APrON Alberta Pregnancy Outcomes and Nutrition

Nicole Letourneau RN PhD FCAHS

& APrON Team

APrON Team

Management Team	Legacy Members	Staff & Trainees
N. Letourneau (current PI) R. Bell D. Dewey C. Field G. Giesbrecht C. Lebel B. Leung C. McMorris	B. J. Kaplan F. Bernier M. Cantell L. Casey M. Eliasziw A. Farmer L. Gagnon L. Goonewardene D. Johnston L. Kooistra D. Manca L. McCargar M. O'Beirne V. Pop, N. Singhal	A. Deane H. Ntanda J. Novick E. Ali M. Grisbrook & many others

THANK YOU to

- **Our participants: Mothers, fathers (& co-parents) and children**
- **APrON Scientific Advisors**
- **All study staff and trainees in Calgary & Edmonton**
- **Funders**

APrON is a longitudinal pregnancy cohort study

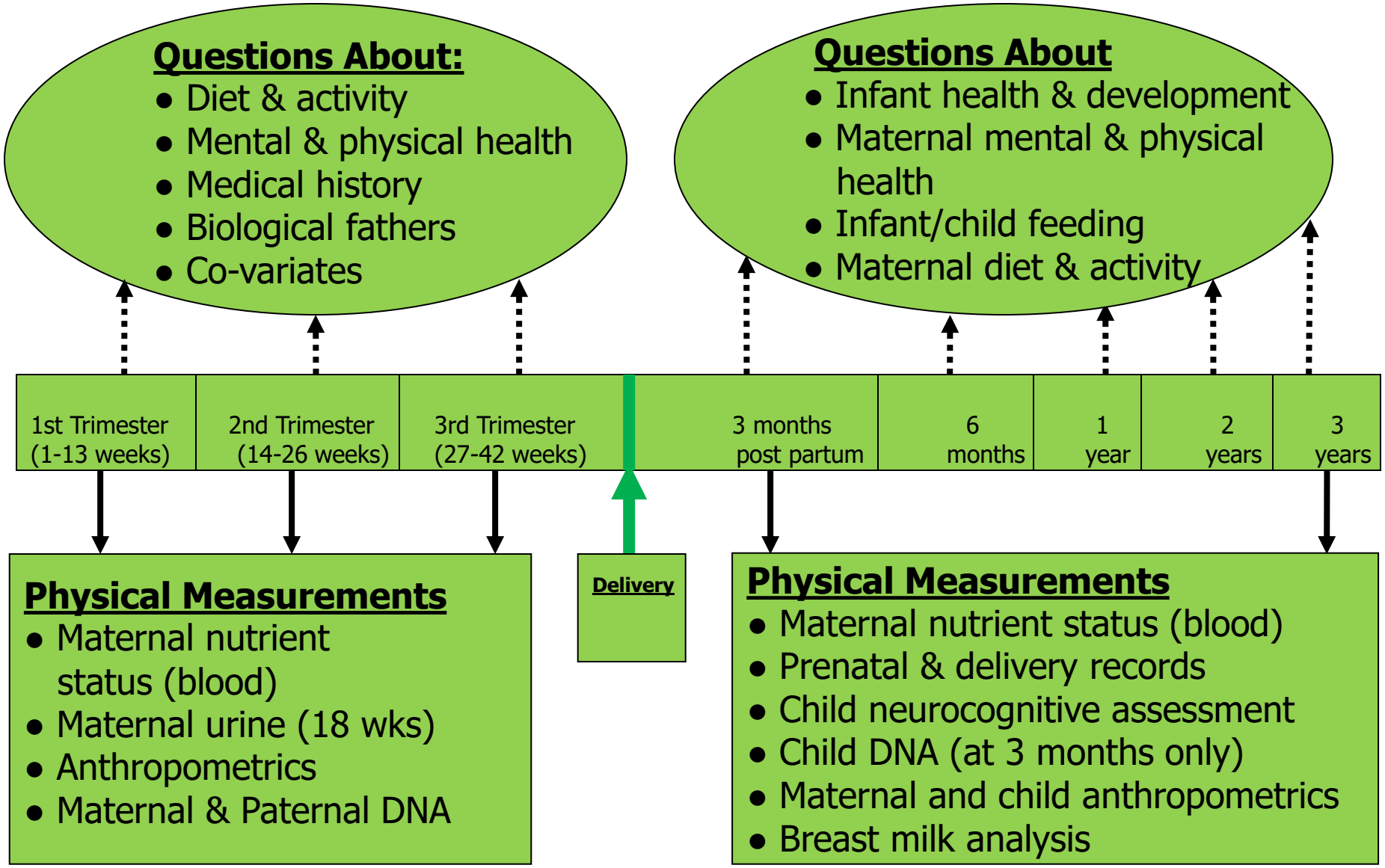
It evolved from 3 health concerns:

- Increasing burden of **mental disorders**
- Increasing burden of **neurodevelopmental disorders**
- **Concerns about nutritional impacts** on mental health and neurodevelopment

Target population

- Pregnant women ≥16 years old
- <27 weeks gestation
- Able to complete questionnaires in English
- Not planning to move out of the city within 6 months of inclusion into study

Measurements



APrON Participants

We have ~2200 mothers, ~1300 fathers and 2225 children enrolled

Time point	# sent questionnaires	# received questionnaires	Response Rate
A or B – baseline survey	2189	2124	97.03%
B – follow-up	539	479	88.87%
C – follow-up	2030	1843	90.79%
E – follow-up	1960	1831	93.42%
F – follow-up	1930	1538	79.69%

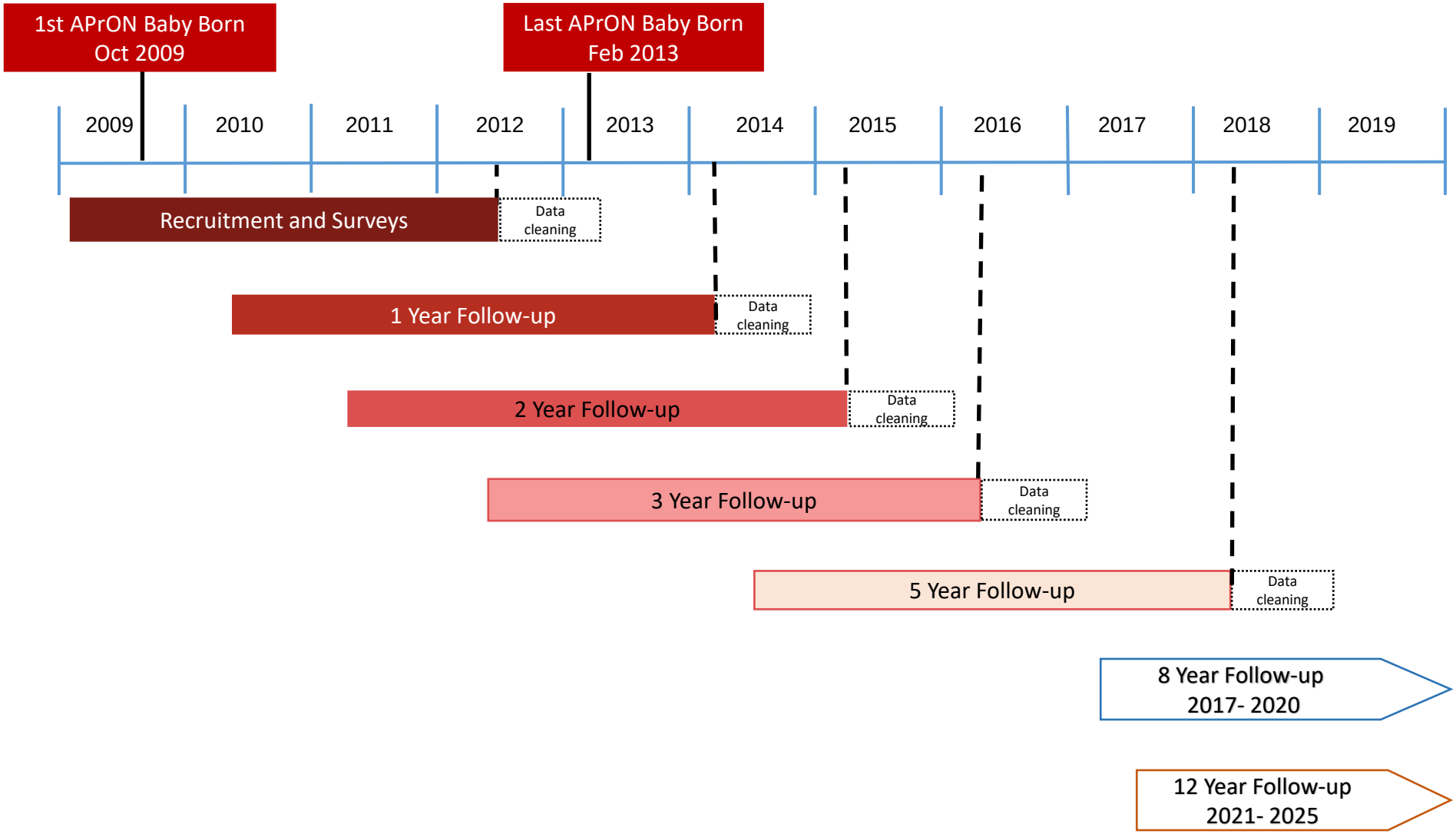
APrON Mothers

Maternal Characteristics (n)	n (%)
Maternal Age (2143)	Mean (SD) 31.1±4.5
Parity (2103)	Nulliparous 1185 (56.3%) Primiparous 714 (33.9%) Multiparous 204 (9.7%)
Marital Status (2104)	Married 1780 (84.6%) Common-law 240 (11.4%) Single 69 (3.3%) Divorced 8 (0.4%) Separated 7 (0.3%)
Maternal Education (2084)	Less than high school diploma 58 (2.8%) Completed high school diploma 200(9.6%) Completed trade, technical 406(19.5%) Completed University 948 (45.5%) Completed post-grad 472(22.6%)
Ethnicity (2098)	Caucasian 1684 (80.3%) Other 414 (19.7 %)
Family Income (2081)	Less than $20,000 66 (3.2%) $20,000-$39,999 121 (5.8%) $40,000-$69,999 279 (13.4%) $70,000-$99,999 467 (22.4%) $100,000 or more 1148 (55.2%)

APrON Children

Child Characteristics (n)	Mean (SD) or n (%)
Gestational Age (wk) (2089)	38.8 ± 2.15
Birth weight (kg) (2079)	3.33 ± 0.54
Gender (2090)	Female 980 (46.9%) Male 1110 (53.1%)

APrON Timeline



Measures of Development

Birth-2 years

- Infant Behavior Questionnaire-revised (IBQ-R)
- Scales of Independent Behaviour-Revised (SIB-R)
- Brief Rating Inventory of Executive Function (BRIEF)
- Child Behavior Checklist (CBCL)

3-5 years

- BRIEF-Preschool
- CBCL
- Behavior Assessment System for Children (BASC) II

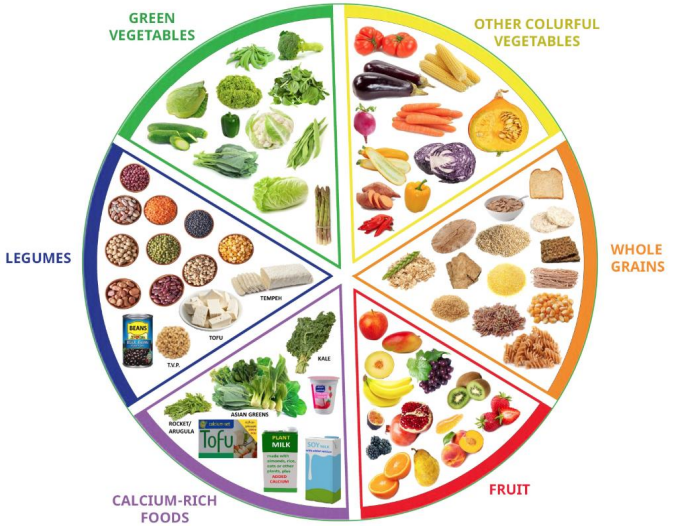
Neurocognitive*

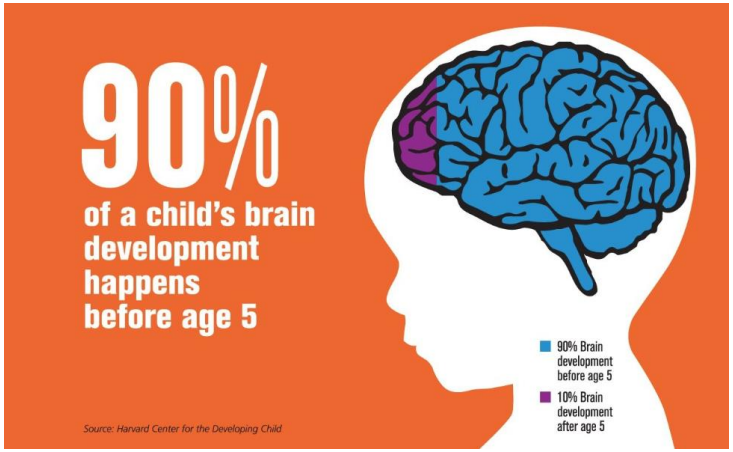
(2, 3 and/or 5 years, n=600)

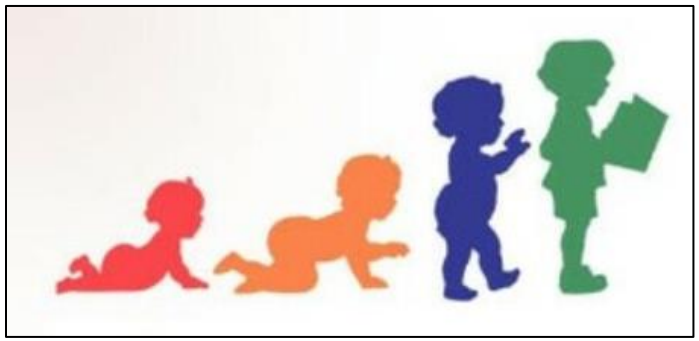
- Bayley II/III
- Weschler Preschool Primary Scale of Intelligence (WPPSI) IV
- NEPSY (Neuropsych Assessment)
- Movement Assessment Battery for Children (MABC) II

