Original Article

Relationships between cardiovascular risk factors and white-coat hypertension diagnosed by home blood pressure recordings in a middle-aged population

Martina A.K. Johansson, Carl Johan Östgren, Jan Engvall, Eva Swahn, Magnus Wijkman, and Fredrik H. Nystrom

Objective: To study risk in white-coat hypertension (WCH) by measurement of coronary artery calcium score (CACS), carotid–femoral pulse-wave velocity (PWV) and carotid plaques.

Methods: Cross-sectional population-based cohort with randomized selection of participants from Linköping, Sweden. An Omron m10-IT oscillometric device was used for clinic and home blood pressures (HBP) in the morning and evening for 1 week.

Results: We recruited 5029 middle-aged and mainly defined WCH as SBP at least 140 mmHg and/or DBP at least 90 mmHg with HBP less than 135/85 mmHg. There were 2680 normotensive participants and 648 had WCH after exclusion of treated participants. More women (59.5%) than men (42.8%, $P < 0.001$) had WCH. We found higher prevalence of CACS greater than 100 compared with less than 100 (12.4 vs. 7.2%, $P < 0.001$), PWV (11.5 ± 1.5 vs. 10.4 ± 1.3 m/s, $P < 0.001$) and a higher prevalence of one or more carotid plaques (59.5 vs. 48%, $P < 0.001$) in participants with WCH than in normotension. Participants with WCH also had more dyslipidemia and higher glucose levels. Normotensive women scored lower on nervousness than women with WCH ($P = 0.022$). After matching of 639 participants with WCH to normotensive participants according to age, gender and systolic HBP the prevalence of a high CACS (12.1 vs. 8.6%, $P = 0.003$,) PWV (11.0 ± 0.068 vs. 11.5 ± 0.068 m/s, estimated marginal means ± SE, $P < 0.001$ by ANOVA) but not more carotid plaques (59.5 vs. 55.6%, $P = 0.23$), remained in the participants with WCH compared with the matched normotensive participants.

Conclusion: WCH is particularly common in middle-aged women, and it displays metabolic dysfunction and increased prevalence of arteriosclerotic manifestations in both genders. As markers of increased cardiovascular risk were present also after matching normotensive and WCH participants according to systolic HBP, age and gender, the presence of WCH signals an increased cardiovascular risk burden that is not fully explained by elevated BP levels at home.

INTRODUCTION

Home blood pressure (HBP) monitoring is recommended in hypertension guidelines as being a part of regular care to diagnose and guide hypertension treatment [1]. It is widely recognized that office BP (OBP) recordings often inaccurately reflects the out-of-office BP levels [2,3]. White-coat hypertension (WCH) is a common example of such deviations and it is defined by having hypertensive BP levels in the office but normal ambulatory or HBP levels [4]. Most analyses of WCH have used a cut-off of less than 140 mmHg/less than 90 mmHg as a normal blood pressure for OBP and less than 135 mmHg/less than 85 mmHg as the corresponding normal HBP level [5]. The increase of BP in the office compared with BP measured outside the office, has been termed the white-coat effect, that is, OBP − HBP or ambulatory blood pressure [6]. However, the specific effect on cardiovascular disease (CVD) that is related to WCH is under debate. Although many

studies have shown increased target organ damage or cardiovascular complications in WCH [7–9], others have demonstrated similar left ventricular mass or prognosis when WCH was compared with a truly normotensive population [10–14]. However, a limitation in the search for determinants of potential risk related to WCH is that differences in other cardiovascular risk factors and actual out of-office BP levels in the two groups was usually not taken into account [8]. These factors limit the determination of the specific blood pressure-related risk of the WCH phenomenon or of the white-coat effect. Indeed, left ventricular mass did not differ in relation to the magnitude of the white-coat effect after matching according to day-time BP levels [15].

