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Cerebral white matter lesions, subjective cognitive failures, and objective neurocognitive functioning: A follow-up study in women after hypertensive disorders of pregnancy

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ABSTRACT

Objective: Hypertensive disorders of pregnancy, like preeclampsia, are a leading cause of maternal and fetal morbidity/mortality worldwide. Preeclampsia can be complicated by the occurrence of convulsions (eclampsia). Women who experienced (pre)eclampsia more frequently report daily cognitive failures and showed increased emotional dysfunction several years later, but are not impaired on objective neurocognitive testing. In addition, women with preterm preeclampsia more often have cerebral white matter lesions (WML) on follow-up. We aimed to determine whether WML presence is related to cognitive dysfunction, anxiety, and depressive symptoms in (pre)eclamptic women. **Method:** Forty-one eclamptic, 49 preeclamptic, and 47 control women who had a normotensive pregnancy completed the Cognitive Failures Questionnaire (CFQ), the Hospital Anxiety and Depression Scale (HADS), and a broad neurocognitive test battery (visual perception and speed of information processing, motor functions, working memory, long-term memory, attention, and executive functioning). All underwent cerebral magnetic resonance imaging (MRI), and WML presence was recorded. Median elapsed time since index pregnancy was 6 years. Average age was 40 years. **Results:** WML were more prevalent in women who had experienced preterm (pre)eclampsia (<37 weeks; 40%) than in controls (21%, $p = .03$). In (pre)eclamptic women, CFQ and HADS scores were higher than those in controls (44 ± 16.1 vs. 36 ± 11.0 , $p < .001$, and 11 ± 6.3 vs. 8 ± 5.5 , $p < .001$). There was no difference in objective cognitive performance as measured by neurocognitive tests. Subjective and objective cognitive functioning, anxiety, and depressive symptoms were not related to WML presence. **Conclusion:** Formerly (pre)eclamptic women report cognitive dysfunction, but do not exhibit overt cognitive impairment when objectively tested on average 6 years following their pregnancy. The presence of WML is not related to objective nor to subjective cognitive impairment, anxiety, and depressive symptoms. Longitudinal studies are needed to study whether the presence of WML is a risk factor for developing objective cognitive impairment in the long term.

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Preeclampsia is a hypertensive multisystem disorder of pregnancy, which is a leading cause of maternal and fetal/neonatal morbidity and mortality and affects 1–7% of all pregnancies. It is characterized by new-onset hypertension (≥ 140 mmHg

systolic or ≥ 90 mmHg diastolic blood pressure) combined with proteinuria after the 20th week of pregnancy. In some cases, the maternal brain is involved in the form of eclamptic seizures, cerebral edema, and/or intracerebral hemorrhage. Recently,

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All authors contributed in writing to the study proposal and the manuscript. I.R.P. and A.M.A. collected the data, J.C.G. evaluated the neuroimaging data, and I.R.P. performed the statistical analysis. I.R.P., A.B., J.C.G., A.M.A., J.G.A., and G.G.Z. discussed the results and commented on the manuscript.

The study was approved by the University Medical Center Groningen (UMCG) Institutional Review Board (Medisch Ethische Toetsingscommissie) in 2004, reference number METC 2004.216. All women signed informed consent.

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it has been shown that, several years later, formerly preeclamptic and eclamptic women report cognitive failures related to memory, attention, and vision-related tasks of everyday life (Andersgaard et al., 2009; Aukes, Wessel, Dubois, Aarnoudse, & Zeeman, 2007; Postma, Bouma, Ankersmit, & Zeeman, 2014; Postma et al., 2013; Wiegman et al., 2012). In the literature, small studies evaluating neurocognitive test performance in preeclamptic women within 1.5 years following the index pregnancy have found impairment pertaining to auditory-verbal memory (Brussé, Duvekot, Jongerling, Steegers, & De Koning, 2008), speed of information processing (Digit Symbol Coding of Wechsler Adult Intelligence Scale-Third Edition, Dutch Version, WAIS-III-NL), and divided attention (Paced Auditory Serial Addition Test; Baecke, Spaanderman, & Van der Werf, 2009), but not on other cognitive tests. In contrast, our recent study evaluating cognitive functioning in a relatively large group of women, on average 6 years following a (pre)eclamptic pregnancy and using a broad range of standardized neurocognitive tests, showed that (pre)eclamptic women do not exhibit overt cognitive impairment when tested objectively several years following their pregnancy (Postma et al., 2014). We argued that the reported cognitive failures may reflect actual neurocognitive dysfunction in complex daily life situations, generally associated with less structure and numerous distractions, which require more flexibility than a quiet, structured test setting. Alternatively, subjective cognitive failures may also be related to emotional factors, as (pre)eclamptic women report more anxiety and depressive symptoms (Baecke et al., 2009; Postma et al., 2014) and more often seem to develop posttraumatic stress disorder, which may persist for several years (Delahaije, Dirksen, Peeters, & Smits, 2013; Porcel et al., 2013). We suggested that cognitive failures in formerly (pre)eclamptic women may be interpreted as a measure of executive control of behavior, in which people who have symptoms of anxiety and depression experience cognitive failures mainly in complex and stressful daily life events.

