

Fetal (Prenatal) Alcohol Impairs Blood Flow and Stroke Recovery in Adult Mice

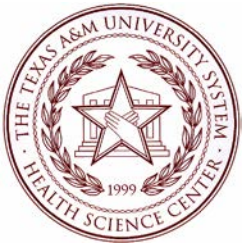
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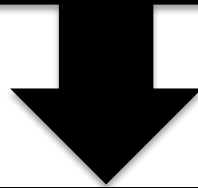
Objectives

- Identify prenatal alcohol exposure (PAE) as a risk factor for adult cardiovascular diseases
- Recognize PAE can amplify/ aggravate the effect of a second adverse life experience in adulthood
- Understand that PAE causes greater disability after brain trauma in adults.

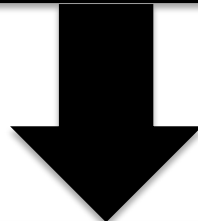


Fetal Origin of Adult Disease (Barker Hypothesis)

In Utero Environment (Adverse
Events/Undernutrition)



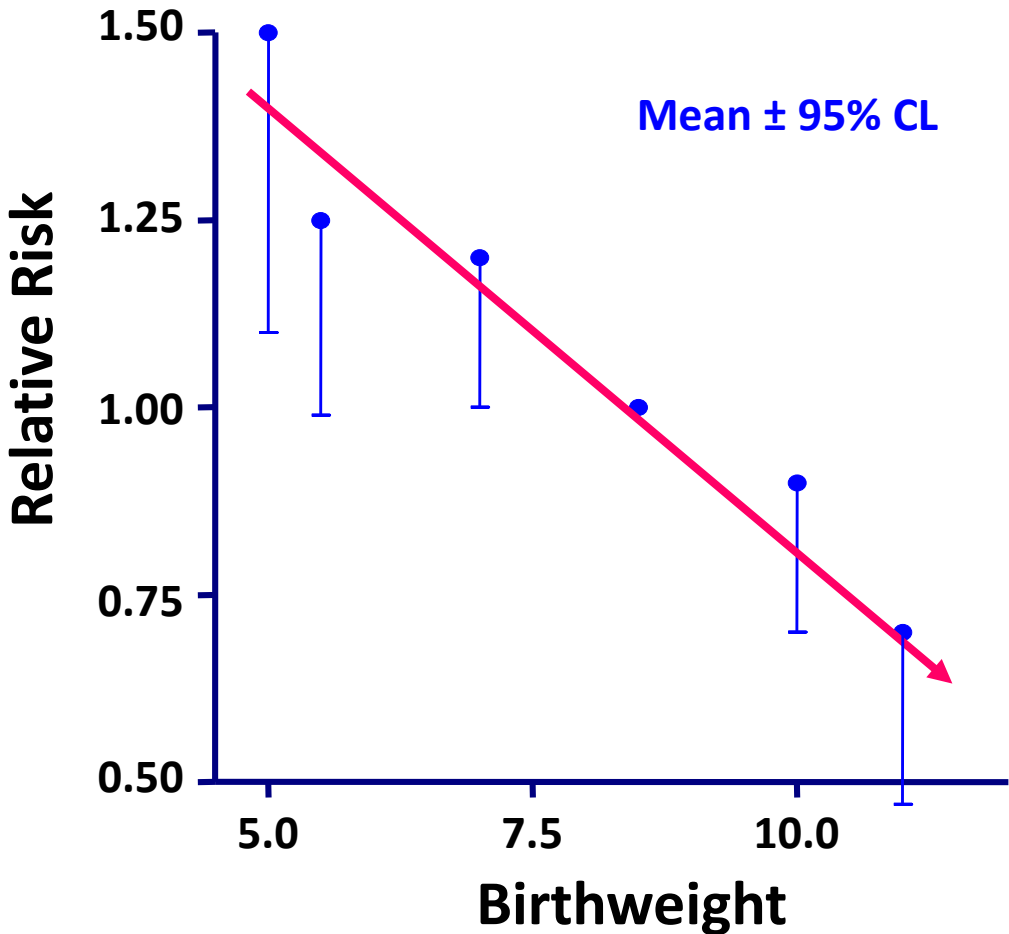
Birth/Infancy (Low Birth weight)



Childhood to Adult (Metabolic to
Cardiovascular diseases)



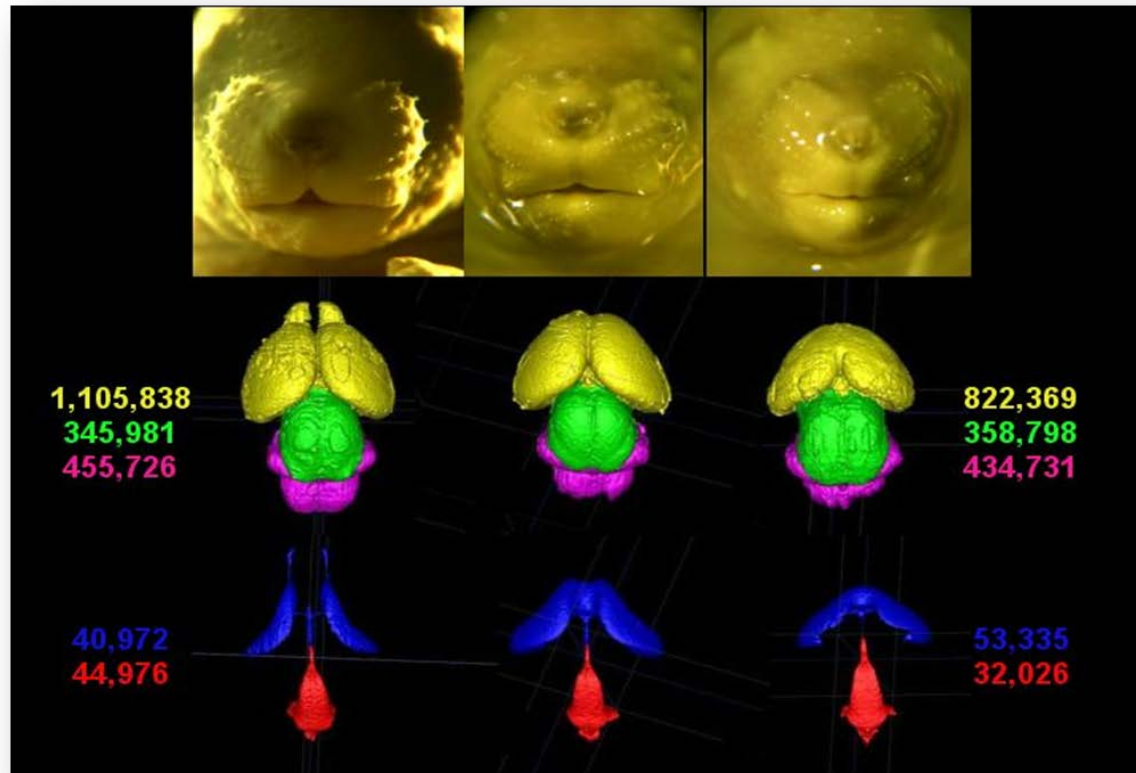
Relative Risk For Coronary Heart Disease, Stroke And Low Birth Weight