An elevated level of several metabolic and inflammatory risk markers has been documented in cross-sectional studies in which participants with WCH have been compared with normotensive participants [13,16]. In the large population-based Italian PAMELA trial, the increase in plasma glucose levels and incidence of new-onset diabetes among 1412 participants was significantly greater in individuals with WCH than in normotensives over a 10-year period [17]. Along with the metabolic alterations, WCH has also been associated with a stronger activation of the sympathetic nervous system [18]. This could imply that these patients have poorer tolerance for stress with an active sympathetic nervous system that also makes them more prone for attaining dysmetabolic side effects. In line with this, the long-term risk for developing sustained hypertension is high in participants with WCH [5,19].

To the best of our knowledge, the relationships between WCH and CVD risk, in which HBP and OBP were measured with the same device, has not been described in any large population-based cohort with randomized selection of participants. Thus, we aimed to characterize WCH in such a cohort to study presence of arteriosclerosis as judged by levels of coronary artery calcium score (CACS), pulse wave velocity (PWV) and presence of carotid plaques.

MATERIALS AND METHODS

Blood pressure data were derived from the town of Linköping as a part of the Swedish CArdioPulmonary bioImage Study (SCAPIS), which is a collaborative project that set out to recruit 30 000 individuals, 50–64 years old, during 2013–2018. The participants all lived in the six Swedish major university cities (Gothenburg, Linköping, Malmö/Lund, Stockholm, Umeå and Uppsala) in which local representatives at the corresponding medical universities ran the trial [20]. For inclusion in the study participants, had to be 50–65 years old and they had to live in one of the selected areas. All participants gave written informed consent for participation in the study, and they had to have the ability to understand instructions and complete questionnaires in the Swedish language. In addition to determining traditional cardiovascular risk factors, the participants underwent extensive imaging using noncontrast-enhanced and contrast-enhanced computer tomography (CT), including calcium scoring of the coronary arteries (CACS) by computed tomography coronary arterial angiography (CTCA) and ultrasonography of the carotid arteries [20]. All participants

filled out extensive electronic questionnaires about known and diagnosed diseases and risk conditions, employment, marital status and educational level on dedicated computers at the trial offices. They also answered questions about exercise habits, smoking, food intake, medications, nutritional supplements and the sense of quality of life [20] including the validated SF-36 health survey [21].

Ethics

Data analysis was approved by the Regional Ethics Committee of Linköping and performed in accordance with the Declaration of Helsinki of 1975. The study was approved by the Regional Ethical Review board in Umeå (# 2010-228-31 M).

Blood pressure measurements

The participants in SCAPIS Linköping were also asked to participate in an additional investigation of a weeklong recording of HBP that was performed in between the two trial days of the SCAPIS protocol. The OBP in SCAPIS was measured by a semi-automatic Omron m10-IT oscillometric device (Omron, Kyoto, Kyoto Prefecture, Japan) during the investigations on the first of the two examination days in SCAPIS. Brachial arterial blood pressure was measured in both arms, and it was registered in the supine position after 5 min rest. The cuff size was adjusted according to arm circumference and the cuff was at level with the heart. The blood pressure registration was repeated with at least 1 min between measurements. If the two results differed more than 10 mmHg (either systolic or diastolic), the measurement was repeated until two subsequent results were within ±10 mmHg after a maximum of four attempts. If the difference was still more than 10 mmHg, the last two measurements were used. The participants did not receive information about the results until all measurements were completed. The mean value from two stable recordings was calculated and defined as OBP. The Omron m10-IT has been found valid, it is technically equivalent to Omron M7 [22]. Participants who accepted participation in the HBP recording were equipped with an identical BP recorder to be used at home. The participants were shown how to use the Omron device in the same manner as at the office, while being at the hospital. The Omron m10-IT recorder was preprogrammed to measure the HBP three times with 1 min between each measurement. The mean value that was presented after the measurements was noted in a notebook, that was provided by the staff, by the participant. This method was preferred, rather than using electronic transfer of the data, as it is similar to clinic routine for HBP recordings in Sweden. All participants were asked to measure the HBP in the seated position, with the cuff at the level of the heart, in the morning and in the evening for 7 days except for the first day in which the morning was spent in the hospital vicinities. Thus, a total of 13 HBP recordings (mean of three each time) were to be executed by the participants. The device and the notebook were handed back to the investigators at the second examination day of the SCAPIS trial and the mean values of the 13 HBP recordings were used in the analyses presented. All patients that were on antihypertensive medication were excluded from the analyses in this report.

