Population Neuroscience

On critical periods and reverse causality. Recent results from the Generation R birth cohort

Longitudinal Developmental Science from Birkenhead to Bangalore Conference

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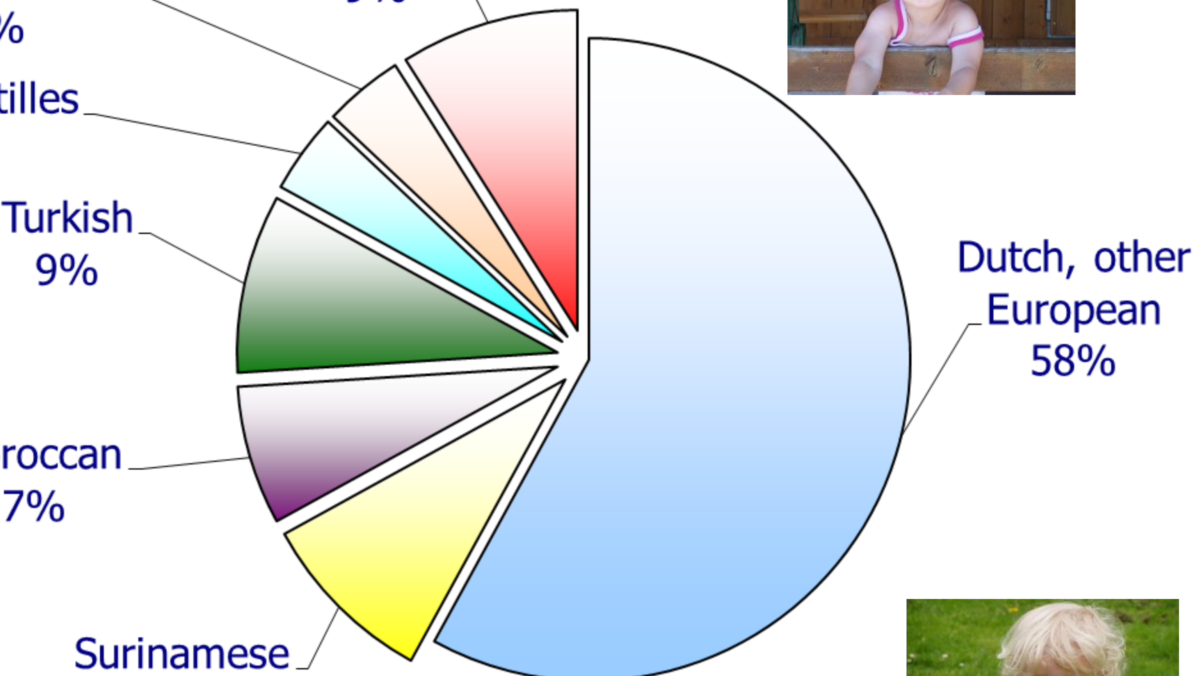
Overview of the presentation

- Introduction
- Shared method variance bias
- Reverse causality
- Critical periods
- My current favourite longitudinal result from Generation R

Design Generation R

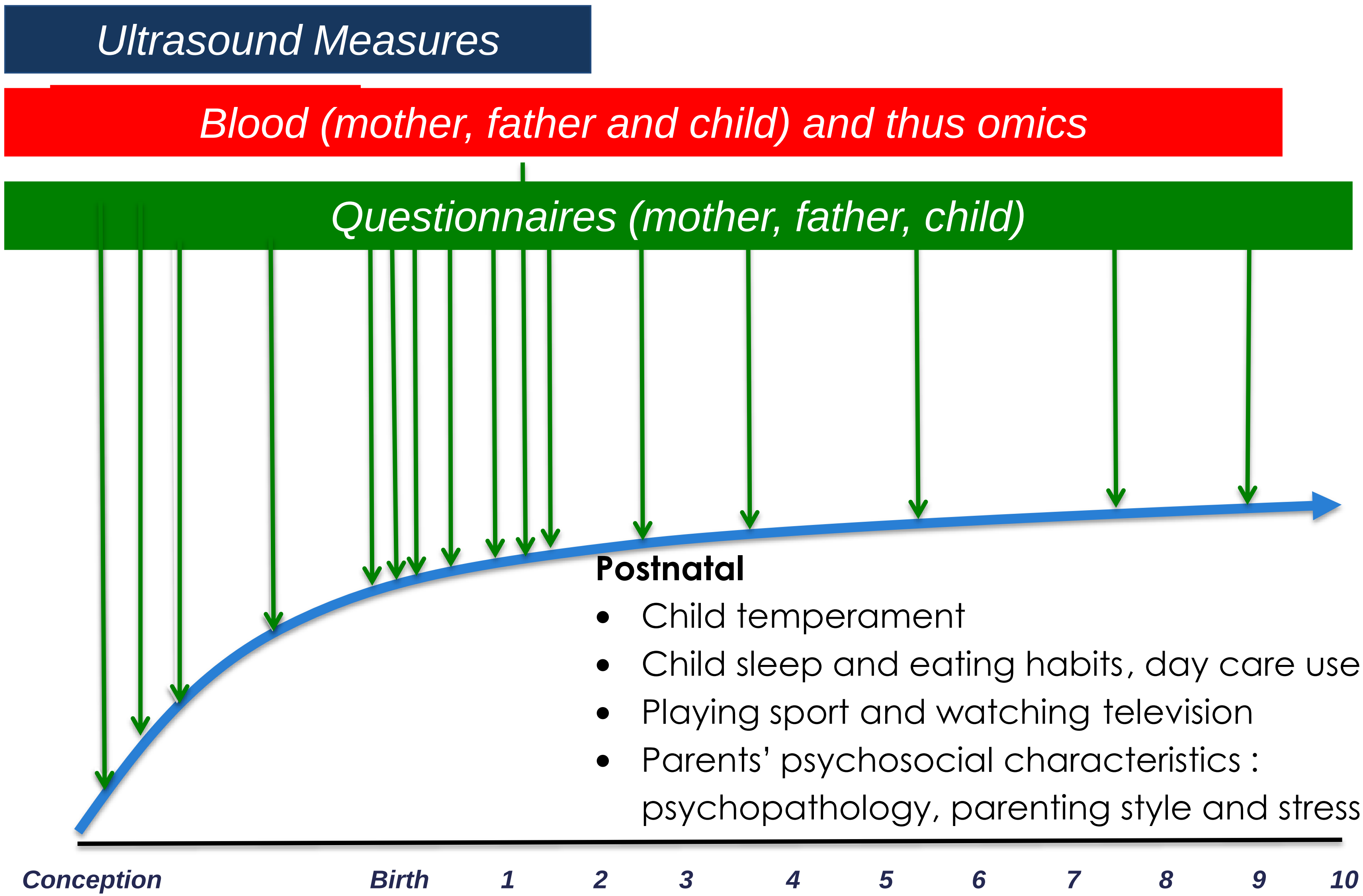
- Prospective cohort design
- From early foetal life
- 9,778 mothers and their children
- Detailed measures in Focus cohort (N=1,106)
- Urban, multi-ethnic population

Generation R: National origins

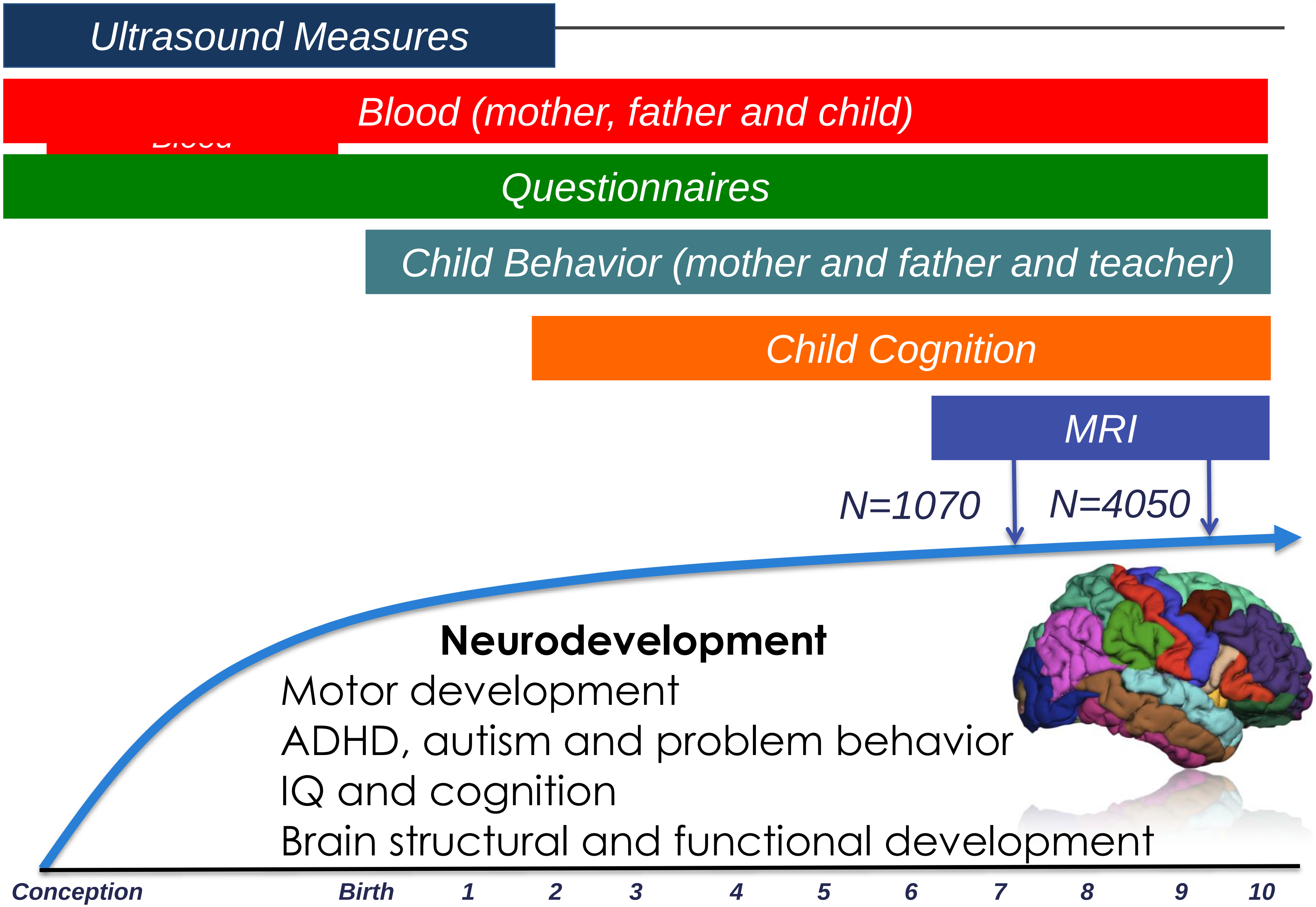


Based on classification according to the CBS, 2004; Missing: (12%)

Overview of design and assessments



Overview of design and assessments



Child assessment to address shared method variance bias

Parental depression and maternal report

	Mother report*				
Life-time depression	%	N	*B*	95% *CI(B)*	*p*-value
			Emotional problems		
Father	15.9	3175	**0.10**	**0.01;0.20**	**0.032**
Mother	27.7	3176	**0.26**	**0.19;0.34**	**0.000**
			Behavioral problems		
Father	15.9	3165	**0.13**	**0.04;0.23**	**0.005**
Mother	27.7	3166	**0.23**	**0.15;0.31**	**0.000**

Ringoot et al., J Clin Epi, 2015

Parental depression and child report

			Child report*		
Life-time depression	%	N	*B*	95% *CI(B)*	*p*-value
			Emotional problems		
Father	15.9	3175	**0.12**	**0.03;0.21**	**0.009**
Mother	27.7	3176	**0.11**	**0.03;0.19**	**0.004**
			Behavioral problems		
Father	15.9	3165	**0.15**	**0.06;0.24**	**0.001**
Mother	27.7	3166	0.06	-0.01;0.14	0.112

Adjusted for parent age at intake, income, marital status, maternal educational level, smoking during pregnancy, child ethnicity, child gender, child age at interview, number of siblings, and verbal abilities of the child