121,700 American Nurses, self report study BMJ 315:396,1997

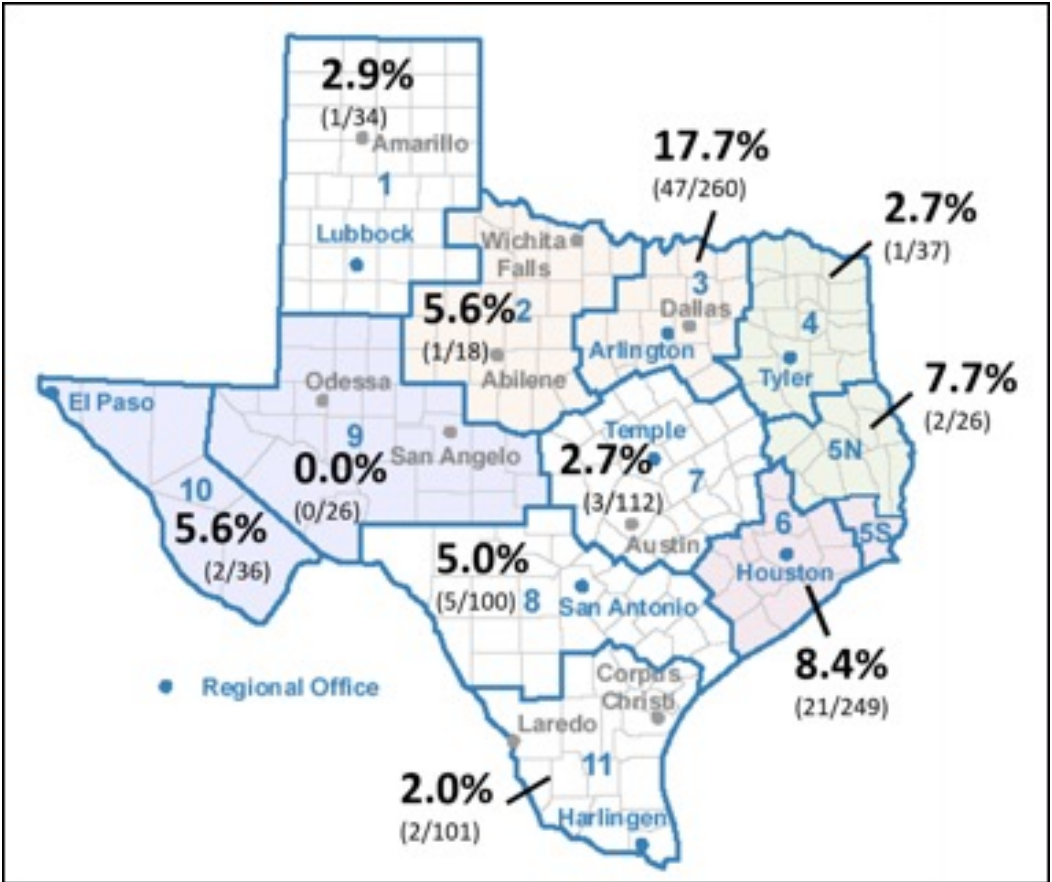
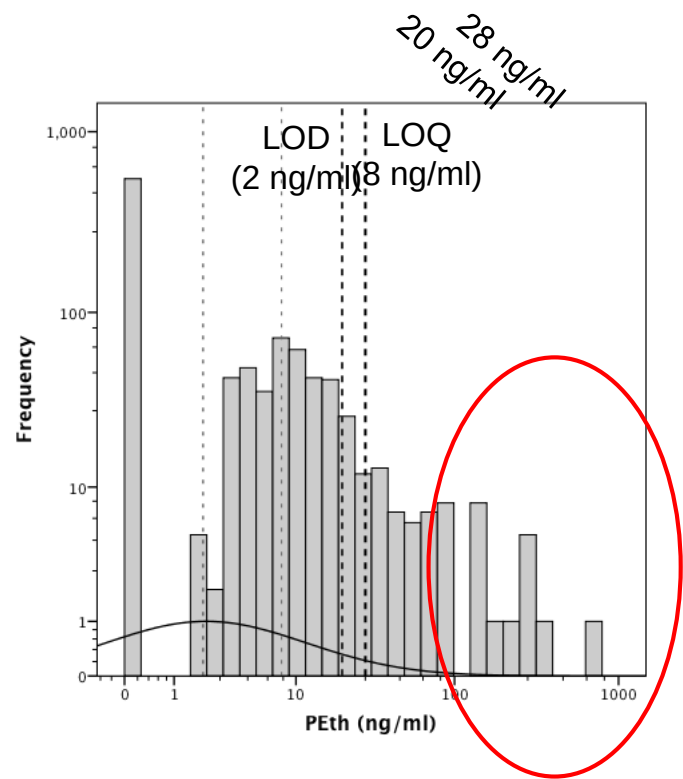


Face and Brain in FASD





Prevalance of PAE in the State of Texas as Assessed by Phosphatidylethanol in Newborn Dried Blood Spot Specimens



HEALTH SCIENCE CENTER
TEXAS A&M UNIVERSITY



Texas Office for Prevention
of Developmental Disabilities
Minding the Minds of Children



THE UNIVERSITY of
NEW MEXICO



Long term effects of low dose prenatal alcohol

Modest fetal growth restriction

(Probyn et al, Repro Fertil Dev, 2012)

Growth deficits in later life (males)

(Probyn et al, Repro Fertil Dev, 2012)

Changes in mammary–lactation

(Probyn et al, Am J Physiol; 2013)

Increased anxiety but no impairments in learning & memory

(Cullen et al, PLoS One, 2013; PLoS one 2014)

Increased fibrosis in the lung

(Probyn et al, J DOHaD, 2014)

Altered metabolic function

(Probyn et al, PLoS One, 2013)

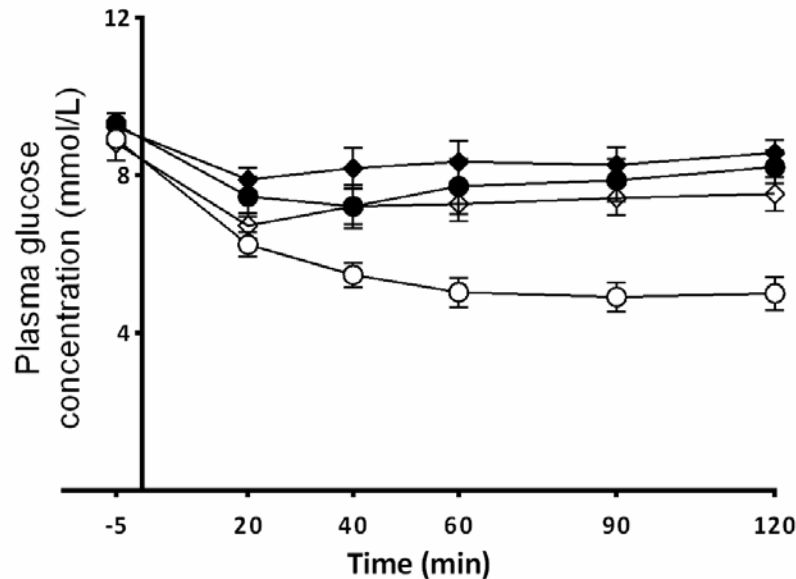
Impaired cardiac function and altered heart structure

(Nguyen et al, Physiol Rep. 2014)

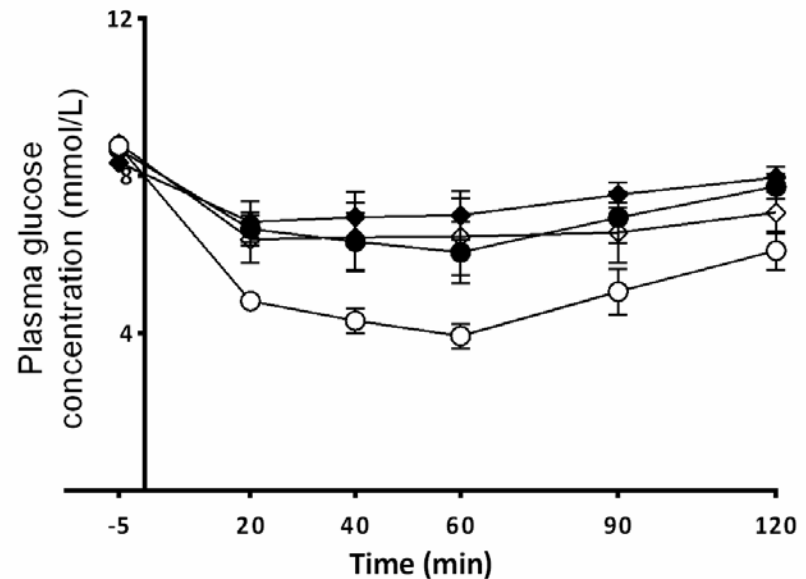


Alcohol around conception causes insulin resistance in male and female offspring at 8 months

MALES



FEMALES



- control control
- control HIF
- ◇ EtOH control
- ◆ EtOH HIF

Gardebjer et al., FASEB 2015



Early Cardiovascular Effects of Prenatal Alcohol Exposure (PAE)