Our group has previously studied the presence of white matter lesions (WML) following (pre)eclampsia and found that women who experienced eclampsia or preterm (pre)eclampsia more often have WML on long-term follow-up than do control women who had a normotensive pregnancy (Aukes, De Groot, Aarnoudse, & Zeeman, 2009;

Aukes et al., 2012). The current study adds a new, interesting question to our previously published studies: Are these WML related to cognitive functioning in women following a (pre)eclamptic pregnancy? We studied the effect of WML in a relatively large group of formerly (pre)eclamptic women and hypothesize that WML in women who had (pre)eclampsia may have an effect on standardized test measures of neurocognitive functioning and may specifically be related to cognitive failures experienced in the completion of daily life activities.

Method

Participants

Formerly eclamptic, preeclamptic, and control women with normotensive pregnancies were enrolled in this retrospective cohort study as part of ongoing follow-up studies assessing long-term cerebral consequences of preeclampsia and eclampsia (Aukes et al., 2009; Aukes et al., 2012; Postma et al., 2014; Wiegman et al., 2014). Women with a diagnosis of eclampsia in their medical history between 1988 and 2005 were identified using the electronic admission, diagnosis, and delivery databases of the University Medical Center Groningen (UMCG), and additional formerly eclamptic women have been recruited to participate in our follow-up studies through collaboration with two other tertiary referral centers: VU University Medical Center Amsterdam and Isala Clinics Zwolle (Aukes et al., 2009; Aukes et al., 2012; Postma et al., 2014; Wiegman et al., 2014). In total, 137 formerly eclamptic women were identified from the UMCG database. Six of these women were excluded, one because diagnosis of eclampsia could not be confirmed, another because of a history of a cerebrovascular accident, and a third as a result of inability to understand Dutch. In addition, three women had died in the interim, two of whom were the result of cerebral complications resulting from eclampsia and one as a result of gynecologic cancer. Of the remaining 131 formerly eclamptic patients, 69 could be reached and were willing to participate. Six of them were subsequently excluded as a result of contraindications for magnetic resonance imaging (MRI) scanning, and 63 women remained. In the original study (Aukes et al., 2009; Aukes et al., 2012), each woman who had eclampsia was

matched for age (within 1 year) and year of index pregnancy (within 2 years) with a woman who had a pregnancy complicated by preeclampsia, and also with a parous control whose pregnancy had been uncomplicated and normotensive. The group of women who had preeclampsia and the group of parous controls has expanded since the original report (Aukes et al., 2009). Parous women in the control group were recruited through the department's electronic delivery database as well as among hospital employees and their family members. Their records were evaluated to confirm that the pregnancy was indeed uneventful and normotensive.

Eclampsia and preeclampsia were defined according to international criteria (Tranquilli et al., 2014). Preeclampsia is defined as new-onset hypertension (≥ 140 mmHg systolic or ≥ 90 mmHg diastolic) combined with proteinuria after the 20th week of pregnancy, and eclampsia is defined as the occurrence of tonic-clonic convulsions in a woman with preeclampsia. Preterm (pre)eclampsia was defined as medically indicated delivery at < 37 weeks of gestational age. Medical records were reviewed for accuracy of diagnosis and to extract clinical and demographic characteristics. Participants were asked to complete a brief questionnaire concerning basic demographic characteristics and medical history. Neurocognitive measurements were performed between November 2008 and January 2012, whereas neuroimaging studies were performed between July 2005 and January 2012.

Exclusion criteria were known epilepsy, a known cerebrovascular accident, demyelinating disorders, a history of intracranial infection or any cranial neurosurgical procedure, the inability to understand Dutch, MRI contraindications, or pregnancy at the moment of testing. For all women, elapsed time since the index pregnancy had to be at least 12 months. During the study, two eclamptic women were excluded as they showed signs of malingering or underachievement, as evaluated by the Amsterdam Short-Term Memory (ASTM) test, a symptom validation test presented as a short-term memory task (Bouma, Mulder, Lindeboom, & Schmand, 2012). The ASTM test is a valid, standardized, and widely used test to indicate malingering. One control was excluded because she had professional knowledge of the neurocognitive tasks. Forty-one of 63 (65%) eclamptic women, 49/74 (66%) formerly preeclamptic women, and 47/75

(63%) controls who underwent MR imaging participated in the neurocognitive test battery and were included (Postma et al., 2014).

Education level was categorized according to the system of Verhage as described in Bouma et al. (2012): 1 being the lowest (less than primary school), and 7 the highest (academic degree). None of the women were in the low education group (Categories 1 and 2). Average was defined as Category 3–5 and high as Category 6–7. The Dutch Adult Reading Test (DART; Dutch version of the National Adult Reading Test) was used to determine premorbid intelligence (Bouma et al., 2012). The DART is a valid, standardized test based on the assumptions that reading ability (of irregular words) is relatively independent of brain disorders, and it is a strong predictor of intelligence in the normal population (Bouma et al., 2012). No significant difference was found between the groups. One participant had sufficient knowledge of the Dutch language to fulfil the tasks, but the DART could not be administered. Another participant was unable to complete the DART due to dyslexia.

This project was approved by the UMCG Medical Ethical Committee, and all women signed informed consent.

Questionnaires

Cognitive Failures Questionnaire (CFQ; subjective cognitive functioning)

The Cognitive Failures Questionnaire (CFQ) evaluates cognitive "failures," or daily mistakes, committed in the completion of daily tasks (Broadbent, Cooper, FitzGerald, & Parkes, 1982). It includes questions like "Do you read something and find you haven't been thinking about it and must read it again?" or "Do you fail to hear people speaking to you when you are doing something else?" Participants were asked to fill out the questionnaire based on their experiences in the past 6 months. The CFQ consists of 25 items, each scored on a 5-point scale (0–4). The total scale ranges from 0–100, with higher scores indicating more cognitive failures.

