Data Supplement for Sandman et al., Cortical Thinning and Neuropsychiatric Outcomes in Children Exposed to Prenatal Adversity: A Role for Placental CRH? Am J Psychiatry (doi: 10.1176/appi.ajp.2017.16121433)

SUPPLEMENTARY RESULTS

Consort diagram and description of MRI cohort

Figure S1 illustrates the selection steps for recruiting 6-9-year-old subjects for the MRI scans from the prospective cohort of 834 initially approached to participate in studies of pregnancy and infant outcomes. ***Table 1*** presents means and tests of significant differences for subjects in the MRI protocol and subjects eligible but not in the MRI protocol. ***Table S1A*** presents parametric analysis of continuous variables for the child, birth outcomes and maternal characteristics. There are no significant differences between these two cohorts of subjects for any variables compared. ***Table S1B*** presents means and nonparametric (Mann-Whitney U tests) tests for categorical variables. A significant difference between the groups was detected for one variable—Mother's cohabitation status. The difference between the groups was primarily related to a higher frequency of "Neither legally married nor cohabitating with partner" in the cohort not participating in the MRI protocol. In summary, these two cohorts are virtually identical.

Cortical volumes associated with total pCRH exposure across gestation

Children exposed to high levels of pCRH throughout fetal life exhibited significant thinning of the whole cortical mantle (12%; ***Table S2A***). Regional analysis indicated that cortical thinning associated with pCRH levels was primarily observed in the temporal (15%) and the frontal (16%) regions (***Table S2A***). Neither average concentrations of pCRH across gestation nor levels at any gestational interval were associated with *increased* cortical thickness either globally or in any cortical region (***Table S2B***).

Tables of FreeSurfer subregional parcellations at 19 and 31 weeks gestation

Tables S3 and ***S4*** present the percentages of FreeSurfer sub-regional parcellations associated with exposure to pCRH at 19 weeks' GA (***Table S3***) and 31 weeks' GA (***Table S4***). In ***Table S3*** it is apparent that the bilateral surface of the frontal regions, specifically the frontal pole is primarily thinner in children exposed to CRH at 19 weeks GA. ***Table S4*** illustrates a somewhat broader association between cortical thinning and later exposure to CRH. However the most striking regional association with pCRH at 31weeks is evident bilaterally in the temporal poles.

Conversion to standard scores

In order to combine the pCRH values, each raw value distribution was converted to a standard z-score distribution. Separately at 19 and 30 weeks, CRH values were converted with the formula:

$$z = (X - \mu) / \sigma$$

…where X is a CRH value, μ is the population mean for CRH, and σ is the standard deviation.

The standard score converts CRH concentrations to a z-score distribution with a mean of 0 and a standard deviation of 1. Values for individuals are expressed in terms of standard deviations from their means. Thus a z-score of 1 indicates the subject has a CRH value that is 1 standard deviation above the mean.

Analysis of logarithmic transformation of pCRH at 19 weeks gestation

A logarithmic transformation of pCRH values at 19 weeks GA was computed to account for potential outliers. The two "outliers" were within normal physiological limits. Moreover, these women had consistently elevated levels across gestation. To perform the transform, a constant was added to the standard scores to eliminate zeros and negative numbers. (The log of a negative number is not a number and that the log of zero is negative infinity). The skewness dropped from 2.7 to 1.35. The relation between transformed CRH levels and cortical thickness for the areas in Figures 2B-D in the main text remained significant (r's 0.26 [$p<.025$]-0.39 $p<.01$]). ***Table S5*** presents the FreeSurfer subregional parcellations for log transformed pCRH. The results are nearly identical with the percentages for non-transformed date in ***Table S3.*** The critical comparisons are highlighted.

Sex Differences—Exploratory analysis

We have reported that the age-related changes (6-9 years of age) in cortical and white mater volume (Muftuler et al, 2011; 2012) were stronger for girls than for boys. Because of the age-related differences in cortical volume, we adjusted for age at the time of testing in all the analyses reported here. The differences in the age-related changes between girls and boys prompted us to test for sex differences in predictors and potential covariates in our cohort. As presented in ***Table S6***, there were no sex differences in the predictors or potential covariates examined in this study. ***Figure S2*** demonstrates that patterns of association between prenatal exposure to elevated pCRH at either 19 or 31 weeks and cortical volumes differ for boys from the combined images. The patterns of association for girls exposed to elevated CRH at 19 weeks gestation differ to the combined images. In contrast, the patterns of association between prenatal exposure at 31 weeks and decreased temporal pole volume for girls are similar to the combined images.

