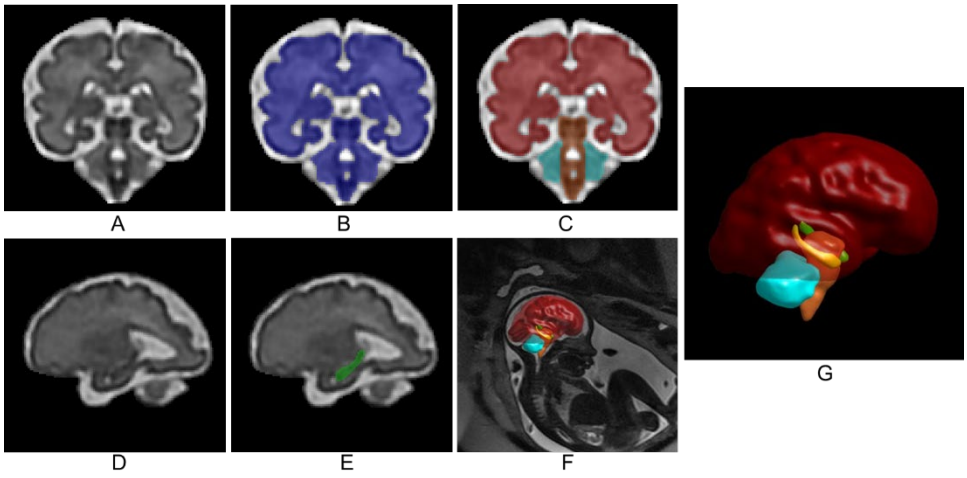
Supplementary Online Content

Wu Y, Kapse K, Jacobs M, et al. Association of maternal psychological distress with in utero brain development in fetuses with congenital heart disease. *JAMA Pediatr*. Published online January 13, 2020. doi:10.1001/jamapediatrics.2019.5316

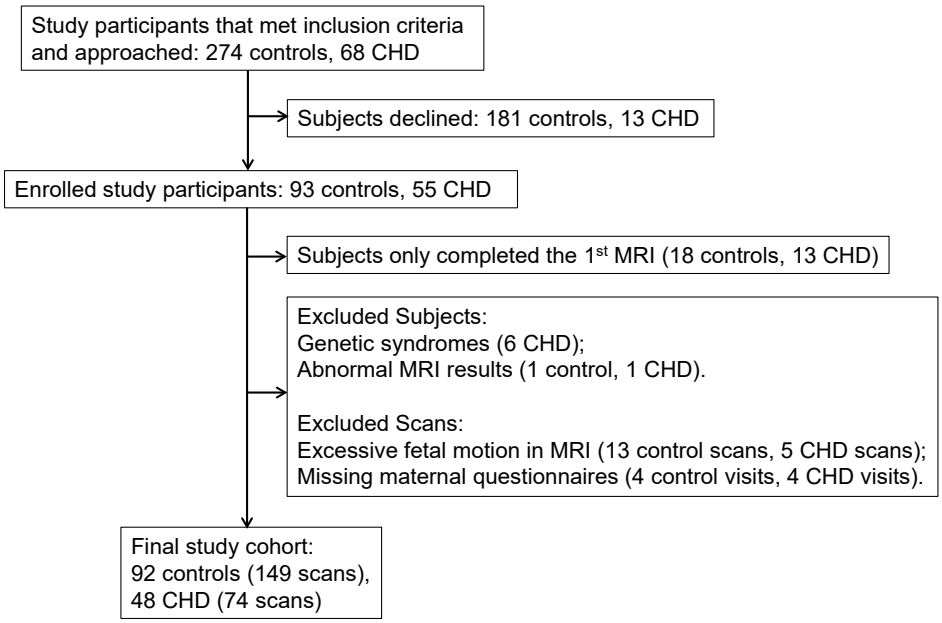
This supplementary material has been provided by the authors to give readers additional information about their work.

eFigure 1. T2-weighted brain MR image segmentation



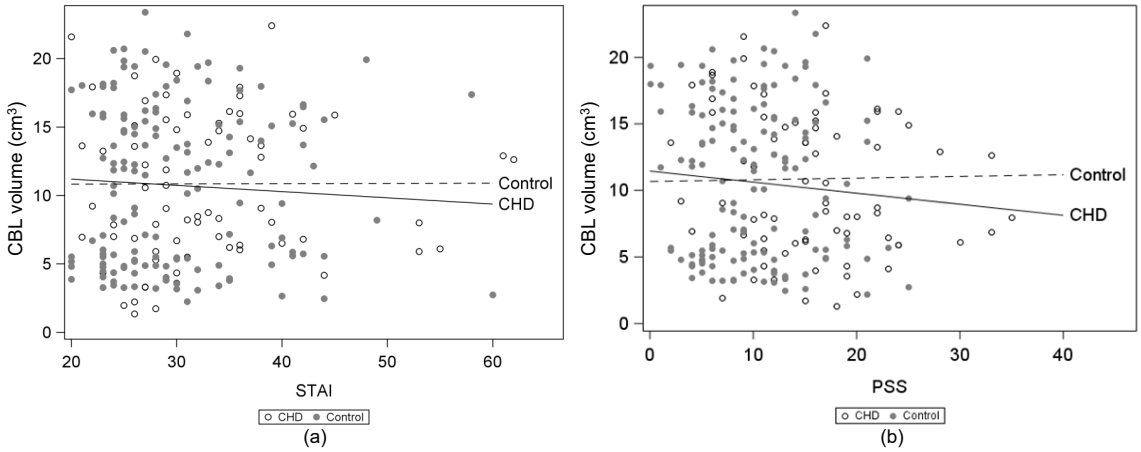
Segmentation of total brain (blue), cerebrum (red), cerebellum (cyan), brainstem (brown), left hippocampus (green), and right hippocampus (yellow) on coronal view (A-C), sagittal view (D-E), 3D view overlaying fetal image (F) and isolated 3D reconstruction (G) of a fetus with congenital heart disease at 30 gestational weeks.

