ORIGINAL ARTICLE

# Aortic Hemodynamics and Cognitive Performance in Postmenopausal Women: Impact of Pregnancy History

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**BACKGROUND**
Studies demonstrate an association between aortic hemodynamics and cognitive function. The impact of pregnancy history on this association is unknown.

**METHODS**
Postmenopausal women (age 59 ± 5 years; years since last pregnancy 35 ± 3) with either a history of preeclampsia (PE; $n = 34$) or a history of a normotensive pregnancy (NP; $n = 30$) underwent cognitive testing: Letter-Number Sequencing, Digit Span, Trail Making Test, and letter and category fluency. Applanation tonometry was used to derive aortic systolic and diastolic blood pressure and augmentation index.

**RESULTS**
Distribution of cognitive scores and aortic hemodynamic measures was similar between the PE and NP groups. Principal component (PC) analysis was used to reduce the 3 aortic hemodynamic measures and the 5 cognitive variables to single summary indices, each representing a weighted average of their respective constituent variables. Using a multivariable linear model based on these PCs that adjusted for pregnancy history and body mass index, the composite index of aortic hemodynamics was associated with the summary cognitive index, whether taking into account a potential interaction with pregnancy history ($P = 0.035$) or not ($P = 0.026$) (interaction $P = 0.178$). Multivariable modeling of individual cognitive tests revealed a differential association for letter fluency by pregnancy history (test for interaction $P = 0.023$); this score correlated with the aortic hemodynamic index in the PE (partial $R^2 = 0.20$), but not the NP (partial $R^2 = 0.00$) group.

**CONCLUSIONS**
Elevated aortic hemodynamics may negatively impact cognitive function in postmenopausal women with specific executive functions, such as letter fluency, being impacted more by a pregnancy history of PE.

*Keywords:* aortic stiffness; blood pressure; cognition; hypertension; menopause; preeclampsia; pregnancy

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A history of preeclampsia (PE), a disorder of pregnancy characterized by high blood pressure during pregnancy, places women at a higher risk of developing cardiovascular disease, stroke, and hypertension compared with women who had a normotensive pregnancy (NP).[1–7] Despite this increase in risk, most studies only evaluate women within several years of the postpartum period. Women after menopause, regardless of pregnancy history, are at an elevated risk for developing cardiovascular diseases such as hypertension.[8] Indeed, postmenopausal women (35 years postpartum) with a history of PE tend to exhibit more cognitive impairment compared with postmenopausal women with a history of a NP.[9] Additionally, women with a history of PE have reduced brain blood flow responses to a vasodilatory stimulus, indicating impaired cerebrovascular reactivity.[10] Thus, postmenopausal women with a history of PE may have a high risk of developing both cardiovascular disease and early cognitive decline.

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Blood pressure of the large central arteries is relevant to brain health. These vessels are proximal to the brain and have an important role in dampening pulsatile blood flow caused by myocardial contraction. A more rigid aorta under high pressure may transmit pulsatile forces into the cerebral microcirculation, a low impedance flow system, causing microvascular damage, and ultimately affecting brain function.[11–13] Consistent with this concept, elevated aortic hemodynamics inversely associate with cognitive test scores in older adults.[14] While hypertension is a risk factor for accelerated cognitive decline,[15,16] elevated aortic blood pressures due to arterial stiffness may appear before a diagnosis of clinical hypertension[17] and be more indicative of subclinical cognitive decline in healthy adults compared with traditionally measured brachial blood pressure.[15,18]

Previously, our group reported that postmenopausal women with higher aortic blood pressure and wave reflection had a greater fraction of white matter hyperintensities in the brain,[19] a biomarker of cognitive decline reflecting areas on the brain burdened with demyelination and axonal loss.[20,21] We sought to extend the study of aortic hemodynamics and cognition by evaluating postmenopausal women with a history of PE, as these women are at a higher risk for cognitive decline. Therefore, we hypothesized that higher aortic blood pressures would associate with lower cognitive performance in women with a history of PE but not in age-matched women with a history of NP.

## METHODS

### Participant recruitment

Women pregnant between 1976 and 1982 in Olmsted County, MN were identified through the medial record linkage Rochester Epidemiology Project as described.[22,23] An exposure was confirmed as PE if a woman had at least 1 preeclamptic pregnancy between 1976 and 1982 and met the standard definition: (i) 2 or more blood pressure readings of a systolic blood pressure (SBP) >140 mm Hg or a diastolic blood pressure (DBP) >90 mm Hg that occur at least 4 hours apart after 20 weeks gestation and (ii) new onset proteinuria, as defined by a urine dipstick 1+, or proteinuria ≥0.300 g/24 hours, or a protein/creatinine ratio equivalent to ≥0.3 g/24 hours. Emergency room visits were not included in the assessment. Forty women with a confirmed history of PE agreed to participate in the main prospective study, along with 40 age- and parity-matched women with a history of NP. Of these 80 women, 64 met inclusion criteria and were retained for the present ancillary study: 30 women had a history of NP and 34 women had a history of PE. For inclusion in this ancillary study, women must have been a resident of Olmsted County or surrounding areas, were nonsmoking, had a body mass index (BMI) <35 kg/m$^2$, were not on hormone replacement therapy, and had no underlying cardiovascular disease. Study procedures were approved by the Institutional Review Board of the Mayo Clinic and were performed according to the Declaration of Helsinki, including obtaining written informed consent from each participant.

### Cognitive testing

Cognitive tests for the current study were selected from a broader 2.5-hour battery of validated tests that were administered in a fixed order to each participant by a trained psychometrist under the supervision of a neuropsychologist.[9] Cognitive tests were selected based on literature suggesting that frontal executive functions are associated with cerebral vascular changes/white matter lesions,[24,25] arterial stiffness,[26,27] and hypertensive pregnancy disorders.[28,29] Digit Span and Letter-Number Sequencing tested attention/working memory, Trail Making Test (Part B) measured cognitive flexibility, and verbal fluency (3 letters and 3 categories) measured search and retrieval strategies, all of which are aspects of frontal executive functioning.

