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Impaired Cognition and Brain Atrophy Decades After Hypertensive Pregnancy Disorders

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Abstract

Background—Hypertensive pregnancy disorders have been associated with subjective cognitive complaints or brain white matter lesions five to ten years after the hypertensive pregnancy. The long-term effects of hypertensive pregnancies on brain structure and cognitive function remain unknown.

Methods and Results—This study included 1279 women who participated in the Family Blood Pressure Project Genetic Epidemiology Network of Arteriopathy (GENOA) study. As part of the ancillary Genetics of Microangiopathic Brain Injury study, a neurocognitive battery was administered; 1075 also had a brain MRI. A history of a hypertensive pregnancy disorder was obtained by self-report using a validated questionnaire. Linear models fit with generalized estimating equations were used to assess the association between hypertensive pregnancy disorders and cognition, adjusting for age, race, education, body mass index, smoking, current hypertension, hypertension duration, and family history of hypertension. Regression models for the brain MRI outcomes also were adjusted for total intracranial volume. Women with histories of hypertensive pregnancy disorders performed worse on all measures of processing speed: Digital Symbol Substitution Test (mean score 41.2 vs 43.4, P=0.005), Trail Making Test Part A (mean seconds 45.1 vs 42.2, P=0.035), and Stroop (mean score 173.9 vs 181.0, P=0.002) and had smaller brain volumes compared to women with histories of normotensive pregnancies (286 vs 297, P=0.023).

Conclusions—Hypertensive pregnancy disorders are associated with worse performance on tests of processing speed and smaller brain volumes decades later. Population-based studies are

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Disclosures

None.

needed to provide critical insight as to the contribution of hypertensive pregnancies to risk of cognitive decline and dementia.

Keywords

hypertension; preeclampsia/pregnancy; cognition; brain imaging; epidemiology

Hypertensive pregnancy disorders are a potential sex-specific risk factor for cognitive impairment and dementia among women.[1] These disorders, which affect approximately 8% of all pregnancies, include gestational hypertension, preeclampsia, eclampsia, chronic hypertension, and preeclampsia or eclampsia superimposed on chronic hypertension. Women with histories of hypertensive pregnancy disorders, especially preeclampsia, are at an increased risk for a subsequent diagnosis of hypertension,[2] cardiovascular disease (CVD),[2,3] and stroke[4] later in life. Several longitudinal studies have established that hypertension,[5,6] stroke,[2,7] and CVD[8] increase the risk of cognitive decline and dementia. Thus, it is possible that women with histories of hypertensive pregnancy disorders also have an increased risk of cognitive decline and dementia. Studies suggest associations between hypertensive pregnancy disorders and subjective cognitive complaints[9,10] or brain white matter lesions on MRI.[11-14] However, these studies had small sample sizes, included few ethnic or racial minorities, and only assessed brain structure and cognitive function five to ten years after the hypertensive pregnancy. The long-term effects of hypertensive pregnancy disorders on brain structure and cognitive function remain unknown. In the present study, we examined associations between hypertensive pregnancy disorders, cognitive performance, and brain MRI findings among a large, multi-ethnic and racial sample of women, mean age of 61 years, enrolled in the Genetic Epidemiology Network of Arteriopathy (GENOA) study, which was a cohort included in the Family Blood Pressure Project (FBPP).

Methods

Study Design

Our analysis included 1279 women who participated in the FBPP GENOA study and who completed the pregnancy history questionnaire during the Phase 2 study examination (2000-2004). GENOA is a multi-center study that started in 1995 and followed a well-characterized cohort of sibships from families with histories of hypertension.[15] Participants were recruited from families in which at least two siblings developed hypertension before age 60. As part of the ancillary study Genetics of Microangiopathic Brain Injury (2001-2005), all had cognitive testing and 1075 women had a MRI for measuring brain and ventricular volumes and white matter lesions. The brain MRI and cognitive function testing were completed, on average, about one year after the GENOA examination. Non-Hispanic white women were recruited in Rochester, Minnesota (N=569). Non-Hispanic black women were recruited in Jackson, Mississippi (N=710).This study was approved by the Institutional Review Boards at the Mayo Clinic and University of Mississippi Medical Center. All subjects provided written informed consent before participating.