Acute Alcohol Exposure Model



↓

**Ultrasound
imaging- pre**

↓

**Alcohol treatment
(intragastric gavage)**

↓

**Ultrasound
imaging-post**

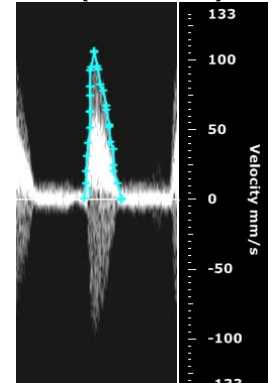
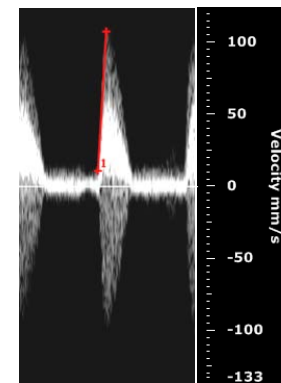
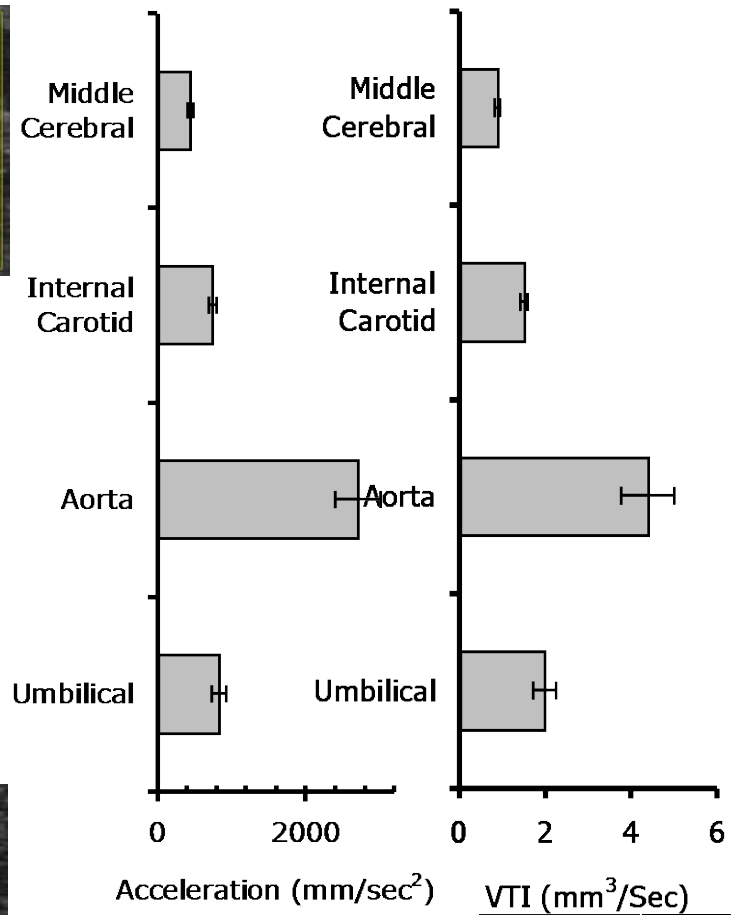
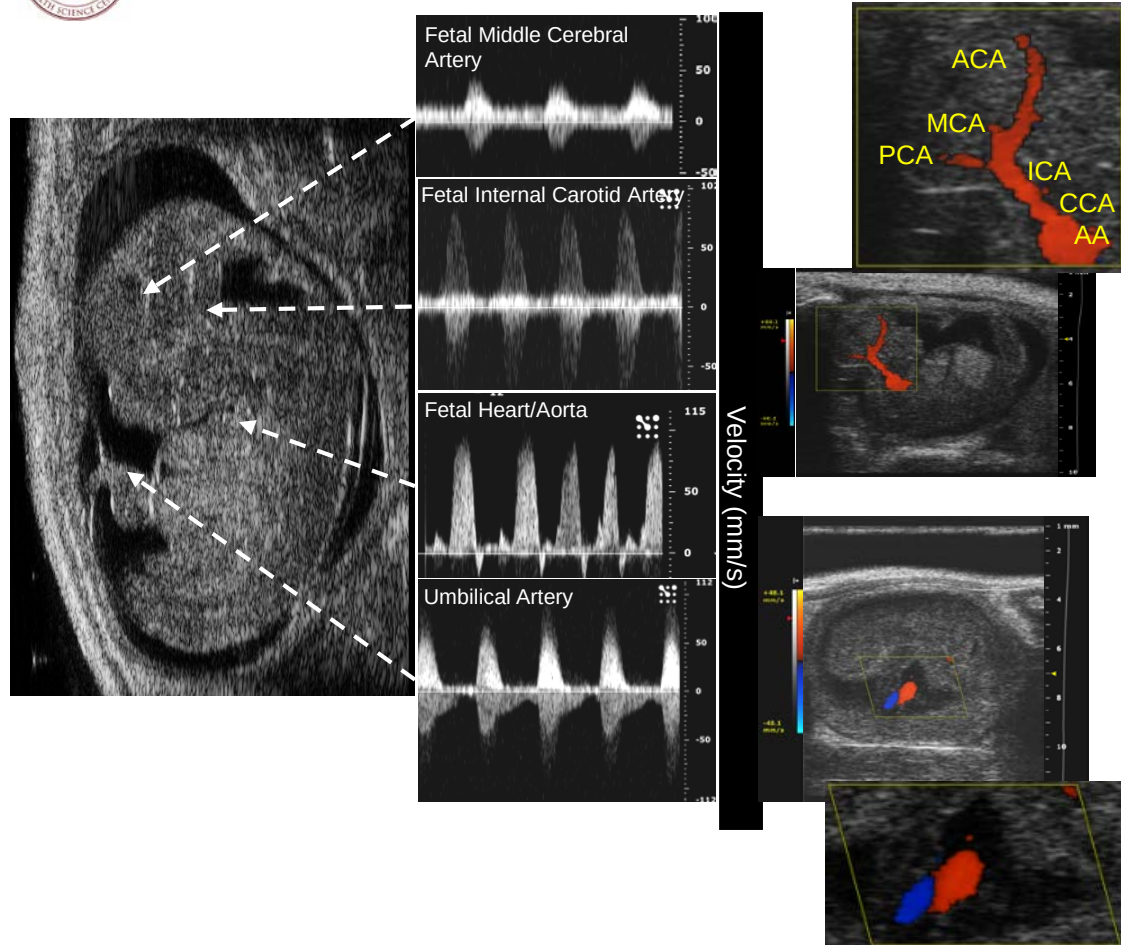


