Different Metabolic Predictors of White-Coat and Sustained Hypertension Over a 20-Year Follow-Up Period
A Population-Based Study of Elderly Men
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Background—The clinical significance of white-coat hypertension is still unclear. Moreover, no study has examined metabolic predictors of white-coat versus sustained hypertension.

Methods and Results—We investigated men (n = 602) in a longitudinal population-based cohort who at age 70 years were identified as normotensive, white-coat hypertensive (office blood pressure [BP] ≥140/90 and daytime ambulatory BP ≥135/85 mm Hg), and sustained hypertensive (office BP ≥140/90 and daytime ambulatory BP ≥135/85 mm Hg). At baseline, when the subjects were aged 50 years, blood glucose, insulin, lipids, and fatty acid composition of the serum cholesterol esters were analyzed. The investigations at age 70 years included determination of insulin sensitivity and target organ damage. At age 50 years, individuals who 20 years later were identified as white-coat hypertensive or sustained hypertensive showed significantly elevated BP, heart rate, and impaired glucose tolerance compared with normotensive subjects but white-coat hypertensive subjects were leaner and had a more favorable serum cholesterol ester fatty acid profile than did sustained hypertensive subjects. At age 70 years, both white-coat and sustained hypertensive subjects showed an impaired insulin sensitivity, elevated blood glucose, and increased serum insulin and heart rate compared with normotensive subjects, but left ventricular mass and urinary albumin excretion were increased only in sustained hypertensive subjects.

Conclusions—These findings indicate that although metabolic abnormalities and elevated heart rate were consistent over time in both hypertensive groups, a lower body mass index and more favorable dietary fat composition predicted the development of white-coat as opposed to sustained hypertension over 20 years. (Circulation. 2002;106:63-68.)

Key Words: hypertension ■ fatty acids ■ insulin

White-coat hypertension is a condition characterized by a persistently raised blood pressure (BP) in the clinical setting in combination with a normal daytime ambulatory BP (ABP), in contrast to sustained hypertension, where an elevated BP is found both at office and ambulatory readings. The clinical relevance of white-coat hypertension is not established, and the question of whether this condition involves an increased cardiovascular risk remains controversial. Results from cross-sectional studies have been contradictory; some indicate an association between white-coat hypertension and hypertensive target organ damage, whereas others do not. However, the degree of target organ damage present in white-coat hypertensive individuals is dependent on the threshold used to define normal ABP. A strict upper limit of normal daytime ABP may identify office hypertensive individuals at low risk for cardiovascular events. Metabolic risk factors related to hypertension contribute to the development of hypertensive target organ damage and atherosclerotic diseases. Hypertension is associated with an abnormal glucose metabolism and dyslipidemia, and insulin resistance may precede hypertension. Although cross-sectional studies have indicated metabolic disturbances in young white-coat hypertensive subjects, the results are inconsistent. Furthermore, prospective studies evaluating risk factors that differentiate between the development of white-coat from sustained hypertension are lacking. There is evidence that dietary factors influence BP, and the Dietary Approaches to Stop Hypertension (DASH) trial indicated that a diet with a reduced total and saturated fat content lowered ABP. The fatty acid composition in serum cholesterol esters (CEs) partly reflects the dietary fat quality over the previous weeks and has been related to BP level. However, it is not known whether the serum fatty acid composition differs between subjects who develop sustained or white-coat hypertension later in life. The present study was performed in white-coat hypertensive, normotensive, and sustained hypertensive individuals.
tensive 70-year-old men who were participants of a longitudi-

dinal population-based health survey since the age of 50

years. The aims were to examine whether metabolic status

and biomarkers of the dietary fat quality could predict the
development of sustained or white-coat hypertension over a
20-year period and to cross-sectionally compare these sub-
groups with regard to metabolic risk factors and target organ
damage, with urinary albumin excretion rate and left ventric-
ular geometry used as measures of organ damage.