Optional Visits—Exploratory analysis

Prenatal visits 15 (N=57) and 35 (N=55) weeks' gestational age (GA) were optional with smaller samples than the “early’ and “late” cohorts. Exploratory analysis indicated that CRH exposure at 15 weeks GA was associated with significant thinning of the frontal cortex—very similar to the findings at 19 weeks GA. The significant association between pCRH and cortical thinning was bilateral but strongest in the right (19% of the structure) compared with 11% in the left frontal region. Regional analyses identified that the lateral frontal pole (40% LH and 65% RH) and the medial orbital frontal [22% LH, 33% RH] regions were the areas in which cortical thinning was most strongly associated with levels of pCRH. Pial maps depict areas of significant thinning linked with fetal pCRH exposure at 15 weeks GA and scatterplots illustrate three subregions of the frontal cortex with the strongest association (***Figure S3***). These results were highly consistent with the findings at 19 weeks GA.

pCRH increases across gestation

The human placenta synthesizes and releases CRH into the maternal and fetal circulation. Placental CRH is identical to hypothalamic CRH in structure, immunoreactivity and bioactivity (Petraglia, Sutton, & Vale, 1989; Sasaki et al., 1987, 1988). We observed the expected elevation of pCRH levels as pregnancy advanced in our cohort **(Figure S4).**

Correlations of *pCRH with* potential maternal, birth and child variables

The findings from **Tables S7A-B** indicate that there are no significant associations between pCRH at 19 and 31 weeks and maternal sociodemographic and mood/anxiety indices. **Table S7C** presents data for the entire sample.

SUPPLEMENTAL METHODS

CRH assay details

Total CRH concentrations were determined by a radioimmunoassay with reported sensitivity of 2.04 pg/ml (RIA; Bachem Peninsula Laboratories, San Carlos, CA). Plasma samples (1-2 ml) were extracted with three volumes of ice-cold methanol, mixed, allowed to stand for 10 minutes at 4°C, and centrifuged at 1700 g and 4°C for 20 minutes (Sandman et al., 2006). Pellets were washed with 0.6 ml methanol, and the combined supernatants were dried down in a Savant SpeedVac concentrator. Reconstituted samples with assay buffer were incubated (100 µl/assay tube) with anti- CRH serum (100 µl) for 48 hours at 4°C, followed by a 24-hour incubation with 125I- CRH at 4°C. Labeled and unlabeled CRH were collected by immunoprecipitation with goat anti-rabbit IgG serum and normal rabbit serum after 90 minutes of incubation at room temperature. Samples were then centrifuged at 1700 g and 4°C for 20 minutes, after which the aspirated pellets were quantified with a gamma scintillation counter. This assay has less than 0.01% cross-reactivity with ovine CRH, 36% cross-reactivity with bovine CRH, and non-detectable reactivity with human ACTH. Intra-assay and inter- assay coefficients ranged from 5% to 15%, respectively.

Subjects with motion artifacts

There were no differences between the subjects excluded because of motion artifacts and those without motion artifacts as described in Table S8 below. We also provide characteristics for the three subjects with “marginal” scans. The summary table presents mean data for the participants who completed the scan, the 7 subjects with motion artifacts and 3 subjects with “marginal” images (who were excluded from the analysis).

TABLE S8. Data for subjects with motion artifacts in their MRI images (excluded from analysis)

	MOTION ARTIFACTS (N=7)	NO MOTION ARTIFACTS (N=97)	MARGINAL(N=3)
AGE (YEARS)	7.2	7.5	7.3
SEX	71%M	50%M	33%M
WISC %TILE	63	67	51
ANXIETY (CBCL)	61	53	52
CRH 15 WKS	-0.57	.16	1.01
CRH 19 WKS	-0.75	-0.01	0.52
CRH 25 WKS	0.14	-0.07	0.54
CRH 31 WKS	-0.54	0.07	0.21
CRH 37 WKS	-0.17	-0.06	-0.01

TABLE S9. pCRH levels (standard scores) at each gestational interval with the percentage of the sample providing complete data at each interval

SAMPLING INTERVAL	pCRH VALUES IN STANDARD SCORES	% OF TOTAL SAMPLE
15 weeks GA (optional)	-0.63 ±0.06 pg/ml	59%
19 Weeks GA	-0.58±0.09 pg/ml	73%
25 Weeks GA	-0.41±0.21 pg/ml	52%
31 Weeks GA	0.27±0.67 pg/ml	82%
~35 Weeks GA (optional)	1.60±0.81 pg/ml	57%

REFERENCES

Muftuler, LT., Davis, EP, Buss, C., Head, K., Hasso, AN, & Sandman, CA. Cortical and subcortical changes in typically developing preadolescent children. *Brain Research*, 2011, 1399, 15-24.

Muftuler, LT, Davis, EP, Buss, C, Solodkin, A, Su, MY, Head, KM, Hasso AN & Sandman, CA. Development of white matter pathway in typically developing preadolescent children. *Brain Research,* 2012, 1466, 33-43 PMID: 22634375.