Ultrasound Imaging- Fetal Blood Flow Analysis



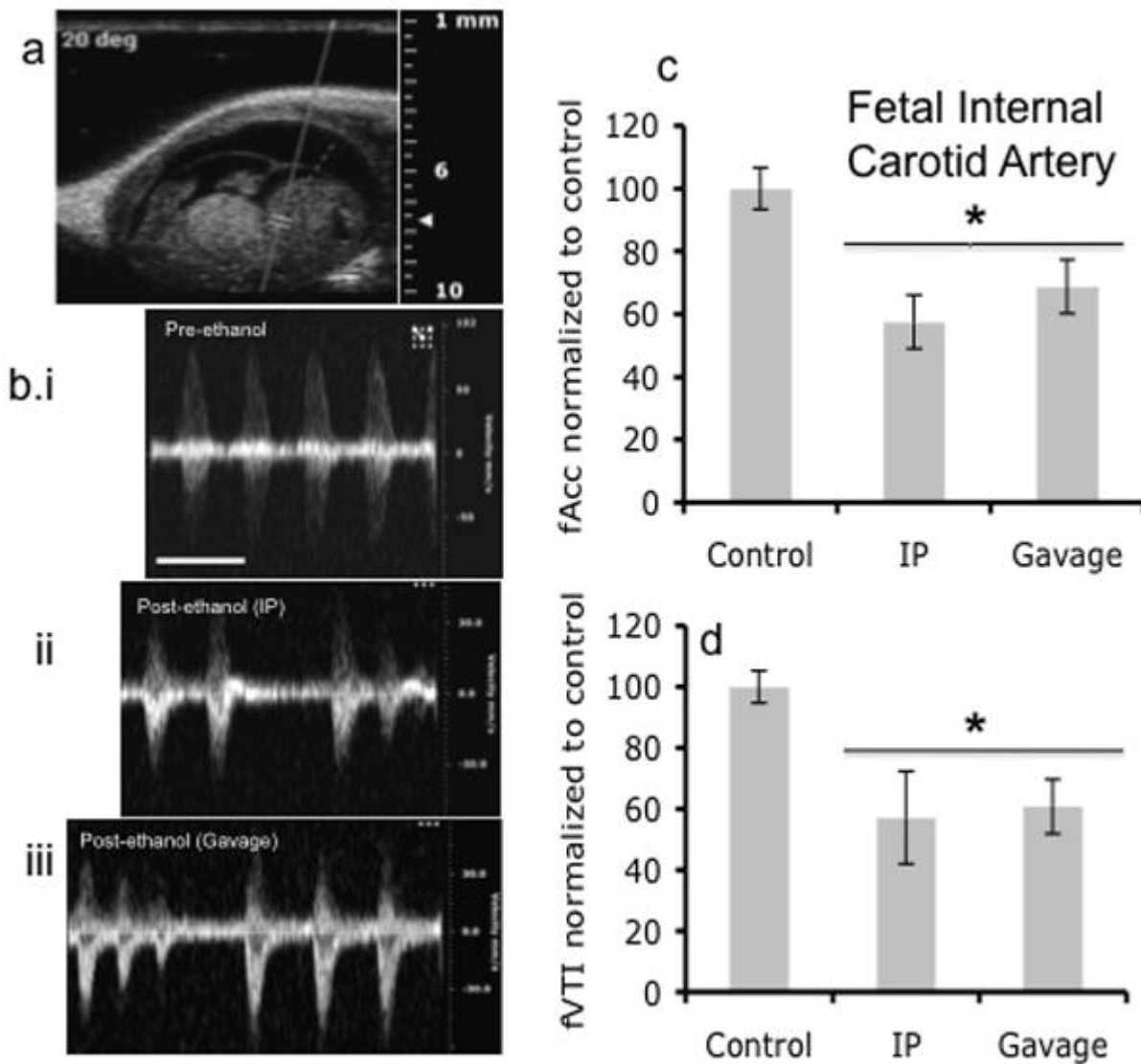


Ultrasound imaging- Fetal Blood flow analysis



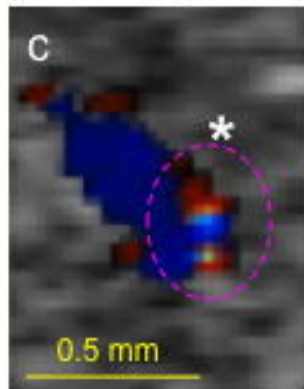
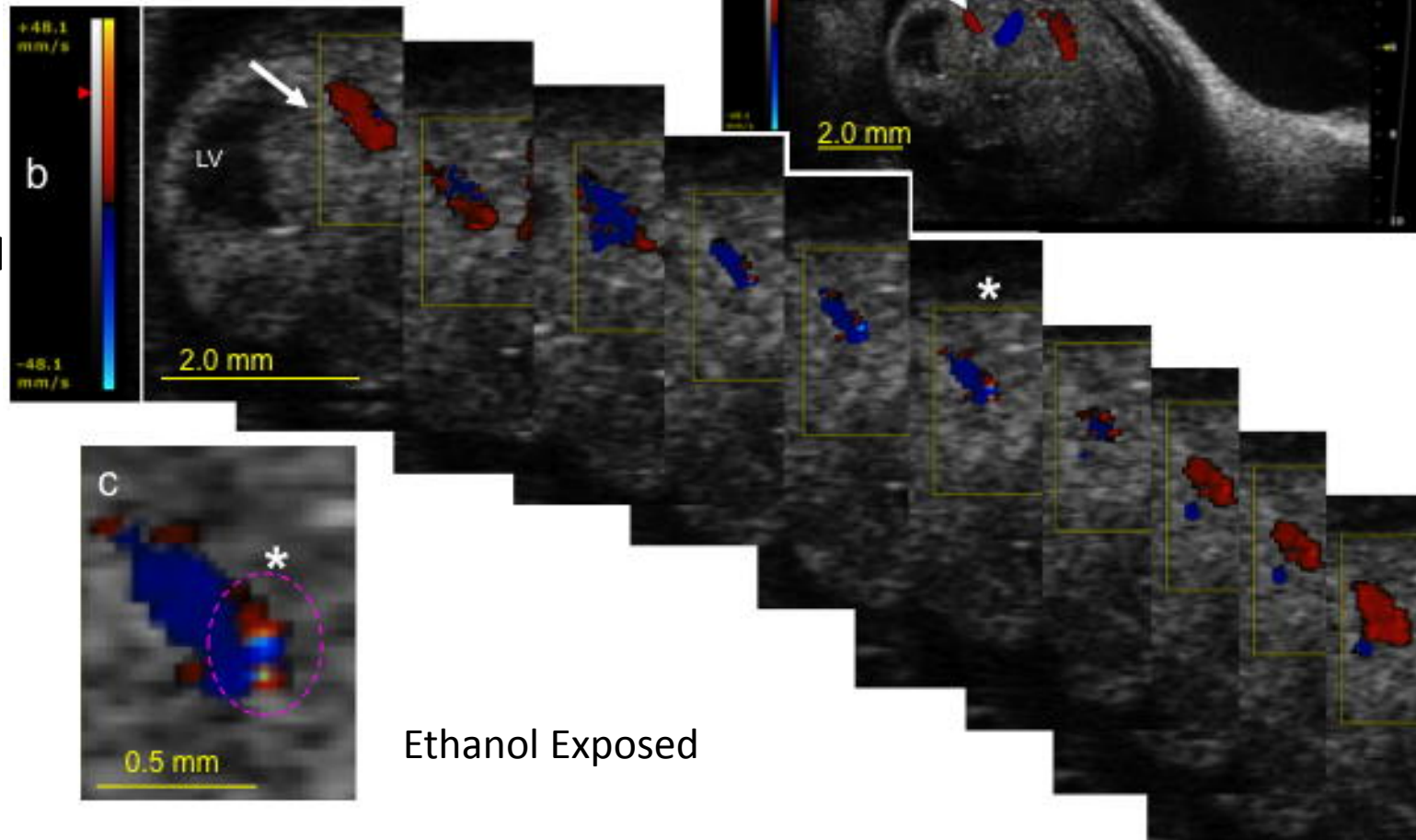
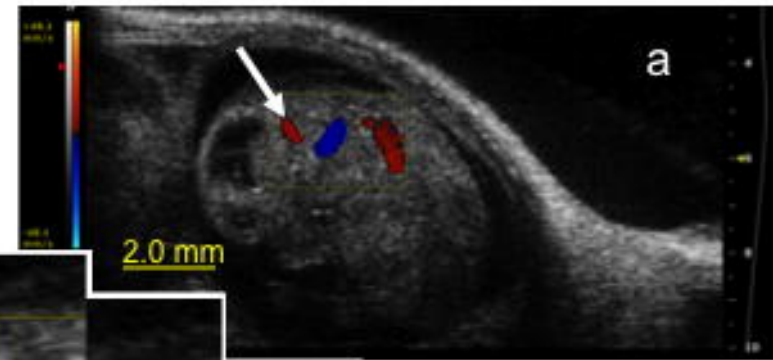