Methods

In 1970 to 1973, all 50-year-old men living in Uppsala County
were invited to a health survey aimed at identifying subjects at risk
for cardiovascular disease (Uppsala Longitudinal Study of Adult Men),
and 2322 of 2841 eligible subjects participated. Twenty years later,
422 subjects had died and 219 had moved out of the Uppsala region.
Of the 1681 men alive and still living in Uppsala, 1221 took part in
a reinvestigation. At age 70 years, valid 24-hour ABP recordings
were collected through a self-administered questionnaire. At age 50
years, none of the subjects in the present study population were

leaving 602 men for the analysis. The ethics committee of

Uppsala University approved the study, and all participants gave

office BP, leaving 602 men for the analysis. The ethics committee of

Uppsala University approved the study, and all participants gave

written informed consent.

Measurements at Age 50 Years

At baseline, anthropometric and supine BP measurements, analysis
of fasting triglyceride and cholesterol concentrations, and intrave-
nous glucose tolerance test were performed as previously de-
scribed. The fatty acid composition in serum CE was analyzed
with gas-liquid chromatography, and the fatty acids are presented
as the relative percentage of the sum of the fatty acids analyzed.
Fasting insulin was analyzed with a specific 2-site immunoradiomet-
ric assay technique. Information on smoking habits was obtained
from interview reports, and data regarding hypertension heredity
were collected through a self-administered questionnaire. At age 50
years, none of the subjects in the present study population were


treated with antihypertensive agents.

Measurements at Age 70 Years

Office BP was measured in the right arm with a sphygmomanometer
at the appropriate cuff size. The recordings were made to the nearest
2 mm Hg twice after 10 minutes of rest with the subject in the supine
position, and the mean of the 2 measurements was used for the
analyses. The resting heart rate (HR) was measured supine as the
pulse rate during 1 minute. Twenty-four–hour ambulatory systolic
BP and diastolic BP were recorded with the use of the Accutracker
2 equipment (Suntech Medical Instruments Inc). Reading and data
editing have been described in a previous study. We defined
white-coat hypertension as office BP ≥140/90 and daytime BP
<135/85 mm Hg and sustained hypertension as office BP ≥140/90
and daytime BP ≥135/85 mm Hg.

The methods for anthropometric measurements and analysis of
fasting serum triglycerides, cholesterol, and nonesterified fatty acids,
as well as oral glucose tolerance test, have previously been de-
scribed. Fasting insulin and proinsulin were analyzed with a
specific 2-site immunoradiometric assay technique. Insulin sensi-
tivity was determined with euglycemic hyperinsulinemic clamp
according to the method described by DeFronzo et al. Slightly
modified. Albumin was measured in urine (Albumin RIA100, Phar-
macia), and the urinary albumin excretion rate (UAER) was

calculated on the amount of urine collected during the night together
with the first sample of urine after rising. Microalbuminuria was
defined as a UAER of 20 to 200 μg/min. M-mode and 2-dimensional
and Doppler echocardiographic examinations were performed in the
first 583 consecutive subjects in the original study population, leaving 288 of the men in the present analysis. The definitions of left

ventricular mass index and relative wall thickness have been de-
scribed previously. Information on previous acute myocardial
infarction was retrieved through the Swedish Hospital Discharge
Register. A dietary assessment was performed with a 7-day precoded
food record that was prepared and validated by the National Food
Administration.

Statistical Analysis

Distributions were tested for normality by Shapiro-Wilk’s test.
Skewed variables were logarithmically transformed. We used
ANOVA to calculate differences in means. Comparisons between
subgroups were performed if the overall F test was significant.
Two-tailed significance values were given, with P<0.05 regarded as
significant. Potential confounders were taken into account by
ANCOVA. Proportional differences between groups were calculated
by the χ2 test. The statistical software package Stata (Stata Corpor-
ration) was used for the analyses.