The Hospital Anxiety and Depression Scale

The Hospital Anxiety and Depression Scale (HADS) is a self-assessment scale, developed to detect states of depression, anxiety, and emotional distress amongst patients with a variety of clinical problems (Spinoven et al., 1997). It consists of 14 items scored on a 4-point scale (0–3). Items were

divided into two subscales: anxiety and depression, both with a maximum score of 21, with higher scores indicating more symptoms.

Neurocognitive tests

Participants completed a battery of 16 standardized, reliable, and valid neurocognitive tests divided into six cognitive domains (Bouma et al., 2012; Lezak, Howieson, Bigler, & Loring, 2012). Tests were administered in a fixed sequence according to standardized instructions for each measure by two advanced doctoral students who were well trained by a neuropsychologist. Measures were scored in a standardized fashion outlined in the administration manual of each test.

Visual perception and speed of information processing

Visual perception was measured using a Dutch *Incomplete Figures Test (GIT-2; Luteijn & Barelds, 2004)*. This task measures perceptual closure (i.e., reconstructing an object from reduced visual information): Participants had to recognize 20 incomplete pictures of familiar objects, persons, or animals. The test was cut off when five subsequent wrong answers were given. The number of correct responses was scored. Visual processing speed was measured using the *Digit Symbol Coding (WAIS-III-NL; Wechsler, 2005)*, *Symbol Search (WAIS-III-NL; Wechsler, 2005)*, and the *Stroop Color-Word Test Part 1 (Word Reading)* and *Part 2 (Color Naming; Hammes, 1971)*. During Digit Symbol Coding, the participant had to fill out as many symbols below numbers as possible in 120 s, using a code at the top of the page (each number corresponded to a symbol). The number of correct symbols was scored. During Symbol Search, the participant had to score whether or not one of two symbols was repeated in a following sequence. The participants were required to complete as many items as possible in 120 s, and the number of correct items was calculated. The Stroop Color-Word Test consists of 100 randomly distributed stimuli, presented in a 10 × 10 table. Part 1 requires the participant to read words (red, green, blue, and yellow) as fast as possible. Part 2 requires colors to be named. Time to completion was recorded.

Motor functions

Visuomotor speed was measured using the *Grooved Pegboard Test*, which consists of a board

with 25 holes, each hole containing a randomly positioned slot. Pegs, with a key on one side, had to be rotated and placed in the holes. The participant had to complete this task as fast as possible for both the dominant and the nondominant hand (Matthews & Kløve, 1964). The *Trail Making Test Part 5 (Motor Speed; Delis-Kaplan Executive Function System, D-KEFS)* requests participants to follow a dotted line with a pencil as fast as possible (Delis, Kaplan, & Kramer, 2007).

Working memory

Visuospatial working memory was assessed using the *Corsi Block-Tapping Test*, consisting of nine black cubes fastened to a black board in a random order (Kessels, Van Zandvoort, Postma, Kapelle, & De Haan, 2000). The digits 1–9 on the cubes are only visible from the side of the examiner. The participant was asked to repeat the sequences, increasing in length, tapped by the examiner. The task was performed forward and backwards and ended after two wrong responses of the same length. A total product score was derived from the number of correct sequences and the block span. The task is considered a nonverbal analogue to *Digit Span (WAIS-III-NL; Wechsler, 2005)*, which was used to measure verbal working memory and consists of sequences of numbers, which had to be repeated by the participant, first forward and then backwards. The length of the sequences was increasing from 2 to 9 digits. The task was ended after two wrong responses of the same length. The number of correct answers was scored. For the *Letter-Number Sequencing Test (WAIS-III-NL; Wechsler, 2005)*, the participant had to repeat sequences of letters and numbers, increasing in length, simultaneously placing the numbers first, in rising order, and then the letters, in alphabetical order. The task was ended after three wrong responses of the same length, and the number of correct answers was scored.

Long-term memory

Visuospatial long-term memory (LTM) was assessed by the Dutch version of the *Location Learning Test* (Administration Procedure II; Kessels, Bucks, Willison, & Byrne, 2012). It consists of 25 compartments on a sheet with 10 everyday objects, located at different positions. It was shown for 15 seconds, and afterwards the participant had to relocate cards with the 10 objects. The test consisted of five consecutive trials, and a total

score was derived. Verbal LTM was measured by the Dutch version of the *Rey Auditory Verbal Learning Test* in which participants had to recall 15 monosyllabic words (regardless of order) in five successive trials (Bouma et al., 2012). The total number of correctly recalled words in all trials was scored.

Attention

Part 1 (Visual Scanning), *Part 2 (Number Sequencing)*, and *Part 3 (Letter Sequencing)* of the *Trail Making Test (D-KEFS)* were used to measure attention (Delis et al., 2007). These conditions were designed to quantify key component skills that are required for performing the Number–Letter Switching condition described below. Sheets with numbers and letters were presented, and in Condition 1, the participant had to blot out only the numbers “3” but not the other numbers, and in Conditions 2 and 3, respectively, numbers and letters had to be connected. Time to completion was recorded.

