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CONTACT: Alzheimer's Association Media Line, 312.335.4078, media@alz.org
AAIC 2022 Press Office, aaicmedia@alz.org

FROM THE ALZHEIMER'S ASSOCIATION INTERNATIONAL CONFERENCE 2022

HISTORY OF HYPERTENSIVE DISORDERS DURING PREGNANCY LINKED TO INCREASED RISK OF DEMENTIA

SAN DIEGO, AUGUST 3, 2022 — Experiences of high blood pressure disorders during pregnancy are associated with an increased risk of vascular dementia and accelerated brain aging, according to studies reported today at the Alzheimer's Association International Conference® (AAIC®) 2022 in San Diego and virtually.

Hypertensive disorders of pregnancy (HDP) — conditions of high blood pressure including chronic/gestational hypertension and preeclampsia — have been strongly linked to heart disease in later life, but, before today, little research has connected these disorders with cognition. The key findings presented at AAIC 2022 include:

- Women with a history of HDP were more likely to develop vascular dementia — a decline in thinking skills caused by conditions that block or reduce blood flow to the brain — later in life, compared to women with non-hypertensive pregnancies.
- Experience of HDP, specifically high blood pressure during pregnancy, was associated with white matter pathology, a predictor of accelerated cognitive decline, 15 years after pregnancy.
- Women with a history of severe preeclampsia had significantly higher levels of beta amyloid, an Alzheimer's-related brain change, as measured in blood, compared to women with non-hypertensive pregnancies.

Affecting nearly 1 in 7 hospital deliveries, HDP is one of the leading causes of morbidity and mortality in birthing persons and fetuses worldwide. These conditions impact Black, Latino, Asian/Pacific Islander and Native American populations at disproportionately high rates.

"This is among the first longitudinal data linking hypertensive disorders of pregnancy with dementia in a large study cohort," said Claire Sexton, D.Phil., senior director of scientific programs and outreach at the Alzheimer's Association. "Considering the serious short- and long-term implications of HDP, early detection and treatment are vital to protect both the pregnant person and baby."

"These data illuminate the importance of prenatal care and monitoring the long-term health of pregnant people," said Sexton. "Those who experience any changes with their memory and cognition should have a discussion with their health care provider."

HDP associated with higher risk of vascular dementia

To explore the association between HDP and later-life dementia, Karen Schliep, Ph.D., MSPH, assistant professor in family and preventive medicine at University of Utah Health, and colleagues, performed a retrospective cohort study among 59,668 women who had experienced a pregnancy.

Women with a history of HDP had a 1.37 times higher adjusted risk of all-cause dementia after taking into account maternal age, year of childbirth and parity than women with non-hypertensive pregnancies. HDP was associated with a 1.64 times higher risk of vascular dementia and 1.49 times higher risk of other related

dementia, but not Alzheimer's disease. Gestational hypertension and preeclampsia/eclampsia showed similar magnitudes in risk for vascular dementia.

"Our results confirm previous findings that preeclampsia is most strongly associated with vascular dementia compared to Alzheimer's or other types of dementia," said Schliep. "They further suggest that vascular dementia risk may be just as high for women with a history of gestational hypertension as for preeclampsia."

HDP associated with white matter pathology 15 years post-pregnancy

Given the well-established association between HDP and long-term cerebrovascular health, Rowina Hussainali, M.Sc., a doctoral student in epidemiology and obstetrics and gynecology at the Erasmus MC Medical Center, Netherlands, and colleagues, aimed to examine the associations between HDP and markers of vascular brain pathology 15 years after pregnancy.

The researchers examined 538 women, 445 with a non-hypertensive pregnancy and 93 with HDP, from the Generation R study. Pregnant women with an expected delivery date between April 2002 and January 2006 were included. Fifteen years later, some of these women underwent magnetic resonance imaging to assess brain tissue volumes as well as other markers that could indicate pathology.

Hussainali and team found women with prior HDP had 38% more white matter pathology (indicative of the wearing away of brain tissue) compared to women with previous non-hypertensive pregnancy. This association was driven by women with gestational hypertension, who had 48% more white matter pathology compared to women with previous normotensive pregnancy. No differences were found with other markers of brain pathology, such as infarcts or cerebral microbleeds. The development of chronic hypertension after pregnancy strengthened this result, especially in women with previous gestational hypertension.

