History of Adverse Pregnancy Outcomes and Cognitive Decline

Laura B. Harrington, PhD, MPH
Assistant Investigator, KPWHRI
Affiliate Assistant Professor, UW Dept. of Epidemiology
laura.b.harrington@kp.org

Sarah Tom, PhD, MPH
Assistant Professor, Columbia University, Depts. of Neurology and Epidemiology
st3144@cumc.columbia.edu

ACT Symposium
May 15, 2024

Outline

- Background: APOs and Cognition / ADRD
- Methods
- Results
- Conclusions and Future Directions

Outline

- Background: APOs and Cognition / ADRD
- Methods
- Results
- Conclusions and Future Directions

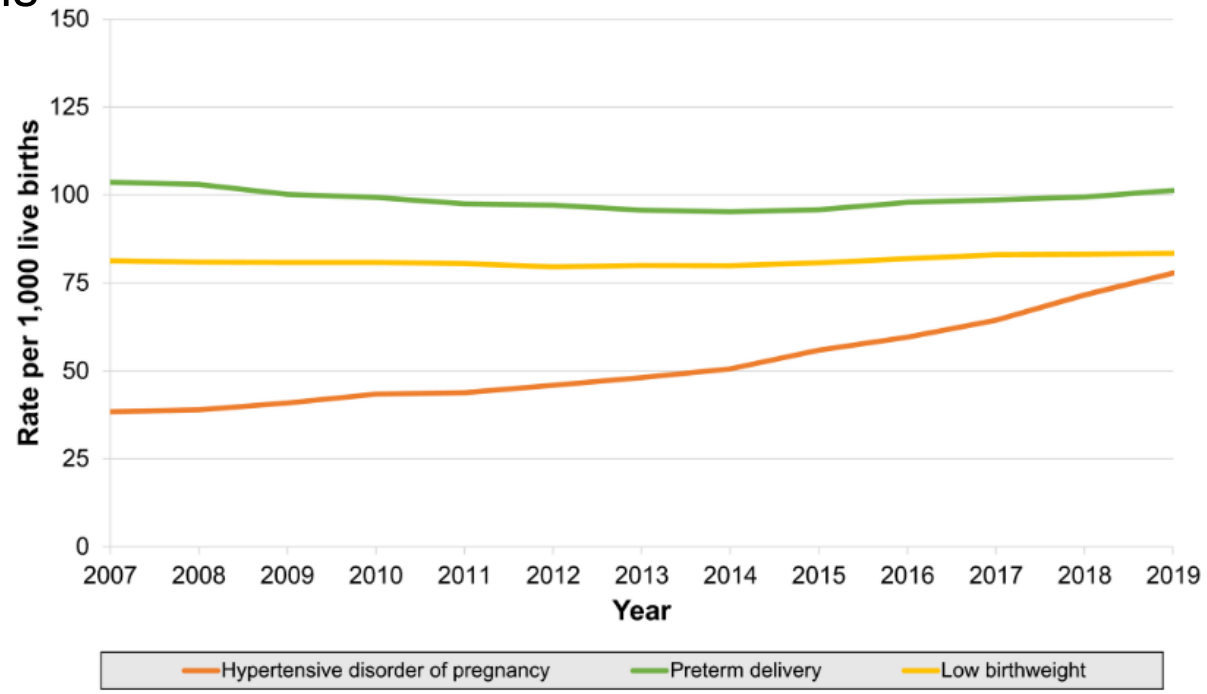
What are APOs?

- APOs = Adverse Pregnancy Outcomes

- APOs can include:
  - Hypertensive disorders of pregnancy (HDP)
    - E.g. gestational hypertension, preeclampsia, eclampsia
  - Preterm birth
  - Gestational diabetes
  - Small-for-gestational-age delivery
  - Placental abruption
  - Pregnancy loss (stillbirth, miscarriage)

How common are APOs?

- APOs complicate ~1 in 5 pregnancies in the United States
- Between 2007 and 2019 - per an analysis of National Center for Health Statistics Natality Files* :
  - age-standardized HDP rates approximately doubled, from 38 to 78 per 1000 live births*



*Freaney et al., JAHA, 2022.

