HARVARD T.H. CHAN
SCHOOL OF PUBLIC HEALTH

Generation R

Population Neuroscience: Research that matters for public health

Family meeting, September 2023

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Overview

- Research until now. Selected examples
- Research ongoing & plans

Learning objectives

- The impact of prenatal exposures on brain development
- The importance of time and timing (life course epidemiology)
- Identify how child neuroimaging might impact public health

Clinical utility

- Genetics: “not really, not yet, not in most cases”

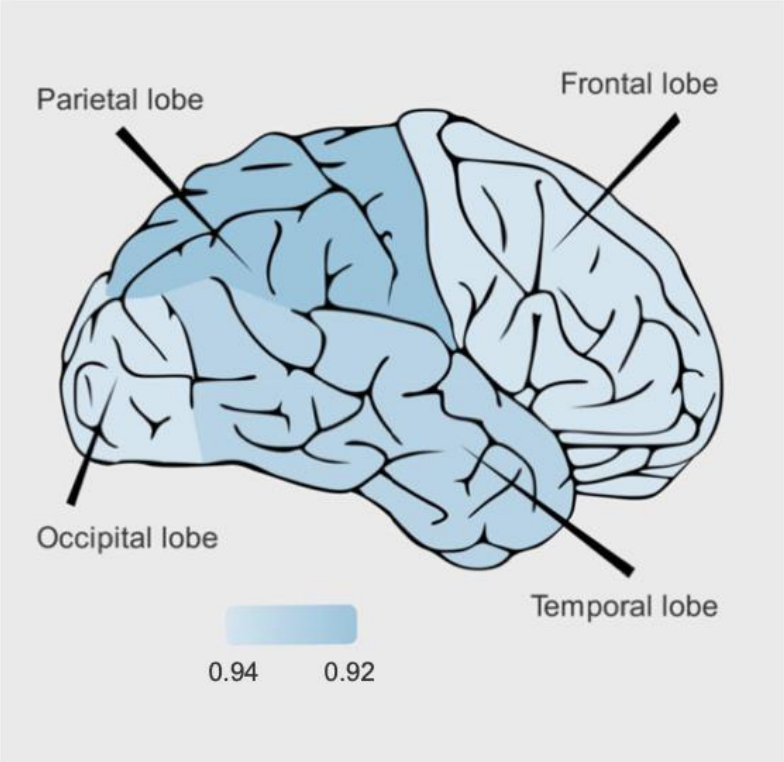
- Brain Imaging in child psychiatry?

  one example only

Does brain imaging help predict adolescent psychotic-like experiences or hallucinations?

- at age 10 years, some in 24%
- at age 14 years, some in 11%
- study in 2042 adolescents with repeated imaging

Smaller baseline grey matter volume is longitudinally related to persistence of hallucinations



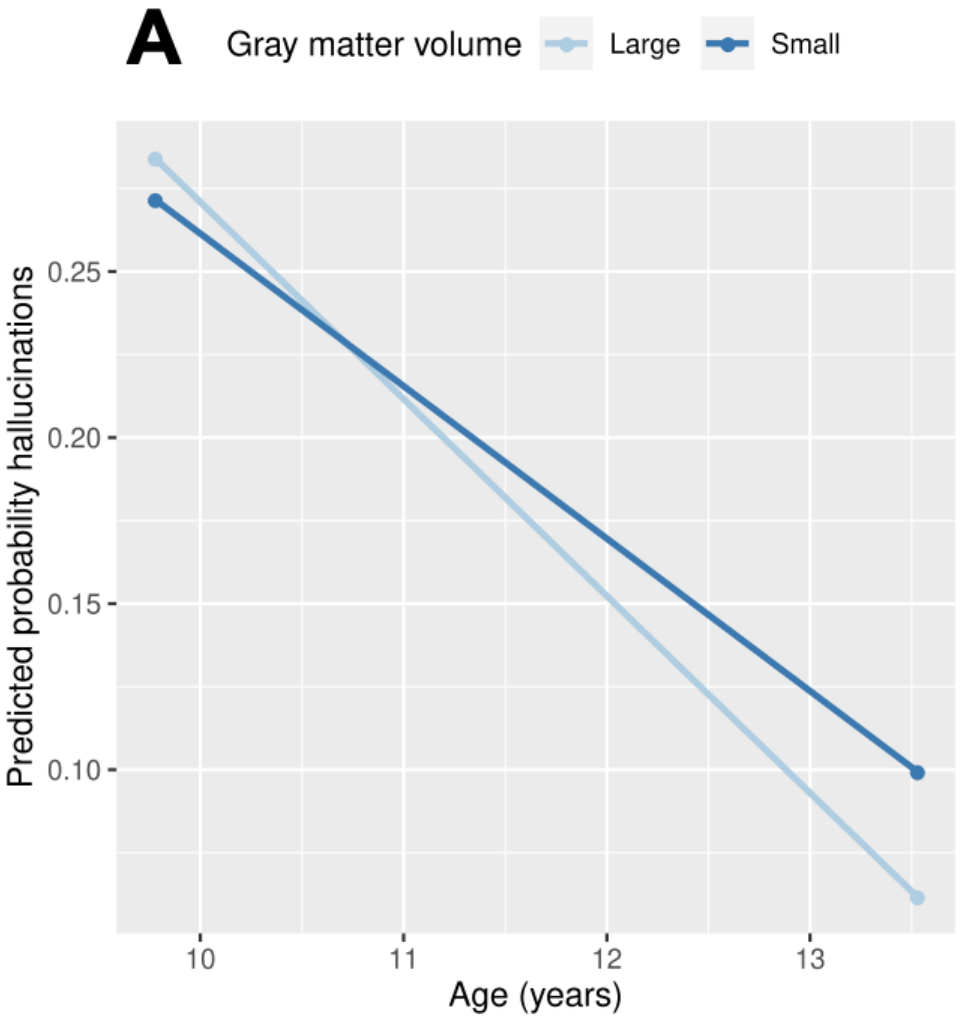
Lobar gray matter volumes related to the persistence of hallucinations. Darker colors indicate stronger associations (expressed in odds ratios, interaction with time).

Steenkamp, ..,Tiemeier, Kushner Biol Psychiat 2022

Grey matter volume is longitudinally related to persistence of hallucinations: 2042 adolescents

No added value
of repeated imaging measures:
No association of baseline symptoms
with change in brain volumes

Exciting question, good data but clinical value?
small effects and unspecific
for brain and for psychiatric outcome



Steenkamp, ..,Tiemeier, Kushner. Biol Psychiat 2022

Focus of this talk: child brain imaging

- **Population Neuroscience**

  an emerging field of research defined by the intersection of neuroscience with epidemiology

- **Prenatal Exposures**

  to environmental chemicals and psychosocial stressors during pregnancy are associated with adverse birth outcomes and neurodevelopment.

Prenatal exposures

Can we identify important intrauterine influences on child development for MCH practice or public health ?

Prenatal exposures

Selected maternal risk factors

- **Depression**
- Stress
- **Antidepressant use: SSRI**
- Diet: Fatty acids
- **Poverty**
- Smoking or cannabis use
- **Thyroid deficiency**
- Folate intake
- Vitamin D deficiency
- **Environmental toxins**, i.e. Organophosphates, Trans-fatty acids

Design Generation R

- Prospective cohort design
- From early foetal life
- 9,778 mothers and their children
- Urban, multi-ethnic population
- Baseline response: 62%

Overview of design and assessments

Ultrasound Measures

Blood (mother, father and child)

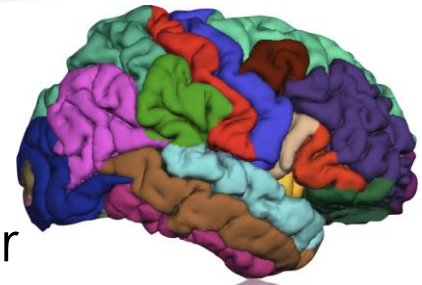
Questionnaires

Child Behavior (mother and father and teacher)

Child Cognition

MRI

N=1070 N=4050 N=3250



Neurodevelopment

Motor development

ADHD, autism and problem behavior

IQ and cognition

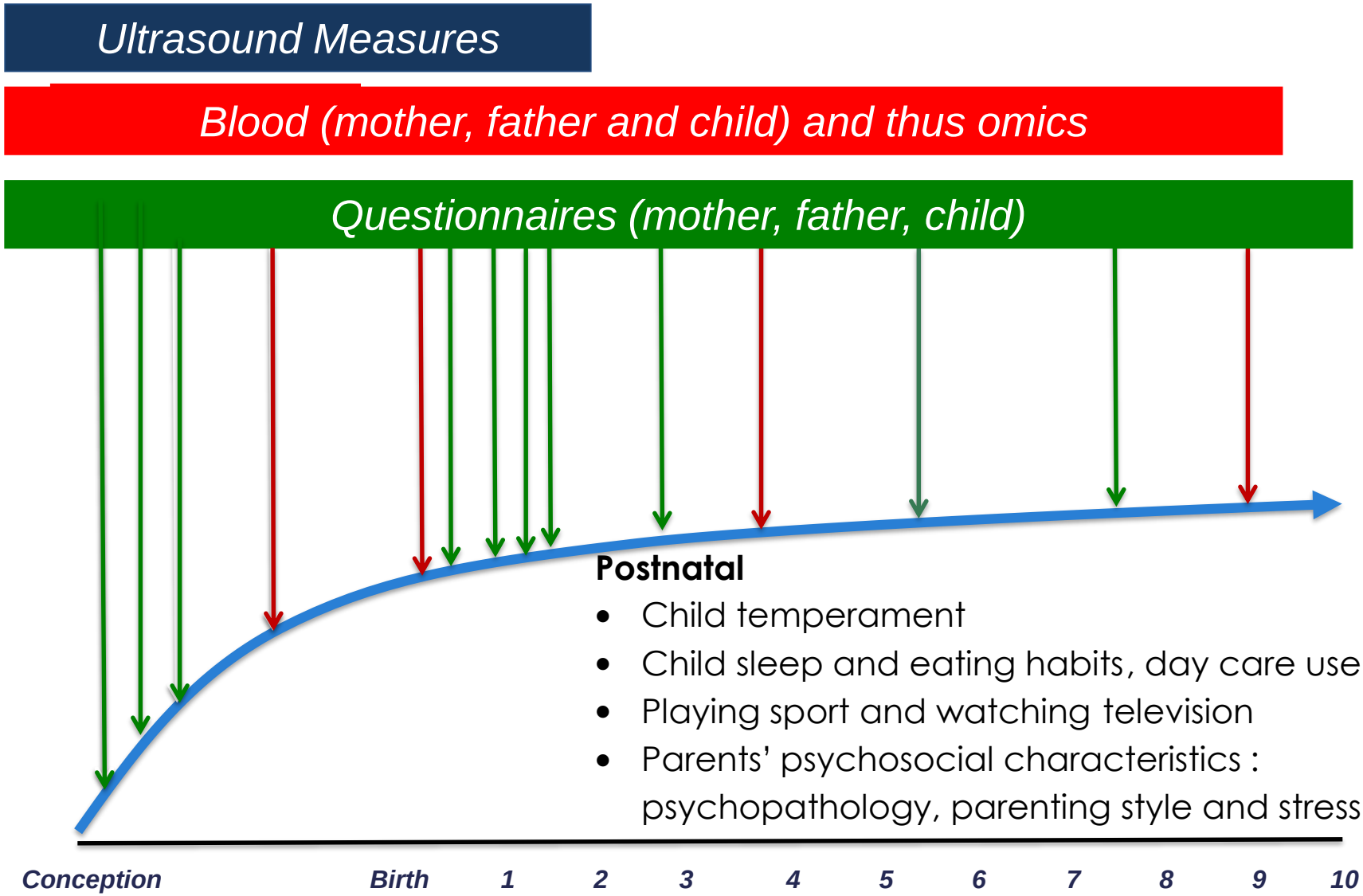
Brain structural and functional development

Conception Birth 1 2 3 4 5 6 7 8 9 10 13 15

Maternal Depression I Timing

Maternal depressive symptoms from fetal life forward and child brain structure at age 10 years

Overview of design and assessments



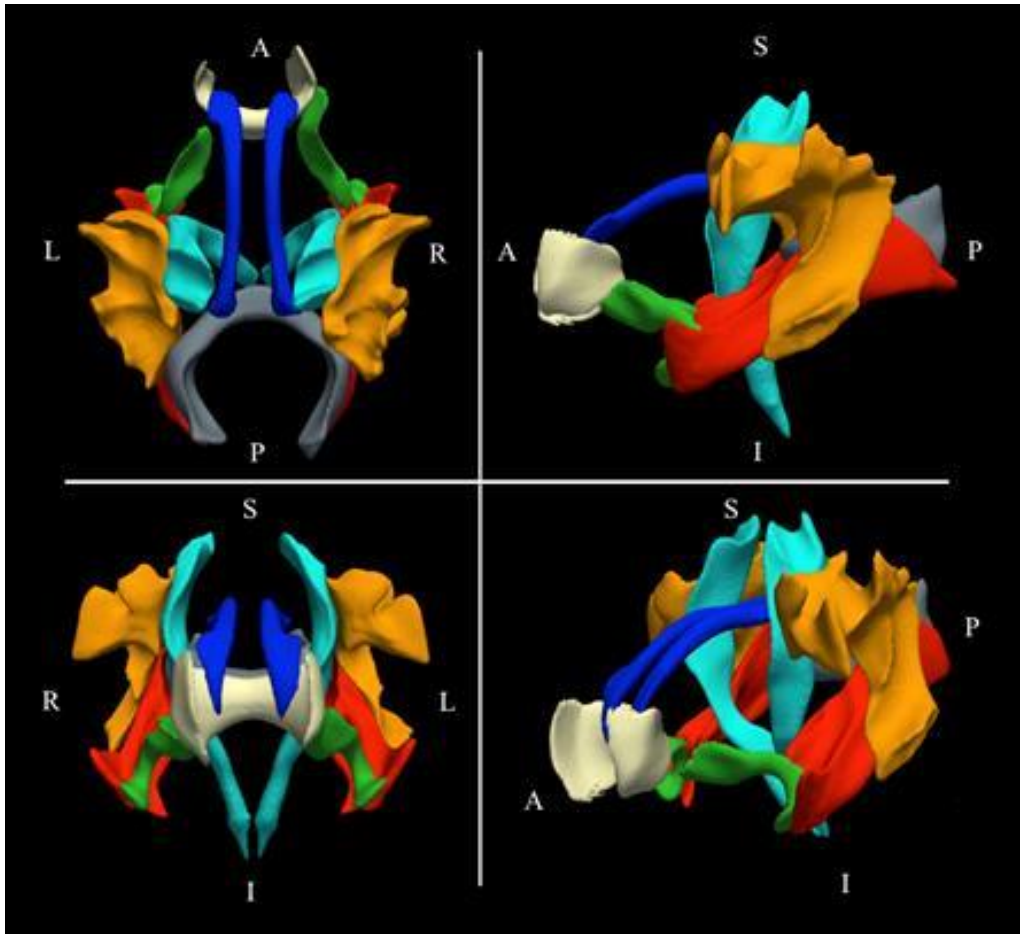
Maternal depressive symptoms at different time points (n>2000)

Maternal depressive symptoms	Global brain volumes (cm^3)			
	Total White Matter		**Total Gray Matter**	
	B (95% CI)	p-value	B (95% CI)	p-value
Prenatal 20 weeks (n=2348)				
	-1.89 (-6.21, 2.43)	.39	-2.32 (-7.75, 3.11)	.40
Postnatal 2 months (n=2083)				
	-3.23 (-7.46, 1.00)	.14	-7.36 (-12.61,-2.12)	.006#
Child 3 years (n=2207)				
	-1.36 (-7.06, 4.35)	.64	0.82 (-6.28, 7.92)	.82
Child 9 years (n=2676)				
	-1.94 (-5.98, 2.11)	.35	-2.17 (-7.22, 2.88)	.40

Model 2 adjusted for child age at scan, child gender, mother age at intake, ethnicity, prenatal maternal education, marriage (partner) status, mother BMI intake, child birth weight, maternal smoking and alcohol intake.