Sandman, C. A., Glynn, L., Dunkel-Schetter, C., Wadhwa, P., Garite, T., Chicz-DeMet, A., & Hobel, C. (2006). Elevated maternal cortisol early in pregnancy predicts third trimester levels of placental corticotropin releasing hormone (CRH): Priming the placental clock. *Peptides, 27*, 1457-1463. doi: 10.1016/j.peptides.2005.10.002

Petraglia, F., Sutton, S., & Vale, W. (1989). Neurotransmitters and peptides modulate the release of immunoreactive corticotropin-releasing factor from cultured human placental cells. *Am J Obstet Gynecol, 160*(1), 247-251. doi: 10.1016/0002-9378(89)90130-0

Sasaki, A., Shinkawa, O., Margioris, A. N., Liotta, A. S., Sato, S., Murakami, O., . . . Yoshinaga, K. (1987). Immunoreactive corticotropin-releasing hormone in human plasma during pregnancy, labor, and delivery. *J Clin Endocrinol Metab, 64*, 224-229. doi: 10.1210/jcem-64-2-224

Sasaki, A., Tempst, P., Liotta, A. S., Margioris, A. N., Hood, L. E., Kent, S. B., . . . Krieger, D. T. (1988). Isolation and characterization of a corticotropin-releasing hormone-like peptide from human placenta. *J Clin Endocrinol Metab, 67*, 768-773. doi: 10.1210/jcem-67-4-768

FIGURE S1. Consort diagram illustrating the selection of subjects from the initial studies to evaluate the influence of stress on pregnancy and infant/child outcomes.

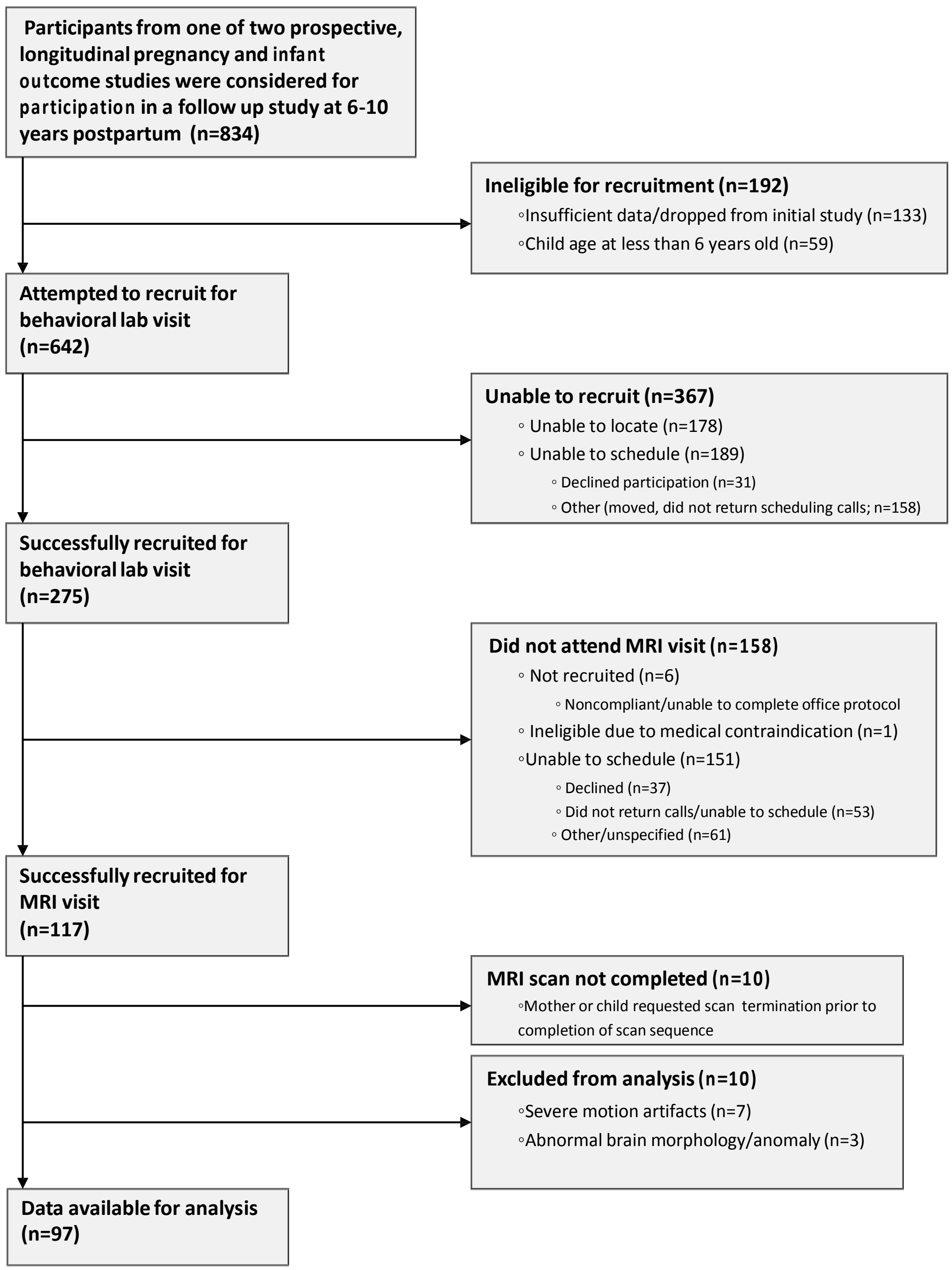
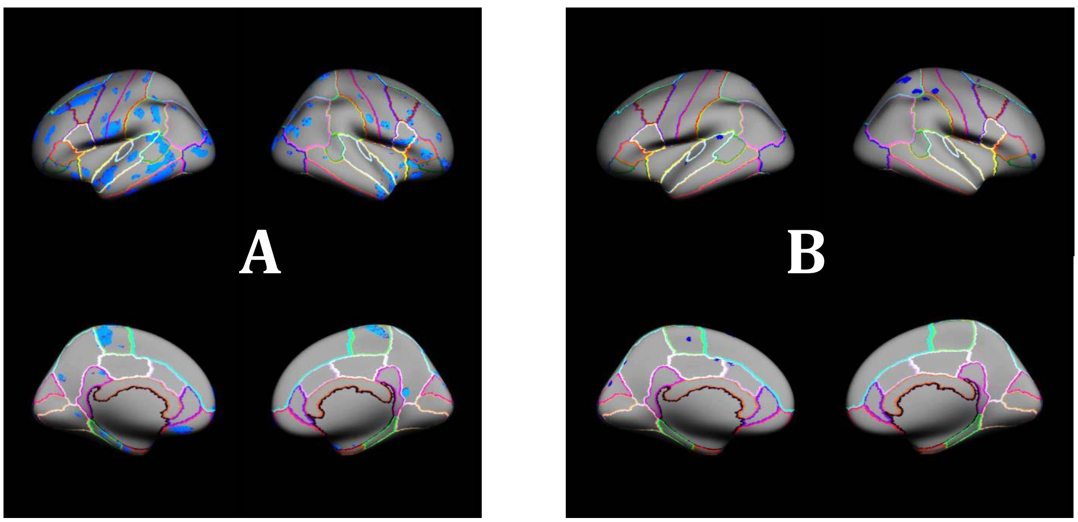