HDP Rate/1000 Live Births – by Race and Ethnicity

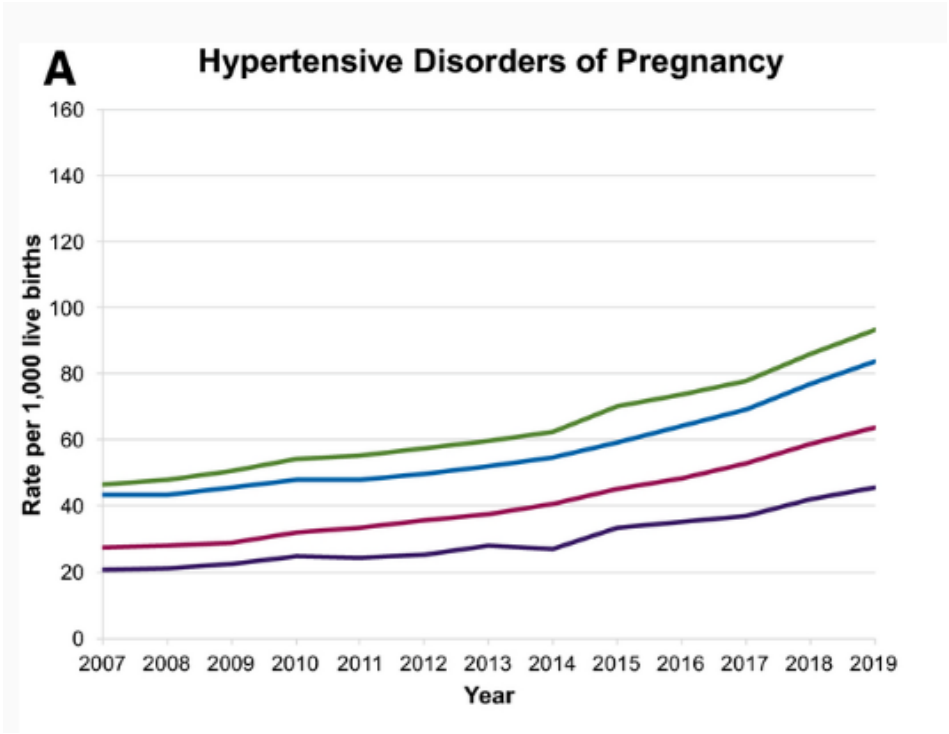


*Figure from Freaney et al., JAHA, 2022.

APOs and Cardiovascular Risk

Circulation

AHA SCIENTIFIC STATEMENT

Adverse Pregnancy Outcomes and Cardiovascular Disease Risk: Unique Opportunities for Cardiovascular Disease Prevention in Women

A Scientific Statement From the American Heart Association

ABSTRACT: This statement summarizes evidence that adverse pregnancy outcomes (APOs) such as hypertensive disorders of pregnancy, preterm delivery, gestational diabetes, small-for-gestational-age delivery, placental abruption, and pregnancy loss increase a woman's risk of developing cardiovascular disease (CVD) risk factors and of developing subsequent CVD (including fatal and nonfatal coronary heart disease, stroke, peripheral vascular disease, and heart failure). This statement highlights the importance of recognizing APOs when CVD risk is evaluated in women, although their value in reclassifying risk may not be established. A history of APOs is a prompt for more vigorous primordial prevention of CVD risk factors and primary prevention of CVD. Adopting a heart-healthy diet and increasing physical activity among women with

Nisha I. Parikh, MD, MPH, Chair
Juan M. Gonzalez, MD
Cheryl A.M. Anderson, PhD
Suzanne E. Judd, PhD
Kathryn M. Rexrode, MD
Mark A. Hlatky, MD
Erica P. Gunderson, PhD
Jennifer J. Stuart, ScD
Dhananjay Vaidya, PhD, Vice Chair

*Parikh, et al., Circulation, 2021.