Paternal report, parental depression and child report

Lifetime depression, (dichotomous)	Child age 3 yr			
	Father report (CBCL)[a]		Mother report (CBCL)[a]	
	B	95% CI	*B*	95% CI
	Emotional problems score $N = 2{,}573$			
Father	***0.25***	***0.14, 0.35**** ***	0.14	0.04, 0.25**
Mother	0.17	0.09, 0.26***	***0.25***	***0.16, 0.33**** ***
	Behavioral problems score $N = 2{,}573$			
Father	***0.24***	***0.13, 0.34**** ***	0.18	0.07, 0.28**
Mother	0.17	0.08, 0.26***	***0.20***	***0.11, 0.28**** ***

Adjusted for parent age at intake, income, marital status, maternal educational level, smoking during pregnancy, child ethnicity, child gender, child age at interview, number of siblings, and verbal abilities of the child

Ringoot et al., J Clin Epi, 2015

Reverse causality
an obvious example: feeding

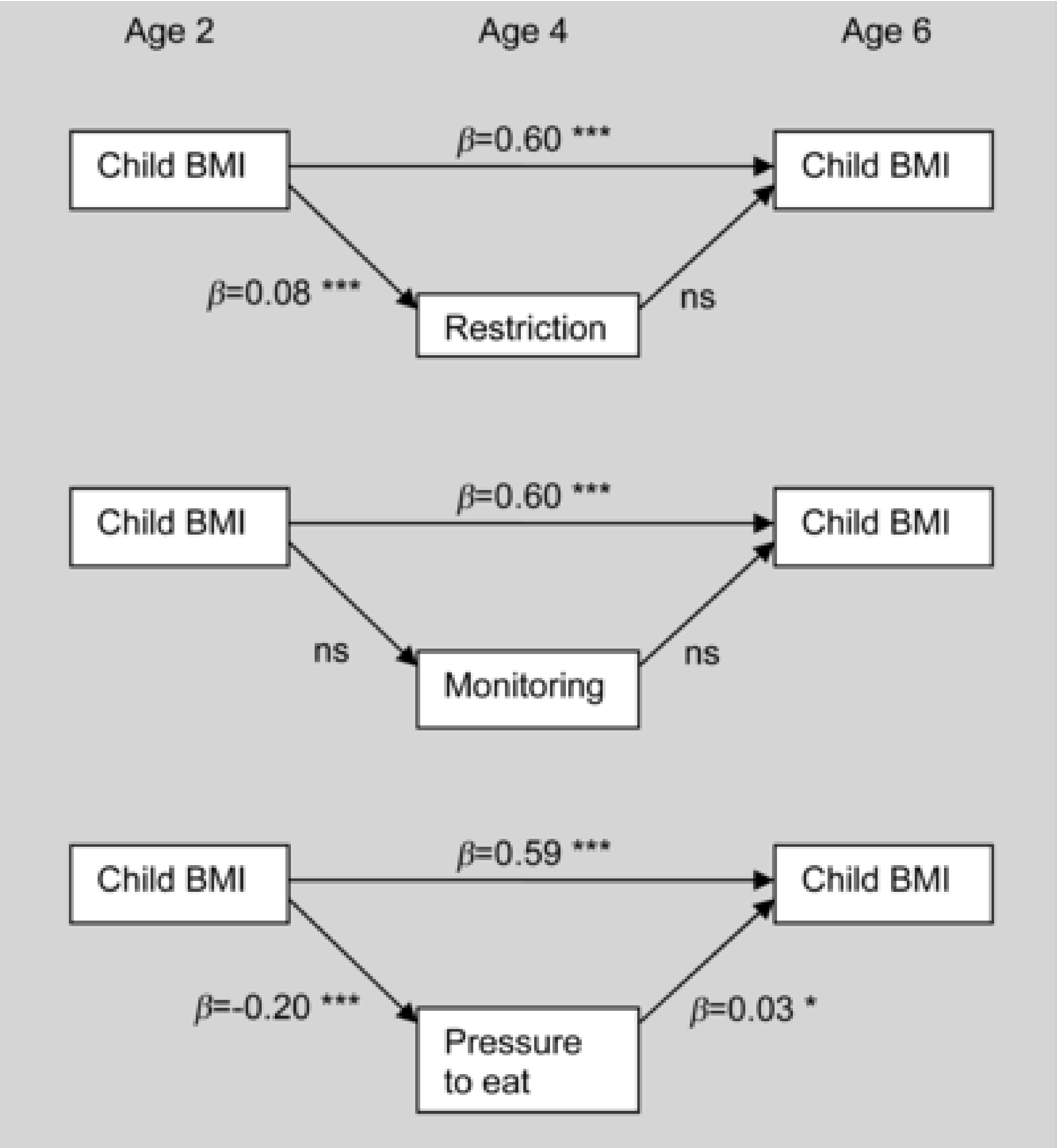
Feeding scales (/SD)	Child BMI SD score	*P*
	BMI at age 4 y	
Feeding at age 2 y		
Pressuring feeding		
Unadjusted	−0.04 (−0.07, −0.01)	0.04
Confounder adjusted	−0.04 (−0.08, −0.01)	0.01
	BMI at age 6 y	
Feeding at age 4 y		
Restriction		
Unadjusted	0.08 (0.05, 0.10)	<0.001
Confounder adjusted	0.07 (0.04, 0.09)	<0.001
Pressure to eat		
Unadjusted	−0.13 (−0.16, −0.10)	<0.001
Confounder adjusted	−0.17 (−0.19, −0.14)	<0.001

Confounders included child age, child ethnicity, maternal education, and maternal BMI.

Feeding and child weight

Feeding scales (/SD)	Child BMI SD score	*P*
	BMI at age 4 y	
Feeding at age 2 y		
Pressuring feeding		
Unadjusted	−0.04 (−0.07, −0.01)	0.04
Confounder adjusted	−0.04 (−0.08, −0.01)	0.01
Further adjusted for child BMI at 2 y	−0.01 (−0.04, 0.01)	0.32
	BMI at age 6 y	
Feeding at age 4 y		
Restriction		
Unadjusted	0.08 (0.05, 0.10)	<0.001
Confounder adjusted	0.07 (0.04, 0.09)	<0.001
Further adjusted for child BMI at age 4 y	0.01 (−0.01, 0.03)	0.25
Pressure to eat		
Unadjusted	−0.13 (−0.16, −0.10)	<0.001
Confounder adjusted	−0.17 (−0.19, −0.14)	<0.001
Further adjusted for child BMI at 4 y	−0.02 (−0.04, −0.01)	0.01

Or as a path-model



Jansen et al.,
Am J Clin Nutri, 2014

Is baseline adjustment overcorrection or does it introduce some collider bias?

- Certainly in studies of Change (delta)

- But to some extent also in longitudinal studies with lagged variables

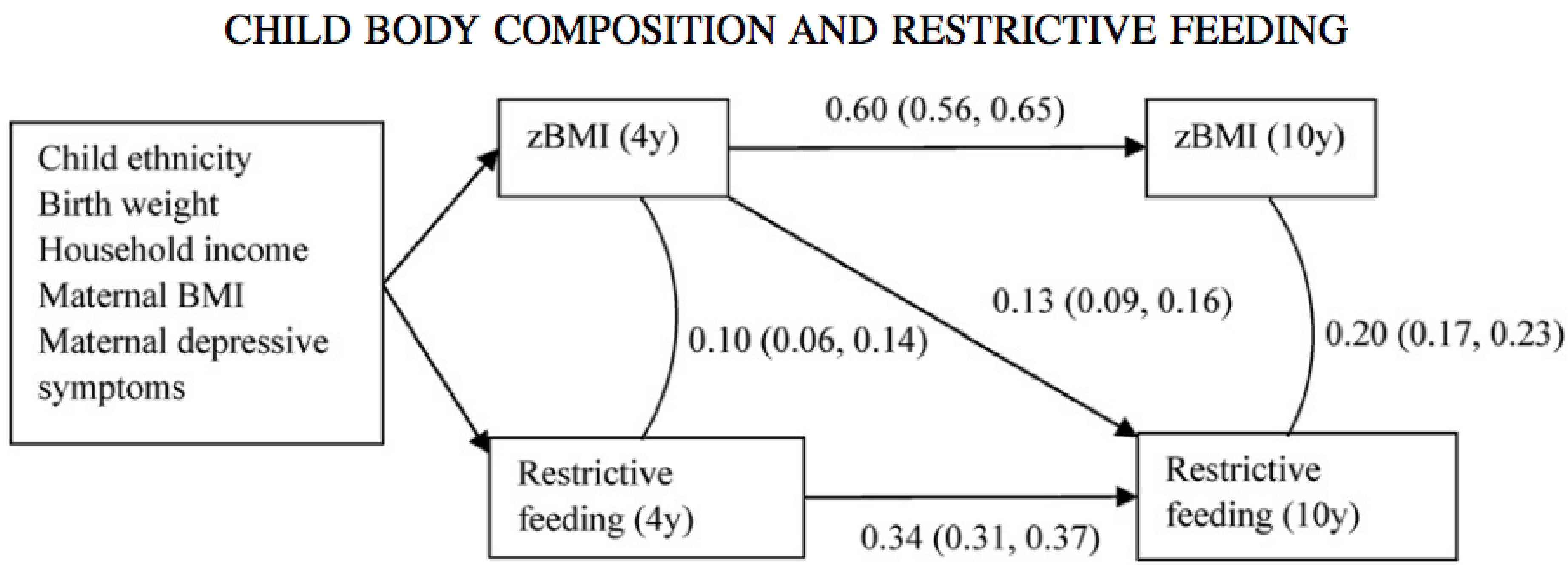
- Peto dubbed this the horse-racing effect: “In a race between fast and slow horses … one would expect to find the faster horses out in front halfway through the race”

Glymour et al. 2005, AJE

Problems with adjustment occur if:

- Measures of the outcome fluctuate because of imperfect measurement reliability or latent variable instability; or
- Change has already occurred prior to the baseline measurement, the rate of change experienced in the past predicts the future rate of change, and exposure is unaffected by baseline function.

Thus with more follow-up and as a cross-laged model



Derks et al.,
Am J Clin Nutri, 2017

Brain and Behaviour: Direction of effects?