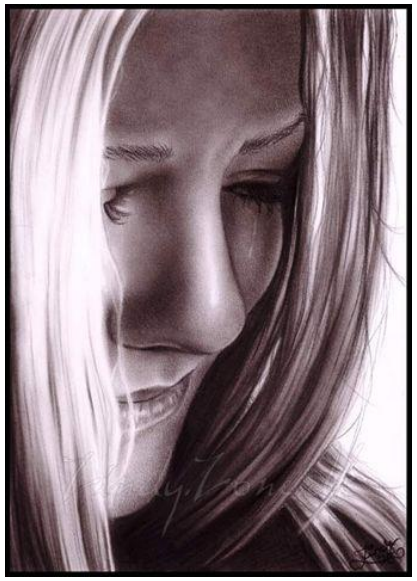
* For more information contact dmdewey@ucalgary.ca

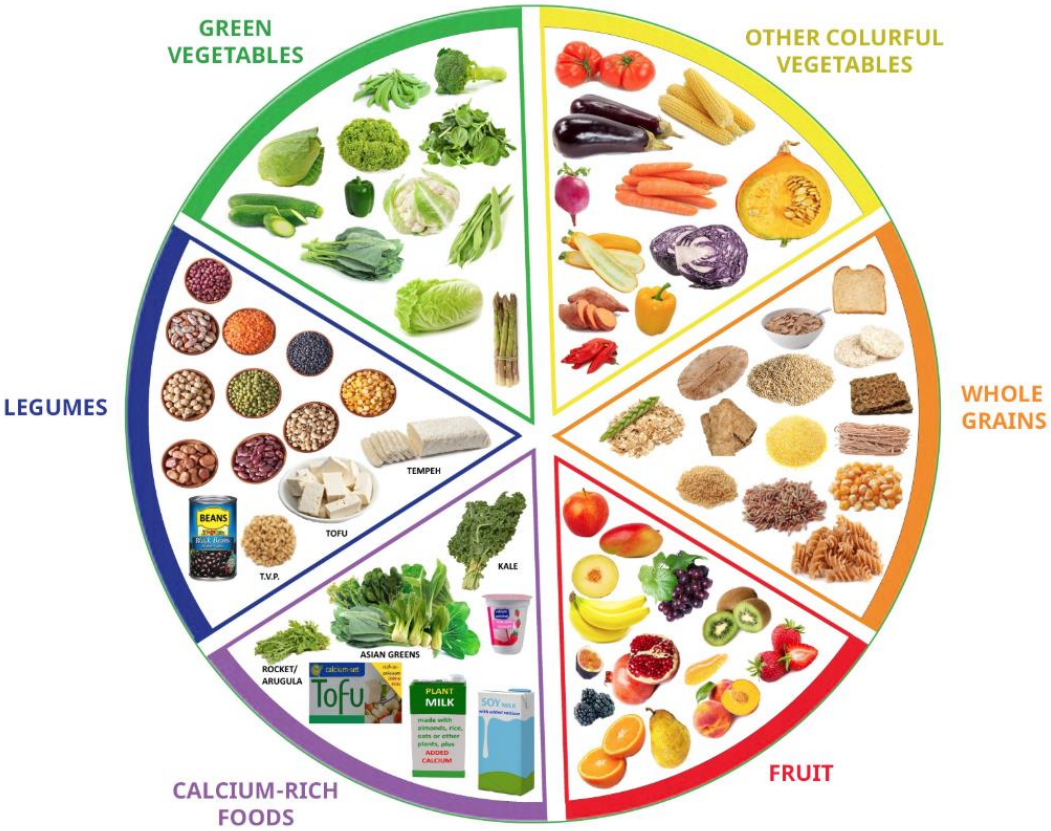
Exemplar Published Findings










GREEN VEGETABLES
OTHER COLURFUL VEGETABLES
LEGUMES
WHOLE GRAINS
FRUIT
CALCIUM-RICH FOODS
TEMPEH
TOFU
T.V.P.
BEANS
KALE
ASIAN GREENS
ROCKET/ ARUGULA
Tofu
PLANT MILK

NRC Research Press

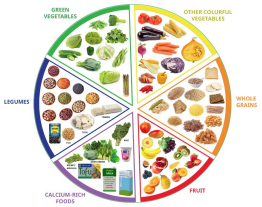
ARTICLE

Folate, vitamin B_{12}, and vitamin B_6 status of a group of high socioeconomic status women in the Alberta Pregnancy Outcomes and Nutrition (APrON) cohort

Faiqa Fayyaz, Flora Wang, René L. Jacobs, Deborah L. O'Connor, Rhonda C. Bell, Catherine J. Field; and the APrON Study Team

Abstract: Folic acid supplementation and food fortification policies have improved folate status in North American women of child bearing age. Recent studies have reported the possible inadequacy of vitamin B_{12} and B_6 in the etiology of neural tube defects in folate-fortified populations. The aims of this study were to describe folate status and its relationship to supplementation and to assess vitamin B_{12} and B_6 status in a cohort of pregnant women. Supplement intake data were collected in each trimester from the first cohort (n = 599) of the Alberta Pregnancy Outcomes and Nutrition (APrON) study. Red blood cell folate (RBCF) and plasma folate, holotranscobalamin, and pyridoxal 5-phosphate were measured. Overt folate deficiency was rare (3%) but 24% of women in their first trimester had suboptimal RBCF concentration (<906 nmol·L^{-1}). The proportion of the cohort in this category declined substantially in second (9%) and third (7%) trimesters. High RBCF (>1360 nmol·L^{-1}) was observed in approximately half of the women during each pregnancy trimester. Vitamin B_{12} and B_6 deficiencies were rare (<1% of the cohort). Women consuming folic acid supplements above the upper level had significantly higher RBCF and plasma folate concentrations. In conclusion, the prevalence of vitamin B_{12} and B_6 deficiency was very low. A quarter of the women had suboptimal folate status in the first trimester of pregnancy and over half the women had abnormally high RBCF, suggesting that supplementation

APrON Alberta Pregnancy Outcomes and Nutrition



Rationale

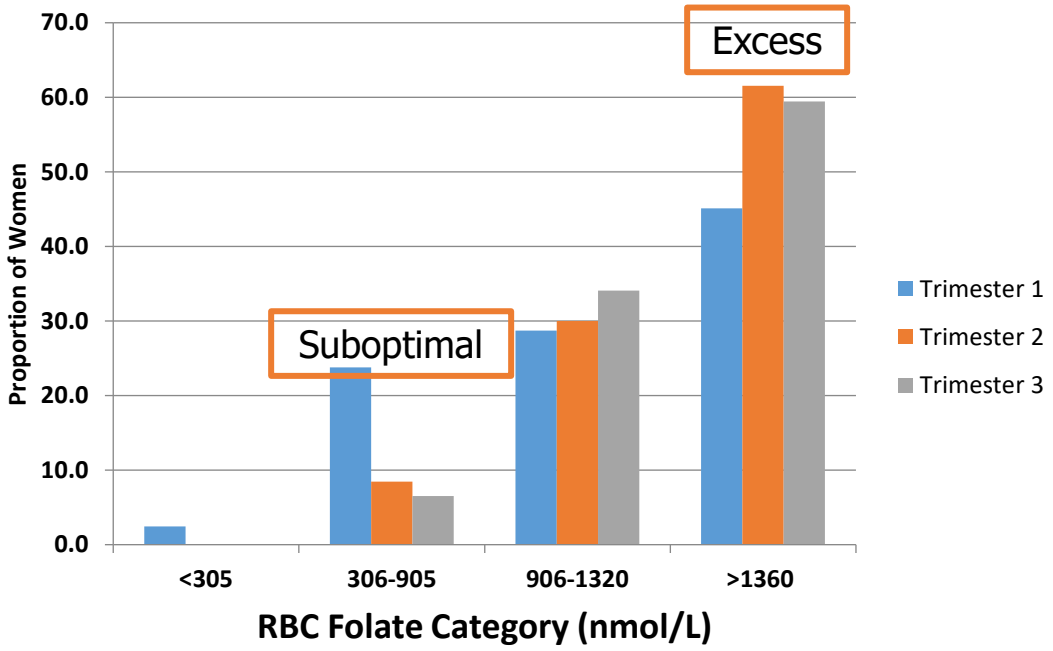
- Folate, Vitamin B12 and B6 are essential for early embryonic development and impact health later in life
- Folic acid fortification of cereal grains became mandatory in Canada in 1998
- Animal models show that folic acid at 20X recommended relates to embryonic delays, growth retardation, and reduced fetal weight and length
- Other negative impacts of high folate status include masking of Vitamin B12 (deficiency) and neurological disruption, cancer, immune function changes and epigenetic regulation disruption

Research Aim and Participants

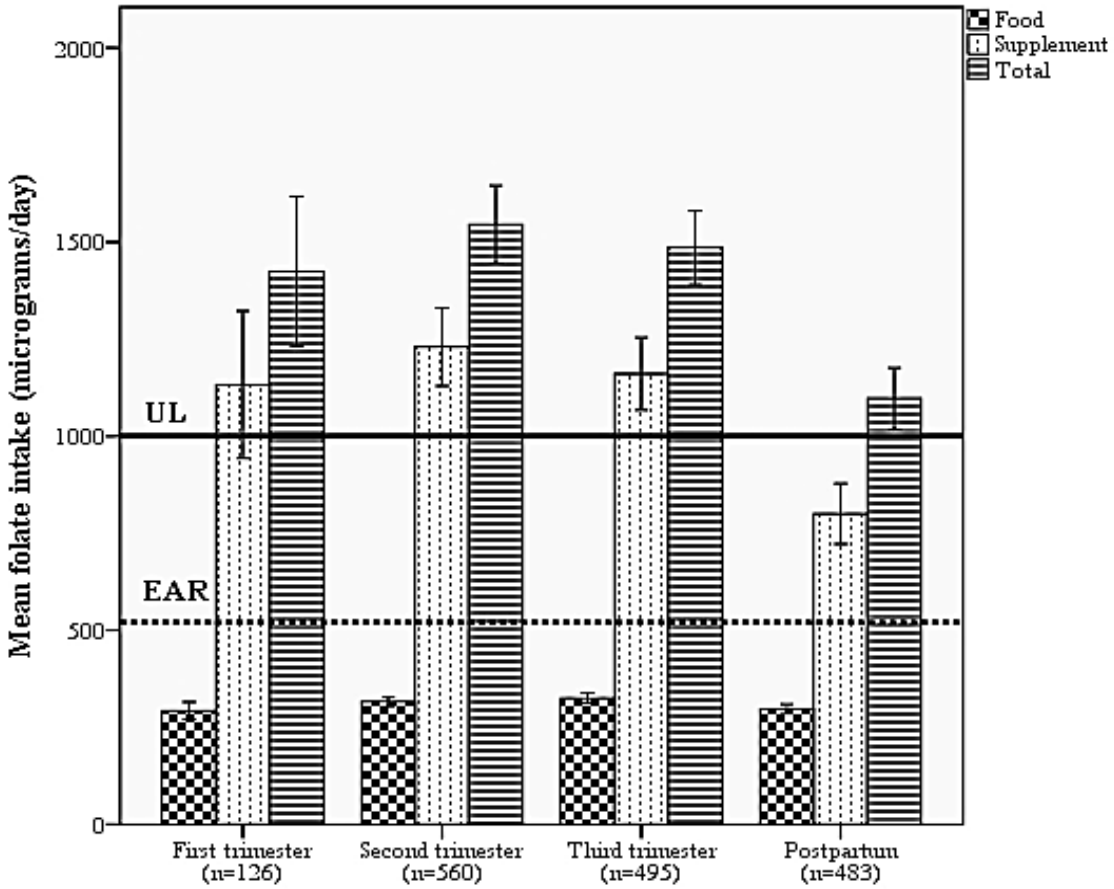
- Describe folate status and relationship to supplementation and to assess Vitamin B12 and B6 in pregnant women
- N=599

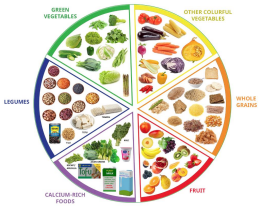
Red Blood Cell Folate Status in APrON Women

	1st Trimester		2nd Trimester		3rd Trimester	
	N	Median (95%CI)	N	Median (95%CI)	N	Median (95%CI)
All Women	122	1280 (1114,1393)	520	1504 (1450,1568)	446	1462 (1421,1529)



Estimated Folate/Folic Acid Intake





Summary

- **Overt folate deficiency was rare**
  - 24% of women had suboptimal RCB folate concentrations (<906 nm/L) at the start of pregnancy
  - **Most had excess folate**
- Women consuming folic acid supplements had high RBC folate and plasma folate concentrations
- Vitamin B12 and B6 deficiency was also rare (<1%)
- **Questions appropriateness of folate supplementation** during pregnancy in women who are healthy and at low risk for nutritional deficiencies

British Journal of Nutrition (2014), **112**, 112–121
doi:10.1017/S0007114514000555

Estimation of choline intake from 24 h dietary intake recalls and contribution of egg and milk consumption to intake among pregnant and lactating women in Alberta

Erin D. Lewis, Fatheema B. Subhan, Rhonda C. Bell, Linda J. McCargar, Jonathan M. Curtis, René L. Jacobs, Catherine J. Field* and the APrON team

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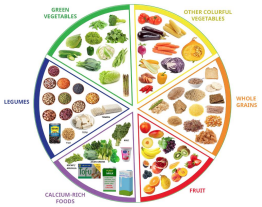
(Submitted 28 August 2013 – Final revision received 30 January 2014 – Accepted 5 February 2014 – First published online 8 April 2014)

Abstract

Despite recommendations for higher choline intakes during pregnancy and lactation, there is limited research regarding maternal intake during these important periods. In the present study, we estimated dietary choline intake during pregnancy and lactation in a population of Albertan women and the contribution of egg and milk consumption to intake. Dietary intake data were collected from the first 600 women enrolled in a prospective cohort study carried out in Alberta, Canada. During the first and/or second trimester, the third trimester and 3 months postpartum, 24 h dietary intake recall data were collected. A database was constructed including foods consumed by the cohort and used to estimate dietary choline intake. The mean total choline intake value during pregnancy was 347 (SD 149) mg/d, with 23 % of the participants meeting the adequate intake (AI) recommendation. During lactation, the mean total choline intake value was 346 (SD 151) mg/d, with 10 % of the participants meeting the AI recommendation. Phosphatidylcholine was the form of choline consumed