Results

Metabolic Characteristics at Age 50 Years

At age 50 years, office systolic BP, diastolic BP, pulse
pressure, and HR were significantly and similarly elevated in
subjects who would be identified as either white-coat
(n=106) or sustained (n=308) hypertensive 20 years later
(Table 1). At age 50 years, both hypertensive groups were
characterized by elevated serum triglycerides, elevated blood
glucose concentration at 60 minutes, and an impaired glucose
tolerance (K value at intravenous glucose tolerance test)
compared with normotensive subjects. However, at age 50
years, a lower body mass index (BMI), lower fasting glucose
levels, and a significantly different serum CE fatty acid
composition with a higher proportion of linoleic acid and
lower proportions of palmitic, arachidonic, eicosapentaenoic,
and docosahexaenoic acid distinguished subjects who 20
years later would be identified as white-coat hypertensive
from sustained hypertensive subjects (Table 2). Smoking
status and family history of hypertension did not differ
between the groups.

Metabolic Characteristics at Age 70 Years

Office and ambulatory BPs at age 70 years in normotensive,
white-coat hypertensive, and sustained hypertensive subjects
are shown in the Figure. In this cross-sectional analysis, both
white-coat and sustained hypertensive subjects differed from
normotensive subjects by increased plasma glucose levels,
increased fasting insulin levels, and a lower insulin sensitivity
index. BMI, waist-to-hip ratio, and proinsulin were, on the
other hand, higher in sustained hypertensive subjects than in
the other two groups. Office HR was higher in both hyper-
tensive groups than in the normotensive group (Table 3).
Serum triglyceride and cholesterol levels did not differ
significantly between the groups. Dietary records showed that
white-coat hypertensive subjects at age 70 years had a lower
fat intake (33.8±5.2 versus 35.3±5.7 [percent of total energy
intake], P=0.01) and a higher carbohydrate intake
(49.2±5.6% versus 47.7±6.0%, P=0.02) than did sustained
hypertensive subjects.

Measurements of Hypertensive Target Organ
Damage at Age 70 Years

Sustained hypertensive subjects had higher UAERs than did
either white-coat hypertensive or normotensive subjects. The
differences between the groups were similar when subjects with UAERs >200 μg/min (n=7, 1% in each group) were excluded from the analysis. The prevalence of microalbuminuria was significantly increased in sustained hypertensive subjects, whereas there was no difference between normotensive and white-coat hypertensive subjects (Table 4). The intraventricular septal thickness, posterior wall thickness, left ventricular mass index, and total peripheral resistance index were all increased in sustained hypertensive subjects compared with the other groups. Ejection fraction did not differ between the groups (Table 4).

**Discussion**

In this study, the first to present longitudinal data about metabolic predictors of white-coat hypertension, 2 important new findings were disclosed. First, an increased HR, increased office BP, and abnormalities in glucose metabolism were consistent over time in both white-coat and sustained hypertensive subjects. Second, subjects who developed white-coat hypertension 20 years later were leaner and showed a more favorable serum CE fatty acid composition at baseline than did sustained hypertensive subjects (see below). In contrast to sustained hypertensive