Executive functioning

Inhibitory control was assessed by *Part 3 (Inhibitory Control)* of the Dutch *Stroop Color–Word Test* (Hammes, 1971). Words were pictured in a different color (e.g., the word “red” was pictured in green), and the colors had to be named. Time to completion was recorded. In addition, an interference score was calculated by subtracting time to completion of part 3 and part 2. *Part 4* of the *Trail Making Test (Number–Letter Switching)* is similar to “Part B” of the original Trail Making Test (Delis et al., 2007). The participant had to switch between connecting numbers and letters, and the task measures divided attention and cognitive flexibility. Contrast scores were calculated for Part 4 versus Part 1 (contrast score 1), Part 4 versus Part 2 (contrast score 2), Part 4 versus Part 3 (contrast score 3), and Part 4 versus Part 5 (contrast score 5). Fluency tasks consisted of the *Verbal Fluency Test* (animals and professions) and the *Figure Fluency Test* (Dutch version of the *Ruff Figure Fluency Test*) for visuospatial fluency (Mulder, Dekker, & Dekker, 2006). The Verbal Fluency Test requires the participant to name as many words in the categories “animals” and “professions” as possible within 1 minute. The number of responses was scored. During the Figure Fluency Test the participant had to draw as many unique patterns as possible within 1 min (5 times), by connecting two or more dots with a straight line. The

number of unique patterns was scored. Planning was measured by the *Tower Test (D-KEFS)*; (Delis et al., 2007). The participant had to place two to five discs from a start to an end position on a base with three sticks, thus building a tower, using as few steps as possible. There were nine items, increasing in difficulty. A total achievement score was calculated.

Cerebral MR imaging protocol

Participants were invited to the Neuro-Imaging Center of the School for Behavioural and Cognitive Neurosciences in Groningen. The detailed MRI protocol has been previously published by our group (Aukes et al., 2009; Aukes et al., 2012; Wiegman et al., 2014). All studies were performed on a 3-T MRI system (Philips Intera; Philips Medical Systems, Best, the Netherlands). An experienced neuroradiologist (J.C.G.), blinded for patient category, rated the presence of WML and other structural brain abnormalities. WML were considered to be present if hyperintense on fluid-attenuated inversion recovery (FLAIR) proton density-weighted and T2-weighted images, and not as hypointense as liquor on T1-weighted images. Correction for inclusion of partial volume misclassification was performed as described previously (Aukes et al., 2012; Wiegman et al., 2014). The number of small (less than 3 mm), medium (3–10 mm), or large (greater than 10 mm) WML were counted. Considering them spherical with a fixed diameter per size category, a total approximated volume for subcortical white matter lesions was determined. Due to the skewed, non-normal distribution of the WML volume, it was not possible to use this quantification of the lesions for further analysis.

Following MR imaging and a period of rest, blood pressure was measured manually with an aneroid sphygmomanometer. Women with a blood pressure of $\geq 140/90$ mmHg or current anti-hypertensive medication use for their high blood pressure were designated as currently hypertensive. In cases of hypertension, the measurement was repeated after 15 minutes.

Statistical analyses

Statistical analysis was performed using IBM Statistical Package for the Social Sciences Version 20 for Windows (SPSS, IBM, Chicago

IL, USA). Raw test scores were used. All data were checked for normality of distribution using distribution curves, Shapiro–Wilks test, and Levene’s test for homogeneity of variance. Small deviations in test scores from a normal distribution due to an outlier were accepted. For measures (Trail Making Test) that were not normally distributed, logarithmic transformation was employed. There were no differences in outcomes between these transformations and non-parametric tests. Formerly preeclamptic and eclamptic women were analyzed as one group ($n = 90$), since no differences in subjective and objective neurocognitive functioning as well as WML presence were found between these two groups in our previous study.

Patient characteristics were analyzed using t test for normally distributed data, Mann–Whitney U test for non-normally distributed data, and χ^2 test for categorical data. Single imputation was used to replace two missing values in the questionnaire (due to a missed question) and two missing values (due to missing test forms) in the tests using estimated means for the whole group. Mean and median values were calculated before and after imputation to ensure the absence of differences. The presence of WML and other structural MRI abnormalities between groups was compared using one-sided Fisher’s Exact Test. WML volume was analyzed using Mann–Whitney U test. A two-way analysis of variance (ANOVA) was conducted to explore the effect of group variable and WML on CFQ and HADS scores. Multivariate analysis using two-way multiple analysis of variance (MANOVA) was performed to explore the impact of the group variable and WML per cognitive domain. Analyses were corrected for age, since the WML positive group was found to be significantly older than the WML negative group. Effect sizes (η^2_p) were calculated in order to estimate the strength of significant effects between groups (Fritz, Morris, & Richler, 2012). An effect size of $\eta^2_p = .01$ was defined as small, $\eta^2_p = .06$ as medium, and $\eta^2_p = .14$ as large (Fritz et al., 2012). Stroop interference score and the Trail Making Test contrast scores were not included in the MANOVA domains, since these scores are not independent of the raw scores. Instead, they were separately analyzed using two-way ANOVA.

In order to detect a medium effect size of $\eta^2 = .06$ on the two-way multivariate analysis of the test domains for four groups [namely (pre)eclampsia

with WML, (pre)eclampsia without WML, controls with WML, and controls without WML], with two predictors (group, WML), with a power of .80 and alpha of .05, inclusion of 34 women in each group was needed (Faul, Erdfelder, Lang, & Buchner, 2007).

Results

Participants

Ninety formerly (pre)eclamptic women and 47 controls underwent both neuroimaging and neurocognitive testing. As shown in Table 1 and as expected, estimated gestational age at delivery and birth weight were significantly lower in women who had a (pre)eclamptic pregnancy. At the time of imaging, (pre)eclamptic women had significantly higher blood pressure and more often used antihypertensive medication than controls.