Zou et al, AJP 2019

Brain connectivity or white matter microstructure



Tracts are group average representations in standard coordinate space.

blue	*cingulum bundle*
gray	*forceps major*
tan	*forceps minor*
red	*inferior longitudinal fasciculus*
orange	*superior long. fasciculus,*
green	*uncinate fasciculus*

R = Right, L = Left, A = Anterior, P = Posterior, I = Inferior, S = Superior

Single time point maternal depression and global white matter infrastructure (DTI) age 9 years

Symptom assessment

Time point	Model	Global FA B	95% CI	P
Prenatal (n=2243)	3	-0.07	(-0.27, 0.11)	0.44
Postnatal 2m (n=2037)	3	-0.22	(-0.41, -0.04)	0.02
Postnatal 3y (n=2183)	3	-0.04	(-0.29, 0.20)	0.74
Postnatal 9y (n=2577)	3	-0.07	(-0.25, 0.10)	0.40

Microstructure and measure of connectivity

Model 1 no covariates.

Model 3 additionally adjusted for child age at scan, child gender, mother age at intake, ethnicity, prenatal maternal education, marriage (partner) status, mother BMI intake, child birth weight, maternal smoking and alcohol intake.

Zou et al, AJP 2019

A commentary: confounding

Maternal Depression and Child Development: Clues to Causal Mechanisms From Potential Confounders

Deanna M. Barch, Ph.D., Cynthia Rogers, M.D.

This issue of the *Journal* includes an important study by Zou and colleagues (1) examining the relationships of prenatal and postnatal (2 months, 3 years, and 10 years) maternal

The authors also raise the possibility that the severity of maternal depression in the postnatal period may be a marker for overall increased maternal depression across offspring

et al. conducted analyses with statistical models
nd did not include covariates representing poten-
ounders that
own effects on
elopment and
including ma-
ucation level,
lcohol use, and
income. These
hemselves can
ctors for both maternal and child depression and

What the authors did not find in the study is, in many ways, as striking and important as what they did find.

Maternal depression and global DTI
Confounding

Time point	Model	Global FA B	95% CI	P
Prenatal (n=2243)	1	-0.28	(-0.46, -0.10)	0.002
	3	-0.07	(-0.27, 0.11)	0.44
Postnatal 2m (n=2037)	1	-0.29	(-0.47, -0.12)	0.001
	3	-0.22	(-0.41, -0.04)	0.02
Postnatal 3y (n=2183)	1	-0.16	(-0.41, 0.08)	0.18
	3	-0.04	(-0.29, 0.20)	0.74
Postnatal 9y (n=2577)	1	-0.18	(-0.35, -0.01)	0.04
	3	-0.07	(-0.25, 0.10)	0.40

Microstructure and measure of connectivity

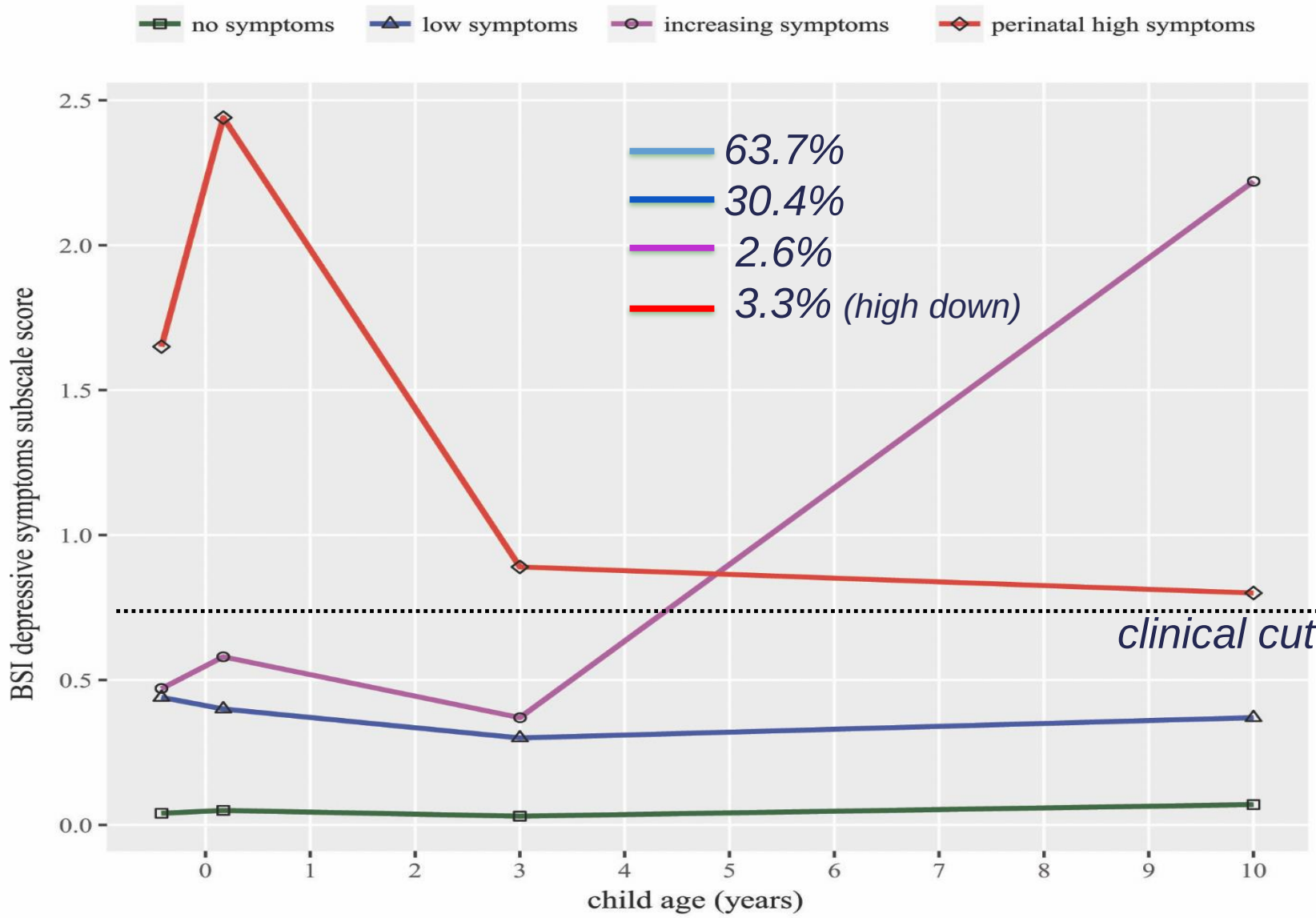
Model 1 no covariates.

Model 3 additionally adjusted for child age at scan, child gender, mother age at intake, ethnicity, prenatal maternal education, marriage (partner) status, mother BMI intake, child birth weight (only postnatal models), maternal smoking and alcohol intake.

Repeatedly measured exposure

- A chance finding?
- Did not study repeatedly measured exposure
- These are non-independent associations
- Typical trajectory, specific groups

Trajectories of maternal depression in 5623 women



Trajectories of maternal depression and brain connectivity in the child

Model	Group	Global FA		
		B	95%CI	P
Model 3	No	Ref	-	-
	Low	-0.14	(-0.30, 0.02)	0.09
	Medium-up	0.21	(-0.37, 0.79)	0.47
	High-down	-0.53	(-1.01, -0.04)	0.034

Model 3 additionally adjusted for child age at scan, gender, maternal ethnicity, maternal age, gestational age at birth, maternal education, marital status, family income, child birth weight, maternal smoking and alcohol intake.

Zou et al, AJP 2019

Critical periods: timing

- Variable exposure is important
- Carry over effects of exposure
- Biological periods of rapid development, a sensitive window
- Candidate exposures for sensitive periods: thyroid hormone, serotonin, vitamin D, hormones

Maternal Depression II and maternal prenatal SSRI use

Time (since exposure)

and timing (adolescence)

Do prenatal exposure effects remain or do the attenuate with age?

ORIGINAL ARTICLE

ONLINE FIRST

Maternal Use of Selective Serotonin Reuptake Inhibitors, Fetal Growth, and Risk of Adverse Birth Outcomes

2012

Hanan El Marroun, PhD; Vincent W. V. Jaddoe, MD, PhD; James J. Hudziak, MD; Sabine J. Roza, MD, PhD; Eric A. P. Steegers, MD, PhD; Albert Hofman, MD, PhD; Frank C. Verhulst, MD, PhD; Tonya J. H. White, MD, PhD; Bruno H. C. Stricker, MD, PhD; Henning Tiemeier, MD, PhD

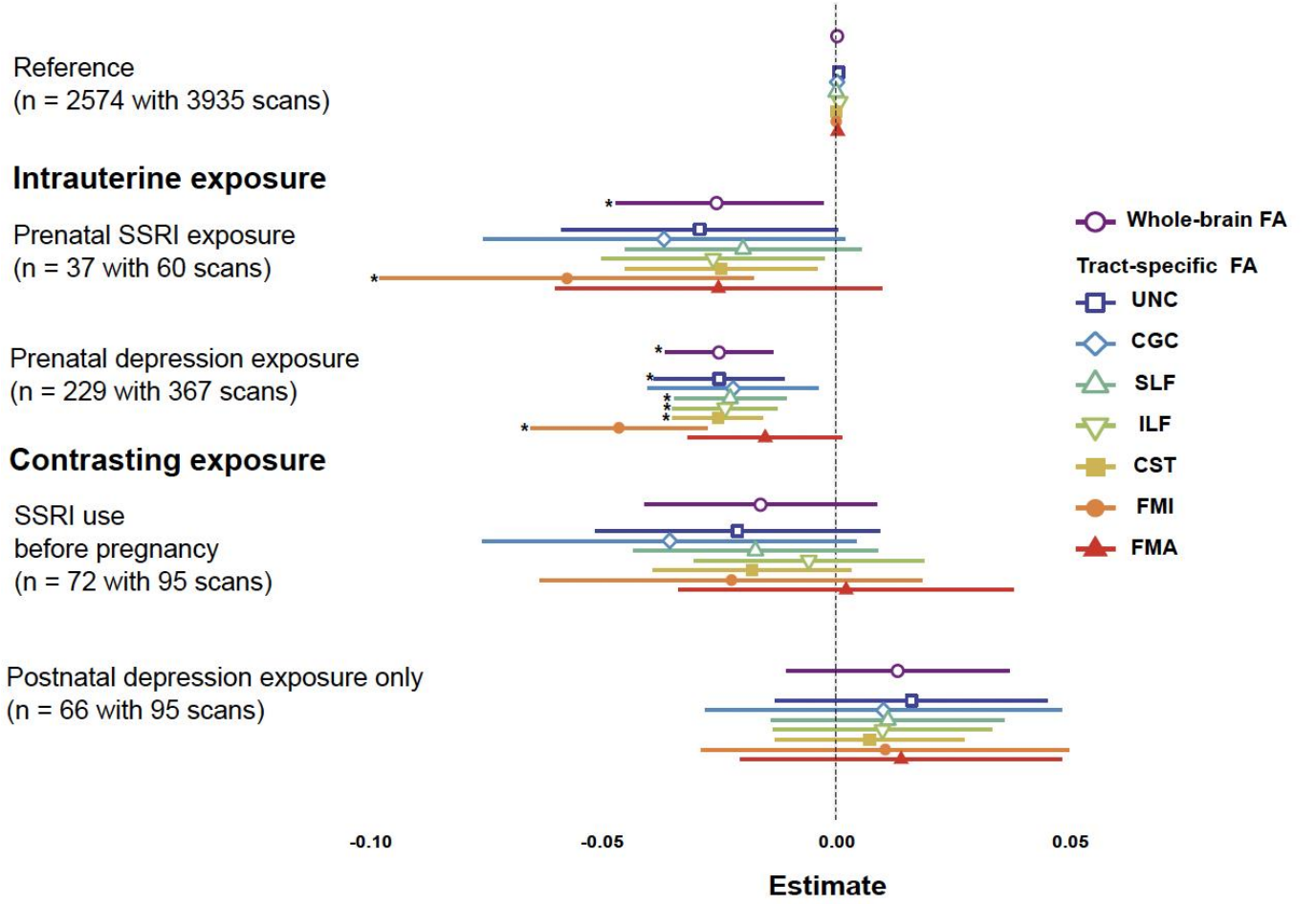
BJPsych | The British Journal of Psychiatry (2014) 205, 95–102. doi: 10.1192/bjp.bp.113.127746

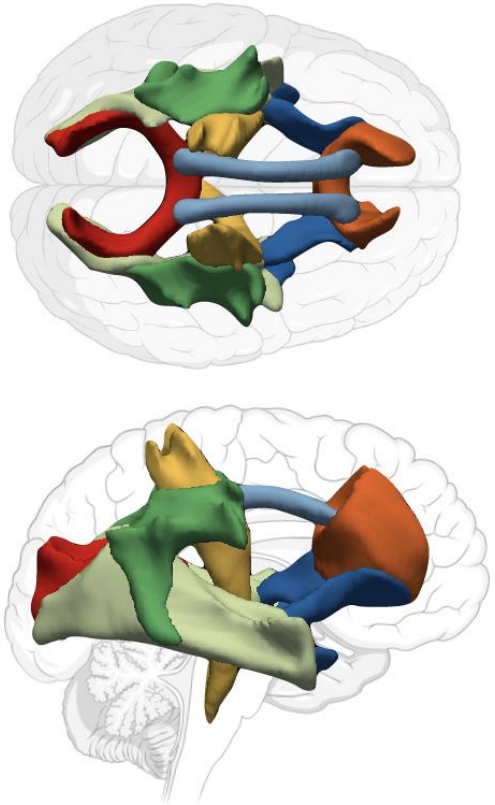
2014

Prenatal exposure to selective serotonin reuptake inhibitors and social responsiveness symptoms of autism: population-based study of young children†

Hanan El Marroun, Tonya J. H. White, Noortje J. F. van der Knaap, Judith R. Homberg, Guillén Fernández, Nikita K. Schoemaker, Vincent W. V. Jaddoe, Albert Hofman, Frank C. Verhulst, James J. Hudziak, Bruno H. C. Stricker and Henning Tiemeier

Intrauterine exposure to maternal SSRI use or depression and white matter at age 7 years