| TABLE 1. Metabolic Characteristics at Age 50 Years in Subjects Defined According to Hypertension Status at Age 70 Years |
|-----------------|-----------------|-----------------|-----------------|-----------------|
|                  | Normotensive Subjects (n=188) | White-Coat Hypertensive Subjects (n=106) | Sustained Hypertensive Subjects (n=308) | ANOVA P Value |
| BMI, kg/m²       | 23.8 (2.6)       | 23.9 (2.5)*     | 24.7 (2.7)†     | 0.0001         |
| Serum triglycerides, mmol/L | 1.59 (0.6)     | 1.76 (0.7)†     | 1.78 (0.9)†     | 0.009          |
| LDL cholesterol, mmol/L       | 5.09 (1.10)    | 5.19 (1.28)     | 5.23 (1.35)     | 0.54           |
| HDL cholesterol, mmol/L       | 1.38 (0.37)     | 1.43 (0.34)     | 1.35 (0.35)     | 0.18           |
| Fasting blood glucose, mmol/L | 4.88 (0.5)     | 4.80 (0.5)*     | 5.0 (0.6)†      | 0.007          |
| Blood glucose +60 min, mmol/L   | 10.2 (2.8)     | 11.0 (2.6)†     | 11.2 (2.9)†     | 0.002          |
| Glucose tolerance, K value     | 1.96 (0.9)      | 1.70 (0.6)†     | 1.73 (0.8)†     | 0.02           |
| Fasting insulin, pmol/L       | 39.0 (23.3)     | 47.7 (46.0)     | 53.8 (37.5)†    | 0.001          |
| Office systolic BP, mm Hg     | 120 (10)        | 129 (12)†       | 130 (13)†       | <0.0001        |
| Office diastolic BP, mm Hg    | 76 (7)          | 80 (7)†         | 81 (8)†         | <0.0001        |
| Office pulse pressure, mm Hg  | 44 (8)          | 49 (11)†        | 49 (10)†        | <0.0001        |
| Office pulse rate, bpm        | 66 (10)         | 68 (10)†        | 67 (10)†        | 0.04           |

Values are presented as mean (SD).
*P<0.05, white-coat vs sustained hypertensive subjects.
†P<0.05 vs normotensive subjects.

| TABLE 2. Fatty Acid Composition in Serum CEs at Age 50 Years in Subjects Defined According to Hypertension Status at Age 70 Years |
|-----------------|-----------------|-----------------|-----------------|-----------------|
|                  | Normotensive Subjects (n=188) | White-Coat Hypertensive Subjects (n=106) | Sustained Hypertensive Subjects (n=308) | ANOVA P Value |
| Palmitic acid (16:0) | 11.5 (1.0)   | 11.3 (1.0)*    | 11.6 (0.9)      | 0.03           |
| Palmitoleic acid (16:1 ω-7) | 3.49 (1.03)  | 3.50 (1.06)    | 3.68 (1.19)     | 0.10           |
| Searic acid (18:0) | 1.11 (0.27)   | 1.19 (0.32)    | 1.20 (0.28)†    | 0.04           |
| Oleic acid (18:1 ω-9) | 19.0 (2.4)   | 18.8 (2.6)     | 19.3 (2.5)      | 0.15           |
| Linoleic acid (18:2 ω-6) | 55.2 (4.5)   | 55.9 (4.7)*    | 54.2 (4.8)†     | 0.006          |
| α-Linolenic acid (18:3 ω-3) | 0.65 (0.16)  | 0.64 (0.16)    | 0.67 (0.17)     | 0.40           |
| γ-Linolenic acid (18:3 ω-6) | 0.60 (0.25)  | 0.65 (0.28)    | 0.71 (0.31)†    | 0.0008         |
| Dihomo-γ-linolenic acid (20:3 ω-6) | 0.54 (0.14)  | 0.54 (0.15)    | 0.57 (0.13)†    | 0.03           |
| Arachidonic acid (20:4 ω-6) | 4.78 (0.92)  | 4.54 (0.98)*   | 4.83 (0.99)     | 0.049          |
| Eicosapentaenoic acid (20:5 ω-3) | 1.30 (0.61)  | 1.17 (0.58)*   | 1.35 (0.56)     | 0.007          |
| Docosahexaenoic acid (22:6 ω-3) | 0.70 (0.21)  | 0.65 (0.19)*   | 0.72 (0.21)     | 0.02           |

Presented as relative amounts, % of total fatty acids. Values are mean (SD).
*P<0.05 white-coat vs sustained hypertensive subjects.
†P<0.05 vs normotensive subjects.
subjects, white-coat hypertensive subjects showed no target organ damage.