WML and subjective cognitive functioning

Formerly (pre)eclamptic women tended to have subcortical WML more often than controls (Table 2, $p = .06$). Women with preterm (pre)eclampsia had subcortical WML approximately twice as often as controls (Table 2, $p = .03$). Although periventricular WML were seen in four (pre)eclamptic women and never in controls, this difference did not reach statistical significance (Table 2).

(Pre)eclamptic women reported more symptoms than controls on the Cognitive Failure Questionnaire (CFQ; Table 2) [two-way ANOVA, $F(3, 133) = 7.75$, $p < .01$, $\eta^2 = .06$]. The presence of WML was not associated with more CFQ symptoms (Table 2) [two-way ANOVA, $F(3, 133) = 0.02$, $p = .89$, $\eta^2 = .00$]. Also, the relationship between WML and CFQ was not different in (pre)eclamptic women compared to controls, as indicated by the interaction factor [two-way ANOVA, $F(3, 133) = 0.22$, $p = .64$, $\eta^2 = .00$]. When the above-mentioned analyses were repeated comparing only women with preterm (pre)eclampsia to controls, the results were similar. Exclusion of those women who had infarctions or periventricular WML ($n = 10$) did not alter the results.

WML, anxiety, and depressive symptoms

(Pre)eclamptic women reported more symptoms than controls on the HADS Total scale (Table 2) [two-way ANOVA, $F(3, 133) = 12.22$, $p < .01$, $\eta^2 = .09$]. They also reported more symptoms on the

Table 1. Overview of participant characteristics.

Characteristic	(Pre)eclampsia (n = 90)	Controls (n = 47)	p
Age (years): <i>M (SD)</i>	39 (6.6)	40 (7.3)	.38
Ethnicity (n Caucasian): n (%)	88 (98)	45 (98)	.74
Elapsed time since index pregnancy (years): <i>Mdn (min-max)</i>	6 (1–20)	6 (1–27)	.50
Birth weight of newborn (g): <i>Mdn (min-max)</i>	1572 (300–4470)	3520 (2210–4620)	<.01
EGA at delivery (weeks): <i>Mdn (min-max)</i>	32 ⁺³ (22–41)	40 (36 ⁺¹ –42 ⁺³)	<.01
Preterm (pre)eclampsia <37 weeks: n (%)	62 (69)		
Nulliparous at index pregnancy: n (%)	69 (77)	21 (45)	<.01
Level of education			.26
Average: n (%)	38 (42)	16 (35)	
High: n (%)	52 (58)	30 (65)	
Current systolic blood pressure (mmHg): <i>Mdn (min-max)</i>	125 (100–175) ^a	120 (95–158) ^b	<.01
Current diastolic blood pressure (mmHg): <i>Mdn (min-max)</i>	80 (60–110) ^a	75 (60–95) ^b	<.01
Current hypertension: n (%)	30 (37) ^a	5 (11) ^b	<.01
Migraine: n (%)	26 (29)	11 (23)	.47
Smoking: n (%)	14 (16)	9 (19)	.61

Note. EGA = estimated gestational age.
^an = 81. ^bn = 45.

Table 2. White matter lesions and the Cognitive Failures Questionnaire in (pre)eclampsia and controls.

Characteristic	Pre(eclampsia) (n = 90)		Controls (n = 47)		p
Subcortical WML: n (%)	32 (36)		10 (21)		.06
WML volume in WML positive women (ml): <i>Mdn (min-max)</i>	0.11 (0.004–2.29)		0.11 (0.02–0.12)		.51
Periventricular WML: n (%)	4 (4)		0 (0)		.18
Infarcts: n (%)	6 (7)		1 (2)		.25
CFQ Total score: <i>M (SD)</i>	44 (16.1)		36 (11.0)		<.001
HADS Total score: <i>M (SD)</i>	11 (6.3)		8 (5.5)		<.001
	WML (n = 32)	No WML (n = 58)	WML (n = 10)	No WML (n = 37)	
CFQ Total score: <i>M (SD)</i>	44 (15.0)	45 (16.7)	33 (8.0)	37 (11.7)	
HADS Total score: <i>M (SD)</i>	12 (6.5)	11 (6.2)	6 (5.1)	9 (5.5)	
	Preterm (pre)eclampsia (n = 62)		Controls (n = 47)		
Subcortical WML: n (%)	25 (40)		10 (21)		.03

Note. WML = white matter lesions; CFQ = Cognitive Failures Questionnaire; HADS = Hospital Anxiety and Depression Scale.

HADS Anxiety subscale [two-way ANOVA, $F(3, 133) = 11.02, p < .01, \eta^2 = .08$] and HADS Depression subscale [two-way ANOVA, $F(3, 133) = 8.43, p < .01, \eta^2 = .06$]. The presence of WML was not associated with HADS Total score (Table 2) [two-way ANOVA, $F(3, 133) = 0.40, p = .53, \eta^2 = .00$]. Women with WML also did not report more symptoms on the HADS Anxiety subscale [two-way ANOVA, $F(3, 133) = 0.14, p = .71, \eta^2 = .00$] and HADS Depression subscale [two-way ANOVA, $F(3, 133) = 0.59, p = .44, \eta^2 = .00$]. The effect of WML was not different between (pre) eclamptic women and controls for the HADS Total score, $F(3, 133) = 3.22, p = .08, \eta^2 = .02$, Anxiety, $F(3, 133) = 2.26, p = .14, \eta^2 = .02$, and Depression, $F(3, 133) = 2.90, p = .09, \eta^2 = .02$, as

indicated by the interaction factor. When the above-mentioned analyses were repeated comparing women with preterm (pre)eclampsia to controls, the results were similar; there was a significant effect of preterm (pre)eclampsia versus controls on CFQ/HADS score, but not of WML presence. Exclusion of those women who had infarctions or periventricular WML did not reveal any different results.