Koc, JAMAPsychiatry, 2023 in press

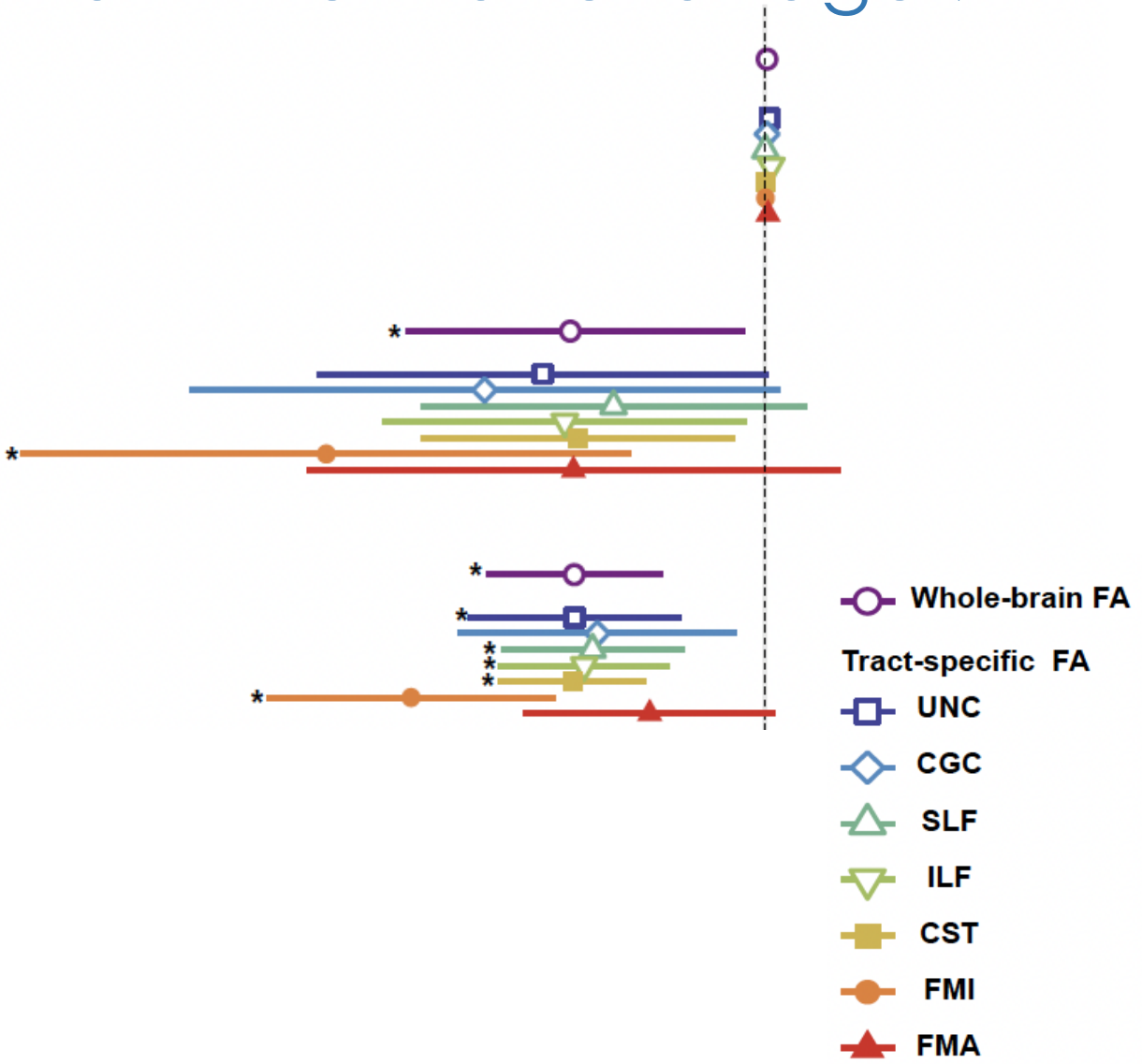
Intrauterine exposure to maternal SSRI use or depression and white matter at age 7

Reference
(n = 2574 with 3935 scans)

Intrauterine exposure

Prenatal SSRI exposure
(n = 37 with 60 scans)

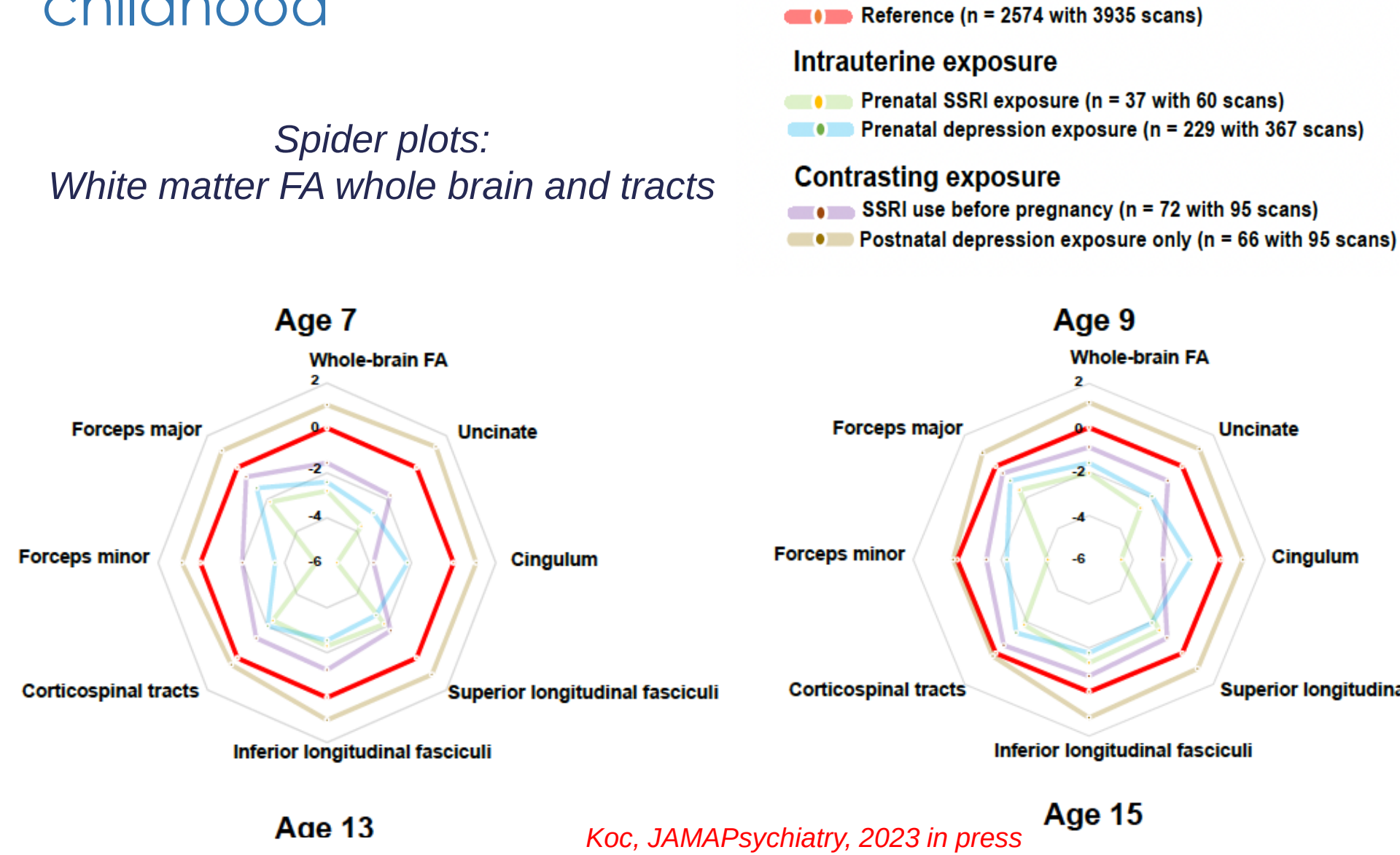
Prenatal depression exposure
(n = 229 with 367 scans)



Koc, JAMAPsychiatry, 2023 in press

Intra-uterine exposure to maternal depression or SSRI and white matter catch-up growth in childhood

Spider plots:
White matter FA whole brain and tracts



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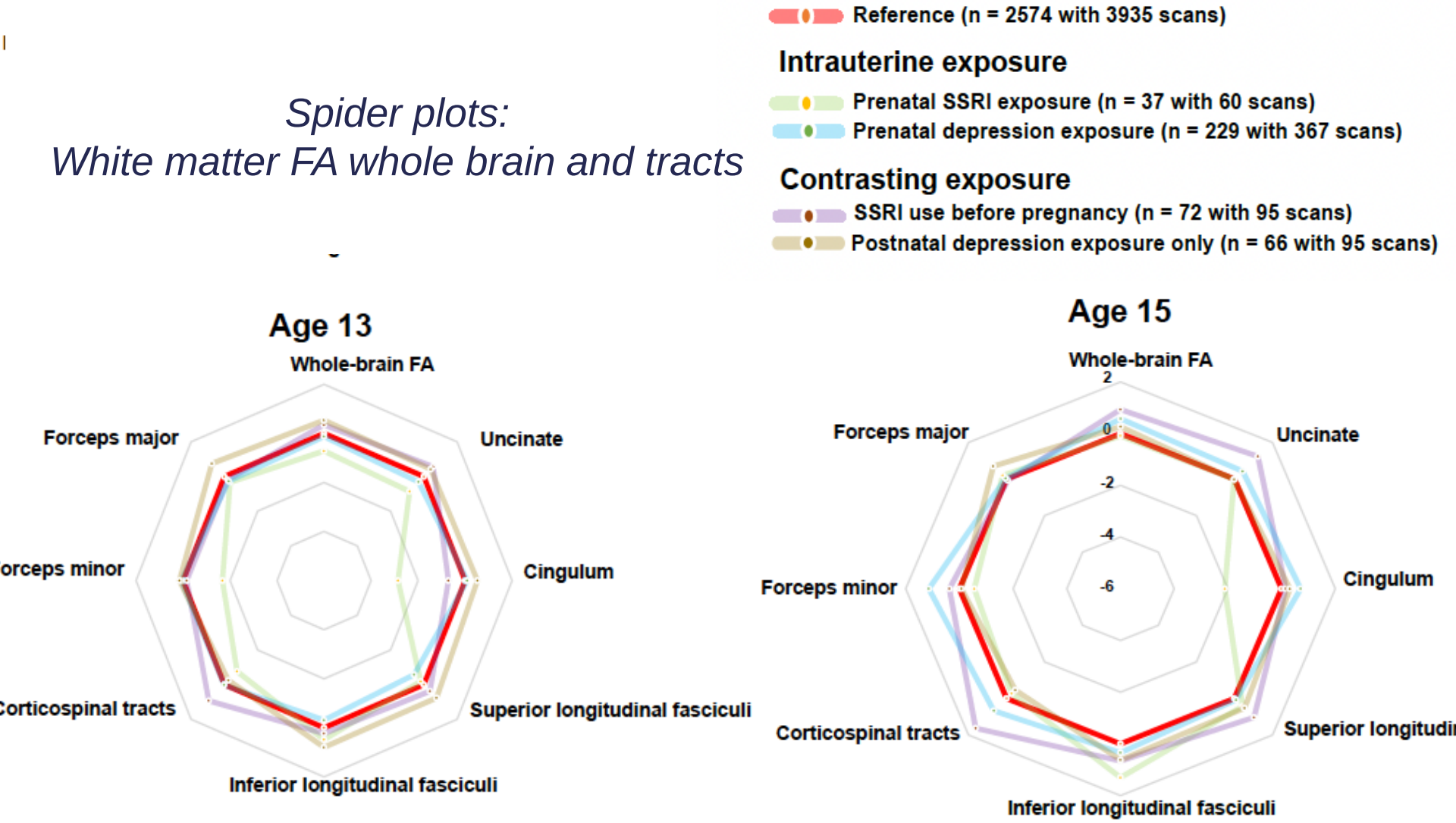
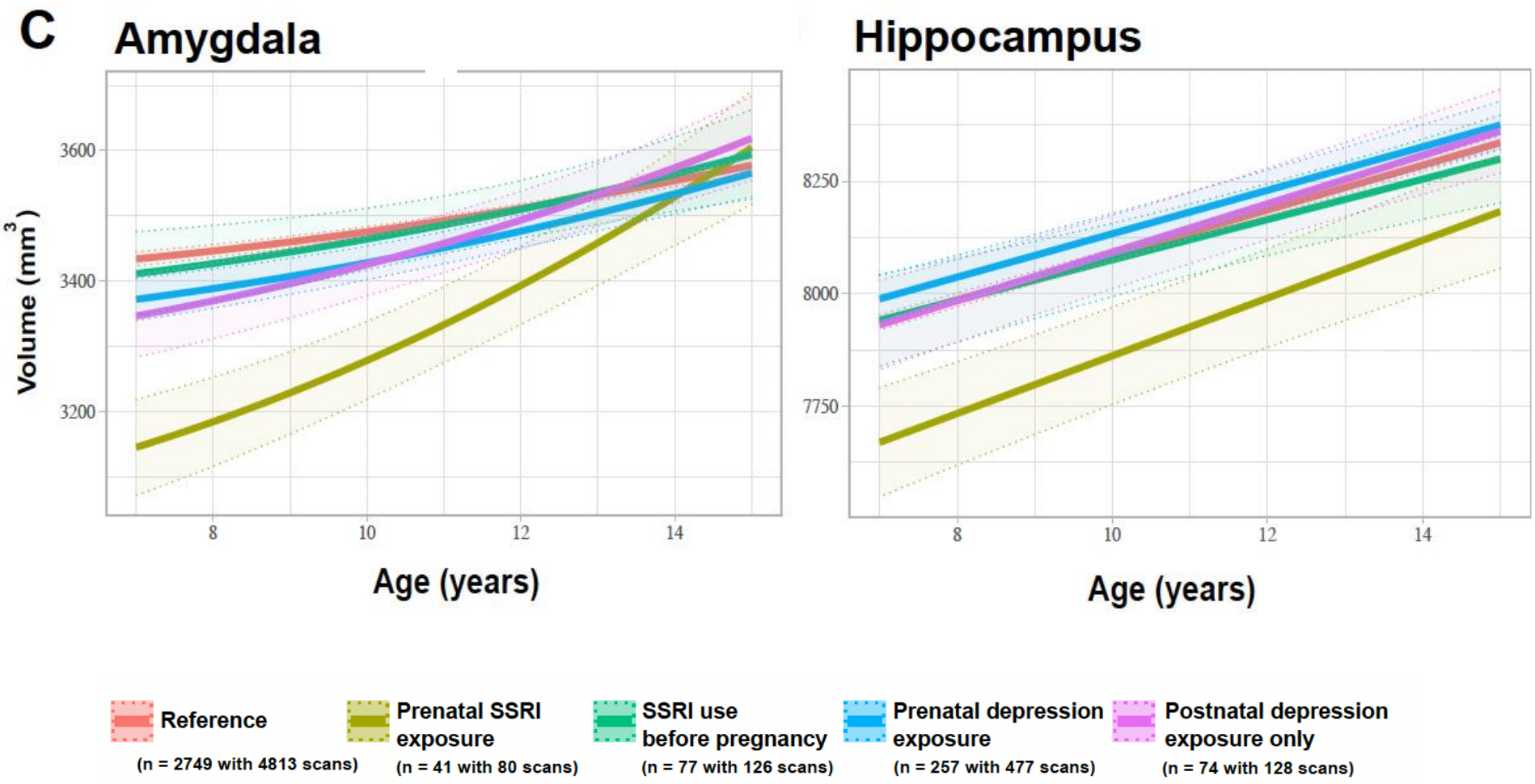


Koc, JAMAPsychiatry, 2023 in press

Intra-uterine exposure to maternal depression or SSRIs and subcortical structure development across childhood



Koc, JAMAPsychiatry, 2023 in press

Time: Many prenatal exposure effects attenuate with age

- Catch up growth and development: Neuroplasticity
- Dilution of effects with age
- Clinical relevance: Little long-term effect of intra-uterine exposure to SSRIs

Poverty

Does poverty impact brain development ?

Social interaction with timing

Background; poverty imaging

- Household income has been associated with brain morphology.

- No study assessed household income from fetal life onward.