The MRI pilot Imaging study of children aged 6 to 8 years

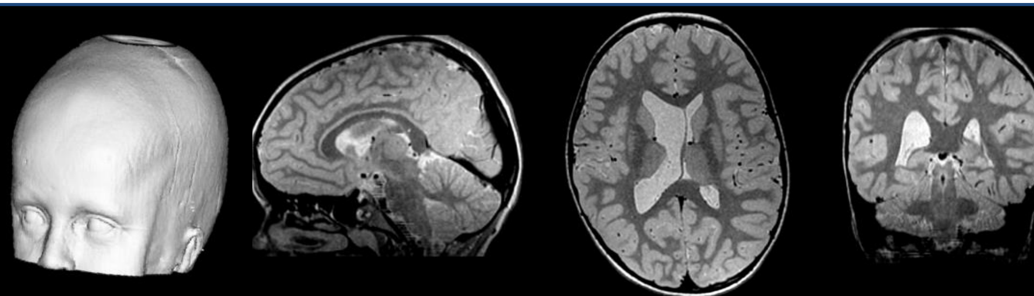
N=1070 of which 760 acceptable quality

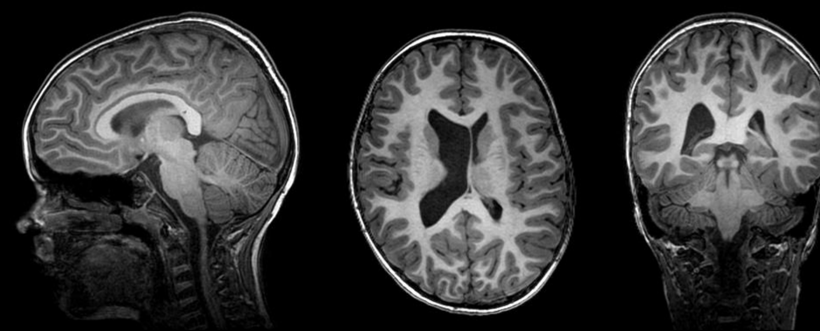
Sequences at MRI

30 minute protocol

Anatomical

Isotropic proton density
Isotropic T1-weighted





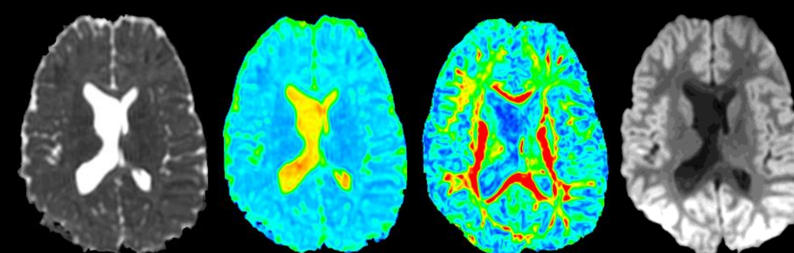
$0.9 \times 0.9 \times 0.9$ mm^3

3.0T – 8ch head coil Discovery MR750

DTI

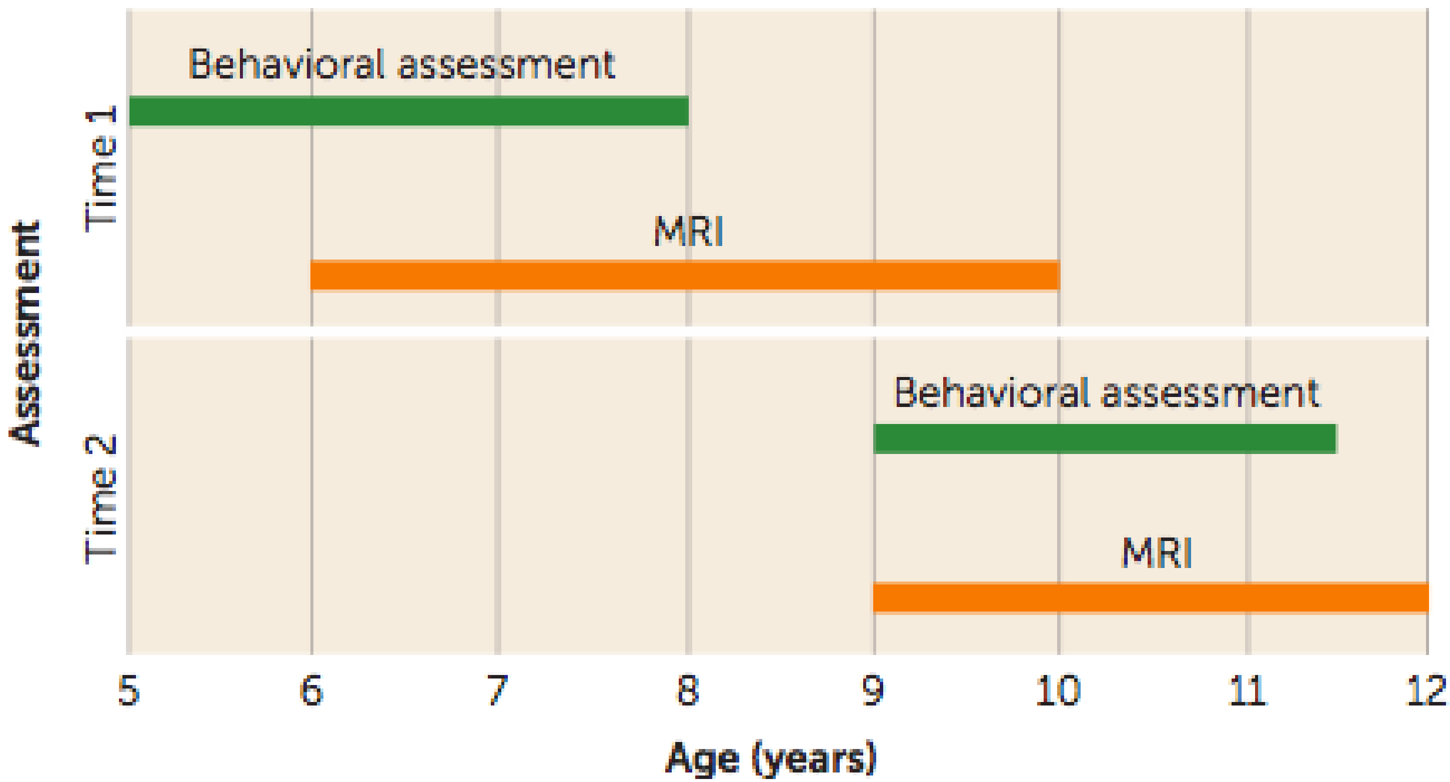
36 direction Diffusion Tensor Scanning

DTI - $2.0 \times 2.0 \times 2.0$ mm^3



A longitudinal imaging study

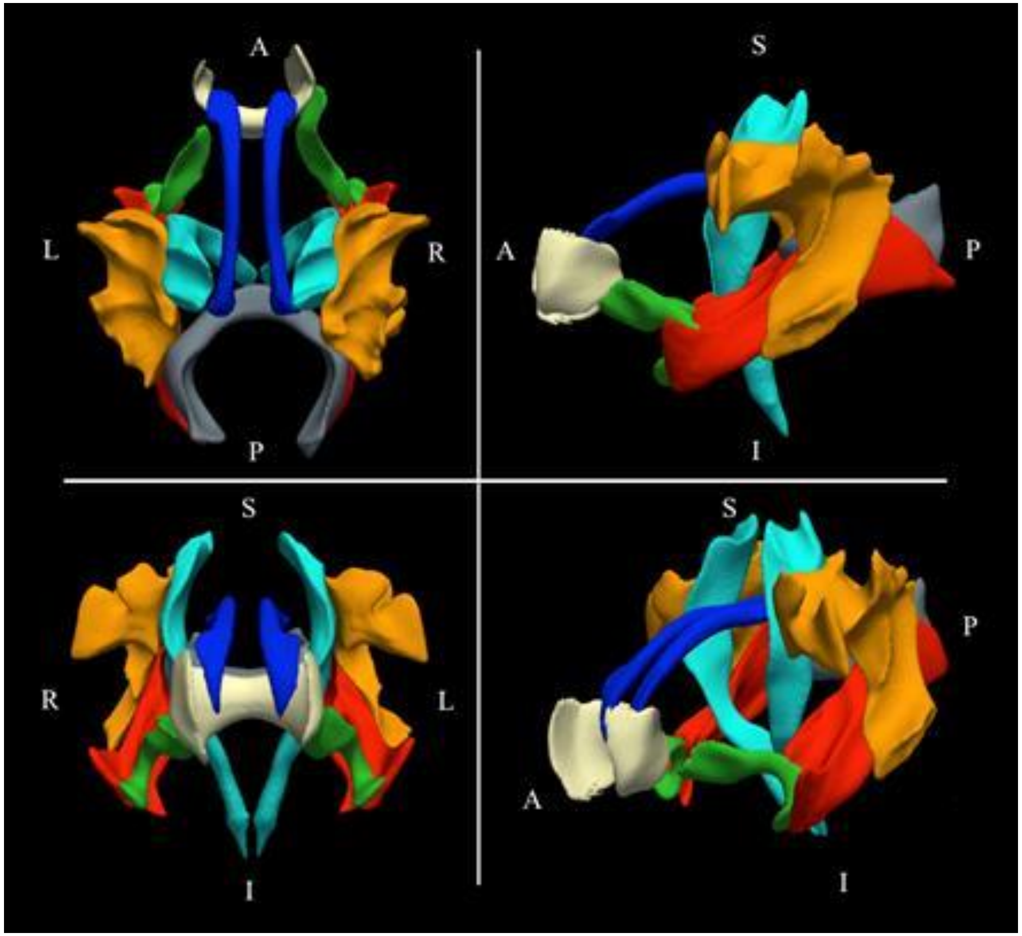
FIGURE 1. Timeline of Data Collection Points in a Study Tracking Brain Development and Dimensional Psychiatric Symptoms in Children[a]



[a] The figure indicates the age ranges of study participants during each type of assessment.

Muetzel et al., Am J Psych, 2017

Change of connectivity in pre-adolescence



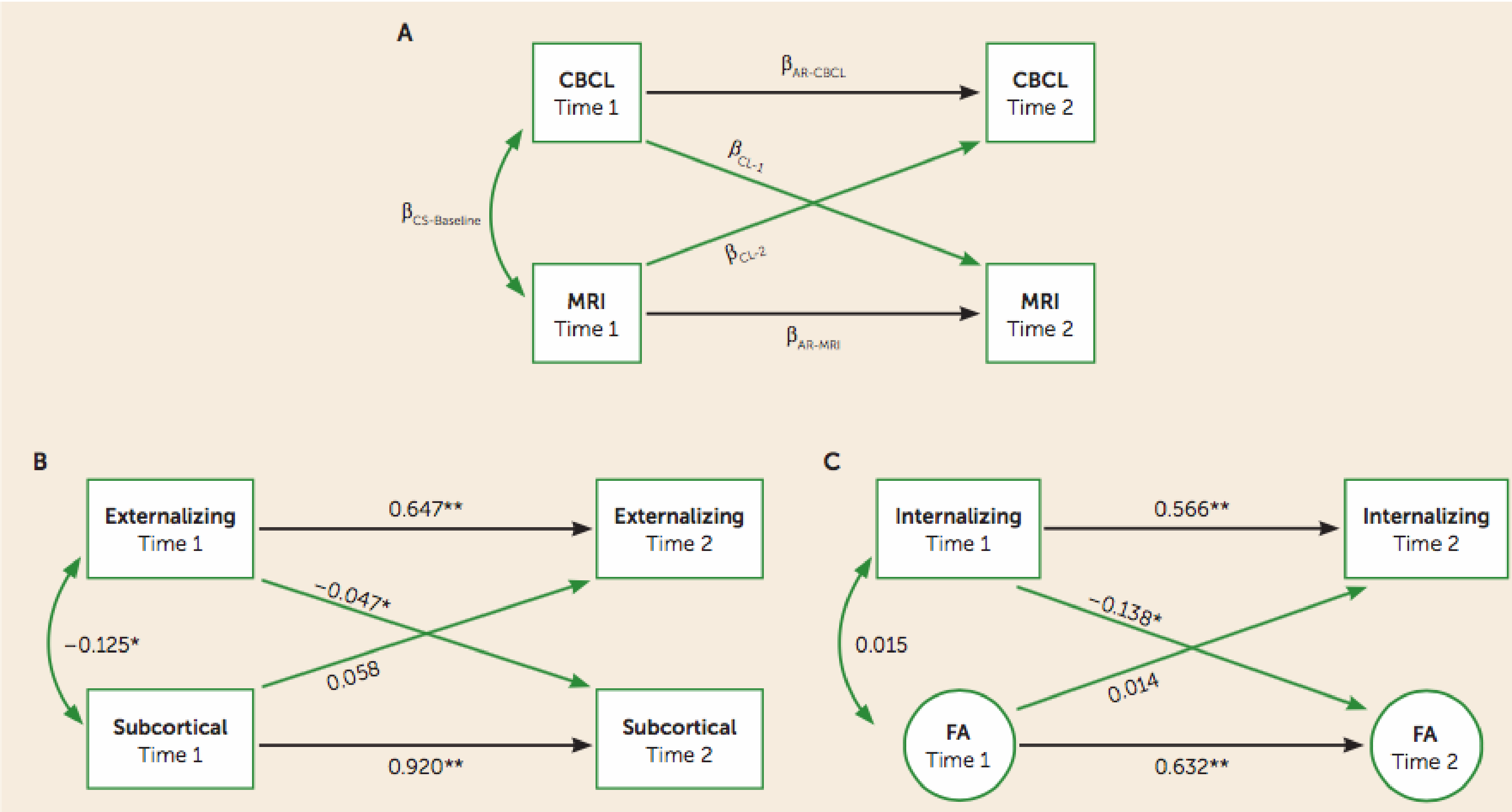
Tracts are group average representations in standard coordinate space.

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

Design of analyses

FIGURE 3. Cross-Lagged Panel Models Applied to Assess Macro- and Microstructural Brain Changes and Dimensional Psychiatric Symptoms in Children[a]



[a] Panel A depicts the general modeling strategy used for cross-lagged panel models. Panel B depicts the cross-lagged panel model where total subcortical volume was associated with broadband externalizing problems, and panel C depicts the cross-lagged panel model where global fractional anisotropy was associated with broadband internalizing problems. Numeric values are standardized structural regression coefficients. AR=autoregressive; CBCL=Child Behavior Checklist; CL=cross-lagged; CS=cross-sectional; FA=fractional anisotropy.

*p<0.01. **p<0.001.

