Scientific Contributions

The Association Between Blood Pressure, Hypertension, and Cerebral White Matter Lesions
Cardiovascular Determinants of Dementia Study

Ewoud J. van Dijk, Monique M.B. Breteler, Reinhold Schmidt, Klaus Berger, Lars-Göran Nilsson, Matthijs Oudkerk, Andrzej Pajak, Susana Sans, Maria de Ridder, Carole Dufouil, Rebecca Fuhrer, Simona Giampaoli, Lenore J. Launer, Albert Hofman, for the CASCADE Consortium

Abstract—Cerebral white matter lesions are frequently observed on magnetic resonance imaging (MRI) scans in elderly people and are associated with stroke and dementia. Elevated blood pressure is presumed one of the main risk factors, although data are almost exclusively derived from cross-sectional studies. We assessed in 10 European cohorts the relation between concurrently and previously measured blood pressure levels, hypertension, its treatment, and severe cerebral white matter lesions. In total, 1805 non-demented subjects aged 65 to 75 years were sampled from ongoing community-based studies that were initiated 5 to 20 years before the MRI. White matter lesions in the periventricular and subcortical region were rated separately using semiquantitative measures. We performed logistic regression analyses adjusted for potential confounders in 1625 people with complete data. Concurrently and formerly assessed diastolic and systolic blood pressure levels were positively associated with severe white matter lesions. Both increases and decreases in diastolic blood pressure were associated with more severe periventricular white matter lesions. Increase in systolic blood pressure levels was associated with more severe periventricular and subcortical white matter lesions. People with poorly controlled hypertension had a higher risk of severe white matter lesions than those without hypertension, or those with controlled or untreated hypertension. Higher blood pressure was associated with an increased risk of severe white matter lesions. Successful treatment of hypertension may reduce this risk; however, a potential negative effect of decreasing diastolic blood pressure level on the occurrence of severe periventricular white matter lesions should be taken into account. (Hypertension. 2004;44:625-630.)

Key Words: hypertension ■ stroke ■ dementia ■ epidemiology ■ ischemia ■ aging

Cerebral white matter lesions are frequently observed on magnetic resonance imaging (MRI) scans in elderly people. These lesions are associated with an increased risk of stroke, cognitive decline, and dementia. Although the exact pathogenesis of these lesions is not fully understood, they are considered to reflect ischemic small vessel disease. Elevated levels of blood pressure are thought to contribute to these lesions.

Hypertension is extremely prevalent in elderly people. Cross-sectional population-based MRI studies have shown a positive association between higher blood pressure and severity of white matter lesions. Longitudinal data are, however, scarce. Midlife blood pressure reportedly is associated with white matter lesions in the elderly. The Rotterdam Scan Study previously found that both an increase and a decrease in blood pressure levels are related to white matter lesions. People with uncontrolled hypertension seem to have a higher prevalence of severe white matter lesions than people without hypertension or with controlled hypertension.

We conducted a study in 10 European cohorts to assess the relation between concurrent and earlier assessed blood pressure levels and cerebral white matter lesions in nondemented elderly. We also assessed the relation between change in blood pressure over time and white matter lesion severity. Finally, we assessed the relation between hypertension, its treatment, and severe white matter lesions.
Methods

Study Population

The Cardiovascular Determinants of Dementia (CASCADE) study is a multicenter collaborative study in Europe, based on 10 ongoing community-based cohorts.13 From the consecutive baseline cohorts 1805 men and women aged 65 to 75 years were randomly selected. Because data on blood pressure-lowering medication were missing for the cohort from the United Kingdom (n = 180), this study was excluded, leaving 1625 participants. Informed consent was obtained at each center in accordance with guidelines from local institutional review boards.

Measurement of Risk Factors

Data collection for CASCADE (ie, concurrent) took place between 1996 and 1998 and included blood pressure measurements, measurements of cardiovascular risk factors, and brain MRI. Also available to CASCADE were blood pressure data collected in previous surveys of the individual cohorts except for Austria and France. For these previous surveys, data on cardiovascular risk factors were not complete in all cohorts.

Blood pressure was measured according to the multinational monitoring of trends and determinants in cardiovascular medicine (MONICA) or a comparable protocol and was similar in all cohorts at all times.14 Blood pressure was measured twice on the right arm in sitting position and, except for Italy, with a random-zero sphygmomanometer. The average of the 2 measurements was used. Hypertension was defined as a systolic blood pressure of ≥160 mm Hg, or a diastolic blood pressure of ≥95 mm Hg, or the use of blood pressure-lowering medication. Subjects who used blood pressure-lowering medication were considered successfully treated if they had systolic and diastolic blood pressures <160 mm Hg and <95 mm Hg, respectively; otherwise, they were classified as poorly controlled.