- Whether the association between low income and child brain morphology differs by
  1) timing of exposure and
  2) minority/majority status

Generation R: National origins

Based on classification according to the CBS, 2004; Missing: (12%)

Methods

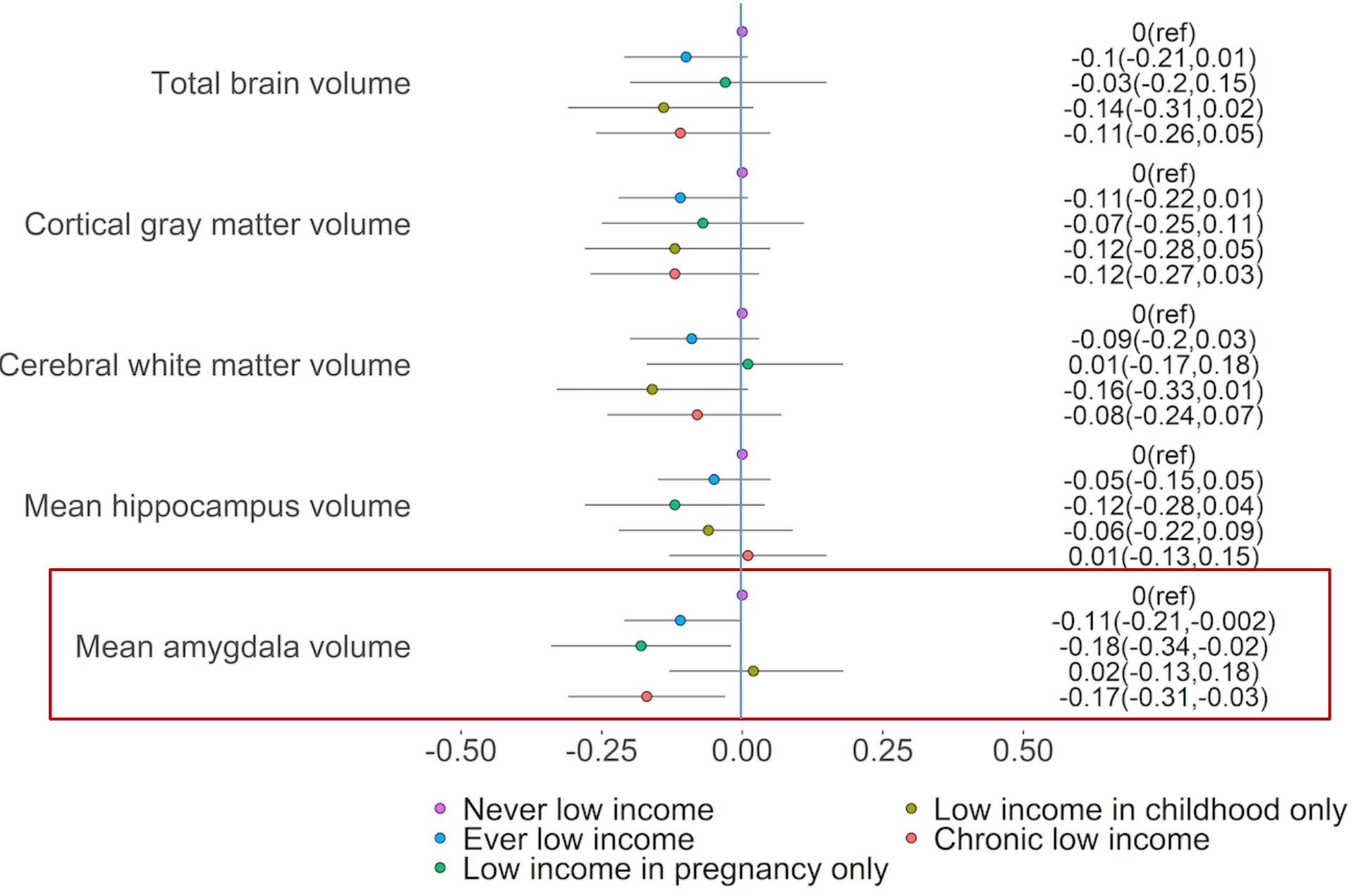
- Data of a total of 2166 children from the Generation R study was analyzed.

- Poverty was defined based on national low-income threshold in Netherlands

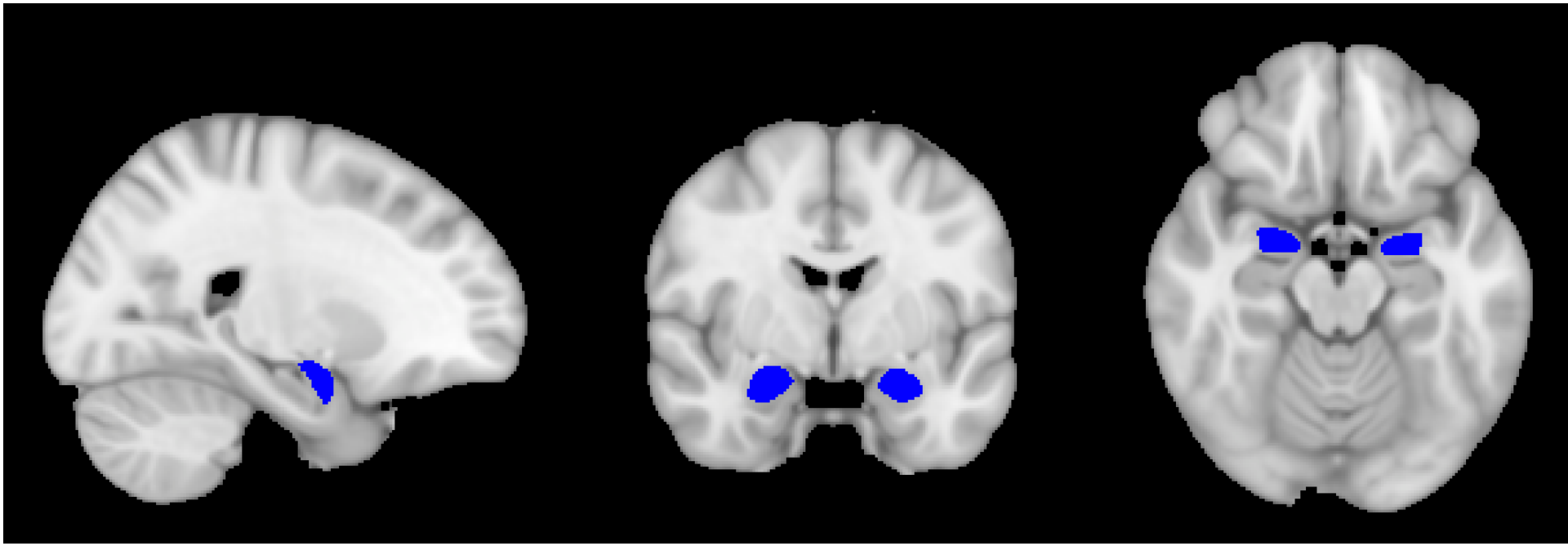
Poverty by race/ethnicity or parental national origin

	Never poverty	Ever poverty	Timing of poverty exposure N=442		
Maternal ethnicity	N = 1724 (79.6%)	N = 442 (20.4%)	Poverty in pregnancy only N = 111 (5.1%)	Poverty in childhood only N = 116 (5.4%)	Chronic poverty pregnancy+ childhood N = 215 (9.9%)
Dutch, %	72.5	26.0	19.8	50.0	16.3
Western, non-Dutch (deleted)					
Non-Western, %	13.5	67.2	69.4	44.8	78.1

Poverty and brain volume



Affected by poverty but in different groups:
White matter and the amygdala



Poverty and brain morphology in the majority of Dutch national origin

Dutch (N = 1365)	Cerebral white matter volume		
	B	95%CI	P-value
Poverty status			
Never-low-income	0	Ref.	
Ever-low-income	**-0.22**	**-0.40; -0.05**	**0.01**
In pregnancy only	-0.07	-0.43; 0.30	0.73
In childhood only	**-0.25**	**-0.48; -0.01**	**0.04**
Chronic poverty	-0.28	-0.59; 0.02	0.07

Koyama, Sci Reports, 2023

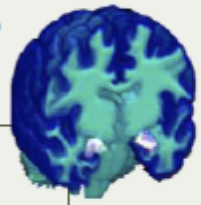
Poverty and brain morphology in the minority of non-Dutch national origin

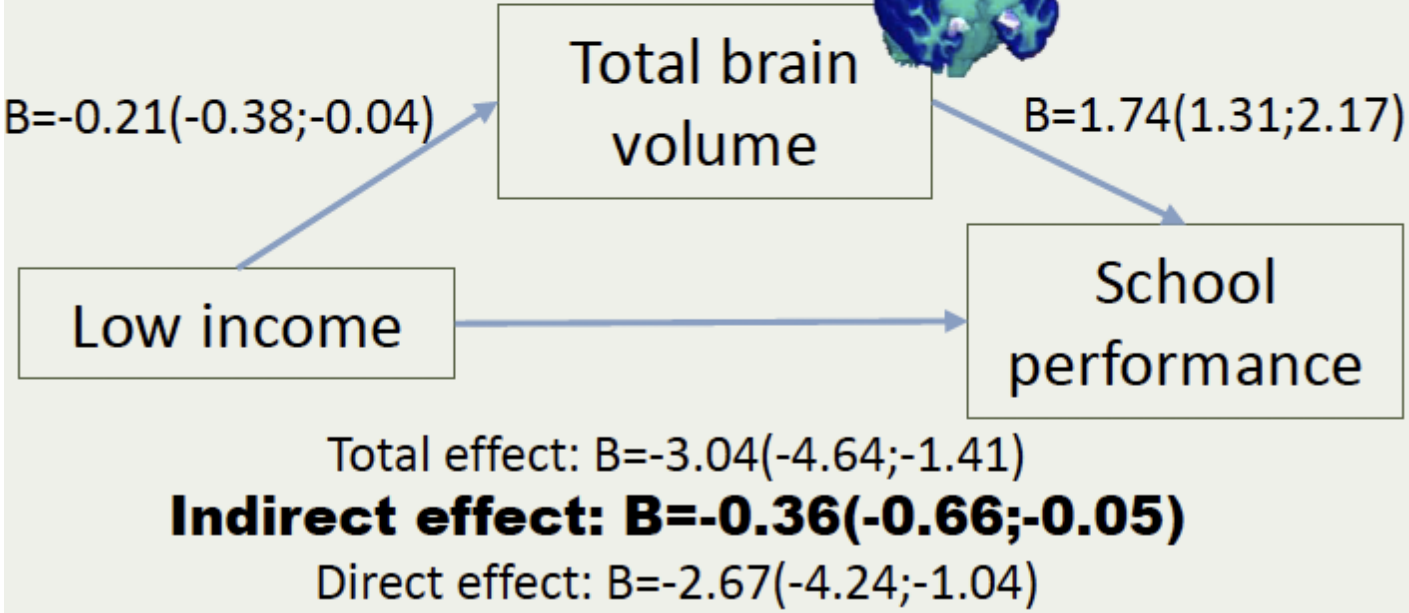
Non-Western (N = 530)		Total brain volume			Amygdala volume		
Poverty status	N	B	95%CI	P-value	B	95%CI	P-value
Never-low-income	233	0	Ref.		0	Ref.	
Ever-low-income	297	-0.02	-0.20; 0.15	0.79	-0.15	-0.31; 0.01	0.06
In pregnancy only	77	0.05	-0.18; 0.28	0.68	**-0.20**	**-0.41; 0.004**	**0.05**
In childhood only	52	-0.04	-0.30; 0.22	0.77	0.01	-0.23; 0.25	0.93
Chronic poverty	168	-0.07	-0.28; 0.14	0.52	**-0.21**	**-0.40; -0.02**	**0.03**

Koyama, Sci Reports, 2023

Functional outcomes

Yet, children from **Dutch majority** group exposed to poverty showed **smaller total brain volume**; which mediated the association between poverty and **poor school performance**.





Koyama, Sci Reports, 2023

Summary

- Early-life poverty exposure and preadolescent brain morphology are associated.
- Differential associations across majority and minority groups were found.
- In the majority group, smaller total brain volume partly explained the association between poverty and poor school performance.
- Distinct vulnerability and mechanism must be discussed: do findings in minority reflect stress by discrimination? Yes, partly, we could show

