Cerebral white matter lesions (WMLs) are highly prevalent in the elderly population and increase the risk of dementia and stroke.\textsuperscript{1} Although believed to be vascular in origin, the exact etiology of WMLs is still unknown. On the basis of pathological and epidemiological studies, blood pressure is considered to be one of the most important factors by damaging the cerebral small vessels.\textsuperscript{2,3} Because blood pressure is modifiable, blood pressure control seems an important candidate for the prevention of WML progression.

The earliest studies demonstrating an association between high blood pressure and WMLs were cross-sectional by design. Although means of blood pressure were calculated over a 5-year period before longitudinal MRI scanning, WML progression was subsequently measured on 2 scans 3.5 years apart. We performed analyses with linear regression models and evaluated adjustments for age, sex, cardiovascular risk factors, and baseline WML volume. In addition, we evaluated whether treatment of hypertension is related to WML progression. Both systolic and diastolic blood pressures were significantly associated with WML progression (regression coefficient [95% confidence interval], 0.08 [0.03; 0.14] mL/y and 0.09 [0.03; 0.15] mL/y per SD increase in systolic and diastolic blood pressure, respectively). Pulse pressure was also significantly associated with WML progression, but not independent from hypertension. After adjustment for baseline WML volume, only systolic blood pressure remained significantly associated: 0.05 (0.00; 0.09) mL/y per SD increase. People with uncontrolled untreated hypertension had significantly more WML progression than people with uncontrolled treated hypertension (difference [95% confidence interval], 0.12 [0.00; 0.23] mL/y). The present study further establishes high blood pressure to precede WMLs and implies that hypertension treatment could reduce WML progression in the general population.

**Key Words:** aging ■ blood pressure ■ epidemiology ■ hypertension ■ pulse pressure ■ white matter lesions/hyperintensities

Cerebral white matter lesions (WMLs) are highly prevalent in the elderly population and increase the risk of dementia and stroke.\textsuperscript{1} Although believed to be vascular in origin, the exact etiology of WMLs is still unknown. On the basis of pathological and epidemiological studies, blood pressure is considered to be one of the most important factors by damaging the cerebral small vessels.\textsuperscript{2,3} Because blood pressure is modifiable, blood pressure control seems an important candidate for the prevention of WML progression.

The earliest studies demonstrating an association between high blood pressure and WMLs were cross-sectional by design, which limits causal inferences.\textsuperscript{4–13} More recently, studies have used longitudinal designs and found similar results.\textsuperscript{14–23} Yet, because WML progression is strongly influenced by the WML load at baseline,\textsuperscript{15} it is unknown to what extent associations of blood pressure with WML progression are affected by the baseline WML load. Moreover, to provide stronger evidence for a temporal relationship, blood pressure should preferably be measured before the window in which WML progression is determined, instead of during this window. In addition, the use of different MRI scanners or scanning protocols when measuring WML progression can possibly lead to systematic biases. Previous studies have addressed 1 or 2 of these issues, but none of them addressed all.

It is also unknown whether the associations between blood pressure and WML progression are present for systolic, diastolic, and pulse pressure. Moreover, the influence of medication use and control of hypertension on WML progression remains unclear. We hypothesized that blood pressure would relate to WML progression even when taking baseline WML load into account and that medication use and adequate control of hypertension would reduce this progression.

We tested this hypothesis in a population-based longitudinal MRI study in which we measured systolic, diastolic, and pulse pressure before MRI scanning; evaluated the influence of the WML load at baseline; and used exactly the same scanners and scanning protocol at baseline and follow-up.
Methods

Study Population and Design

The study is based on participants from the Rotterdam Study, a population-based cohort study in The Netherlands that investigates determinants of various chronic diseases among the elderly people. The original study population consisted of the general population aged 55 years and older within the Ommoord area, a suburb of Rotterdam. In 2000, the cohort was expanded with 3011 people (265 years) who were living in the study area and had not been included before.

For this report, we used data from a random subset of the latter cohort expansion, which underwent 3 visits: visit 1 (in the year 2000), visit 2 (2005–2006), and visit 3 (2008–2010). At visits 1 and 2, blood pressure and cardiovascular determinants were assessed. At visits 2 and 3, MRI scanning was performed. Figure 1 displays the design used and the timings of the various longitudinal measurements. No blood pressure measurements were available at visit 3.