Early Effects of PAE



PAE Is Associated with Flow Reversal

Control



Ethanol exposed

Ethanol Exposed



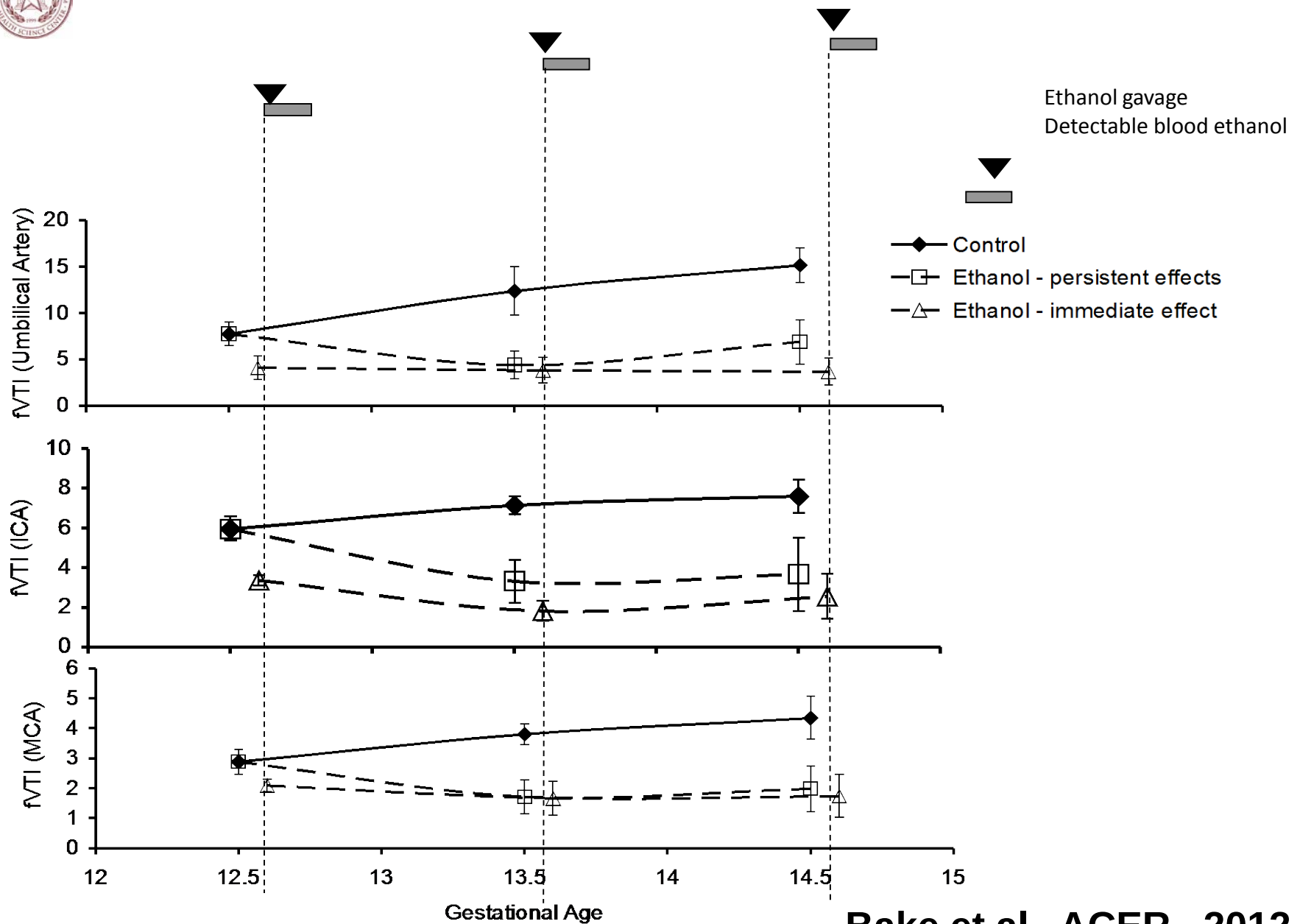
Summary

A single dose of ethanol significantly reduced blood flow in the developing fetus

