Annals of Internal Medicine REVIEW

Cardiovascular Events and Mortality in White Coat Hypertension

A Systematic Review and Meta-analysis

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Background: The long-term cardiovascular risk of isolated elevated office blood pressure (BP) is unclear.

Purpose: To summarize the risk for cardiovascular events and all-cause mortality associated with untreated white coat hypertension (WCH) and treated white coat effect (WCE).

Data Sources: PubMed and EMBASE, without language restriction, from inception to December 2018.

Study Selection: Observational studies with at least 3 years of follow-up evaluating the cardiovascular risk of WCH or WCE compared with normotension.

Data Extraction: 2 investigators independently extracted study data and assessed study quality.

Data Synthesis: 27 studies were included, comprising 25 786 participants with untreated WCH or treated WCE and 38 487 with normal BP followed for a mean of 3 to 19 years. Compared with normotension, untreated WCH was associated with an increased risk for cardiovascular events (hazard ratio [HR], 1.36 [95% CI, 1.03 to 2.00]), all-cause mortality (HR, 1.33 [CI, 1.07 to 1.67]), and cardiovascular mortality (HR, 2.09 [CI, 1.23 to 4.48]); the risk of WCH was attenuated in studies that included stroke in the definition of cardiovascular events (HR, 1.26 [CI, 1.00 to 1.54]). No significant association was found between treated WCE and cardiovascular events (HR, 1.12 [CI, 0.91 to 1.39]), all-cause mortality (HR, 1.11 [CI, 0.89 to 1.46]), or cardiovascular mortality (HR, 1.04 [CI, 0.65 to 1.66]). The findings persisted across several sensitivity analyses.

Limitation: Paucity of studies evaluating isolated cardiac outcomes or reporting participant race/ethnicity.

Conclusion: Untreated WCH, but not treated WCE, is associated with an increased risk for cardiovascular events and all-cause mortality. Out-of-office BP monitoring is critical in the diagnosis and management of hypertension.

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Hypertension, the foremost preventable cause of disability and premature mortality worldwide (1), is diagnosed most commonly with in-office blood pressure (BP) measurements. However, recent guidelines strongly recommend out-of-office BP monitoring (including ambulatory BP monitoring [ABPM] and self– or home BP monitoring [HBPM]) for the diagnosis and management of hypertension (2–4). Increased use of out-of-office BP monitoring in recent decades has led to the identification of several BP phenotypes with different prognostic implications regarding long-term cardiovascular risk (5–7). These BP phenotypes, which require a combination of in-office and out-of-office BP readings to ascertain, include sustained normotension (that is, normal in-office and out-of-office BP in persons not receiving antihypertensive treatment), controlled hypertension (normal in-office and out-of-office BP in persons receiving antihypertensive treatment), masked hypertension (normal in-office but elevated out-of-office BP), white coat hypertension (WCH) (elevated in-office but normal out-of-office BP, described as WCH in persons not receiving antihypertensive treatment and as white coat effect [WCE] or white coat uncontrolled hypertension in those receiving antihypertensive treatment), and uncontrolled hypertension (elevated in-office and out-of-office BP).

Despite guideline recommendations, real-world practice has been slow to adopt out-of-office BP monitoring (8). The clinical inertia surrounding out-of-office BP monitoring seems to be driven by several provider-, patient-, and policy-related factors (9, 10). A major barrier is skepticism over the utility of screening for isolated office hypertension (that is, untreated WCH and treated WCE) due to unclear evidence (9). The burden and risks of WCH, in particular, differ across studies. In a systematic review for the U.S. Preventive Services Task Force, Piper and colleagues (11) reported that the prevalence of WCH ranged from 5% to 65% in studies using ABPM and 16% to 55% in those using HBPM. They also found that WCH carried a higher cardiovascular risk than normotension in several studies but that these findings were not consistent across studies (11). Furthermore, the authors noted that studies of treated WCE showed no increased risk for adverse cardiovascular outcomes. Likewise, previous meta-analyses demonstrated weak association of WCH with cardiovascular risk and weak or no association with all-cause mortality (12, 13). However, these meta-analyses did not adequately explore factors contributing to the inconsistent findings across studies. Moreover, several additional studies evaluating the association between WCH and adverse cardiovascular outcomes were subsequently published.

In this meta-analysis, we aimed to thoroughly assess the association of untreated WCH and treated

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WCE with future cardiovascular events and all-cause mortality. This information might promote more widespread adoption of out-of-office BP monitoring as standard of care and may inform policy changes to provide greater reimbursement and support for out-of-office BP monitoring in routine practice.