Design of analyses

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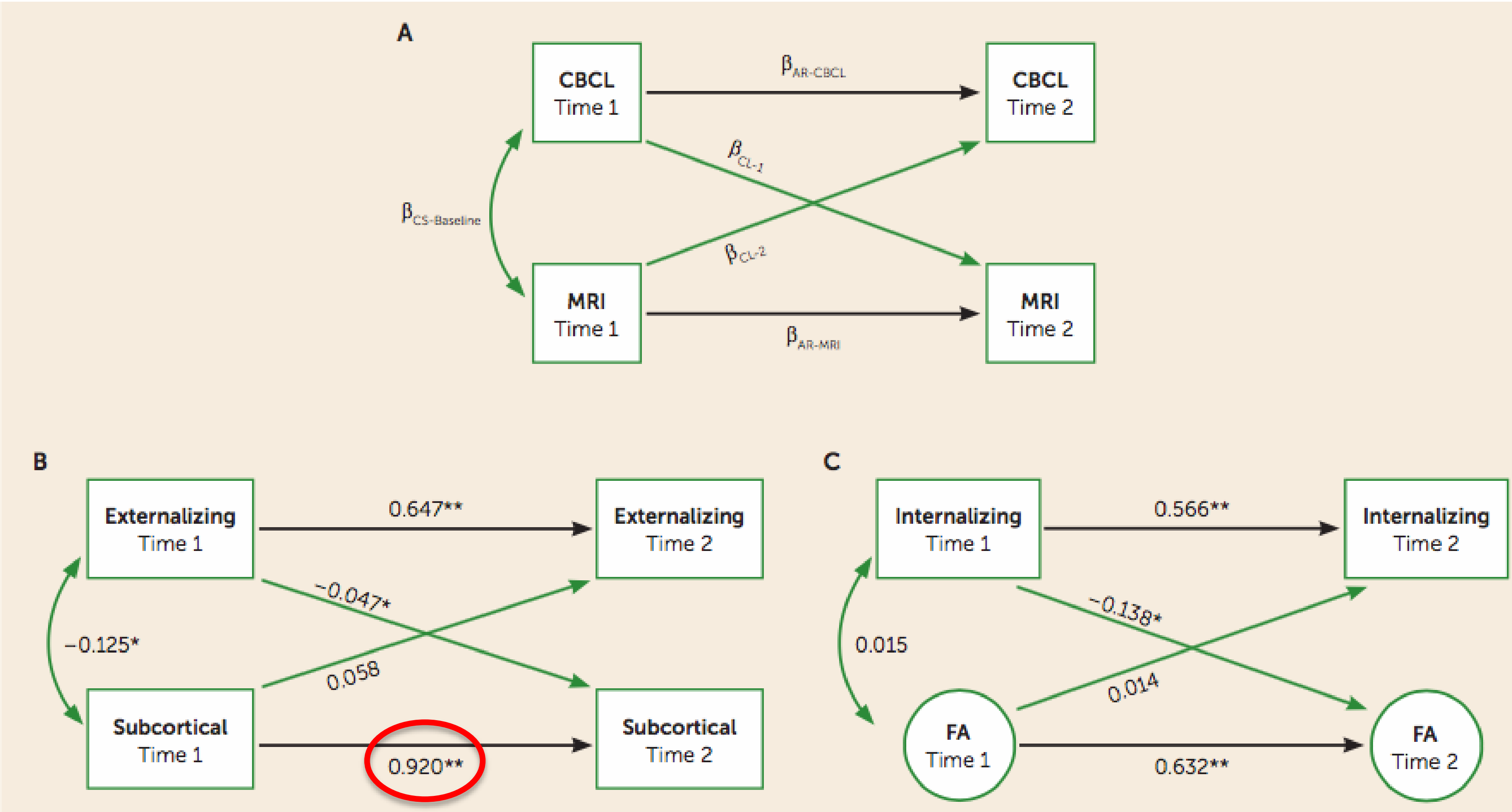

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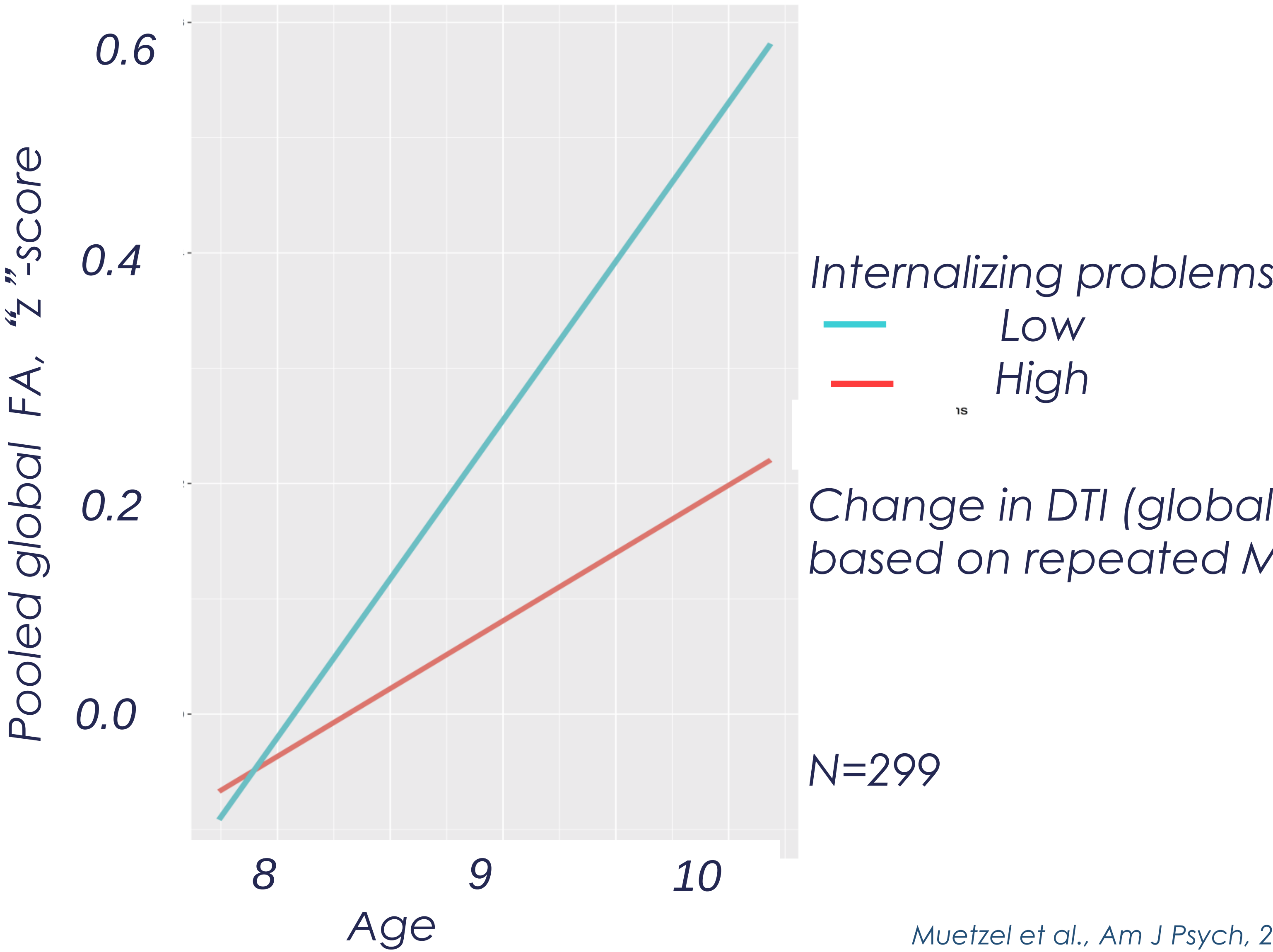
Internalizing problems and the change of connectivity