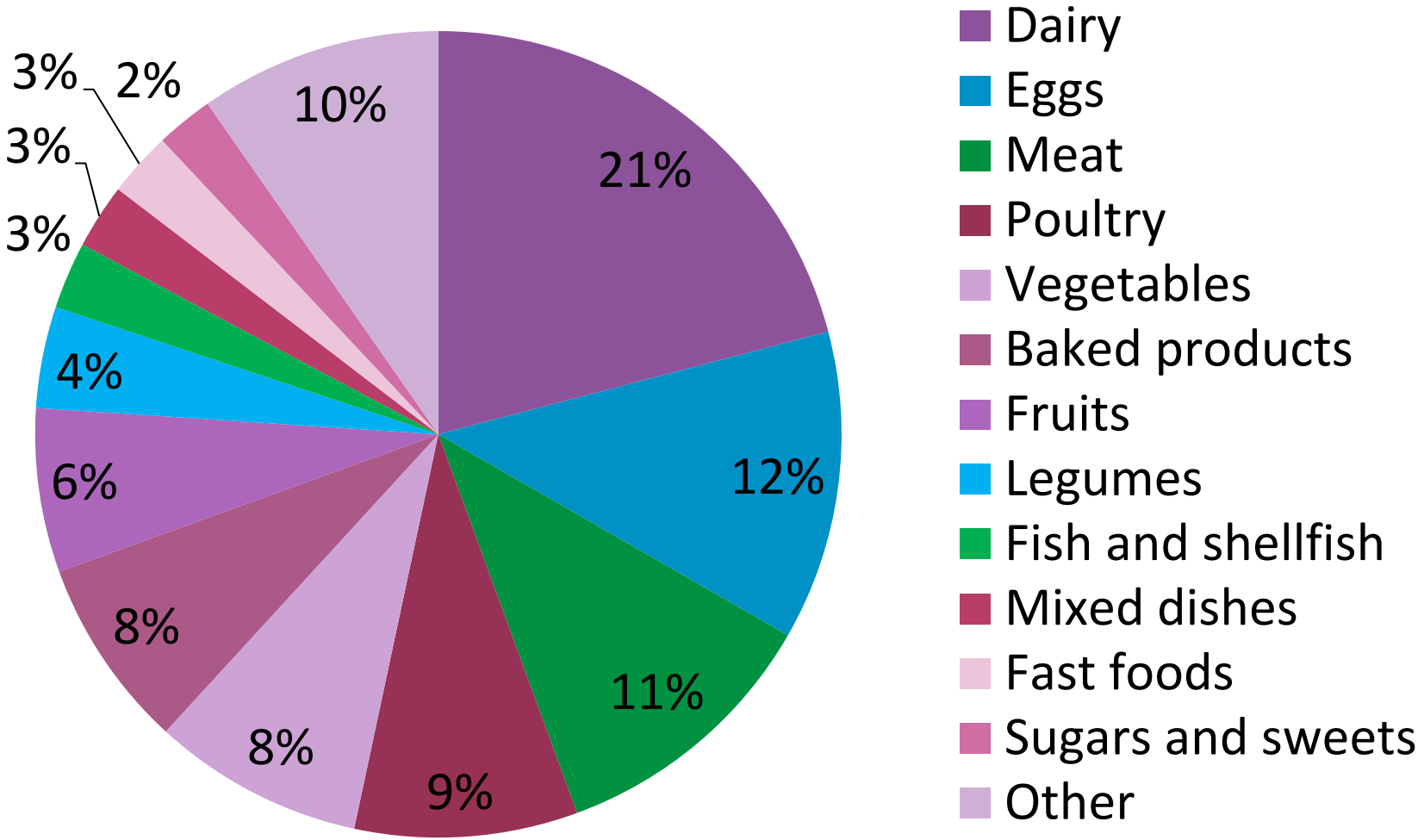
Rationale

- Choline has been recognized as an essential nutrient since 1998
- Needs increase in pregnancy and lactation
  - Plays vital role in fetal development, particularly brain
- Little human data available to estimate requirements
- Adequate Intake (AI) values:
  - Pregnancy 450 mg/d
  - Lactation 550 mg/d
- Nutrient databases (USDA and CNF) have limited choline information

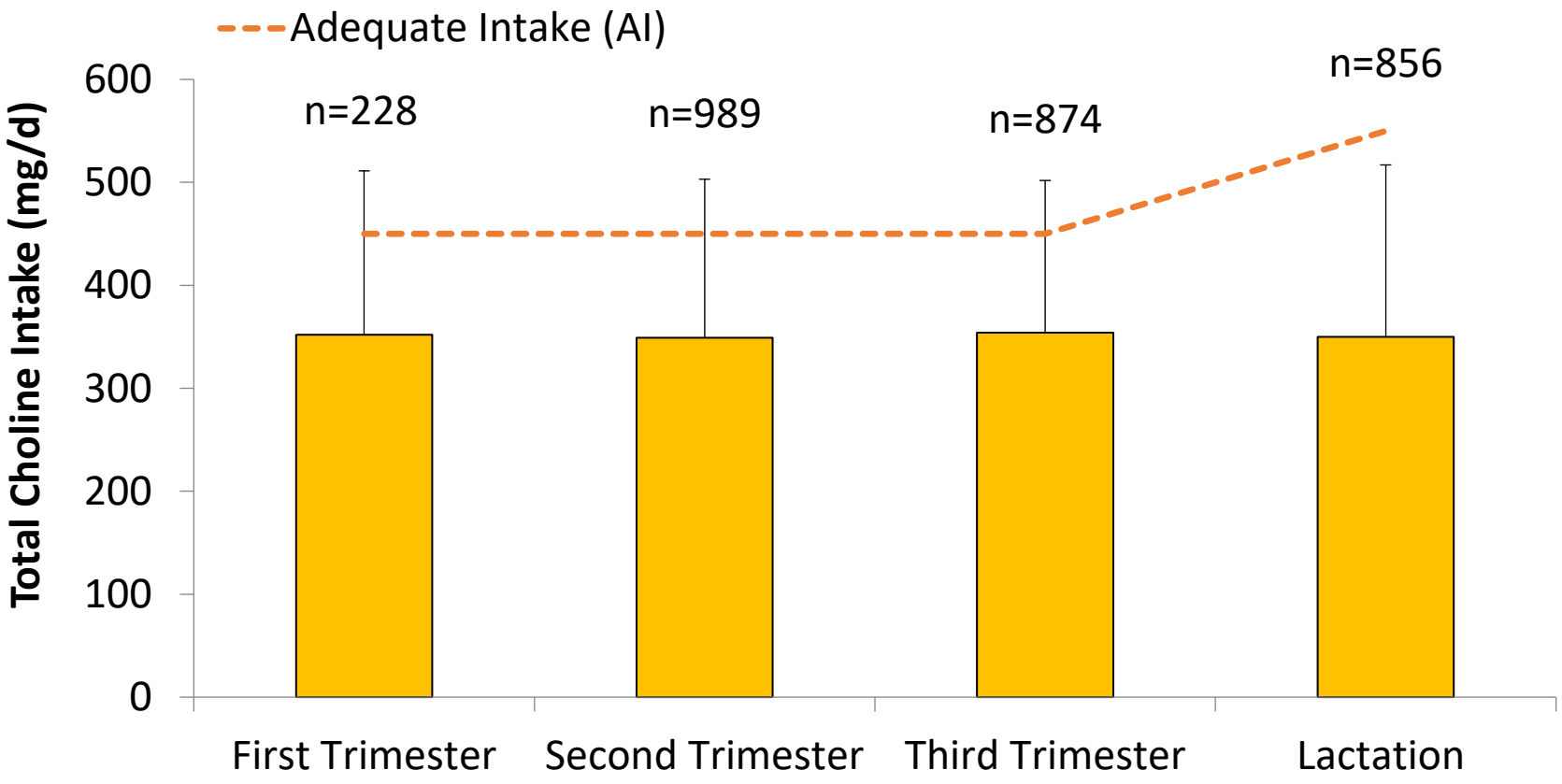
Research Aim and Participants

- Estimate dietary intake of choline during pregnancy
- N=600

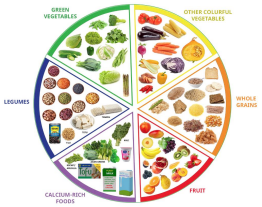
Dairy, eggs, and meat are major food categories contributing to total choline intake in pregnancy



Choline Intake in Pregnancy and Lactation



Daily recommendations met by 23% in pregnancy and 10% in lactation

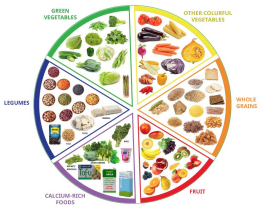


Summary

- **Average choline intake was below Adequate Intake (AI)**
  - <25% of APrON women met AI during pregnancy
  - <10% of APrON women met AI during lactation

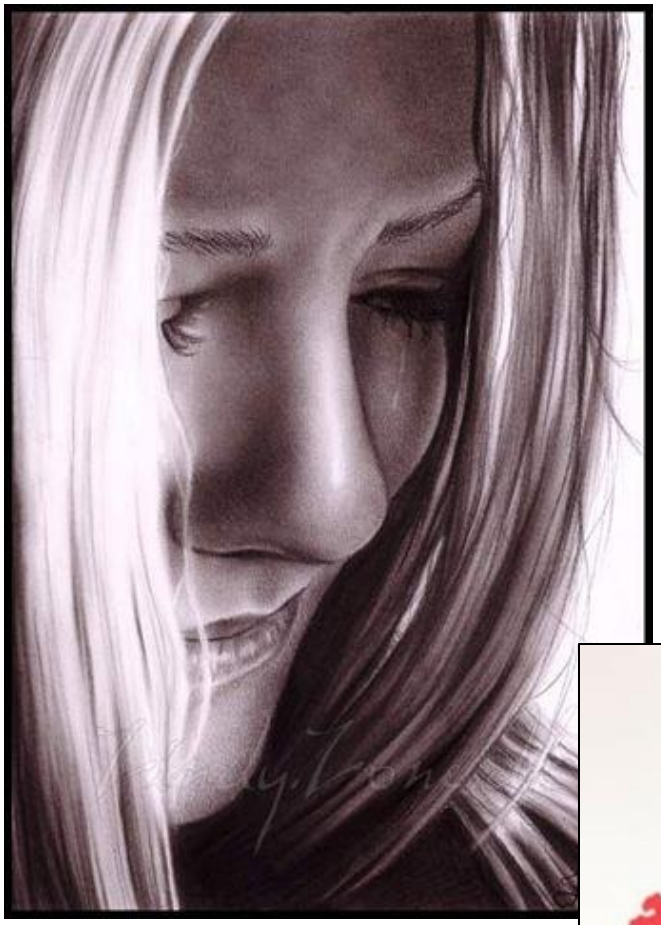
- **Milk and egg consumption were major contributors to total choline intake**

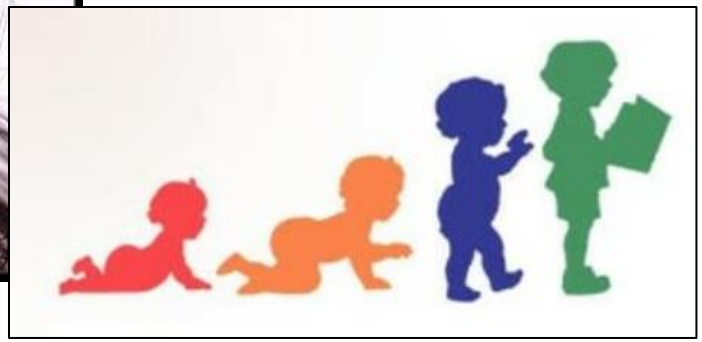
- Aug 2016: European Food Safety Authority used this information in revision of their Dietary Reference Values for Choline



Policy Impact

Lewis ED, Subhan FB, Bell RC, McCargar LJ, Curtis JM, Jacobs RL, Field CJ and team AP, 2014. Estimation of choline intake from 24 h dietary intake recalls and contribution of egg and milk consumption to intake among pregnant and lactating women in Alberta. British Journal of Nutrition, 112, 112–121.





Journal of Developmental Origins of Health and Disease

cambridge.org/doh

Original Article

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Key words:
adverse; child behaviour; internalizing and externalizing behaviour; maternal anxiety; maternal depression

Intergenerational transmission of adverse childhood experiences via maternal depression and anxiety and moderation by child sex

N. Letourneau, D. Dewey, B. J. Kaplan, H. Ntanda, J. Novick, J. C. Thomas, A. J. Deane, B. Leung, K. Pon, G. F. Giesbrecht and the APrON Study Team

Department of Pediatrics, University of Calgary, Child Development Center, Calgary, AB, Canada

Abstract

Adverse childhood experiences (ACEs) of parents are associated with a variety of negative health outcomes in offspring. Little is known about the mechanisms by which ACEs are transmitted to the next generation. Given that maternal depression and anxiety are related to ACEs and negatively affect children's behaviour, these exposures may be pathways between maternal ACEs and child psychopathology. Child sex may modify these associations. Our objectives were to determine: (1) the association between ACEs and children's behaviour, (2) whether maternal symptoms of prenatal and postnatal depression and anxiety mediate the relationship between maternal ACEs and children's behaviour, and (3) whether these relationships are moderated by child sex. Pearson correlations and latent path analyses were undertaken using data from 907 children and their mothers enrolled the Alberta Pregnancy Outcomes and Nutrition study. Overall, maternal ACEs were associated with symptoms of anxiety and depression during the perinatal period, and externalizing problems in children.

APrON Alberta Pregnancy Outcomes and Nutrition

Rationale

- Research has revealed the within-generation impact of ACEs on children and adults over their lifespan.
- Prenatal and postnatal depression and anxiety have been linked to internalizing and externalizing behavioural problems in their children.
- Growing evidence suggests that mothers' exposures to ACEs may also increase children's risk for behavioural problems.