METHODS

Data Sources and Searches

All steps of the review and meta-analysis were performed by using a predefined protocol (**Supplement**, available at Annals.org) completed on 5 July 2018 in accordance with MOOSE (Meta-analysis of Observational Studies in Epidemiology) guidelines (14). Publications were identified by searching PubMed and EMBASE from inception to 10 December 2018, without language restriction. Search algorithms incorporated *hypertension*, *blood pressure*, and several terms related to WCH, in-office BP, out-of-office BP monitoring, and cardiovascular outcomes (**Supplement**). Additional publications were identified by manual review of reference lists of relevant studies, reviews, and meta-analyses.

Study Selection

Publications were eligible for inclusion if they were studies in adult humans that reported associations of WCH or WCE with nonfatal cardiovascular events (including incident coronary artery disease, myocardial infarction, angina, stroke, transient ischemic attack, peripheral artery disease, revascularization procedure, and hospitalization for congestive heart failure), fatal cardiovascular events, or all-cause mortality; had a mean follow-up of at least 3 years; and provided a reference group of persons with normotension or controlled hypertension. Two investigators independently screened abstracts and reviewed full texts to determine eligibility. Any discrepancies were resolved by a third reviewer.

Data Extraction and Quality Assessment

Two investigators independently extracted data from each eligible publication by using a standardized form (**Supplement**). Data extracted included cohort name; year of publication; country and location of the study; study design; inclusion and exclusion criteria; type and duration of out-of-office BP measurement; criteria for diagnosis of WCH or WCE; number of study participants overall and with WCH or WCE; number of participants receiving antihypertensive treatment at baseline; number of participants with a history of diabetes, cardiovascular disease, or chronic kidney disease; number of participants who were current smokers and were male; mean age, body mass index, and duration of follow-up; covariates included in statistical adjustment; outcomes reported and outcome definitions; adjusted risk estimates, separated by antihypertensive treatment status (treated, untreated, or treated and untreated combined); and type of outcome (fatal and nonfatal cardiovascular event, fatal cardiovascular event, or all-cause mortality). Any discrepancies were resolved by a third reviewer. Study authors were contacted directly by the lead author if a publication met all inclusion criteria but did not report the outcomes in a way that could be extracted for meta-analysis (for example, if 95% CIs were not reported).

Quality of the evidence was evaluated by 2 investigators using a modified QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies 2) tool to assess individual study bias for each outcome (**Supplement**). The QUADAS-2 tool assesses whether a study has low, high, or unclear risk of bias across 4 domains: patient selection, index test (modified to reflect the quality of the ABPM or HBPM assessment), reference standard (modified to reflect the quality of the in-office BP), and flow and timing (15). The modified tool incorporated quality of the statistical analyses, handling of confounding, and outcome assessment. Confounding was considered to be adequately addressed if adjustment was made for age, sex, previous cardiovascular events, antihypertensive medication, and at least 2 additional covariates among smoking status, lipid levels, diabetes mellitus, body mass index, kidney function, left ventricular hypertrophy, clinic BP, and alcohol use. Studies were determined to have a high risk of bias in the handling of confounding if the same covariates were used for analyzing cardiovascular events and all-cause mortality without otherwise accounting for potential differential confounding (for example, participant exclusion for important risk factors for all-cause mortality, such as cancer or high infectious risk). The primary analyses were restricted to studies determined to have a low risk of bias across at least 5 of 7 domains of the modified QUADAS-2.

Data Synthesis and Analysis

Meta-analyses were performed by calculating pooled log hazard ratios using random-effects inverse-variance models, with profile likelihood estimation (16–18) and Bartlett correction (in analyses of more than 5 studies) (19) to address heterogeneity across the relatively small number of studies. All analyses incorporated multivariable-adjusted hazard ratios to quantify the association between WCH or WCE and each of the outcomes, with normotension or controlled hypertension as the reference group. The primary analyses were stratified by baseline antihypertensive treatment status reported in each study (WCH [untreated], WCE [treated], or combined). The primary outcomes evaluated were fatal and nonfatal cardiovascular events and all-cause mortality. Heterogeneity was assessed by Cochran *Q* test and quantified with the I^2 index (20) in analyses of 3 or more studies. Begg rank correlation (21) and Egger weighted linear regression (22) tests were planned to assess for small study effects (that is, publication bias). However, these tests do not perform well with fewer than 10 studies contributing to a given estimate, and consequently they were omitted.

In instances with more than 1 publication from the same cohort, data from the most recent and applicable report were used for the primary analyses; other publi-

cations from that cohort were included in pertinent subgroup analyses if the data were not available from the most recent publication.

Analyses were performed with the admetan and metabias packages in Stata, version 15.1 (StataCorp).