### Aortic hemodynamics

Participants arrived at the Clinical Research Unit at Mayo Clinic after a 4-hour fast and 24 hours without caffeine, alcohol, or vigorous exercise. After resting supine for at least 10 minutes, brachial SBP, brachial DBP, and mean arterial pressure (MAP) were measured using an oscillomeric noninvasive brachial blood pressure cuff (Datex Ohmeda CardioCap5 Anesthesia Monitor, GE Healthcare, Fairfield, CT). The measurements were made in triplicate with 2 minutes supine rest in between measurements. Aortic hemodynamics were assessed in the supine position using applanation tonometry. High-fidelity radial artery pressure waveforms were recorded from the radial pulse on the right wrist.[19,30] A generalized transfer function corrected for upper limb pressure amplification and generated the corresponding aortic pressure waveform (Sphygmocor, Atcor Medical, Sydney, Australia). Radial waveforms were calibrated using brachial SBP and brachial DBP. The software automatically calculated the following variables: (i) aortic SBP, (ii) aortic DBP, and (iii) augmentation index (AIx; reflected wave amplitude divided by pulse pressure expressed as a percentage). AIx was adjusted for a heart rate of 75 bpm.[31] AIx is a characteristic of wave reflection, with higher values indicating amplified wave reflection due to increased aortic stiffness. Consecutive trials (3–5 recordings) with sufficient operator index and quality were averaged for each participant.

### Data analysis and statistics

Descriptive statistics (mean ± standard deviation and quartile values for continuous variables, or percentages and counts for categorical variables) were computed for study participants by pregnancy history. Spearman rank correlation coefficients were used to estimate the strength of relationship between each hemodynamic measure and each cognitive test and were interpreted as weak ($|r_s| < 0.3$), moderate ($|r_s| = 0.3–0.5$), or strong ($|r_s| \geq 0.5$). Due to the interdependency of the hemodynamic variables (aortic SBP, aortic DSP, and Alx) and multiplicity problems that arise from examining multiple individual correlations separately by group, data reduction was undertaken to achieve more interpretable statistical test results. Principal component (PC)

analysis was used to reduce the joint variation of 3 aortic hemodynamic variables (aortic SBP, aortic DBP, and AIx) and 5 cognitive scores (Digit Span, Letter-Number Sequencing, Trail Making Test B, letter fluency, and category fluency) to their most important dimensions, whereby each series of variables is replaced by a summary scale scored by the first PC. This scoring process involved first transforming the original variables to normal scores (mean 0, variance 1) and then optimally combining these standardized measures into a summary variable that adequately captures the data's information. Ordinary least squares regression modeling was used to assess the relationship between the PCs summarizing aortic hemodynamic and cognitive score variables, with interaction terms incorporated to allow for the possibility of differential patterns by pregnancy history. For *post hoc* analysis, a second least squares multivariable model was fitted with the original scales of the cognitive tests by modeling all of them as separate variables. The individual cognitive scores were assessed for independent and differential associations not as responses but as predictor variables, since reversing the model equation to make the aortic hemodynamics PC a single outcome was more computationally convenient. In addition, we repeated the first regression analysis by focusing on dimensions of brachial measured pressures and assessing the summary measure, using MAP or pulse pressure, as it correlates with the cognitive PC. We controlled for BMI in all regression models due to observed differences between women with and without a history of PE. These analyses were primarily done using Statistical Analysis Software SAS, version 9.4 (SAS Institute, Cary, NC).

## RESULTS

### Participant characteristics

By study design, the original 2 groups of 40 women with histories of NP and PE were matched for age and parity. In the 64 women retained for this ancillary study (Table 1), there were no significant differences in years since pregnancy, education, and brachial SBP, brachial DBP, or MAP. BMI was significantly higher in women with a history of PE compared with women with a history of NP ($P = 0.008$). Women with a history of PE also had a higher incidence of currently diagnosed hypertension defined by use of antihypertensive medications or if the average SBP or DBP was at least 140 or at least 90 mm Hg, respectively ($P = 0.003$). There were no significant differences in aortic hemodynamics between groups (Table 2). Additionally, there were no group differences in any of the raw scores for the cognitive measures (Table 3).

### Correlation results

No moderate correlations were observed between aortic hemodynamics and raw cognitive test scores in the overall group of women or in the subgroup with a history of NP (Table 4). However, in women with a history of PE, aortic SBP and aortic DBP had moderate, negative correlations with Letter-Number Sequencing ($r_s = -0.39$ and $-0.43$, respectively) and with letter fluency ($r_s = -0.35$ and $-0.42$, respectively); with lower scores representing worse performance. In women with a history of PE, a weak to moderate positive correlation was found between aortic blood pressures and Trail Making Test B, where higher scores on the cognitive test indicate worse performance ($r_s = 0.28$ and 0.34 for aortic SBP and aortic DBP, respectively).

### Principal components

Data reduction was performed on the 3 aortic hemodynamic variables and 5 cognitive test variables to minimize the impact of multiplicity problems from testing the statistical significance of these relationships and because of the interdependency among variables in each set of measurements. From the PC analysis, the first hemodynamic PC adequately summarized the component variables explaining 75% of