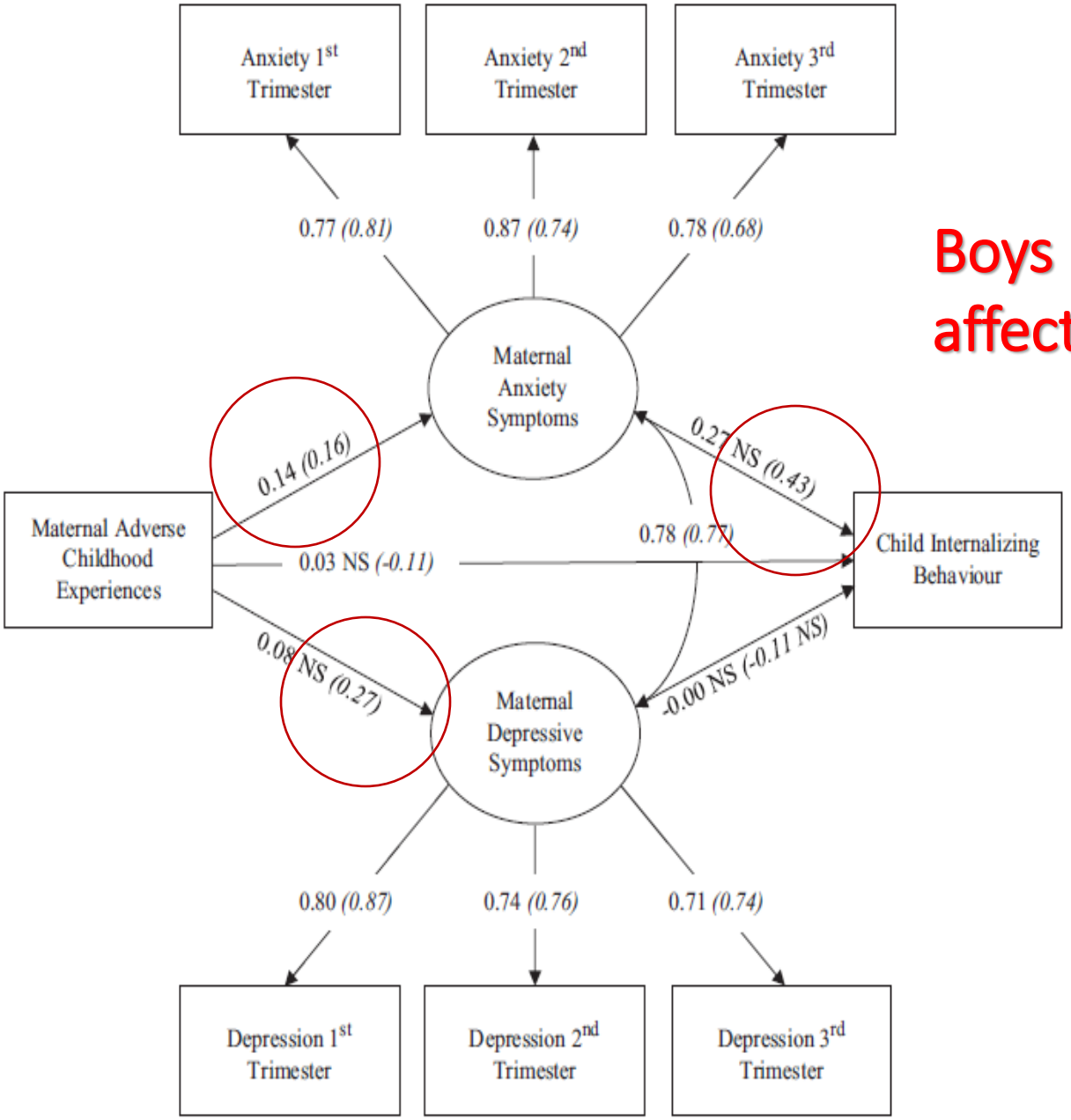
Research Aim and Participants

- Understand the association between maternal ACEs, depression and anxiety and children's behavior
- N=907

Table 5. Overall indirect effects of maternal adverse childhood experiences (ACEs) on externalizing and internalizing behaviour

Model	95% bias corrected CI for indirect effect	Model Fit
Prenatal Exposures		
ACEs → Depression → Externalizing	-0.001 – 0.055	Chi-Sq(41) = 43.4, *P* = 0.37 RMSEA=0.008 [0.000, 0.025] TLI: = 0.99 SRMR = 0.023
ACEs → Anxiety → Externalizing	-0.010 – 0.085	
ACEs → Depression → Internalizing	-0.033 – 0.020	Chi-Sq(41) = 40.3, *P* = 0.50 RMSEA=0.000 [0.000, 0.022] TLI = 1.00 SRMR = 0.023
ACEs → Anxiety → Internalizing	0.022 – 0.143	
Postnatal Exposures		
ACEs → Depression → Externalizing	0.007 – 0.076	Chi-Sq(41)=65.1, *P* = 0.01 RMSEA=0.026 [0.013, 0.037] TLI = 0.98 SRMR = 0.018
ACEs → Anxiety → Externalizing	-0.033 – 0.050	
ACEs → Depression → Internalizing	0.001 – 0.063	Chi-Sq(41) = 67.1, *P* = 0.006 RMSEA=0.027 [0.014, 0.038] TLI = 0.98 SRMR = 0.019
ACEs → Anxiety → Internalizing	-0.018 – 0.066	

CI = confidence interval; RMSEA = root mean square error of approximation which is a parsimony-adjusted index in which values closer to 0 represent a good fit and cut-off representing good fit is RMSEA < 0.08; TLI = Tucker–Lewis Index. A TLI of 0.95, indicates the model of interest improves the fit by 95% relative to the null model. Cut-off for good fit is TLI ⩾0.95; SRMR = standardized root mean square residual which is the square-root of the difference between the residuals of the sample covariance matrix and the hypothesized model. Cut-off for good fit is SRMR <0.08. Covariates included were: maternal education, ethnicity, social support, household annual income, and child age and sex.



Boys more affected

Fig. 2. Standardized parameter estimates for the moderated mediator model for child internalizing behaviour. Parameter estimates are for girls and boys (*in brackets*). Non-significant associations are designated as NS, otherwise all associations were significant at $P < 0.05$.

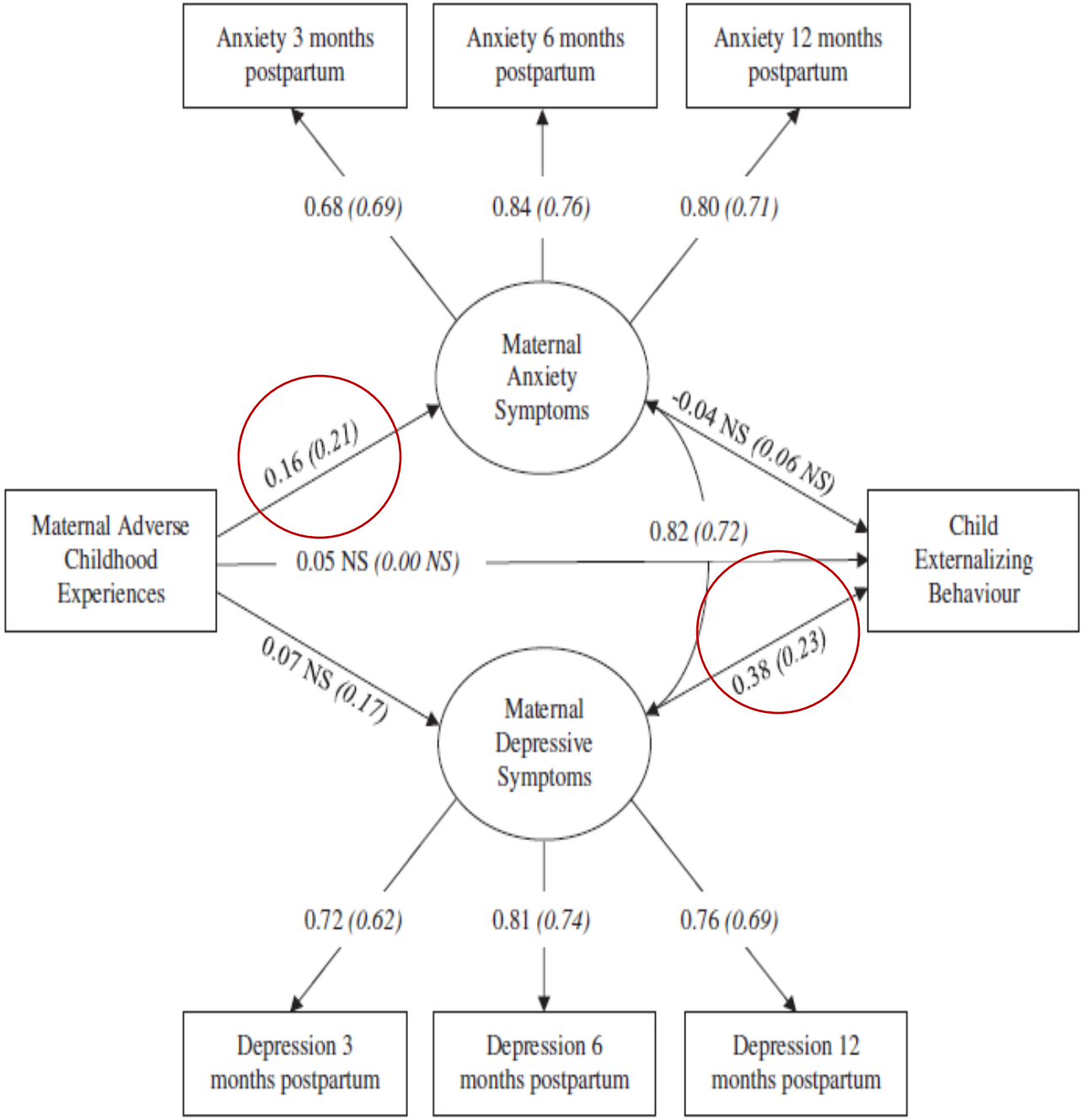


Fig. 3. Standardized parameter estimates for the moderated mediator model for child externalizing behaviour. Parameter estimates are for girls and boys (*in brackets*). Non-significant associations are designated as NS, otherwise all associations were significant at $P < 0.05$

Summary

- Mothers exposure to ACEs is associated with their prenatal depression and anxiety and externalizing problems in children.

- Together, maternal depression and anxiety is associated with the effects of maternal ACEs on children's internalizing and externalizing behaviours.

- It was found that boys were more vulnerable to the indirect effects of maternal ACEs than girls.

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RESEARCH ARTICLE

WILEY Developmental Psychobiology

Biological embedding of perinatal social relationships in infant stress reactivity

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Email: ggiesbre@ucalgary.ca

Funding information
Alberta Innovates–Health Solutions; Canadian Child Health Clinician Scientist Program; Canadian Institutes of Health Research; Alberta

Abstract

Whereas significant advances have been made in understanding how exposure to early adversity "gets under the skin" of children to result in long term changes in developmental outcomes, the processes by which positive social relationships become biologically embedded remain poorly understood. The aim of this study was to understand the pathways by which maternal and infant social environments become biologically embedded in infant cortisol reactivity. Two hundred seventy-two pregnant women and their infants were prospectively assessed during pregnancy and at 6 months postpartum. In serial mediation analyses, higher perceived social support from partners during pregnancy was associated with lower infant cortisol reactivity or larger decreases in cortisol in response to a stressor at 6 months of age via lower self-reported prenatal maternal depression and higher mother–infant interaction quality. The findings add to our understanding of how perinatal social relationships become biologically embedded in child development.

KEYWORDS
biological embedding, cortisol reactivity, mother-infant interaction quality, social support

APrON Alberta Pregnancy Outcomes and Nutrition

Rationale

- Early life exposures have extraordinary potency to direct developmental trajectories because they calibrate the function of the stress response systems, which regulate a wide range of adaptive functions.
- The processes by which positive social relationships become biologically embedded remain poorly understood.

Research Aim and Participants

- Understand how positive social relationships are biologically embedded in children.
- Determine if **prenatal social support** is indirectly associated with the regulation of infant stress response.
- N=272

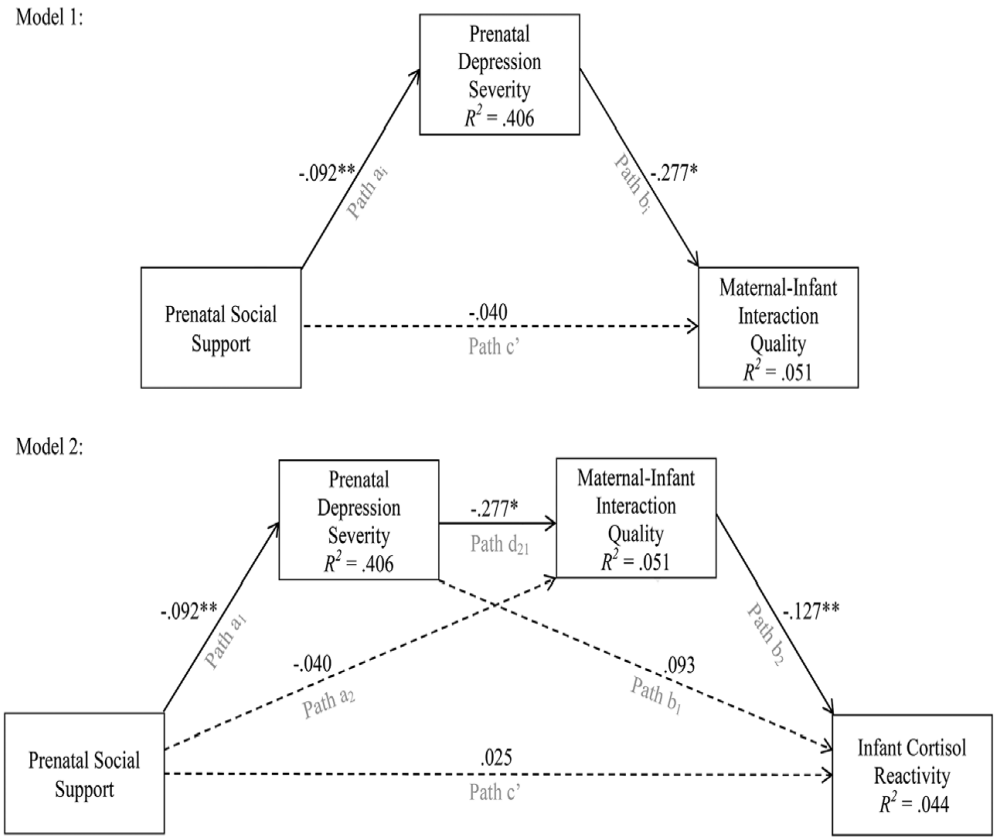


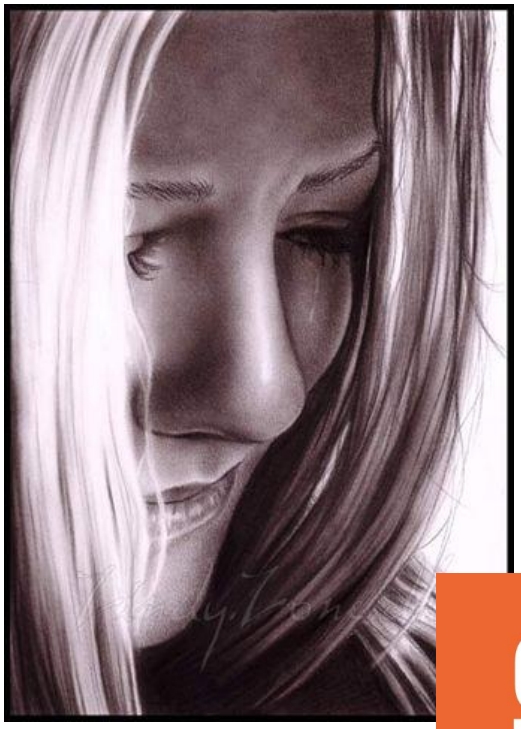
FIGURE 1 Longitudinal path models examining the relations between prenatal social support, prenatal depression severity, maternal–infant interaction quality, and infant cortisol reactivity. Unstandardized estimates are displayed. Significant paths are represented by solid lines, non-significant paths are represented by dashed lines

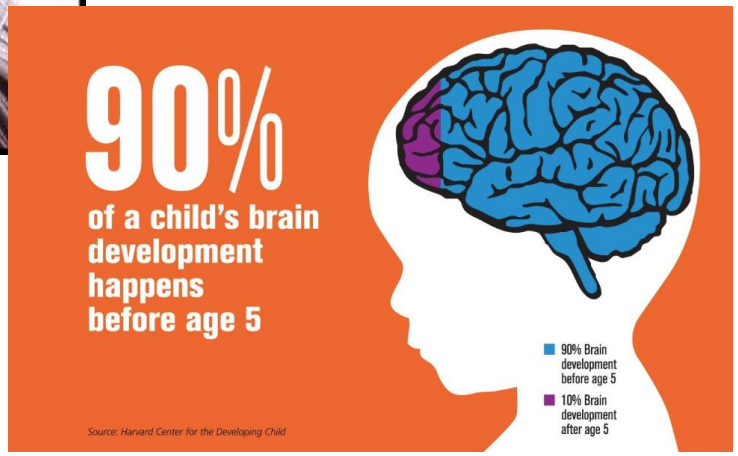
Summary

- Women who reported higher perceived social support in early pregnancy reported less prenatal depression symptoms.