FIGURE S2. Pial maps (A) from FreeSurfer illustrating statistically significant areas of cortical thinning associated with total concentration of prenatal levels of pCRH across gestation (N=97). Representative scatterplots (B-D) of the significant associations between pCRH and cortical thinning in cortical subregions (B r=0.26, p<0.01: C r=0.36, p<0.001: D r=0.37, p<0.001).

Figure S2: The association between exposure to pCRH and cortical volumes for girls and boys

19 WEEKS GESTATION

GIRLS		BOYS	
LH	RH	LH	RH



31 WEEKS GESTATION

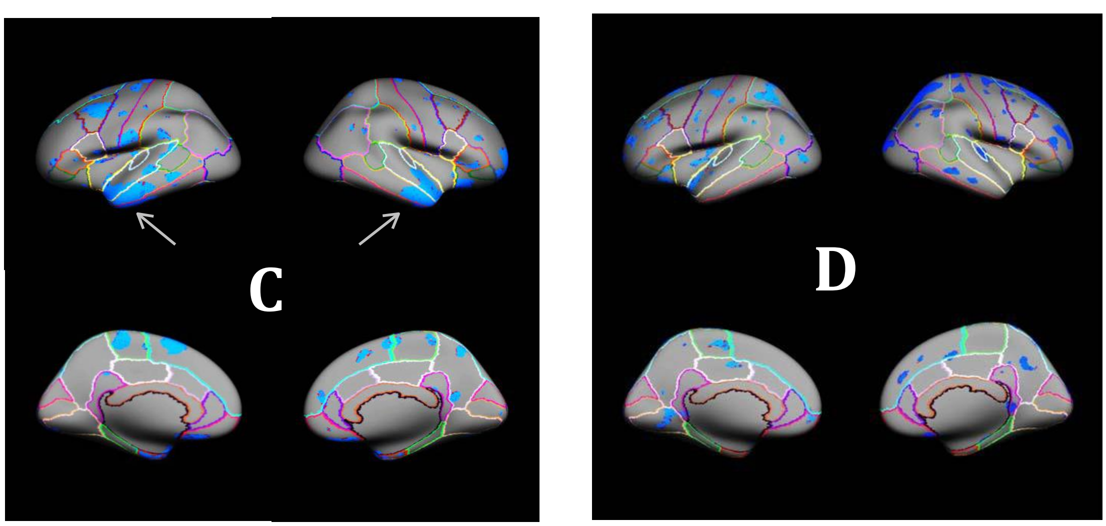


FIGURE S3. Pial maps (A) from FreeSurfer statistically significant areas of cortical thinning associated with prenatal levels of pCRH at 15 weeks' gestation (N=57). Representative scatterplots (B-D) of the significant associations between pCRH and cortical thinning in cortical subregions (B r=0.31, p<0.01: C r=0.42, p<0.001: D r=0.55, p<0.001).