**Table 1.** Characteristics of participants

| Variable | History of NP ($n = 30$) | History of PE ($n = 34$) | $P$ value |
|---|---|---|---|
| Age at study consent (years) | 59.3 ± 4.8 (58.6, 55.4–62.5) | 59.2 ± 4.8 (59.2, 56.1–62.4) | 0.968 |
| Time since pregnancy (years) | 35.4 ± 2.7 (34.5, 33.7–36.2) | 35.4 ± 3.2 (34.9, 33.0–37.1) | 0.742 |
| Body mass index (kg/m$^2$) | 25.7 ± 4.4 (24.7, 22.4–28.6) | 28.8 ± 4.7 (28.4, 25.5–32.6) | 0.008 |
| Heart rate (beats/min) | 63.7 ± 8.4 (64.0, 56.7–70.0) | 64.0 ± 8.6 (63.5, 59.0–70.0) | 0.914 |
| Brachial systolic blood pressure (mm Hg) | 131.4 ± 20.7 (125.5, 121.0–139.0) | 131.3 ± 17.9 (127.2, 117.7–143.3) | 0.914 |
| Brachial diastolic blood pressure (mm Hg) | 76.0 ± 9.8 (75.7, 71.7–82.3) | 77.6 ± 9.4 (77.0, 71.0–84.0) | 0.590 |
| Mean arterial pressure (mm Hg) | 94.5 ± 12.8 (92.8, 87.0–102.9) | 95.6 ± 12.0 (94.2, 86.7–106.1) | 0.672 |
| Hypertension | 20.0% (6) | 55.9% (19) | 0.003 |
| Education | | | 0.753 |
| High school or less | 10.0% (3) | 14.7% (5) | |
| Some college/technical school | 50.0% (15) | 52.9% (18) | |
| College graduate or higher | 40.0% (12) | 32.4% (11) | |

Characteristics of participants are reported as percentage (number) or mean ± standard deviation (median, 25th–75th percentiles); $P$ values are from Pearson $\chi^2$ test or Wilcoxon rank sum test. Abbreviations: NP, history of normotensive pregnancy; PE, history of preeclampsia.

**Table 2.** Aortic hemodynamics

| Variable | History of NP (*n* = 30) | History of PE (*n* = 34) | *P* value |
|---|---|---|---|
| Aortic systolic blood pressure (mm Hg) | 122.9 ± 19.9 (118.4, 113.7–126.0) | 122.5 ± 17.5 (119.8, 111.7–135.0) | 0.904 |
| Aortic diastolic blood pressure (mm Hg) | 77.0 ± 10.2 (77.5, 71.0–83.0) | 77.7 ± 9.3 (79.2, 70.7–84.0) | 0.638 |
| Augmentation index (percentage) | 34.4 ± 7.0 (34.2, 30.7–40.0) | 36.1 ± 8.5 (36.5, 29.7–41.0) | 0.360 |
| Augmentation index adjusted for a HR of 75 bpm (percentage) | 28.7 ± 6.9 (30.0, 24.7–33.7) | 30.8 ± 8.5 (32.3, 25.7–35.0) | 0.234 |

Aortic hemodynamic data are reported as mean ± standard deviation (median, 25th–75th percentiles), and compared with Wilcoxon rank sum tests. Abbreviations: HR, heart rate; NP, history of normotensive pregnancy; PE, history of preeclampsia.

**Table 3.** Scores on cognitive testing

| Cognitive function | Cognitive test | History of NP (*n* = 30) | History of PE (*n* = 34) | *P* value |
|---|---|---|---|---|
| Attention/working memory | Digit Span | 16.5 ± 3.9 (16, 14–18) | 16.2 ± 3.4 (16, 14–18) | 0.892 |
| | Letter-Number Sequencing | 10.0 ± 2.1 (10, 9–11) | 9.9 ± 2.2 (9, 8–11) | 0.498 |
| Cognitive flexibility | Trail Making Test B[a] | 59.5 ± 13.7 (57, 53–64) | 69.2 ± 32.6 (63, 49–75) | 0.349 |
| Verbal fluency | Letter Fluency | 42.1 ± 11.1 (41, 33–50) | 41.2 ± 11.2 (42, 36–46) | 0.893 |
| | Category Fluency | 54.8 ± 9.5 (58, 48–63) | 51.1 ± 12.0 (50, 42–61) | 0.247 |

Scores on cognitive tests are reported as mean ± standard deviation (median, 25th–75th percentiles), and compared with Wilcoxon rank sum tests. Abbreviations: NP, history of normotensive pregnancy; PE, history of preeclampsia.
[a]Time in seconds, with higher score showing worse performance.

**Table 4.** Correlation coefficients between aortic hemodynamic and cognitive function variables

| | | | Spearman correlations | | |
|---|---|---|---|---|---|
| Cognitive function | Cognitive test | Hemodynamic variable | $r_{s\,ALL}$ (*n* = 64) | $r_{s\,NP}$ (*n* = 30) | $r_{s\,PE}$ (*n* = 34) |
| Attention/working memory | Digit Span | ASBP | −0.08 | −0.00 | −0.14 |
| | | ADBP | −0.21 | −0.26 | −0.21 |
| | | AIx | 0.00 | −0.14 | 0.09 |
| | Letter-Number Sequencing | ASBP | −0.23 | 0.03 | −0.39[a] |
| | | ADBP | −0.23 | 0.01 | −0.43[a] |
| | | AIx | −0.08 | −0.16 | −0.04 |
| Cognitive flexibility | Trail Making Test B[b] | ASBP | 0.15 | −0.11 | 0.28 |
| | | ADBP | 0.13 | −0.16 | 0.34[a] |
| | | AIx | 0.09 | 0.08 | 0.10 |
| Verbal fluency | Letter Fluency | ASBP | −0.15 | 0.14 | −0.35[a] |
| | | ADBP | −0.14 | 0.19 | −0.42[a] |
| | | AIx | −0.18 | −0.11 | −0.19 |
| | Category Fluency | ASBP | −0.11 | −0.08 | −0.17 |
| | | ADBP | −0.11 | −0.07 | −0.21 |
| | | AIx | 0.03 | 0.10 | −0.02 |

Spearman correlation coefficients between aortic hemodynamic and cognitive function variables. Abbreviations: ADBP, aortic diastolic blood pressure (mm Hg); AIx, augmentation index (percentage; adjusted for a HR of 75 bpm); ASBP, aortic systolic blood pressure (mm Hg); HR, heart rate; NP, history of normotensive pregnancy; PE, history of preeclampsia. Data are $r_s$ (Spearman correlation).
[a]Moderate correlation ($0.3 \le r_s < 0.5$).
[b]Higher score showing worse performance.

