Hypertensive organ damage predicts future cognitive performance: A 9-year follow-up study in patients with hypertension

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Hypertension is associated with cognitive deficits, probably caused by cerebral small vessel disease. The authors examined whether additional presence of cardiac and renal organ damages, and their combined presence, are associated with future cognitive performance. In 78 patients with essential hypertension (mean age 51.2 ± 12.0 years), brain damage was determined by MRI features, cardiac damage by left ventricular mass index (LVMI), and renal damage by estimated glomerular filtration rate (eGFR) and albuminuria. At 9-year follow-up, neuropsychological assessment was performed. LVMI was associated with future lower cognition (P = 0.032), independent of age, sex, premorbid cognition, and brain damage, but eGFR and albuminuria were not. The presence of 2 or 3 types of organ damage compared to none was associated with future lower cognition. Increasing number of hypertensive organ damages, and cardiac damage independently of brain damage, might indicate a more severe hypertensive disease burden and could help to identify patients at risk of cognitive problems.
1 | INTRODUCTION

The brain is one of the target organs affected by hypertension. Hypertension is a major risk factor for cerebral small vessel disease (cSVD), which in turn leads to brain damage that can be made visible on brain MRI. These imaging markers of cSVD are strongly associated with cognitive function. Other types of hypertensive organ damage, such as cardiac and renal damages, have also been linked to lower cognitive function or increased risk of cognitive impairment.7-11 Organ damage could be regarded as marker of the severity of hypertensive disease.12 Little research has investigated the combined effect of different sites of organ damage on cognitive function. One study showed that an increasing number of signs of cardiac and renal damages were associated with decline in memory performance.13 However, whether cardiac and renal damages are also associated with cognition independently of brain damage is unknown. No study combined the presence of hypertensive cardiac, renal, and cerebral damages and investigated their independent impact on cognitive performance. Investigating the implications of combined and organ-specific hypertensive organ damage could help identifying patients at high risk of developing cognitive problems.

We investigated whether brain, cardiac, and renal damages, and their combined presence, are predictive of lower cognitive performance 9 years later. We hypothesize that an increasing presence of hypertensive organ damages negatively influences cognitive performance. In addition, we examined whether cardiac and renal hypertensive organ damages are predictive of future lower cognitive performance, independent of cSVD, and what these types of hypertensive organ damage add, in addition to cSVD, in explaining cognitive function.

2 | METHODS

2.1 | Study population

Patients with essential hypertension were recruited from the hypertension outpatient clinic of the Department of Internal Medicine of Maastricht University Medical Centre, the Netherlands, for a study on brain damage in patients with essential hypertension (HYBRiD). Hypertension was defined as off-medication, clinically measured conventional blood pressure ≥140 mm Hg systolic or ≥90 mm Hg diastolic, or both. Details about the HYBRiD study have been described before. Exclusion criteria were documented diabetes, renal failure, ischemic or valvular heart disease, atrial fibrillation, history of transient ischemic attacks or stroke, and obstructive sleep apnea syndrome. All patients received a brain MRI, an echocardiography, and a timed urine collection over a 24-hour period and routine laboratory investigations. Three off-medication office blood pressure measurements were taken, and the systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP) from the second and third measurements were averaged. Patients who were using antihypertensive medication were instructed to discontinue treatment at least 2 weeks before these BP measurements. Information about vascular risk factors (body mass index, smoking, and the presence of hypercholesterolemia) was obtained. Nine years later, patients were invited for follow-up study, which included a neuropsychological assessment. The Medical Ethics Committee of the Maastricht University Medical Centre approved this study, and all participants gave written informed consent.

