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Relationship between cord blood arachidonic acid level and further parental factors with the risk of overweight in the offspring until the age of 10 years

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Relationship between arachidonic acid levels in cord blood and growth during the first 10 years of life

Elisabeth Thiering, Berthold Koletzko, Claudia Glaser, Joachim Heinrich, Hans Demmelmair

As obesity is a powerful risk factor for a variety of diseases, the increasing prevalence represents a tremendous challenge for the healthcare systems worldwide. Adverse effects of obesity are particularly serious if obesity starts early in life and causes long term exposure of organs to excess body fat. There are convincing indications that fetal environment can have a programming effect, which contributes to the risk of developing obesity already during childhood (Gillman et al, 2008).

Although current knowledge about mechanisms which contribute to early childhood obesity is limited, there is some evidence that the composition of dietary fatty acids during pregnancy may influence the risk of the offspring to become overweight or obese. Polyunsaturated fatty acids influence adipogenesis as their metabolites bind to nuclear receptors, which act as regulators of fat cell formation (Madsen et al, 2005), thereby providing a molecular link between fatty acid status and fat cell development. Of particular importance for adipogenesis seems arachidonic acid, the major long chain polyunsaturated fatty acid of the linoleic acid derived n-6 series (Demmelmair et al, 1999). Arachidonic acid is converted into prostacyclin and prostaglandins, which influence differentiation of primary preadipocytes into adipocytes. While for n-3 series long chain polyunsaturated fatty acids (eicosapentaenoic acid, docosahexaenoic acid) an inhibitory effect on preadipocytes differentiation is widely accepted the situation is less clear for arachidonic acid, which can have inhibiting or stimulating effects depending on glucose and insulin levels (Massiera et al, 2003; Madsen et al, 2005; Madsen et al, 2010).

Although the observed increase of the intake of n-6 fatty acids during the last decades and the increase in childhood obesity agree with the assumption that arachidonic acid stimulates adipose tissue formation (Ailhaud et al, 2008), the hypothesis has not been tested so far in a birth cohort study. With the aim to investigate the relationship between arachidonic acid levels and later anthropometric development the fatty acid composition of cord blood phosphoglycerides was studied in the very well characterized LISA birth cohort. For this cohort growth data until the age of 10 years are available.

In the influences of lifestyle-related factors on the immune system and the development of allergies in childhood study (LISAplus), parents of neonates admitted to maternity hospitals in Munich, Leipzig, Wesel, and Bad Honnef, Germany were contacted. In total, 3097 healthy neonates with a birth weight over 2500g and gestational age over 37 weeks were recruited between December 1997 and January 1999. LISAplus was designed as a population based study and has been followed up at the age of six, twelve and 18 months and two, four, six and ten years (Heinrich et al, 2002; Zutavern et al, 2006). Fifty seven percent were followed until the age of 10 years.

The study population for this analysis was restricted to the study area of Munich in order to avoid differences which are related to region. Data from a total of 681 infants from Munich metropolitan area were analyzed.

Height and weight measurements were obtained at seven points of time between birth and the age of 2 years via medical records. Analyses of growth curves were restricted to singletons with at least three postnatal growth measurements. For cross-sectional analyses of body mass index age and sex standardized values were obtained according to the German national standard by Kromeyer-Hauschild (Kromeyer-Hauschild et al, 2001).

Serum obtained from cord blood was stored at -80ºC until fatty acid analysis according to the method developed by Glaser et al (Glaser et al, 2010). This method enables a precise quantification of phosphoglyceride bound fatty acids including arachidonic acid and all further major long chain polyunsaturated fatty acids.

Growth modeling was performed using Reed1 nonlinear random-effects models, as described previously (Simondon et al, 1992; Tzoulaki et al, 2010). Childhood overweight was characterized by exceeding the 90^{th} percentile at any time point during childhood versus a low-moderate body mass index below the 50^{th} percentile. For the total population the raw model (model 1) was sequentially adjusted for parental education and age of the mother (model 2), all model 2 confounders plus height of the mother, gestational age, gestational weight gain, maternal body mass index before pregnancy, maternal smoking during pregnancy (model 3), all model 3 confounders plus postnatal ETS exposure of the child, weight of the mother at child's age 6 (model 4).

Statistical significance was defined by a two-sided alpha level of 5%. All statistical analyses were performed using R 2.10.1(R Developement Core Team, 2009).