APOs and Cardiovascular Risk

Table 2. APOs and Associations With Mortality and CVD Outcomes

Pregnancy outcome/ reproductive risk factors	Outcome association	Strength of Evidence*
Hypertensive disorders of pregnancy (preeclampsia, gestational hypertension)	↑ Atherosclerotic CVD (including coronary heart disease, peripheral vascular disease, and ischemic stroke)	A
	↑ Hemorrhagic stroke	B
	↑ Heart failure	B
GD	↑ Atherosclerotic CVD	A
Preterm delivery	↑ Atherosclerotic CVD	A
SGA	↑ Atherosclerotic CVD	A
Large for gestational age	↑ Atherosclerotic CVD	B
Placental abruption	↑ Atherosclerotic CVD	A
Miscarriages/stillbirths	↑ Atherosclerotic CVD	A

APO indicates adverse pregnancy outcome; CVD, cardiovascular disease; GD, gestational diabetes; and SGA, small for gestational age.

See Supplemental Table 1 for specific studies and references.

*Strength of Evidence A indicates multiple consistent cohort studies, meta-analyses of such studies, or both. Strength of Evidence B indicates fewer available studies or inconsistencies in the evidence.

*Figure from Parikh et al., Circulation, 2021.

APOs associated with later life ADRD?

- History of APOs may be associated with later life development of Alzheimer's disease and related dementias (ADRD)

- Multiple potential pathways proposed:
  - Shared risk factors (e.g. hypertension)
  - Common pathophysiological features (e.g. vascular endothelial dysfunction, angiogenic dysregulation, changes in cerebral vasoreactivity)
  - Social influences (e.g. financial stress, traumatic birthing experiences, and exposure to systemic racism

Hypertensive Disorders of Pregnancy & Cognition / ADRD

- History of hypertensive disorders of pregnancy (HDP) associated with:
  - Longitudinal declines in global cognition and attention / executive function z scores[1]
  - Reduced cognitive function at 14-years post-pregnancy[2]
  - Lower scores on measures of processing speed [3,4]
    - Digit Symbol Substitution Test (DSST)[3,4],Stroop Test of executive function[3,4], and Trail Making Test Part A[4]
  - Smaller brain volume[4]
  - Long-term differences in executive functioning[5]
  - Dementia risk (preeclampsia HR=3.5; 95% CI: 2.0 to 6.1)[6]

- But, no evidence of an association in some studies with:
  - Cognitive level[1,7]
  - Working memory[3]
  - Cognitive performance in memory, language, or executive function[4]

[1]Mielke et al., Neurology, 2023; [2]Adank et al., Neurology, 2021; [3]Dayan et al., Hypertension, 2018; [4]Mielke et al., Circ Cardiovasc Qual Outcomes, 2016; [5]Alers et al., AJOG, 2023; [6]Basit et al., BMJ, 2018.; [7]Fields et al., AJOG, 2017.

Other APOs & Cognition / ADRD

- Most studies do not evaluate APOs other than HDP in relation to cognitive outcomes
- Few aging cohorts include pregnancy history
- Swedish registry data:
  - History of APOs associated with higher risk of vascular dementia[1]
    - APOs = hypertensive disorders of pregnancy, preterm birth, and fetal growth restriction
- Bogalusa Heart Study:
  - No association of APOs with midlife cognition[2]
    - APOs = gestational diabetes, hypertensive disorders of pregnancy, preterm birth, and low birth weight infant

[1]Andolf et al., BJOG, 2020; [2]Harville, Am J Geriatr Psychiatry, 2020.

NIA-funded R21 (09/20-06/23)

- PI: Eliza Miller
  - Co-Is: Harrington; Tom
- "Pregnancy complications and the development of Alzheimer's Disease and Related Dementias in Women in the Adult Changes in Thought Study"

- Aim: **To evaluate the association between any APO history and cognition and cognitive decline**, among female ACT study participants born in or after 1940, with evidence of ≥1 child or pregnancy (n=444).