Prenatal maternal thyroid function

Timing again

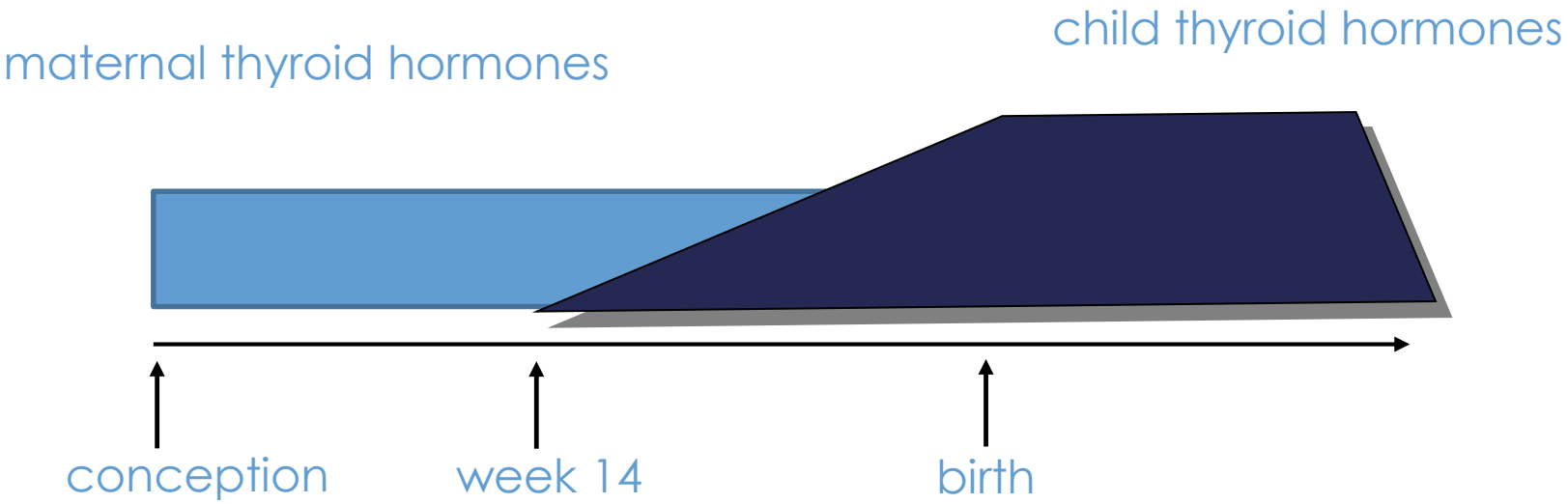
Thyroid and brain

neurogenesis

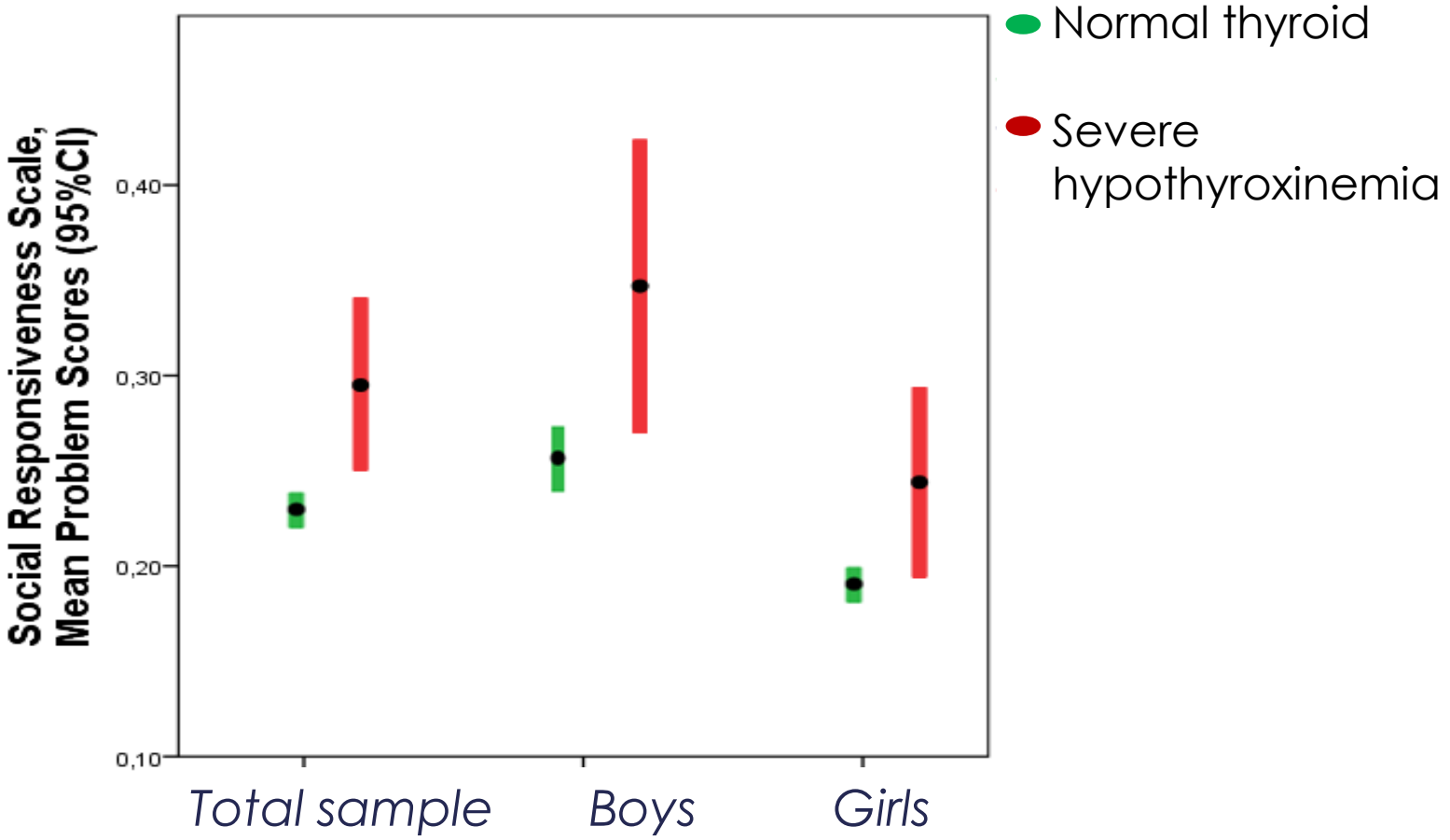
neural migration

synapse formation

myelination

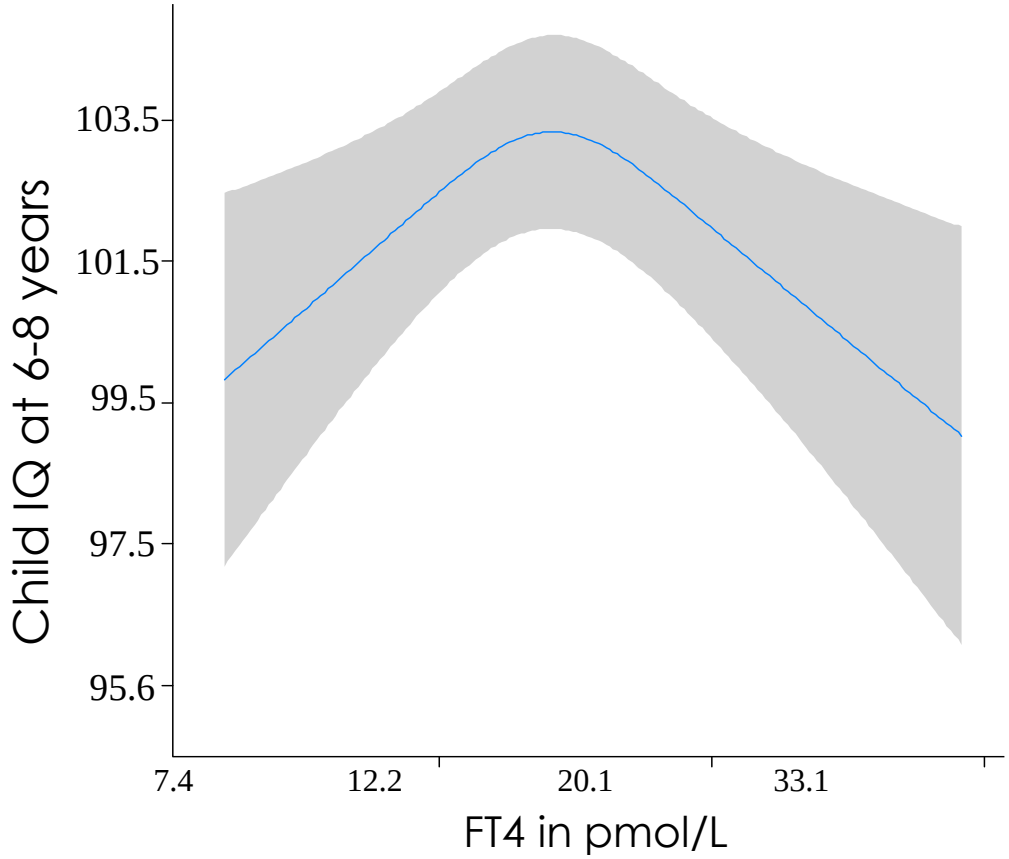


Maternal hypothyroxinemia and autistic traits at 6 years



Roman & Ghassabian et al. 2013 Ann Neurol

Maternal free T4 and offspring IQ



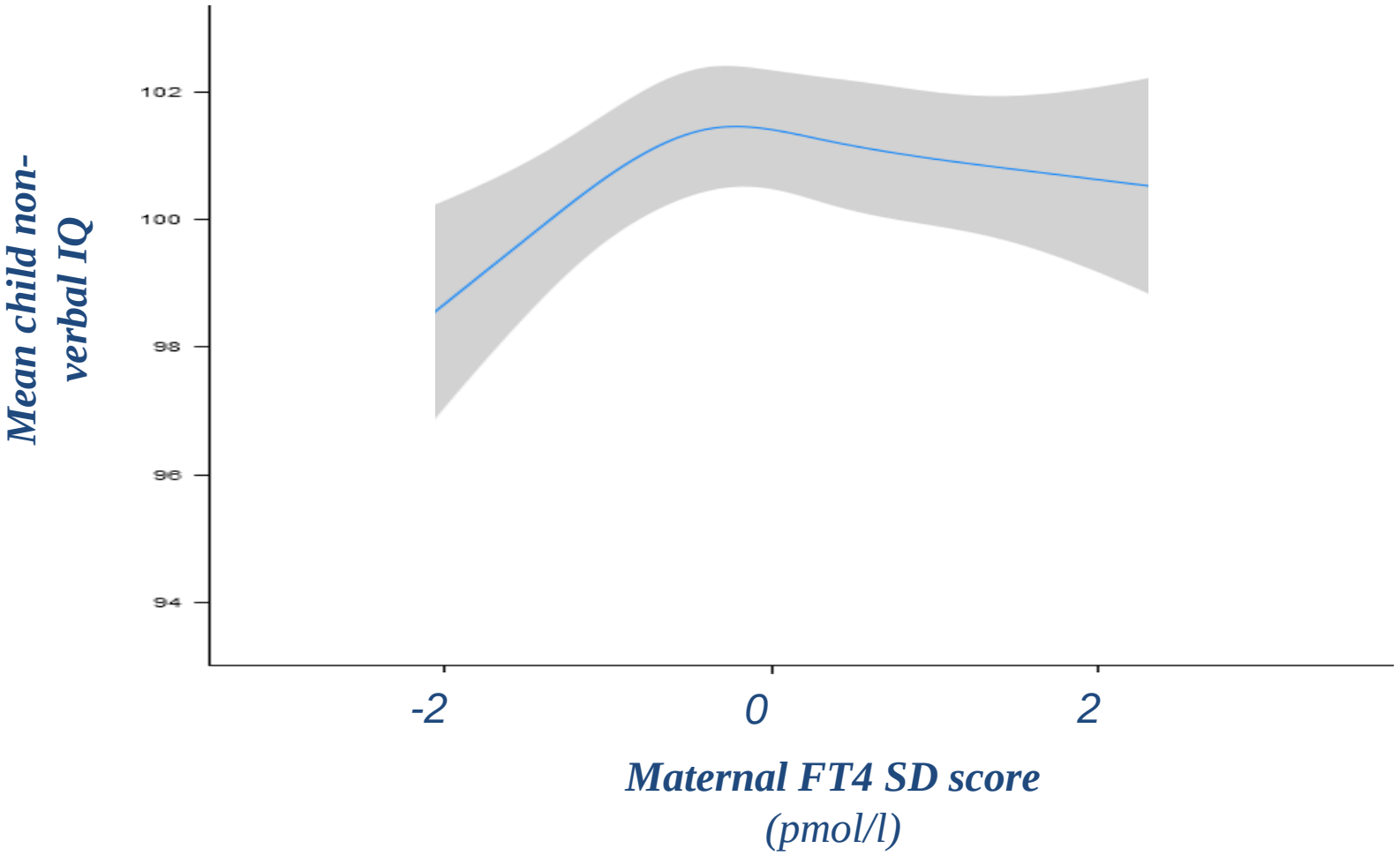
n=3839

P = 0.003

Adjusted for child age, sex, gestational age at blood sampling, hCG, maternal age, smoking, BMI, parity, education level, ethnicity, fetal gender and birth weight.

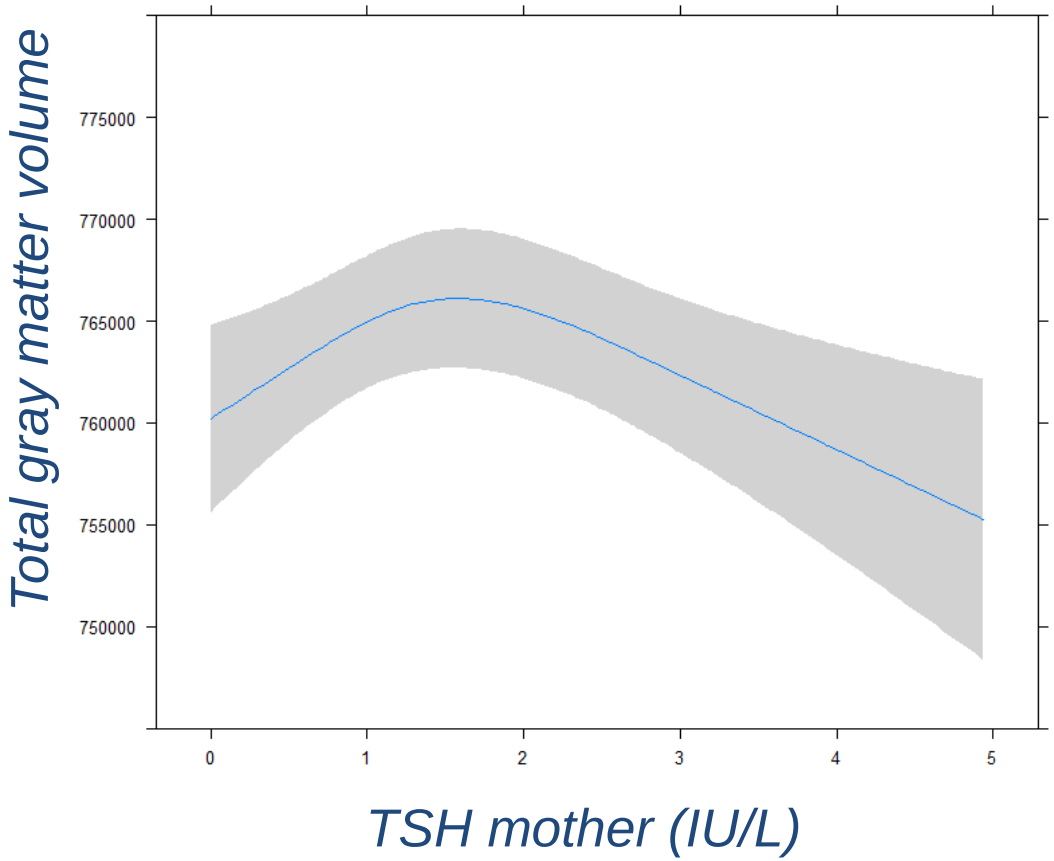
Korevaar et al. 2015, Lancet Endo

Replication in ALSPAC and INMA study: IQ



Korevaar et al. 2015, Lancet Endo

Maternal TSH during pregnancy and child grey matter age 9/10 years



N=2083 children

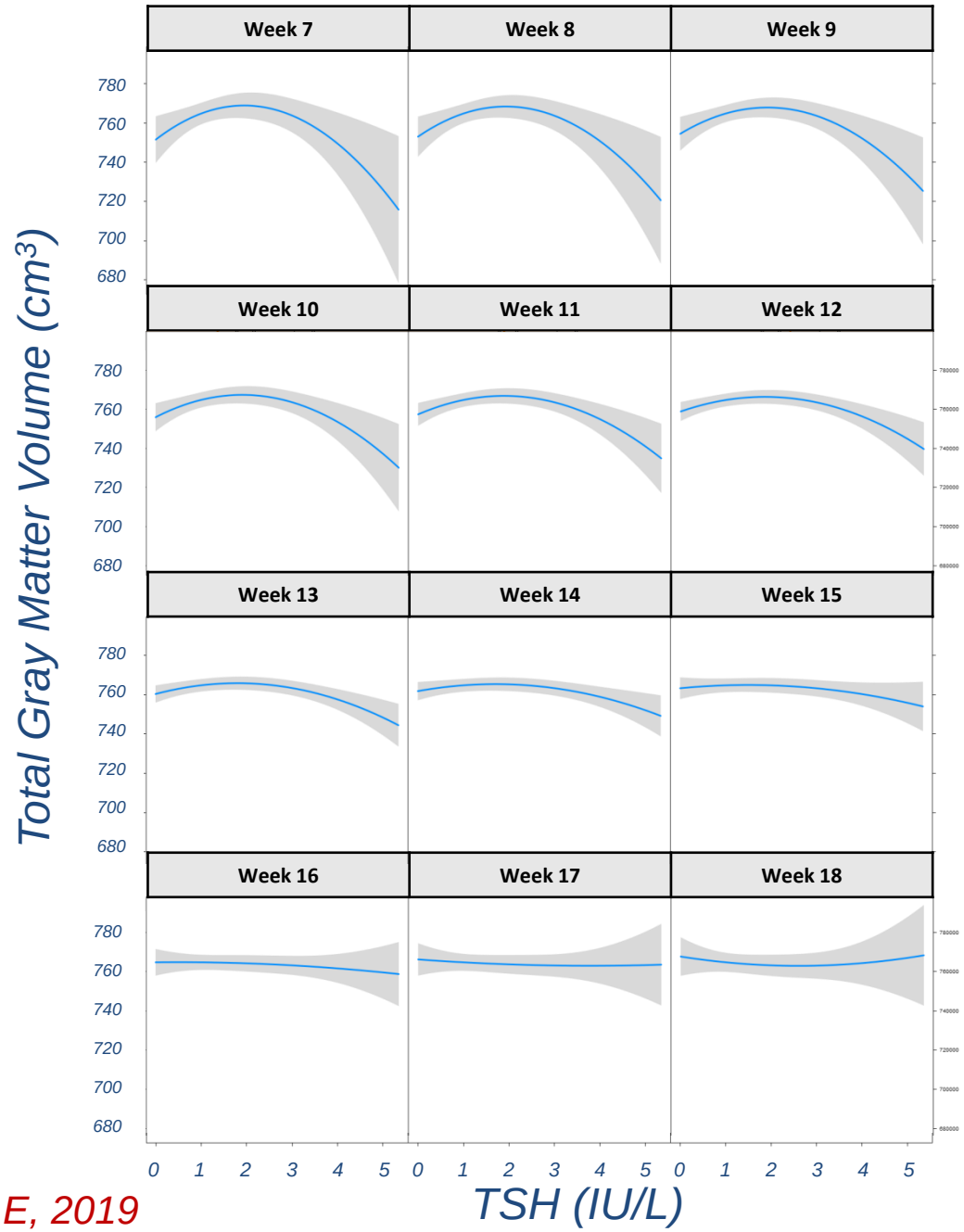
p=0.0006
for quadratic term

Watch out for the X-axis: High TSH indicative of low thyroid levels
Flipped as compared to prior figure

Timing in pregnancy analysis

Gestational age at assessment: timing and sensitive period ?

Analyses per week of TSH assessment



N=2083 children

Prenatal screening not recommended but discussed in clinical guidelines

Jansen, Lancet D& E, 2019

Timing

- Sensitive period to maternal thyroid
- Need not reflect less overall thyroid dependency of brain (view it as measurement error if you rely on maternal thyroid)
- Major clinical and research implications – interventions must start early

Do you know what trans-fatty acids are?

