



Magnus, M., Hughes, A. D., Williams, C. E. M., Chaturvedi, N., Catov, J., & Fraser, A. (2018). Hypertensive Disorders During Pregnancy and Offspring Retinal Microvasculature During Adolescence. *Journal of the American College of Cardiology*, 72(11), 1318-1320.
<https://doi.org/10.1016/j.jacc.2018.06.057>

Peer reviewed version

License (if available):
CC BY-NC-ND

Link to published version (if available):
[10.1016/j.jacc.2018.06.057](https://doi.org/10.1016/j.jacc.2018.06.057)

[Link to publication record in Explore Bristol Research](#)
PDF-document

This is the author accepted manuscript (AAM). The final published version (version of record) is available online via Elsevier at <https://doi.org/10.1016/j.jacc.2018.06.057> . Please refer to any applicable terms of use of the publisher.

University of Bristol - Explore Bristol Research

General rights

This document is made available in accordance with publisher policies. Please cite only the published version using the reference above. Full terms of use are available:
<http://www.bristol.ac.uk/pure/about/ebr-terms>

**Hypertensive disorders during pregnancy and offspring retinal microvasculature
during adolescence**

Maria C. Magnus PhD ^{1,2,3*}, Alun D. Hughes MD PhD ⁴, Cathy Williams PhD ², Nishi
Chaturvedi MD PhD ⁴, Janet Catov PhD ⁵, and Abigail Fraser PhD ^{1,2}

¹ MRC Integrative Epidemiology Unit at the University of Bristol, Bristol, United Kingdom

² Department of Population Health Sciences, Bristol Medical School, Bristol, United
Kingdom

³ Centre for Fertility and Health, Norwegian Institute of Public Health, Oslo, Norway

⁴ Institute of Cardiovascular Science, University College London, London, United Kingdom

⁵ Department of Epidemiology, University of Pittsburgh, Pittsburgh, United States

*Corresponding author:

Maria Christine Magnus

MRC Integrative Epidemiology Unit at the University of Bristol

Oakfield House Oakfield Grove

BS8 2BN Bristol

United Kingdom

Disclosures: The authors have no relationships with industry to disclose.

Offspring of mothers with hypertensive disorders during pregnancy (HDP) have increased risk of cardiovascular disease (CVD) (1). Whether this is due to a direct *intra uterine* effect, such as maternal inflammation, endothelial dysfunction or poor placentation linked pre-eclampsia (PE), or shared genetics or environment, which is more likely to be linked to gestational hypertension (GH), remains undetermined (1). Regardless, it is proposed that microvascular changes that predate CVD events by decades could play a role (2). Retinal scans are a non-invasive way to directly observe the human microvasculature. We therefore examined whether exposure to maternal HDP was associated with retinal microvascular features in adolescent offspring in a UK pregnancy cohort.

We included 1,082 singletons with information on maternal HDP and retinal microvasculature at age 13 from the Avon Longitudinal Study of Parents and Children (ALSPAC). Ethical approval was granted by the ALSPAC Law and Ethics Committee and local research ethics committees. Women without pre-existing hypertension were classified with gestational hypertension (GH) if they had systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg on at least 2 occasions first occurring after 20 gestational weeks. Pre-eclampsia (PE) was defined as GH in combination with proteinuria (≥ 30 g/dL). We compared children of mothers with GH and PE to children of mothers without pre-existing hypertension. Measures of retinal microvasculature included arteriolar diameters, venular diameters, arteriolar length diameter ratio, arteriolar tortuosity, arteriovenous ratio and optimality deviance. The multivariable linear regression models adjusted for sex, age at retinal scans, and ametropia (Model 1), in addition to maternal age, parity, education, pre-pregnancy BMI, smoking and grandparental history of CVD (Model 2).

A total of 159 mothers (15%) had GH, while 18 (2%) had PE. The mean age of the children at the time of the retinal scans was 12.8 years (standard deviation 0.2). Maternal GH showed modest associations with offspring retinal venular diameter, adjusted mean difference

2.62 microns (95% CI: 0.26, 4.98), and arteriovenous ratio, adjusted mean difference -0.02 (95% CI: -0.04, -0.01) (Table). Similar associations were not observed for PE, with an adjusted mean difference of 0.94 microns (95% CI: -5.50, 7.38) for retinal venular diameter, and an adjusted mean difference of -0.01 (95% CI: -0.05, 0.04) for arteriovenous ratio (Table). There was no strong evidence of any additional associations. Excluding children with childhood-onset diabetes (N=3), did not change results.