At visit 2, 1073 people were randomly selected for this study from the full cohort expansion (N=3011), because MRI scanning was implemented only from visit 2 onward and could not be performed in the full cohort. Hereto, we used a simple random sampling procedure. After excluding people with previous clinical stroke (n=35), dementia (n=4), or those who had MRI contraindications (n=94), a total of 944 people was eligible. From these, 877 participated and gave written informed consent. Because of physical inabilities, imaging could not be performed in 12 persons, leaving 865 people who underwent MRI scanning. From these, 731 people had a second MRI at visit 3, and of these 699 people had good-quality MRI data of both scans.

After excluding 19 people with MRI-defined cortical infarcts, which hampered the assessment of WMLs, and 15 people with missing information on blood pressure measures, 665 people remained for the current analysis. All measurements were performed at the Rotterdam Study Research Center, which is a single site. The Institutional Review Board (Erasmus MC, Rotterdam, The Netherlands) approved the study.

Blood Pressure, Hypertension, and Antihypertensive Medication

At visits 1 and 2 (5.3 years later; see Figure 1), systolic and diastolic blood pressure were measured twice on the right arm with a random zero sphygmomanometer by a trained research physician after the participant had been sitting quietly for ≥5 minutes. A standard cuff or, if applicable, a large cuff was used. Pulse pressure was defined as systolic blood pressure minus diastolic blood pressure. To gain robust measures of blood pressure, we computed 5-year means of blood pressure measures (mean of blood pressure measure at visit 1 summed with the mean of blood pressure measure at visit 2, and divided by 2). Hypertension was defined as systolic blood pressure ≥140 or diastolic blood pressure ≥90 mm Hg or receiving antihypertensive treatment at either of the 2 visits. Antihypertensive medication was assessed during a home interview. At the research center, a physician ascertained the indication for which the medication had been prescribed.

MRI and WML Progression

Brain MRI was performed at visits 2 and 3 (3.5 years apart; see Figure 1). At both visits, we used the same MRI scanner and imaging protocol and applied exactly the same image postprocessing steps and segmentation method. We used a 1.5-T scanner (GE Healthcare) with an 8-channel head coil and included T1-weighted, proton density–weighted, and fluid-attenuated inversion recovery sequences. Postprocessing steps have been described elsewhere and include a conventional k-nearest-neighbor brain tissue classifier extended with WML segmentation. Using this classifier, we obtained quantitative measures of WML volume and intracranial volume (in mL). WML progression was assessed by subtracting the WML volume (in mL) at the first measurement from the WML volume (in mL) at the second measurement. This number was subsequently divided by the time between scans (in years) to obtain the annual WML progression (in mL/year). Infarcts were classified as described previously.

Cardiovascular Risk Factors

Body mass index, total cholesterol, high-density lipoprotein cholesterol, triglycerides (only measured at visit 1), diabetes mellitus, alcohol consumption (only measured at visit 2), and smoking were determined by interview and laboratory and physical examination at visits 1 and 2. Body mass index was calculated by dividing weight (kg) by the square of height (m²). The waist/hip ratio was defined as the ratio between the waist circumference (cm) and the hip circumference (cm). We considered diabetes mellitus present when a person was taking oral antidiabetics or insulin, or if fasting plasma glucose was ≥7 mmol/L (≥126 mg/dL). A physician assessed participants’ smoking habits, and smoking status was further classified as current, former, or never. Alcohol intake was quantified as units per week. Cardiovascular disease (coronary heart disease, heart failure, or atrial fibrillation) was assessed during interview and verified by reviewing medical records and through automated linkage of the study database with files from general practitioners. For the analyses, we computed means for the continuous covariates at visits 1 and 2 and determined the ever presence of a condition between visits 1 and 2 for dichotomous variables. Apolipoprotein E (ApoE)-ε4 genotyping was performed as previously described.

Statistical Analyses

We investigated how systolic blood pressure, diastolic blood pressure, and pulse pressure were related to WML volume cross-sectionally and annual WML progression longitudinally, using linear regression models, adjusted for age, sex, and intracranial volume in model I, and additionally for cardiovascular risk factors (antihypertensive medication, total cholesterol, high-density lipoprotein cholesterol, triglycerides, body mass index, alcohol consumption, smoking, and diabetes mellitus) in model II. For the analyses regarding WML progression, we also applied a model III with adjustments for baseline WML volume, to assess whether possible associations were explained by WML accumulated before the first scan.