WML and objective cognitive functioning

In Table 3, test results are shown comparing both formerly (pre)eclamptic women and controls with and without WML. Neither the presence of WML nor a history of (pre)eclampsia

Table 3. Multivariate analysis of neurocognitive test domains.

Cognitive domain	Function	Test	Measure	Preeclampsia (n = 90)		Controls (n = 47)		F(3, 131) ^a	p	Effect size η^2_p
				WML (n = 32)	No WML (n = 58)	WML (n = 10)	No WML (n = 37)			
<i>Visual perception and speed of information processing</i> WML Group WML × Group	Perceptual closure	Dutch Incomplete Figures Test (GIT-2)	Total score (accuracy)	13 (2.9)	13 (2.8)	13 (2.9)	13 (3.0)	0.28	.93	.01
		Digit Symbol Coding (WAIS-III-NL)	Total score (accuracy)	81 (14.9)	83 (12.7)	82 (15.3)	81 (13.0)	0.87	.51	.03
	Visual perceptual speed	Symbol Search (WAIS-III-NL)	Total score (accuracy)	36 (6.4)	37 (3.8)	38 (9.2)	38 (7.5)	0.51	.77	.02
		Stroop Color-Word Test	Part 1: Word Reading (time)	44 (5.9)	45 (9.6)	44 (10.1)	42 (7.3)			
			Part 2: Color Naming (time)	55 (8.8)	56 (10.7)	53 (7.3)	54 (8.7)			
<i>Motor functions</i> WML Group WML × Group	Visuomotor speed	Grooved Pegboard	Score dominant hand (time)	67 (9.4)	65 (9.7)	67 (14.2)	64 (6.5)	0.79	.50	.02
			Score nondominant hand (time)	71 (9.2)	74 (12.2)	77 (17.8)	71 (10.8)	2.36	.07	.05
		Trail Making Test (D-KEFS)	Part 5: Motor Speed (time)	21 (1.3)	25 (1.5)	20 (1.2)	20 (1.3)	1.97	.12	.04
<i>Working memory (WM)</i> WML Group WML × Group	Visuospatial WM	Corsi Block-Tapping Test	Total product score (accuracy)	103 (31.7)	97 (26.0)	108 (25.3)	107 (25.7)	1.00	.39	.02
			Total score (accuracy)	15 (3.3)	15 (3.2)	16 (4.2)	15 (3.6)	0.94	.42	.02
	Verbal WM	Letter-Number Sequencing (WAIS-III-NL)	Total score (accuracy)	11 (1.7)	10 (1.8)	12 (2.5)	10 (2.1)	0.77	.51	0.02
<i>Long-term memory (LTM)</i> WML Group WML × Group	Visuospatial LTM	Location Learning Test	Total score (accuracy)	18 (13.2)	16 (14.6)	19 (12.5)	14 (12.9)	1.06	.35	.02
		15-Word Learning Test	Total score (accuracy)	46 (6.9)	46 (7.8)	45 (9.0)	48 (8.4)	0.03	.98	.00
	Verbal LTM	Trail Making Test (D-KEFS)	Part 1: Visual Scanning (time)	18 (1.2)	18 (1.3)	18 (1.4)	19 (1.4)	0.39	.68	.01
<i>Attention</i> WML Group WML × Group	Visual scanning	Trail Making Test (D-KEFS)	Part 2: Number Sequencing (time)	28 (1.3)	27 (1.4)	27 (1.6)	27 (1.4)	0.57	.64	.01
			Part 3: Letter Sequencing (time)	25 (1.3)	27 (1.3)	26 (1.4)	25 (1.4)	0.21	.89	.01
	Visual scanning and sequencing							0.61	.61	.01

(Continued)

Table 3. (Continued).

Cognitive domain	Function	Test	Measure	Pre(eclampsia) (n = 90)		Controls (n = 47)		F(3, 131) ^a	Effect size η^2_p
				WML (n = 32)	No WML (n = 58)	WML (n = 10)	No WML (n = 37)		
				Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)		
Executive functioning	Inhibitory control	Stroop Color-Word Test	86 (16.7)	84 (26.5)	82 (18.8)	81 (16.4)	1.51	.19	
	Divided attention and cognitive flexibility	Trail Making Test (D-KEFS)	68 (1.4)	64 (1.3)	59 (1.4)	62 (1.4)	1.17	.33	
		Verbal fluency task	44 (9.3)	44 (9.7)	41 (10.4)	46 (10.9)	1.08	.37	
		Figure fluency task	98 (18.7)	97 (21.5)	110 (23.9)	98 (15.0)			
Visuospatial fluency	Tower test (D-KEFS)	18 (3.6)	18 (3.8)	19 (1.9)	18 (3.7)				
	Planning								

Note. Results are expressed as mean (SD); time is in seconds. WML = white matter lesions; WM = working memory; LTM = long-term memory; WAIS-III-NL = Wechsler Adult Intelligence Scale-Third Edition, Dutch Version; D-KEFS = Delis-Kaplan Executive Function System.

^aTwo-way multivariate analysis of variance (MANOVA) test statistics of between-group effect.