Assessment of Hypertensive Pregnancy

We used a standardized, previously validated questionnaire administered by trained interviewers to determine whether a woman had a history of hypertension in pregnancy.[16] Women were asked, “Have you had at least one pregnancy lasting more than six months?” Women who responded “yes” were asked how many pregnancies they had and,” during any of these pregnancies (which lasted more than 6 months), did a physician ever tell you that you had high blood pressure or hypertension?”

Cognitive Testing

A neuropsychological assessment was offered to all participants using a standardized protocol to assess global cognition and domains of memory, language, executive function, and processing speed. Global cognition was assessed by the Mini-Mental State Examination (MMSE, range 0-30).[17] Tests of memory included the Rey Auditory Verbal Learning Test (RAVLT) delayed recall (range 0-15)[18] and the Wechsler Adults Intelligence Scale II Incidental Learning Task (range 0-93).[19] Language was assessed using the FAS, a measure of letter fluency, and the Animal Naming Task, a measure of category (animals) fluency.[18] Executive function was assessed by the Trail-Making Test (TMT) Part B (TMT-B).[20] A greater time to completion (in seconds) indicated worse performance. Processing speed was measured using the Wechsler Adult Intelligence Scale Revised Digit Symbol Substitution Task and TMT-A.[18] A greater time to completion (in seconds) on the TMT-A indicated worse performance. We also included the Stroop test, a measure of both processing speed and cognitive flexibility.[21] The Stroop test involved three trials. In the WORD trial, the subject read words of color names printed in black ink. In the COLOR trial, the subject identified colors. Finally, in the COLOR-WORD response inhibition trial, the subject named the color in which a word was presented, while ignoring the printed word. Scoring for each trial type is based on the number of correct responses in 45 seconds. The sum of the three trials was used as the final score (range 0-93). Higher scores indicate better cognitive performance.

MRI Assessment

All MRI scans were performed on identically equipped Signa 1.5 T MRI scanners (GE Healthcare) and images were centrally processed at the Mayo Clinic. Symmetric head positioning with respect to orthogonal axes was verified by a series of short scout scans. Total intracranial volume (TIV; head size) was measured from T1-weighted spin echo sagittal images, each set consisting of 32 contiguous 5 mm thick slices with no interslice gap, field of view = 24 cm, matrix = 256 × 192, obtained with the following sequence: scan time = 2.5 min, echo time = 14 ms, repetitions = 2, replication time = 500 ms.[22] Total brain and white matter lesion volumes (cm^3) were determined from axial fluid-attenuated inversion recovery (FLAIR) images, each set consisting of 48 contiguous 3-mm interleaved slices with no interslice gap, field of view = 22 cm, matrix = 256 × 160, obtained with the following sequence: scan time = 9 min, echo time = 144.8 ms, inversion time = 2600 ms, repetition time = 11 seconds, bandwidth = +/- 15.6 kHz, one signal average. Interactive imaging processing steps were performed by a trained image analyst who had no knowledge of the subjects’ personal or medical histories or biological relationships. A fully automated

algorithm was used to segment each slice of the edited multi-slice FLAIR sequence into voxels assigned to one of three categories: brain, cerebrospinal fluid, or white matter lesion. The mean absolute error of this method was 1.4% for brain volume and 6.6% for white matter lesion volume, and the mean test-retest coefficient of variation was 0.3% for brain volume and 1.4% for white matter lesion volume.[23] The difference between TIV and brain volume provided a measure of brain atrophy. White matter hyperintensities in the corona-radiata and periventricular zone, as well as infarcts in the central gray matter, were included in the global white matter lesion volume measurements. Brain scans with cortical infarctions were excluded from the analyses because of the distortion of the white matter lesion volume estimates that would be introduced into the automated segmentation algorithm.

Assessment of Covariates

All measurements were performed by trained technicians who followed standardized protocols. Height was measured with the participant standing with her heels together, without shoes, against a vertically mounted ruler. Weight was measured using an electronic balance with participants wearing lightweight clothes. Body mass index (BMI) was calculated as weight (kg)/height^2 (m^2). 'Ever' smoked was defined as a lifetime history of having smoked ≥100 cigarettes. Diabetes was defined as a self-report of a physician diagnosis of diabetes and use of hypoglycemic medications, or a fasting serum glucose concentration of at least 126 mg/dl. Hypertension was defined as a self-reported physician diagnosis of hypertension and prescription antihypertensive medication use, or an average systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg. Hyperlipidemia was defined as the use of a lipid-lowering medication or an abnormal lipid measurement (total cholesterol ≥200 mg/dl, triglycerides ≥150 md/dl, or high density lipoprotein (HDL) ≤40 mg/dl). Serum concentrations of total cholesterol, triglycerides, and HDL cholesterol were measured on the same analyzer.