Additionally, the following exploratory analyses were conducted. We evaluated additional adjustments for cardiovascular disease and ApoE-ε4 carrier status and tested for interaction of ApoE-ε4 carrier status with systolic blood pressure, diastolic blood pressure, or pulse pressure. In addition, we adjusted pulse pressure for the presence of hypertension to see whether pulse pressure had additional value beyond hypertension. We evaluated the addition of quadratic terms of systolic blood pressure, diastolic blood pressure, or pulse pressure were related to WML volume cross-sectionally and annual WML progression longitudinally, using linear regression models, adjusted for age, sex, and intracranial volume in model I, and additionally for cardiovascular risk factors (antihypertensive medication, total cholesterol, high-density lipoprotein cholesterol, triglycerides, body mass index, alcohol consumption, smoking, and diabetes mellitus) in model II. For the analyses regarding WML progression, we also applied a model III with adjustments for baseline WML volume, to assess whether possible associations were explained by WML accumulated before the first scan.

Additionally, the following exploratory analyses were conducted. We evaluated additional adjustments for cardiovascular disease and ApoE-ε4 carrier status and tested for interaction of ApoE-ε4 carrier status with systolic blood pressure, diastolic blood pressure, or pulse pressure. In addition, we adjusted pulse pressure for the presence of hypertension to see whether pulse pressure had additional value beyond hypertension. We evaluated the addition of quadratic terms of systolic blood pressure, diastolic blood pressure, or pulse pressure to explore whether J-shaped relationships were present. We repeated all analyses with waist/hip ratio as covariate instead of body mass index.

Finally, we evaluated the relationship between hypertension treatment and WML progression by constructing 4 mutually exclusive groups of people: normotensives, controlled treated hypertensives, uncontrolled treated hypertensives, and untreated hypertensives. These 4 groups were defined as follows based on the mean blood pressure of visits 1 and 2, and the use
Table 1. Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Variable</th>
<th>Visit 1</th>
<th>Visit 2</th>
<th>Visit 3</th>
<th>P Value for Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>61.6 (5.0)</td>
<td>66.9 (5.0)</td>
<td>70.4 (5.0)</td>
<td>NA</td>
</tr>
<tr>
<td>Female</td>
<td>52%</td>
<td>52%</td>
<td>52%</td>
<td>NA</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>138 (19)</td>
<td>143 (18)</td>
<td>...</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>78 (10)</td>
<td>81 (10)</td>
<td>...</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Pulse pressure, mmHg</td>
<td>60 (14)</td>
<td>62 (15)</td>
<td>...</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Antihypertensive medication</td>
<td>22%</td>
<td>34%</td>
<td>...</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.84 (0.95)</td>
<td>5.73 (0.93)</td>
<td>...</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>HDL, mmol/L</td>
<td>1.39 (0.37)</td>
<td>1.44 (0.38)</td>
<td>...</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.33 [0.80]</td>
<td>...</td>
<td>...</td>
<td>NA</td>
</tr>
<tr>
<td>Body mass index</td>
<td>26.8 (3.5)</td>
<td>27.5 (3.6)</td>
<td>...</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Alcohol, units/wk</td>
<td>...</td>
<td>6 [14]</td>
<td>...</td>
<td>NA</td>
</tr>
<tr>
<td>Current smoker</td>
<td>16%</td>
<td>11%</td>
<td>...</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Diabetes mellitus*</td>
<td>8%</td>
<td>9%</td>
<td>...</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Cardiovascular disease†</td>
<td>6%</td>
<td>7%</td>
<td>...</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Values are means (SD), percentages, or median [interquartile range]. NA indicates not applicable.

Fasting glucose ≥7.0 mmol/L (≥126 mg/dL) or receiving glucose-lowering drugs.

†The presence of coronary heart disease, heart failure, or atrial fibrillation.

Results

Characteristics of the study population are represented in Table 1. The mean (SD) age of the population was 61.6 (5.0) years at visit 1, 66.9 (5.0) years at visit 2, and 70.4 (5.0) years at visit 3. The age range was 55 to 82 years at visit 1, 60 to 87 years at visit 2, and 64 to 91 years at visit 3. In Table S1 (online-only Data Supplement), the associations between blood pressure measures and cross-sectionally assessed WML volume are represented.

