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Short Communication

Association between maternal c-reactive protein levels in pregnancy and growth trajectories of head circumference during the first year of postnatal life – A secondary data analysis of a case-control study on autism

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1. Introduction

Elevated levels of c-reactive protein (CRP) and other markers of inflammation during pregnancy have been associated with offspring neurodevelopmental disorders [1]. Higher levels of maternal CRP have also been associated with newborn brain connectivity in regions involved in emotion regulation and theory of mind [2]. Understanding brain changes that may precede diagnosis of neurodevelopmental disorders could help elucidate points for prevention [2].

Existing research utilizes head circumference (HC) as a proxy for brain growth. In prematurely born neonates, elevated CRP was associated with smaller HC [3]. This association was also found in neonates with normal birth weight [4]. In contrast, a study in Nepal found that higher levels of prenatal α1-acid glycoprotein, another acute-phase reactant, but not CRP was associated with smaller HC [5]. The limited research in this area has primarily been in the context of preterm/low-birth weight and none have considered longitudinal changes in HC. We extend this research by observing the association of prenatal maternal CRP with velocity of HC (HGV) and total head growth (HG) over the first year of life.

2. Methods

The present study is based on a secondary analysis of data from a completed case-control investigation on autism nested in a national birth cohort using a matched subsample of 906 (688 male: 218 female) offspring previously described with available well baby visit data [6]. We define our outcome variables as rate or speed of change (HGV) [7] and cumulative growth (HG) within a given period of months. HGV was derived using the Bayesian inversion method. Analyses included linear mixed effect models with subject specific random intercept and: (1) HG as dependent variables, CRP, time interval (0–4, 4–8, or 8–12 months), and time interval × CRP interaction as predictor variables; (2) estimated HGV as dependent variables, CRP, time (age 3, 4, 6, 9, or 12 months), and time × CRP interaction as predictor variables. Associations of CRP were considered continuously and as quintiles. SAS, version 9.4 (SAS Institute Inc., Cary NC) and R growthrate package were used for analyses. Ethical approval was given by the Institutional Review Boards of the hospital district of Southwest Finland, National Institute for Health and Welfare, and New York State Psychiatric Institute.

3. Results

The study sample of parents had a mean maternal age of 29.7 years (SD = 5.20) and paternal age of 32.4 years (SD = 6.16) at the time of delivery. The majority came from urban communities (63.4%) in the Western (31.5%) and Southern (46.8%) regions of Finland and had mid-range income (49.1%). Neonates were born on average at term gestational age (39.4 weeks; SD = 1.6) and normal birth weight (3588.7 g; SD = 534.5), and the majority (75.9%) were male. The average gestational week of blood draw was 10.8 weeks (SD = 3.4). Models were adjusted for autism diagnosis, gestational week at blood draw, parity, region, and socioeconomic status.

There were significant associations with CRP and head growth during the first year of life; in addition we identified dose response (level of CRP) effects related to HG (Table 1). There was an association between CRP (continuous), in the 0–4 month interval, and lower HG. The association of CRP (continuous) with HG at 4–8 months differed significantly

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Table 1
Association between maternal c-reactive protein (CRP) and head growth and velocity at 0–12 months of age.