- Perceived social support has a positive indirect association with maternal-infant interaction quality via its association with lower maternal depressive symptoms reported during pregnancy.

- Higher maternal-infant interaction quality was associated with lower infant cortisol reactivity or larger decreases in cortisol in response to the frustration stressor.




90%
of a child's brain development happens before age 5
90% Brain development before age 5
10% Brain development after age 5
Source: Harvard Center for the Developing Child

Archival Report

Biological Psychiatry

Prepartum and Postpartum Maternal Depressive Symptoms Are Related to Children's Brain Structure in Preschool

Catherine Lebel, Matthew Walton, Nicole Letourneau, Gerald F. Giesbrecht, Bonnie J. Kaplan, and Deborah Dewey

ABSTRACT

BACKGROUND: Perinatal maternal depression is a serious health concern with potential lasting negative consequences for children. Prenatal depression is associated with altered brain gray matter in children, though relations between postpartum depression and children's brains and the role of white matter are unclear.

METHODS: We studied 52 women who provided Edinburgh Postnatal Depression Scale (EPDS) scores during each trimester of pregnancy and at 3 months postpartum and their children who underwent magnetic resonance imaging at age 2.6 to 5.1 years. Associations between maternal depressive symptoms and magnetic resonance imaging measures of cortical thickness and white matter structure in the children were investigated.

RESULTS: Women's second trimester EPDS scores negatively correlated with children's cortical thickness in right inferior frontal and middle temporal regions and with radial and mean diffusivity in white matter emanating from the inferior frontal area. Cortical thickness, but not diffusivity, correlations survived correction for postpartum EPDS. Postpartum EPDS scores negatively correlated with children's right superior frontal cortical thickness and with diffusivity in white matter originating from that region, even after correcting for prenatal EPDS.

CONCLUSIONS: Higher maternal depressive symptoms prenatally and postpartum are associated with altered gray matter structure in children; the observed white matter correlations appear to be uniquely related to the postpartum period. The reduced thickness and diffusivity suggest premature brain development in children exposed to higher maternal perinatal depressive symptoms. These results highlight the importance of ensuring optimal women's mental health throughout the perinatal period, because maternal depressive symptoms appear to increase children's

Rationale

- Few studies have examined the associations between maternal depression and children's brain structure.
- Current studies are limited to infants or school-aged children. Leaving a critical gap in knowledge of brain abnormalities during early childhood.
- Understanding the brain abnormalities associated with perinatal depressive symptoms can highlight brain regions sensitive to such effects and provide information about potential mechanisms linking maternal depression with negative behavioral and cognitive outcomes.

Research Aim and Participants

- Understand the associations between perinatal depressive symptoms and brain structure in preschool-aged children.
- N=52

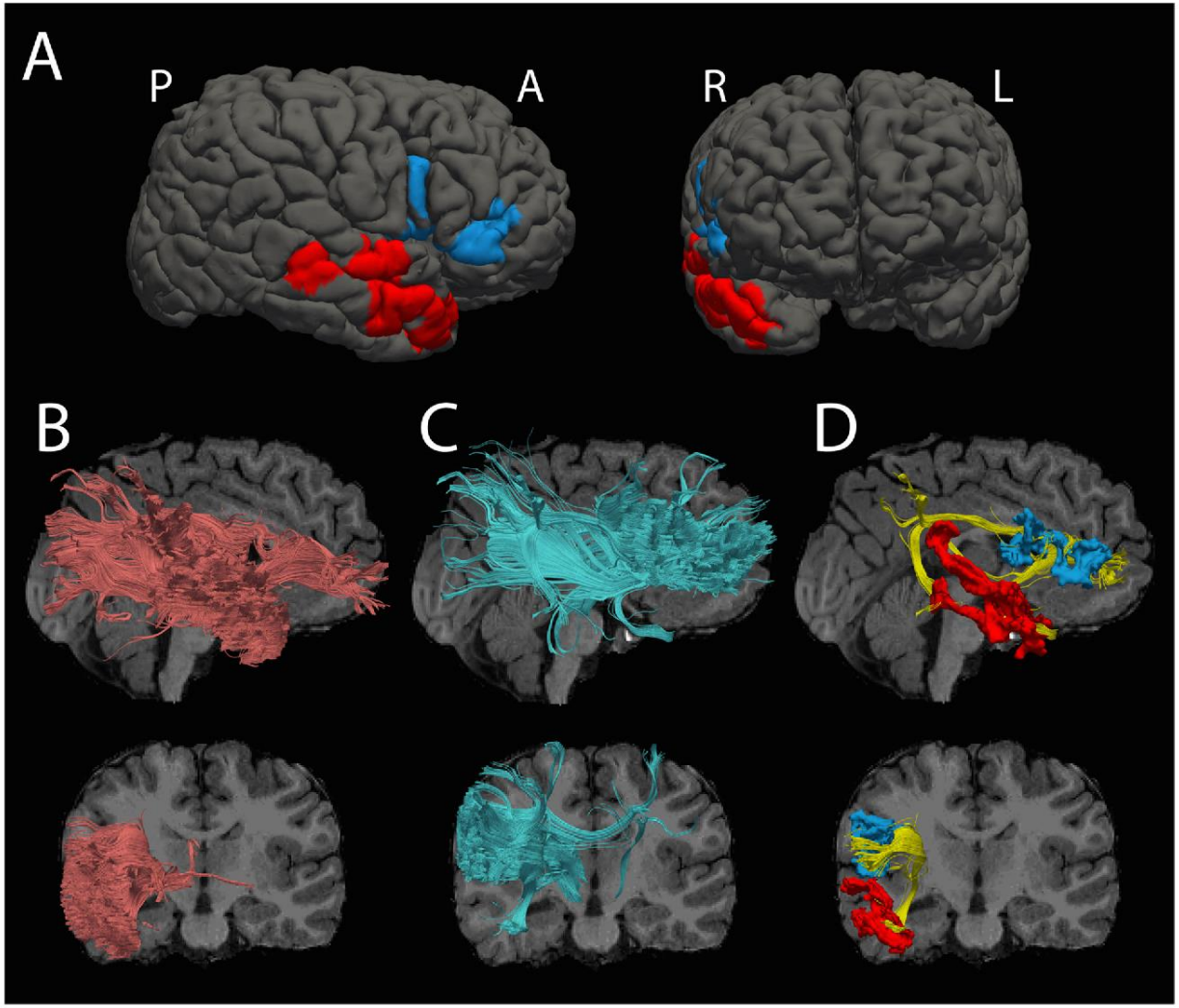


Figure 1. Brain areas with significant associations to maternal prenatal depression scores. Two regions demonstrated significant negative correlations between cortical thickness and second trimester maternal depressive symptoms: **(A)** a cluster in the right middle temporal region (red) and a cluster in the right inferior frontal region spanning the pars orbitalis and pars triangularis (blue). The white matter fibers emanating from each of these two regions: **(B)** pink—fibers emanating from the middle temporal area included the uncinate and inferior longitudinal fasciculi; **(C)** cyan—fibers emanating from the inferior frontal area included the uncinate, arcuate, and inferior fronto-occipital fasciculi are shown, as well as the fibers that pass through both regions; **(D)** yellow—primarily the lateral portions of the uncinate and arcuate fasciculi. Fibers from the inferior frontal region demonstrated a significant negative correlation between maternal second trimester depressive symptoms and radial and mean diffusivity. Correlations of second trimester Edinburgh Postnatal Depression Scale with cortical thickness, but not those with diffusivity, remained significant after controlling for postpartum depressive symptoms. A, anterior; L, left; P, posterior; R, right.

Summary

- Observed associations between children's cortical thickness and maternal depressive symptoms in the second trimester and postpartum only, suggests that these may be vulnerable times for child's brain development.

- Thinner cortex and lower diffusivity was observed and suggest altered brain development and earlier brain maturation in children who were exposed to higher levels of maternal depressive symptoms.

- Results suggest that children exposed to higher levels of maternal depressive symptoms can result in premature brain development and reduced plasticity.

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Environmental Health

RESEARCH Open Access

Prenatal maternal and childhood bisphenol a exposure and brain structure and behavior of young children

Melody N. Grohs[1,2], Jess E. Reynolds[2,3], Jiaying Liu[4], Jonathan W. Martin[4,5], Tyler Pollock[2,3,6], Catherine Lebel[2,3,7†], Deborah Dewey[2,7,8,9,10*†] and the APrON Study Team

Abstract

Background: Bisphenol A (BPA) is commonly used in the manufacture of plastics and epoxy resins. In North America, over 90% of the population has detectable levels of urinary BPA. Human epidemiological studies have reported adverse behavioral outcomes with BPA exposure in children, however, corresponding effects on children's brain structure have not yet been investigated. The current study examined the association between prenatal maternal and childhood BPA exposure and white matter microstructure in children aged 2 to 5 years, and investigated whether brain structure mediated the association between BPA exposure and child behavior.

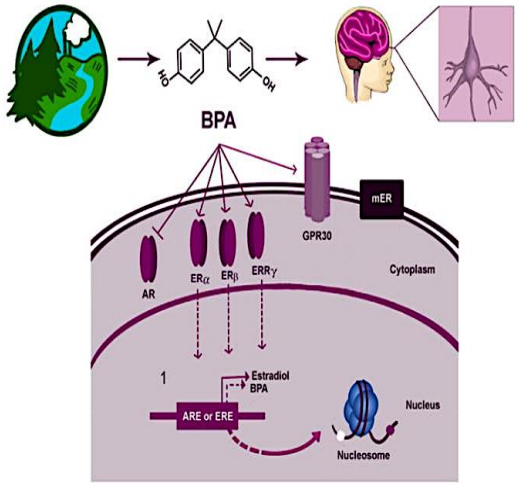
Alberta Pregnancy Outcomes and Nutrition

Rationale

- BPA is an endocrine disrupting chemical (ECDs).
  - In North America, over 90% of the population has detectable levels of urinary BPA.
  - BPA can pass through the placenta and cross the blood brain barrier, meaning the fetal brain is likely exposed during gestation.
- Mounting evidence that show early life exposure to EDCs may play a role in the increasing prevalence of neurobehavioral and neurodevelopmental deficits worldwide.
- Animal studies show that white matter is particularly sensitive to early exposure to BPA suggesting that it is an important avenue to investigate in order to better understand the effects of BPA in humans.

Research Aim and Participants

- Investigate the associations between prenatal & postnatal BPA exposure and white matter structure in preschool aged children.
- N = 98



Human Research

Wolstenholme, J. T. et al., (2011).

Bisphenol A

Brain White Matter

?

