Hypertensive disorders of pregnancy and long-term risk of maternal stroke
A systematic review and meta-analysis

Matthew Brohan[1,2], Fionn P. Daly[2], Louise Kelly[3], Fergus P. McCarthy[4], Ali S. Khashan[1], Karolina Kublickiene[5], Peter M. Barrett[1]

1. School of Public Health, University College Cork, Cork, Ireland
2. School of Medicine, University College Cork, Cork, Ireland
3. Department of General Medicine, Beaumont Hospital, Dublin, Ireland
4. Irish Centre for Maternal & Child Health, University College Cork, Cork, Ireland
5. Division of Renal Medicine, Department of Clinical Intervention, Science and Technology, Karolinska Institutet, Stockholm, Sweden

Introduction

- Hypertensive disorders of pregnancy (HDP) are common and place significant strain on the body[1]
- HDP are associated with long-term negative cardiovascular outcomes[2]
- The risk that HDP present to the neurovascular system in later life is less established
- There is a lack of consensus on the association between HDP subtypes and stroke subtypes[3,4]
- As stroke is a relatively common pathology[5], it is important to establish if women with HDP are at a higher risk of stroke in later life - and if there is an association between HDP subtypes and stroke subtypes

Aims

1. To provide a synthesis of the available literature on the association between HDP and long-term risk of maternal stroke
2. To examine the association between individual HDP (preeclampsia [PE], gestational hypertension [GH], chronic hypertension [CH], and superimposed preeclampsia on chronic hypertension) and ischaemic and haemorrhagic stroke separately

Methods

DATA SOURCES:

Databases PubMed, Web of Science, and CINAHL were searched from inception to 01/06/21

Papers were included if the following criteria were met:

- case-control or cohort studies,
- conducted on human participants,
- available in English,
- measuring the exposure of a history of HDP (PE, GH, CH, or superimposed PE on CH), and the outcome of maternal ischaemic stroke or haemorrhagic stroke
- the outcome occurred at least 3 months postpartum

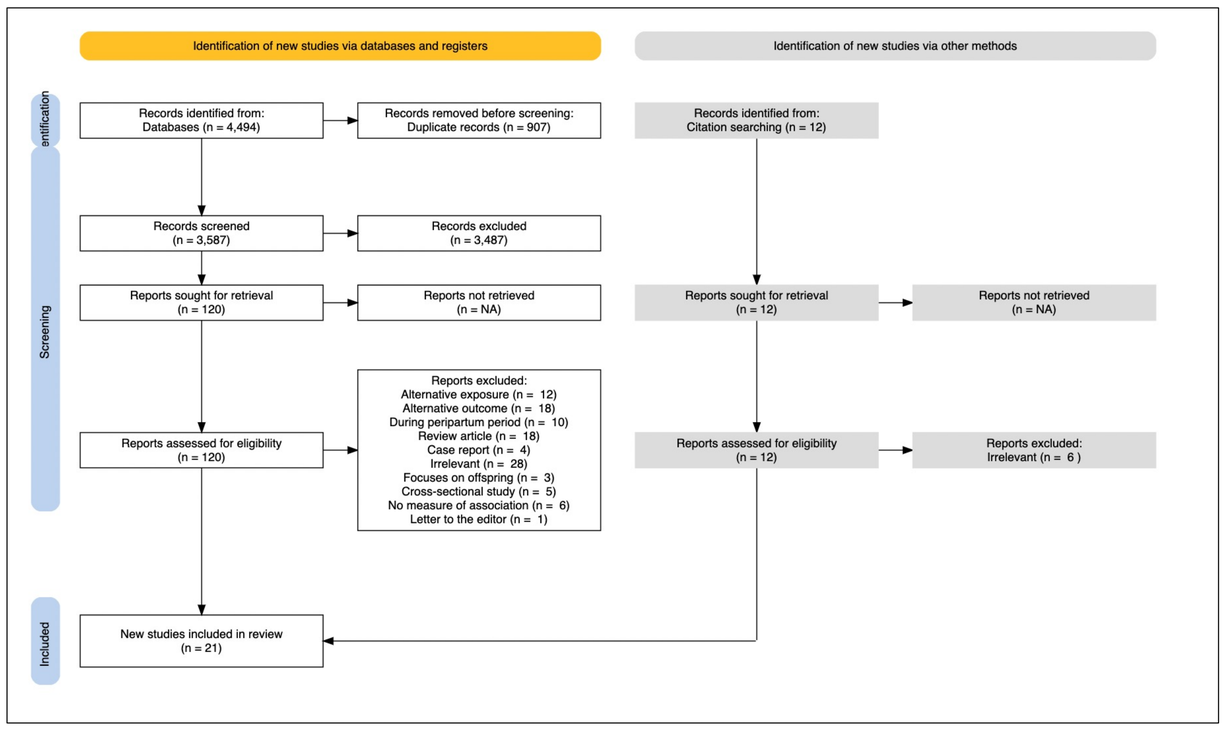

Figure 1: PRISMA flow diagram of study selection

DATA APPRAISAL AND SYNTHESIS METHODS:

