

## BACKGROUND

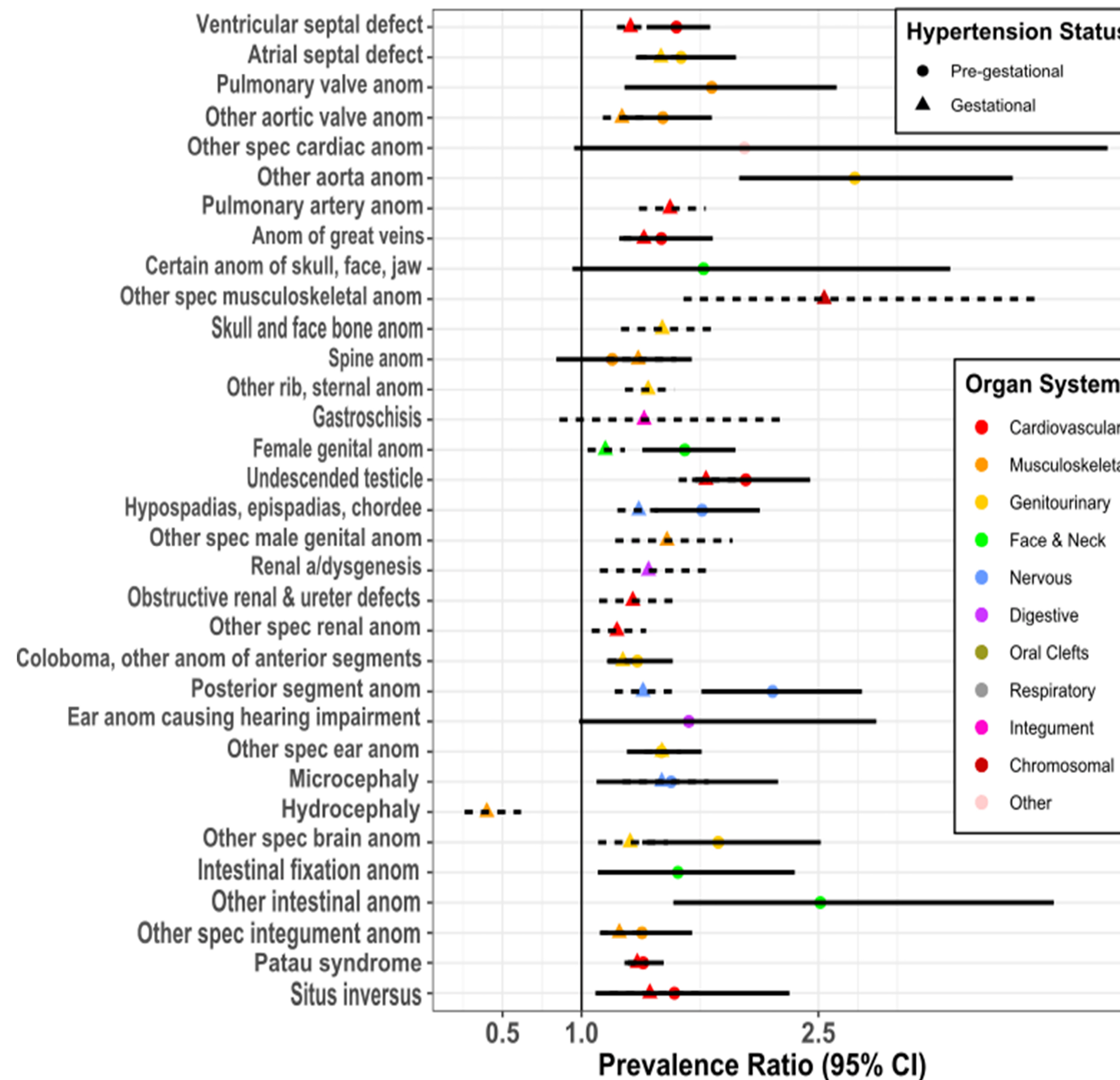
Maternal hypertension has been associated with congenital heart disease<sup>1</sup>. However, there remain questions about the broader range of birth defects associated with hypertension and differences in risk among offspring of women with pre-gestational vs. gestational diagnosis. We evaluated associations using data from one of the world's largest population-based active birth defects surveillance systems and a novel statistical approach.

## PURPOSE

To determine prevalence of birth defects associated with pre-gestational and gestational hypertension.

## METHODS

We performed a phenome-wide association study (PheWAS) to evaluate risk of a broad range of birth defects among offspring of women with hypertension, overall and stratified by timing of diagnosis, among all livebirths (N>6,500,000) and birth defects cases regardless of pregnancy outcome (N>290,000) in Texas during 2005-2015. We randomly divided data into discovery (60%) and replication (40%) partitions and used Poisson regression to estimate prevalence ratios (PRs) and 95% confidence intervals (CIs) for any birth defect and 130 specific defects with >10 cases diagnosed among exposed offspring. Multivariable models were adjusted for maternal age, race/ethnicity, education, previous livebirths, and BMI. Birth defects associated with maternal hypertension at a Bonferroni-adjusted threshold ( $p < 3.8E-4$ ) in discovery were re-tested in replication; those associated with maternal hypertension at  $p < 0.05$  and with the same direction of effect were considered statistically significant. To maximize precision, we estimated PRs and 95% CIs for replicated defects in the pooled dataset.



**Fig 1:** Prevalence ratios for associations between pre-gestational and gestational hypertension and birth defects, which are identified and color-coded by organ system. Only birth defect associations that replicated are included in this figure.

## RESULTS

Maternal hypertension was associated with:

- increased prevalence of any birth defect ( PR 1.32, 95% CI 1.30-1.34)
- non-isolated birth defects (PR 1.38, 95% CI 1.35-1.40)
- 27 specific birth defects, including novel (e.g., microcephaly) and previously reported phenotypes (e.g., hypospadias, ventricular septal defects).

Pre-gestational compared to gestational hypertension was a stronger risk factor for:

- any birth defect (PR 1.38, 95% CI 1.34-1.43 vs. 1.28, 95% CI 1.26-1.30)
- non-isolated birth defects (PR 1.47, 95% CI 1.41-1.54 vs. 1.35, 95% CI 1.32-1.38)
- several specific birth defects (Figure 1)

## CONCLUSION

Our findings suggest that maternal hypertension is associated with a broad range of structural birth defects across organ systems. Nearly 30 structural birth defects were differentially associated with pre-gestational and gestational hypertension. Increased risk of birth defects may be a result of reduced uteroplacental perfusion<sup>2</sup>. Further studies are needed to elucidate the genetic and environmental factors underlying these associations.

## REFERENCES

1. Lei, Y., Ludorf, K. L., Yu, X., Benjamin, R. H., Gu, X., Lin, Y., Finnell, R. H., Mitchell, L. E., Musfee, F. I., Malik, S., Canfield, M. A., Morrison, A. C., Hobbs, C. A., Van Zutphen, A. R., Fisher, S., & Agopian, A. J. (2021). Maternal Hypertension-Related Genotypes and Congenital Heart Defects. *American journal of hypertension*, 34(1), 82-91.
2. Fisher, S. C., Van Zutphen, A. R., Werler, M. M., Romitti, P. A., Cunniff, C., Browne, M. L., & National Birth Defects Prevention Study (2018). Maternal antihypertensive medication use and selected birth defects in the National Birth Defects Prevention Study. *Birth defects research*, 110(19), 1433-1442. <https://doi.org/10.1002/bdr2.1372>