Role of the Funding Source

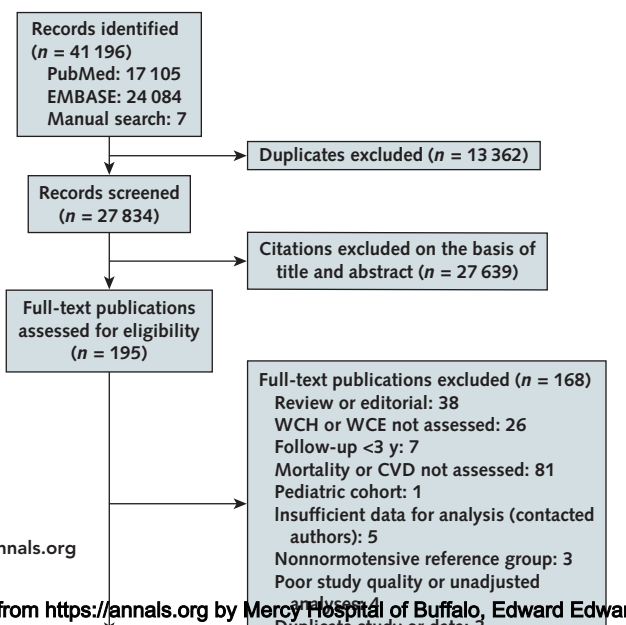
The funding source had no role in the study design or implementation.

RESULTS

The search strategy identified 27 publications that were eligible for inclusion from 29 unique cohorts, involving 25 786 persons with WCH or WCE and 38 487 with normotension or controlled hypertension (Figure 1 and Supplement Table 1, available at Annals.org). Two studies were based in North America, 13 in Europe, 7 in Asia, and 5 across several regions. Fourteen studies reported funding from government, university, medical society, or research foundation grants; 3 reported only industry sponsorship; 4 reported a combination of industry and government or foundation funding; and 6 (encompassing 4 distinct cohorts) did not report any source of funding. Six studies were population based, 11 recruited participants from outpatient clinics, and 10 included patients who were referred for ABPM or to a specialized hypertension clinic. Eighteen studies assessed out-of-office BP with ABPM, 7 with HBPM, and 2 with both methods. To diagnose WCH or WCE, 15 studies used a daytime out-of-office BP threshold of less than 135/85 mm Hg, 7 used a 24-hour threshold of less than 130/80 mm Hg, and 5 used a different threshold (such as 125/80 mm Hg) or combined both thresholds.

Mean study-specific participant age ranged from 43 to 72 years (median, 56 years) (Supplement Table 2, available at Annals.org), with a mean follow-up of 3 to 19 years (median, 8 years). After 3 studies were excluded because of overlapping cohort-specific data with regard to the primary outcomes, 24 studies were included in the primary analyses. All studies included in the primary analyses demonstrated a low risk of bias in at least 5 of 7 domains of the modified QUADAS-2 tool (Supplement Table 3, available at Annals.org). All multivariable models, at minimum, accounted for age, sex, and prior cardiovascular events (Supplement Table 4, available at Annals.org); 25 studies incorporated antihypertensive medication in the models, and all studies adjusted for at least 2 additional covariates among smoking status, lipid levels, diabetes mellitus, body mass index, kidney function, and left ventricular hypertrophy. Nine studies that evaluated both cardiovascular events and all-cause mortality used the same models for both outcomes without clear justification.

Figure 1. Evidence search and selection.



Cardiovascular Events

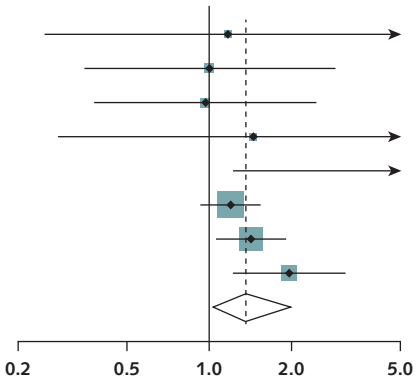
Twenty-one studies reported risk for fatal and nonfatal cardiovascular events among participants with WCH or WCE versus those with normotension or controlled hypertension (Figure 2). In the primary analyses of studies stratified by antihypertensive treatment status, participants with WCH had a higher risk for cardiovascular events than those with normotension (hazard ratio [HR], 1.36 [95% CI, 1.03 to 2.00]), whereas patients with WCE had no increased risk for cardiovascular events (HR, 1.12 [CI, 0.91 to 1.39]). In the primary analyses of studies that did not stratify by antihypertensive treatment status, WCH or WCE was not associated with increased risk for cardiovascular events overall compared with normotension or controlled hypertension (HR, 1.26 [CI, 0.95 to 1.73]); however, restricting the analyses to unstratified studies in which fewer than half of the participants were receiving antihypertensive treatment showed an increased risk for cardiovascular events associated with WCH or WCE (HR, 1.42 [CI, 1.00 to 2.15]). These findings were more robust when the analyses were restricted to studies in which fewer than 20% of participants were receiving antihypertensive treatment (HR, 2.45 [CI, 1.31 to 4.30]).