Behavior

Altered:

Internalizing Behavior (Increased anxiety, depression)

Externalizing Behavior (Increased aggression, attention deficits)

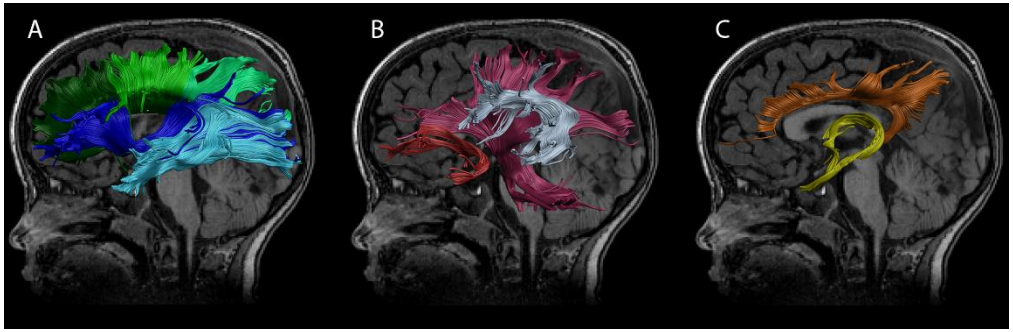
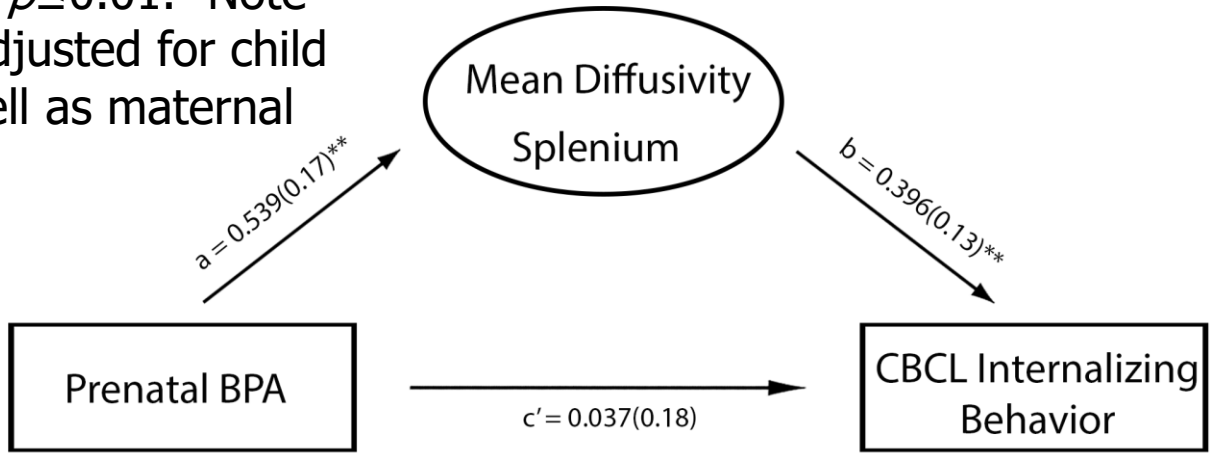
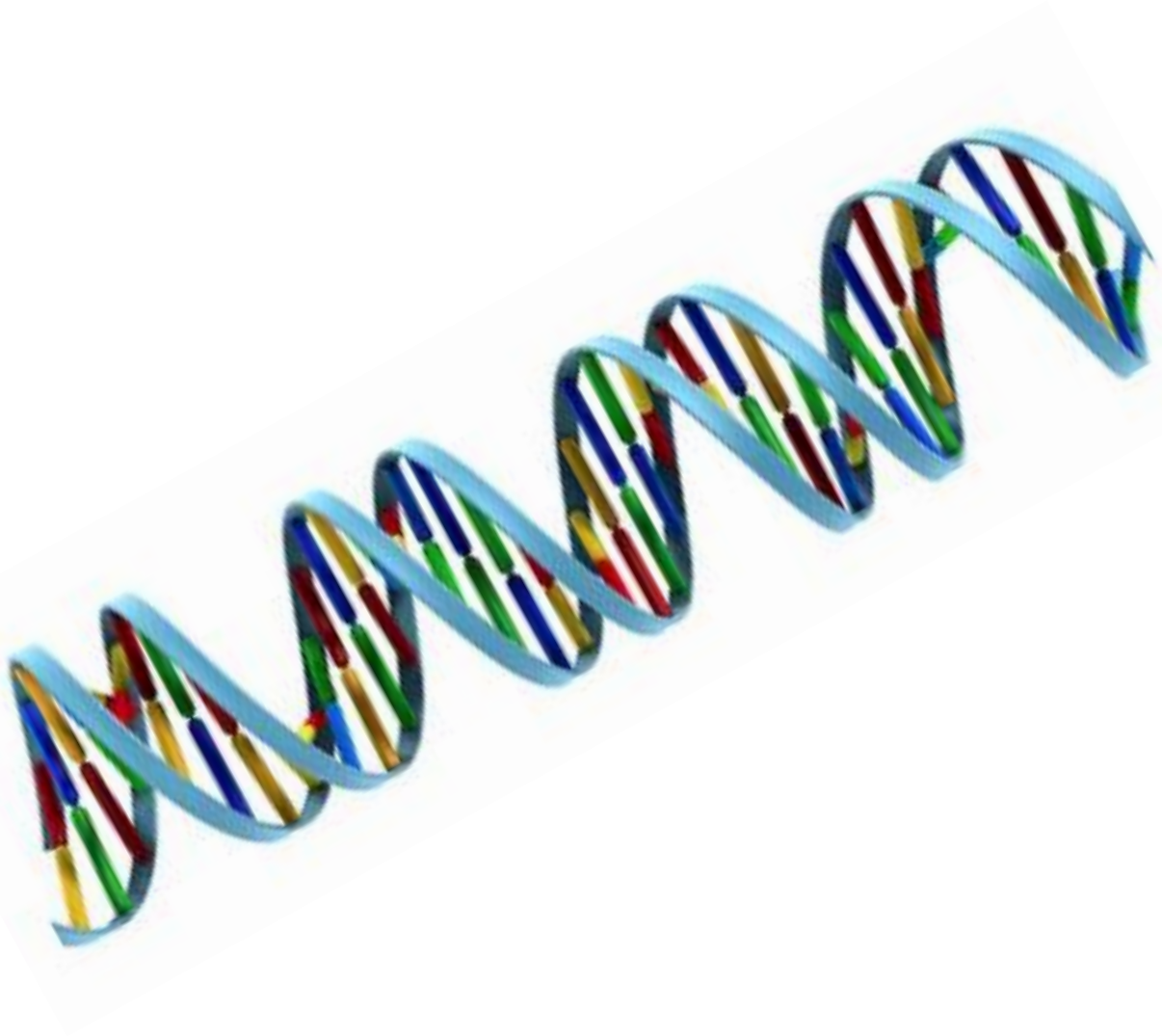


Figure 2: Mediation model in which prenatal BPA levels and child white matter microstructure of the splenium were examined in relation to child internalizing behavior. Standardized beta coefficients, and standard errors in brackets, are reported; *$p \leq 0.05$, **$p \leq 0.01$. Note that the final model was adjusted for child sex and age at scan, as well as maternal urinary creatinine.



Summary

- Findings suggest that prenatal period is more sensitive to BPA exposure.
- Evidence found for young children exposed to greater BPA levels prenatally to have altered white matter microstructure.
- Findings suggest children who were exposed to higher doses of BPA during the **second trimester** were associated with microstructural alterations in inferior and posterior white matter tracts of young children.
- Findings provides support for the hypothesis that underlying alterations in white matter microstructure may be a mechanism by which early life exposure to BPA induces negative behavioral outcomes.



Original Quantitative Research Report

Parenting Interacts With Plasticity Genes in Predicting Behavioral Outcomes in Preschoolers

Canadian Journal of Nursing Research
0(0) 1–18

DOI: 10.1177/0844562119863612
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SAGE

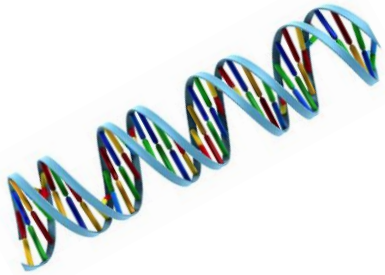
Nicole L. Letourneau[1,2,3], A. P. Jason de Koning[4], Bikram Sekhon[1], Henry N. Ntanda[2], Michael Kobor[5], Andrea J. Deane[2], Alexander M. Morin[5], Deborah Dewey[2], Tavis S. Campbell[6], Gerald F. Giesbrecht[2], and the APrON Study Team

Abstract

Background: Public health and pediatric nurses typically focus on supporting parenting to reduce the likelihood of children's behavioral problems. Studies have identified interactions between early exposures to stress in caregiving and child genotype in predicting children's behavioral problems, such that certain genotypes connote greater differential susceptibility or plasticity to environmental stressors. We sought to uncover the interaction between observational measures of parent–child relationship quality and genotype in predicting early-onset behavioral problems in 24-month-olds, using prospective methods.

Methods: We conducted a secondary analysis of data collected on a subsample of 176 women and their infants enrolled during pregnancy in the ongoing Alberta Pregnancy Outcomes and Nutrition (APrON) cohort study. Inclusion criteria required mothers to be ≥18 years of age, English speaking and ≤22 weeks gestational age at enrollment. Genetic data were obtained from blood leukocytes and buccal epithelial cell samples, collected from infants at three months of age. For each child, the presence of plasticity alleles was determined for *BDNF, CNR1, DRD2/ANKK1, DRD4, DAT1, 5-HTTLPR*, and *MAOA*

APrON Alberta Pregnancy Outcomes and Nutrition



Rationale

- Belsky & Beaver (2011) created plasticity index from allelic variants
  - *DAT1-10r, DRD2, DRD4-7r, 5HTTLPR-s, MAOA-2r* and *MAOA-3r*
- Scores ranging from 0 (none of the alleles) to 5 (all of them)
- This index has been used in subsequent studies of G x E interaction (e.g. Belsky, 2015)

- Early life: parent-child relationship regulates child response to stress before child can self-regulate.
  - (Conradt & Ablow, 2010; Letourneau, Watson, Duffett-Leger, Hegadoren, & Tryphonopoulos, 2011)

- Well established that low quality parent-child relationships portend behavioural problems in children (e.g. multiple Harvard Center reviews)
- High quality parent-child relationships are considered protective
  - Buffer impacts of stress on child development

Research Aim and Participants

- Determine interaction between parent-child relationship and biomarkers of differential susceptibility, and children's behavioural problems in a normal sample.

- N = 176

Internalizing Behaviours

AIC-Best Regression Models for Child Internalizing Behaviours Using Plasticity Index

Model	<AIC>	Δ <AIC>	AIC weight	Cumulative Prob
Fixed + Unresponsive * Plasticity Index	1028.467		0.517	0.517
Fixed + (Sensitive + Unresponsive) * Plasticity Index	1030.745	2.278	0.166	0.683
Fixed + Controlling * Plasticity Index	1031.748	3.281	0.100	0.783
Fixed + (Controlling + Unresponsive) * Plasticity Index	1032.009	3.542	0.088	0.871
Fixed + Sensitive * Plasticity Index	1032.591	4.124	0.066	0.937

Regression Coefficients and Statistic for Gene x Parent-Child Relationship on Internalizing Behaviours Using Plasticity Index

Predictor	Mean effect	SE	Average P-value	% Imput. P <0.05
Plasticity Index	-1.087	0.522	0.043	70
Ethnicity	-1.070	0.821	0.195	0
Unresponsive	-0.674	0.346	0.057	40
Unresponsive*Plasticity Index	0.153	0.070	0.034	80
Infant Age	0.438	0.117	0.000	100
Sex	0.604	0.685	0.379	0

Externalizing Behaviours

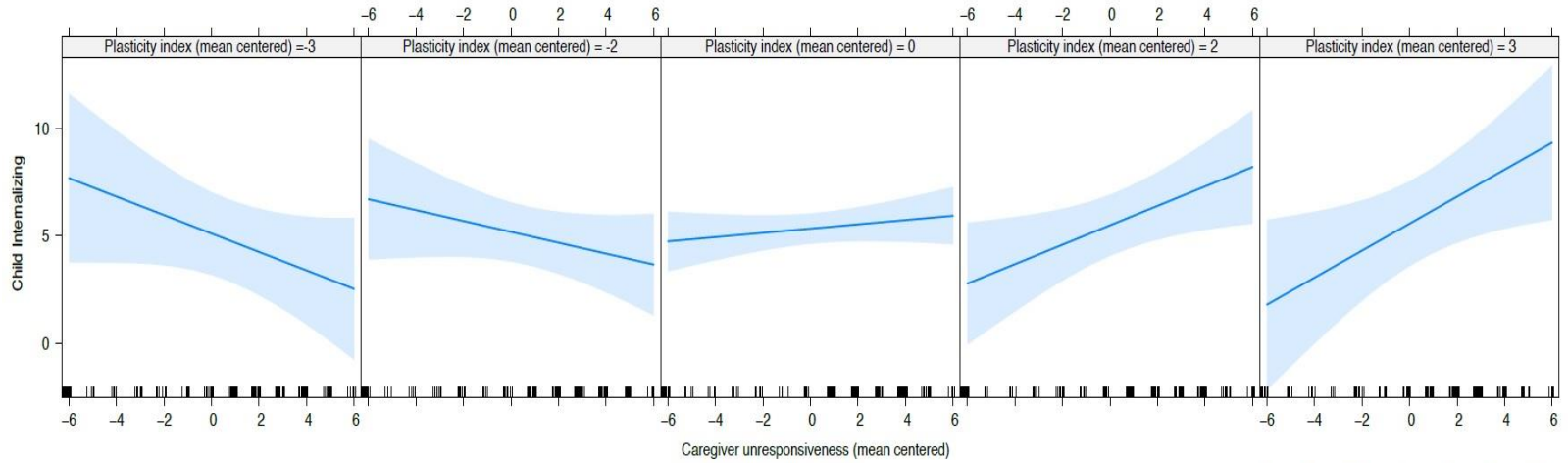
AIC-Best Regression Models Considered for Externalizing Behaviours

Model	<AIC>	Δ <AIC>	AIC weight	Cumulative P
Fixed + Controlling*(CNR1-A + DAT1-9-repeat)	1164.910		0.050	0.050
Fixed + Unresponsive*CNR1-A	1166.155	1.245	0.027	0.077
Fixed + Controlling*(CNR1-T + CNR1-A + DAT1-9-repeat)	1166.464	1.555	0.023	0.101
Fixed + Controlling*(CNR1-A)	1166.649	1.740	0.021	0.122
Fixed + Unresponsive*(CNR1-T + CNR1-A)	1166.659	1.749	0.021	0.143

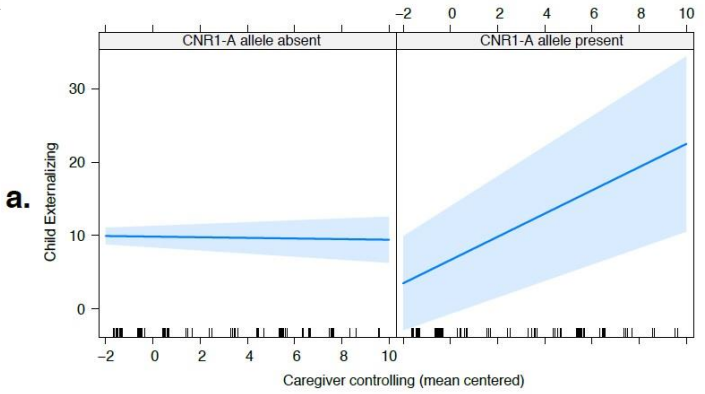
Regression Coefficients and Statistics for Regression of Gene x Parent-Child Relationship on Externalizing Behaviours