the variance. Each component contributed a similar positive loading (aortic SBP = 0.608, aortic DBP = 0.620, AIx adjusted for a HR of 75 bpm = 0.497) that, when combined, reflects an average aortic hemodynamic summary index. When the PC analysis was repeated on the cognitive test variables, the summary variable scored by the cognitive PC explained 52% of the total variation with similar loadings (Digit Span = 0.426, Letter-Number Sequencing = 0.464,

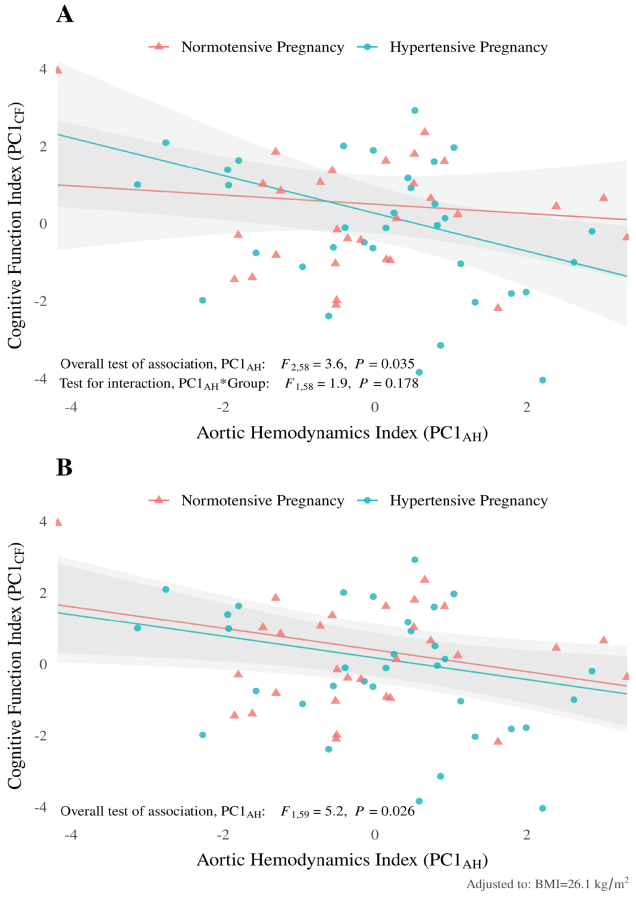


**Figure 1.** Overall relationship between 2 principal components, aortic hemodynamic summary index and cognitive summary index, as described by 2 linear models with and without an interaction term for pregnancy history. Both models were adjusted for potential confounding effects of BMI. (**a**) The model estimated trend of how the derived aortic hemodynamic summary index relates to the cognitive summary index when a separate slope is estimated for each group. From this model, the overall test of association, when taking the potential interaction with pregnancy history into account, showed statistical significance ($F_{2,58}$ = 3.6, $P$ = 0.035), while the test for interaction (i.e., difference between trends) was nonsignificant ($F_{1,58}$ = 1.9, $P$ = 0.178). (**b**) The relationship between principal components when the model is fitted without interaction by formulating a common slope for the 2 groups. The association estimated by this model was statistically significant ($F_{1,59}$ = 5.2; $P$ = 0.026), with higher levels of aortic hemodynamics correlating with lower values of cognitive function. Abbreviation: BMI, body mass index.

Trail Making Test B = 0.420, letter fluency = 0.433, category fluency = 0.484) across the constituent variables. Thus, this PC also could also be interpreted as an average summary of its component measures, with lower scores indicating worse cognitive function. Neither the cognitive test PC nor the aortic hemodynamics PC differed between women with a history of NP and women with a history of PE ($P$ = 0.540 and $P$ = 0.432, respectively).

### Ordinary least squares regression of the PCs

An ordinary least squares regression was performed to determine the potential of an overall or differential association between the aortic hemodynamic summary index and the cognitive summary index. BMI was included in the model as a covariate to adjust for possible confounding effects. The global test for the association when taking the potential interaction of pregnancy history into account (i.e., 2 df overall test for whether the 2 indices are correlated in either group) showed significance ($F_{2,60}$ = 3.6, $P$ = 0.035) (Figure 1a). There was no evidence that the association between the cognitive summary index and the aortic hemodynamic summary index differed by PE status (global test for interaction, $F_{1,58}$ = 1.9, $P$ = 0.178) (Figure 1a). When analyzed as a main effect (in a model without pregnancy history interaction) the aortic hemodynamic summary index significantly associated with the cognitive summary index ($F_{1,59}$ = 5.2, $P$ = 0.026) (Figure 1b). The result was similar when controlling for antihypertensive medications (data not shown). A graphical illustration of these findings (Figure 1b) suggested that higher levels of the aortic hemodynamic summary index correlated with lower values of the cognitive summary index.

### *Post hoc* linear regression analysis of the PCs

To determine which individual scales of cognition may be driving the association between aortic hemodynamics and cognitive indices, a *post hoc* linear regression analysis was performed using the original 5 cognitive variables instead of the single PC. While the global test showed no association (either overall or differentially by group) between the 5 cognitive variables and the aortic hemodynamic summary index ($F_{10,50}$ = 1.5, $P$ = 0.152 for global test of association, with partial $R^2$ = 0.24; and $F_{5,50}$ = 1.7, $P$ = 0.155 for global test for interaction), the partial test for association of the aortic hemodynamic summary index and letter fluency score was significant and differed by pregnancy history ($F_{2,50}$ = 4.2, $P$ = 0.020 for overall association; $F_{1,50}$ = 5.5, $P$ = 0.023 for interaction, Figure 2). The interaction effect (illustrated in Figure 2 by nonparallel slopes of the 2 trend lines, and in Figure 3 by the difference in partial $R^2$ values from group-stratified model fits) suggests that, among women with a history of PE, a worsening aortic hemodynamic summary index was associated with decreasing letter fluency score (partial $R^2$ = 0.20), whereas for women with a history of NP, no association was found (partial $R^2$ = 0.00). These results were not adjusted for multiple testing.