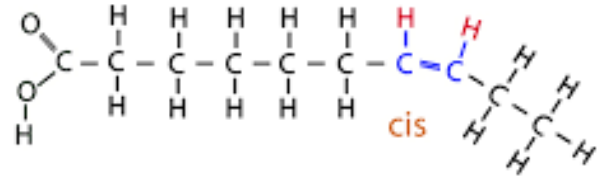
Calendar time ☺ and brain growth over time

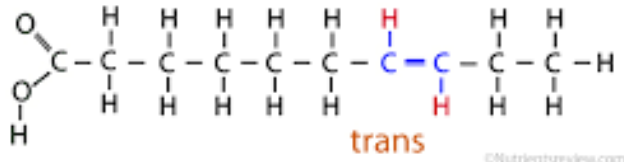
Trans-fatty acids

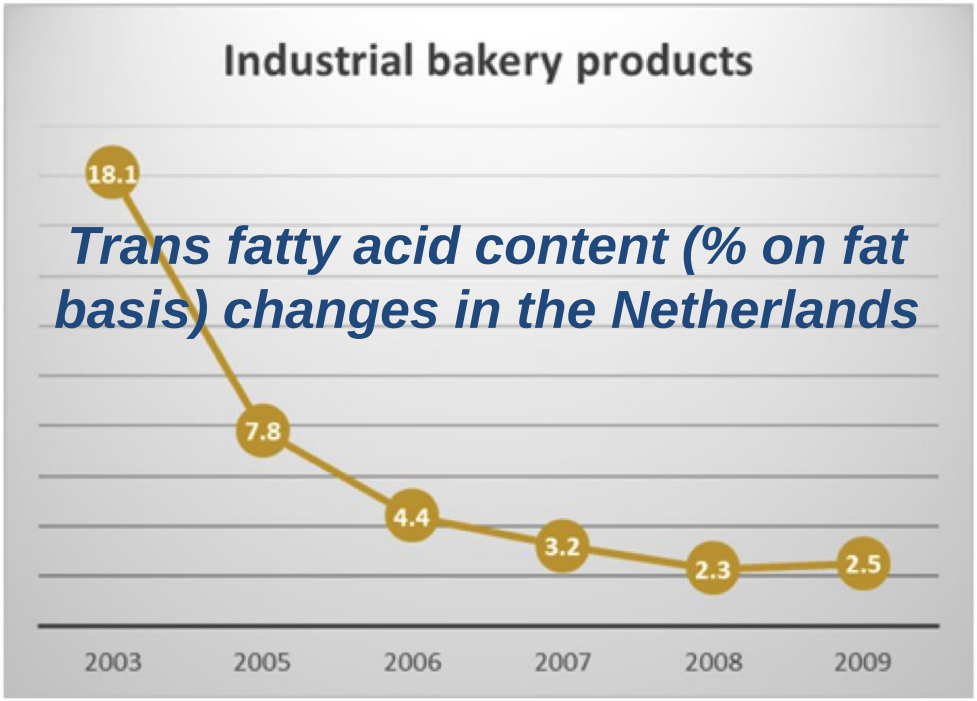
Trans-fatty acids are found in fried foods, commercial baked goods, processed foods and margarine

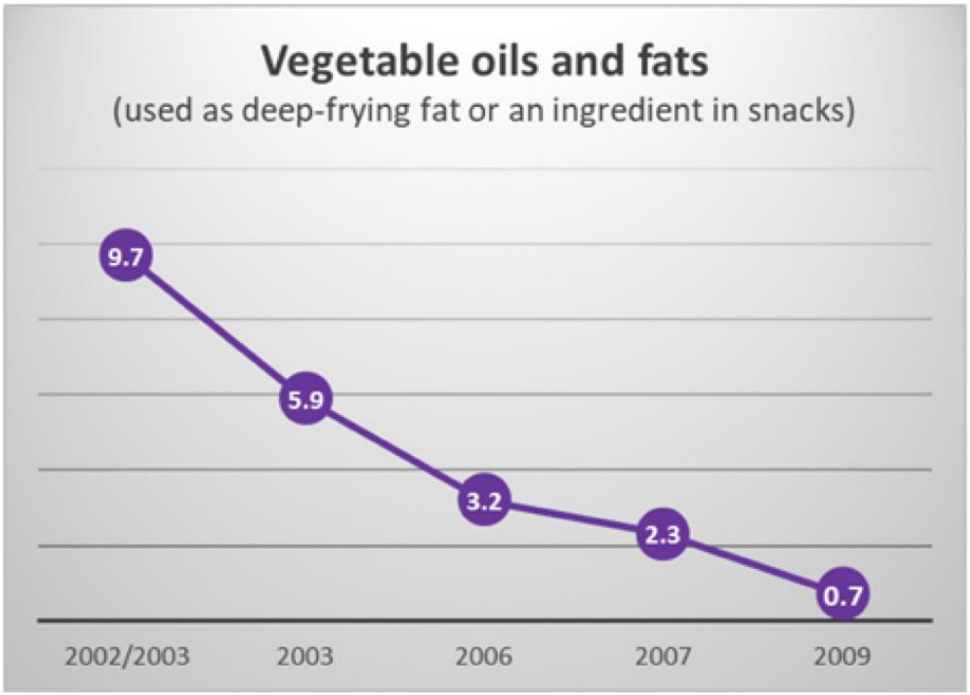
ADAM.

Cis- and Trans-Fatty Acids

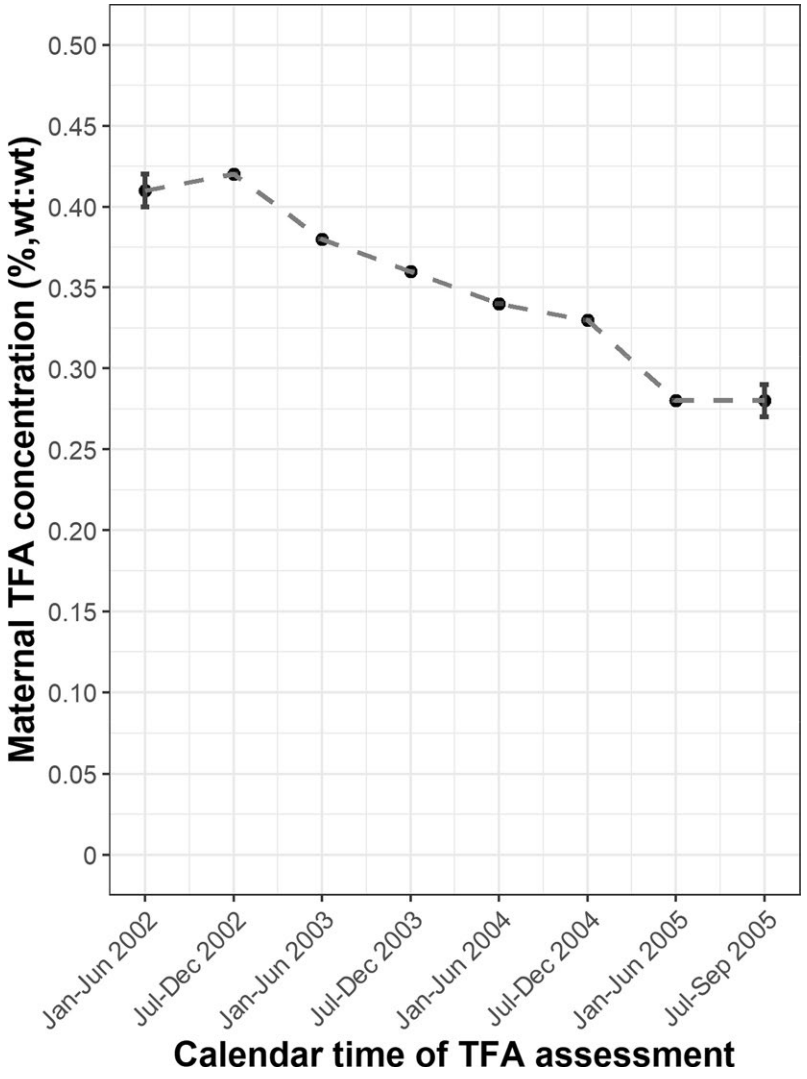








Inclusion of participant and mean TFA levels



Zou et al., EJE, 2022

A relation of TFA with fetal head size

Table 2 Maternal trans fatty acid concentration during pregnancy in relation to fetal head circumference and head circumference growth

Maternal TFA concentration	Fetal HC at single assessments[a]						Fetal HC growth rate across assessments[b] (n = 6517)		
	Second trimester (n = 6792)			Third trimester (n = 6625)					
	B	95% CI	*p*-value	B	95% CI	*p*-value	B	95% CI	*p*-value
Model 1	0.13	0.01, 0.24	0.03	−0.26	−0.43, −0.08	0.004	−0.04	−0.05, −0.02	< 0.001
Model 2	0.12	0.004, 0.24	0.04	−0.30	−0.47, −0.12	< 0.001	−0.04	−0.06, −0.02	< 0.001
Model 3	0.07	−0.05, 0.19	0.24	−0.33	−0.51, −0.15	< 0.001*	−0.04	−0.06, −0.02	< 0.001*

TFA Trans fatty acid, *HC* Head circumference

Zou et al., EJE, 2022

Calendar time is related to head size
A causal or instrumental variable analysis

Model		Fetal HC in the third trimester[a]			Fetal HC growth rate across assessments[b]		
		B	95% CI	*p*-value	B	95% CI	*p*-value
1	*Calendar time*	−0.77	−1.0, −0.51	<0.001	−0.11	−0.13, −0.09	<0.001
2		−0.66	−0.91, −0.40	<0.001	−0.10	−0.12, −0.08	<0.001
3		−1.0	−1.2, −0.79	<0.001	−0.11	−0.14, −0.09	<0.001

HC Head circumference

Instrumental variable analysis on maternal trans fatty acids concentration during pregnancy in relation to fetal HC in the third trimester (n = 6383) and HC growth across assessments in the second and third trimesters (n = 6280) was performed using two-stage least squares estimation. Calendar time of maternal trans fatty acids assessment was used as the instrumental variable. The raw values of maternal trans fatty acids concentration were log-transformed to obtain a normal distribution

Zou et al., EJE, 2022

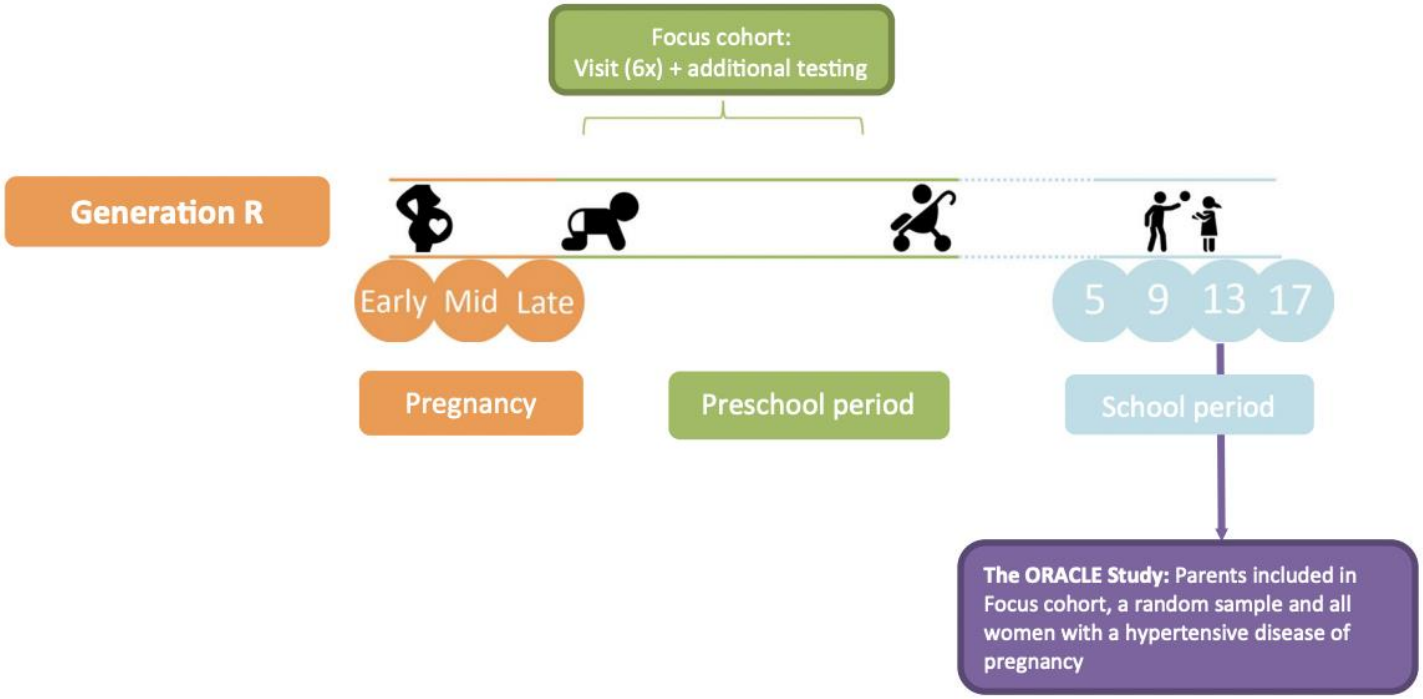
Imaging research of high public health relevance

- Establishing causal mechanism
- Reduction of Trans-fatty acids helps
- Low- and middle-income countries (e.g., East Europe, South Asia) have high TFA products in fried food and oil

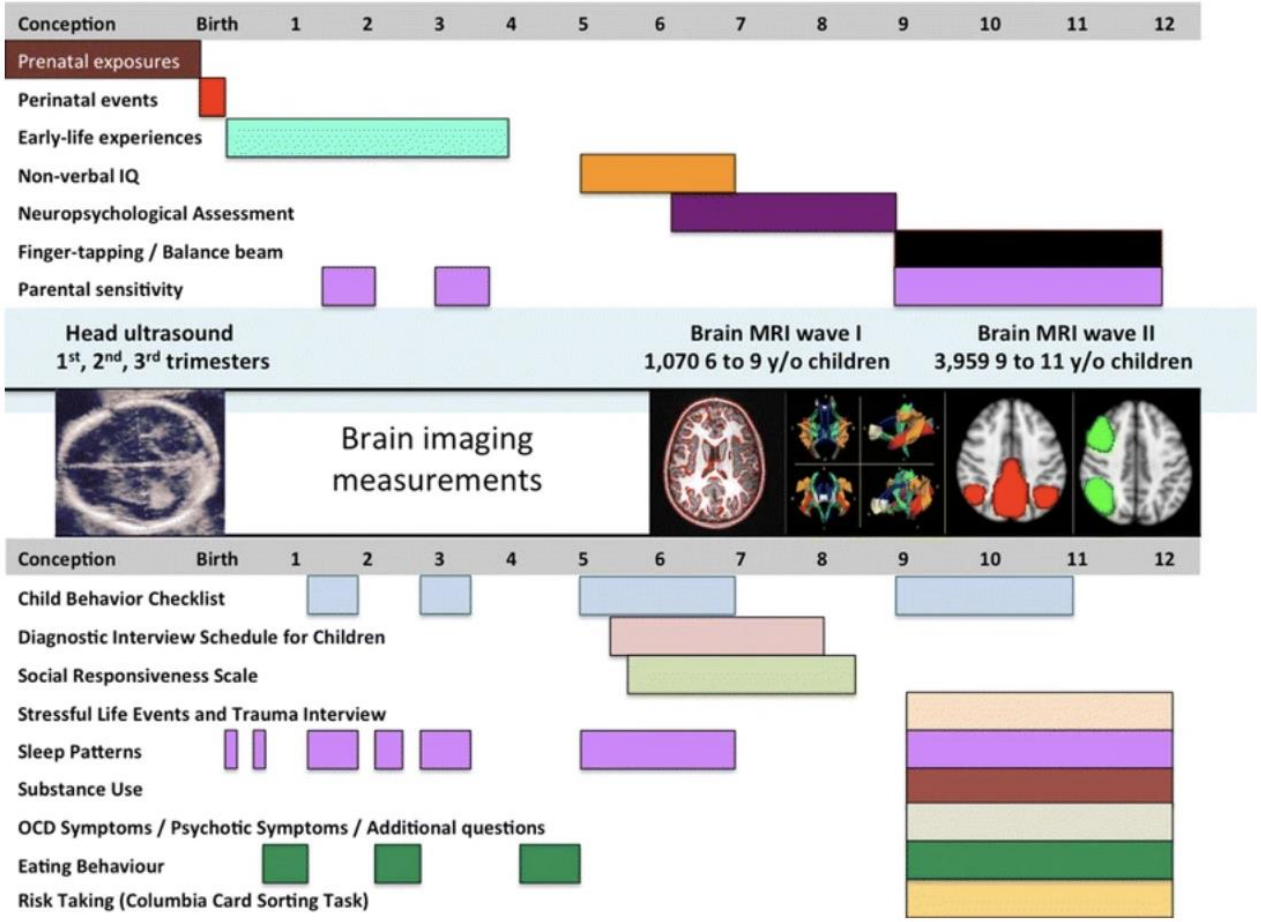
Population neuroscience

- Brain imaging can unravel mechanisms if studies are sufficiently large: etiology
- Not useful as a diagnostic or prognostic tool
- Meaningful clinical prediction using neuroimaging in child psychiatry will remain elusive in next 10 years
- Public health relevance: occasionally