Head Growth and Velocity														Total Head Growth													
		Unadjusted		Adjusted[a]		Adjusted[b]		Adjusted[c]				Unadjusted		Adjusted[a]		Adjusted[b]		Adjusted[c]			
Continuous ln(CRP)												*Continuous ln(CRP)*															
Age in months		**t-value**	**p**	**t-value**	**p**	**t-value**	**p**	**t-value**	**p**			**Age in months**		**t-value**	**p**	**t-value**	**p**	**t-value**	**p**	**t-value**	**p**						
3		−0.87	0.39	−0.94	0.34	−0.20	0.84	−0.12	0.91			**0 to 4**		**−3.37**	**−0.0008**	**−3.37**	**0.0008**	**−2.11**	**0.04**	**−2.16**	**0.03**						
Difference from ln(CRP) at 3 months												*Difference from ln(CRP) at 0–*4 months															
4		0.08	0.93	0.08	0.94	−0.04	1.00	−0.06	0.95			**4 to 8**		**3.24**	**0.00**	**3.24**	**0.001**	**2.15**	**0.03**	**2.18**	**0.03**						
6		0.75	0.45	0.75	0.45	0.03	1.00	−0.02	0.98			**8 to 12**		1.51	0.13	1.51	0.13	0.92	0.36	0.94	0.35						
9		0.07	0.94	0.07	0.94	−0.76	0.45	−0.78	0.43																		
12		−0.02	0.98	−0.02	0.98	−0.90	0.37	−0.89	0.37																		
Interaction	**df**	**F-value**	**p**	**df**	**F-value**	**p**	**df**	**F-value**	**p**	**df**	**F-value**	**p**		**Interaction**	**df**	**F-value**	**p**	**df**	**F-value**	**p**	**df**	**F-value**	**p**	**df**	**F-value**	**p**		
	4	0.21	0.93	4	0.21	0.93	4	0.42	0.80	4	0.40	0.81			2	**5.25**	**0.005**	2	**5.25**	**0.005**	2	2.33	0.10	2	2.40	0.09		
Quintile CRP												*Quintile CRP*															
Age in months		**t-value**	**p**	**t-value**	**p**	**t-value**	**p**	**t-value**	**p**			**Age in months**		**t-value**	**p**	**t-value**	**P**	**t-value**	**p**	**t-value**	**p**						
3	**0–20%**	**(Ref)**		(Ref)	–	(Ref)	–	(Ref)	–			**0 to 4**	**0–20%**	(Ref)	–	(Ref)	–	(Ref)	–	(Ref)	–						
	20–40%	0.03	0.97	0.08	0.94	−0.79	0.43	−0.65	0.51				**20–40%**	**−2.83**	**0.00**	**−2.84**	**0.00**	−1.80	0.07	−1.48	0.14						
	40–60%	−1.20	0.23	−1.24	0.21	**−2.00**	**0.05**	−1.67	0.09				**40–60%**	**−2.25**	**0.02**	**−2.26**	**0.02**	−1.74	0.08	−1.91	0.06						
	60–80%	−1.38	0.17	−1.36	0.17	−1.24	0.21	−0.74	0.46				**60–80%**	**−2.58**	**0.01**	**−2.59**	**0.01**	−0.97	0.33	−0.74	0.46						
	80–100%	−0.61	0.54	−0.68	0.50	−0.49	0.63	−0.46	0.64				**80–100%**	**−4.00**	**<0.00**	**−4.00**	**<0.00**	**−2.61**	**0.01**	**−2.52**	**0.01**						
Difference from quintile CRP at 3 months												*Difference from quintile CRP at 0 to* 4 months															
4	**0–20%**	–	–	–	–	–	–	–	–			**4 to 8**	**0–20%**	–	–	–	–	–	–	–	–						
	20–40%	−0.17	0.87	−0.17	0.87	0.13	0.90	0.16	0.87				**20–40%**	1.91	0.06	1.91	0.06	1.21	0.23	1.28	0.20						
	40–60%	0.37	0.71	0.37	0.71	0.91	0.36	0.89	0.37				**40–60%**	**2.09**	**0.04**	**2.09**	**0.04**	1.75	0.08	1.80	0.07						
	60–80%	0.55	0.58	0.55	0.58	0.68	0.50	0.69	0.49				**60–80%**	**2.25**	**0.02**	**2.25**	**0.02**	1.22	0.22	1.25	0.21						
	80–100%	−0.20	0.84	−0.20	0.84	−0.21	0.84	−0.21	0.83				**80–100%**	**3.67**	**0.0003**	**3.67**	**<0.00**	**2.51**	**0.01**	**2.56**	**0.01**						
6	**0–20%**	–	–	–	–	–	–	–	–			**8 to 12**	**0–20%**	–	–	–	–	–	–	–	–						
	20–40%	−0.72	0.47	−0.72	0.47	−0.09	0.92	0.03	0.98				**20–40%**	1.53	0.18	1.53	0.13	1.21	0.23	1.39	0.16						
	40–60%	1.24	0.21	1.24	0.21	**2.00**	**0.05**	**2.01**	**0.04**				**40–60%**	0.92	0.36	0.92	0.36	0.71	0.48	0.81	0.42						
	60–80%	1.00	0.32	1.00	0.32	1.08	0.28	1.10	0.27				**60–80%**	1.15	0.25	1.15	0.25	0.45	0.65	0.51	0.61						
	80–100%	0.38	0.70	0.38	0.70	−0.07	0.95	−0.08	0.93				**80–100%**	**2.02**	**0.04**	**2.02**	**0.04**	1.42	0.16	1.49	0.14						
9	**0–20%**	–	–	–	–	–	–	–	–																		
	20–40%	−0.72	0.47	−0.72	0.47	0.02	0.98	0.14	0.89																		
	40–60%	1.12	0.26	1.12	0.26	1.68	0.09	1.66	0.10																		
	60–80%	0.67	0.50	0.67	0.50	0.49	0.63	0.53	0.59																		
	80–100%	−0.11	0.91	−0.11	0.91	−0.49	0.63	−0.49	0.62																		
12	**0–20%**	–	–	–	–	–	–	–	–																		
	20–40%	−0.01	0.99	−0.01	0.99	0.62	0.54	0.63	0.53																		
	40–60%	1.09	0.28	1.09	0.28	1.55	0.12	1.57	0.12																		
	60–80%	0.82	0.41	0.82	0.41	0.73	0.47	0.79	0.43																		
	80–100%	−0.19	0.85	−0.19	0.85	−0.61	0.54	−0.62	0.53																		
Interaction	**df**	**F-value**	**p**	**df**	**F-value**	**p**	**df**	**F-value**	**p**	**df**	**F-value**	**p**		**Interaction**	**df**	**F-value**	**p**	**df**	**F-value**	**p**	**df**	**F-value**	**p**	**df**	**F-value**	**p**		
	16	0.53	0.93	16	0.53	0.93	16	0.80	0.69	16	0.77	0.72			8	1.80	0.07	8	1.80	0.07	8	0.98	0.45	8	1.05	0.40		