Table 2 shows the relationship of systolic blood pressure, diastolic blood pressure, and pulse pressure with annual WML progression. All values mentioned below represent regression coefficients. Both systolic and diastolic blood pressures were significantly associated with WML progression, even after adjustment for age, sex, intracranial volume, and cardiovascular risk factors for WML progression (95% confidence interval [CI] per SD increase in systolic blood pressure: 0.08 (0.03; 0.14) mL/y and 0.09 (0.03; 0.15) mL/y per SD increase in diastolic blood pressure. After adjustment for baseline WML volume only, the association between systolic blood pressure and WML progression remained statistically significant: 0.05 (95% CI, 0.00; 0.09) mL/y per SD increase in systolic blood pressure (P<0.05). Pulse pressure was also significantly associated with WML progression (0.06 [95% CI, 0.00; 0.11] mL/y per SD increase in pulse pressure; P<0.05), although this value attenuated and lost statistical significance after adjustment for the presence of hypertension (−0.02 [95% CI, −0.05; 0.09] mL/y per SD increase in pulse pressure; P=0.58), or adjustment for baseline WML volume (0.04 [95% CI, 0.00; 0.08] mL/y per SD increase in pulse pressure; P=0.09). Addition of quadratic terms of systolic blood pressure, diastolic blood pressure, or pulse pressure to any of the models was not significant. After additional adjustments for the presence of cardiovascular disease, the effect estimates remained unchanged. Adjustment for ApoE-ε4 carriership did not change the effect estimates either. No interaction between ApoE-ε4 and systolic blood pressure, diastolic blood pressure, and pulse pressure was observed (all P>0.20). No differences were observed when body mass index was replaced by the waist/hip ratio as covariate in the analyses.

Figure 2 displays the WML progression on top of the baseline WML volume for (1) normotensives (n=255), (2) controlled treated hypertensives (n=83), (3) uncontrolled treated hypertensives (n=155), and (4) uncontrolled untreated hypertensives (n=172). We found that the largest amount of WML progression was observed in the uncontrolled untreated hypertensives group. When taking into account the baseline WML load, the WML progression in this group was statistically significantly higher than in the uncontrolled treated hypertensives group with a difference (0.12 [0.00; 0.23] mL/y; P<0.05). Furthermore, we observed that across people with persistent normal blood pressure, controlled treated hypertension, uncontrolled treated hypertension, and uncontrolled untreated hypertension, there was a trend of increasing annual WML progression (P=0.01).

Discussion

In this longitudinal MRI study, we found that high systolic blood pressure and high diastolic blood pressure were...
founder, the true effect estimate of the association between baseline WML load may be part of the causal chain. However, baseline WML load is a form of overadjustment because the baseline WML load could also act as a confounder, the true effect estimate of the association between blood pressure and WML progression probably lies between the adjusted and unadjusted effect estimates. Another consideration is that we investigated the 5-year mean blood pressure and not the change in blood pressure over 5 years in relation to WML progression. However, blood pressure is highly variable over time and shows considerable regression to the mean.²¹ In our study, we therefore decided to use the average over 5 years instead of the change over 5 years. We also note that our study only had 2 measurements of WML volume, preventing us to assess nonlinear trends over time.

High blood pressure has consistently been associated with cross-sectionally measured WML burden and with longitudinally measured WML progression.¹⁴,¹⁵,¹⁷,²¹ With respect to differences in the associations for systolic blood pressure versus diastolic blood pressure, studies have been inconsistent both for cross-sectionally measured WML burden and longitudinally measured WML progression. Some studies found associations for 1 of the 2, others for both. We found both systolic and diastolic blood pressures to be related to WML progression, but only systolic blood pressure to be related to WML progression after taking into account the already present WML load. Yet, this does not per se imply that systolic blood pressure is more important than diastolic blood pressure in WML progression because the distribution of systolic blood pressure is possibly more favorable to find associations. We also investigated whether pulse pressure would give additional information beyond the presence of hypertension. Pulse pressure has been associated with cross-sectionally measured WML load in several studies.⁶,³²,³³ However, we found that the association of pulse pressure with WML progression attenuated and lost statistical significance after taking into account the presence of hypertension. Perhaps the use of pulse wave velocity or other better indirect measures of arterial stiffness would be more sensitive to pick up an association with WML progression in future studies.

We found that per SD increase in systolic blood pressure, WML volume increased with 0.08 mL/y. For diastolic blood pressure, this was 0.09 mL/y. This corresponds to 23% and 25% of the mean annual WML progression in our population, respectively. Several studies found WML progression associated with cognitive decline.⁵,⁶,²³,⁵⁴,⁵⁵ This implies that high blood pressure could affect cognition via WMLs.