At age 50 years, the subjects later to be identified as white-coat hypertensive had an impaired glucose tolerance as judged by glucose determinations after a glucose challenge. Furthermore, the BP level was similar at age 50 years in those defined as white-coat and sustained hypertensive 20 years later, and both groups showed elevated HRs, indicating sympathetic overactivity and, thus, an increased risk of developing hypertension and insulin resistance. However, the 2 groups differed in terms of BMI and serum CE fatty acid composition. An increased proportion of palmitic acid, γ-linolenic acid, and dihomo-γ-linolenic acid and low levels of linoleic acid in serum CEs have previously been associated with insulin resistance and predicted diabetes in this population. In the present study, a similar CE fatty acid pattern was seen in 50-year-old subjects who later developed sustained hypertension, a finding that remained true after exclusion of subjects with diabetes at age 70 years. In contrast, the higher proportion of linoleic acid and lower proportion of palmitic acid observed in white-coat hypertensive subjects indicate a higher relative intake of vegetable fat and a lower intake of foods containing saturated fat. The serum CE fatty acid composition is influenced by dietary factors but also by genetically determined differences in fatty acid uptake and enzymatic activity. A high proportion of linoleic acid in serum can reduce the levels of eicosapentaenoic and docosahexaenoic acid, commonly regarded as favorable, through a decreased conversion of α-linolenic acid to long-chain ω-3 fatty acids because these series are competitors for the same enzymatic systems. Similarly, the slightly lower proportion of arachidonic acid observed in the white-coat hypertensive subjects may have been caused by a decreased desaturase activity secondary to a high intake of linoleic acid. Previous data have shown that the serum fatty acid composition of 70-year-old men reflects that of the same men 20 years earlier, which implies that subjects with more favorable dietary fat intakes at age 50 years maintain these habits. In the present study, a lower BMI, lower self-reported total fat intake, and serum biomarkers of dietary fat quality were consistent in white-coat hypertensive subjects, supporting the possibility that dietary factors in combination with genetic disposition may have protected high-risk subjects from developing persistently elevated BP and organ damage. Still, because the white-coat group also developed insulin resistance, it could be speculated that sympathetic overactivity may have had a greater impact on this development than the fatty acid profile. Our findings suggest that in a state of increased sympathetic drive, the influence of dietary fat intake and obesity is of potential importance for the development of sustained hypertension and target organ damage.

| TABLE 3. Metabolic Characteristics at Age 70 Years |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
|                                | NormalSubjectsn = 188          | White-Coat Hypertensive Subjectsn = 106 | Sustained Hypertensive Subjectsn = 308 | ANOVA P Value |
| BMI, kg/m²                      | 24.8 (2.8)                     | 25.3 (3.0)*                        | 26.3 (3.3)†                       | <0.0001 |
| Waist-to-hip ratio              | 0.93 (0.05)                    | 0.93 (0.05)*                       | 0.94 (0.05)†                      | 0.001  |
| Serum triglycerides, mmol/L     | 1.30 (0.6)                     | 1.37 (0.6)                         | 1.36 (0.7)                        | 0.4    |
| LDL cholesterol, mmol/L         | 3.93 (0.87)                    | 3.93 (0.89)                        | 3.96 (0.92)                       | 0.91   |
| HDL cholesterol, mmol/L         | 1.31 (0.34)                    | 1.37 (0.35)                        | 1.33 (0.36)                       | 0.40   |
| Fasting plasma glucose, mmol/L  | 5.3 (0.9)                      | 5.6 (1.4)†                         | 5.8 (1.3)†                        | <0.0001|
| Plasma glucose +120 min, mmol/L | 6.9 (3.1)                      | 7.9 (4.2)†                         | 8.2 (3.7)†                        | <0.0001|
| M, mg · min⁻¹ · kg⁻¹/(100 mU/L) | 6.05 (2.5)                     | 5.6 (2.7)†                         | 5.2 (2.4)†                        | 0.002  |
| Insulin, pmol/L                 | 42.4 (41.8)                    | 54.8 (90.7)†                       | 49.5 (31.3)†                      | 0.002  |
| Proinsulin, pmol/L              | 6.4 (5.4)                      | 7.4 (8.9)†                         | 8.6 (8.1)†                        | 0.0003 |
| Serum nonesterified fatty acids, mmol/L | 0.47 (0.2) | 0.50 (0.2) | 0.52 (0.2)‡ | 0.003 |
| Office HR, bpm                  | 63 (8)                         | 67 (9)‡                            | 66 (9)‡                            | 0.0001 |
| Daytime HR, bpm                 | 73 (11)                        | 76 (13)†                           | 76 (11)†                           | 0.04   |
| Nighttime HR, bpm               | 60 (9)                         | 63 (12)                            | 61 (10)‡                           | 0.2    |