Diabetes was defined as a history of diabetes confirmed by the treating physician or use of oral antidiabetics or insulin or a fasting glucose level ≥7 mmol/L, or a nonfasting glucose level ≥11.1 mmol/L. Smoking status was categorized as never, former, and current cigarette smoking. Hypercholesterolemia was defined as a total cholesterol level ≥6.5 mmol/L. Body mass index was calculated as weight divided by height squared.

White Matter Lesions

The core protocol included T1-, T2-, and proton density-weighted MR images.13 The same mobile MRI machine (1.0-T; Siemens, Germany) was sent to Spain, Italy, Poland, Sweden, and UK. The other cohorts acquired images on a 1.0-T or a 1.5-T machine using comparable MRI protocols.

White matter lesions were considered present if visible as hyperintense on proton density-weighted and T2-weighted images, without prominent hypointensity on T1-weighted scans. Periventricular white matter lesion grades were rated semiquantitatively (range 0 to 9).7,12 For subcortical white matter lesions, a total volume was approximated.7,12 Three raters, trained by one neuroradiologist, scored all images. Both intrarater and inter-rater studies (n = 100) showed a good to excellent agreement (κ = 0.79 to 0.90, r = 0.88 to 0.95).7,12

Data Analysis

White matter lesion distributions were dichotomized at the upper quintile to represent severe white matter lesions (for periventricular white matter lesion grade ≥4 and for subcortical white matter volume ≥1.5 mL).7,11,12 We calculated relative risks as estimated by odds ratios by means of multivariate logistic regression.

Changes in blood pressure were calculated as change in mm Hg per year and subsequently grouped in 5 categories based on inspection of the blood pressure data only. Because of a J-shape association with change in diastolic blood pressure reported earlier in the Dutch cohorts, we repeated this analysis excluding the participants form these 2 cohorts to confirm this association in the other cohorts.12 Adjustment was made for age, sex, study site, and potential confounding cardiovascular risk factors measured. Analyses with previous blood pressure data were additionally adjusted for differences in follow-up time.

Before data pooling, we assessed heterogeneity by formal testing of the study×blood pressure interaction. The German cohort showed deviant results; hence, we assessed pooled estimates with and without this cohort.

We performed logistic regression analysis with dummy variables for people with untreated, successfully treated, and poorly controlled hypertension to estimate the relative risks for severe white matter lesions compared with people with no hypertension.

Results

Table 1 presents characteristics of the study participants overall and stratified by study site. Blood pressure levels, the prevalence of hypertension, and elevated blood pressure were highest in Poland and lowest in Spain and France. Additional data are available online at http://www.hypertensionaha.org.

Higher concurrent and previous diastolic and systolic blood pressures were equally associated with an increased risk of severe white matter lesions (Figures 1 and 2). The estimates for the German cohort in relation to white matter lesions were significantly different from the others. The

| TABLE 1. Characteristics of the Study Cohorts Overall and Stratified on Study Site |
|--------------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|
| Characteristics          | Total (n = 1625) | Austria (n = 169) | France (n = 192) | Germany (n = 194) | Italy (n = 167) | NL-RS (n = 233) | NL-ZS (n = 267) | Poland (n = 154) | Spain (n = 110) | Sweden (n = 139) |
| Age, y (n)               | 70 (3)           | 68 (2)           | 68 (3)           | 71 (3)           | 70 (3)           | 70 (3)           | 70 (3)           | 70 (3)           | 69 (4)           |
| Woman                    | 51               | 46               | 60               | 51               | 55               | 48               | 49               | 49               | 46               | 53               |
| SBP (conscious), mm Hg   | 146 (21)         | 148 (19)         | 133 (18)         | 145 (17)         | 149 (20)         | 145 (19)         | 150 (22)         | 155 (26)         | 136 (19)         | 151 (23)         |
| SBP (previous), mm Hg    | 137 (20)         | NA               | NA               | 139 (18)         | 151 (20)         | 134 (19)         | 132 (16)         | 143 (22)         | 130 (17)         | 137 (20)         |
| DBP (conscious), mm Hg   | 82 (12)          | 87 (9)           | 77 (11)          | 83 (9)           | 79 (11)          | 78 (11)          | 82 (12)          | 90 (13)          | 73 (10)          | 87 (12)          |
| DBP (previous), mm Hg    | 80 (11)          | NA               | NA               | 82 (10)          | 84 (10)          | 74 (11)          | 82 (10)          | 81 (12)          | 75 (10)          | 88 (10)          |
| Use of BP medication     | 34               | 27               | 34               | 45               | 26               | 35               | 31               | 48               | 20               | 32               |
| Hypertension*            | 50               | 47               | 38               | 57               | 44               | 46               | 55               | 71               | 26               | 61               |