TABLE 1. Baseline characteristics

Variable	Normotension N = 2680	Participants with WCH N = 648	P between groups P value
Age (years)	56.6 ± 4.32	58.2 ± 4.5	<0.001
Gender (males/females, %)	46/54	44/56	0.479
Office SBP (mmHg)	119.3 ± 9.6	144.3 ± 8.9	<0.001
Office DBP (mmHg)	76.7 ± 6.4	90.1 ± 5.9	<0.001
Home SBP (mmHg)	112.4 ± 9.2	122.6 ± 7.3	<0.001
Home DBP (mmHg)	72.8 ± 5.9	78.3 ± 4.7	<0.001
Calcium score[a] (% given the number 1)	7.2	12.4	<0.001
Carotid plaques[b] (% given the number 1)	48.0	59.5	<0.001
Pulse wave velocity (m/s)[c]	10.4 ± 1.3	11.5 ± 1.5	<0.001
Total cholesterol (mmol/l)	5.5 ± 1.0	5.7 ± 1.1	<0.001
LDL cholesterol (mmol/l)	3.3 ± 0.9	3.47 ± 0.99	<0.001
Triglycerides (mmol/l)	1.1 ± 0.6	1.3 ± 0.8	<0.001
HbA1c (mmol/mol)	35.2 ± 5.0	36.1 ± 7.1	0.003
Fasting blood glucose (mmol/l)	5.5 ± 0.8	5.8 ± 1.4	<0.001
High sensitive CRP (mg/l)	1.6 ± 3.1	1.7 ± 2.2	0.343
Plasma creatinine (μmol/l)	79.6 ± 14.0	78.9 ± 13.8	0.257
BMI (kg/m^2)	25.6 ± 3.8	26 ± 5.1	<0.001
Waist (cm)	88.9 ± 11.5	92.7 ± 12.2	<0.001
Smoker (%)	231/8.6%	40/6.2%	0.025

Baseline data means ± SD, except for CACS and carotid plaques in which the proportions (%) of dichotomized values of number are presented. The comparisons between groups were done with independent samples t test with exception of CACS and carotid plaques in which chi-square was used. CRP, C-reactive protein; WCH, white-coat hypertension.
[a]Missing values in the total cohort (i.e. of 5029 participants): 160, and in the total group presented in Table 1: 75. Values less than 100 were set as 0 and values of 100 or more as 1 because of skewed distribution for calculation of the P value by chi-square.
[b]Missing values in the total cohort: 2 and none in the total group in Table 1. Values less than 1 were set as 0 and values of 1 or more as 1 because of skewed distribution for calculation of chi-square.
[c]Missing values in the total cohort: 1666 and in the total group presented in Table 1: 996.
WCH was defined as a systolic OBP of at least 140 mmHg and/or diastolic OBP at least 90 mmHg combined with HBP less than 135 mmHg/less than 85 mmHg. Normotensive participants had OBP less than 140 mmHg/less than 90 mmHg and HBP less than 135 mmHg/less than 85 mmHg.

WCH was defined as having a systolic OBP at least 140 mmHg and/or DBP at least 90 mmHg with a concomitant HBP less than 135 mmHg/less than 85 mmHg.

Pulse wave velocity

The results from carotid–femoral PWV were used to assess arterial stiffness, and it was measured by using a Sphygmocor Xcel (SphygmoCor system, model MM3, AtCor Medical, Sydney, Australia). The participants were instructed to refrain from caffeine and heavy meals for 3 h, nicotine for 4 h and alcohol for 12 h prior to the PWV determination, which was recorded on a separate third day of investigations as an additional investigation that was also offered to the participants. Blood pressure cuffs were attached to the upper left arm and to the right thigh, 10–20 cm below the groin. The distance between the femoral pulse acquisition site and the upper margin of the thigh cuff was subtracted from the distance between the carotid receptor and the high and multiplied by 0.8. The PWV was measured twice and the mean value was calculated.