- Middle cerebral artery
- Internal Carotid Artery
- Aorta
- Umbilical artery



Short-term effect of single dose of ethanol

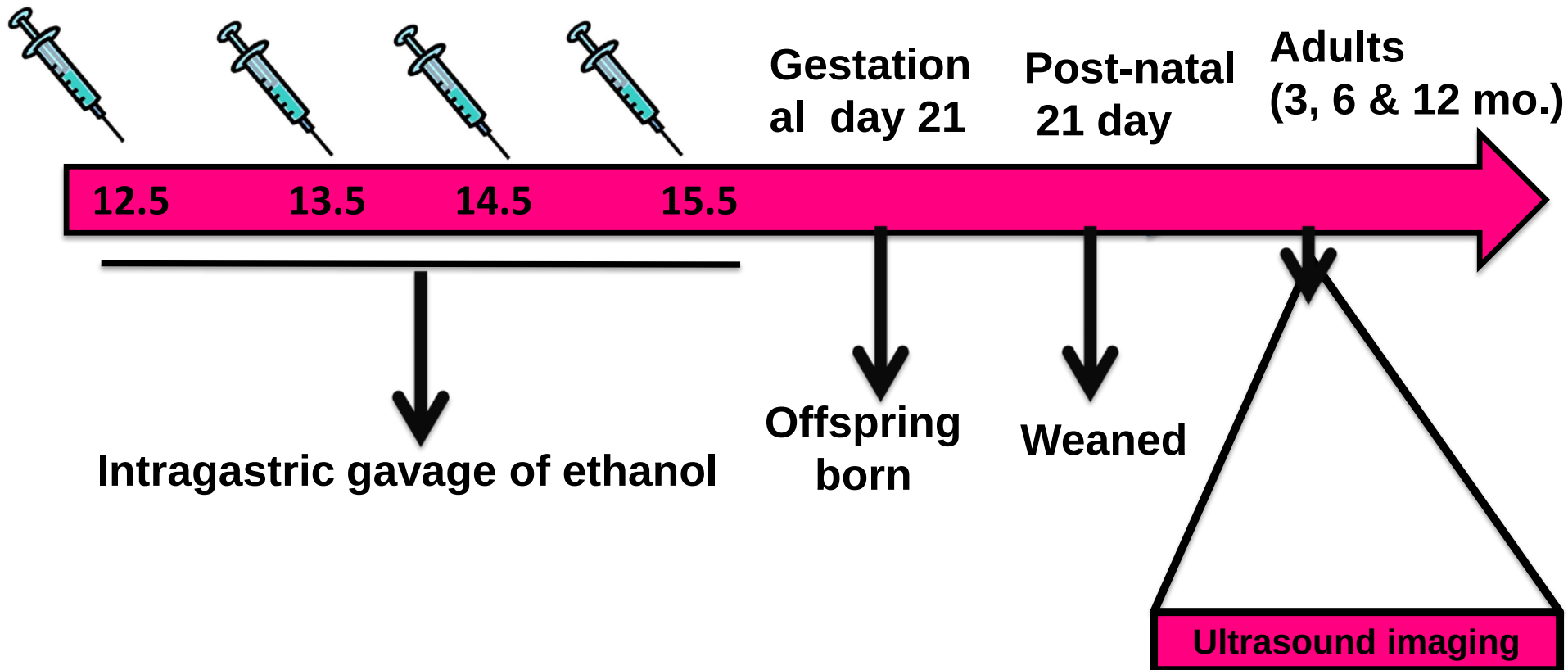




Effects of Prenatal Alcohol Exposure Persist Across A Lifetime

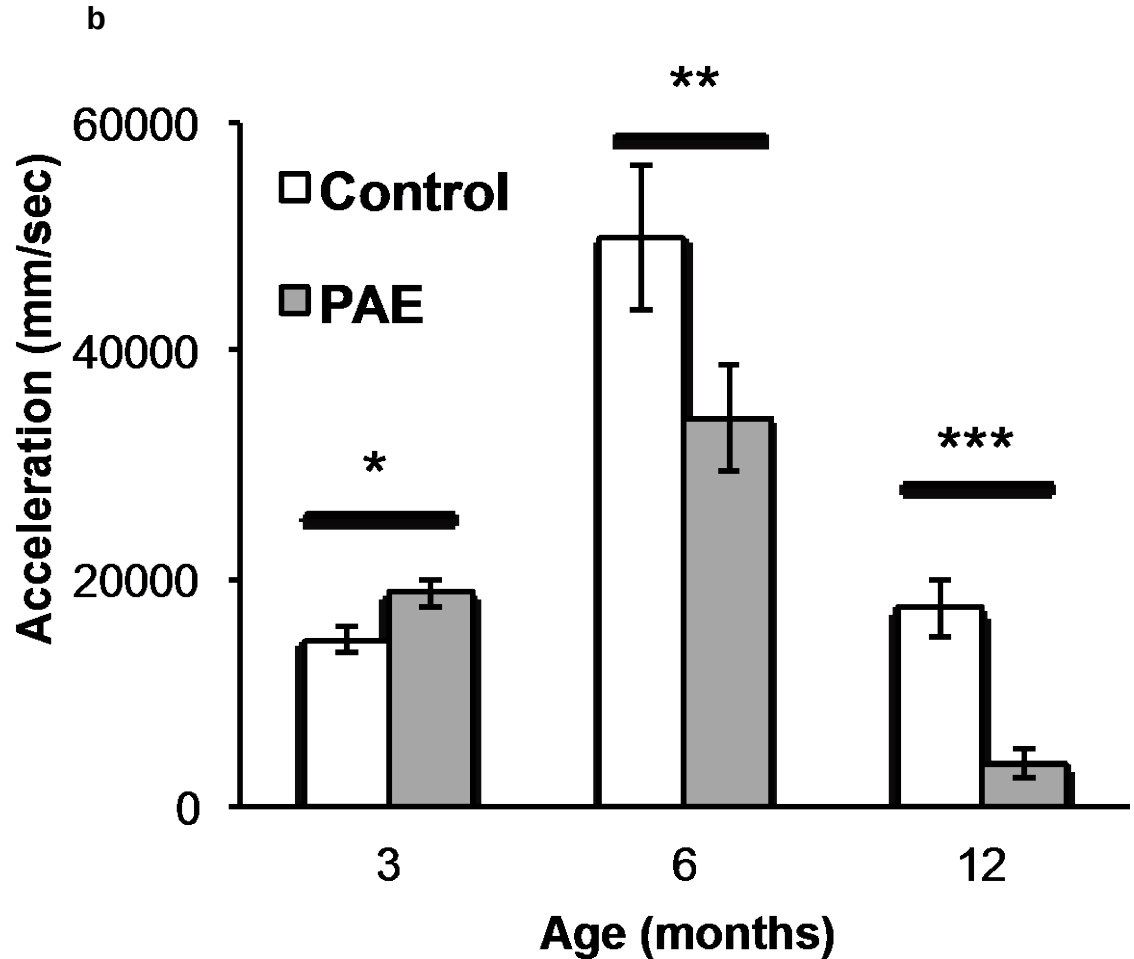
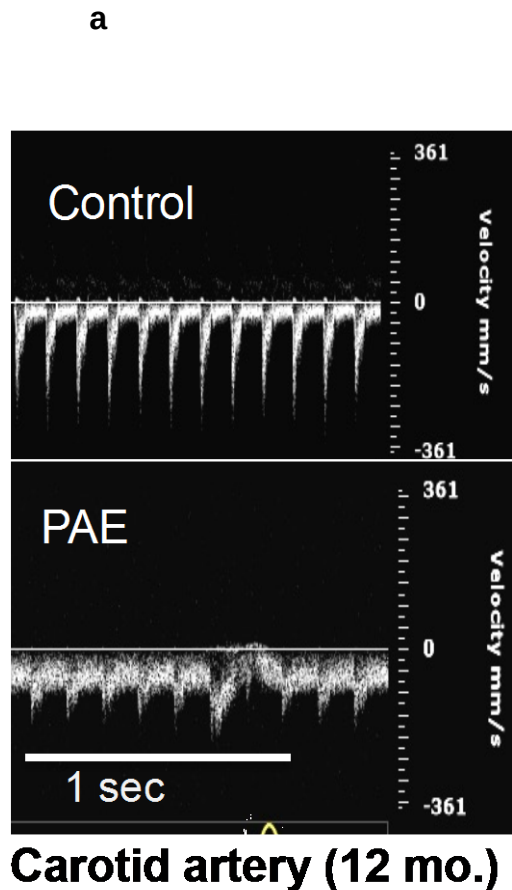


Multiple Binge Exposure Model





Effects of 1st trimester-equivalent exposure on late cardiovascular effects on the offspring





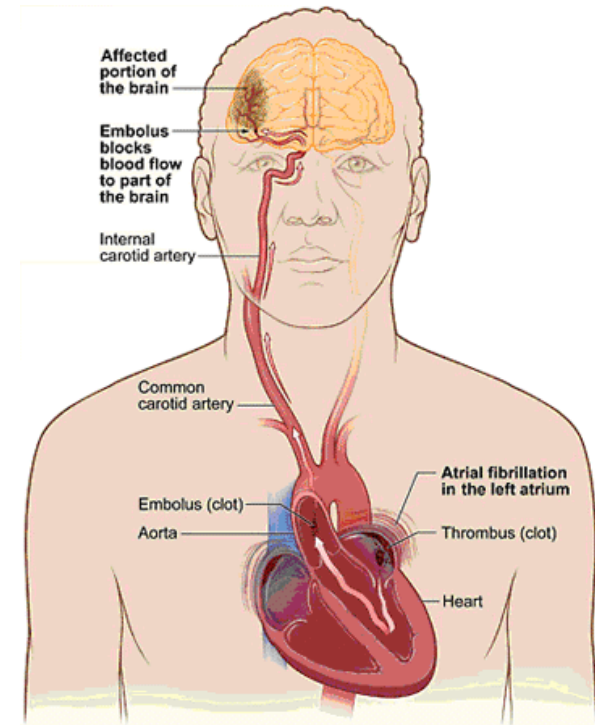
Summary

Fetal alcohol exposed adults showed region specific blood flow acceleration in

1. Carotid artery ✓
2. Intra-renal (lobar) artery ✓
3. Renal artery X
4. Femoral Artery X



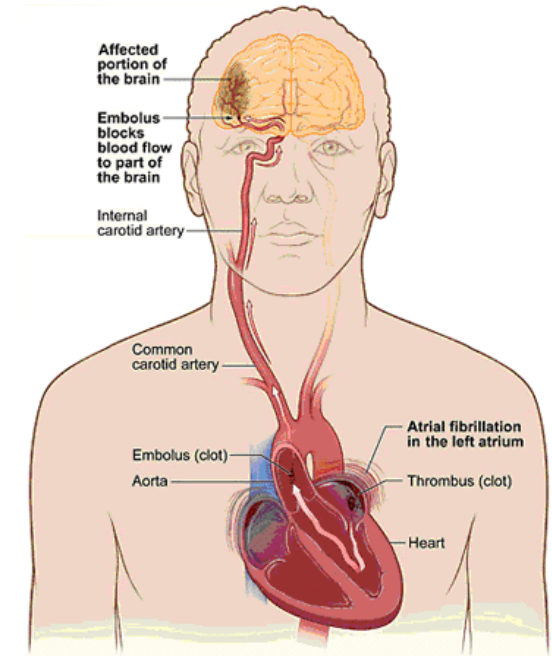
Do early developmental life events affect outcomes from cardiovascular/cerebrovascular disease?





Stroke Epidemiology

- Stroke is the 5th leading cause of death and the leading cause of long term disability
- Yearly cost of \$74 billion for stroke care
- 795,000 people will experience a new or recurrent stroke
- Sharp increase in stroke in young adults of both sexes (Ramirez et al., 2016; Tibaek et al., 2016).





Experimental Plan

**Prenatal Alcohol
Exposure**



Second Hit

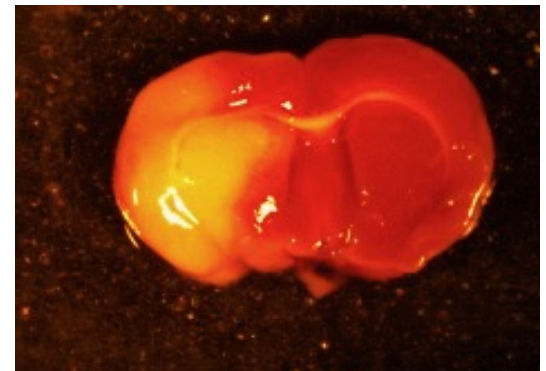
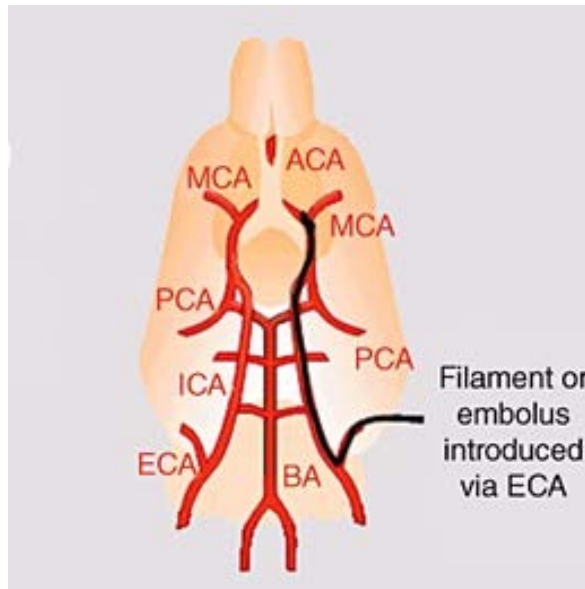
MCA occlusion at 3 mo.