Statistics

Differences in the baseline characteristics of women, by having a history of a hypertensive pregnancy disorder, with cognitive and MRI data were evaluated using chi-square tests for categorical variables (presented as absolute numbers with percentages) and One-way ANOVA for continuous variables (expressed as mean values with SDs). The associations between having had a history of a hypertensive pregnancy disorder and either cognitive function or MRI characteristics were estimated using linear models fit with generalized estimating equations (GEE), accounting for sibship clustering. All variables in Table 1 were initially examined as potential confounders. Only covariates that differed between women with and without a history of hypertensive pregnancies (or nulliparous women) were included in the GEE models. Model 1 was adjusted for age, race, education, BMI, smoking, hypertension, and family history of hypertension. Model 2 was adjusted for all the covariates from Model 1 and, in addition, with hypertension duration, which was assessed for women with current hypertension. The duration of hypertension was unknown for 81 of 898 (9%) hypertensive women; for these women, the duration of hypertension was not imputed. Values for the cognitive testing data that were not normally distributed were log transformed. The *P* values corresponding to the log transformed data are presented in tables, while the descriptive values (means ± 95% CIs for mean) are converted to antilog for easier

interpretation of the cognitive test scores. The total volume of brain injury was assessed as an MRI composite measure of brain atrophy and white matter lesion volume. Because the MRI measures and the cognitive domain scores used different measurement units, the relationship between the two was assessed in the form of z-scores (ie, standardized cognitive domains and total standardized volume of brain injury). Composite measures for memory, processing speed and language domains were constructed from tests constituting each domain to reduce measurement error and floor and ceiling effects of individual tests. A standardized z-score was created for each individual measure, and z-scores were averaged within a domain to create the composite. Standardized outcomes and predictors were then modeled to facilitate comparison between models, where a beta coefficient of -0.5 is interpreted as a 0.5-standard deviation (SD) decrease in cognitive score outcome being associated with 1-SD increase in total brain injury. Sensitivity analyses were performed by excluding five women with clinical diagnoses of dementia and adjusting for recent self-reported symptoms of depression and nervousness. A second sensitivity analysis was performed by including nulliparous women in all models. We also adjusted models for abnormal estimated glomerular filtration rate (eGFR<60 mL/min per 1.73m^2). As these additional analyses did not alter the results, they are not reported. Statistical analysis was performed using SPSS (SPSS for Windows, version 21.0, SPSS, Chicago, IL). P<0.05 was considered to be statistically significant.

Results

Participant Characteristics

Among the 1279 women with cognitive data, 208 (16.3%) had histories of hypertensive pregnancy disorders. The frequency of hypertensive pregnancies (n=176; 16.4%) was similar among the 1075 women with a MRI. There were no differences in demographic, medical, or cognitive characteristics between women who did and did not have a brain MRI. Compared to women with previous normotensive pregnancies, women with previous hypertensive pregnancies were younger, had higher BMIs, were more frequently hypertensive, and more frequently reported a parental history of hypertension (Table 1). Compared to nulliparous women, women with previous hypertensive pregnancies were more frequently Non-Hispanic black, had a lower education, had higher BMIs, were more frequently hypertensive, and more frequently reported a parental history of hypertension. There were no differences between women with and without (normotensive or nulliparous) a history of hypertensive pregnancy with respect to diabetes, dyslipidemia, or a family history of coronary heart disease.

History of Hypertensive Pregnancy Disorders and Cognitive Function

In multivariable analyses, women with histories of hypertensive pregnancy disorders performed worse on all three measures of processing speed: Digital Symbol Substitution Test (mean score 41.2 vs 43.4, P=0.005), Trail Making Test Part A (mean seconds 45.1 vs 42.2, P=0.035), and the Stroop (mean score 173.9 vs 181.0, P=0.002) (Table 2, Model 1). There were no associations between having a history of a hypertensive pregnancy disorder and cognitive performance in memory, language, or executive function. Additionally adjusting for hypertension duration in the models did not alter the results except for Trail

Making Test Part A, where differences between the groups were attenuated (mean seconds 43.7 vs 42.1, *P*=0.238) (Table 2, Model 2). The results were not different when nulliparous women were included or when the models were adjusted for abnormal eGFR (data not shown).