All-Cause Mortality

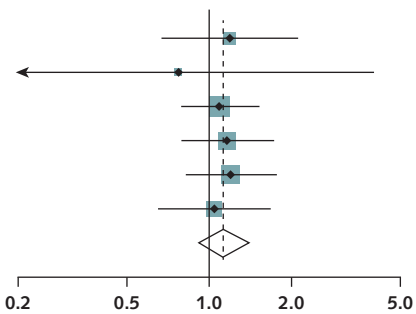
Eleven studies reported on all-cause mortality risk in WCH or WCE relative to normotension or controlled hypertension (Figure 3). The primary analyses of studies stratified by antihypertensive treatment status demonstrated an increased mortality risk in participants with WCH (HR, 1.33 [CI, 1.07 to 1.67]) versus those with normotension or controlled hypertension. No increase in mortality risk was observed in participants with WCE (HR, 1.11 [CI, 0.89 to 1.46]). In studies that did not stratify by antihypertensive treatment status, WCH or WCE was associated with an increased risk for death (HR, 1.46 [CI, 1.03 to 2.08]) if fewer than half of the participants were receiving treatment, but not if at least half were receiving treatment (HR, 1.34 [CI, 0.82 to 2.18]). These findings were corroborated after the analyses were restricted to studies in which fewer than 20% of participants were receiving treatment (HR, 2.00 [CI, 1.16 to 3.47]).

Figure 2. Cardiovascular event risk in WCH and WCE.

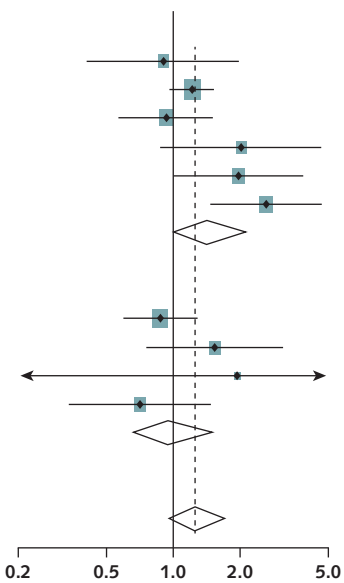
Study, Year (Reference)	Total Participants, *n*	HR (95% CI)
Verdecchia et al, 1994 (23)	1392	1.17 (0.25–5.33)
Fagard et al, 2005 (24)	359	1.00 (0.35–2.90)
Pierdomenico et al, 2008 (25)	2037	0.97 (0.38–2.46)
Mancia et al, 2013 (26)	1589	1.45 (0.28–7.51)
Sung et al, 2013 (27)	1257	5.59 (1.22–25.55)
Asayama et al, 2014 (28)	8237	1.20 (0.93–1.54)
Stergiou et al, 2014 (29)	6458	1.42 (1.06–1.91)
Banegas et al, 2018 (30)	63 910	1.96 (1.22–3.15)
Overall (I^2 = 0.0%; *P* = 0.379)		1.36 (1.03–2.00)



Study, Year (Reference)	Total Participants, *n*	HR (95% CI)
Bobrie et al, 2004 (31)	4939	1.18 (0.67–2.10)
Shimada et al, 2008 (32)	2896	0.77 (0.15–3.96)
Franklin et al, 2012 (33)	7295	1.09 (0.79–1.52)
Stergiou et al, 2014 (29)	6458	1.16 (0.79–1.72)
Pierdomenico et al, 2017 (34)	1191	1.20 (0.82–1. 76)
Banegas et al, 2018 (30)	63 910	1.04 (0.65–1.66)
Overall (I^2 = 0.0%; *P* = 0.992)		1.12 (0.91–1.39)



Study, Year (Reference)	Total Participants, *n*	Participants Receiving Treatment, %	HR (95% CI)
<50% receiving BP treatment			
Fagard et al, 2005 (24)	359	32	0.90 (0.40–2.00)
Hansen et al, 2007 (35)	7030	22	1.22 (0.96–1.53)
Hänninen et al, 2012 (36)	2046	23	0.93 (0.56–1.52)
Mancia et al, 2013 (26)	1589	19	2.04 (0.87–4.78)
Tientcheu et al, 2015 (37)	3027	21	1.98 (0.99–3.95)
Ntineri et al, 2018 (38)	665	15	2.67 (1.48–4.80)
Subgroup (I^2 = 46.8%; *P* = 0.051)			1.42 (1.00–2.15)
≥50% receiving BP treatment			
Hermida et al, 2012 (39)	3344	62	0.87 (0.59–1.29)
Minutolo et al, 2014 (40)	512	89	1.55 (0.75–3.19)
Wang et al, 2017 (41)	588	75	1.96 (0.12–32.12)
Fujiwara et al, 2018 (42)	4261	79	0.70 (0.33–1.49)
Subgroup (I^2 = 0.0%; *P* = 0.417)			0.94 (0.65–1.52)
Heterogeneity between groups: *P* = 0.066			
Overall (I^2 = 47.5%; *P* = 0.045)			1.26 (0.95–1.73)