"These data clearly indicate that a history of HDP was associated with more damage to the brain 15 years after pregnancy — damage that could have lasting impacts on cognition," said Hussainali. "Women with a history of HDP should be evaluated and treated early for hypertension and other cardiovascular risk factors."

Preeclampsia linked to increased markers of brain inflammation

Preeclampsia is a severe hypertensive disorder of pregnancy that affects up to 5-8% of pregnancies. A large body of data indicates that women with a history of preeclampsia have an accumulation of health risk factors later in life, including heart disease. As severe preeclampsia has been associated with the highest risks for cerebrovascular disease, Sonja Suvakov, M.D., Ph.D., postdoctoral research fellow and assistant professor of medicine at Mayo Clinic, and team, explored whether vesicles — small fluid-filled pouches — released from brain cells would be detectable in women years after their affected pregnancies.

The researchers found that women with a history of severe preeclampsia had significantly higher concentrations of extracellular vesicles positive for amyloid beta, a protein that makes up one of the hallmark brain lesions of Alzheimer's. They also found a significant increase of extracellular vesicles positive for markers of brain endothelium damage and inflammation. Similarly, circulating levels of beta amyloid were also increased.

"These findings indicate that women with a history of preeclampsia have increased levels of markers of neurovascular damage which may negatively impact their cognitive skills," said Suvakov. "Further research is required to fully understand the neurodegenerative and cognitive risks that a history of hypertensive disorders confers on women throughout life."

About the Alzheimer's Association International Conference® (AAIC®)

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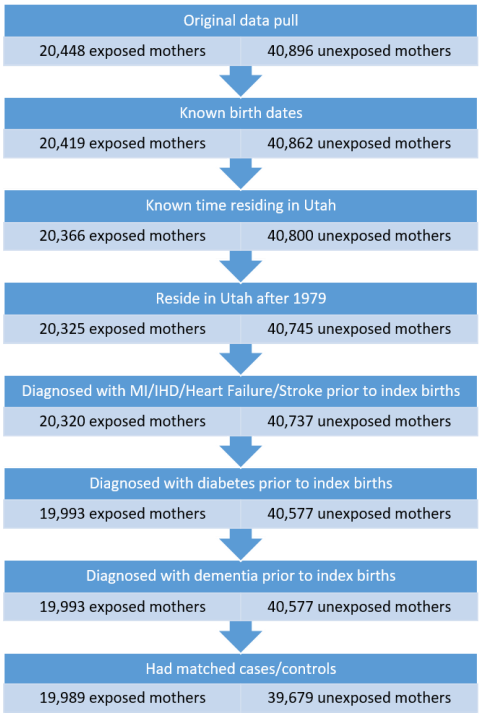
- Karen Schliep, Ph.D., MSPH, et al. What subtypes are driving the association between hypertensive disorders of pregnancy and dementia? Findings from an 80-year retrospective cohort study (Funders: National Institute on Aging, National Center for Research Resources, National Cancer Institute)
- Rowina Hussainali, M.Sc., et al. Hypertensive disorders of pregnancy and markers of vascular brain pathology after 15 years: a prospective cohort study (Funders: Preeclampsia Foundation; Coolsingel Foundation; Erasmus MC, Erasmus University Rotterdam, Netherlands Organization for Health Research and Development, Netherlands Organization for Scientific Research, Ministry of Health, Welfare and Sport; Ministry of Youth and Families; European Research Council)
- Sonja Suvakov, M.D., Ph.D., et al. Circulating extracellular vesicles of neurovascular origin are elevated in women with severe preeclampsia years after their affected pregnancies