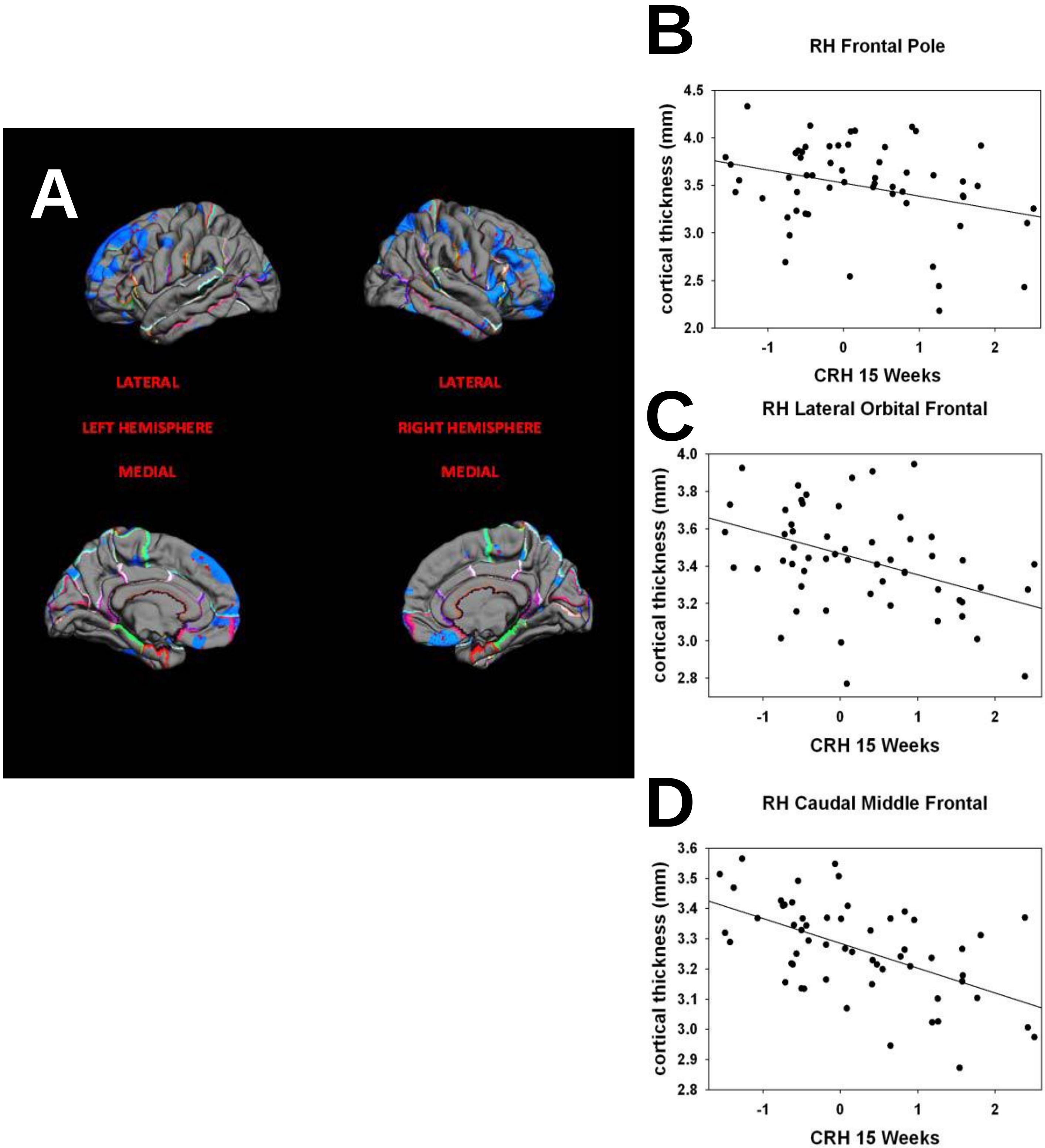


TABLE S1A. Comparing Subjects in the MRI Protocol With Subjects Not in Protocol

		N	Mean					
		N	MEAN	Std. Deviation		d	F	SI
Child's age (IN YEARS) at lab visit	noMRI	167	7.1442	.84140	Between Groups	1	1.895	.17
	mri	108	7.0029	.81599	Within Groups	273		
	Total	275	7.0887	.83289	Total	274		
Mother's age (IN YEARS) at lab Visit	noMRI	167	37.6072	5.31953	Between Groups	1	.008	.93
	mri	108	37.6683	6.21935	Within Groups	273		
	Total	275	37.6312	5.67888	Total	274		
Maternal age (IN YEARS) at delivery	noMRI	167	30.4630	5.28280	Between Groups	1	.085	.77
	mri	108	30.6654	6.10207	Within Groups	273		
	Total	275	30.5425	5.60877	Total	274		
Final GAB (in WEEKS)	noMRI	167	39.1711	1.58407	Between Groups	1	.031	.86
	mri	108	39.2051	1.55102	Within Groups	273		
	Total	275	39.1844	1.56842	Total	274		
birth weight (in grams)	noMRI	163	3414.28	527.684	Between Groups	1	.345	.55
	mri	105	3454.73	584.401	Within Groups	266		
	Total	268	3430.13	549.880	Total	267		
Apgar score at five minutes	noMRI	163	8.9	.28	Between Groups	1	1.691	.19
	mri	106	9.0	.23	Within Groups	267		
	Total	269	8.9	.26	Total	268		
Total number of OB Risks	noMRI	156	.3	.60	Between Groups	1	.478	.49
	mri	98	.3	.62	Within Groups	252		
	Total	254	.3	.61	Total	253		
Years of school completed	noMRI	167	15.20	2.10	Between Groups	1	.120	.72
	mri	108	15.11	1.88	Within Groups	273		
	Total	275	15.16	2.01	Total	274		
WAIS: POI index score	noMRI	165	100.87	16.631	Between Groups	1	2.251	.13
	mri	107	103.94	16.277	Within Groups	270		
	Total	272	102.08	16.531	Total	271		
STAI- MEAN Score	noMRI	163	1.7387	.47346	Between Groups	1	.061	.80
	mri	108	1.7244	.46147	Within Groups	269		
	Total	271	1.7330	.46791	Total	270		
BDI - Total MEAN score	noMRI	161	.3304	.38080	Between Groups	1	.624	.43
	mri	108	.2948	.33531	Within Groups	267		
	Total	269	.3161	.36300	Total	268		