Vertical dashed lines represent the value of the overall pooled HR; large, open diamonds represent the overall pooled HR and 95% CI; shaded boxes represent the individual study weights; and small, solid diamonds represent the HR of each study. BP = blood pressure; HR = hazard ratio; WCE = white coat effect; WCH = white coat hypertension. **Top.** Untreated WCH. **Middle.** Treated WCE. **Bottom.** Results not stratified by antihypertensive treatment.

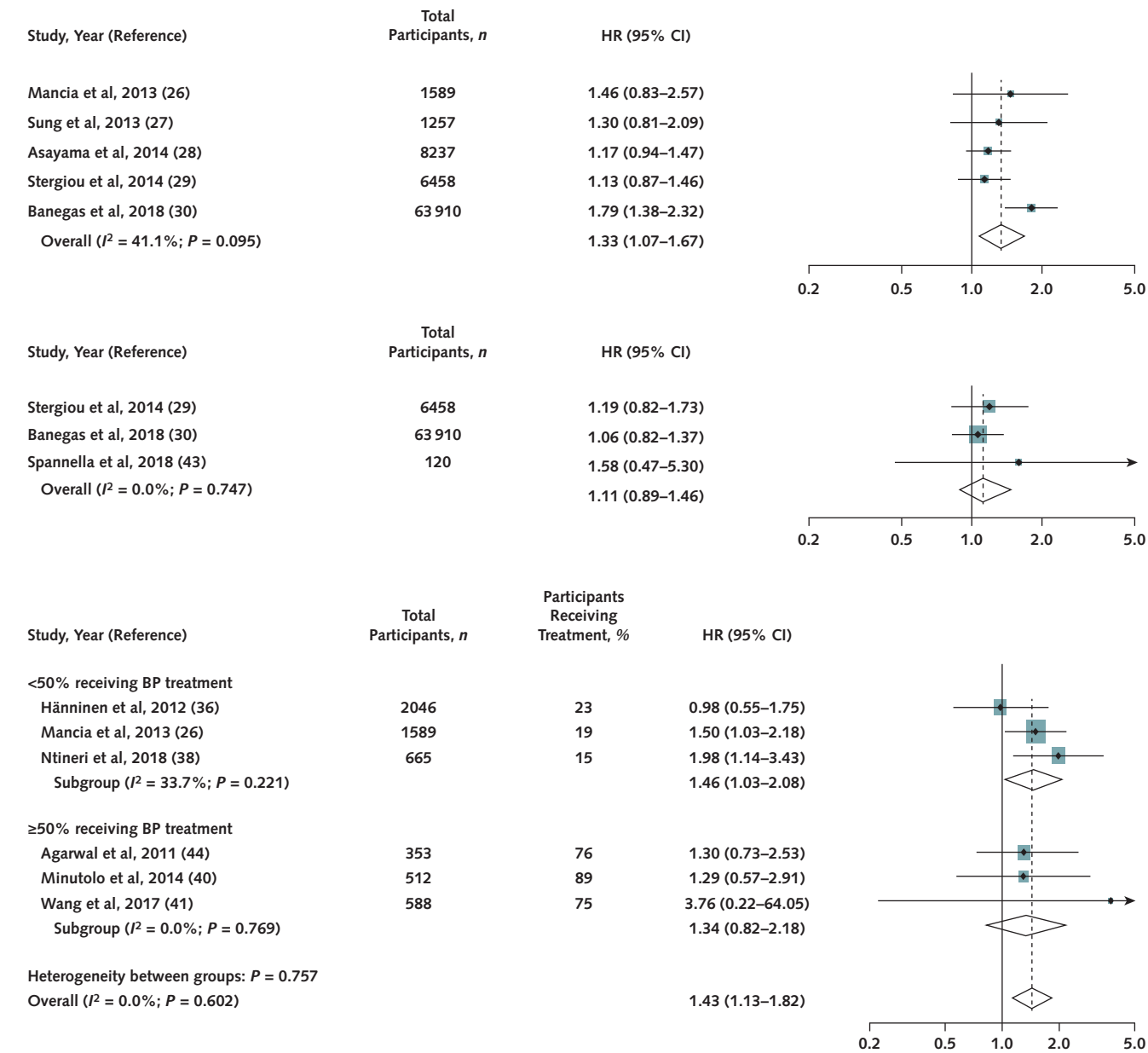
Sensitivity Analyses by Outcome Definitions