Numbers are unadjusted means (standard deviation) or percentages. NL-RS indicates Netherlands Rotterdam Study; NL-ZS, Netherlands Zoetermeer Study; SBP, systolic blood pressure; DBP, diastolic blood pressure; NA, not assessed.

*Blood pressure ≥160/95 mm Hg or use of blood pressure-lowering medication.
pooled fully adjusted relative risks (without Germany) of concurrently measured diastolic (per 5 mm Hg) and systolic (per 10 mm Hg) blood pressure were, respectively, 1.15 (95% CI, 1.09 to 1.23) and 1.13 (95% CI, 1.06 to 1.21) for severe periventricular white matter lesions and 1.14 (95% CI, 1.07 to 1.21) and 1.12 (95% CI, 1.05 to 1.19) for severe subcortical white matter lesions. Additional adjustment for length of follow-up time or body mass index did not alter the association between previously assessed blood pressure and severe white matter lesions.

Both a decrease and an increase in diastolic blood pressure were associated with a more than doubled risk of severe periventricular white matter lesions compared with stable blood pressure levels over time (Table 2). Additional adjustment for blood pressure-lowering medication did not change these associations. The same pattern was observed in relation to severe subcortical white matter lesions; however, these effects were not statistically significant. These J-shape associations with changes in diastolic blood pressure became slightly stronger after exclusion of the 2 Dutch cohorts, in which this association was described before. A clear increase in systolic blood pressure was associated with a higher risk of severe white matter lesions (Table 3).

Hypertension is strongly related to severe white matter lesions (Table 4). People who were treated for high blood pressure and still had elevated levels had the highest risk of severe white matter lesions, compared with people without hypertension. They also had a significantly higher risk of severe white matter lesions than people with untreated or controlled hypertension. People with untreated or successfully treated hypertension had comparable risks of severe white matter lesions. Exclusion of the German cohort did not alter these results.
**Discussion**

This study demonstrates that concurrently and formerly assessed higher systolic and diastolic blood pressure levels are associated with a higher prevalence of severe periventricular and subcortical white matter lesions. These findings were observed in all individual cohorts from different European countries except for Germany. People with a clear increase and clear decrease in diastolic blood pressure had more periventricular white matter lesions compared with people whose blood pressure remained stable. Increase in systolic blood pressure was associated with a higher prevalence of severe periventricular and subcortical white matter lesions. Uncontrolled hypertension was strongly related to more severe white matter lesions.

The strengths of this study are its large number of participants originating from different countries, reflecting the wide range of cardiovascular risk in Europe, and its longitudinal design in blood pressure measurements. Individual studies on risk factors of white matter lesions are often difficult to compare because of methodological differences. The standardized blood pressure and white matter lesions assessment and comparable study designs made it possible to pool the individual studies in CASCADE.

Some methodological limitations of this study need to be considered. First, participants had to be survivors of the cohort they originated from. People with high blood pressure levels or extreme changes in blood pressure levels over time may have preferentially died and hence will be underrepresented. If this nonparticipation was preferential in people with severe white matter lesions, which could be caused by possible shared vascular risk factors and susceptibility with myocardial infarction and stroke, then selection bias would have led to underestimation of the real associations.

A second potential source of selection bias was the incomplete response. Nonresponse was most likely in people with high blood pressure and more severe white matter lesions. Therefore, selection may have biased our results most likely toward an underestimation of the real associations.

Third, the association between blood pressure and white matter lesions might be confounded by other cardiovascular risk factors, study site, or length of follow-up time. However, adjustment for these factors did not significantly alter the association between blood pressure and white matter lesions, which suggests that white matter lesions are independently related to blood pressure levels and changes.