- Three reviewers extracted data and appraised study quality following the Meta-analyses of Observational Studies in Epidemiology (MOOSE)[6] and PRISMA-P[7] guidelines and using the Newcastle-Ottawa scale for risk of bias assessment[8]

MAIN OUTCOMES AND MEASURES:

- Primary outcome- any stroke (undifferentiated)
- Secondary outcomes- ischaemic stroke and haemorrhagic stroke
- The protocol for this systematic review was registered on PROSPERO (CRD42021254660)

PRELIMINARY ANALYSIS:

- Review Manager (Cochrane Collaboration) software, version 5.4
- Adjusted estimates inputted into Review Manager using the inverse variance method
- Preliminary analysis generated forest plots and observed the pooled associations between each exposure (HDP, PE, GH, CH and superimposed PE on CH) and each of the outcomes (any stroke, ischaemic stroke and haemorrhagic stroke)

SUBGROUP ANALYSIS:

- This took place in cases where 10 or more studies examined an association[9].
- Where possible, subgroup analyses were completed by study type, study location, method of data ascertainment and study quality

Results

- 21 studies included (8,057,165 study participants)
- 5 studies reported on >1 outcome of interest
- HDP significantly associated with any stroke, aRR 1.76 (95% CI, 1.41-2.20)
- PE significantly associated with any stroke, aRR 1.71 (95% CI, 1.50-1.96), ischemic stroke, aRR 1.68 (95% CI, 1.17-2.43), and hemorrhagic stroke, aRR 2.45 (95% CI, 1.36-4.41)
- GH significantly associated with any stroke, aRR 1.23 (95% CI, 1.20-1.26), and ischemic stroke, aRR 1.38 (95% CI, 1.14-1.67)
  - However, the association with haemorrhagic stroke was not statistically significant, aRR 2.06 (95% CI 0.65-6.65).
- Too few studies to conduct a meta-analysis for either CH, or superimposed PE on CH, with maternal stroke.

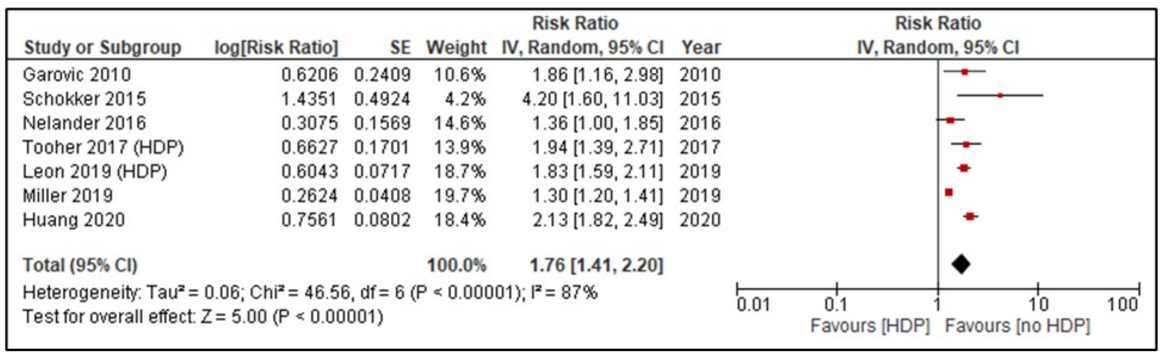

Figure 2: Forest plot of HDP (exposure) and any stroke (outcome)

