



High Early Childhood Insulin Increases Asthma Risk Independent of Obesity

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Rationale

Asthma and obesity are major, interconnected public health challenges that usually have their origins in childhood, and for which the relationship is strengthened among those with insulin resistance. We hypothesized that high insulin in early life confers increased risk for asthma, independent of obesity.

Methods

Participants were enrolled in the **Tucson Children's Respiratory Study (TCRS)**, a non-selected birth cohort designed to assess early life risk factors for subsequent respiratory outcomes, which has had continuous follow up for over 36 years.

- Non-fasting serum samples were collected at age 6 years.
 - Insulin, leptin, c-reactive protein (CRP), and interleukin (IL)-6 levels were measured by multiplex (Human Multi-Analyte Profile panel version 1.6, Myriad Rules Based Medicine, Austin TX).
- Lung function testing was performed at age 6 by measurement of maximal forced expiratory flow at functional residual capacity (V_{max}FRC).
- Bronchial hyper-reactivity (BHR) to cold, dry air at age 6 was defined as a drop of V_{max}FRC greater than the 90th percentile of decline for reference children (Lombardi et al, AJRCCM 1997).
- Allergy skin prick testing was performed at age 6 to a panel of locally relevant allergens.
 - Atopy was defined as one or more positive skin test.
 - Serum IgE was measured by PRIST, log transformed.
- Physician-diagnosed asthma with symptoms in the past year was determined at assessments from age 6 to 36 years.
- Body mass index (BMI) was assessed at age 6 using standard methods in 303 of the participants included in these analyses; participant-reported height and weight was available for an additional 35 participants.
- Generalized estimating equation models were used to assess the association between insulin levels at age 6 and subsequent asthma from 8 to 36 years.

Results

Analyses were limited to 342 TCRS participants at age 6 who had at least one subsequent asthma assessment and age 6 insulin measurement. Insulin levels at age 6 were divided into quartiles. Because non-fasting insulin levels were higher in females (n=179) than in males (n= 163) (median (interquartile range) 5.14 uIU/mL (3.05, 8.39) uIU/mL vs 4.61 (1.85, 8.0) uIU/mL, respectively, P=0.045), quartiles were generated separately by sex. In 98 of the 342 included samples (29%), insulin levels were lower than the minimum detectable concentration (0.67 uIU/ml). We identified participants in the highest quartile of non-fasting insulin, hereafter called 'high insulin', and compared them with participants in the other three quartiles combined, hereafter called 'low insulin'.

Table 1. Relation of early life factors to high non-fasting insulin at age 6yr

Factors	Group	n	% with High Insulin	p
Ethnicity	Non-Hispanic White	215	27.4	
	Hispanic White	83	22.9	
	Other	44	22.7	0.642
Ever Maternal Asthma	No	310	25.2	
	Yes	27	33.3	0.352
Maternal Smoking during pregnancy	No	285	25.6	
	Yes	50	26.0	0.954
Maternal Age at Delivery	<28 yr	179	25.1	
	>=28 yr	163	26.4	0.793
Ever Breastfed in the first 6 months	No	50	26.0	
	Yes	288	25.4	0.922
Day Care first 6 months	No	306	25.5	
	Yes	27	25.9	0.960
Indoor Dogs in infancy	No	231	27.7	
	Yes	110	21.8	0.245
Maternal Smoking first year after birth	No	281	26.3	
	Yes	59	23.7	0.678

Table 2. Relation of high non-fasting insulin at age 6yr to concurrent factors

Factors at age 6	Low Insulin		High Insulin		P ANOVA		
	n	%	n	%			
Skin Test Positive	251	36.7	87	46.0	0.125		
Cold Air Responsive	148	14.2	29	29.3	0.024		
Asthma at age 6	253	11.1	88	13.6	0.519		
	n	Mean	95% CI	n	Mean	95% CI	P ANOVA
BMI	251	15.8	15.6, 16.0	87	16.6	16.0, 17.1	0.002
V _{max} FRC*, ml/s	198	1198	1149, 1249	64	1102	1029, 1180	0.047
Total IgE*, IU/ml	252	36.7	29.7, 45.4	88	45.3	31.0, 66.1	0.329

*Geometric mean, 95%CI

Figure 1: The proportion of participants with asthma at each age, by low vs high non-fasting insulin

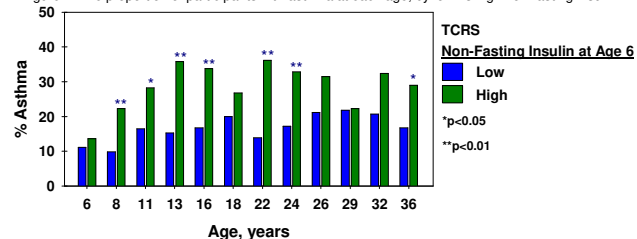


Table 3. Relation of high non-fasting insulin at age 6 yr to asthma ages 6-36, longitudinal model, compared with low insulin.

	Odds Ratio	95% CI	p	N	Observations
1 High Non-Fasting Insulin	2.06	1.35, 3.16	0.001	342	3399
2 Limited to those with age 6 BMI					
High Fasting Insulin	1.97	1.28, 3.03	0.002	338	3361
3 Adjusted for age 6 BMI					
High Fasting Insulin	1.95	1.26, 3.02	0.003	338	3361
BMI	1.02	0.92, 1.13	0.717		
4 Adjusted for age 6 BMI and Leptin					
High Fasting Insulin	1.92	1.24, 2.98	0.004	338	3361
Leptin	1.32	0.67, 2.59	0.417		
5 Adjusted for age 6 BMI and CRP					
High Fasting Insulin	1.95	1.26, 3.02	0.003	338	3361
CRP	0.96	0.72, 1.29	0.779		
6 Adjusted for age 6 BMI and IL-6*					
High Fasting Insulin	1.95	1.26, 3.02	0.003	338	3361
IL-6	1.13	0.72, 1.78	0.599		

Conclusion

High early life insulin is related to subsequent asthma diagnosis through age 36. This effect is independent of concurrent obesity and other related inflammatory markers. Early life lung function and bronchial hyperreactivity implicate possible mechanisms underlying this phenotype.

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