To assess brachial pressure parameters, single summary measures based on brachial MAP and brachial pulse pressure were calculated and correlated with the cognitive summary index in a regression analysis, which yielded similar findings. There was an overall association between the cognitive PC and brachial measured MAP or pulse pressure ($P$ = 0.038 both), independent of BMI and pregnancy history; however, the associations did not differ significantly by pregnancy history (test for interaction $P$ = 0.149 and $P$ = 0.411, respectively).

## DISCUSSION

There are two important findings from this study. First, using a composite index of aortic hemodynamics and cognitive function by PC analysis, there was a negative

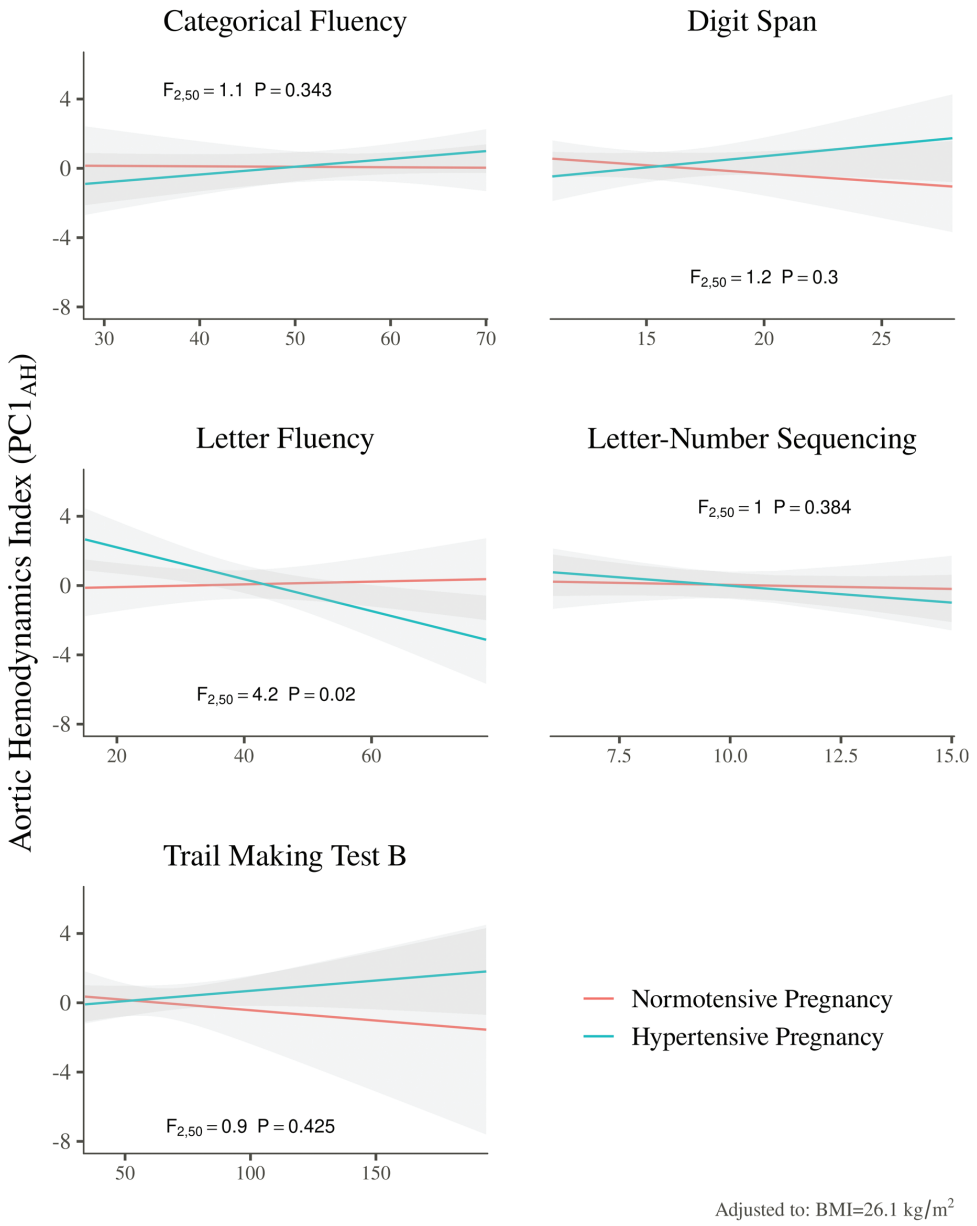


**Figure 2.** Partial effects plot relating raw cognitive test scores to the derived aortic hemodynamics summary index by normotensive vs. preeclamptic pregnancy history. A least squares multivariable model was fitted for relating the 5 separate cognitive scores simultaneously to the aortic hemodynamics summary index, allowing for a possible interaction in the association of each score with the grouping variable for pregnancy history. BMI was included in the model as a covariate. Inside each panel, the model estimated trend is shown by a regression line for each group (with nonparallel slopes suggestive of an interaction) and is adjusted for BMI and the other cognitive test variables in the model by setting them to medians. The partial test statistics and *P* values displayed in the plot are based on a 2 df. *F*-test for any association—whether overall or differentially by group—between that cognitive scale and the aortic hemodynamic summary index (i.e., an assessment of whether an association is present in either group). Of the 5 cognitive variables analyzed, only letter fluency, a measure of language and executive functioning, showed a significant association (overall, $P = 0.020$; differential, $P = 0.023$). Lower scores correlated with higher aortic hemodynamic values in the PE group, whereas no association was observed in the NP group (partial $R^2 = 0.20$ and 0.00, respectively). Abbreviations: BMI, body mass index; NP, normotensive pregnancy; PE, preeclampsia.

association of higher (worse) aortic hemodynamic index with lower (worse) cognitive function index that was independent of pregnancy history. These results are consistent with and expand observations from other studies that demonstrate an association between aortic blood pressure characteristics with cognitive performance.[14] The large vessels, such as the aorta, dampen the pulsatile blood flow caused by myocardial contraction. An increase in arterial rigidity would negatively impact the dampening function and transmit the large pulsatile forces into the cerebral microcirculation.[11–13] Evidence to support this concept comes from studies showing that hypertension increases the risk for developing cognitive decline, and that arterial stiffness and aortic blood pressure measures may increase prior to clinically relevant changes in brachial blood pressure.[32]