  - *Hypothesis:* *On average, those who experienced one or more APOs would have lower global cognition at any age at or above 65 and faster cognitive decline than those with no history of APOs.*
    - *APOs = hypertensive disorders of pregnancy, preterm birth, small-for-gestational-age infant, low birth weight infant, or stillbirth*

Outline

- Background: APOs and Cognition / ADRD
- Methods
- Results
- Conclusions and Future Directions

ACT Sample

- Women born ≥ 1940 and enrolled 1994 – 2020 with one of the following:
  - ≥ 1 pregnancy or child reported at ACT enrollment
  - ≥ 1 pregnancy abstracted from chart review
  - Presence of obstetric history in the electronic health records

- Focus on participants who likely were members of KPWA during reproductive years.

- *n = 444*

Exposure Variable

Primary: Any APO

Adverse Pregnancy Outcomes	
Hypertensive disorders of pregnancy	Gestational hypertension Preeclampsia Eclampsia
Preterm birth	Spontaneous or medically indicated birth prior to 37 weeks gestation
Low birth weight	<2500 g
Small-for-gestational-age infant	Based on gestational age and birth weight < 10th percentile
Stillbirth	

- Three trained abstractors
  - Inter-rater reliability of 24 charts: all scores over 75%
    - 88% for history of hypertension
    - 96% for history of preeclampsia

Outcome Variable

- Cognitive Assessment Short Inventory (CASI)
  - Global cognition
  - Enrollment and every two years
  - ***Primary Outcome***
- Subdomains (Mukherjee et al., 2023)
  - Memory
  - Executive function
  - Language
  - Visuospatial functioning
- Item response theory transformation (Crane et al., 2008)
  - Non-linearity

Covariates Self-reported at Enrollment

- Demographic
  - Race and ethnicity
  - Birth year
- Social determinants of health
  - Marital status
  - Educational attainment
- Health-related factors
  - Smoking status
  - Vascular conditions
  - Current medications

Statistical Analysis

- To account for repeat measures of cognition, linear regression with generalized estimating equations

- Assess relationship between the level of cognition at any age and change in cognition over 4 years of follow-up (interaction between age and APO history), adjusting for
  - Age
  - Birth cohort
  - Education
  - Marital status (at ACT enrollment)