In sensitivity analyses evaluating differential reporting of cardiovascular events (Table), WCH was associated with increased cardiovascular mortality (HR, 2.09 [CI, 1.23 to 4.48]), whereas WCE was not (HR, 1.04 [CI, 0.65 to 1.66]). Risk from WCH was attenuated in a limited number of studies that reported fatal and nonfatal stroke (WCH: HR, 1.15 [CI, 0.61 to 2.16]; combined WCH and WCE: HR, 1.27 [CI, 0.53 to 2.31]). Studies that included stroke in the definition of cardiovascular events also demonstrated lower risk from WCH (HR, 1.26 [CI, 1.00 to 1.54]) than those that did not include stroke in the definition of cardiovascular events (HR, 2.09 [CI, 1.23 to 4.48]).

Sensitivity Analyses by Study Design Characteristics

Several analyses were performed to explore potential sources of heterogeneity and differences in outcomes across the treatment groups. In subgroup analyses of study design characteristics (Supplement Table 5, available at Annals.org), the overall results were sim-

Figure 3. All-cause mortality risk in WCH and WCE.



Vertical dashed lines represent the value of the overall pooled HR; large, open diamonds represent the overall pooled HR and 95% CI; shaded boxes represent the individual study weights; and small, solid diamonds represent the HR of each study. BP = blood pressure; HR = hazard ratio; WCE = white coat effect; WCH = white coat hypertension. **Top.** Untreated WCH. **Middle.** Treated WCE. **Bottom.** Results not stratified by antihypertensive treatment.

Table. Subgroup Analyses, by Reporting of Outcome Events in Participants With WCH or WCE Compared With Participants With Normotension or Controlled Hypertension

Outcome Definition	WCH (Untreated)			WCE (Treated)			Combined WCH and WCE		
	Studies, *n*	HR (95% CI)	I^2, % (*P* Value)*	Studies, *n*	HR (95% CI)	I^2, % (*P* Value)*	Studies, *n*	HR (95% CI)	I^2, % (*P* Value)*
Fatal CVD events (i.e., cardiovascular mortality)	3	2.09 (1.23–4.48)	0 (0.393)	1	1.04 (0.65–1.66)	–	2	1.74 (0.90–3.43)	–
Only fatal and nonfatal stroke reported	1	1.15 (0.61–2.16)	–	–	–	–	2	1.27 (0.53–2.31)	–
Included stroke in definition of CVD									
Yes	5	1.26 (1.00–1.54)	0 (0.866)	5	1.14 (0.94–1.39)	0 (0.984)	9	1.22 (0.90–1.68)	48.0 (0.046)
No	3	2.09 (1.23–4.48)	0 (0.393)	1	1.04 (0.65–1.66)	–	1	2.04 (1.87–4.78)	–
Included CHF in definition of CVD									
Yes	3	1.27 (1.00–1.59)	0 (0.587)	4	1.15 (0.94–1.40)	0 (0.984)	7	1.33 (0.96–1.98)	54.1 (0.040)
No	5	1.82 (1.08–2.85)	0 (0.432)	2	1.02 (0.49–1.88)	–	3	1.05 (0.52–2.21)	13.8 (0.166)

CHF = congestive heart failure; CVD = cardiovascular disease; HR = hazard ratio; WCE = white coat effect; WCH = white coat hypertension.
* I^2 value was not reported in analyses of <3 studies because of insufficient statistical power to assess for heterogeneity.

ilar regardless of level of bias (based on the modified QUADAS-2 tool). Results also were similar to those of the primary analyses when restricted to studies that used ABPM (as opposed to HBPM) to determine WCH or WCE; had a mean participant age of 55 years or greater; used validated BP monitors; used a daytime BP threshold of less than 135/85 mm Hg for defining WCH or WCE; recruited participants for the study (as opposed to them being referred for indication-specific ABPM); had at least 2000 participants; had a mean follow-up of at least 5 years; were published after 2012; and included persons with a history of cardiovascular disease, chronic kidney disease, or diabetes. The elevated risk for cardiovascular events associated with WCH dissipated in the 1 study that did not use validated BP monitors (HR, 1.20 [CI, 0.93 to 1.54]) and in studies that had referred participants (HR, 1.31 [CI, 0.92 to 1.98]), had fewer than 2000 participants (HR, 1.56 [CI, 0.71 to 4.01]), had less than 5 years of follow-up (HR, 1.87 [CI, 0.84 to 3.36]), were published in 2012 or earlier (HR, 1.01 [CI, 0.53 to 1.97]), used HBPM (HR, 1.42 [CI, 0.88 to 2.31]), defined WCH by using a 24-hour BP threshold of less than 130/80 mm Hg (HR, 1.36 [CI, 0.91 to 2.33]), had a mean participant age less than 55 years (HR, 1.21 [CI, 1.00 to 1.51]), or excluded persons with previous cardiovascular disease (HR, 0.98 [CI, 0.44 to 2.20]).