History of Hypertensive Pregnancy Disorders and Brain MRI Measures

Women with histories of hypertensive pregnancy disorders had smaller brain volumes compared to women with histories of normotensive pregnancies (286 vs 297, *P*=0.023) in multivariable models (Model 1, Table 3). Women with histories of hypertensive pregnancy disorders also had greater mean white matter lesion volumes (8.9 vs 8.1, *P*=0.182), but this difference did not reach statistical significance. Inclusion of hypertension duration in the models did not alter the results (Model 2, Table 3). Results did not differ when nulliparous women were included, or when the models were adjusted for abnormal eGFR (data not shown).

Relationship Between Cognitive Function and Brain MRI Measures

Lastly, we examined the association between domain-specific cognitive function and the total standardized volume of brain injury, a composite measure of brain atrophy and white matter lesion volume (Table 4). Among all domains, better cognitive functioning was associated with a lower volume of brain injury. Faster processing speed was most significantly associated with a lower volume of brain injury among women with (b = -0.36, *P*=0.004) and without (b = -0.16, *P*=0.005) a history of a hypertensive pregnancy disorder. Better performance on tests of memory (b = -0.08, *P*=0.034) and executive function (b= -0.12, *P*=0.019) were also associated with a lower volume of brain injury among women with histories of normotensive pregnancies. Better performance on tests of language (b = -0.19, *P*=0.019) was associated with a lower volume of brain injury among women with histories of hypertensive pregnancies (Table 4, Models 1). Inclusion of hypertension duration in the models did not alter the results in women with histories of a hypertensive pregnancy disorder, but the results were attenuated for tests of memory in women who were normotensive while pregnant (b = -0.06, *P*=0.082) (Table 4, Model 2).The results did not differ when nulliparous women were included in the normotensive pregnancy group, or when the models were adjusted for abnormal eGFR (data not shown).

Discussion

Our results indicate that women with histories of a hypertensive pregnancy disorder, compared to those who were normotensive while pregnant, perform more poorly on tests of processing speed decades after the hypertensive pregnancy. No differences in memory, language and/or executive function were observed between the groups. In addition, women with histories of a hypertensive pregnancy disorder had greater brain atrophy and a trend towards a greater degree of white matter lesion volume. As hypertensive pregnancy disorders are increasingly recognized as a CVD risk factor, cognitive decline and brain changes may be mediated solely by subsequent diagnoses of hypertension or cardiovascular disease. Alternatively, hypertensive pregnancy disorders may represent a risk factor that is independent of the effects of cardiovascular disease. In the present study, after adjusting for

CVD, hypertension, hypertension duration and a family history of hypertension, the association between having a history of a hypertensive pregnancy disorder and both processing speed and brain atrophy remained significant. These results suggest that hypertensive pregnancies are independent predictors of impaired brain structure and cognitive function and may identify those women at greater risk of future dementia.

Our previous study in the FBPP cohort demonstrated that, compared to women who had normotensive pregnancies, women who had hypertensive pregnancies were more likely to develop hypertension and stroke, even after controlling for traditional risk factors.[2] Our subsequent studies, using either all FBPP cohorts as a whole or the component network cohorts individually, also showed that women with histories of a hypertensive pregnancy disorder were at greater risk for peripheral artery disease,[24] left ventricular hypertrophy,[25] and metabolic abnormalities that increase the risk of CVD, including elevated C-reactive protein[26] and homocysteine.[27] Taken together, these findings identify hypertensive pregnancy disorders as an additional sex-specific CVD risk factor.