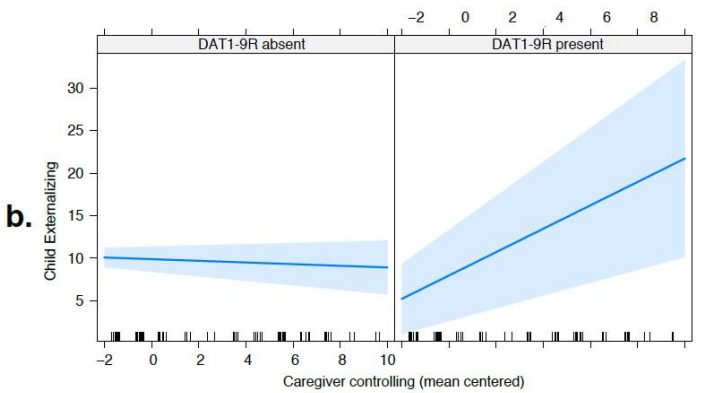
Predictor	Mean effect	SE	Average P-value	% Imput. P <0.05
CNR1-A	-7.132	3.333	0.037	70
DAT1 9-repeat	-4.474	2.250	0.064	50
Ethnicity	-0.974	1.185	0.413	0
Controlling	-0.122	0.155	0.435	0
Infant Age	0.417	0.052	0.000	100
Controlling*DAT1 9- repeat	1.220	0.557	0.036	60
Sex	1.475	1.012	0.148	0
Controlling*CNR1-A	1.622	0.623	0.010	100

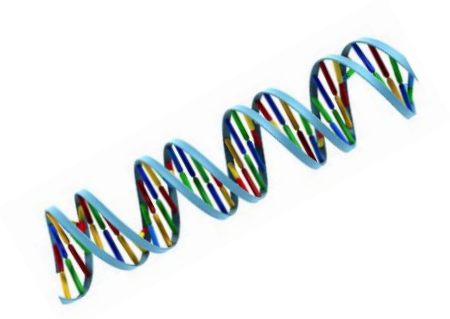
Effect of Interactive Terms in the AIC-Best Model Explaining Internalizing Behaviours



Effect Display for Interactions in the AIC-Best Model Explaining Child Externalizing Behaviour







Summary

- INTERNALIZING BEHAVIOUR:
  - Higher scores on plasticity index interacted with higher parental unresponsiveness in predicting more problem behaviours
  - Higher scores on plasticity index interacted with lower parental unresponsiveness in predicting fewer problem behaviours
- EXTERNALIZING BEHAVIOUR:
  - *CNR1-A* plasticity allele interacted with *higher* parental controlling behaviours in predicting *more* problem behaviours
  - *CNR1-A* interacted with *lower* parental controlling behaviours in predicting *fewer* problem behaviours
  - Similar outcomes for those who possessed *DAT1-9r* plasticity allele

Giesbrecht *et al. Environmental Health* (2017) 16:47
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Environmental Health

RESEARCH Open Access

Prenatal bisphenol a exposure and dysregulation of infant hypothalamic-pituitary-adrenal axis function: findings from the APrON cohort study

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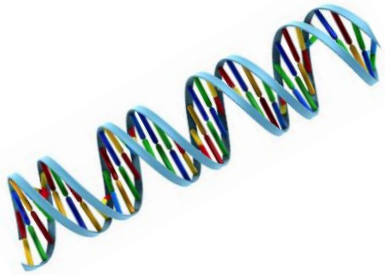
Abstract

Background: Animal models show that prenatal bisphenol A (BPA) exposure leads to sexually dimorphic disruption of the neuroendocrine system in offspring, including the hypothalamic-pituitary-adrenal (HPA) neuroendocrine system, but human data are lacking. In humans, prenatal BPA exposure is associated with sex-specific behavioural problems in children, and HPA axis dysregulation may be a biological mechanism. The objective of the current study was to examine sex differences in associations between prenatal maternal urinary BPA concentration and



Rationale

- Expressed concern for the potential effects of BPA exposure on brain development and behaviour in fetuses, infants and children.
  - (as reported by the National Institute of Environmental Health)
- Mechanisms by which BPA exposure is associated with these behavioural outcomes are not known. The HPA axis is a potential mechanism because it mediates many effects of early life exposure on development.
- The potential effect of BPA exposure on the development of the hypothalamic-pituitary-adrenal (HPA) neuroendocrine system has only recently been investigated in computer and rodent models.

Research Aim and Participants

- Examine sex differences in associations between prenatal maternal urinary BPA concentration and HPA axis function in 3 month old infants.
- N = 132

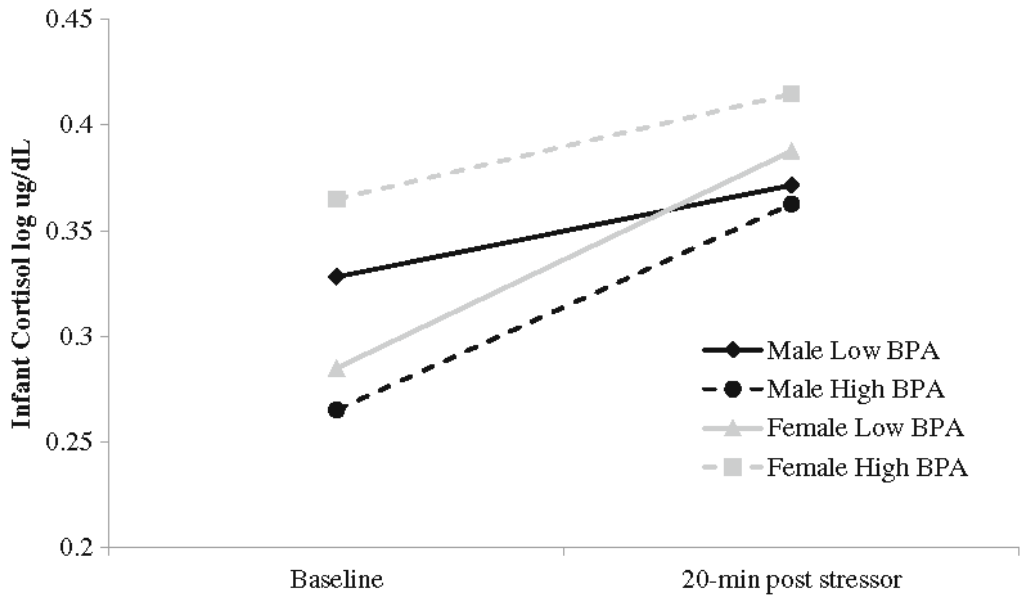
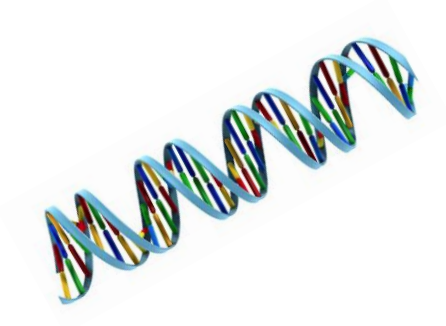


Fig. 1 Infant baseline cortisol and cortisol reactivity as a function of maternal urinary total BPA concentration and infant sex



Summary

- Findings suggest fetal/infant sex plays a critical role in the association between maternal BPA concentration and children's HPA axis function.

- For females, elevated maternal BPA was associated with elevated baseline cortisol, whereas in males it was associated with decreased baseline cortisol.

- The greater maternal urinary total BPA concentration was associated with attenuation of infant cortisol reactivity in female infants but potentiation of cortisol reactivity in male infants.

The PedBE clock accurately estimates DNA methylation age in pediatric buccal cells

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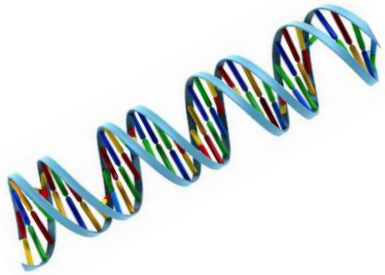
Edited by Marla B. Sokolowski, University of Toronto, Toronto, ON, Canada, and accepted by Editorial Board Member Gene E. Robinson August 23, 2019 (received for review February 19, 2019)

The development of biological markers of aging has primarily focused on adult samples. Epigenetic clocks are a promising tool for measuring biological age that shows impressive accuracy across most tissues and age ranges. In adults, deviations from the DNA methylation (DNAm) age prediction are correlated with several age-related phenotypes, such as mortality and frailty. In children, however, fewer such associations have been made, possibly because DNAm changes are more dynamic in pediatric populations as

clock has been applied to many independent datasets, each showing strong correlations with chronological age. Deviations between DNAm age and chronological age, referred to as DNAm age acceleration, are associated with several age-related health variables, with higher epigenetic age associated with an increase in mortality, cognitive decline, and a decrease in time until death (2).



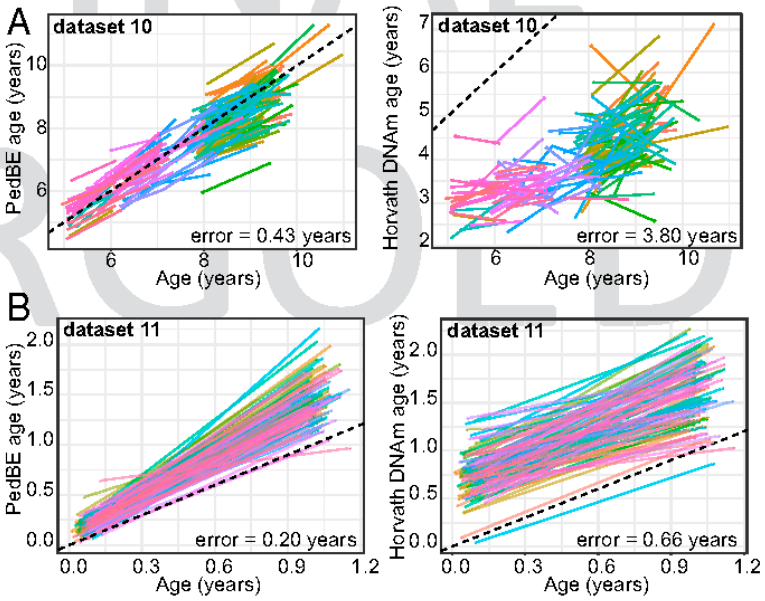
Rationale

- DNA methylation is the most studied mark in human population epigenetics.
- Epigenetic age, based on CpG methylation and often referred to as DNA methylation (DNAm) age, has emerged as a highly accurate estimator of chronological age.
- However, current epigenetic clocks are not very accurate in the pediatric age range perhaps because DNA methylation changes much faster in children.

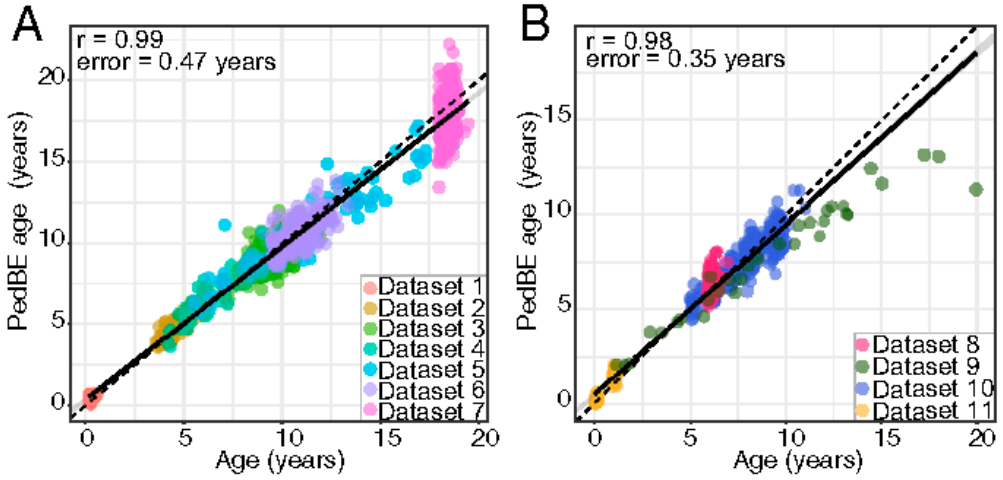
Research Aim and Participants

- Aimed to develop a highly accurate, non-invasive, biological measure of age specific to pediatric samples using buccal epithelial cell DNAm.
- N = 139

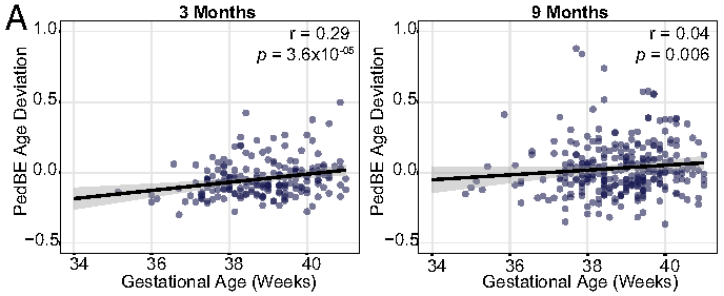
Longitudinal data demonstrated higher accuracy of the PedBE clock as compared to the pan-tissue Horvath DNAm clock.

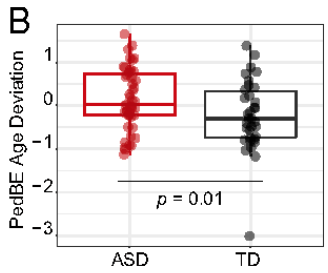


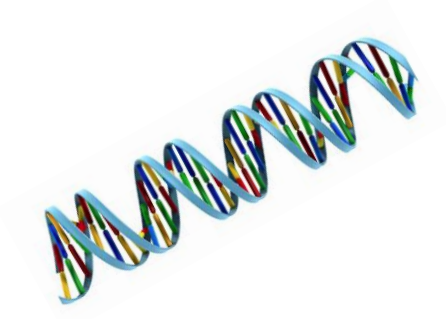
Pediatric buccal DNA methylation age accurately predicted chronological age.



PedBE deviation was associated with gestational age at 3 and 9 mo and individuals diagnosed with ASD in independent cohorts.