Calcification of the coronary arteries

CACS was assessed in noncontrast-enhanced images from a state-of-the-art multislice computed tomography scanner (Siemens, Somatom Definition Flash, Siemens Medical Solution, Forchheim, Germany). Imaging and analyses were performed using a calcium scoring protocol [23]. The calcium content in each coronary artery was measured and summed to produce a total CACS score according to international standards [24]. An Agatston

score greater than 0 defined presence of coronary artery calcification.

Ultrasonography of carotid arteries

Atherosclerosis in the carotid arteries was assessed according to a standardized protocol with a Siemens Acuson S2000 ultrasound scanner equipped with a 9L4 linear transducer (Siemens). The left and right carotid artery were insonated and atherosclerotic plaques in the common carotid artery, bulb or in the internal carotid artery fulfilling the Mannheim consensus [25] were identified. Visually detected plaques in the carotid arteries were recorded as the number of total plaques. Thus, significant carotid atherosclerosis was defined by the presence of at least one plaque in the carotid arteries.

Statistical analyses

Statistical estimates were calculated using IBM SPSS 27 software (IBM Corporation, Somers, New York, USA). An Independent Samples t test was used for the comparisons between the WCH and normotensive groups seen in Table 1 except for CACS and number of carotid plaques, which were compared by chi-square after dichotomization (CACS <100 set as 0 and 100 or more set as 1, absence of carotid plaques set as 0 and 1 or more plaques set as 1) in Table 1. Comparisons between the matched participants (for age, gender, and home SBP) were performed with a full factorial ANOVA-test in which a matching number for each pair was entered as the covariate. However, comparison of CACS score and presence of carotid plaques were performed by Logistic

TABLE 2. Comparison of normotensive participants and participants with white-coat hypertension after matching for age, gender and home SBPs

Variable	Normotension N = 639	Participants with WCH N = 639	P value between groups by ANOVA (except calcium score and carotid plaques)
Age (years)	57.4 ± 0.17	58.1 ± 0.17	
Gender (men/women, %)	44.4/55.6	44.4/55.6	
Office SBP (mmHg)	128.0 ± 0.32	146.8 ± 0.32	<0.001
Office DBP (mmHg)	80.5 ± 0.22	90.4 ± 0.22	<0.001
Home SBP (mmHg)	123.1 ± 0.25	122.6 ± 0.249	0.159
Home DBP (mmHg)	78.3 ± 0.17	78.3 ± 0.17	0.919
Calcium score[a] (% given the number 1)	8.6	12.1	0.003
Carotid plaques[a] (% given the number 1)	55.6	59.5	0.23
Pulse wave velocity (m/s)[b]	11.0 ± 0.068	11.5 ± 0.068	<0.001
Total cholesterol (mmol/l)	5.47 ± 0.041	5.76 ± 0.041	<0.001
LDL cholesterol (mmol/l)	3.28 ± 0.037	3.48 ± 0.037	<0.001
Triglycerides (mmol/l)	1.19 ± 0.028	1.26 ± 0.028	0.045
HbA1c (mmol/mol)	35.9 ± 0.25	36.0 ± 0.25	0.77
Fasting blood glucose (mmol/l)	5.7 ± 0.045	5.79 ± 0.045	0.18
High sensitive CRP (μmol/l)	2.0 ± 0.12	1.7 ± 0.12	0.063
Plasma creatinine (mg/dl)	78.4 ± 0.55	79.0 ± 0.55	0.42
BMI (kg/m^2)	26.9 ± 0.16	26.8 ± 0.16	0.62
Waist (cm)	92.5 ± 0.47	92.4 ± 0.47	0.92