Values are mean (SD).
*P <0.05 white-coat vs sustained hypertensive subjects.
†P <0.05 vs normotensive subjects.
It has been suggested that part of the increased cardiovascular risk in white-coat hypertension is attributable to coexisting risk factors rather than the raised office BP per se.\(^28\) Consequently, in studies where white-coat hypertension was related to carotid artery atherosclerosis,\(^3\) insulin resistance and impaired glucose tolerance, being independent risk factors for an increased carotid intima-media thickness,\(^29,30\) may have accounted for part of this relationship. Thus, although no hypertension-related target organ damage was detected in the present study, white-coat hypertension cannot be regarded a benign phenomenon because these subjects display metabolic abnormalities that are powerful risk factors for future atherosclerotic events.

Left ventricular hypertrophy (LVH) is a commonly used measure of hypertensive target organ damage, but the variation in 24-hour BP only explains \(\sim 30\%\) of the variation in left ventricular mass.\(^31\) An unfavorable serum CE fatty acid profile with a high proportion of saturated fatty acids and a low proportion of linoleic acid has previously been shown to predict LVH over 20 years,\(^28\) indicating that the fatty acid pattern is an important long-term determinant of LVH. Endothelial dysfunction is associated with LVH,\(^32\) and because endothelium-dependent vasodilation is related to fatty acid composition of serum CEs,\(^33\) this may represent a possible link between the fatty acid profile, sustained hypertension, and LVH.

Microalbuminuria is a marker of organ damage in both hypertension and diabetes. In the present study, diabetes was more prevalent in sustained hypertensive subjects (14.3%) than in white-coat hypertensive subjects (8.5%) and normotensive subjects (5.9%) at age 70 years (\(P<0.05\)). However, the differences in UAER between the groups remained after adjustment for either fasting blood glucose or diabetes, which suggests that the elevated ABP may have contributed to the renal impairment.

The choice of upper limit of normal ABP is of critical importance when evaluating the risk associated with white-coat hypertension. In the present study, a daytime BP of \(<135/85\) mm Hg defined white-coat hypertension, a threshold based on a number of studies of ABP normality in different populations.\(^19\) This limit is also close to the daytime pressure (137/83 mm Hg) that by linear regression analysis corresponded to an office BP of 140/90 mm Hg in the present study population.\(^18\) A more restrictive definition (130/80 mm Hg) was used in a separate analysis to investigate the importance of the upper limit of normal ABP level, but it did not substantially change the results (data not shown).

A possible limitation of the present study is the absence of ABP monitoring at baseline. Some of the findings may have been the result of chance because of multiple comparisons, and therefore, they need to be reproduced in future studies. Moreover, extrapolation of these results to women and other ethnic groups should be done with caution.

In conclusion, a more favorable serum CE fatty acid profile and lower BMI predicted white-coat as opposed to sustained hypertension over 20 years. Both white-coat and sustained hypertensive subjects showed consistently increased HR, elevated office BP, and metabolic disturbances. Although these data do not indicate causality, our findings suggest that in a state of sympathetic overactivity, an unfavorable dietary fat intake and obesity may be important contributors to the development of sustained hypertension and target organ damage.

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