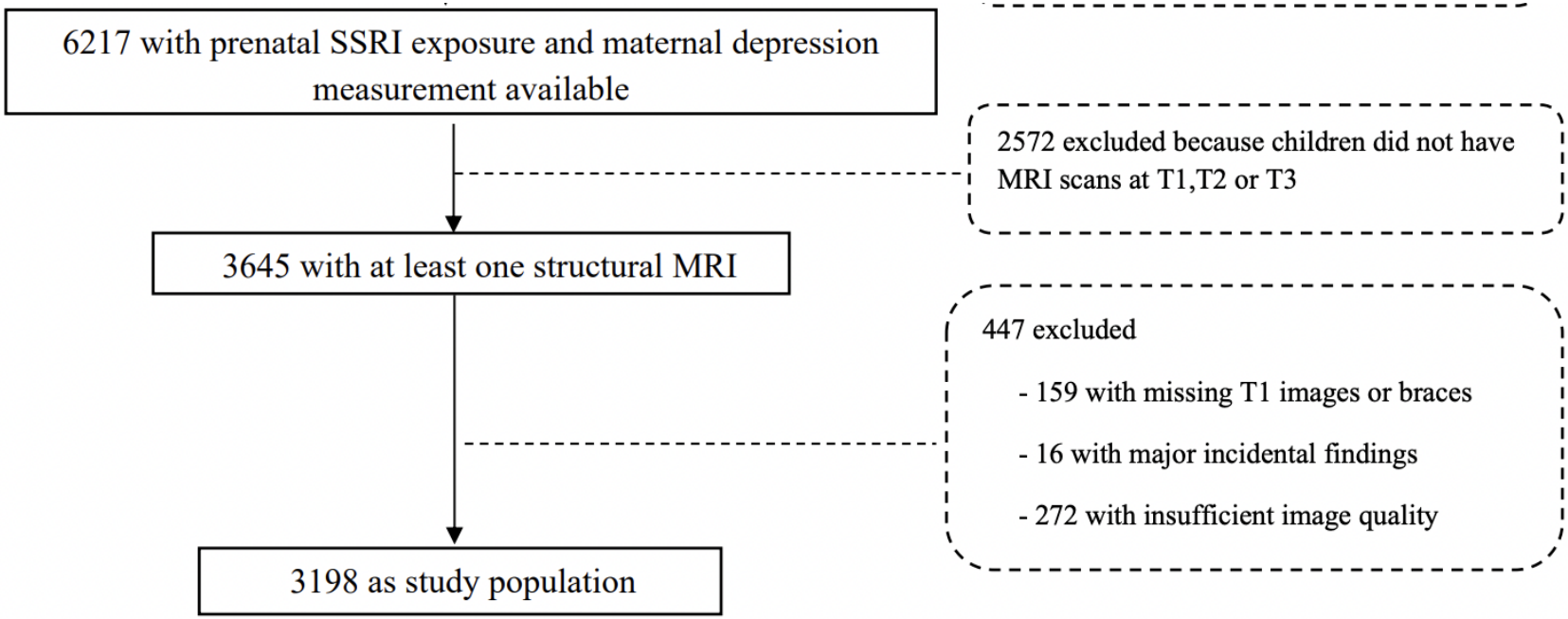
Ongoing research: ORACLE



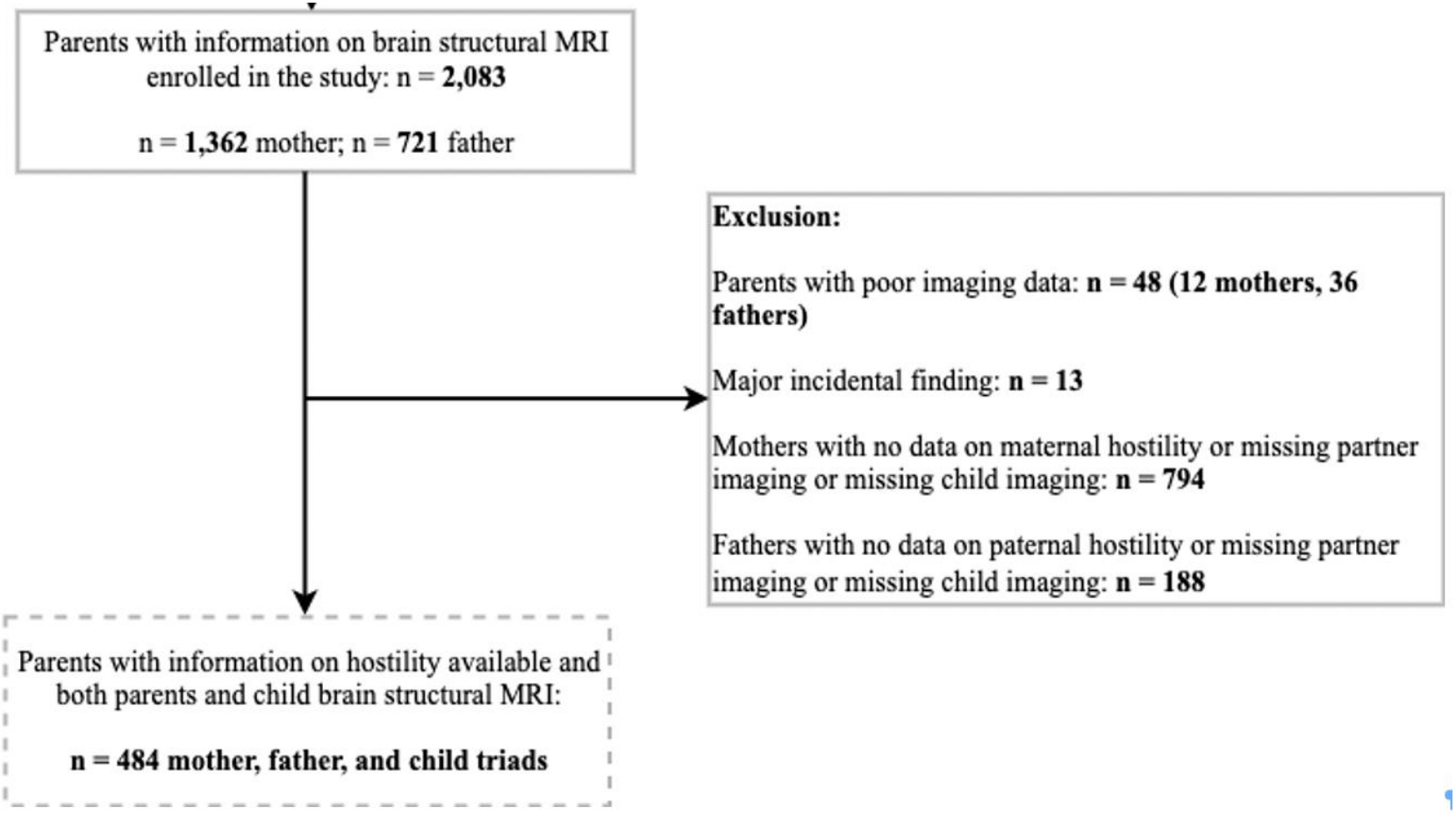
Imaging: The numbers vary and always get smaller



Child imaging in Generation R

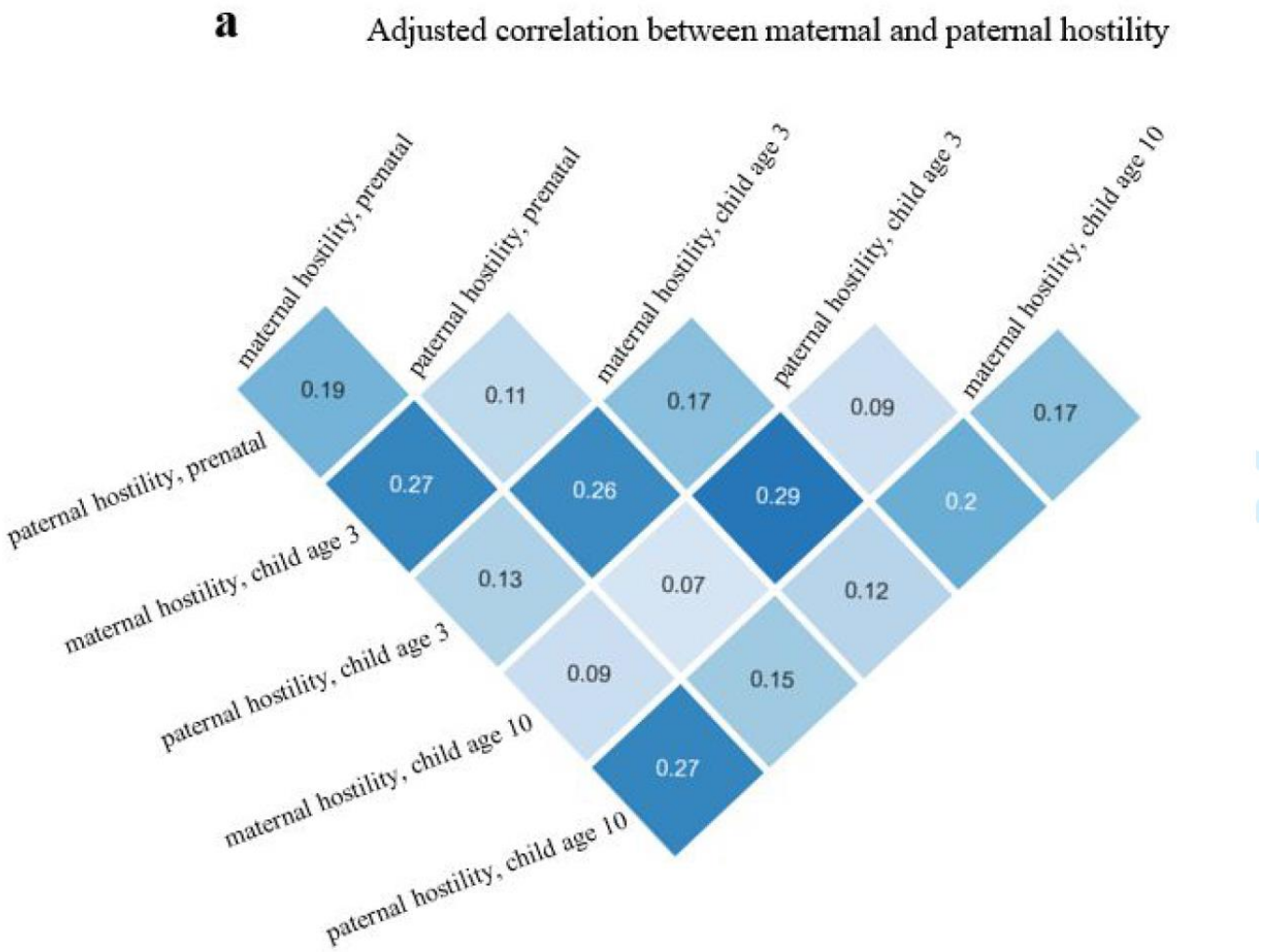


Imaging data parents ORACLE

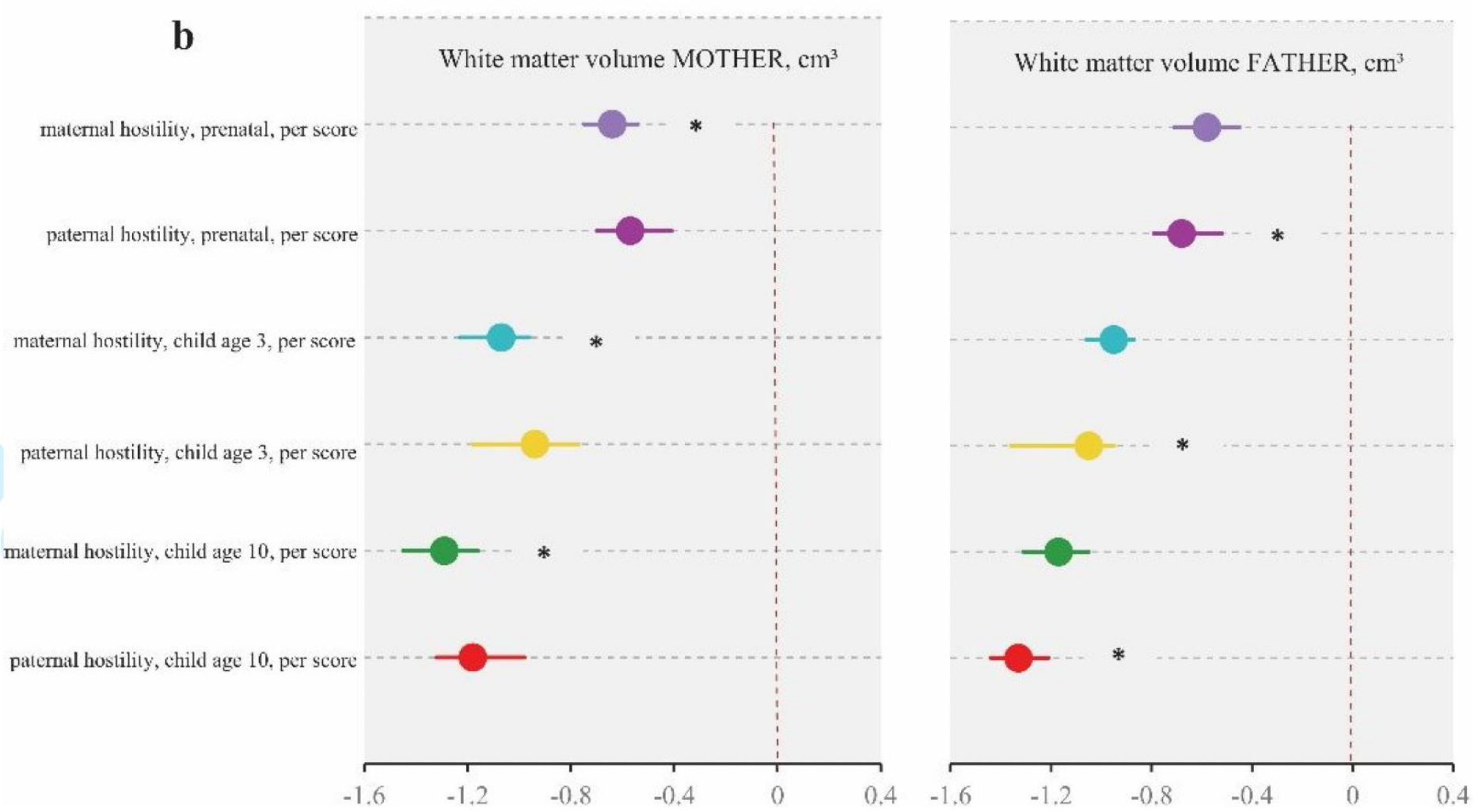


It takes three: Parental hostility, brain morphology and child externalizing problems in a parent-offspring neuroimaging trio design