Discussion

(Pre)eclamptic women reported more subjective cognitive problems in daily life and reported more anxiety and depressive symptoms at, on average, 6 years follow-up than control women who had a normotensive pregnancy. (Pre)eclamptic women did not show cognitive impairment as measured by extensive objective neurocognitive testing. (Pre)eclamptic women more often have WML on neuroimaging. However, in contrast to our expectation, the presence of WML was not related to subjective or objective measures of cognitive functioning nor to anxiety and depressive symptoms in (pre)eclamptic women or in women who had a normotensive pregnancy.

Subcortical WML, which are thought to be related to hypertension and cardiovascular risk factors, are found more often in women with

was significantly associated with worse scores on any of the neurocognitive test domains. The effect of WML was not different between (pre)eclamptic women and controls, as indicated by the interaction factors. The Stroop interference score was 29 (18.3) for (pre)eclamptic women and 27 (11.3) for controls. The results did not show significant main effects of group [two-way ANOVA, $F(3, 133) = 0.009, p = .92$] and WML [two-way ANOVA, $F(3, 133) = 0.03, p = .86$], and the interaction factor was also not significant [two-way ANOVA, $F(3, 133) = 0.07, p = .79$]. The contrast scores of the Trail Making Test observed for (pre)eclamptic women and controls, respectively, were as follows: contrast score 1: 49 (21.3) and 45 (24.2); contrast score 2: 40 (20.7) and 36 (20.6); contrast score 3: 42 (20.1) and 39 (19.6); and contrast score 5: 44 (21.4) and 45 (22.8). There were no significant effects of group, WML, and the interaction factor on any of the contrast scores ($p > .05$). Results were not different when comparing women with preterm (pre)eclampsia to controls, except for a significant effect of preterm (pre)eclampsia on the motor functions domain, $F(3, 103) = 3.69, p = .02$, which was the result of a significant difference in the Trail Making Test Part 5 (motor speed), $F(3, 103) = 7.94, p < .01$. Exclusion of those women who had infarctions or periventricular WML did not alter the results.

(pre)eclampsia, and the prevalence of these WML was especially high in women with preterm (pre) eclampsia. This is in line with the finding that women with preeclampsia, and especially those women with preterm preeclampsia, have an increased risk of hypertension and ischemic and hemorrhagic stroke in later life (Bellamy, Casas, Hingorani, & Williams, 2007).

WML were not related to objective neurocognitive deficits. This study covers a broad range of neurocognitive functions and incorporates sensitive tests for measuring cognitive impairment. Therefore, other factors need to be taken into consideration to explain the lack of a relationship between WML and objective neurocognitive deficits.

First, young women with an average age of 40 years may not yet suffer overt sequelae related to WML due to the compensational capacity of the brain. Not the mere presence of WML, but more so their severity may prove to be the main determinant of impaired cognitive functioning. With aging, the WML burden may increase and gray matter volume decrease, and the aging brain may have reduced ability to compensate for cognitive dysfunction (DeBette & Markus, 2010). Indeed most associations between WML and cognitive impairment are found in older people (De Groot et al., 2000; Sachdev, Wen, Christensen, & Jorm, 2005). Although one could expect that the WML volume would be larger in (pre)eclamptic women than in controls, we did not find a significant difference between these two groups. The two groups are comparable with respect to WML volume.

Second, WML location may play a role. Both subcortical and periventricular WML are related to hypertensive disease and coincide often. However, mainly periventricular, more than subcortical, WML seem to be associated with cognitive impairment and dementia (Bolandzadeh, Davis, Tam, Handy, & Liu-Ambrose, 2012; De Groot et al., 2001; Gootjes et al., 2004; Kuller et al., 2010; Taki et al., 2011). Periventricular WML are thought to disrupt long connections from subcortical structures to cortical areas, whereas subcortical WML are thought to disrupt intermediate cortico-cortical connections (Filley, 1998; Kim, MacFall, & Payne, 2008). In the present study, most WML were located in the subcortical regions, and only four women had periventricular WML. This may, at least partially,

play a role in the lacking relationship of WML presence with cognitive functioning.

We also hypothesized that WML would specifically be related to self-reported cognitive failures (CFQ) in formerly (pre)eclamptic women. However, we were not able to show a relationship between WML presence and CFQ results. A possible explanation for this finding is that the CFQ has a strong relationship with anxiety and depressive symptoms in formerly (pre)eclamptic women (Postma et al., 2014). (Pre)eclampsia is a serious life event, in which women who are more sensitive to stress may be more likely to develop anxiety and depressive symptoms. In a previous study, depression and anxiety in early pregnancy seem to be associated with increased risk of (pre)eclampsia, and it is possible that symptoms of anxiety and depression were already present prior to the index pregnancy (Kurki, Hiilesmaa, Raitasalo, Mattila, & Ylikorkala, 2000). The higher CFQ scores may therefore have a more psychosocial explanation. Alternatively, but related to the psychosocial explanation, we hypothesize that higher CFQ scores could be the result of dysfunction in executive control, in which a higher burden of anxiety and depressive symptoms leads women to experience cognitive failures mainly in complex and stressful daily life events. This interpretation is in agreement with the view that the CFQ reflects a strong interaction between negative emotions like stress and anxiety and cognition. The CFQ measures problems related to frequent lapses of memory—for example, failures of attention in daily life, distractibility, forgetfulness, forgetting people's names (retrieval problems), and losing task goals during task execution and was developed by Broadbent et al. to measure cognitive failures, which make a person vulnerable to showing bad effects of stress (Broadbent et al., 1982). It may be viewed as a reflection of a person's experience of difficulties with executive functioning in everyday life (e.g., "Do you have trouble making up your mind?" and "Do you start doing one thing at home and get distracted into doing something else (unintentionally)?"). It may be difficult to capture these difficulties using a neurocognitive test battery in a laboratory environment, since executive functioning is especially appealed to in new, complex and unknown situations, in which rapid and efficient adjustment of behavior to the environment is needed because routine solutions do not suffice. Therefore, even when a person functions well in a