2.2 | Assessment of brain damage

On baseline brain MRI scans (axial T2-weighted, FLAIR, and T2* gradient echo sequences, Intera 1.5-T, Philips Medical Systems, Best, the Netherlands), two experienced vascular neurologists rated MRI markers of cSVD, after reaching satisfactory inter-rater agreements. The inter-rater agreement statistics have been previously reported. An ordinal scale representing the total burden of cSVD was created. Definitions and rating method have been described in detail before. In short, the presence of each of the four MRI markers for cSVD (white matter hyperintensities (WMH), lacunes, cerebral microbleeds, and perivascular spaces) was counted to retrieve a total cSVD burden score (ranging from 0 to 4). WMH were assessed according to the Fazekas scale. The presence of WMH was defined as periventricular WMH Fazekas score 3 (irregular hyperintensities extending into the deep white matter) and/or deep WMH Fazekas score 2 or 3 (confluent hyperintensities). Perivascular spaces were rated at the level of the basal ganglia as mild, moderate, or extensive. One point was awarded for moderate or extensive perivascular spaces. Lacunes and cerebral microbleeds were assessed according to the international consensus definition, and for both lacunes and cerebral microbleeds, one point was awarded in the total cSVD score if at least one lacune or cerebral microbleed was present. Brain damage was considered present in case of a cSVD score ≥1.

2.3 | Assessment of cardiac damage

Left ventricular mass, assessed at baseline by two-dimensional M-mode and Doppler echocardiography (Sonos 5500, Hewlett-Packard, Andover, MA, USA), was estimated according to Devereux’s formula (Penn convention) and indexed to body surface area. The left ventricle dimensions and wall thicknesses were measured according to recommendations. Cardiac damage was considered present in case of left ventricular hypertrophy (LVH), defined as a left ventricular mass index (LVMI) >115 g/m² for men and >95 g/m² for women.

2.4 | Assessment of renal damage

The urinary albumin excretion (UAE) was measured in a timed 24-hour urine collection by means of nephelometry (BN ProSpec® System, Dade Behring Inc, Deerfield, IL, USA), with a detection limit of 2.2 mg/L. Microalbuminuria was defined as a UAE >30 and <300 mg/24 hours. Renal function was considered to be impaired in case of an estimated glomerular filtration rate (eGFR; calculated with CKD-EPI) <60 mL/minute. Hypertension-related renal damage
was considered to be present in case of microalbuminuria and/or impaired renal function.

Results of reproducibility analyses for both cardiac and renal damages have been described before. 12

2.5 | Neuropsychological assessment

Cognitive performance was measured at 9-year follow-up with an extensive neuropsychological assessment, as has been described before. 20 We determined an overall cognition score by averaging domain scores of memory, executive function, and information processing speed. Memory domain was measured with the Rey Auditory Verbal Learning Test 21 (immediate recall, delayed recall, and delayed recognition) and the Digit Span Forward (subtest of Wechsler Adult Intelligence Scale (WAIS)-III). Executive function domain was measured with the Stroop Color-Word Test 23 (SCWT) interference score (time of part 3 minus mean time of parts 1 and 2), Trail Making Test 24 (TMT) interference score (time of part 2 minus time of part 1), Category (animals and professions) 25 and Letter Fluency, 26 Letter-Number Sequencing (subtest of WAIS-III), and Digit Span Backward (subtest of WAIS-III). Information processing speed domain was measured with the Symbol Substitution Coding (subtest of WAIS-III), TMT part A, and SCWT parts 1 and 2. Test scores were transformed into standardized values (z-scores), by dividing the difference between the individual raw score and the sample mean by the sample standard deviation, which results in sample mean = 0 and standard deviation (SD) = 1 for each test. For each patient, domain scores were calculated by averaging these z-scores of the tests within that domain.

The Dutch Adult Reading Test (DART) was used as a measure of prior cognitive ability. 27 By correcting for the DART, associations with cognitive function actually represent a lifetime change in cognitive performance.

The Rotterdam-Cambridge Cognitive Examination (R-CAMCOG) was used to determine the presence of possible dementia, defined as a score <34. 28

2.6 | Statistical analysis

Baseline characteristics of all included patients were reported as mean and SD or median and interquartile range (IQR) for normally and non-normally distributed characteristics, respectively, and absolute number and percentage for categorical characteristics.