Full factorial ANOVA (analysis of variance) with matched (for age, gender and home SBP) and grouped variables for comparison between normotensives and WCH. Data are estimated marginal means ± SE, except for CACS and carotid plaques in which the proportion of the number 1 after dichotomization is given and the P value calculated by Logistic regression (see Statistics section for details). WCH was defined as a systolic OBP of at least 140 mmHg and/or diastolic OBP at least 90 mmHg combined with HBP less than 135 mmHg/less than 85 mmHg. Normotensive participants had OBP less than 140 mmHg/less than 90 mmHg and HBP less than 135 mmHg/less than 85 mmHg. Data in both groups were calculated by estimated marginal means and are means and standard errors, except for CACS and carotid plaques. CRP, C-reative protein; LDL, low-density lipoprotein.
[a]Dichotomized values were used in the calculation of the P value by logistic regression, see Statistics section for details.
[b]Missing values in 191 participants in each group, data were also corrected for heart rate.

regression after dichotomization in Table 2. A two-sided *P* value less than 0.05 was considered statistically significant.

RESULTS

A total of 8715 participants were randomly selected and recruited for SCAPIS Linköping. The participation rate was 58% and 5057 participants joined the trial. A total of 5029 of these participants agreed to also perform the HBP recording for 1 week, rendering a participation rate of 99.4% of the participants in SCAPIS Linköping. There were complete registrations of all 13 HBP in 87.3% of the participants and all had at least five registrations performed, 99% had at least nine registrations. There were 2680 participants with normotension (OBP below 140/90 mmHg and HBP below 135/85 mmHg) and 648 had WCH after exclusion of the participants who were on antihypertensive drugs according to the questionnaire (*n* = 912). There were 1666 participants who had missing values on PWV, 160 participants had missing values on CACS and two participants had missing values on carotid ultrasound. The lack of data on PWV was mainly as this investigation did not have full capacity in the start of SCAPIS Linköping, hence most recordings from PWV were from the later time-period of the recruitment of participants.

The WCH was particularly common in women compared with men (proportion of WCH in participants with hypertensive levels of OBP: 59.5% in women 42.8% in men, *P* < 0.001 between genders). As seen in Table 1, participants with WCH had a higher CACS, more prevalence of carotid plaques and higher PWV than normotensive participants, and these statistical differences were not affected after separate calculations according to gender (all

P < 0.005). Participants with WCH also displayed several other signs of increased risk for cardiovascular disease compared with normotensive participants. They had larger waist circumferences (*P* < 0.001 also after correction for gender) less favourable cholesterol levels, and higher fasting glucose levels (Table 1).

As the HBP were higher in WCH than in participants with normotension (Table 1), and as this could increase arteriosclerotic development per se, we matched for gender, age and home SBP and analysed the data by using ANOVA and logistic regression. As shown in Table 2, participants with WCH still had a higher CACS and PWV but not a higher prevalence of carotid plaques than the normotensive participants after the matching that resulted in a nonsignificant difference of HBP between the groups. The matched participants with WCH correspondingly also displayed signs of increased risk for cardiovascular disease compared with normotensive participants, having higher cholesterol levels and serum triglycerides (Table 2).

In a first general analysis of the data on stress markers, we found gender differences in queries regarding sense of harmony or stress (*P* < 0.01 for both comparisons between genders). Hence, we analysed the data separately in men and women. In response to the question 'how much of the last four weeks have you felt calm and peaceful?' with 0 being 'all of the time'; 1 'most of the time'; 2 'some of the time'; 3 'a little of the time' and 4 'none of the time', normotensive women scored similar points as women with WCH (normotensives: 1.27 ± 0.71, WCH 1.21 ± 0.69, *P* = 0.16). In response to the question 'how much of the last four weeks have you been a very nervous person?' with the same response alternatives as in the former question,

normotensive women scored higher points as compared with women with WCH (normotensives: 1.92 ± 1.0, WCH 1.80 ± 1.0, $P = 0.022$), that is, a result suggestive of less frequent sense of being nervous in normotensive women. In the men, there were no such difference in feeling 'calm and peaceful' (normotensives 1.09 ± 0.7 WCH 1.08 ± 0.69 $P = 0.86$) or being nervous (normotensives 1.71 ± 0.96 WCH 1.73 ± 1.02 $P = 0.88$) during the last 4 weeks when comparing the corresponding groups.

