Cerebral white matter lesions (WMLs) are highly prevalent in the elderly population and increase the risk of dementia and stroke. 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. 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. More recently, studies have used longitudinal designs and found similar results. Yet, because WML progression is strongly influenced by the WML load at baseline, 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.\textsuperscript{24} 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.\textsuperscript{24}

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.\textsuperscript{23} 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. Hereeto, 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 cuff. A standard cuff participant had been sitting quietly for 5 minutes. A standard cuff was performed as previously described.\textsuperscript{30} 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 by reviewing medical records and through automated linkage of the study database with files from general practioners.\textsuperscript{29} 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.\textsuperscript{30}

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 carriership and tested for interaction of ApoE-ε4 carriership 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 for J-shaped relationships. We explored whether pulse pressure had additional value beyond hypertension. 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

![Figure 1. Schematic overview of the study design. BP indicates blood pressure; and WML, white matter lesion.](image-url)
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, mm Hg</td>
<td>60 (14)</td>
<td>62 (15)</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>22%</td>
<td>34%</td>
<td>...</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Anithypertensive medication</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>NA</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>High-density lipoprotein, 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>NA</td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>16%</td>
<td>38%</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.
‡Adjusted for age, sex, intracranial volume, and baseline WML volume.

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, or 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 controlled 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...
Figure 2. Hypertension treatment and white matter lesion (WML) progression. This figure shows the mean WML progression in mL (95% confidence interval [CI]; black bars) for 4 blood pressure categories. Categories were defined as follows based on their mean blood pressure and medication use in the 5 years before the first scan: (1) normotensives: study participants with normal mean blood pressure and receiving no antihypertensive medication during this period (n=255); (2) controlled treated hypertensives: study participants with normal mean blood pressure and receiving antihypertensive medication during this period (n=83); (3) uncontrolled treated hypertensives: study participants with hypertensive mean blood pressure and receiving antihypertensive medication during this period (n=155); and (4) uncontrolled untreated hypertensives: study participants with hypertensive mean blood pressure and receiving no antihypertensive medication during this period (n=172). Hypertensive mean blood pressure was defined as diastolic blood pressure ≥90 mm Hg or systolic blood pressure ≥140 mm Hg. A statistically significant difference in WML progression was observed between the uncontrolled untreated hypertensives group and the uncontrolled treated hypertensives group, after adjustment for age, sex, intracranial volume, time between scans, and the baseline WML load (P<0.05).

Hypertension treatment and white matter lesion (WML) progression. This figure shows the mean WML progression in mL (95% confidence interval [CI]; black bars) for 4 blood pressure categories. Categories were defined as follows based on their mean blood pressure and medication use in the 5 years before the first scan: (1) normotensives: study participants with normal mean blood pressure and receiving no antihypertensive medication during this period (n=255); (2) controlled treated hypertensives: study participants with normal mean blood pressure and receiving antihypertensive medication during this period (n=83); (3) uncontrolled treated hypertensives: study participants with hypertensive mean blood pressure and receiving antihypertensive medication during this period (n=155); and (4) uncontrolled untreated hypertensives: study participants with hypertensive mean blood pressure and receiving no antihypertensive medication during this period (n=172). Hypertensive mean blood pressure was defined as diastolic blood pressure ≥90 mm Hg or systolic blood pressure ≥140 mm Hg. A statistically significant difference in WML progression was observed between the uncontrolled untreated hypertensives group and the uncontrolled treated hypertensives group, after adjustment for age, sex, intracranial volume, time between scans, and the baseline WML load (P<0.05).

A possible limitation of this study is that although the response rate was high, selective dropout could have occurred during the follow-up period. Nevertheless, we believe that if present, this would have led to an underestimation of the results found. Another consideration is that adjustment for baseline WML load is a form of overadjustment because the baseline WML load may be part of the causal chain. However, 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. 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. 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. 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. 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. 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. 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. 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 Research Institute for Diseases in the Elderly; the Ministry of Education, Culture, and Science; the Ministry of Health, Welfare, and Sports; the European Commission (DG-XII); and the Municipality of Rotterdam. Grants: NWO 918-46-615, 948-00-010 and 916.13.054, Alzheimer’s Association New Investigator Research Grant-09-13168, and Medische Verhaaren received funding from the Dutch Heart Foundation (Nederlandse Hartstichting), grant 2009B102.

Disclosures

None.

References

1. Debette S, Markus HS. The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: systematic review and meta-analysis. BMJ. 2010;341:c3666.
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

Benjamin F.J. Verhaaren, Meike W. Vernooij, Renske de Boer, Albert Hofman, Wiro J. Niessen, Aad van der Lugt and M. Arfan Ikram

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

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/61/6/1354

Data Supplement (unedited) at:
http://hyper.ahajournals.org/content/suppl/2013/03/25/HYPERTENSIONAHA.111.00430.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/
HIGH BLOOD PRESSURE AND CEREBRAL WHITE MATTER LESION PROGRESSION IN THE GENERAL POPULATION

Benjamin F.J. Verhaaren, MD,1,2 Meike W. Vernooij, MD, PhD,1,2 Renske de Boer, PhD,2,3 Albert Hofman, MD, PhD;1 Wiro J. Niessen, PhD;2,3,4 Aad van der Lugt, MD, PhD;2 M. Arfan Ikram, MD, PhD.1,2

Departments of 1Epidemiology, 2Radiology, 3Medical Informatics, Erasmus MC University Medical Center, Rotterdam, the Netherlands. 4Faculty of Applied Sciences, University of Technology, Delft, the Netherlands.

Correspondence: M.A. Ikram, MD, PhD, Department of Epidemiology, Erasmus MC University Medical Center, P.O. Box 2040, 3000 CA, Rotterdam, the Netherlands. Fax: +31107043489. Tel: +31107043391. E-mail: m.a.ikram@erasmusmc.nl.
## 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.