We investigated whether an increasing number of sites with organ damage (brain, cardiac, and/or renal damage) were associated with future cognitive performance (overall cognition score) using multivariable linear regression analysis, corrected for age, sex, and DART score. Next, we tested the associations between the individual organ damages (cSVD score, LVMI, eGFR, and UAE, as continuous variables) and cognitive performance (overall cognition score). We performed univariable linear regression analyses to estimate crude associations and subsequently performed multivariable linear regression in which we corrected for age, sex, and DART score. In addition, for the analyses of LVMI, eGFR, and UAE, we repeated the multivariable linear regression with addition of the cSVD score. For all regression analyses, we computed the coefficient of variation ($R^2$), to examine how much of the variance in cognitive performance (overall cognition score) was explained by LVMI, eGFR, or UAE, on top of age, sex, DART score, and cSVD score.

In exploratory analyses, we examined the associations between SBP, DBP, and MAP and cSVD score, LVMI, eGFR, and UAE with Pearson’s correlation, and the number of sites with organ damage with Spearman’s correlation.

IBM SPSS Statistics 22 software was used for all analyses. Results were considered significant at $P < 0.05$.

3 | RESULTS

3.1 | Participants

Of the 218 patients in the HYBRiD study at baseline, 193 (88.5%) patients had complete baseline data on brain, cardiac, and renal damages. Of these, 78 (40.4%) completed the follow-up including cognitive testing after 9 years. Reasons for exclusion during follow-up were as follows: no consent to be contacted for follow-up ($n = 18$), not interested ($n = 70$), cerebrovascular event during follow-up ($n = 7$), death ($n = 4$), contraindications for MRI ($n = 4$), neuropsychological assessment not possible ($n = 3$), unreachable ($n = 3$), and other reasons ($n = 6$).

The mean follow-up period was 9.05 year (SD = 0.13). Included patients ($n = 78$) did not differ from excluded patients ($n = 115$) in age (mean (SD): 51.2 ± 12.0 vs 52.0 ± 12.7 years, respectively, $P = 0.670$), sex (male: 56.4% vs 47.0%, respectively, $P = 0.197$), LVMI (mean (SD): 88.2 ± 18.5 vs 90.1 ± 21.9, $P = 0.544$), eGFR (mean (SD): 82.9 ± 16.6 vs 82.4 ± 19.5, $P = 0.843$), or UAE (median (IQR): 12(7-20) vs 15(9-27, $P = 0.211$). Baseline characteristics are shown in Table 1.

At follow-up, three patients had an R-CAMCOG score <34, indicating possible dementia.

3.2 | Hypertensive organ damage

At baseline, twenty-nine patients had no organ damage, 31 had damage of 1 organ, 15 had 2 organ damages, and 3 had damage of all 3 organs. The distribution of the types of organ damage is shown in Table 2.

The presence of 2 or 3 sites with organ damage was associated with future lower cognitive performance ($B = -0.36$ (95% CI = -0.67 to -0.05), $P = 0.023$, and $B = -0.77$ (95% CI = -1.37 to -0.18), $P = 0.012$, respectively) compared to having no organ damage, but having organ damage only at one site was not ($B = -0.16$ (95% CI = -0.42 to 0.11), $P = 0.238$).

Cerebral small vessel disease score was associated with lower cognitive performance in unadjusted and adjusted analyses (Table 3). LVMI was associated with lower cognition in unadjusted analysis and after correction for age, sex, and DART score and additionally for cSVD score (Table 3). eGFR and UAE were both not associated with cognitive performance (Table 3).
In addition, we investigated how much variance in future cognitive performance was explained by baseline hypertensive organ damage. Age, sex, and DART score explained 44.7% of the variance in cognitive performance. The cSVD score explained an additional 5.2%. On top of age, sex, DART score, and cSVD score, 3.1% was explained by LVMI, while eGFR and UAE explained only 0.2% and 0.1%, respectively.

### 3.3 Exploratory analyses

Since types of organ damage are thought to result from hypertension, we examined the correlations between SBP, DBP, and MAP and organ damages. Results are shown in Table 4. SBP was correlated with all types of organ damage, while DBP and MAP were correlated with 2 or 3 of the types of organ damages. Number of sites of organ damage was significantly correlated with SBP, DBP, and MAP.