Although CVD is a well-recognized risk factor for cognitive decline and dementia, there is a dearth of information as to the effects of hypertensive pregnancies on brain structure and cognitive function, and whether such an association might be solely mediated by CVD. One pilot study compared cognitive performance between ten severely preeclamptic and ten normotensive pregnant women three to eight months postpartum. The severely preeclamptic women had significantly lower scores on a test of auditory-verbal memory, but not on tests of attention/concentration or executive functioning.[28] Two additional studies examining the effects of hypertensive pregnancies on cognition, approximately six to eight years after the affected pregnancy, when the average age of the women was 30-40 years, found that women with preeclampsia and eclampsia (30-50 women per group) reported worse subjective cognitive function.[9,10] However, a comprehensive neuropsychological battery was not conducted. In the current study, we systematically examined the association between having a history of a hypertensive pregnancy and domain-specific cognitive functioning among a large group of 1279 women of different racial and ethnic backgrounds. We found that women with histories of a hypertensive pregnancy had poorer cognitive performance, especially in processing speed, decades later, when the average age of the women was about 60 years. While the significant associations had modest effect sizes, on a population scale even a modest shift in the distribution of cognitive scores can result in an increased public health burden from cognitive impairment (ie., the lower the scores at a given age, the sooner one crosses the threshold for impairment as function declines with age). Importantly, adjusting for CVD and known CVD risk factors did not attenuate the results, suggesting that hypertensive pregnancy disorders may be independent risk factors for cognitive decline.

Some studies have suggested associations between having a history of a hypertensive pregnancy and brain white matter lesions on MRI.[11-14] For example, previous neuroimaging studies in women with severe forms of preeclampsia demonstrated significant white matter lesions.[11] Neuroradiological abnormalities, in the form of vasogenic edema at the time of delivery, persisted in a few patients up to eight weeks postpartum, presumably caused by gliosis in response to infarction. Subsequent studies suggested greater white matter lesion burden five to seven years after the affected pregnancies.[11-14] Our study suggests even

longer-term adverse effects of hypertensive pregnancies, such that these affected women have greater brain atrophy decades after their pregnancies compared to women who had normotensive pregnancies. There was also a trend for white matter lesions. Further, our results indicate that cognitive impairment occurs in the setting of structural brain changes for women with a mean age of 61 years. Thus, women with histories of hypertensive pregnancy disorders may need to be closely monitored for signs and symptoms of cognitive decline, and their modifiable risk factors need to be treated adequately.

Limitations of this study warrant consideration. First, all hypertensive pregnancy disorders were pooled for this analysis, as the study was too small to examine the effects of preeclampsia alone. Future studies are needed to determine whether women with histories of preeclamptic or eclamptic pregnancies are at even greater risk of adverse structural and functional brain changes compared to women with histories of gestational hypertension. Second, brain scans with cortical infarctions were excluded from the analyses due to distortion of the volume estimates. This would potentially bias the results towards the null such that the effects of a hypertensive pregnancy disorder on brain structure could be even more pronounced. Third, GENOA enrolled sibships with a familial predisposition to hypertension. Therefore, the results may not be generalizable to low-risk women or to the general population. Fourth, survival bias may have affected the results because women participated in this cross-sectional study decades after their pregnancies. Fifth, the reported associations may be due to shared risk factors between hypertensive pregnancy disorders and cognitive decline or brain atrophy. Alternatively, hypertension in pregnancy may be indicative of long-term vascular abnormalities that may elevate the risk for cognitive decline and brain atrophy. Our study cannot differentiate between these two possible mechanisms but sets the stage for future studies that will be adequately designed and powered to address the underlying mechanisms. Lastly, pregnancy history was determined by self-report. However, the pregnancy history questionnaire was previously validated, demonstrating 80% sensitivity and 90% specificity for the determination of preeclampsia.[16]

Despite these limitations, our study clearly showed that women with histories of hypertensive pregnancy disorders, compared to women with histories of normotensive pregnancies, demonstrate cognitive decline in the setting of MRI-based brain atrophy. To date, hypertensive pregnancy disorders have been identified as a risk factor by the AHA guidelines for prevention of CVD[29] and stroke[30] (Guidelines for the Prevention of Stroke in Women: A Statement for Healthcare Professionals from the American Heart Association/ American Stroke Association). Population-based studies that would address and confirm the association between having a history of a hypertensive pregnancy and future cognitive decline are needed. They may provide critical insight as to the contribution of sex-specific risk factors to the risk of dementia in women.

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WHAT IS KNOWN

- Previous studies suggest associations between hypertensive pregnancy disorders and subjective cognitive complaints or brain white matter lesions on MRI five to ten years after the hypertensive pregnancy.
- The long-term effects of hypertensive pregnancy disorders on brain structure and cognitive function, assessed using a comprehensive neuropsychological battery, have not been reported.

WHAT THE STUDY ADDS

- Women with a history of hypertensive pregnancy disorders perform more poorly on tests of processing speed decades after the hypertensive pregnancy compared to women with normotensive pregnancies.
- Women with a history of hypertensive pregnancy disorders also had greater brain atrophy decades later.
- The results remained after adjusting for traditional cardiovascular risk factors, suggesting that hypertensive pregnancies are independent predictors of impaired cognition and brain structure.