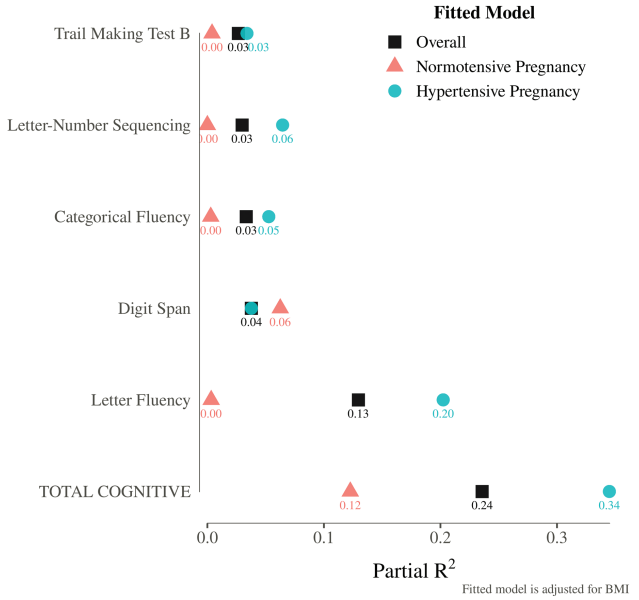


**Figure 3.** Partial correlation of the raw cognitive scores with the derived aortic hemodynamics summary index. Both the overall and group-stratified least squares multivariable models presented are adjusted for BMI. The partial $R^2$ measures from the "Overall" model combine the pregnancy history interaction effects with the corresponding cognitive test main effects. For each model, the "TOTAL COGNITIVE" result displayed in the plot represents the joint effect of all 5 individual cognitive tests in the multivariable model. Abbreviation: BMI, body mass index.

The second finding of this study is that measures of individual aortic hemodynamics and the PC aortic hemodynamic summary index correlated with specific cognitive test scores in women with a history of PE, but not NP. Specifically, the PC aortic hemodynamic summary index associated with the letter fluency test only in women with a history of PE. Collectively, these results suggest that pregnancy history has an impact on the relationship between aortic hemodynamics and cognition.

These associations between elevated aortic hemodynamics and declines in cognitive function provide evidence linking a history of PE to long-term effects on brain health. A history of PE has been associated with decreased cerebrovascular reactivity,[10] specific regions of brain atrophy (i.e., occipital lobe volume),[33] and a trend for greater incidence of clinically diagnosed cognitive impairment.[9] Additionally, there is a higher incidence of white matter lesions following a preeclamptic event with follow-up ranging from immediately post pregnancy to years later.[34–37] These changes in brain structures may be responsible for poor cognitive outcomes. Yet, reported findings on PE history and cognition have been controversial and many studies do not include a long-term follow-up. One study reported no difference in executive function or sustained attention a decade after the incident pregnancy.[38] In contrast, lower scores for motor speed, attention, learning, and memory were reported less than 1 year after the incident event[39,40] and 7 years post pregnancy[28] in women with a history of PE compared with women with a history of NP. It is important to note, however, that the time to follow-up, types of cognitive tests, and current health status of the participants may contribute to these apparent disparate results.

The exact mechanism by which the event of PE, or the predisposition to develop PE due to underlying vascular dysfunction, influences cognition is unknown. Women in both groups had relatively low cardiometabolic risk[23]; however, women in the PE group had greater prevalence of hypertension and use of antihypertensive medications compared with women in the NP group. Importantly, results did not change when controlling for antihypertensive medications. The current study adds to the existing literature by including the measurement of aortic hemodynamics, suggesting that changes in large artery function may influence brain structure and are associated with poorer cognition in women with a history of PE.

Although we are unable to control for cumulative lifestyle and behavioral factors, a strength of this study was that women were evaluated 35 years post pregnancy on average. This study was cross-sectional, thus limiting evaluation of the vascular and cognitive profiles to a single time point. However, the women were age and parity matched including number of births, geographical location, and type of birth. Additionally, the women in this study represent a unique cohort in that women with preexisting cardiovascular disease were excluded. There were no group differences in aortic blood pressures and AIx as women had low cardiometabolic risk by Framingham risk score and hypertension was controlled using antihypertensive medications. It was not possible to determine how long the individuals had been exposed to hypertension before the initiation of antihypertensive therapy. Additional studies are needed to address duration of hypertension relative to initiation of medication use on cognition in women such as those with a history of PE. Future studies are necessary to determine the relationships between aortic hemodynamics and cognition among hypertensive women who did not have PE.

PC analysis was used to identify similarly weighted contributions of the individual measures of aortic systolic pressure, aortic diastolic pressure, and AIx adjusted for a heart rate of 75 bpm to derive an aortic hemodynamic summary index. The consistency of these contributors provides an integrated measure of aortic hemodynamics that has not been used previously to assess associations of central hemodynamics with cognition. The integrated aortic hemodynamic summary index represents an integrated measure of physiologically related individual measures. Similarly, PC analysis was used to create a cognitive summary index. It is unclear why performance on letter fluency may be impacted more than other aspects of executive functioning by aortic hemodynamics in women with a history of PE. It is possible that letter fluency, which is a more challenging search and retrieval task than category fluency, is an early indicator of impending executive dysfunction. In addition, it may be that the brain regions and circuits recruited for these tasks are differentially affected by aortic hemodynamics. Regardless, word-finding difficulties are a common complaint expressed by postmenopausal women who present to the clinic with cognitive concerns. To gain a better understanding of how brain regions associated with cognition in general and executive functions in particular are impacted by a history of PE,

and to help determine the long-term trajectory, these results need to be confirmed in larger cohorts.

The present study demonstrated that measures of aortic hemodynamics may be associated with lower cognitive performance in postmenopausal women. Future studies could address the influence of elevated aortic hemodynamics and vascular function as predictors of cognitive decline, especially in women relative to their pregnancy histories.