Our findings indicate that children born to mothers with GH (but not PE) have a greater venular diameter and a lower arteriovenous ratio. In contrast to findings from the Generation R cohort which examined children at age six, our findings do not support a narrower arteriolar diameter among children exposed to HDP (3). The differences between our findings and those from Generation R may be explained by the fact that they measured retinal microvasculature at age 6 instead of age 13, or the fact that they did not separate GH from PE, as they grouped both conditions into HDP. However, both narrower arterioles and wider venules are known to predict future hypertension and CVD events (4). It is therefore plausible that there might be a microvascular pathway linking HDP and increased CVD risk in offspring (4). The associations of maternal GH - but not of PE - with offspring cardiovascular health are also in line with associations previously reported for offspring blood pressure in ALSPAC (5). A potential explanation may be that GH is more likely driven by underlying genetic predisposition and lifestyle characteristics, whilst PE is driven by a specific pregnancy profile, e.g. placentation. In conclusion, our results indicate that children of mothers with GH have a wider venular diameter and lower arteriovenous ratio. This might be explained by a common role of genetic or lifestyle characteristics linked to CVD risk.

Please note: Drs. Magnus and Fraser work at the MRC Integrative Epidemiology Unit which receives infrastructure funding from the UK Medical Research Council (MC_UU_12013/5) and are also funded by a UK MRC fellowship awarded to Dr. Fraser (MR/M009351/1).

References

1. Thoulass JC, Robertson L, Denadai L et al. Hypertensive disorders of pregnancy and adult offspring cardiometabolic outcomes: a systematic review of the literature and meta-analysis. *J Epidemiol Community Health* 2016;70:414-22.
2. Li LJ, Ikram MK, Wong TY. Retinal vascular imaging in early life: insights into processes and risk of cardiovascular disease. *J Physiol* 2016;594:2175-203.
3. Yesil GD, Gishti O, Felix JF et al. Influence of Maternal Gestational Hypertensive Disorders on Microvasculature in School-Age Children: The Generation R Study. *Am J Epidemiol* 2016;184:605-615.
4. Newman AR, Andrew NH, Casson RJ. Review of paediatric retinal microvascular changes as a predictor of cardiovascular disease. *Clin Exp Ophthalmol* 2017;45:33-44.
5. Fraser A, Nelson SM, Macdonald-Wallis C, Sattar N, Lawlor DA. Hypertensive disorders of pregnancy and cardiometabolic health in adolescent offspring. *Hypertension* 2013;62:614-20.

Table The mean difference in measures of retinal microvasculature between offspring of mothers with hypertensive disorders during pregnancy and offspring of normotensive mothers (n=1,082)

Measure of microvasculature	Gestational hypertension Mean difference (95% CI)	Pre-eclampsia Mean difference (95% CI)	Direction of the association between the microvascular measures and later cardiovascular risk
Arteriolar diameter, microns			↓
Model 1	0.19 (-1.60, 1.98)	0.42 (-4.52, 5.35)	
Model 2	0.27 (-1.57, 2.12)	0.93 (-4.10, 5.97)	
Venular diameter, microns			↑
Model 1	3.08 (0.78, 5.37)	1.25 (-5.08, 5.57)	
Model 2	2.62 (0.26, 4.98)	0.94 (-5.50, 7.38)	
Arteriolar length diameter ratio (LDR)			↑
Model 1	-0.37 (-0.93, 0.19)	-0.83 (-2.37, 0.72)	
Model 2	-0.39 (-0.97, 0.18)	-0.95 (-2.53, 0.62)	
Arteriolar tortuosity			↓
Model 1	-0.002 (-0.006, 0.002)	-0.004 (-0.015, 0.007)	
Model 2	-0.001 (-0.006, 0.003)	-0.003 (-0.014, 0.009)	
Arteriovenous ratio			↓
Model 1	-0.03 (-0.04, -0.01)	-0.01 (-0.06, 0.03)	
Model 2	-0.02 (-0.04, -0.01)	-0.01 (-0.05, 0.04)	
Optimality deviance ^a			↑
Model 1	-0.002 (-0.017, 0.012)	0.009 (-0.032, 0.050)	
Model 2	-0.003 (-0.019, 0.013)	0.008 (-0.034, 0.049)	

CI=confidence interval.

Model 1 Adjusted for age, sex and ametropia.

Model 2 Adjusted for age sex and ametropia, in addition to maternal age, parity, education, pre-pregnancy BMI, smoking during pregnancy and genetic predisposition to cardiovascular disease (parental history of hypertension, stroke or heart disease).

^a For a theoretically optimal bifurcation, the optimality ratio should be 0.79, and the optimality deviance was calculated as the absolute value of the optimality ratio minus 0.79.

Multiple imputation of missing covariate information conducted using chained equations.