Influence analyses demonstrated no meaningful differences in the HRs for cardiovascular events upon omission of each study from the primary analyses (**Supplement Table 6**, available at Annals.org).

DISCUSSION

Our findings from 27 studies involving more than 64 000 patients who had in-office and out-of-office BP monitoring demonstrate that untreated WCH is associated with an increased risk for cardiovascular events and all-cause mortality compared with normotension, whereas treated WCE is not associated with an elevated risk. These results persisted across many sensitivity analyses.

Our literature review identified several previous systematic reviews and meta-analyses that evaluated WCH and longitudinal cardiovascular risk (12, 13, 45). These reviews reported data from fewer studies than the current review and performed limited sensitivity analyses to explore differences across the studies. Several studies evaluating the longitudinal association of WCH and adverse cardiovascular outcomes and mortality have been published since the earlier reviews (30, 34, 37, 38, 40–43, 46), providing more robust data and greater opportunity for detailed sensitivity analyses. Moreover, previous meta-analyses used fixed-effects modeling as the analytic approach, which does not adequately address differences in study design and participant characteristics observed across the studies (47). In contrast to previous meta-analyses, we used random-effects modeling with profile likelihood estimation, which is particularly suited to address the presence of these types of dissimilarities (16, 17). We also included studies in patients with diabetes and chronic kidney disease, which previously were excluded (12). We instead performed sensitivity analyses that showed no meaningful differences in studies that included these groups.

The current review supports and expands on earlier findings in several ways. Similar to previous reviews (12, 13), we determined that WCH is associated with an increased risk for cardiovascular events. Unlike previous meta-analyses, we had sufficient statistical power to also demonstrate an increased risk for all-cause and cardiovascular mortality in WCH. We were also able to explore the effect of cause-specific outcomes on the findings across studies. Most notably, WCH did not seem to be associated with an increased risk for stroke (42, 46, 48, 49). To support this observation further, the cardiovascular risk of WCH was attenuated in studies that included stroke in the definition of cardiovascular events (23–25, 28, 29). We also evaluated potential factors contributing to inconsistent outcomes in studies that combined participants with untreated WCH and those with treated WCE. An increased risk for cardio-

vascular events and death associated with WCH or WCE was seen in studies in which fewer than half of the participants were receiving antihypertensive treatment at baseline (24, 26, 35–38), which was corroborated when analyses were restricted to studies in which fewer than 20% of participants were receiving treatment at baseline (26, 38). No increase in risk was observed in studies in which at least half of the participants were receiving treatment at baseline (39–42, 44). These findings suggest that the risk for cardiovascular events and death in studies combining WCH and WCE is probably driven by the proportion of participants with untreated WCH. We conclude that future studies evaluating the association of WCH with adverse cardiovascular outcomes would benefit from stratifying by baseline antihypertensive treatment status and reporting stroke outcomes separate from other cardiovascular outcomes.

We found that differences in study design characteristics may explain many discrepancies in findings across studies. For example, studies that had a mean participant age of less than 55 years or excluded persons with previous cardiovascular disease were associated with a mitigated risk for cardiovascular events in WCH. These findings are consistent with detailed subgroup analyses by Franklin and colleagues (50) in the International Database of Ambulatory Blood Pressure in Relation to Cardiovascular Outcomes, which suggest that the long-term cardiovascular risk of WCH is largely associated with older age and higher baseline cardiovascular risk. However, these findings may be related to follow-up that was too short to observe events in younger, lower-risk populations. The cardiovascular risk of WCH was attenuated in studies with shorter follow-up (<5 years, which also was correlated with an earlier study year). In the 2 studies that reported rates of progression to sustained hypertension, participants with WCH had an approximately 3- to 4-fold increased risk for sustained hypertension compared with those with normotension over 7 to 10 years of follow-up (26, 37). Longer follow-up may be associated with increased risk for cardiovascular events in WCH because of greater conversion to sustained hypertension.