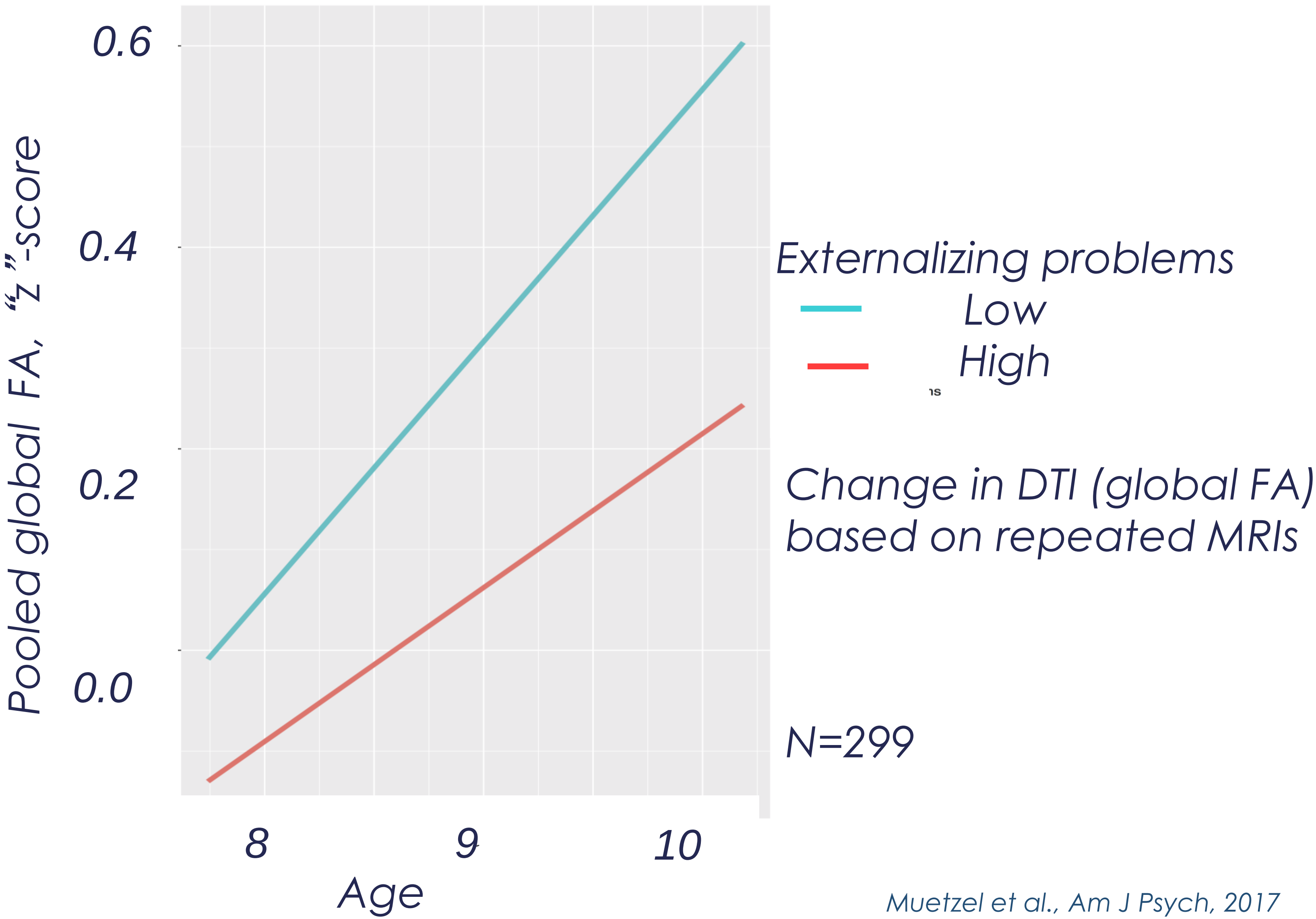


Change in DTI (global FA) based on repeated MRIs

N=299

Muetzel et al., Am J Psych, 2017

Externalizing problems and the change of connectivity

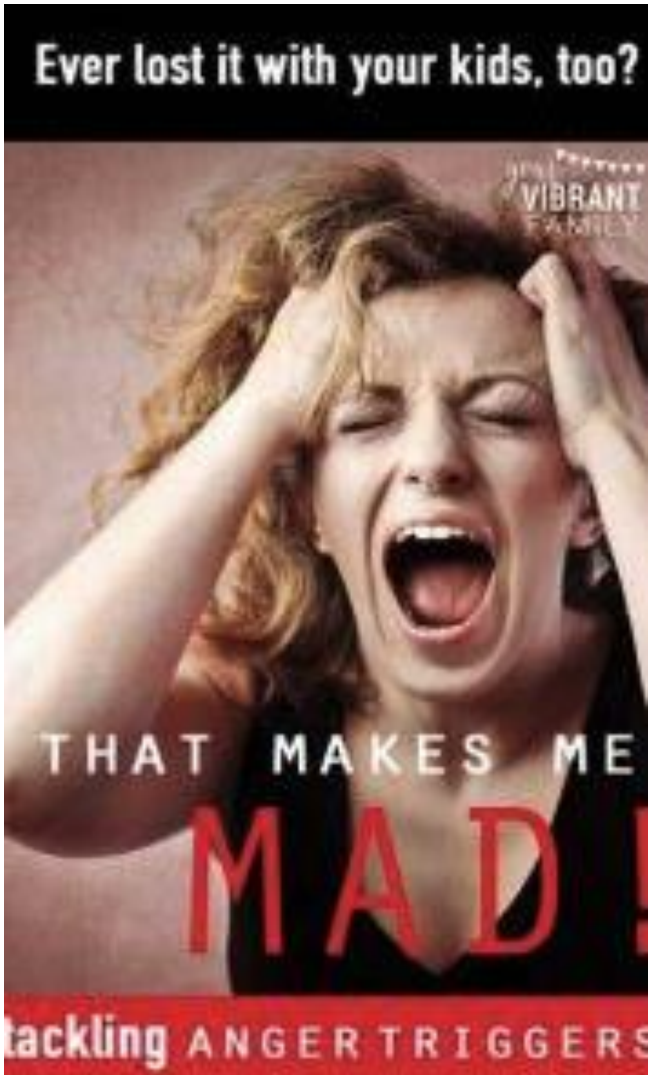


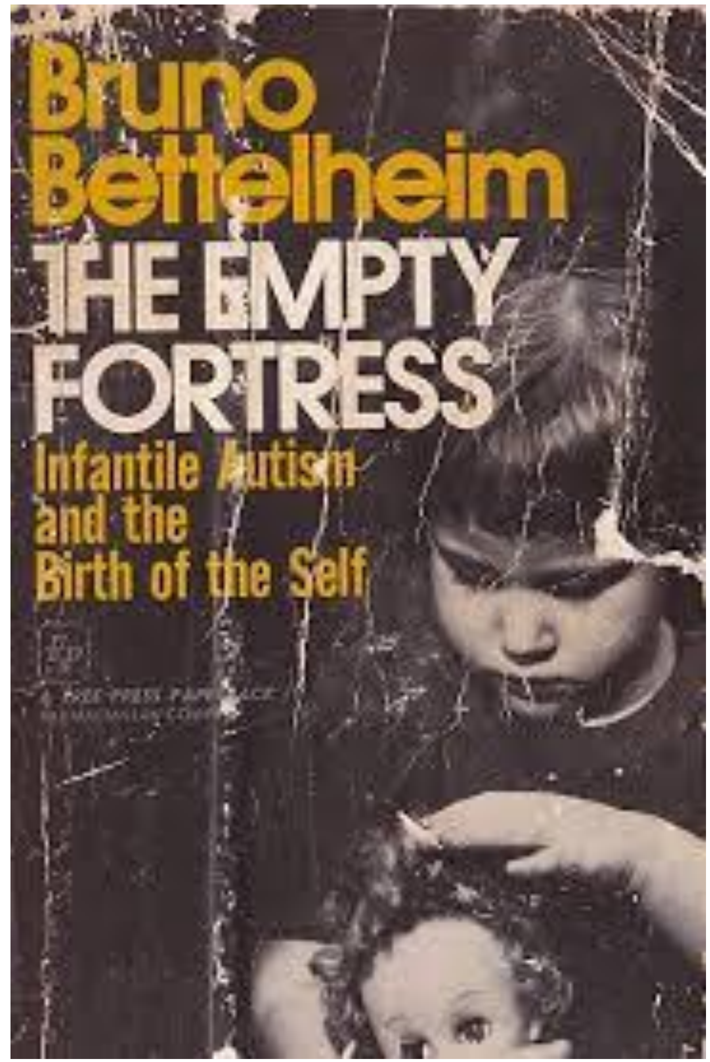
Change in DTI (global FA) based on repeated MRIs

N=299

Muetzel et al., Am J Psych, 2017

Reversed causality: Refrigerator mums, double bind and other myths





A reinterpretation of the direction of effects in studies of socialization.

By Bell, Richard Q.

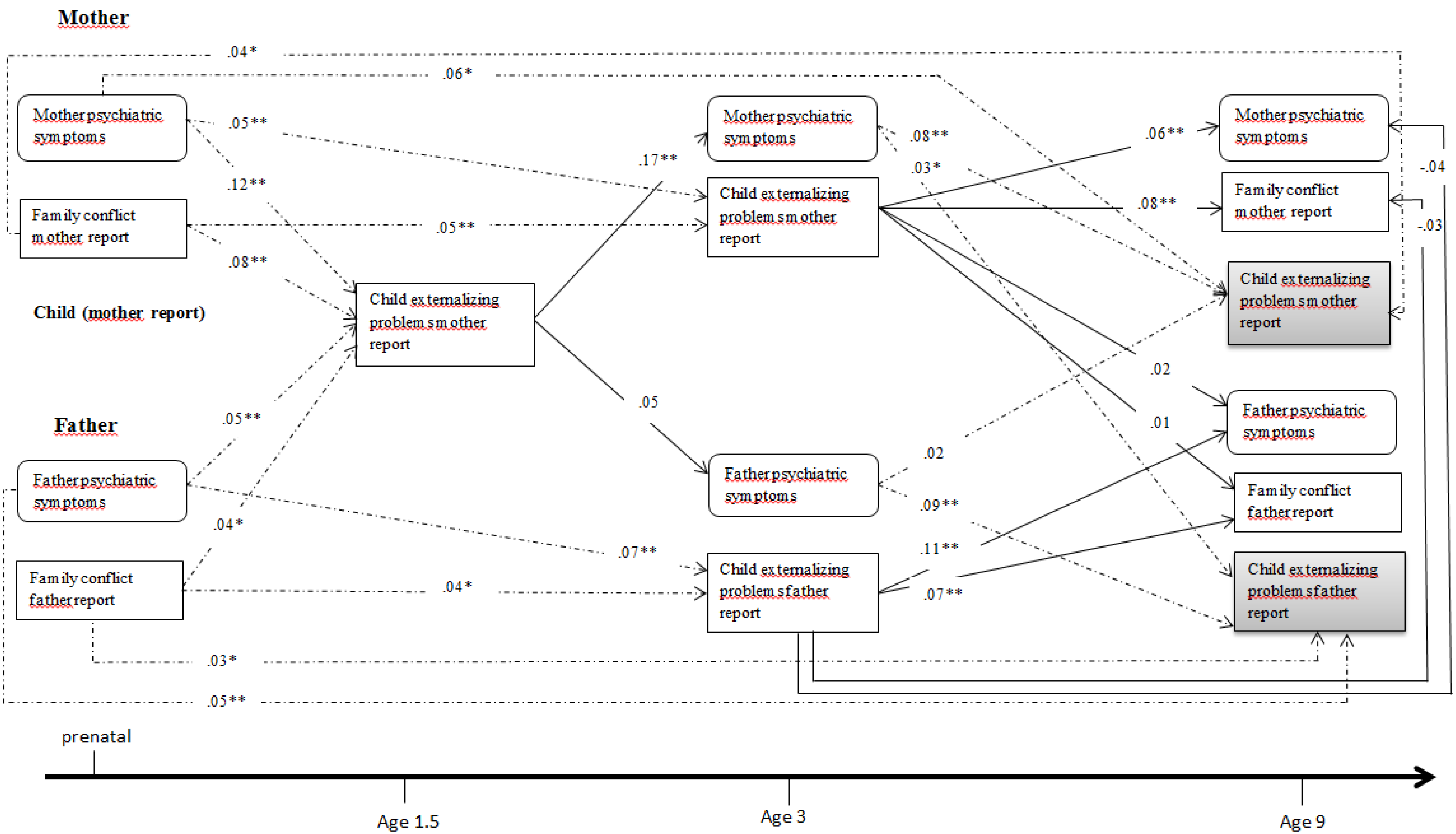
Psychological Review, Mar 1968, 81-95

STUDIES ARE SUMMARIZED INDICATING THAT THE BASIC MODEL OF SOCIALIZATION, THE ACTION OF A PARENT ON A CHILD, IS TOO LIMITED TO ACCOMMODATE DATA EMERGING FROM RECENT STUDIES OF HUMAN AND ANIMAL SS. A SET OF PROPOSITIONS IS PRESENTED CONCERNING THE EFFECTS OF CONGENITAL FACTORS IN CHILDREN ON PARENT BEHAVIOR. THIS SYSTEM IS APPLIED TO CURRENT FINDINGS IN SEVERAL MAJOR AREAS. CURRENT LITERATURE ON SOCIALIZATION, BASED LARGELY ON CORRELATIONS BETWEEN PARENT AND CHILD BEHAVIOR, CAN BE REINTERPRETED PLAUSIBLY AS INDICATING EFFECTS OF CHILDREN ON PARENTS. A CORRELATION DOES NOT INDICATE DIRECTION OF EFFECT. IT IS FELT THAT THE EFFECT OF CHILDREN ON PARENTS CAN NO LONGER BE DISMISSED AS ONLY A LOGICAL BUT IMPLAUSIBLE ALTERNATIVE EXPLANATION OF A CORRELATION

From child to parent: the associations of child problem behavior with parental psychopathology and family functioning

- The parent-child relation interwoven in cycles of reciprocal causality
- Child-parent effects are less strong than parent-child effects
- N = 5536 for externalizing behavior and N = 5518 for internalizing behavior
- the bidirectional associations of child problem behavior with parental psychopathology and family conflict across childhood

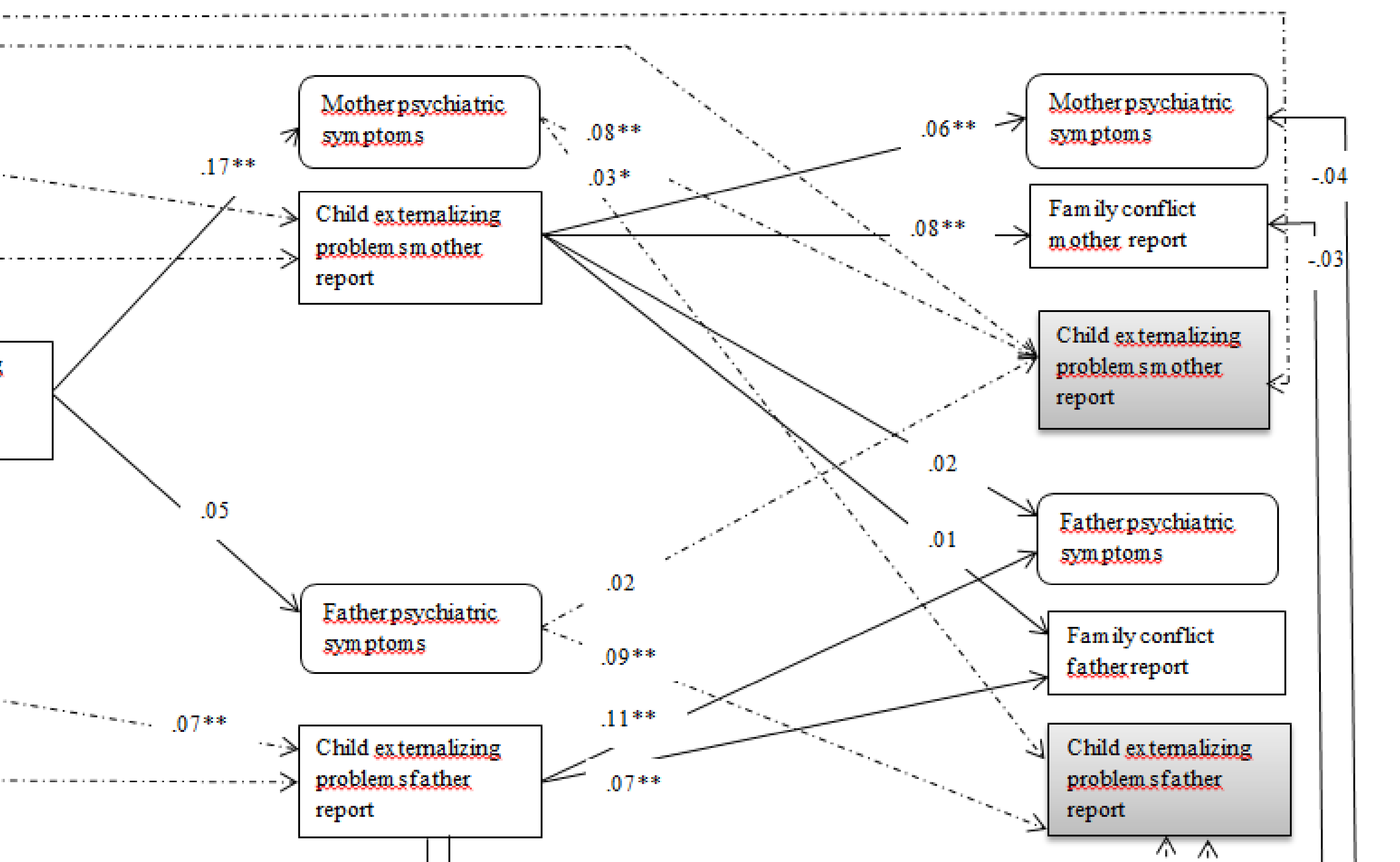
Figure 1. Bidirectional associations of parental psychopathology, family conflict and child externalizing problems.