TABLE S1B. Nonparametric Tests of Differences Between Subjects in MRI Protocol With Subjects Eligible But Not in MRI Protocol

CHILD SEX
P<0.22 (ns)

SUBJECTS NOT IN MRI PROTOCOL

	Frequency	Percent
male	71	42.5
female	96	57.5

SUBJECTS IN MRI PROTOCOL

	Frequency	Percent
male	54	50.0
female	54	50.0

CHILD ETHNICITY
P<0.32 (ns)

SUBJECTS NOT IN MRI PROTOCOL

	Frequency	Percent
Hispanic	28	16.8
non-hispanic white	78	46.7
African American or Black	15	9.0
Asian	11	6.6
Multi-Ethnic	35	21.0

SUBJECTS IN MRI PROTOCOL

	Frequency	Percent
Hispanic	27	25.0
non-hispanic white	45	41.7
African American or Black	5	4.6
Asian	8	7.4
Multi-Ethnic	23	21.3

MOTHERS ETHNICITY
P<0.27 (ns)

SUBJECTS NOT IN MRI PROTOCOL

	Frequency	Percent
Hispanic	33	19.8
non-hispanic white	84	50.3
African American or Black	17	10.2
Asian	13	7.8
Multi-Ethnic	19	11.4
other	1	.6

SUBJECTS IN MRI PROTOCOL

	Frequency	Percent
Hispanic	30	27.8
non-hispanic white	48	44.4
African American or Black	6	5.6
Asian	16	14.8
Multi-Ethnic	7	6.5
other	1	.9

HOUSEHOLD INCOME PREVIOUS YEAR
P<0.52(ns)

SUBJECTS NOT IN MRI PROTOCOL

	Frequency	Percent
under $20,000	6	3.6
$20,001 - $40,000	15	9.0
$40,001 - $60,000	20	12.0
$60,001 - $80,000	26	15.6
$80,001 - $100,000	18	10.4
over $100,000	81	48.5

SUBJECTS IN MRI PROTOCOL

	Frequency	Percent
under $20,000	5	4.7
$20,001 - $40,000	8	7.4
$40,001 - $60,000	10	9.3
$60,001 - $80,000	19	17.6
$80,001 - $100,000	19	17.6
over $100,000	51	47.2

MOTHER'S COHABITATION STATUS
P<0.01

SUBJECTS NOT IN MRI PROTOCOL

	Frequency	Percent
Legally Married	122	73.1
Legally married, but currently separated/not living w partner	4	2.4
Cohabitating w partner, but not legally married	11	6.6
Neither legally married nor cohabitating w partner	28	16.8

SUBJECTS IN MRI PROTOCOL

	Frequency	Percent
Legally Married	93	86.1
Legally married, but currently separated/not living w partner	2	1.9
Cohabitating w partner, but not legally married	8	7.4
Neither legally married nor	5	4.6

TABLE S1C. Comparing pCRH Levels in Subjects in the MRI Protocol With Subjects Eligible But Not in the Protocol

		N	SD		df	F	SIG
wk15 CRH - MEAN	noMRI	85	.1777844	Between Groups	1	.011	.917
	mri	65	.1602163	Within Groups	148		
wk19 CRH - MEAN	noMRI	129	-.0705060	Between Groups	1	.176	.675
	mri	77	-.0075490	Within Groups	204		
wk25 CRH - MEAN	noMRI	87	.0099925	Between Groups	1	.241	.624
	mri	60	-.0673128	Within Groups	145		
wk31 CRH - MEAN	noMRI	114	-.0230650	Between Groups	1	.646	.423
	mri	84	.0709460	Within Groups	196		
: wk37 CRH - MEAN	noMRI	86	.0355027	Between Groups	1	.322	.572
	mri	65	-.0576674	Within Groups	149		

TABLE S2A. Percentage of whole cortex and the different cortical regions that are significantly thinner in children exposed as fetuses to Placental CRH across gestation (Average) and at five separate gestational intervals