*** AAIC 2022 news releases may contain updated data that does not match what is reported in the following abstracts.

Proposal ID: 62343
Title: What subtypes are driving the association between hypertensive disorders of pregnancy and dementia? Findings from an 80-year retrospective cohort study
Background: We recently found that women with, versus without, a history of HDP had a higher hazard of all-cause dementia, vascular dementia (VaD), and other/unspecified dementia, but not Alzheimer's disease (AD). Here, we assess associations of HDP subtypes with later life dementias.
Methods: We performed a retrospective cohort study among women with at least 1 singleton pregnancy (1939–2019) in Utah. Classification of HDP was done via birth certificates (text string, 1939–1977; ICD9 codes, 1978–1988; and check boxes with additional text, 1989–2013) with death certificates and inpatient records used for validation. Classification of dementia was assessed using ICD 9/10 codes via death, inpatient, and Medicare records. HDP exposed women (n=19,989) were one-to-two matched with unexposed women (n=39,679) by 5-year age groups, year of childbirth, and parity at the time of pregnancy (Figure 1). Cox regression models were used to estimate adjusted Hazard Ratios (aHR) and 95% CI for HDP subtypes with all-cause and specific dementias.
Results: HDP pregnancies were comprised of preeclampsia/eclampsia (65.9%) and gestational hypertension (33.5%). The remaining HDP cases were due to HELLP syndrome (0.6%), which we did not evaluate here due to small case count. Incidence of dementia over follow-up (1979–2019) was 4.1%; of these, 70% were other/unspecified, 24% were AD, and 6% were VaD. Women with a history of preeclampsia/eclampsia, compared to unexposed, had a 1.38 higher hazard of all-cause dementia, while women with gestational hypertension had a 1.36 higher hazard (Table 1). Breaking down by dementia subtypes, women with a history of preeclampsia/eclampsia had a 1.51 higher hazard of other/unspecified dementia, while women with gestational hypertension had a 1.31 higher hazard. The strength of association of gestational hypertension with VaD was 2.75, nearly double that for preeclampsia/eclampsia, which was 1.58. HDP subtypes were not associated with AD.
Conclusion: Our results are in line with the largest study to date conducted in Denmark that found preeclampsia to be most strongly associated with VaD compared to other dementia subtypes. Our results further suggest that risk of VaD may be just as high for women with a history of gestational hypertension as for preeclampsia.

Presenting Author
Karen Schliep, Ph.D., MSPH (Karen.Schliep@utah.edu)
University of Utah, United States

Flow chart of selecting exposed and unexposed mothers from the Utah Population Database (1939 to 2019)



Hazard ratios for all-cause dementia and dementia subtypes by history of HDP subtype, adjusted for index child's birth year and birth order and mothers' age at index birth.

History of Preeclampsia / Eclampsia	Dementia overall HR (95% CI)	Vascular dementia HR (95% CI)	Alzheimer's disease HR (95% CI)	Other/unspecified dementia HR (95% CI)
Exposed	1.38 (1.26, 1.50)	1.58 (1.11, 2.24)	1.04 (0.87, 1.24)	1.51 (1.36, 1.68)
Unexposed	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
History of Gestational Hypertension				
Exposed	1.36 (1.03, 1.79)	2.75 (0.90, 8.40)	1.18 (0.52, 2.68)	1.31 (0.96, 1.80)
Unexposed	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]

Proposal ID: 62354
Title: Hypertensive disorders of pregnancy and markers of vascular brain pathology after 15 years: a prospective cohort study
Background: Substantial evidence suggests an association between hypertensive disorders of pregnancy (HDP) and long term cerebrovascular health. We aimed to determine the associations between HDP and markers of vascular brain pathology fifteen years after pregnancy
Method: This was a nested cohort study embedded in a population-based prospective cohort followed from early pregnancy. We included 538 women, 445 (82.7%) with normotensive index pregnancies and 93 (17.2%) with HDP in the index pregnancy. Fifteen years after pregnancy (median of 14.6 years 90% range 14.0; 15.7), women had a mean age of 46.5 years (SD = 4.2). These women underwent magnetic resonance imaging to assess brain tissue volumes as well as white matter hyperintensities (WMH), lacunar infarcts, and cerebral microbleeds as markers of vascular brain pathology.
Result: Women with prior HDP had 38% (95% CI: [8% ; 75%]) higher WMH volume compared to women with previous normotensive pregnancy. This association was driven by women with gestational hypertension, who had 48% (95% CI: [11% ; 95%]) higher WMH volume compared to women with previous normotensive pregnancy. No differences were found with infarcts or cerebral microbleeds. The development of chronic hypertension after pregnancy strengthened this result, especially in women with previous gestational hypertension.
Conclusion: A history of HDP was associated with more WMH burden fifteen years after pregnancy. This effect was driven by women with previous gestational hypertension. The development of chronic hypertension after pregnancy contributed to this effect. Women with a history of HDP should be evaluated and treated early for hypertension and other cardiovascular risk factors.