Statistically significant values of $p < 0.05$ are shown in **bold**.
Abbreviations: CRP, c-reactive protein, ln, loglinear, df, degrees of freedom, p, p-value.
[a] Adjusted for autism diagnosis.
[b] Adjusted for gestational week of blood draw, parity, region of birth, and socioeconomic status.
[c] Adjusted for gestational age at birth, birthweight, child sex, province of birth, degree of urbanization, maternal age, paternal age, and socioeconomic status.

from that at 0–4 months. This pattern of association between CRP and HG at 0–4 months remained when CRP was considered by quintiles. For example, CRP in quintile 5 was associated with reduced HG at 0–4 months relative to quintile 1 across all models. These relationships differed significantly at 4–8 months versus 0–4 months in each model.

When observing HGV, ln(CRP) (continuous) was not associated with HGV. When CRP was considered as quintiles, the mid-quintile (40–60%) was significantly associated with lower HGV at 3-months and higher HGV at 6- months.

4. Discussion

We demonstrate a significant relationship between prenatal CRP exposure and HG during the first 12 months of life. The influence of CRP on growth differs by age windows and level of CRP exposure (dose). This is supportive of existing research using non-human models showing altered brain volume, both total [8] and region specific in infants [8]. This identified time window may represent a 'sensitive' period of influence of early maternal immune exposure. This observable anthropometric change in growth, may also suggest the utility of HC changes as a marker of brain development. Our results also suggest a sensitivity of level of maternal inflammation exposure, as quintile analyses demonstrated differences in association with head growth.

Limitations include that as a secondary analysis of a completed case-control study on autism there was a higher proportion of males than is representative of the sex of the live births for the national population. There were also limited clinical details regarding the mother-infant dyad that could affect the levels of CRP, such as infection, inflammatory disease, prolonged labor, method of delivery, or medications used. Some of our findings including mid-quintile associations with maternal CRP and HGV may lack sufficient power to detect an effect particularly after controlling for potential confounds. Future studies that include a greater sample size with long-term follow-up will help to further elucidate these relationships. These studies can also consider non-linear growth and additional potential confounds, mediators, and moderators that may alter these relationships.

Future studies observing variability in immune marker levels across pregnancy can help to better understand the effects of low-grade systematic inflammation *in utero* [5] and its potential longitudinal effect on physical and neurological development of full-term infants.

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Declaration of competing interest

The authors have no conflict of interest to disclose.

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