Table 1

Participant Characteristics by History of Hypertensive Pregnancy Disorders Among Women With Cognitive and MRI Data

Characteristic	With cognitive data			With MRI data		
	Nulliparous (n = 112)	Normotensive Pregnancy (n = 959)	Hypertensive Pregnancy (n = 208)	Nulliparous (n = 103)	Normotensive Pregnancy (n = 796)	Hypertensive Pregnancy (n = 176)
Age (yrs), mean±SD	57±11	61±9	58±10[a]	57±11	61±9	58±10[a]
Race, n (%)			[b]			[b]
Non-Hispanic White	68 (61)	412 (43)	89 (43)	65 (63)	378 (47)	84 (48)
Non-Hispanic Black	44 (39)	547 (57)	119 (57)	38 (37)	418 (53)	92 (52)
Education, n (%)			[b]			[b]
Less than high school (≤8 years)	2 (2)	54 (6)	16 (8)	2 (2)	40 (5)	13 (7)
Partial high school (9-11 years)	4 (3)	107 (11)	26 (12)	3 (3)	80 (10)	17 (10)
High school graduate/GED (12 years)	29 (26)	366 (38)	68 (33)	25 (24)	310(39)	59 (34)
Post high school (>12 years)	77 (69)	432 (45)	98 (47)	73 (71)	366 (46)	87 (49)
Body mass index (kg/m^2), mean±SD	32±7	31±6	34±7[a,b]	32±7	31±6	33±6[a,b]
Ever smoked, n (%)	38 (34)	340 (36)	57 (27)	38 (34)	291 (37)	49 (28)[a]
eGFR<60 mL/min per 1.73m^2, n (%)	5 (4.5)	62 (6.5)	16 (7.7)	4 (3.9)	48 (6.1)	13 (7.4)
Diabetes, n (%)	20 (18)	197 (21)	46 (22)	20 (18)	151 (19)	37 (21)
Hypertension, n (%)	85 (76)	713 (74)	185 (89)[a,b]	85 (76)	578 (73)	155 (88)[a,b]
Duration of hypertension, yrs[†], mean±SD	17±13	15±11	22±13 [a,b]	18±13	15±10	22±13 [a,b]
Dyslipidemia, n (%)	55 (49)	466 (49)	89 (43)	55 (49)	378 (48)	78 (44)
Family history of hypertension, n (%)	88 (79)	747 (78)	180 (87) [a]	88 (79)	618 (78)	155 (88)[a,b]
Family history of CHD, n (%)	49 (44)	401 (42)	102 (49)	49 (44)	338 (43)	89 (51)

GED indicates general educational development.

eGFR Estimated glomerular filtration rate

CHD coronary heart disease

[†]Duration of hypertension is shown for women with current hypertension.

[a]Significant difference (P<0.05) compared to women with normotensive pregnancies.

[b]Significant difference (P<0.05) compared to nulliparous women.

Table 2

Cognitive Performance by a History of Normotensive or Hypertensive Pregnancy Disorders

	Normotensive Pregnancy (n = 959)		Hypertensive Pregnancy (n = 208)	
Cognitive Testing	**Model 1**	**Model 2**	**Model 1**	**Model 2**
Global cognition				
Mini Mental State Examination (range 0-30)	27.9 (27.8-28.0)	27.9 (27.8-28.1)	27.9 (27.7-28.2)	28.0 (27.7-28.3)
Memory				
Rey Auditory Verbal Learning Test(range 0-15)	8.4 (8.2-8.6)	8.4 (8.2-8.6)	8.1 (7.7-8.5)	8.3 (7.9-8.8)
Wechsler Adult Intelligence Scale-IIIIncidental Learning Task	5.0 (4.8-5.1)	5.0 (4.8-5.1)	5.0 (4.6-5.3)	5.0 (4.6-5.4)
Processing Speed				
Digital Symbol Substitution Test (range 0-93)	43.4 (42.8-44.0)	43.6 (42.9-44.3)	41.2[a] (39.8-42.6)	41.6[a] (40.1-43.0)
Trail Making Test Part A, seconds[†]	42.2 (41.2-43.2)	42.1 (41.0-43.2)	45.1[a] (42.6-47.6)	43.7 (41.3-46.3)
Stroop: Processing Speed, Executive Function	181.0 (179.2-182.9)	180.9 (178.9-182.8)	173.9[a] (169.7-178.0)	175.9[a] (171.6-180.3)
Language				
FAS, number of words	31.5 (30.8-32.2)	31.3 (30.5-32.1)	31.8 (30.2-33.4)	31.8 (30.1-33.5)
Animal naming, number of animals	16.7 (16.5-17.0)	16.8 (16.5-17.0)	16.4 (15.8-17.0)	16.4 (15.8-17.1)
Executive function				
Trail Making Test Part B, seconds[†]	116.3 (113.0-119.7)	115.9 (112.5-119.5)	115.6 (108.3-123.5)	112.1 (104.5-120.1)