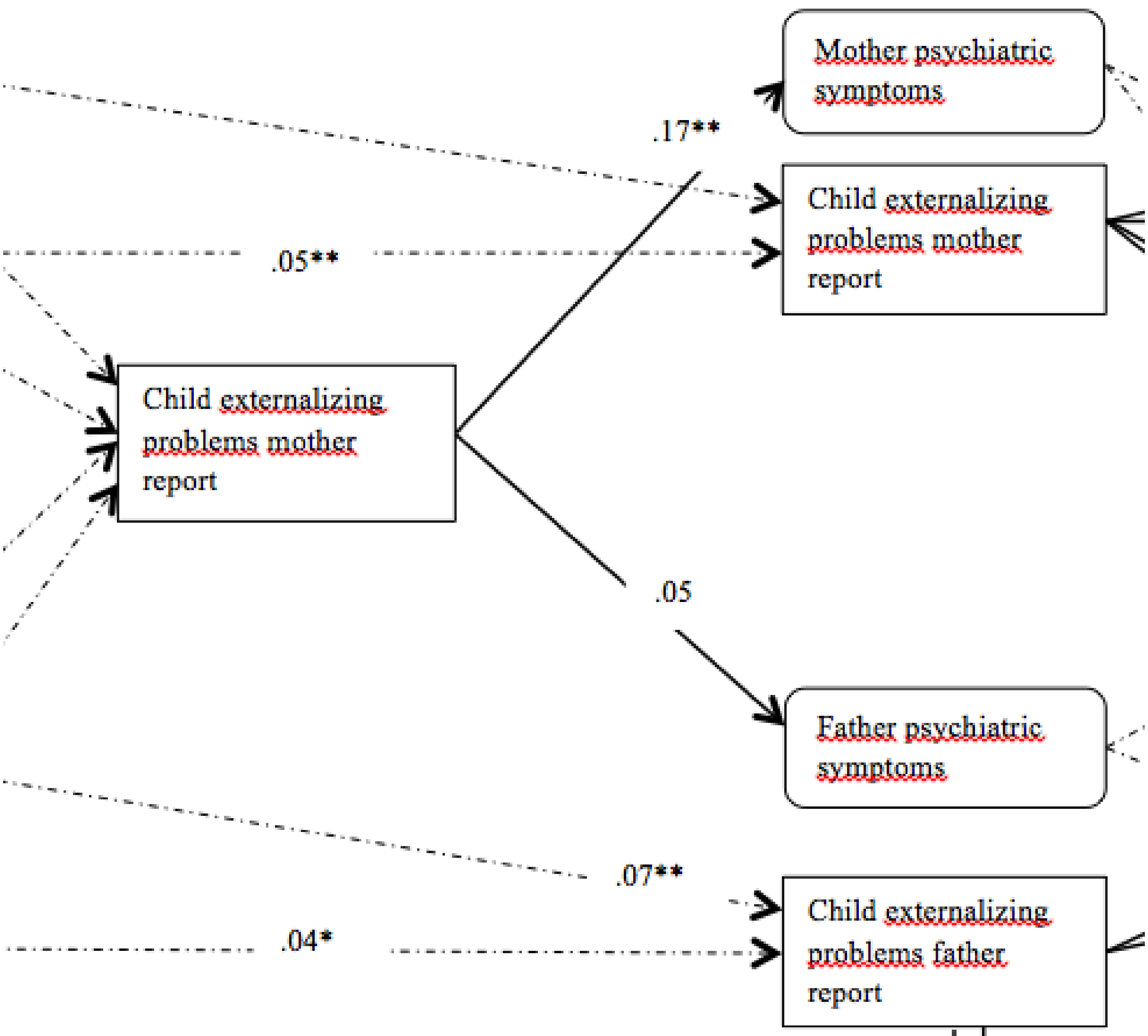


Note: Cross-lagged structural equation modeling of parental psychopathology, family conflict and child externalizing problems. Numeric values are standardized path regression coefficients averaged from 10 imputed datasets. The models are adjusted for age, ethnicity, education and religion, gestational age at birth, child's sex, child's age, prenatal parental psychopathology and prenatal family conflict reported by mother and father. (RMSEA =0.02; CFI=0.99; TLI=0.92). Unidirectional associations of parental psychopathology and family conflict mother and father reports are not presented in the figure to enhance readability.

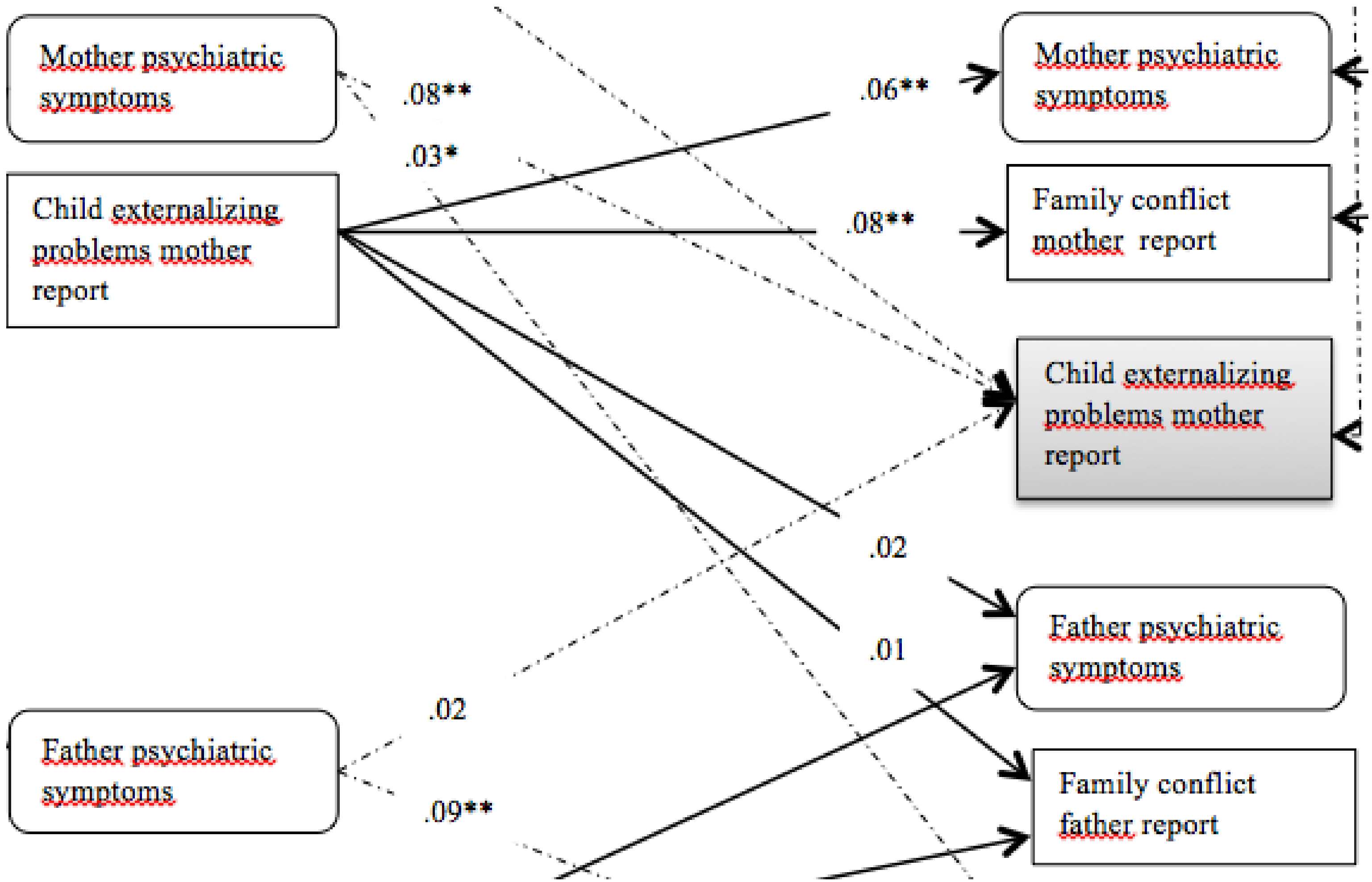
*p<0.01. **p<0.001.

athology, family conflict and child externalizing problems.




Mother psychiatric symptoms
.17**
Child externalizing problems mother report
.05**
Child externalizing problems mother report
.05
Father psychiatric symptoms
.07**
Child externalizing problems father report
.04*

Reverse causality or single method bias



Take home message

- Single-informant, single-method, shared method (variance), reporter or information bias is a known yet underestimated problem

- Beware during data collection
- Single reporter data is (largely) not acceptable in developmental science – psychiatry
- The common practice in adult psychiatric research is no excuse

Take home message

- Psychiatric epidemiology is the discipline of <u>reversed causality</u>

- The association is always the other way round and sometimes bi-directional

- We rarely have the data to demonstrate bi-directionality even if we measured exposure and outcome repeatedly (as we would ideally need 3 or more not too stable measures

Prenatal exposures

Maternal risk factors

- Family distress
- **Depression**
- Smoking and cannabis use
- SSRI use
- Fatty acids
- Thyroid deficiency
- Folate intake
- Vitamin D deficiency
- *Organophosphates*