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## DISCLOSURE

The authors declared no conflict of interest.

## REFERENCES

1. Alosco ML, Brickman AM, Spitznagel MB, Garcia SL, Narkhede A, Griffith EY, Raz N, Cohen R, Sweet LH, Colbert LH, Josephson R, Hughes J, Rosneck J, Gunstad J. Cerebral perfusion is associated with white matter hyperintensities in older adults with heart failure. *Congest Heart Fail* 2013; 19:E29–E34.
2. Bellamy L, Casas JP, Hingorani AD, Williams DJ. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. *BMJ* 2007; 335:974.
3. Garovic VD, Bailey KR, Boerwinkle E, Hunt SC, Weder AB, Curb D, Mosley TH Jr, Wiste HJ, Turner ST. Hypertension in pregnancy as a risk factor for cardiovascular disease later in life. *J Hypertens* 2010; 28:826–833.
4. Ghossein-Doha C, Spaanderman M, van Kuijk SMJ, Kroon AA, Delhaas T, Peeters L. Long-term risk to develop hypertension in women with former preeclampsia. *Reprod Sci* 2014; 21:846–853.
5. Irgens HU, Roberts JM, Reisæter L, Irgens LM, Lie RT. Long term mortality of mothers and fathers after pre-eclampsia: population based cohort study. Pre-eclampsia and cardiovascular disease later in life: who is at risk? *BMJ* 2001; 323:1213–1217.
6. McDonald SD, Malinowski A, Zhou Q, Yusuf S, Devereaux PJ. Cardiovascular sequelae of preeclampsia/eclampsia: a systematic review and meta-analyses. *Am Heart J* 2008; 156:918–930.
7. Nelander M, Cnattingius S, Åkerud H, Wikström J, Pedersen NL, Wikström AK. Pregnancy hypertensive disease and risk of dementia and cardiovascular disease in women aged 65 years or older: a cohort study. *BMJ Open* 2016; 6:e009880.
8. Mosca L, Benjamin EJ, Berra K, Bezanson JL, Dolor RJ, Lloyd-Jones DM, Newby LK, Piña IL, Roger VL, Shaw LJ, Zhao D, Beckie TM, Bushnell C, D'Armiento J, Kris-Etherton PM, Fang J, Ganiats TG, Gomes AS, Gracia CR, Haan CK, Jackson EA, Judelson DR, Kelepouris E, Lavie CJ, Moore A, Nussmeier NA, Ofili E, Oparil S, Ouyang P, Pinn VW, Sherif K, Smith SC Jr, Sopko G, Chandra-Strobos N, Urbina EM, Vaccarino V, Wenger NK; American Heart Association. Effectiveness-based guidelines for the prevention of cardiovascular disease in women—2011 update: a guideline from the American Heart Association. *J Am Coll Cardiol* 2011; 57:1404–1423.
9. Fields JA, Garovic VD, Mielke MM, Kantarci K, Jayachandran M, White WM, Butts AM, Graff-Radford J, Lahr BD, Bailey KR, Miller VM. Preeclampsia and cognitive impairment later in life. *Am J Obstet Gynecol* 2017; 217:74.e1–74.e11.
10. Barnes JN, Harvey RE, Miller KB, Jayachandran M, Malterer KR, Lahr BD, Bailey KR, Joyner MJ, Miller VM. Cerebrovascular reactivity and vascular activation in postmenopausal women with histories of preeclampsia. *Hypertension* 2018; 71:110–117.
11. Cooper LL, Woodard T, Sigurdsson S, van Buchem MA, Torjesen AA, Inker LA, Aspelund T, Eiriksdottir G, Harris TB, Gudnason V, Launer LJ, Mitchell GF. Cerebrovascular damage mediates relations between aortic stiffness and memory. *Hypertension* 2016; 67:176–182.
12. Mitchell GF. Effects of central arterial aging on the structure and function of the peripheral vasculature: implications for end-organ damage. *J Appl Physiol (1985)* 2008; 105:1652–1660.
13. O'Rourke MF, Safar ME. Relationship between aortic stiffening and microvascular disease in brain and kidney: cause and logic of therapy. *Hypertension* 2005; 46:200–204.
14. Lim SL, Gao Q, Nyunt MS, Gong L, Lunaria JB, Lim ML, Ling A, Lam CS, Richards AM, Ling LH, Ng TP. Vascular health indices and cognitive domain function: Singapore longitudinal ageing studies. *J Alzheimers Dis* 2016; 50:27–40.
15. Hajjar I, Goldstein FC, Martin GS, Quyyumi AA. Roles of arterial stiffness and blood pressure in hypertension-associated cognitive decline in healthy adults. Novelty and significance. *Hypertension* 2016; 67:171–175.
16. Iadecola C, Yaffe K, Biller J, Bratzke LC, Faraci FM, Gorelick PB, Gulati M, Kamel H, Knopman DS, Launer LJ, Saczynski JS, Seshadri S, Zeki Al Hazzouri A; American Heart Association Council on Hypertension; Council on Clinical Cardiology; Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing; Council on Quality of Care and Outcomes Research; and Stroke Council. Impact of hypertension on cognitive function: a scientific statement from the American Heart Association. *Hypertension* 2016; 68:e67–e94.
17. McEniery CM, Cockcroft JR, Roman MJ, Franklin SS, Wilkinson IB. Central blood pressure: current evidence and clinical importance. *Eur Heart J* 2014; 35:1719–1725.
18. Pase MP, Himali JJ, Mitchell GF, Beiser A, Maillard P, Tsao C, Larson MG, DeCarli C, Vasan RS, Seshadri S. Association of aortic stiffness with cognition and brain aging in young and middle-aged adults: the Framingham Third Generation Cohort Study. *Hypertension* 2016; 67:513–519.
19. Barnes JN, Harvey RE, Zuk SM, Lundt ES, Lesnick TG, Gunter JL, Senjem ML, Shuster LT, Miller VM, Jack CR Jr, Joyner MJ, Kantarci K. Aortic hemodynamics and white matter hyperintensities in normotensive postmenopausal women. *J Neurol* 2017; 264:938–945.
20. Gordon BA, Najmi S, Hsu P, Roe CM, Morris JC, Benzinger TL. The effects of white matter hyperintensities and amyloid deposition on Alzheimer dementia. *Neuroimage Clin* 2015; 8:246–252.
21. Habes M, Erus G, Toledo JB, Zhang T, Bryan N, Launer LJ, Rosseel Y, Janowitz D, Doshi J, Van der Auwera S, von Sarnowski B, Hegenscheid K, Hosten N, Homuth G, Völzke H, Schminke U, Hoffmann W, Grabe HJ, Davatzikos C. White matter hyperintensities and imaging patterns of brain ageing in the general population. *Brain* 2016; 139:1164–1179.
22. St Sauver JL, Grossardt BR, Leibson CL, Yawn BP, Melton LJ 3rd, Rocca WA. Generalizability of epidemiological findings and public health decisions: an illustration from the Rochester Epidemiology Project. *Mayo Clin Proc* 2012; 87:151–160.
23. White WM, Mielke MM, Araoz PA, Lahr BD, Bailey KR, Jayachandran M, Miller VM, Garovic VD. A history of preeclampsia is associated with a risk for coronary artery calcification 3 decades later. *Am J Obstet Gynecol* 2016; 214:519.e1–519.e8.
24. Smith EE, Salat DH, Jeng J, McCreary CR, Fischl B, Schmahmann JD, Dickerson BC, Viswanathan A, Albert MS, Blacker D, Greenberg SM.