Presenting author:
Rowina Hussainali, M.Sc. (r.hussainali@erasmusmc.nl)
Erasmus MC University Medical Center, Netherlands

Proposal ID: 62360
Title: Circulating extracellular vesicles of neurovascular origin are elevated in women with severe preeclampsia years after their affected pregnancies
Background: Preeclampsia (PE), a pregnancy specific hypertensive disorder, has been associated with elevated risk for strokes, cognitive decline, and smaller brain volumes later in life. As severe PE has been associated with the highest risks for cerebrovascular disease, we hypothesized that circulating extracellular vesicles (EVs) of neurovascular origin will be detectable in women years after severe PE as a marker of persistent neurovascular damage and amyloid-β.
Method: A cohort of 40 women with histories of normotensive pregnancies (control group) and age- and parity-matched to 40 women with history of mild (n=33) and severe (n=7) PE were identified using the Rochester Epidemiology Project. Diagnosis of severe PE was ascertained based on clinical criteria (Table). While none of the women had any major cardiovascular events, our previous study of this cohort has demonstrated that total gray matter volumes were smaller in women with a history of preeclampsia and late-life hypertension compared with the other groups. Blood-borne EVs derived from neurovascular cellular activation were determined by standardized digital flow cytometry. Plasma concentration of

amyloid-β was measured by ELISA. Differences among the groups were tested by ANOVA, with the least difference test for *post hoc* analysis. The association between EVs and MRI brain imaging was assessed by Pearson correlation coefficient.
Result: Women with history of severe PE had a significantly higher concentration of amyloid-β carrying EVs compared to controls (p=0.003). EVs positive for the markers of blood-brain barrier- endothelial damage (LDL-R) and inflammatory coagulation pathway activator (tissue factor), were significantly higher in women with history of severe PE compared to controls (p=0.008 and p=0.002, respectively), as well as to the women with history of mild PE. Plasma concentration of total amyloid-β was also significantly greater in women with history of severe vs. mild PE (p=0.037) (Table). The number of tissue factor positive EVs was negatively correlated with total gray matter volume (cm3) ($p<0.05$).
Conclusion: Women with a history of severe PE demonstrate elevated levels of markers of neuroinflammation and neurovascular damage, as well as greater amyloid-β secretion. Excessive inflammation may contribute to previously described brain atrophy in these women.

Presenting Author:
Sonja Suvakov, M.D., Ph.D. (suvakov.sonja@mayo.edu)
Mayo Clinic, Minnesota, United States

Table. Concentration of blood borne extracellular vesicles (EVs) and those of soluble amyloid β after normotensive and preeclamptic (PE) pregnancies

Variable	Comparison by group			
	Control n=40	Mild PE n=33	Severe PE n=7[a]	P value
Amyloid-β positive EVs/ µL plasma	2.6±0.4	2.5±0.4	15.9±14.2	0.003* 0.004**
LDL-R[b] positive EVs/ µL plasma	4.1±0.6	3.8±0.6	12.3±8.7	0.008* 0.007**
Tissue factor positive EVs/ µL plasma	13.1±1.3	22.1±3.4	40.5±21.9	0.002* 0.041**
Total plasma amyloid-β, pg/mL	8.1±2.8	3.7±1.3	16.5±9.3	0.037**

[a] Severe PE diagnosis was based on clinical criteria that that include severe hypertension, thrombocytopenia, impaired liver function tests, progressive renal insufficiency, pulmonary edema, and new onset neurological deficits

[b] LDL-R, low-density lipoprotein receptor

* severe PE vs. control

** severe PE vs. mild PE