eFigure 2. Flow diagram summarizing our subject recruitment in this study



Six fetuses with congenital heart disease (CHD) were excluded for genetic syndromes/chromosomal findings which included Trisomy 13 (2 subjects), Chromosome 11 deletion, Chromosome 15q13.3 deletion, DiGeorge Syndrome, and CHARGE Syndrome. Abnormal MRI results included intraventricular hemorrhage (1 control) and lissencephaly (1 CHD) at the 1st fetal MRI.

eFigure 3. Associations between maternal trait anxiety (a) or stress (b) and fetal cerebellar volume in CHD and controls



Maternal trait anxiety (STAI) and stress (PSS) are negatively associated with cerebellar (CBL) volumes in fetuses with congenital heart disease (CHD), but associations are relatively unchanged in controls.

eTable 1. Maternal psychological distress scales in controls (92 subjects; 149 visits) and CHD (48 subjects; 74 visits) as well as in women with 2 visits (57 controls, 26 CHD subjects)

Mean (SE)	Controls	CHD	P value[a]	1st visit	2nd visit	P value[b]
SSAI	29.5 (0.9)	37.0 (1.8)	**< .001**	30.2 (0.9)	29.2 (0.9)	.11
STAI	30.7 (0.8)	33.2 (1.3)	.10	30.6 (0.8)	29.6 (0.7)	**.01**
PSS	10.6 (0.6)	15.8 (1.0)	**< .001**	12.4 (0.7)	10.2 (0.6)	**< .001**
EPDS	4.0 (0.4)	7.3 (0.7)	**< .001**	4.6 (0.4)	4.2 (0.4)	.17

Abbreviations: SE, standard error; SSAI, Spielberger State Anxiety Inventory; STAI, Spielberger Trait Anxiety Inventory; PSS, Perceived Stress Scale; EPDS, Edinburgh Postnatal Depression Scale; CHD, congenital heart disease.

[a] P value based on generalized estimating equations, controlling for gestational age

[b] P value based on paired t-test

P value with bolding denotes significant after adjusting for multiple testing

eTable 2. Congenital heart disease diagnoses

(N=48 subjects)	N (%)
SV with aortic obstruction	13 (27)
Hypoplastic left heart syndrome and variants	11 (23)
Complex SV (Unbalanced atrioventricular canal defect with coarctation/arch hypoplasia)	2 (4)
SV without aortic obstruction	4 (8)
Complex SV (Double outlet right ventricle with pulmonary atresia or stenosis)	3 (6)
Double inlet left ventricle	1 (2)
2V with aortic obstruction	6 (13)
Ventricular septal defect with coarctation	2 (4)
Complex 2V (Double outlet right ventricle with coarctation/arch hypoplasia)	2 (4)
Coarctation of the aorta	1 (2)
Atrioventricular canal defect with coarctation	1 (2)
2V without arch obstruction	25 (52)
Transposition of the great arteries	8 (17)
Tetralogy of Fallot	7 (15)
Truncus arteriosus	3 (6)
Atrioventricular canal defect with heterotaxy	3 (6)
Double outlet right ventricle with pulmonary stenosis or atresia	3 (6)
Total anomalous pulmonary venous return	1 (2)

Abbreviations: SV, single ventricle; 2V, two ventricles.

eTable 3. Brain volumes in SV vs 2V CHD, and CHD fetuses with vs without aortic obstruction

Mean (cm^3)	SV CHD (17 subjects; 24 scans)	2V CHD (31 subjects; 50 scans)	P value	CHD without aortic obstruction (29 subjects; 44 scans)	CHD with aortic obstruction (19 subjects; 30 scans)	P value
TBV	183.77	190.37	.28	183.67	194.17	.14
CBR	169.83	176.23	.27	169.74	179.97	.13
BS	3.86	3.91	.61	3.87	3.93	.47
CBL	10.40	10.39	.98	10.26	10.58	.43
LH	0.50	0.54	.09	0.53	0.52	.51
RH	0.54	0.57	.28	0.56	0.56	.86

Abbreviations: SV, single ventricle; 2V, two ventricle; CHD, congenital heart disease; TBV, total brain volume; CBR, cerebrum; BS, brainstem; CBL, cerebellum; LH, left hippocampus; RH, right hippocampus.
Results of least squares means estimates from generalized estimating equations, controlling for gestational age and gender.

eTable 4. Brain volumes in CHD fetuses with one and more maternal stressors (stress, anxiety, and/or depression)

Mean (cm^3)	1 stressor (13 subjects; 15 scans)	2 stressors (15 subjects; 15 scans)	All 3 stressors (10 subjects; 12 scans)	P value
TBV	185.27	178.57	179.14	.44
CBR	171.76	165.50	165.59	.42
BS	3.77	3.76	3.84	.66
CBL	9.86	9.45	9.79	.66
LH	0.49	0.49	0.48	.92
RH	0.53	0.52	0.52	.70

Abbreviations: TBV, total brain volume; CBR, cerebrum; BS, brainstem; CBL, cerebellum; LH, left hippocampus; RH, right hippocampus.
Results of least squares means from generalized estimating equations, controlling for gestational age and gender.