- Age as the time axis

Outline

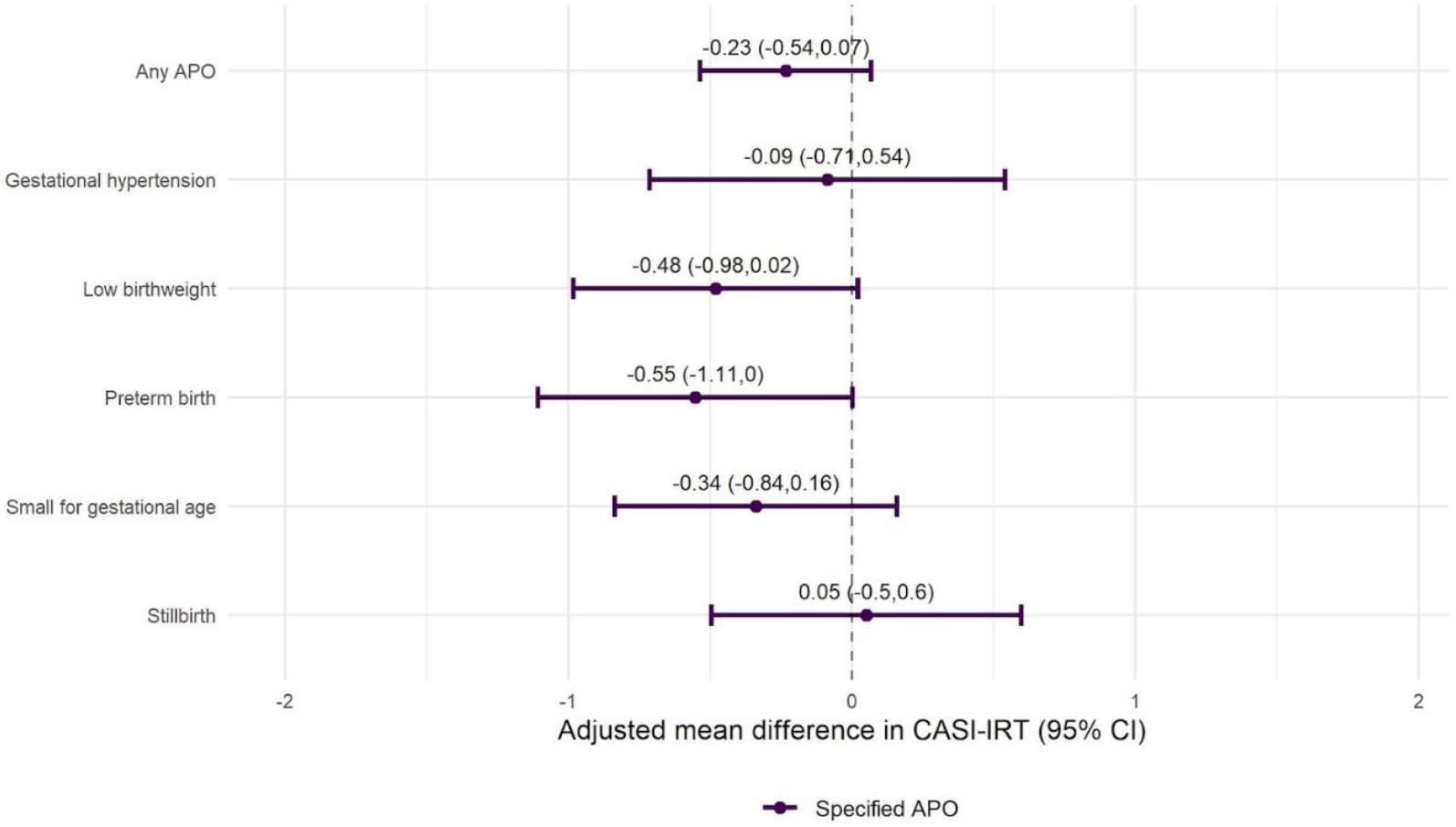
- Background: APOs and Cognition / ADRD
- Methods
- Results
- Conclusions and Future Directions

Descriptive Results

- 13% (n = 59/444) of the sample ever experienced an APO.
  - US women age ≥ 50 years in 2013-2014: 15% (Miller et al., 2022)