Values shown are mean and 95% confidence intervals for the mean.

Model 1 adjusted for age, race, education, BMI, smoking, hypertension, family history of hypertension and accounted for familial clustering.

Model 2 adjusted for all variables from Model 1 plus duration of hypertension

[†]For all tests except the Trail Making Test, Parts A and B, a higher score indicates better performance. For Trail Making Test, Parts A and B, p values were initially derived from natural log transformed test values. Inverse logarithm values are presented in this table to better display performance on the cognitive test.

Table 3

MRI Measures of Study participants by a History of Normotensive or Hypertensive Pregnancy Disorders

MRI Characteristics	Normotensive Pregnancy (n = 796)			Hypertensive Pregnancy (n = 176)		
	Non-adjusted	Model 1	Model 2	Non-adjusted	Model 1	Model 2
Total intracranial volume†	1355 (1347-1363)	/	/	1360 (1344-1376)	/	/
Ventricle volume	21.0 (20.2-21.9)	20.7 (20.0-21.5)	20.8 (20.0-21.6)	18.8 (17.4-20.2)	20.3 (18.6-21.9)	19.9 (18.1-21.6)
Brain atrophy	287 (282-291)	286 (282-290)	285 (281-289)	293 (284-301)	297[a] (288-305)	296[a] (287-305)
White matter lesion volume	8.3 (7.8-8.8)	8.1 (7.7-8.6)	8.2 (7.7-8.7)	8.0 (6.8-9.3)	8.9 (7.9-9.9)	8.3 (7.3-9.5)

Values shown are mean with 95% confidence interval for mean.

†The model for total intracranial volume is univariate.

Model 1 adjusted for age, BMI, smoking, hypertension, family history of hypertension, total intracranial volume, and accounted for familial clustering.

Model 2 adjusted for all variables from Model 1 plus duration of hypertension.

[a]Significant difference (P<0.05) compared to women with normotensive pregnancies.

Table 4

Relationship Between Standardized Cognitive Domains and Total Standardized Volume of Brain Injury by a History of Hypertensive Pregnancy Disorders

Cognitive domain	Normotensive Pregnancy (n = 796)		Hypertensive Pregnancy (n = 176)	
	Model 1 Standardized β (95% CI for β)	Model 2 Standardized β (95% CI for β)	Model 1 Standardized β (95% CI for β)	Model 2 Standardized β (95% CI for β)
Global cognition	-0.02 (-0.08 to 0.04)	-0.02 (-0.08 to 0.05)	-0.09 (-0.21 to 0.07)	-0.03 (-0.17 to 0.11)
Memory	-0.08* (-0.13 to -0.01)	-0.06 (-0.12 to 0.01)	-0.12 (-0.29 to 0.04)	-0.15 (-0.32 to 0.01)
Processing speed	-0.16* (-0.23 to -0.04)	-0.14* (-0.24 to -0.05)	-0.36* (-0.54 to -0.11)	-0.30* (-0.52 to -0.08)
Language	-0.04 (-0.10 to 0.03)	-0.04 (-0.11 to 0.03)	-0.19* (-0.34 to -0.03)	-0.17* (-0.32 to -0.02)
Executive function	-0.12* (-0.17 to -0.01)	-0.09* (-0.17 to -0.01)	-0.18 (-0.34 to 0.03)	-0.13 (-0.31 to 0.06)

Model 1 adjusted for age, race, education, BMI, smoking, hypertension, family history of hypertension and accounted for familial clustering.

Model 2 adjusted for all variables from Model 1 plus duration of hypertension

* indicates statistical significance at $p<0.05$