We also determined that the risk from WCH was diminished in studies that used a mean 24-hour BP of less than 130/80 mm Hg rather than a daytime BP of less than 135/85 mm Hg to define WCH or WCE (23, 28, 30). The differences in findings across BP thresholds are supported by a study by Asayama and colleagues (28), who demonstrated that compared with daytime or nighttime BP alone, using 24-hour BP to define WCH eliminated the increased risk for cardiovascular events associated with WCH. In addition, the adverse cardiovascular risks of WCH were attenuated in studies that included persons who were referred for ABPM and not actively recruited from a broader population. We suspect that this finding represents the effects of selection bias. In particular, control groups identified as having an indication for ABPM may have greater underlying risk at baseline than persons with normotension in the community, biasing the results toward the null. Use of HBPM, as opposed to ABPM, was also associated with attenuation in the cardiovascular risk of WCH, consistent with recent studies suggesting that ABPM may be superior to HBPM as an indicator of cardiovascular risk in masked hypertension (51, 52). Moreover, we found that use of an unvalidated BP monitor mitigated the association of WCH with adverse cardiovascular events, potentially reflecting measurement error (53).

The recent trial by Banegas and colleagues (30), included in this meta-analysis, was a Spanish registry study of 63 910 persons who had 24-hour ABPM, with a median follow-up of 4.7 years. This study was by far the largest included in the meta-analysis, and its results paralleled our overall findings. Mean age, frequency of prior cardiovascular events, and smoking status in the Spanish registry study approximated the medians across the included cohorts, although the Spanish study had a higher proportion of participants with diabetes mellitus (20% vs. a median of 11%). This study subjectively seemed to have a substantial effect on the results of our meta-analysis; however, influence analyses demonstrated no objective difference in the overall results when this study was excluded. Although the Spanish registry study had several limitations (such as referral for diagnostic ABPM rather than study-specific recruitment), we infer that the large sample size and the authors' careful attention to antihypertensive treatment status contributed to highly generalizable results. To be specific, participants were stratified by antihypertensive treatment status, with further adjustment by number (and in sensitivity analyses, type) of antihypertensives among those with treated hypertension. In addition, the authors evaluated cardiovascular mortality and all-cause mortality separately, which was done in only a few studies in our meta-analysis.

The current meta-analysis has several important limitations. Much like previous meta-analyses (12, 13, 45), our review is limited by the use of observational cohort studies, which are prone to unmeasured confounding that may not be adequately addressed by robust study-specific adjustment and meta-analytic methods. In addition, several subgroup analyses were limited to a very small number of studies. For example, only 1 study reported the association of untreated WCH alone (that is, not combined with treated WCE) with fatal and nonfatal stroke (48), and no studies reported the association between untreated WCH and other distinct cardiovascular end points (such as ischemic coronary disease). We suspect the dearth of publications evaluating the association of WCH with stroke may be related to consistently negative findings in studies in which it was assessed. Finally, few studies reported race/ethnicity (37, 44), precluding examination of risk differences in potentially high-risk minority groups.

Findings from this review have important clinical and public health implications. In conjunction with the elevated cardiovascular risk previously associated with masked hypertension (54), the elevated cardiovascular risk associated with WCH underscores the importance of recent guidelines recommending out-of-office BP

screening for the diagnosis of hypertension (2, 3). These findings advocate policies to support broader implementation of out-of-office BP monitoring in routine clinical practice. To promote widespread use of out-of-office BP monitoring, more comprehensive insurance reimbursement and provider training are needed (10). Furthermore, this review supports the need for additional studies, specifically those evaluating cardiovascular risk of WCH in ethnic minority groups, risk for isolated cardiac end points (such as stroke and ischemic heart disease) in WCH, and approaches to reduce cardiovascular risk in persons with WCH.

In conclusion, persons with untreated WCH, but not those with treated WCE, have a markedly increased risk for cardiovascular events and all-cause mortality compared with persons with normal BPs. The cardiovascular risk of WCH was particularly evident in studies of older patients, studies that used ABPM with daytime BP less than 135/85 mm Hg as the threshold for BP control, studies with at least 5 years of follow-up, and studies that excluded stroke from the definition of cardiovascular events. These findings support more widespread use of out-of-office BP monitoring in the diagnosis and management of hypertension. Untreated patients with isolated office hypertension should be monitored closely for transition to sustained hypertension (26, 37), whereas patients receiving treatment may be harmed by overly aggressive management (11, 55). Taking into account recommendations from the recent hypertension guideline from the American College of Cardiology and American Heart Association (2) and the increased cardiovascular risk associated with WCH, we encourage lifestyle modifications (including improved diet, exercise, weight loss, reduction in alcohol use, and smoking cessation) in all patients found to have WCH. This systematic review and meta-analysis highlights the importance of future trials to evaluate interventions to reduce cardiovascular risk in WCH.

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Reproducible Research Statement: *Study protocol:* See the Supplement (available at Annals.org). *Statistical code:* Available from Dr. J.B. Cohen (e-mail, jco@pennmedicine.upenn.edu). *Data set:* See **Supplement Tables 1** to **6** (available at Annals.org). Additional data are available from Dr. J.B. Cohen (e-mail, jco@pennmedicine.upenn.edu).

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