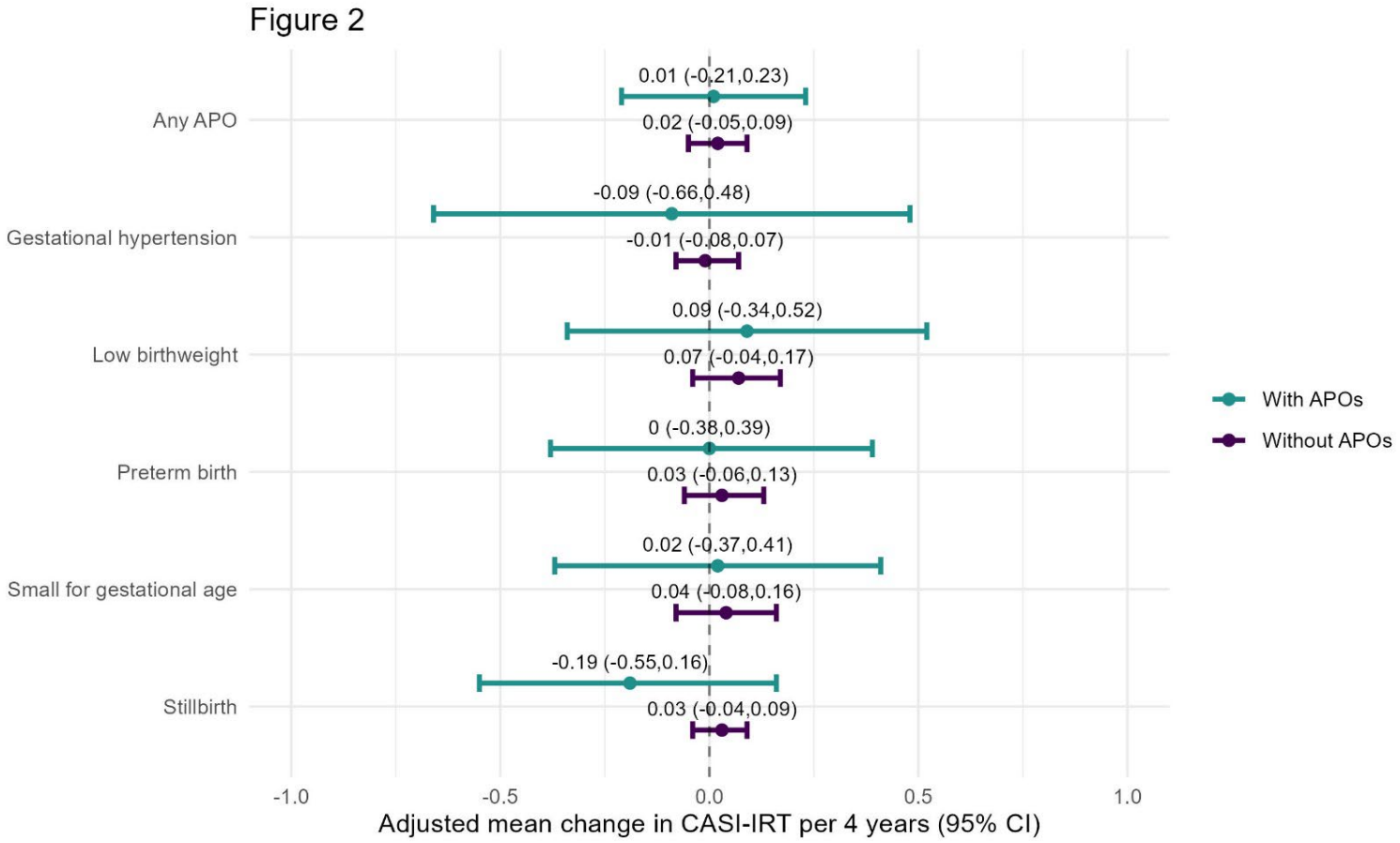
- Compared to those never experiencing an APO, those ever experiencing an APO:
  - ***Higher*** age at first birth (28 vs. 26 years)
  - ***More likely*** to be born in 1946-1952, compared to 1940 – 1945 (42% vs. 32%)
  - ***Younger*** age at death, among decedents (73 vs 74 years)
  - ***Similar*** educational attainment, measured blood pressure, age at ACT enrollment, and follow-up in ACT

Relationship between APOs and Cognition Level



Similar results for cognitive domain outcomes.

Relationships between APOs and 4-year Change in Cognition



Similar results for cognitive domain outcomes.

Outline

- Background: APOs and Cognition / ADRD
- Methods
- Results
- Conclusions and Future Directions

Strengths & Limitations

- Strengths
  - Abstracted pregnancy data
  - Repeated measure of cognition
- Limitations
  - Median age at enrollment of 68 years
  - Short follow-up
  - Missing pregnancy data

Conclusions

- Suggestion that history of APOs associated with lower cognition, though imprecisely measured.
- No association between history of APOs and cognitive change.

Future Directions

- Monitoring these associations as participants age
  - Increased power for evaluating additional outcomes in cognitive change, dementia, neuroimaging, neuropathology
- Expanding the understanding of relationships between APOs and life course reproductive health
- Investigating the pathways from APOs to cognitive aging

Acknowledgements

- ACT participants
- ACT study staff
  - Abstractors: Becky Lederman, Mary Lyons, Margie Wilcox
- ACT investigators
  - Laura Gibbons
  - Paul Crane
- Scientific Team and Co-authors
  - Kristi Chau, Paige Wartko, Roxanne Muiruri, Chloe Krakauer, Linda McEvoy, Andrea LaCroix, Eliza Miller (PI)
- Funding
  - NIA (R21AG069111)

Thank you!

Questions?

laura.b.harrington@kp.org

st3144@cumc.columbia.edu