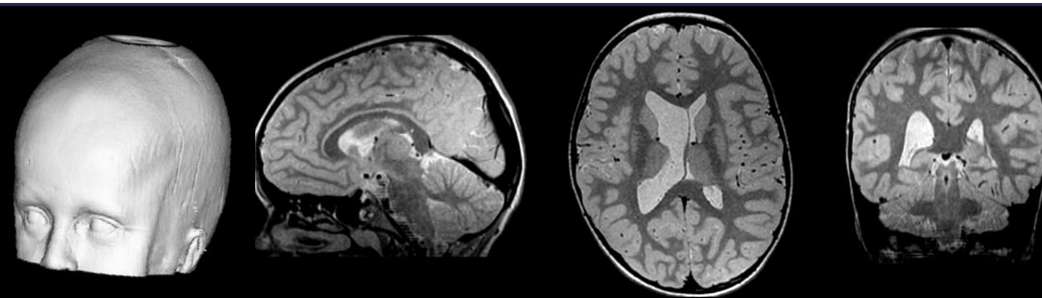
Critical periods & Maternal depression

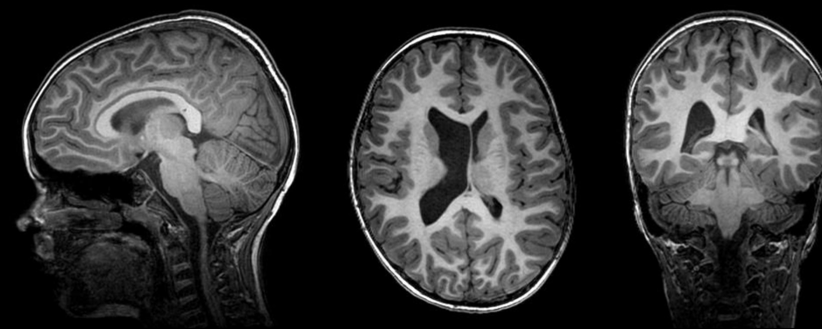
Sequences at MRI

30 minute protocol

Anatomical

Isotropic proton density
Isotropic T1-weighted





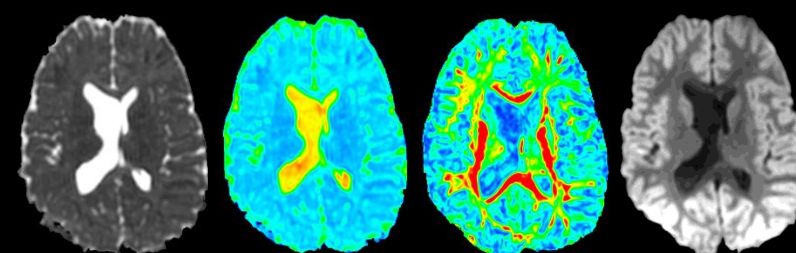
0.9 x 0.9 x 0.9 mm^3

3.0T – 8ch head coil Discovery MR750

DTI

36 direction Diffusion Tensor Scanning

DTI - 2.0 x 2.0 x 2.0 mm^3

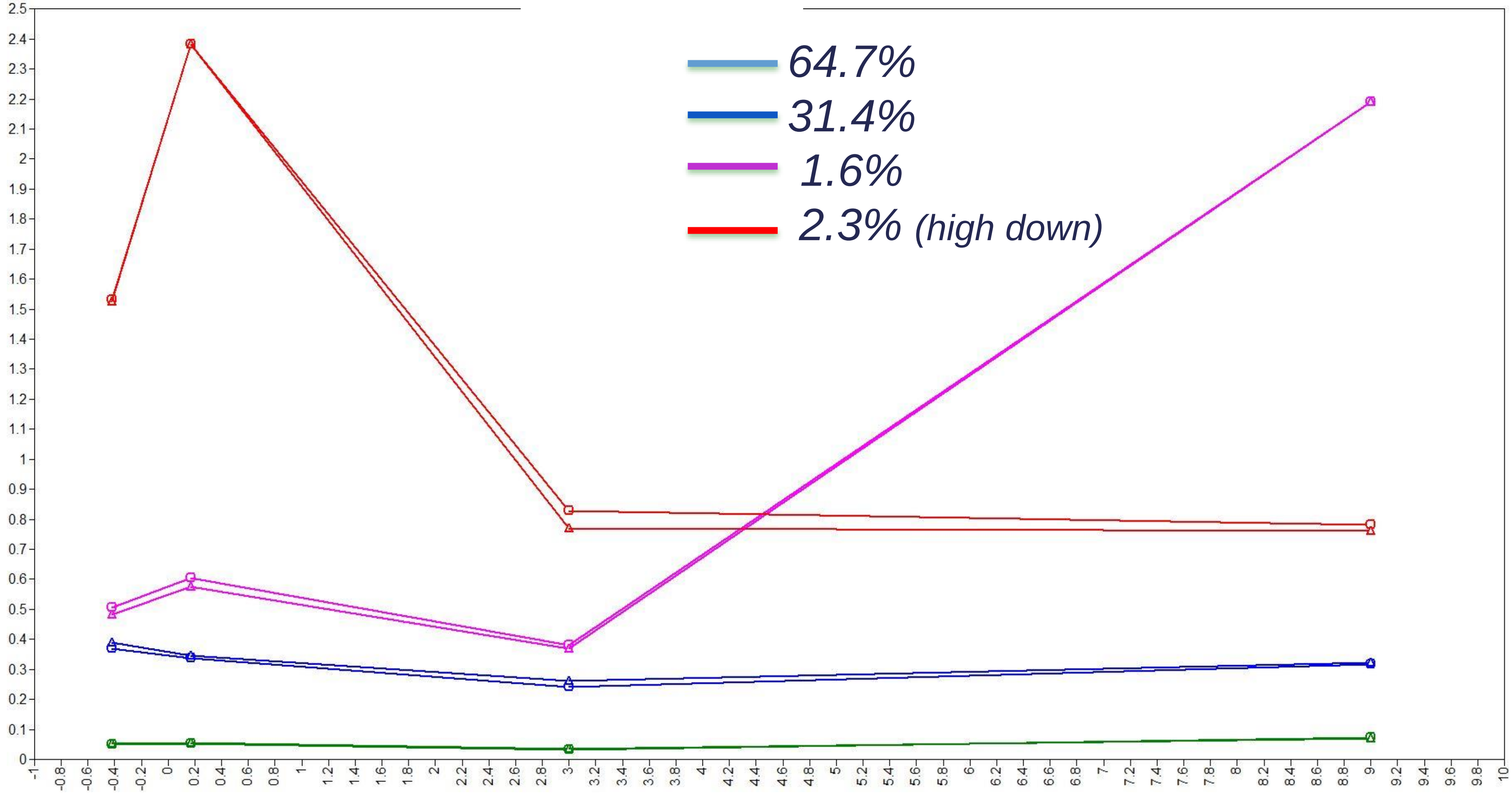


Single time point maternal depression and global DTI age 9 years

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

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.

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 1	No (n=1851)	ref	-	-
	Low (n=703)	-0.23	(-0.39 -0.07)	0.005
	Medium-up (n=37)	0.02	(-0.56, 0.61)	0.946
	High-down (n=56)	-0.80	(-1.28, -0.32)	0.001
Model 3	No	Ref	-	-
	Low	-0.14	(-0.30, 0.02)	0.097
	Medium-up	0.21	(-0.37, 0.79)	0.472
	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.

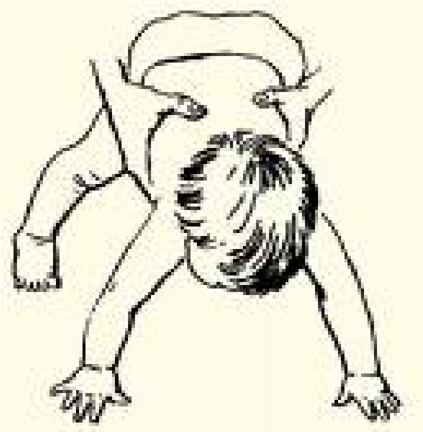
Critical periods

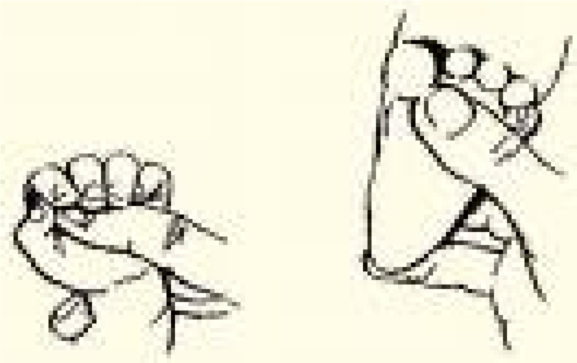
- Variable exposure
- Carry over effects of exposure
- Biological periods of rapid development, sensitive window etc.
- Thyroid hormone, serotonin, vitamin D, hormones

Causes and consequences of neuromotor development in infants

PhD student: Tamara van Batenburg-Eddes

Age-adapted Touwen neurological examination/neuromotor assessment





Senses, reflexes, responses and tonus

The assessment

Subscale	*Position*	*Item description*	*Answering categories*		
			Optimal	*Non-optimal*	*Non-optimal*
Tone	Supine	Resting posture	Semi-flexed legs; slight abduction at the hips	Legs flat on the surface	Legs stretched
		Adductor angle	> 80° - < 140°	> 140°	< 80°
		Popliteal angle	90°-130°	130°-180°	< 90°
		Ankle angle	> 20° - < 90°	< 20°	> 90°
		Head preference	No	Yes	
		Opening & closing hands	Yes	Sometimes closed	Always closed
		Alternating leg movements	Yes	Decreased	Absent
		Grasps with one hand	Yes	Decreased	Absent
		Hyperextension	No	Sometimes	Yes
		Dyskinesia	No	Sometimes	Yes
	Supine-to- sit	Traction response	Arms moderately flexed	Arms fully extended, no resistance	Strong resistance, flexion elbows, legs extended
		Traction response-head control	Active lift of head	Head lag	Exaggerated
	Horizontal	Ventral Tone	Normal tone	Low tone	Back and limbs stretched

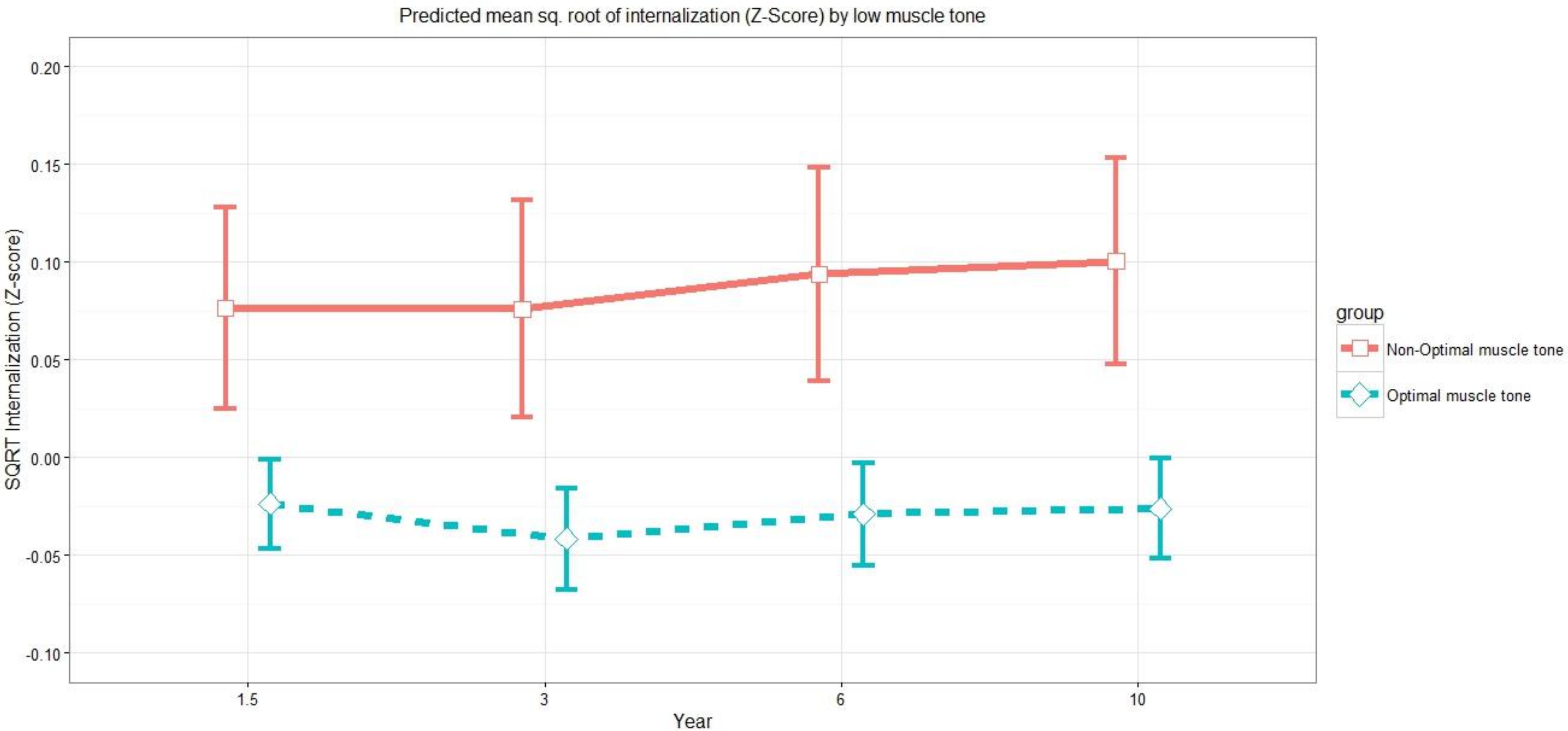
Generation R

Erasmus MC

Polygenic risk score for schizophrenia, n=1,174

Schizophrenia	Non-optimal neuro-motor development		
	OR (95% CI)	*p*	*Number of SNPs*
$P_T < 0.0005$	1.14 (1.00; 1.29)	**0.05**	**2,965**
$P_T < 0.001$	1.14 (1.00; 1.29)	**0.04**	**4,148**
$P_T < 0.005$	1.14 (1.01; 1.30)	**0.04**	**9,547**
$P_T < 0.01$	1.14 (1.01; 1.30)	**0.03**	**13,916**
$P_T < 0.05$	1.15 (1.02; 1.30)	**0.03**	**34,947**
$P_T < 0.1$	1.12 (0.99; 1.27)	0.08	52,256
$P_T < 0.5$	1.12 (0.99; 1.26)	0.08	126,674