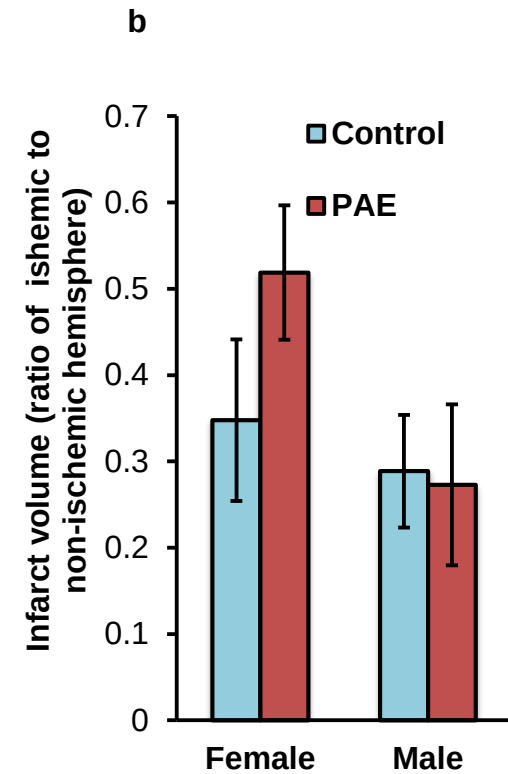
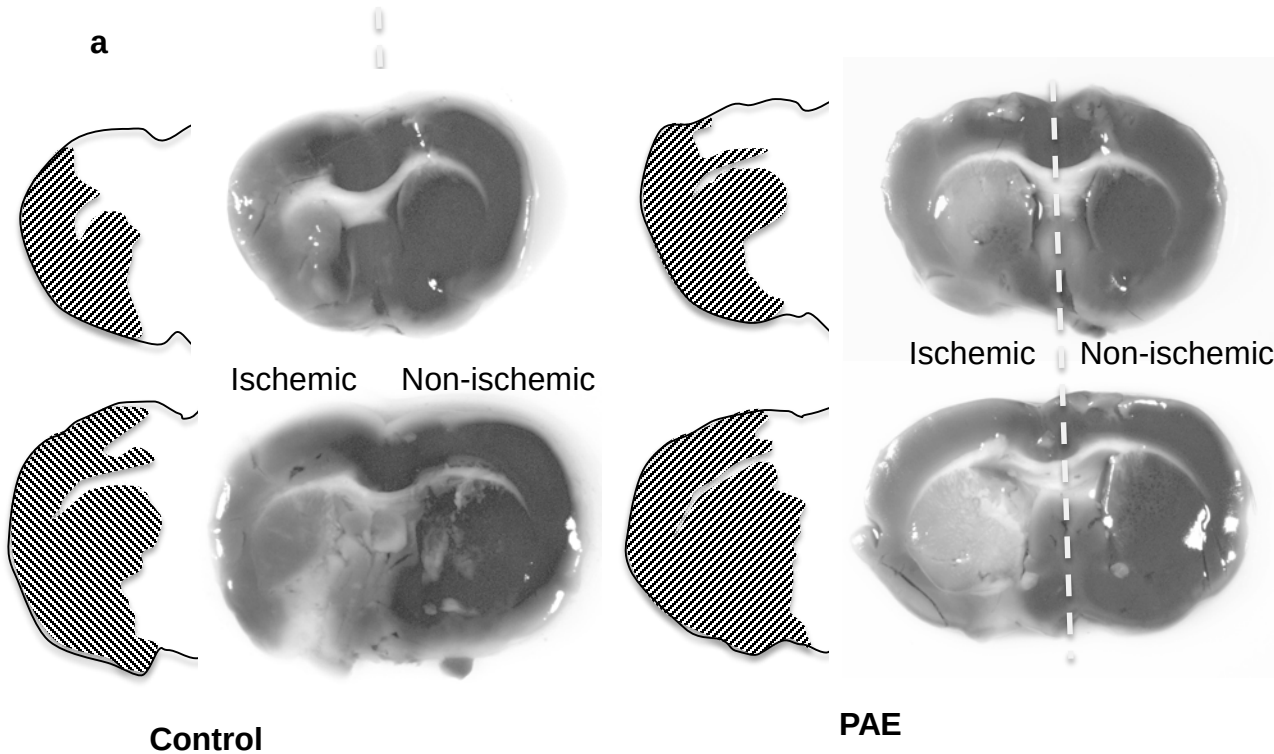
**24h post
stroke**