THINNER	Average N=97	15 Weeks N=57	~19 Weeks N=70	~25 Weeks N=50	~30 Weeks N=79	~35 Weeks N=55
Whole Brain	12	10	6	9	12	6
Frontal Cortex	16	15	8	11	15	7
Parietal Cortex	10	9	5	13	10	3
Temporal Cortex	15	6	9	4	19	10
Occipital Cortex	3	3	4	6	2	1
Cingulate/Limbic	0	1	0	4	0	2

TABLE S2B. Percentage of whole cortex and the different cortical regions that are significantly thicker in children exposed as fetuses to Placental CRH across gestation (Average) and at five separate gestational intervals

THICKER	Average	15 Weeks	~19 Weeks	~25 Weeks	~30 Weeks	~35 Weeks
Whole Brain	1	2	4	3	1	1
Frontal Cortex	0	1	4	2	0	0
Parietal Cortex	1	3	4	2	0	1
Temporal Cortex	0	1	2	4	1	0
Occipital Cortex	4	3	5	6	4	9
Cingulate/Limbic	4	4	5	3	9	5

TABLE S3. Percentage of structures of the frontal and temporal lobes that are thinner in children exposed to placental CRH at 19 weeks gestation. The results are presented for the left (LH) and right (RH)hemisphere.

LH Medial Surface Frontal	Percent of Structure	RH Medial Surface Frontal	Percent of Structure
Orbital Frontal	10	Orbital Frontal	0
Paracentral	23	Paracentral	7

LH Lateral Surface Frontal	Percent of Structure	RH Lateral Surface Frontal	Percent of Structure
Superior Frontal	5	Superior Frontal	0
Rostral Middle Frontal	11	Rostral Middle Frontal	8
Frontal Pole	69	Frontal Pole	78
Pars Triangularis	0	Pars Triangularis	10
Parsorbitalis	6	Parsorbitalis	9
Lateral Orbital Frontal	9	Lateral Orbital Frontal	15
Parsopercularis	0	Parsopercularis	21
Caudal Middle Frontal	32	Caudal Middle Frontal	2
Precentral	5	Precentral	6
Insula	3	Insula	4

LH Lateral Surface Temporal	Percent of Structure	RH Lateral Surface Temporal	Percent of Structure
Superior Temporal	26	Superior Temporal	10
Transverse Temporal	0	Transverse Temporal	0
Middle Temporal	7	Middle Temporal	8
Post Sup Temp sulcus	19	Post Sup Temp sulcus	0
Inferior Temporal	12	Inferior Temporal	6
Fusiform	0	Fusiform	0
Parahippocampal	0	Parahippocampal	0
Entorhinal	0	Entorhinal	0
Temporal Pole	0	Temporal Pole	14

TABLE S4. Percentage of structures of the frontal and temporal lobes that are thinner in children exposed to placental CRH at 31 weeks gestation. The results are presented for the left (LH) and right (RH)hemisphere.

LH Medial Surface Frontal	Percent of Structure	RH Medial Surface Frontal	Percent of Structure
Orbital Frontal	10	Orbital Frontal	16
Paracentral	43	Paracentral	8

LH Lateral Surface Frontal	Percent of Structure	RH Lateral Surface Frontal	Percent of Structure
Superior Frontal	12	Superior Frontal	6
Rostral Middle Frontal	4	Rostral Middle Frontal	24
Frontal Pole	0	Frontal Pole	9
Pars Triangularis	19	Pars Triangularis	19
Parsorbitalis	6	Parsorbitalis	9
Lateral Orbital Frontal	19	Lateral Orbital Frontal	31
Parsopercularis	13	Parsopercularis	14
Caudal Middle Frontal	26	Caudal Middle Frontal	25
Precentral	12	Precentral	17
Insula	18	Insula	0

LH Lateral Surface Temporal	Percent of Structure	RH Lateral Surface Temporal	Percent of Structure
Superior Temporal	35	Superior Temporal	24
Transverse Temporal	0	Transverse Temporal	12
Middle Temporal	27	Middle Temporal	27
Post Sup Temp sulcus	7	Post Sup Temp sulcus	0
Inferior Temporal	13	Inferior Temporal	14
Fusiform	4	Fusiform	5
Parahippocampal	2	Parahippocampal	3
Entorhinal	9	Entorhinal	5
Temporal Pole	66	Temporal Pole	98

TABLE S5. Percentages of structures of the frontal and temporal lobes that are thinner in children exposed to pCRH at 19 weeks gestation using log transformed CRH values. Values can be compared with findings in Table S2. Highlights show the nearly identical results for the transformed and the z-scored data.