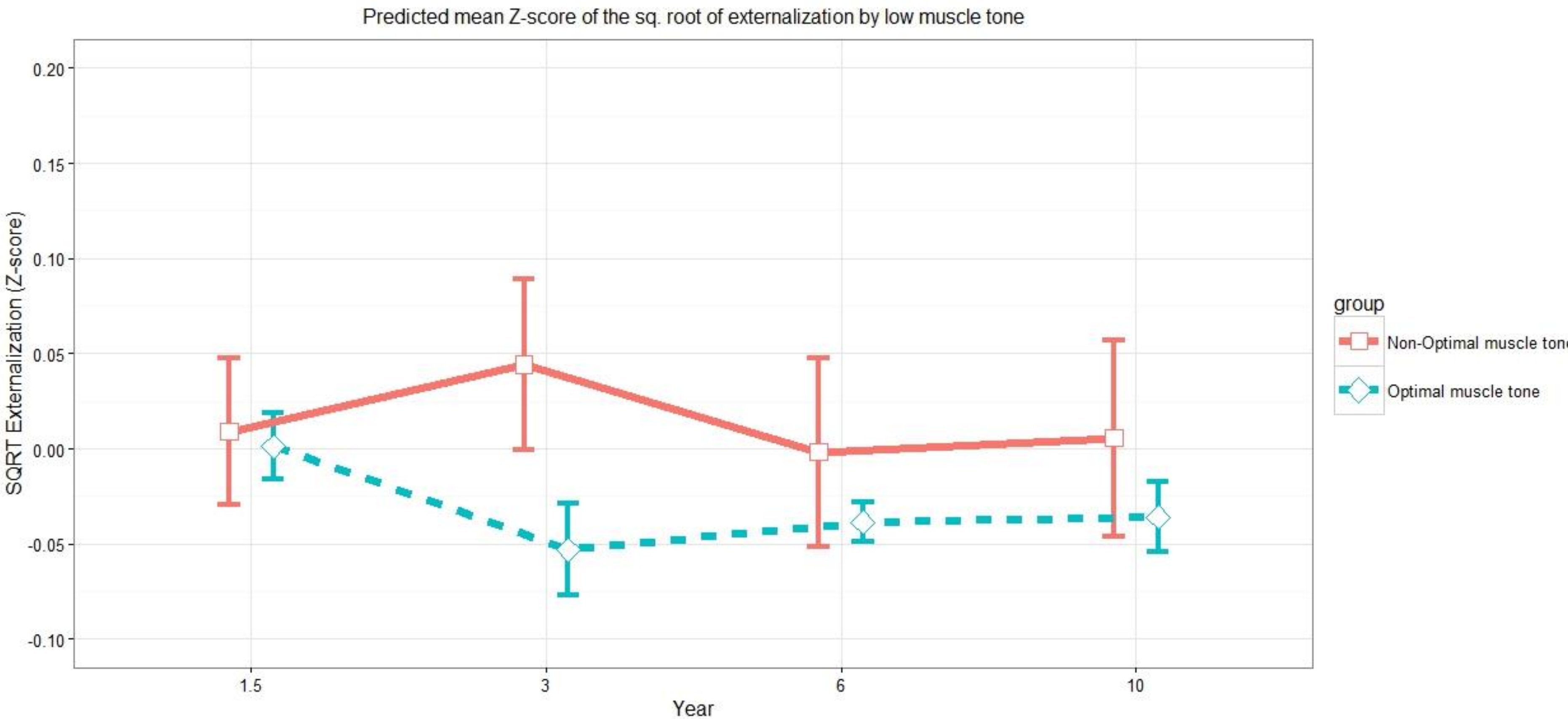
Optimal/non-optimal muscle tone at age weeks and development of internalizing symtpoms



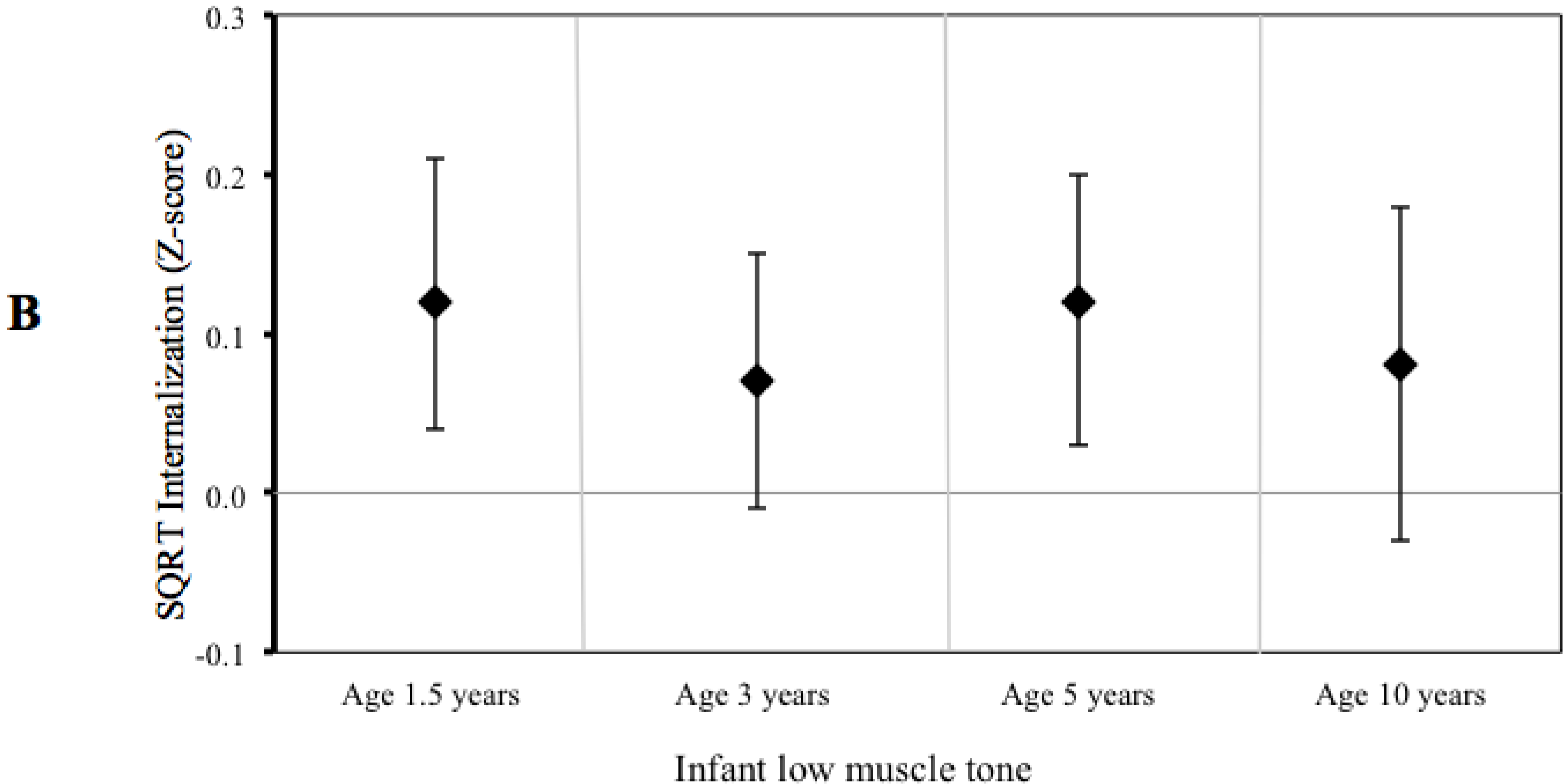
Generation R

Erasmus MC

Optimal/non-optimal muscle tone at age weeks and development of externalizing symptoms

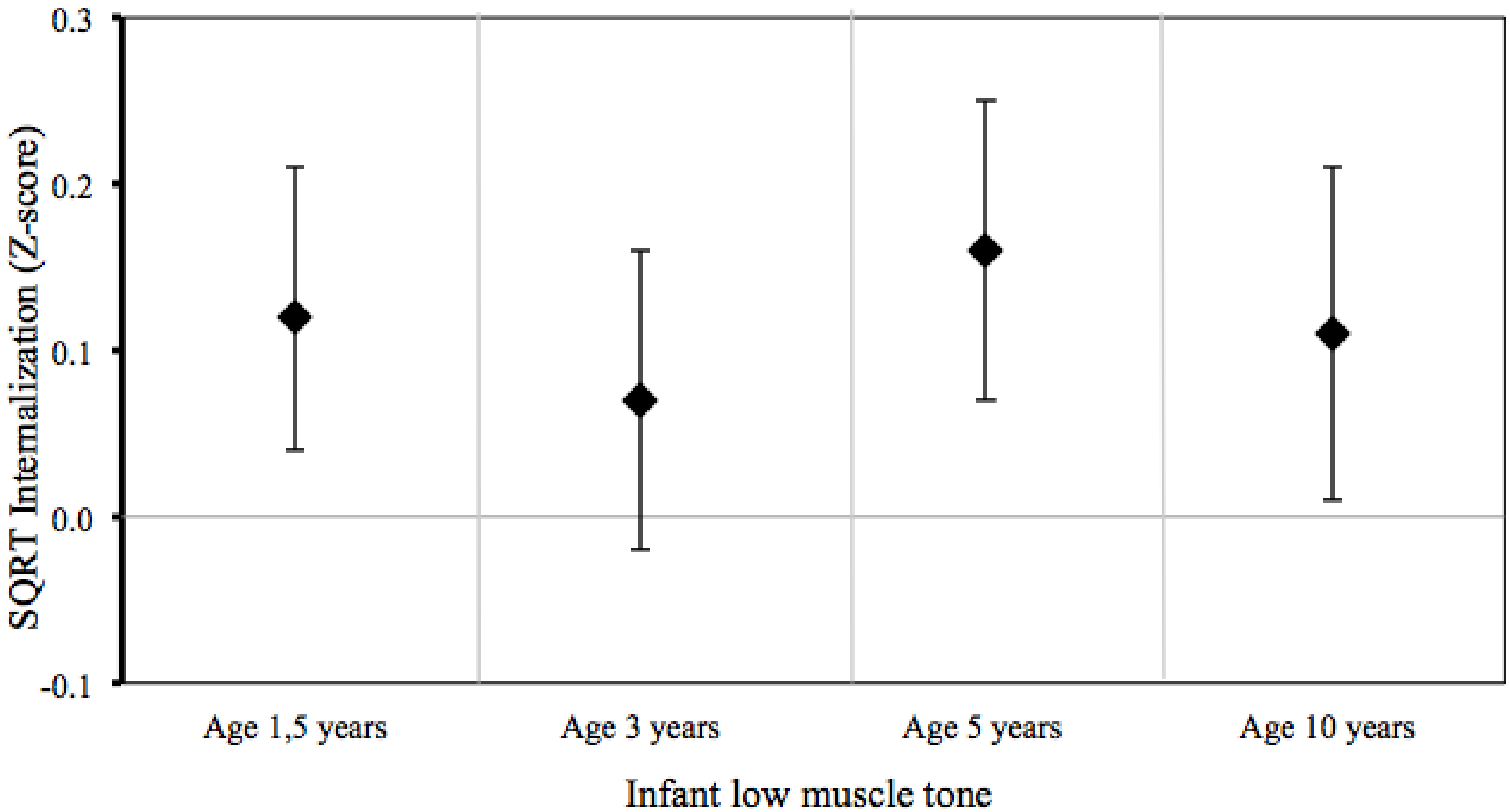


An analysis adjusted for previous visits



Supplementary Figure 2. The associations of low muscle tone and internalizing per each visit, adjusted for internalizing scores at previous visits

An analysis adjusted for previous visits



Repeated measures analyses

Growth models are rarely used correctly

Little interaction with time/age is modeled

Too much trajectory analyses while behaviour rarely justifies latent class assumption and model rarely improves above continuous analyses

You always find trajectories (think of an exception) and quite often parallel trajectories are found

Thank you !

The children

Fadila Serdarevic   *Marinus v. IJzendoorn & Marian Bakermans*   *Rene Veenstra*