- Infarct analysis
- Behavioral tests



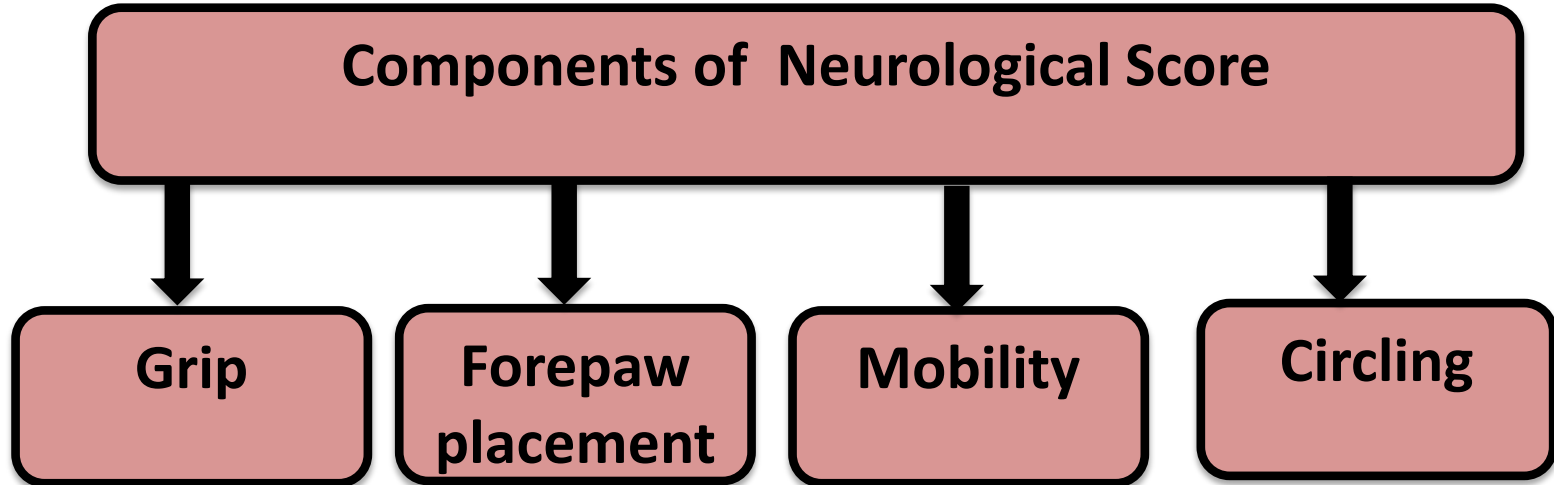
Impact of PAE on Brain infarction





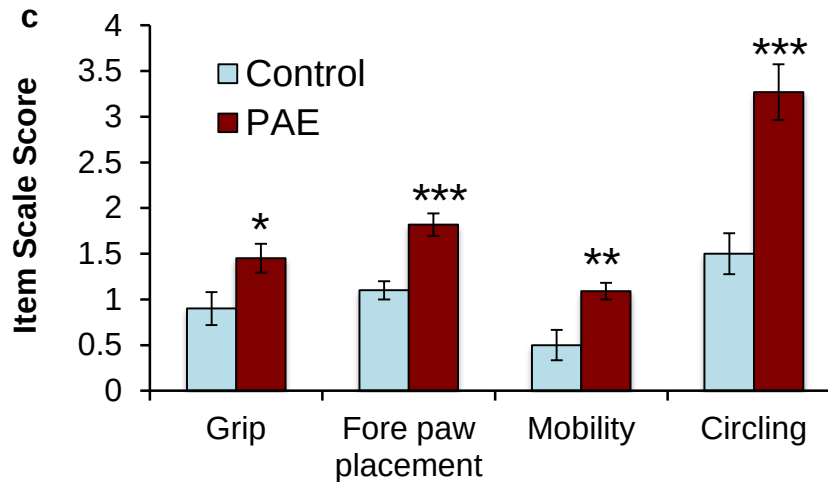
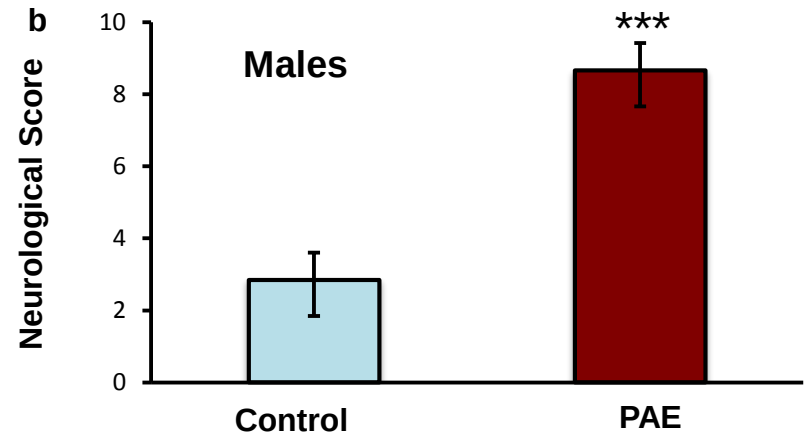
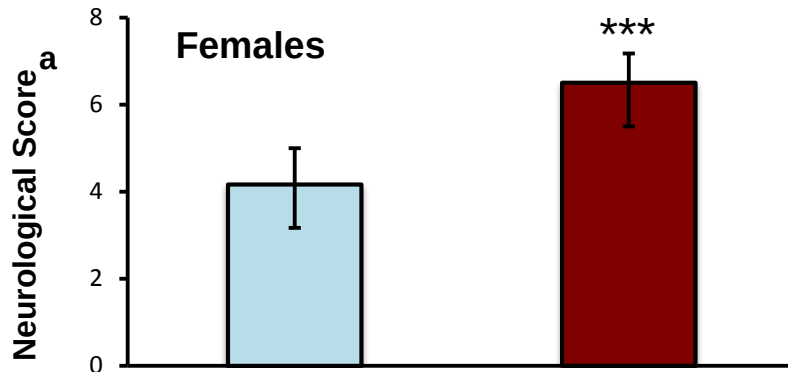
Neurological Status

Neurological Severity Score: A tool used by investigators to assess multiple deficits induced by stroke in animals.



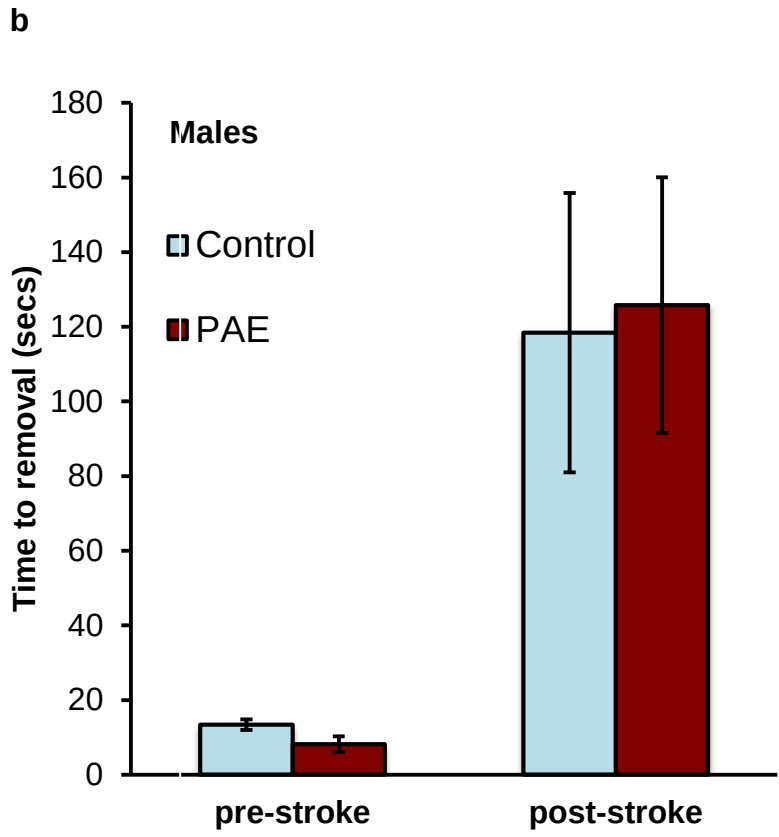
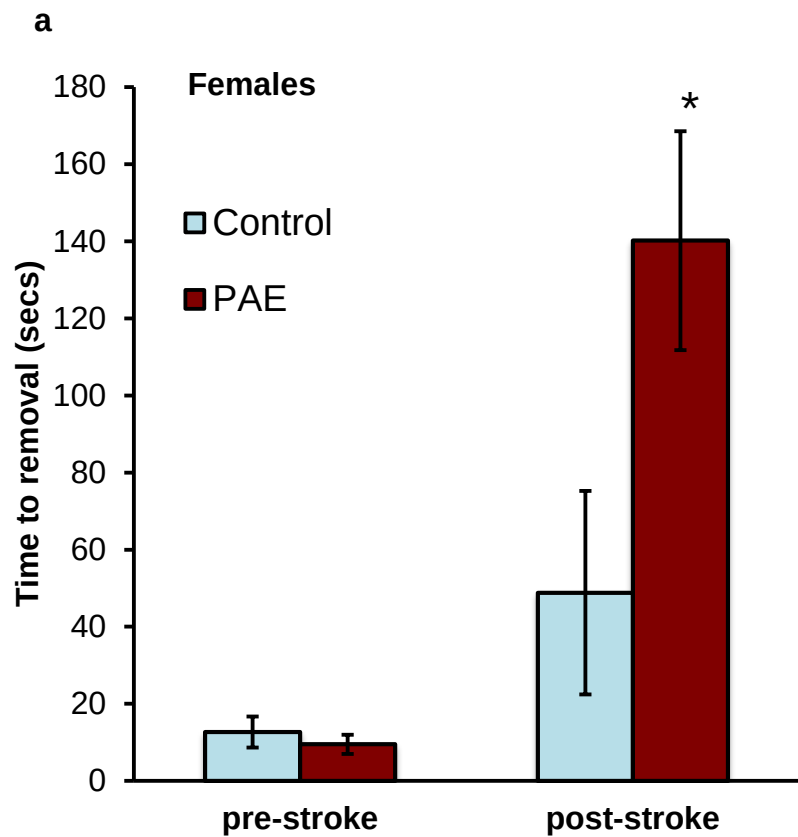


Post-stroke Neurological Scores in Young Adult PAE mice





Sensorimotor Function: Adhesive Removal Test





Conclusions

- ◆ **Doppler ultrasound analysis: Prenatal ethanol exposure resulted in significant arterial resistance in carotid arteries of young mice but hypoperfusion in middle-aged mice**
- ◆ **MCAo in fetal alcohol exposed adults caused severe neurological deficits at 24 h post-stroke as evidenced by high neurological scores.**
- ◆ **Prenatal ethanol exposure persistently alters vascular function and impairs post stroke recovery.**
- ◆ **We need to be better prepared to anticipate the outcomes of adult onset diseases in the FASD population and to strategically plan prevention and rehabilitation strategies.**

Acknowledgements

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