LH Medial Surface Frontal	Percent of Structure	RH Medial Surface Frontal	Percent of Structure
Orbital Frontal	0.0842	Orbital Frontal	0.0000
Paracentral	0.2370	Paracentral	0.0484
LH Lateral Surface		RH Lateral Surface	0.0000
Superior Frontal	0.0470	Superior Frontal	0.0000
Rostral Middle Frontal	0.0810	Rostral Middle Frontal	0.0638
Frontal Pole	0.5302	Frontal Pole	0.7600
Pars Triangularis	0.0000	Pars Triangularis	0.0844
Parsorbitalis	0.0929	Parsorbitalis	0.0400
Lateral Orbital Frontal	0.0777	Lateral Orbital Frontal	0.1479
Parsopercularis	0.0000	Parsopercularis	0.1819
Caudal Middle Frontal	0.3100	Caudal Middle Frontal	0.0233
Precentral	0.0438	Precentral	0.0493
Insula	0.0197	Insula	0.0383
LH Lateral Surface Temporal	Percent of Structure	RH Lateral Surface Temporal	Percent of Structure
Superior Temporal	0.1718	Superior Temporal	0.0923
Transverse Temporal	0.0000	Transverse Temporal	0.0000
Middle Temporal	0.0626	Middle Temporal	0.0726
Post Sup Temp sulcus	0.1743	Post Sup Temp sulcus	0.0000
Inferior Temporal	0.0956	Inferior Temporal	0.0397
Fusiform	0.0000	Fusiform	0.0000
Parahippocampal	0.0000	Parahippocampal	0.0000
Entorhinal	0.0000	Entorhinal	0.0000
Temporal pole	0.0000	Temporal pole	0.1100

TABLE S6. Exploratory Analysis of Sex Differences

		N	Mean	Std. Deviation	df	F	Sig.
Child's age (IN YEARS)	male	54	6.9983	**Between Groups**	1	.003	.954
	female	54	7.0075	**Within Groups**	106		
Mother's age (IN YEARS)	male	54	37.2519	**Between Groups**	1	.482	.489
	female	54	38.0847	**Within Groups**	106		
Final GAB (in WEEKS)	male	54	39.2011	**Between Groups**	1	.001	.979
	female	54	39.2090	**Within Groups**	106		
Birthweight percentile by sex	male	51	53.431	**Between Groups**	1	.035	.852
	female	52	54.481	**Within Groups**	101		
Apgar score at five minutes	male	53	9.02	**Between Groups**	1	.658	.419
	female	53	8.98	**Within Groups**	104		
Total number of OB Risks	male	50	.36	**Between Groups**	1	.203	.653
	female	48	.42	**Within Groups**	96		
WISC - Percentile rank	male	54	68.9130	**Between Groups**	1	.463	.498
	female	54	65.3759	**Within Groups**	106		
CBCL - Internalizing Total	male	54	5.3889	**Between Groups**	1	.085	.771
	female	54	5.6481	**Within Groups**	106		
CBCL - Externalizing Total	male	54	6.1296	**Between Groups**	1	.025	.874
	female	54	5.9444	**Within Groups**	106		
wk19 CRH - MEAN	male	38	-.2509275	**Between Groups**	1	3.519	.065
	female	39	.2295890	**Within Groups**	75		
: wk31 CRH - MEAN	male	44	.0633554	**Between Groups**	1	.009	.926
	female	40	.0792957	**Within Groups**	82		
CESD Z-SCORE	male	51	-.1351109	**Between Groups**	1	.023	.880
	female	50	-.1090865	**Within Groups**	99		
STAI - Z-SCORE	male	51	-.0698441	**Between Groups**	1	.009	.927
	female	50	-.0524384	**Within Groups**	99		

TABLE S7A. Correlations Among CRH Levels and Maternal Characteristics

	CRH Level Week 19	CRH Level Week 31	Mother's age	Years of school completed	Household income-previous year	WAIS: POI index score	Trait Anxiety	CESD (Depression)	Beck Depression Index
CRH Level Week 19	1								
CRH Level Week 31	.386**	1							
Mother's age	-.041	-.053	1						
years of school completed	.024	-.025	.214*	1					
household income-previous	-.037	-.108	.299**	.595**	1				
WAIS: POI index score	.025	.085	.125	.489**	.501**	1			
Trait Anxiety	.218	.037	.035	-.318**	-.442**	-.162	1		
CESD (Depression)	.040	-.031	-.003	-.326**	-.331**	-.197*	.573**	1	
Beck Depression Index	.086	.097	.083	-.190*	-.398**	-.188	.703**	.524**	1

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

TABLE S7B. Correlations Among CRH Levels, Birth Outcomes and Child Sex

	CRH Level Week 19	CRH Level Week 31	Child's sex	GAB	Apgar score at five minutes	Total number of OB Risks
CRH Level Week 19	1					
CRH Level Week 31	.386**	1				
Child's sex	.212	.010	1			
GAB	.020	-.170	.003	1		
Apgar score at five minutes	.046	-.117	-.079	.036	1	
Total number of OB Risks	-.047	.201	.046	-.255*	-.183	1

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

TABLE S7C. Correlations Among CRH, Gestational Age at Birth and Birth Weight in Total Sample (N=578–791)

	GAB	Birth weight	wk19 CRH	wk31 CRH
GAB	1			
Birth weight	.654**	1		
wk19 CRH	-.023	-.071	1	
wk31 CRH	-.256**	-.283**	.209**	1

**. Correlation is significant at the 0.01 level (2-tailed).