### TABLE 1 Patient baseline characteristics

|                          | All patients (n = 78) |
|--------------------------|-----------------------|
| Age, mean (SD), y        | 51.2 (12.0)           |
| Male sex, No. (%)        | 44 (56.4%)            |
| SBP, mm Hg, median (IQR) | 161 (150-181)         |
| DBP, mm Hg, mean (SD)    | 101 (11)              |
| MAP, mm Hg, mean (SD)    | 123 (14)              |
| Duration of hypertension, months, median (IQR) | 38 (14-126) |
| Hypercholesterolemia, No. (%) | 23 (29.5%) |
| Current smoking, No. (%) | 14 (17.9%)            |
| Body mass index, mean (SD) | 27.3 (4.3)         |
| DART score, median (IQR) | 85 (74-92.5)          |
| LVMI, mean (SD), g/m²    | 88 (18)               |
| eGFR, mean (SD), mL/min/1.73 m² | 83 (17) |
| UAE, median (IQR), mg/24 h | 12 (7-20)       |
| cSVD score 0, No. (%)    | 39 (50%)              |
| cSVD score 1, No. (%)    | 28 (35.9%)            |
| cSVD score 2, No. (%)    | 5 (6.4%)              |
| cSVD score 3, No. (%)    | 5 (6.4%)              |
| cSVD score 4, No. (%)    | 1 (1.3%)              |

cSVD, cerebral small vessel disease; DART, Dutch adult reading test; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; IQR, interquartile range; LVMI, left ventricular mass index; MAP, mean arterial pressure; SBP, systolic blood pressure; SD, standard deviation; UAE, urinary albumin excretion.

In addition, we investigated how much variance in future cognitive performance was explained by baseline hypertensive organ damage. Age, sex, and DART score explained 44.7% of the variance in cognitive performance. The cSVD score explained an additional 5.2%. On top of age, sex, DART score, and cSVD score, 3.1% was explained by LVMI, while eGFR and UAE explained only 0.2% and 0.1%, respectively.

### TABLE 2 Distribution and number of sites with organ damages

| Number of organ damages | 0   | 1   | 2   | 3   |
|-------------------------|-----|-----|-----|-----|
| Number of patients (%)  |     |     |     |     |
| n = 29 (37.2%)          |     |     |     |     |
| n = 31 (39.7%)          |     |     |     |     |
| n = 15 (19.2%)          |     |     |     |     |
| n = 3 (3.8%)            |     |     |     |     |

| Number of patients with: | Presence of brain damage | Presence of cardiac damage | Presence of renal damage |
|--------------------------|--------------------------|---------------------------|------------------------|
|                          | 0 (0%)                   | 21 (67.7%)                | 15 (100%)              |
|                          | 21 (67.7%)               | 6 (40.0%)                 | 3 (100%)               |
|                          | 0 (0%)                   | 5 (16.1%)                 | 9 (60.0%)              |
|                          |                          | 5 (16.1%)                 | 3 (100%)               |

### DISCUSSION

We showed that an increasing number of sites with hypertensive organ damage (brain, cardiac, and/or renal damage) were associated with lower cognitive performance after 9 years of follow-up. In addition, our results showed that cardiac damage is associated with cognitive performance after 9 year, independently of brain MRI damage.

The mechanisms underlying hypertension-related cognitive changes are not fully known, but are thought to be mainly induced by cSVD. cSVD is represented by visible MRI brain damage, but is also associated with microstructural brain damage and cerebrovascular functional alterations such as hypoperfusion. These factors also relate to cognitive function, and thus, cSVD score determined by standard brain MRI only partly represents the impact of hypertension and cSVD on cognitive function. Therefore, we examined whether additional clinical effect markers of hypertension, namely other types of organ damage, could predict future cognitive dysfunction, on top of visible MRI brain damage.

Not surprisingly, cSVD score predicted the largest proportion of variance in cognitive performance, but cardiac damage was also independently associated with cognitive performance. Our results are in agreement with previous studies that showed associations between cardiac damage and cognitive function. However, as these studies did not investigate this association independently of brain damage, these results might be due to a high correlation between hypertensive cardiac damage and brain damage. We could not show an association between renal damage (determined by either eGFR or UAE) and cognitive performance. This is contradicting with the results of previous studies, which might be caused by the small sample size of our study.