We did not observe differences between the cohorts from the different European countries with respect to the association between blood pressure and white matter lesions, except for Germany. There was no north–south gradient as seen in cardiovascular mortality. We do not have a biological explanation for the deviant results in the German cohort. Selection, as mentioned, may have preferentially affected the German study. Additional analyses for the deviant findings in the German study confirm a clear selection effect (nonparticipation).

---

**TABLE 2. Odds Ratios (95% CI) of Change in Systolic Blood Pressure Per Year for Severe White Matter Lesions (Exclusive of Germany)**

<table>
<thead>
<tr>
<th>Severe White Matter Lesions</th>
<th>Change in Systolic Blood Pressure Per Year</th>
<th>Periventricular</th>
<th>Subcortical</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Model 1</td>
<td>Model 2</td>
</tr>
<tr>
<td>&lt;−2.5 mm Hg/y</td>
<td>1.2 (0.7–2.2)</td>
<td>1.0 (0.6–1.6)</td>
<td>1.0 (ref)</td>
</tr>
<tr>
<td>−2.5 to 0 mm Hg/y</td>
<td>1.9 (0.9–4.0)</td>
<td>1.3 (0.7–2.7)</td>
<td>1.0 (ref)</td>
</tr>
<tr>
<td>0 to 2.5 mm Hg/y</td>
<td>1.6 (0.9–2.8)</td>
<td>1.4 (0.9–2.2)</td>
<td>1.0 (ref)</td>
</tr>
<tr>
<td>2.5 to 5 mm Hg/y</td>
<td>1.4 (0.7–2.7)</td>
<td>1.6 (0.9–3.0)</td>
<td>1.0 (ref)</td>
</tr>
<tr>
<td>&gt;5 mm Hg/y</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Model 1 adjusted for age, sex, diabetes, smoking, hypercholesterolemia, and study site.
Model 2 as model 1 and the 2 Dutch cohorts excluded.
participants had a significant higher blood pressure, more vascular comorbidities, and a lower self-perceived general health status than participants of the German cohort.

Concurrent and previous diastolic and systolic blood pressure levels had similar magnitudes of association to more severe white matter lesions in this sample of nondemented people. The main hypothesis regarding this association is that long-standing hypertension causes structural changes of the cerebral small vessels, such as thickening of the vessel walls with narrowing of the lumen, hyalinisation of the media resulting in stiffness, and tortuous elongation. Together these changes lead to increased vascular resistance and, hence, hypoperfusion. Furthermore, long-standing hypertension may impair cerebral autoregulation. In healthy people, the mean arterial pressure remains within limits to assure perfusion during fluctuations in systemic blood pressure. These limits may shift upwards with chronic hypertension, resulting in transient falls in cerebral blood flow during periods of lower blood pressure. Episodic of hypotension may then lead to hypoperfusion and ischemia of the white matter. Yet another pathogenetic mechanism may be involved. Hypertension may cause disturbances in the blood–brain barrier, which may cause lesions in the white matter by cerebral edema, activation of astrocytes, destructive enzymes, or other toxins that pass through the damaged vessel walls.

This study confirms the association between decrease in diastolic blood pressure and periventricular white matter lesions that was observed in the Rotterdam Scan Study. Most vulnerable for hypoperfusion are the areas that are already marginally perfused and lack a collateral circulation. The periventricular white matter represents such an arterial border zone, which in combination with insufficient autoregulation is highly sensitive for drops in blood pressure levels. Hypotension might be contributed to a too aggressive antihypertension treatment in elderly people with upshifted autoregulation limits. People with the highest blood pressure levels in the past, who are therefore at high risk, are most likely to have substantial drops in blood pressure caused by treatment, change in lifestyle, and aging. A drop in diastolic blood pressure may also be a consequences of arterial stiffening as part of progression of atherosclerosis, which is associated with white matter lesions.

We found that people with hypertension had a higher risk of severe white matter lesions than those without hypertension, and that people with poorly controlled hypertension had a higher risk than those with controlled hypertension. These observed associations are compatible with reported data on whites in a comparable age range. Adequate control of hypertension may lead to a lesser degree of cerebral small vessel disease. However, people with successfully treated hypertension had the same risk of severe white matter lesions as those with nontreated hypertension. A potential adverse effect of too aggressive treatment in a part of the treatment group or less severe hypertension or shorter duration of hypertension in the untreated group may explain this lack of difference.

**Perspectives**

Our results may offer potential therapeutic possibilities in preventing and reducing the attendant cognitive decline and dementia. A randomized clinical trial would be needed to evaluate the effect of treatment of hypertension on the development of white matter lesions and its possible consequences. The potential adverse effect of lowering the diastolic blood pressure should be borne in mind and data on white matter lesion progression should be noticed.