Correlations between MRI white matter lesion location and executive function and episodic memory. *Neurology* 2011; 76:1492–1499.
25. Au R, Massaro JM, Wolf PA, Young ME, Beiser A, Seshadri S, D'Agostino RB, DeCarli C. Association of white matter hyperintensity volume with decreased cognitive functioning: the Framingham Heart Study. *Arch Neurol* 2006; 63:246–250.
26. Zhong W, Cruickshanks KJ, Schubert CR, Carlsson CM, Chappell RJ, Klein BE, Klein R, Acher CW. Pulse wave velocity and cognitive function in older adults. *Alzheimer Dis Assoc Disord* 2014; 28:44–49.
27. Tsao CW, Seshadri S, Beiser AS, Westwood AJ, Decarli C, Au R, Himali JJ, Hamburg NM, Vita JA, Levy D, Larson MG, Benjamin EJ, Wolf PA, Vasan RS, Mitchell GF. Relations of arterial stiffness and endothelial function to brain aging in the community. *Neurology* 2013; 81:984–991.
28. Postma IR, Bouma A, Ankersmit IF, Zeeman GG. Neurocognitive functioning following preeclampsia and eclampsia: a long-term follow-up study. *Am J Obstet Gynecol* 2014; 211:37.e1–37.e9.
29. Postma IR, Groen H, Easterling TR, Tsigas EZ, Wilson ML, Porcel J, Zeeman GG. The brain study: cognition, quality of life and social functioning following preeclampsia; an observational study. *Pregnancy Hypertens* 2013; 3:227–234.
30. Harvey RE, Barnes JN, Hart EC, Nicholson WT, Joyner MJ, Casey DP. Influence of sympathetic nerve activity on aortic hemodynamics and pulse wave velocity in women. *Am J Physiol Heart Circ Physiol* 2017; 312:H340–H346.
31. Wilkinson IB, MacCallum H, Flint L, Cockcroft JR, Newby DE, Webb DJ. The influence of heart rate on augmentation index and central arterial pressure in humans. *J Physiol* 2000; 525(Pt 1):263–270.
32. Mitchell GF, van Buchem MA, Sigurdsson S, Gotal JD, Jonsdottir MK, Kjartansson Ó, Garcia M, Aspelund T, Harris TB, Gudnason V, Launer LJ. Arterial stiffness, pressure and flow pulsatility and brain structure and function: the Age, Gene/Environment Susceptibility—Reykjavik Study. *Brain* 2011; 134:3398–3407.
33. Raman MR, Tosakulwong N, Zuk SM, Senjem ML, White WM, Fields JA, Mielke MM, Lesnick TG, Bailey KR, Jack CR Jr, Miller VM, Garovic VD, Kantarci K. Influence of preeclampsia and late-life hypertension on MRI measures of cortical atrophy. *J Hypertens* 2017; 35:2479–2485.
34. Aukes AM, de Groot JC, Aarnoudse JG, Zeeman GG. Brain lesions several years after eclampsia. *Am J Obstet Gynecol* 2009; 200:504.e1–504.e5.
35. Soma-Pillay P, Suleman FE, Makin JD, Pattinson RC. Cerebral white matter lesions after pre-eclampsia. *Pregnancy Hypertens* 2017; 8:15–20.
36. Wiegman MJ, Zeeman GG, Aukes AM, Bolte AC, Faas MM, Aarnoudse JG, de Groot JC. Regional distribution of cerebral white matter lesions years after preeclampsia and eclampsia. *Obstet Gynecol* 2014; 123:790–795.
37. Zeeman GG, Fleckenstein JL, Twickler DM, Cunningham FG. Cerebral infarction in eclampsia. *Am J Obstet Gynecol* 2004; 190:714–720.
38. Postma IR, Wessel I, Aarnoudse JG, Zeeman GG. Neurocognitive functioning in women with a history of eclampsia: executive functioning and sustained attention. *Am J Perinatol* 2010; 27:685–690.
39. Baecke M, Spaanderman ME, van der Werf SP. Cognitive function after pre-eclampsia: an explorative study. *J Psychosom Obstet Gynaecol* 2009; 30:58–64.
40. Brussé I, Duvekot J, Jongerling J, Steegers E, De Koning I. Impaired maternal cognitive functioning after pregnancies complicated by severe pre-eclampsia: a pilot case-control study. *Acta Obstet Gynecol Scand* 2008; 87:408–412.