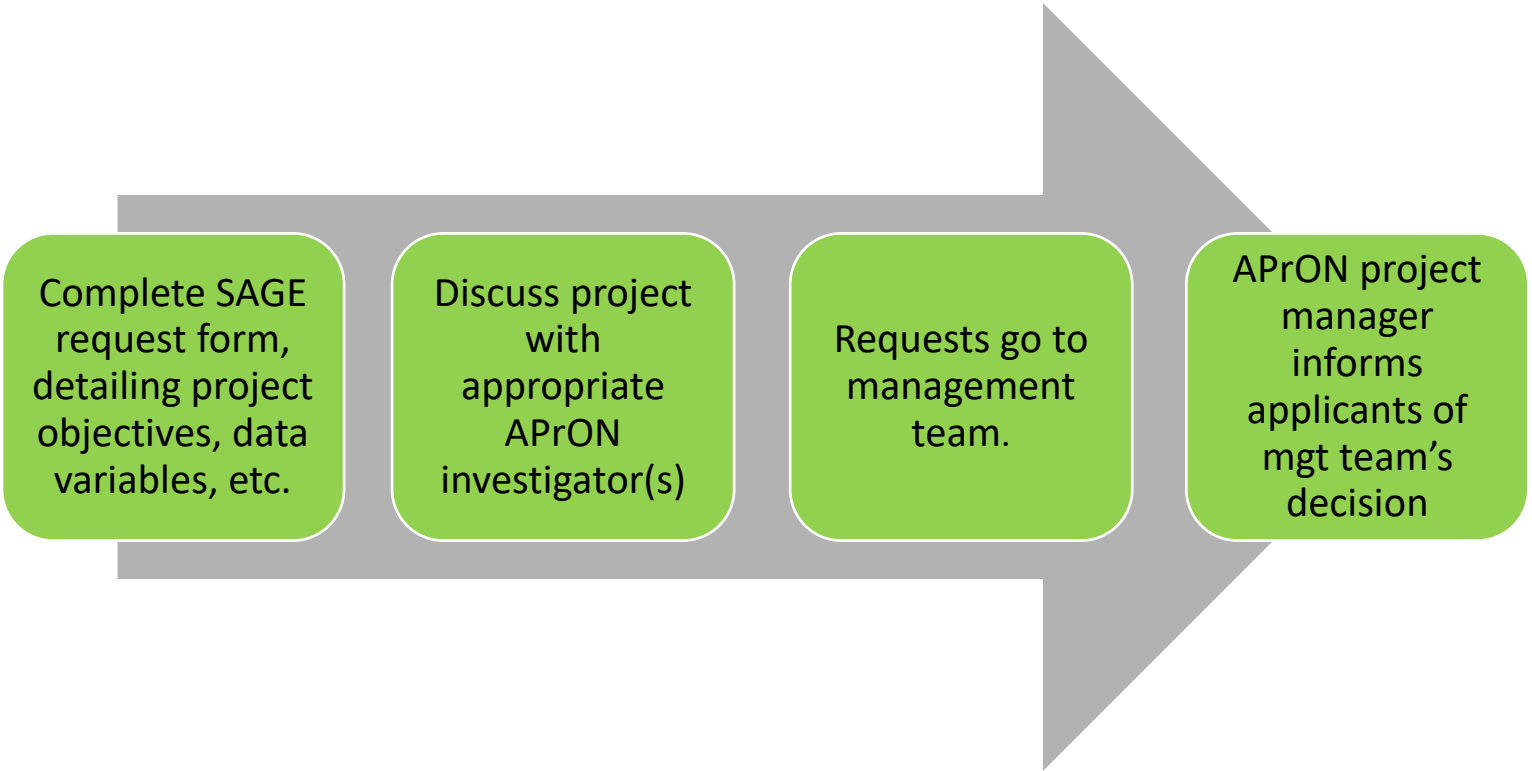
Summary

- Pediatric buccal DNA methylation age accurately predicted chronological age.
- The Pediatric-Buccal-Epigenetic (PedBE) clock was characterized in additional cohorts, showcasing the accuracy in longitudinal data, the performance in nonbuccal tissues and adult age ranges, and the association with obstetric outcomes.
- Findings show infants with a higher gestational age had an older PedBE age.
- PedBE age in children with a neurodevelopmental disorder, ASD, which showed a higher PedBE age than those considered to be typically developing.

Data Access: SAGE

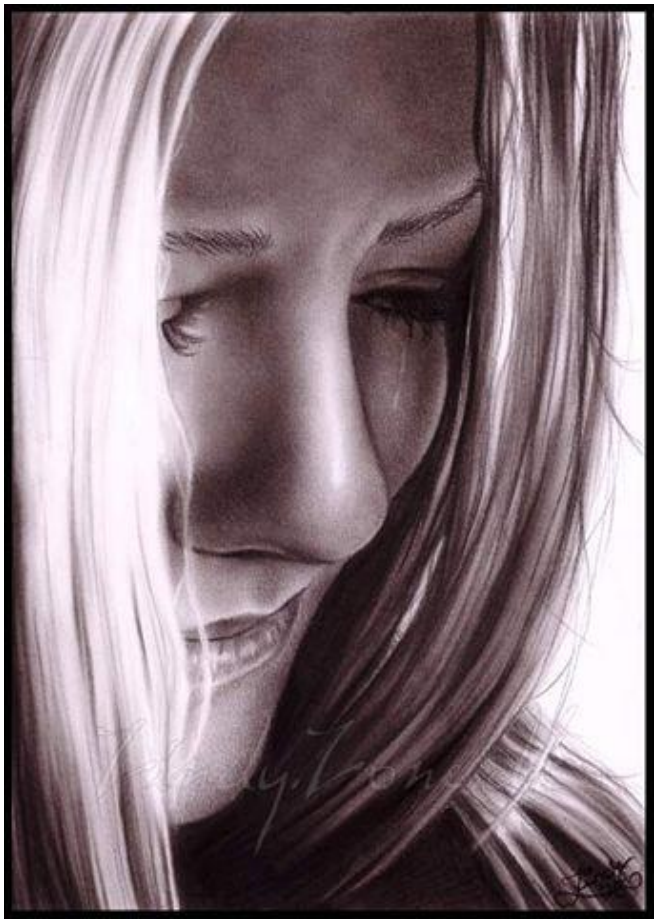
Secondary Analysis to Generate Evidence
https://policywise.com/sage/

Partnership project to support and manage the use of administrative and research data



APrON Alberta Pregnancy Outcomes and Nutrition

Extra Slides



The Buffering Effect of Social Support on Hypothalamic-Pituitary-Adrenal Axis Function During Pregnancy

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Objective: Recent studies suggest that effective social support during pregnancy may buffer adverse effects of maternal psychological distress on fetal development. The mechanisms whereby social support confers this protective advantage, however, remain to be clarified. The aim of this study was to assess whether individual differences in social support alter the covariation of psychological distress and cortisol during pregnancy. **Methods:** Eighty-two pregnant women's psychological distress and cortisol were prospectively assessed in all three trimesters using an ecological momentary assessment strategy. Appraisal of partner social support was assessed in each trimester via the Social Support Effectiveness questionnaire. **Results:** In multilevel analysis, ambulatory assessments of psychological distress during pregnancy were associated with elevated cortisol levels (unstandardized $\beta = .023$, $p < .001$). Consistent with the stress-buffering hypothesis, social support moderated the association between psychological distress and cortisol (unstandardized $\beta = -.001$, $p = .039$), such that the covariation of psychological distress and cortisol increased with decreases in effective social support. The effect of social support for women with the most effective social support was a 50.4% reduction in the mean effect of distress on cortisol and a 2.3-fold increase in this effect for women with the least effective social support scores. **Conclusions:** Pregnant women receiving inadequate social support secrete higher levels of cortisol in response to psychological distress as compared with women receiving effective social support. Social support during pregnancy may be beneficial because it decreases biological sensitivity to psychological distress, potentially shielding the fetus from the harmful effects of stress-related increases in cortisol.
Key words: social support, psychological distress, salivary cortisol, pregnancy, HPA axis, biobehavioral coherence.

APrON = Alberta Pregnancy Outcomes and Nutrition; **GA** = gestational age; **HPA** = hypothalamic-pituitary-adrenal; **PDA** = personal digital assistant; **POMS** = Profile of Mood States; **SSE** = Social Support Effectiveness questionnaire.

experience within fetal development. Maternal cortisol may reach the fetus directly, passing across the placenta despite (partial) conversion of cortisol to its inert form by 11β-hydroxysteriod type 2 (16,17). Active cortisol can then easily pass through the

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Research Aim and Participants

SAMPLE

n = 82 women

All reported that they were in a romantic relationship.

MEASURES

- Cortisol
  - Self-collected **saliva** at home for 2 days (did this 3 times)
- Perceived Social Support from Romantic Partner
  - Social Support Effectiveness Questionnaire (SSEQ)

OBJECTIVES

Understand if individual differences in social support alter psychological distress and cortisol during pregnancy.

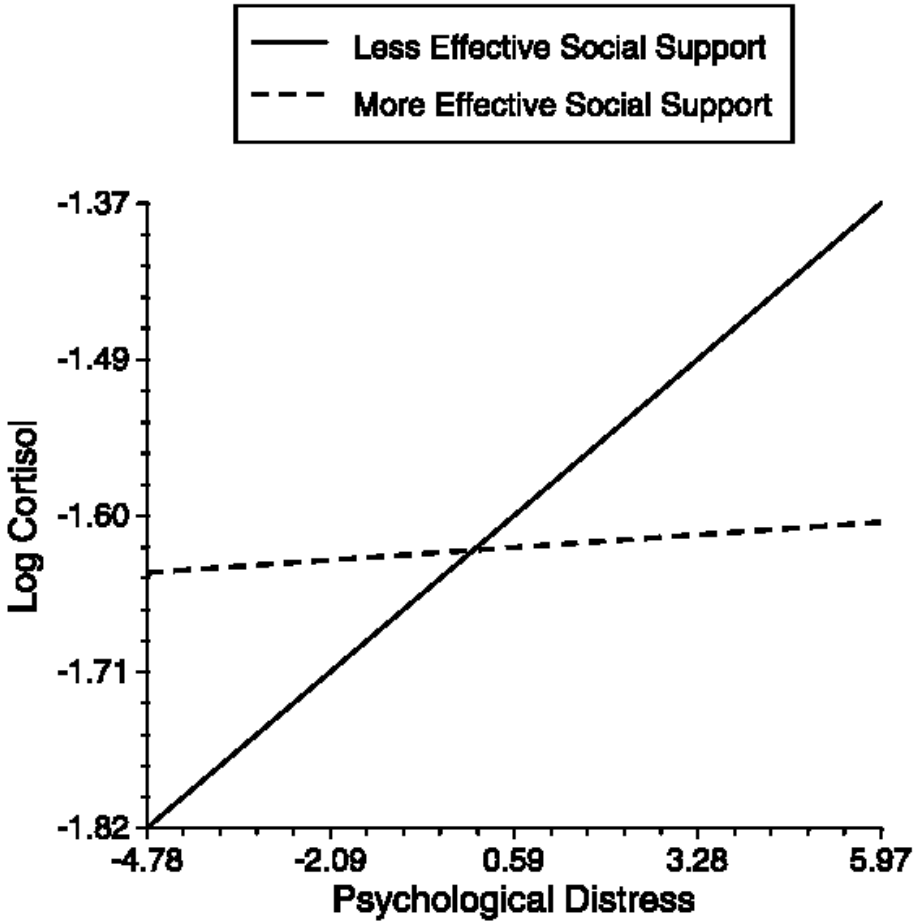
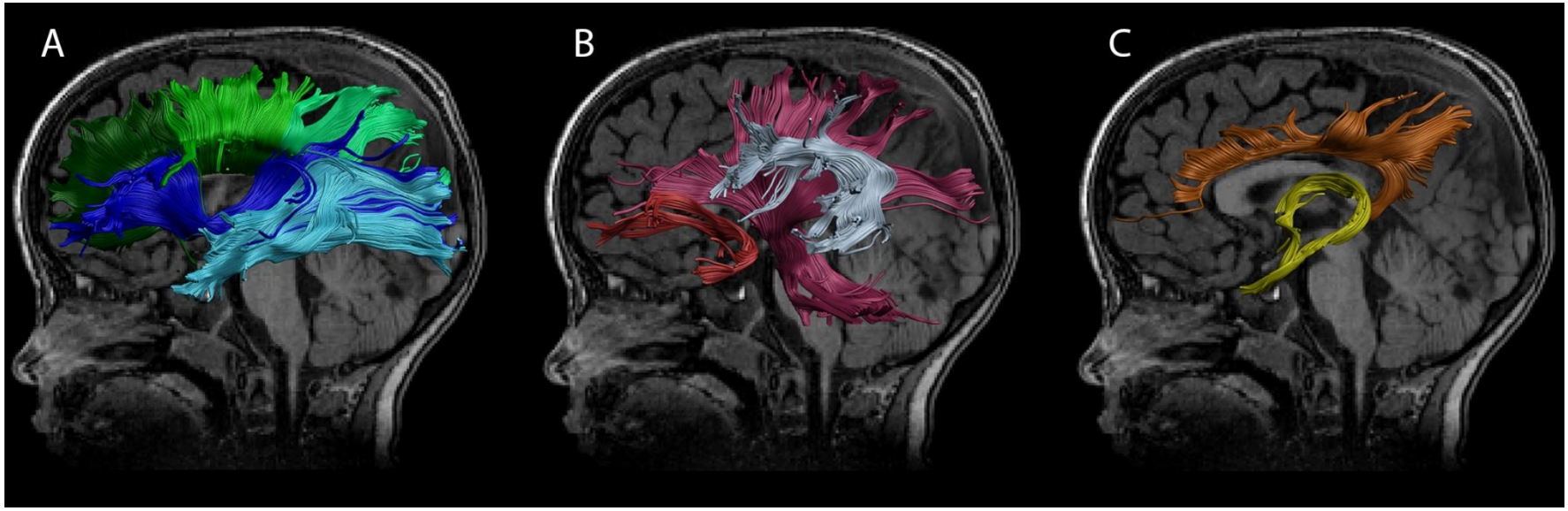


Figure 1. Within-person association between psychological distress and cortisol as a function of social support. More effective social support = mean of upper quartile; less effective social support = mean of lower quartile.

Summary

- Women with relatively higher levels of perceived effective social support had lower psychological distress scores.
- Effective social support weakened the within-person association between psychological stress and cortisol.
- Social support shows it can be a buffer to the effects of psychological distress on the maternal HPA axis during pregnancy.

White Matter Tracts



Fractional Anisotropy (FA) & Mean Diffusivity (MD)

Isolated white matter tracts. A) dark green: genu of corpus callosum, lime green: body of corpus callosum, mint green: splenium of corpus callosum, dark blue: left inferior fronto-occipital fasciculus (IFO), light blue: left inferior longitudinal fasciculus (ILF); B) pink: left pyramidal, silver: left superior longitudinal fasciculus including the arcuate fasciculus (SLF), red: left uncinate fasciculus (UF); C) orange: left cingulum bundle, yellow: fornix. Tracts are shown on a T1-weighted image from a male 3.7 years of age.

Summary

- Children with a higher scores on the plasticity index interacted with higher parental unresponsiveness in predicting more child internalizing problem behaviours, such as anxiety or depression.

- Children with higher scores on the plasticity index interacted with higher parental responsiveness, predicting fewer internalizing behaviours in children.

- Children with the CNR1-A plasticity allele and experienced more controlling caregiver behaviour had significantly more externalizing behaviours.

- Children with the CNR1-A plasticity allele and experienced lower controlling caregiver behaviour actually showed fewer externalizing behaviour.