**Acknowledgments**

Core funding for the collaborative work is provided by the European Union Directorate General XII. Siemens BV, the Netherlands, is gratefully acknowledged for the use of the mobile MRI machine. Imation International BV provided assistance for the MRI film. We thank Bart Schraa and Dani Kraus for technical support, Rafal Motyl and Jan Cees de Groot for reading the MRI scans, and Rene Molhoek for data management. Many other national and international funding agencies have provided assistance to the individual study centers, as have study center staffs: Austria; “Steiermärkische Krankenanstalten GmbH,” the Austrian National Bank; “Jubiläumsfonds,” the Austrian Science Fund, Italy; Roberto Amici, Luigi Palmieri, Franco Scianna for data collection and management, Il Progetto CUORE—Epidemiology and prevention of ischemic heart disease—of the Italian Ministry of Health, France, the INSERM, Merck, Sharp and Dohme-Chibret Laboratories (West Point, NY), and the EISAI Company, Germany, the German Research Society (Deutsche Forschungs Gemeinschaft), the Cooperative Health Research in the Augsburg Region (KORA), the Netherlands, the Netherlands Organization for Scientific Research (NWO), the Health Research and Development Council (ZON), the National Institutes of Health, the Internationale Stichting Alzheimer Onderzoek (ISAO), and the Royal Netherlands Academy of Arts and Sciences. Poland, the Jagiellonian University Medical School, Ewa Kawałec, Roman Topór-Madry, Andrzej Szczudlik, Agnieszka Słowiak, Rafal Motyl, Miroslawa-Orlowiejska-Gillert, Spain, the Department of Health and Social Security of Catalonia, Sweden, the Bank of Sweden Tercentenary Foundation, Swedish Council for Planning and Coordination of Research, Swedish Council for Research in the Humanities and Social Sciences, and the Swedish Council for Social Research. United Kingdom, the Occupational Health and Safety Agency and the Council of Civil Service Unions.

---

**TABLE 4. Odds Ratios (95% CI) of Hypertension and Its Treatment Status for Severe White Matter Lesions Compared to Normotensives Who Did Not Use Blood Pressure-Lowering Medication**

<table>
<thead>
<tr>
<th>Severe White Matter Lesions</th>
<th>No Hypertension</th>
<th>Hypertension</th>
<th>Hypertension Treatment Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=814)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Periventricular</td>
<td>1.0 (ref)</td>
<td>1.6 (1.3–2.2)</td>
<td>1.5 (1.0–2.2)</td>
</tr>
<tr>
<td>(n=811)</td>
<td></td>
<td></td>
<td>1.4 (1.0–2.0)</td>
</tr>
<tr>
<td>Subcortical</td>
<td>1.0 (ref)</td>
<td>1.4 (1.1–1.8)</td>
<td>1.1 (0.8–1.7)</td>
</tr>
<tr>
<td>(n=811)</td>
<td></td>
<td></td>
<td>1.3 (0.9–1.8)</td>
</tr>
<tr>
<td>Adjusted for age, sex, diabetes, smoking, hypercholesterolemia, and study site.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

1. Adequate control of hypertension may lead to a lesser degree of cerebral small vessel disease. However, people with successfully treated hypertension had the same risk of severe white matter lesions as those with nontreated hypertension. A potential adverse effect of too aggressive treatment in a part of the treatment group or less severe hypertension or shorter duration of hypertension in the untreated group may explain this lack of difference.

---

van Dijk et al. Blood Pressure and Cerebral White Matter Lesions 629
References


The Association Between Blood Pressure, Hypertension, and Cerebral White Matter Lesions: Cardiovascular Determinants of Dementia Study
Ewoud J. van Dijk, Monique M.B. Breteler, Reinhold Schmidt, Klaus Berger, Lars-Göran Nilsson, Matthijs Oudkerk, Andrzej Pajak, Susana Sans, Maria de Ridder, Carole Dufouil, Rebecca Fuhrer, Simona Giampaoli, Lenore J. Launer and Albert Hofman for the CASCADE Consortium

Hypertension. 2004;44:625-630; originally published online October 4, 2004; doi: 10.1161/01.HYP.0000145857.98904.20
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2004 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

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/44/5/625

Data Supplement (unedited) at:
http://hyper.ahajournals.org/content/suppl/2004/11/04/44.5.625.DC1