The result that an increasing number of sites with hypertensive organ damage are predictive of lower cognitive performance underlines the importance of considering total hypertensive organ damage.
damage instead of only determining damage in one or two organs. Previous results showed that there is only limited overlap between different sites of hypertensive organ damage, as organ damage can co-occur, but can also remain restricted to one organ. We are aware of one other study that investigated the implications of combined hypertensive organ damages. In this study, number of organ damages was based on LVH, impaired renal function, and albuminuria. It was shown that the presence of 2 or 3 organ damages was associated with decline in memory performance (but not executive function), compared to having no organ damage.

We did not correct for blood pressure in our analyses since the different forms of organ damages are intermediate variables in the causal pathway between hypertension and cognitive dysfunction. Adjusting for blood pressure would blunt the association between organ damage (an intermediate effect of the hypertension) and cognition. In our cohort, all 3 types of organ damage were indeed correlated with SBP, DBP, and/or MAP. The number of sites with organ damage was also correlated with blood pressure.

An important strength of the study is the extensive neuropsychological assessment. By combining multiple neuropsychological tests into one overall cognition score, we lower the intrindividual variability. Future research, with larger sample sizes, could further investigate various cognitive domains. The long follow-up time of 9 years is a strength of our study, but this was also coupled with a high dropout rate: of 193 patients included at baseline only 78 completed follow-up. It is possible that cognitively worse patients were less likely to participate in the follow-up measurements. The small sample size resulted in small numbers of patients in some of the categories of organ damages. Another limitation is the lack of neuropsychological assessment at baseline, which withheld us from determining cognitive decline over the 9 years of follow-up. However, since we used the DART score to control for prior cognitive performance, results actually reflect associations with a lifetime change in cognitive performance. The lack of blood pressure measurements during the 9 years of follow-up is another limitation of our study, as this could have provided more information about blood pressure control.

In conclusion, the load of organ damage, that is having an increasing number of sites with hypertensive organ damage, is associated with future lower cognitive performance. Cardiac damage is also associated with lower cognitive performance independently of brain damage. The presence of damage in multiple organs might indicate a higher hypertensive disease burden, which might not all be visible on brain MRI (yet). These results could help to identify patients at high risk of developing cognitive problems.

### TABLE 3  Associations between organ damage and cognitive performance (overall cognition composite score)

| cSVD score | LVMI | eGFR | UAE |
|------------|------|------|-----|
| B (95% CI) | B (95% CI) | B (95% CI) | B (95% CI) |
| Unadjusted linear regression | | | |
| −0.237 (−0.390 to −0.084) | −0.009 (−0.017 to −0.001) | 0.024 | 0.008 (−0.001 to 0.017) | 0.077 |−0.001 (−0.005 to 0.003) | 0.574 |
| Corrected for age, sex, DART score | | | |
| −0.173 (−0.298 to −0.048) | −0.008 (−0.014 to −0.002) | 0.010 | −0.001 (−0.009 to 0.007) | 0.881 |−0.002 (−0.004 to 0.001) | 0.232 |
| Corrected for age, sex, DART score, and cSVD score | | | |
| NA | NA | −0.007 (−0.013 to −0.001) | 0.032 | −0.002 (−0.010 to 0.006) | 0.624 |−0.001 (−0.003 to 0.002) | 0.714 |

### TABLE 4  Correlations between blood pressure levels and organ damage

| cSVD score | LVMI | eGFR | UAE | Number of organ damages |
|------------|------|------|-----|-------------------------|
| SBP | r = 0.294, P = 0.009 | r = 0.406, P < 0.001 | r = −0.248, P = 0.029 | r = 0.388, P < 0.001 | r = 0.286, P = 0.011 |
| DBP | r = 0.194, P = 0.089 | r = 0.319, P = 0.004 | r = 0.034, P = 0.767 | r = 0.334, P = 0.003 | r = 0.276, P = 0.014 |
| MAP | r = 0.273, P = 0.016 | r = 0.405, P < 0.001 | r = −0.119, P = 0.298 | r = 0.403, P < 0.001 | r = 0.326, P = 0.004 |

cSVD, cerebral small vessel disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; LVMI, left ventricular mass index; NA, not applicable; UAE, urinary albumin excretion.
CONFLICT OF INTEREST

None.

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