How hostility between parents transpires to the child: parents

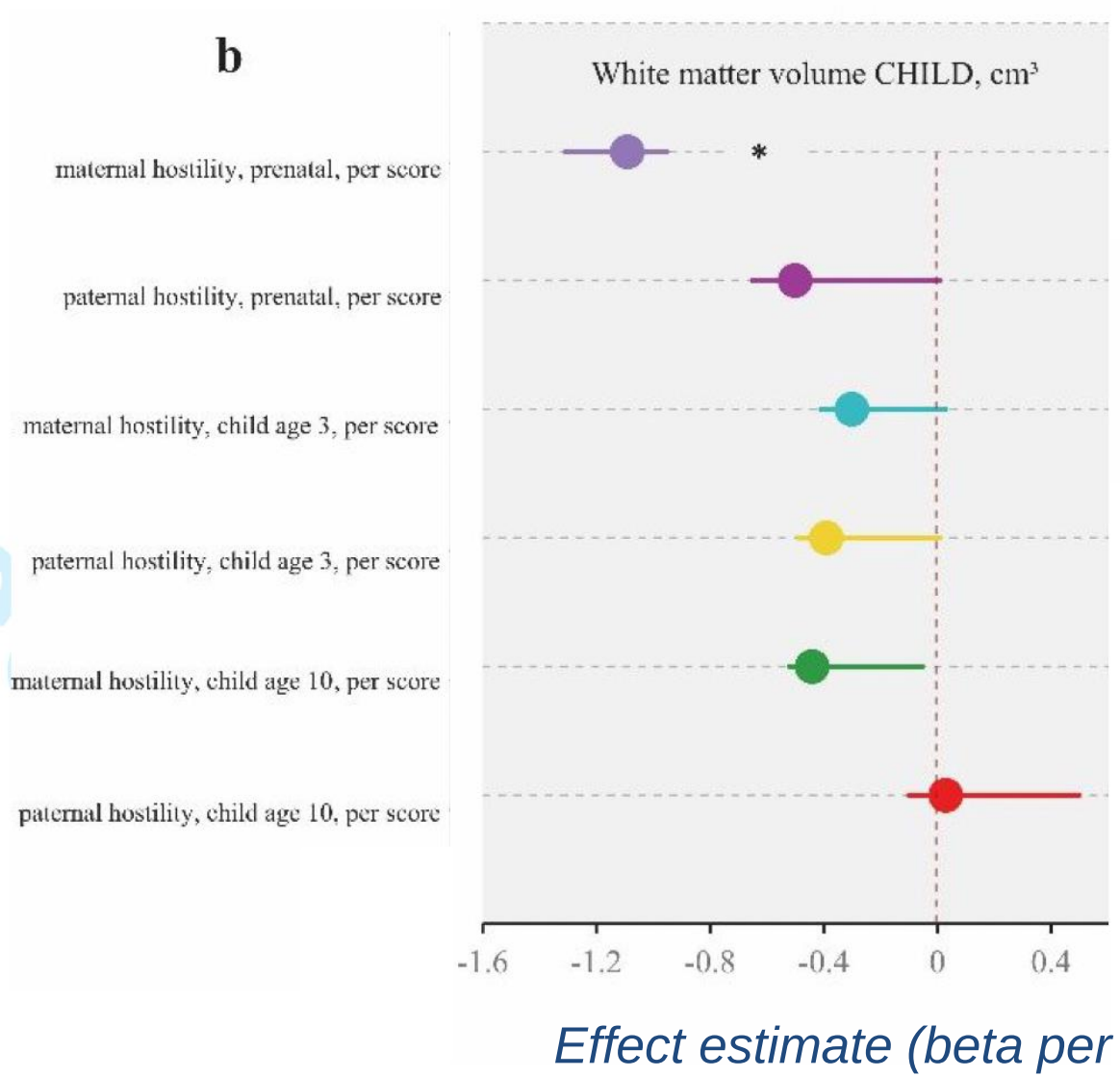


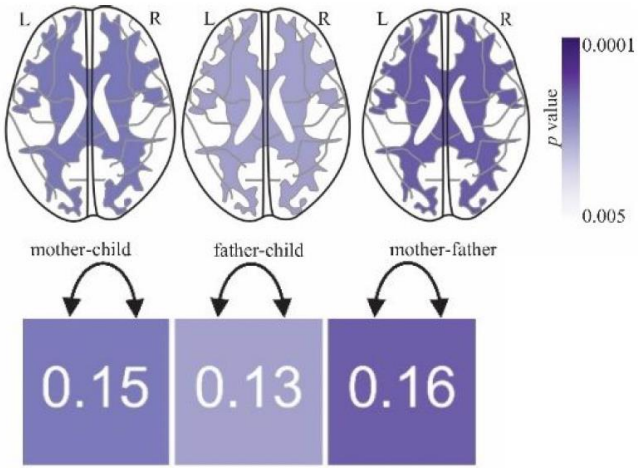
Parental hostility and parental white matter volume



- *Effect estimate (beta per hositility score)*

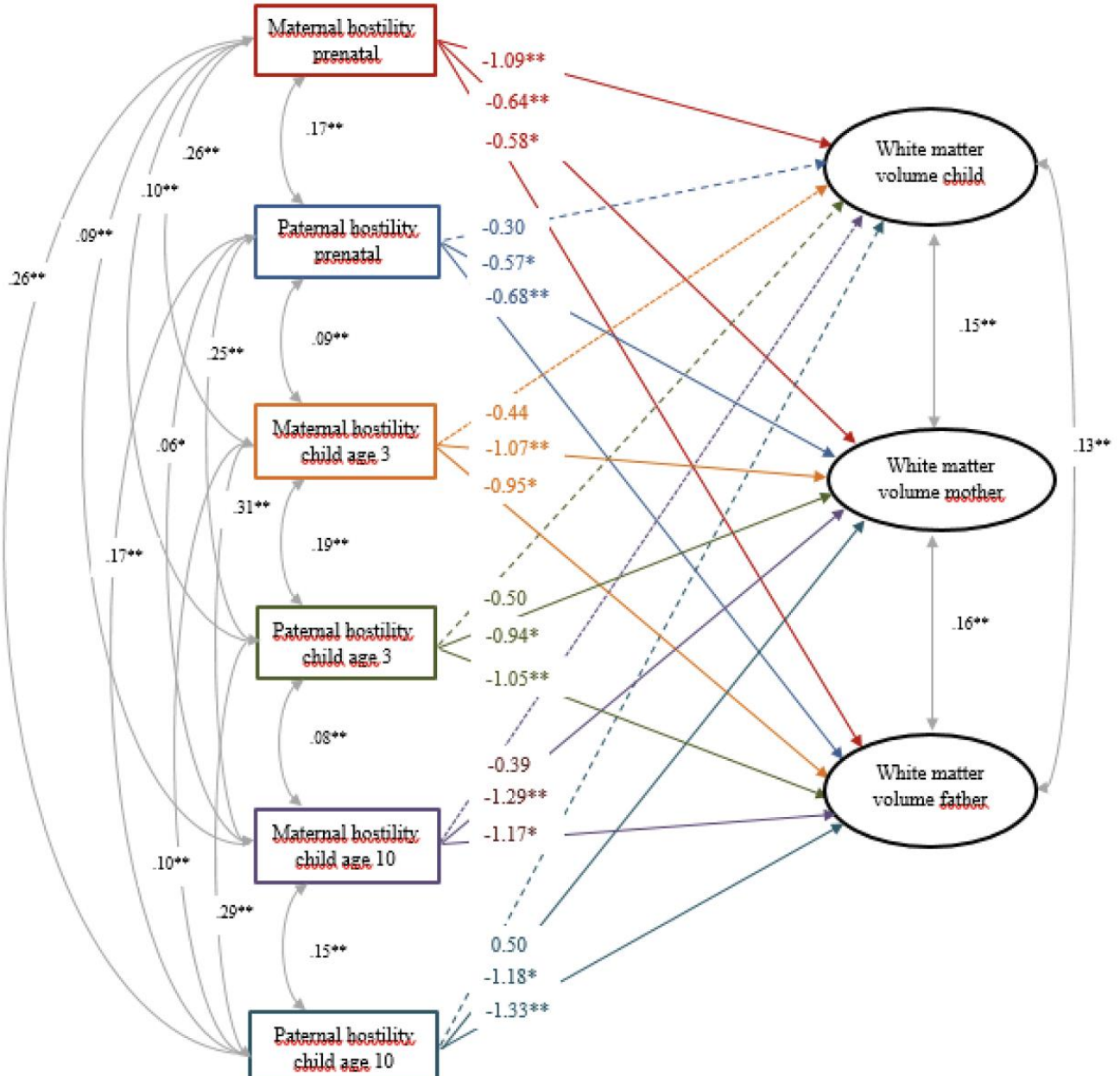
Parental hostility and child white matter volume



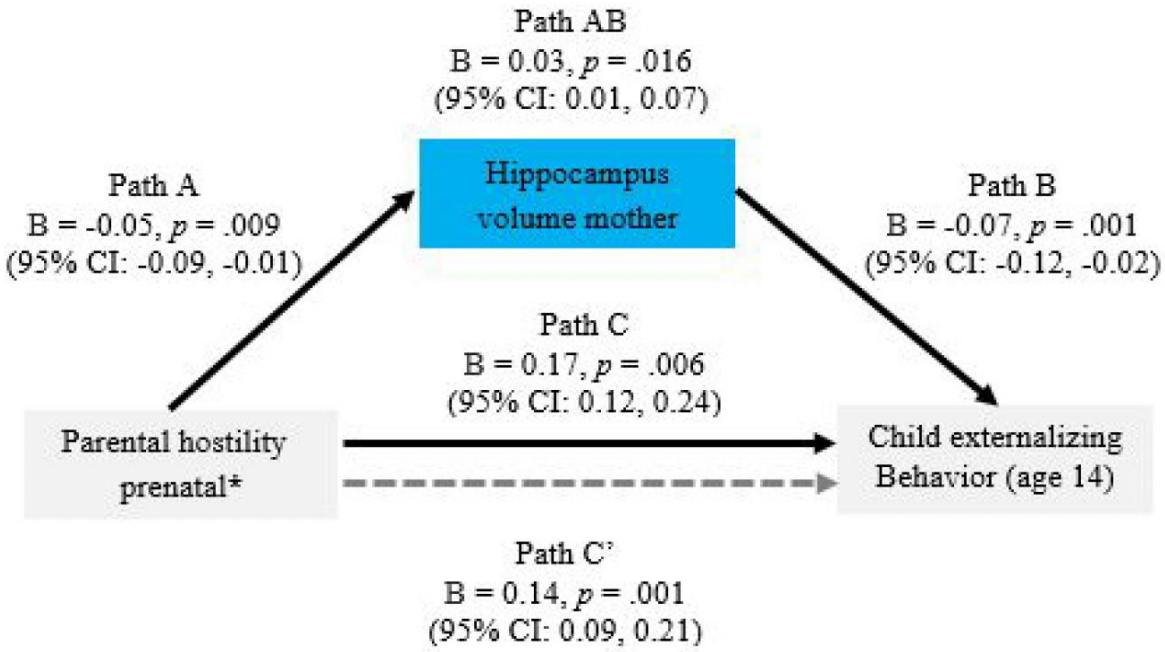


Effect estimate (beta per hositility score)

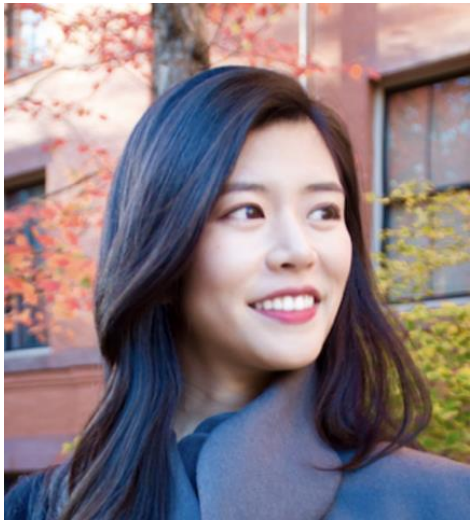
Hostility and white matter volume



Can this help explain child behavior?



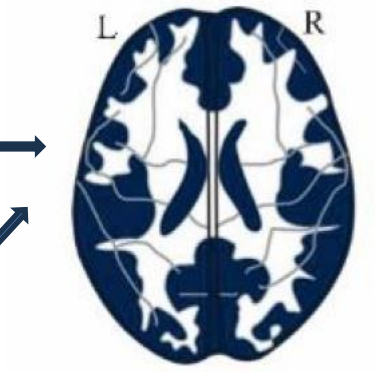
New Project Plans



Yenee Soh, Harvard

Maternal brain

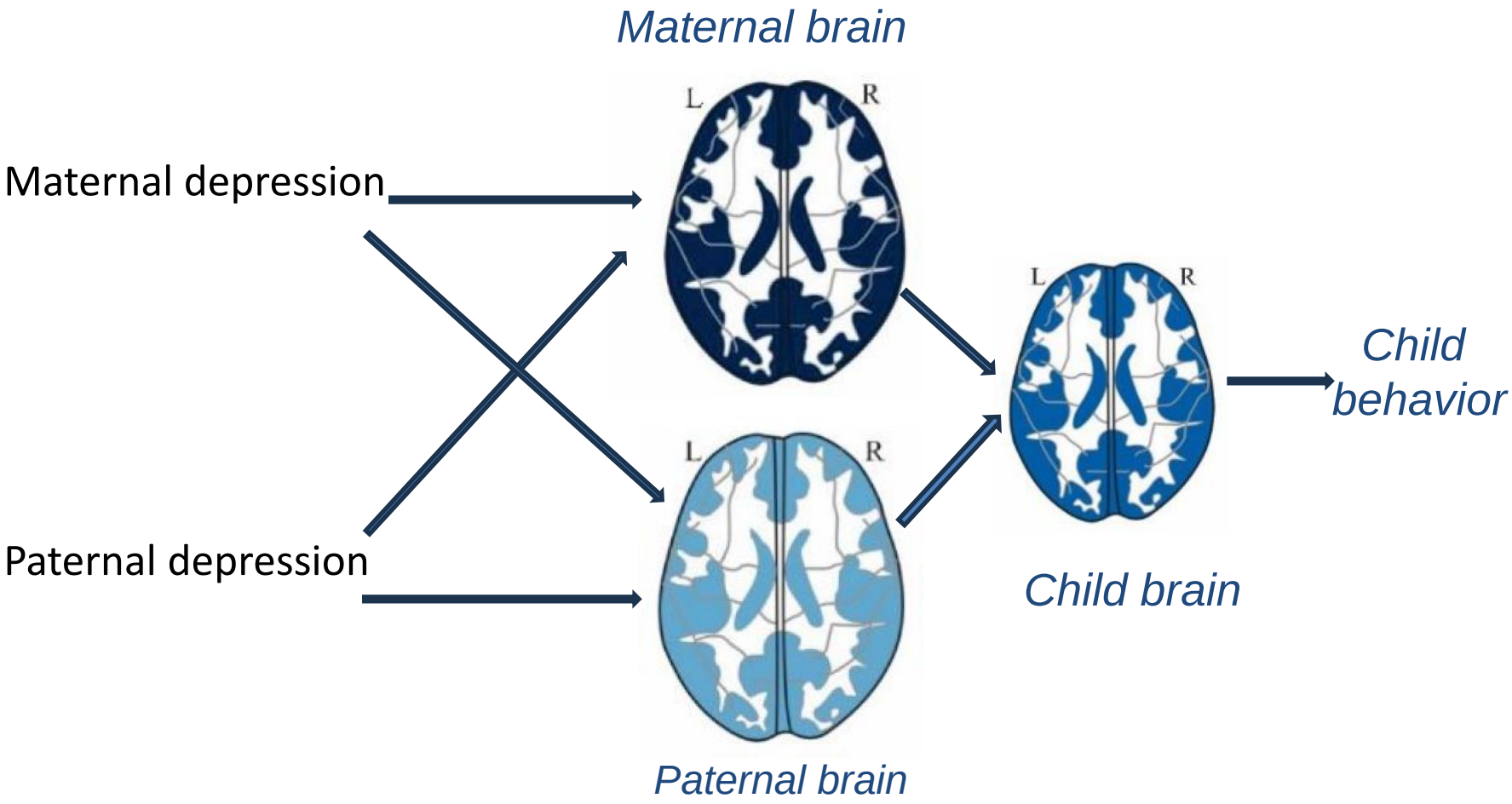
Maternal depression



Paternal depression

Paternal brain

New Project Plans



The children

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Thank you !