DISCUSSION

In this large randomly selected population-based cohort, we found that WCH was very common. In women, the majority of the patients with hypertension based on OBP had normal HBP levels, the exact figure amounting to 59%. The other major finding in this cohort, dedicated to find early signs of CVD, was that the participants with WCH had a higher prevalence of metabolic risk markers for CVD, and also more prevalent arteriosclerotic manifestations in the form of higher CACS and more carotid arterial plaques. However, the interpretation of the origin of these findings were hampered, as in many earlier smaller trials, by the fact that also the actual HBP levels were higher in the WCH group than in truly normotensive participants. We compensated for this fact with the maneuver of matching each WCH patient with a normotensive participant of similar gender, age and home SBP. Interestingly, even after such adaptations of HBP levels, we still found signs of metabolic disease in the form of higher triglycerides and cholesterol levels in WCH compared with normotensive participants. We also found more arteriosclerotic manifestations in the coronary arteries in participants with WCH and a higher PWV. This suggests that the dyslipidemia and vascular disease in aorta and coronary arteries were independent of HBP levels in the participants with WCH.

In the search for potential mechanisms for the dysmetabolic manifestations in WCH, we turned our attention to lifestyle factors in the groups. Women with WCH, determined by traditional cut offs, reported a more frequent sense of nervousness than the truly normotensive participants of the same gender. This question was based on the often used, and validated, SF36 form [26]. In men, there were no such apparent differences in sense of stress. A general and sustained sense of stress has been related to elevated and dysfunctional diurnal cortisol release in several trials [27–29]. Hence, it is possible that this linkage in the women might be a cause of the poor metabolic profile. Indeed, we have earlier reported that the white-coat phenomenon, determined by ambulatory blood pressure, is positively related to plasma cortisol levels in the morning [30].

Earlier smaller trials have suggested that many patients with WCH often develop overt hypertension during long-term follow-up [5,13,19]. Our data with more prevalent signs of metabolic disease in the group of WCH is in line with an increased tendency for arteriosclerosis and hence to develop systolic hypertension. Women with WCH had significantly more carotid plaques and higher CACS score than normotensive women, supporting the idea that this phenomenon was linked to stress and increased cortisol levels as it coincides with positive responses to the questionnaire data on nervousness.

Our new data from a large population-based cohort suggest that middle-aged participants with WCH do carry overt CVD risk factors that seem not to be related to HBP levels per se.

Limitations

There was a high missingness of PWV measurements because of limited capacity for these measurements and a 3-month gap between the start of the main study and the initiation of PWV measurements. Also, as this was a cross-sectional study, the data cannot be used to determine cause and effect. We also acknowledge that a major limitation of home BP recording compared with 24-h ambulatory BP is the absence of information about night-time BP levels, which appear to be a major determinant of cardiovascular risk and target organ damage. Indeed, some patients with normal home BP can have high night-time BP, a potential cause of 'masked' hypertension [31]. The use of home BP in this study, is therefore, acknowledged as a limitation because of lack of night-time BP data.

In conclusion, the increased risk for arteriosclerotic disease was likely not caused by higher HBP levels in participants with WCH as they remained after close matching for age, gender and home SBP. Elevated PWV and CACS stood out as remaining markers of cardiovascular risk in participants with WCH matched for systolic HBP, and so were several signs of dyslipidemia. In the search for mechanisms of the risks linked with WCH, we found that women with WCH reported a more frequent sense of nervousness. A more detailed investigation of these lifestyle factors would be of interest and the prospective data from SCAPIS will soon generate outcome data on such topics by usage of national registries for determination of actual cardiovascular disease [20]. Our data suggest that it could be clinically beneficial to make an extra effort to address dysmetabolic risk markers in WCH to potentially reduce the risk for developing sustained hypertension and premature CVD.

ACKNOWLEDGEMENTS

Conflicts of interest

The authors of this article declare that they had no conflicts of interest regarding the population-based descriptive study

presented herein. The results have not been published elsewhere, previously. But they will in part be presented orally at the upcoming ESH/EASD conference 2021.

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