structured test setting, there may still be problems in novel and complex situations of everyday life in which the individual needs to initiate, plan, organize, and monitor his own behavior (e.g., self-initiation, self-organizing, self-monitoring, and evaluating their purposeful behavior; Chaytor & Schmitter-Edgecombe, 2003; Van der Linden, Keijsers, Eling, & Van Schaijk, 2005). There is substantial evidence that high levels of uncontrollable or prolonged stress can have a detrimental effect on prefrontal cognitive abilities, specifically attention, working memory, and executive control of behavior (Arnsten, 2009). We observed that (pre)eclamptic women indeed showed enhanced levels of stress like anxiety and depression. Moreover, there is growing evidence that a complex functional network of brain regions is involved in regulating the interplay between cognition and emotion, involving the dorsolateral prefrontal cortex, the midcingulate cortex, and the amygdala (Okon-Singer, Hendler, Pessoa, & Shackman, 2015). However, we could not find evidence that the subcortical white matter regions were involved in tasks that rely on the executive control of complex and stressful tasks. This could explain why the CFQ is not related to WML observed in (pre)eclamptic women. Further studies using ecologically valid tests for executive functioning are needed to test the hypothesis that the CFQ is related to executive functioning in daily life in this population of formerly (pre)eclamptic women.

WML may be an early risk factor for later development of objective cognitive impairment, specifically in (pre)eclamptic women who maintained cognitive failures and symptoms of anxiety and depression several years after delivery. Advanced MRI techniques, such as diffusion-weighted imaging (DWI), might be needed to detect microstructural alterations in the white matter (Jokinen et al., 2013). Cerebral microbleeds are, in older people, related to increased risk factors of vascular disease (Van Norden et al., 2013).

As far as we know, this is the first study to report on the presence of cerebral white matter lesions and its relationship with subjective as well as objective cognitive functioning and anxiety and depressive symptoms in a relatively large group of formerly (pre)eclamptic women. Moreover, it is one of the few studies in the literature to report on the relationship of WML and neurocognitive functioning in such a young cohort in general. There are some limitations to this study,

which should be mentioned. The measurements in this study have a cross-sectional design. Therefore, the study does not provide imaging data of participants prior to or during their index pregnancy; whether WML were present prior to the index pregnancy is therefore unknown. This design also limits conclusions related to cause-effect relationships and possible changes in cognitive functioning in daily life due to pregnancy in and of itself. Second, although a sample size calculation was performed, the sample size of this study is considerably smaller than studies performed in older people, and there were a low number of controls with WML, which may have led to a Type II error. We calculated that 34 women with WML were needed in each group in order to obtain sufficient power, and this criterion was not completely met due to the low number of controls with WML. Third, another limitation is the lack of quantitative analyses for evaluating the effect of WML. Fourth, approximately 65% of the women who participated in our previous studies (Aukes et al., 2009; Aukes et al., 2012) could be contacted again and were willing to participate in this neurocognitive study, which may have given rise to selection bias. It is possible that participating women experience more cognitive dysfunction than nonparticipating women; however, most nonparticipating women could not be contacted because of change of address and/or phone number. Other nonparticipating women mentioned the time and travel burden as the main reason not to participate, although some declined because of fear of confrontation with the traumatic experience of their complicated pregnancy. Fifth, elapsed time since index pregnancy shows a wide range, which reflects the rare incidence of eclampsia. Sixth, the effect of subsequent pregnancies following the index pregnancy cannot be excluded. Last, the formal diagnosis of current hypertension in these women cannot be made, since measurements were not performed on multiple days.

Conclusion

In summary, cerebral subcortical WML are more prevalent following preterm (pre)eclampsia. Formerly (pre)eclamptic women report cognitive dysfunction, but do not exhibit overt cognitive impairment when objectively tested on average 6 years following their pregnancy. The presence of WML is not related to objective nor to subjective cognitive impairment, anxiety, and depressive symptoms. Subjective cognitive failures seem to

be related to symptoms of anxiety and depression years after the (pre)eclamptic pregnancy, and we hypothesize that they reflect executive functioning in complex and stressful daily life events. Our results should not trivialize the perceived cognitive dysfunction that these women report nor does it exclude the possibility that (subgroups of) these women develop cognitive impairment in later life. This study has important clinical implications for the follow-up of women who experience subjective cognitive problems following a (pre)eclamptic pregnancy, since these problems seem to be complex and related to stressful activities of everyday life. Following a (pre)eclamptic pregnancy, attention may be paid to adequate psychosocial treatment and follow-up, focusing on dysexecutive and emotional problems in daily life. Interventions, such as psycho-education, providing women with advice on maintaining an organized structure in daily life, and cognitive behavioral therapy or Eye Movement Desensitization and Reprocessing (EMDR) may be beneficial (Ayers, McKenzie-McHarg, & Eagle, 2007; Spikman, Boelen, Lamberts, Brouwer, & Fasotti, 2010; Stramrood et al., 2012). Future studies in women who experienced eclampsia and preeclampsia should focus on long-term follow-up (20–30 years) of cerebral structural abnormalities and cognitive functioning and adequate treatment options.

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