Our finding that people with uncontrolled treated hypertension have significantly less WML progression than people with uncontrolled untreated hypertension implies that treatment of hypertension is important in slowing down WML progression. These results are in-line with a recent observational study that found treatment of people with high systolic blood pressure to be related to less WML progression.²¹ Recently, also randomized controlled trials have been investigating the effect of extra blood pressure–lowering treatment compared with standard treatment on WML progression in stroke patients.⁶,³⁷ One trial found a protective effect of extra treatment, whereas the other did not find a difference. Yet, as participants in these trials were stroke patients, the question remains whether the WMLs in these patients are etiologically similar to the WML disease in the general population.

In conclusion, in this longitudinal MRI study, we found that high blood pressure precedes WML progression. Furthermore,
we found that hypertension treatment is associated with less WML progression. Our study therefore further establishes high blood pressure as a strong risk factor for WMLs and implies that treatment of hypertension could lead to less WML progression in the general population. Further studies are needed to assess whether preventing WML development is also relevant to prevent cognitive decline and clinical disease.

**Perspectives**

The results of our study suggest that antihypertensive treatment would be beneficial in preventing WML progression in the general population. To further elucidate the relationship between blood pressure and WML, additional studies with >2 longitudinal measures of blood pressure and WMLs are desirable. Examination of interactions between blood pressure and other risk factors could possibly detect deleterious risk profiles. Including change in cognition as an outcome measure could throw light on the clinical implications of change in blood pressure and WML volume. Still, clinical trials are the best way to establish that blood pressure control is beneficial in the slowing or prevention of WML progression.

**Sources of Funding**

This study was funded by Erasmus MC, University Medical Center Rotterdam, and Erasmus University Rotterdam; The Netherlands Organisation of Scientific Research (NWO); The Netherlands Organisation for Health Research and Development (ZonMw); The Ministry of Education, Organisation for Health Research and Development (ZonMw); The Organisation of Scientific Research (NWO); The Netherlands Heart Foundation. Antiserum New Investigator Research Grant-09-13168, and Medische Research Institute for Diseases in the Elderly; the Ministry of Education, Organisation for Health Research and Development (ZonMw); The Organisation of Scientific Research (NWO); The Netherlands Heart Foundation. Longitudinal measures of blood pressure and WMLs are desirable in further elucidating the relationship between blood pressure and WMLs. Our study therefore further establishes that treatment of hypertension could lead to less WML progression and implies that treatment of hypertension could lead to less WML progression in the general population. Further studies are needed to assess whether preventing WML development is also relevant to prevent cognitive decline and clinical disease.

**References**

What Is New?

• Our study provides strong and much needed confirmatory evidence that high blood pressure is a risk factor for progression of cerebral white matter lesion in the aging general population.

What Is Relevant?

• Our study further adds to the evidence, suggesting that treatment of hypertension may decrease the risk of white matter lesions.

Summary

In this longitudinal MRI study, we found that high blood pressure precedes cerebral white matter lesion progression and that treatment of hypertension is associated with less progression.
High Blood Pressure and Cerebral White Matter Lesion Progression in the General Population

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Hypertension. 2013;61:1354-1359; originally published online March 25, 2013; doi: 10.1161/HYPERTENSIONAHA.111.00430

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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HIGH BLOOD PRESSURE AND CEREBRAL WHITE MATTER LESION PROGRESSION IN THE GENERAL POPULATION

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**SUPPLEMENTARY TABLE**

**Table S1. Blood pressure and cross-sectional WML volume**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Scan 1</th>
<th>Scan 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure</td>
<td>0.11 (0.04; 0.18)</td>
<td>0.13 (0.06; 0.20)</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>0.12 (0.05; 0.19)</td>
<td>0.13 (0.05; 0.20)</td>
</tr>
<tr>
<td>Pulse pressure</td>
<td>0.08 (0.01; 0.15)</td>
<td>0.10 (0.03; 0.17)</td>
</tr>
</tbody>
</table>

Values are log-transformed millilitres of white matter lesion volume (95%-confidence interval) per standard deviation increase of blood pressure (mean of the measures at visit 1 and 2), adjusted for age, sex, intracranial volume, antihypertensive medication, total cholesterol, HDL-cholesterol, triglycerides, body mass index, alcohol consumption, smoking and diabetes. Values are derived from linear regression models.

Abbreviations: WML = white matter lesion, HDL = high-density lipoprotein.