Table 1 Study population characteristics of the 681 children from the Munich study centre of the LISAplus study

		n/N or N	% or mean (sd)
Gender	male	368/ 681	54.0 %
	female	313/ 681	46.0 %
Parental education	low	42/ 676	6.2 %
	medium	107/ 676	15.8 %
	high	527/ 676	78.0 %
Gestational age	[weeks]	678	39.9 (1.2)
Gestational weight gain	[kg]	667	14.2 (4.3)
Maternal smoking during pregnancy	no	574/ 646	88.9 %
	light (1-10 cigarettes)	56/ 646	8.7 %
	heavy (>10 cigarettes)	16/ 646	2.5 %
Exclusive breastfeeding	no	132/ 643	20.5 %
	1-4 months	195/ 643	30.3 %
	>4 months	316/ 643	49.1 %
Postnatal ETS exposure	no	407/605	67.3 %
	medium (<50% of years)	94/605	15.5 %
	high (>50% of years)	104/605	17.2 %
Maternal age at child's birth	[years]	675	32.6 (4.1)
Maternal height	[cm]	680	168.8 (6.1)
Maternal body mass index	before pregnancy	673	22.2 (3.5)
	at birth of the child	666	27.2 (3.5)

	child's age 6 years	541	22.5	(3.4)
body mass index kg/m^2	at birth	667	12.7	(1.1)
	age 1 week	636	12.1	(1.1)
	age 1 month	646	14.5	(1.4)
	age 3 month	646	16.1	(1.5)
	age 6 month	635	16.6	(1.5)
	age 1 year	641	16.6	(1.3)
	age 2 years	603	16.0	(1.3)
	age 4 years	553	15.4	(1.2)
	age 5 years	522	15.1	(1.3)
	age 10 years	278	16.9	(2.4)

Table 2 Concentration and percentage contribution of polyunsaturated long chain n-6 fatty acids to phosphoglyceride total fatty acids in cord blood

	concentration (mg/l)			**fatty acid composition (%)**		
	mean	**(sd)**	**iqr**	**mean**	**(sd)**	**iqr**
C20:2	2.34	(0.6)	1.90-2.70	0.36	(0.1)	0.30-0.41
C20:3	33.63	(7.5)	28.5-38.6	5.20	(0.8)	4.63-5.69
C20:4	116.26	(21.9)	101.3-129.0	17.96	(1.6)	17.1-19.0
C22:4	4.89	(1.3)	4.00-5.60	0.76	(0.2)	0.64-0.84
C22:5	5.93	(2.1)	4.40-7.10	0.92	(0.3)	0.71-1.08

Table 3 Results of the sequential adjusted logistic regression models between long chain ω-6 fatty acids and childhood obesity (defined as exceeding the 90th percentile of sex and age standardized values)

		model 1[a]			**model 2[b]**			**model 3[c]**			**model 4[d]**		
		OR	CI	p-val	OR	CI	p-val	OR	CI	p-val	OR	CI	p-val
BMI ever >90th percentile vs. <50th percentile	C20:2	0.96	0.77;1.20	0.711	0.96	0.77;1.21	0.740	0.96	0.76;1.23	0.759	1.00	0.77;1.30	0.985
	C20:3	1.01	0.81;1.25	0.947	0.98	0.79;1.22	0.846	1.10	0.87;1.39	0.437	1.08	0.83;1.39	0.574
	C20:4	**0.76**	**0.62;0.93**	**0.009**	**0.76**	**0.61;0.93**	**0.009**	**0.79**	**0.64;0.99**	**0.044**	***0.78***	***0.60;1.01***	***0.058***
	C22:4	0.86	0.70;1.06	0.157	0.88	0.71;1.08	0.209	**0.79**	**0.62;1.00**	**0.048**	0.83	0.65;1.07	0.148
	C22:5	0.94	0.76;1.16	0.549	0.94	0.76;1.16	0.552	0.91	0.72;1.15	0.415	0.88	0.68;1.13	0.312

* per interquartile range increase in percent of fatty acid composition

* boldface p<0.05, italic boldface p<0.10

a model 1: adjusted for sex and age

b model 2: adjusted for all model 1 confounder, parental education, age of the mother

c model 3: adjusted for all model 2 confounder, height of the mother, gestational age, gestational weight gain, maternal bmi before pregnancy, maternal smoking during pregnancy, breastfeeding

d model 4: adjusted for all model 3 confounder, postnatal ETS exposure of the child, weight of the mother at child's age 6

The evaluation of the data does not confirm an adipogenic effect of arachidonic acid percentage in cord blood phosphoglycerides, rather there is an indication that the risk to become overweight might be decreased by high arachidonic acid values in cord blood. The current statistical analysis does not fully exclude a modulating effect of obesity risk by arachidonic acid, as other fatty acids (especially of the n-3 series) might have a stronger effect. If confirmed by further analyses, the data obtained from the LISA cohort do not suggest a potential for obesity prevention by decreased n-6 fatty acid and especially arachidonic acid levels during early in life.

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