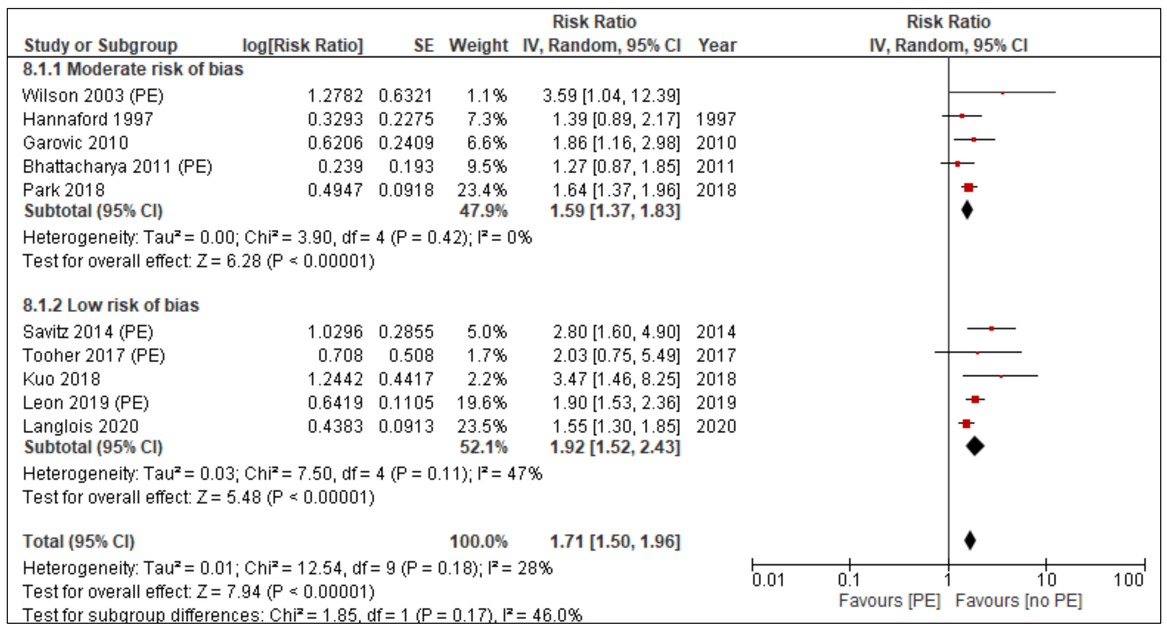

Figure 3: Subgroup analysis of PE and stroke by study quality

Key Discussion Points

- HDP appear to be associated with any undifferentiated stroke, ischaemic stroke and haemorrhagic stroke
- Women with a history of HDP appear to be more likely to develop stroke in later life than those without a history of HDP
- The observed associations may differ by stroke subtype:
  - PE and GH may be positively associated with any undifferentiated stroke and ischaemic stroke
  - PE appears to be associated with long term risk of haemorrhagic stroke while GH does not conclusively appear to be
- Notable lack of data available on individual exposure to CH and superimposed PE on CH
- HDP are prevalent in the community- although while the individual relative risk of stroke is low, the absolute long-term risk of stroke arising following exposure to HDP may be large

Conclusions

- In this systematic review and meta-analysis, exposure to HDP, including preeclampsia and gestational hypertension, appears to be associated with an increased risk of any stroke, and ischaemic stroke in later life
- Women who experience HDP may warrant preventive interventions to reduce their long-term risk of stroke

References

1. Lao TT. The mother--the long-term implications on metabolic and cardiovascular complications.7. Best Pract Res Clin Obstet Gynaecol. 2015;29(2):244-55.
2. Arnott C, Nelson M, Ramirez MA, Hyett J, Gale M, Henry A, et al. Maternal cardiovascular risk 8. after hypertensive disorder of pregnancy. Heart. 2020;106(24):1927-33..
3. Wu R, Wang TT, Gu RH, Xing DX, Ye CX, Chen Y, et al. Hypertensive Disorders of Pregnancy and Risk of Cardiovascular Disease-Related Morbidity and Mortality: A Systematic Review and 9. Meta-Analysis. Cardiology. 2020;145(10):633-47.
4. Warlow C. Epidemiology of stroke. The Lancet. 1998;352:S1-S4.
5. Umesawa M, Kobashi G. Epidemiology of hypertensive disorders in pregnancy: prevalence, risk factors, predictors and prognosis. Hypertension Research. 2017 Mar;40(3):213-20.
6. Brooke BS, Schwartz TA, Pawlik TM. MOOSE Reporting Guidelines for Meta-analyses of Observational Studies. JAMA surgery. 2021.
Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Bmj. 2021;372.
Wells G, Shea B, O'connell D, Petersen J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. Canada: Department of Epidemiology and Community Medicine, University of Ottawa. 2020.
Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al. Cochrane handbook for systematic reviews of interventions: John Wiley & Sons; 2019.