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Plasma IL-1 Receptor Antagonist Concentration Has an Inverse Association With Birth Weight in Prepubertal Children

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Context: Birth size has an impact on later cardiometabolic risk that is strongly related to low-grade inflammation.

Objective: To evaluate plasma interleukin-1 receptor antagonist (IL-1ra) concentrations in relation to birth size and cardiometabolic and inflammatory markers in prepubertal children.

Design: A cohort study. Anthropometric data were recorded. Fasting blood samples were collected for plasma analyses of IL-1ra, alanine transaminase, total cholesterol, high- and low-density lipoprotein cholesterols, triglyceride, glucose, and serum analyses of 25-hydroxyvitamin D [25(OH)D] and high-sensitivity C-reactive protein (hs-CRP) concentrations.

Participants: Forty-nine large for gestational age (LGA), 56 appropriate for gestational age, and 23 small for gestational age (SGA) children at 5 to 8 years of age were examined.

Main Outcome Measures: Differences in IL-1ra concentrations among the birth-size groups and associations between IL-1ra and other metabolic markers were assessed.

Results: Body mass index (BMI) standard deviation score (SDS)-adjusted plasma IL-1ra concentrations were highest in the SGA- and lowest in the LGA-born children ($P = 0.015$). Age- and sex-adjusted IL-1ra concentrations had strongest associations with BMI SDS ($P < 0.001$) and hs-CRP ($P < 0.001$, also when further adjusted for BMI SDS).

Conclusions: Prepubertal children born SGA had the highest and those born LGA the lowest IL-1ra concentrations in this study cohort. Most associations found between IL-1ra and the studied metabolic parameters were weight related, but the association with hs-CRP remained strong after adjustment for BMI. It seems that at prepuberty, SGA children have a stronger inflammatory state than LGA children and may thus be at a greater risk for later metabolic disturbances.

Freeform/Key Words: birth size, cardiometabolic risk, catch-up growth, large for gestational age, low-grade inflammation, small for gestational age

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; AGA, appropriate for gestational age; AI, atherogenic index; ALT, alanine transaminase; β, standardized risk; BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; FDR, false discovery rate; GLM, general linear model; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment for insulin resistance; hs-CRP, high-sensitivity C-reactive protein; IL-1ra, interleukin-1 receptor antagonist; LDL-C, low-density lipoprotein cholesterol; LGA, large for gestational age; SDS, standard deviation score; SGA, small for gestational age; TG, triglyceride; WHtR, waist-to-height ratio.

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Birth size affects the cardiovascular risk in adulthood through prenatal programming (the leading hypothesis), and indicators of this risk can already be seen in childhood and adolescence [1]. Children born small or large for gestational age (SGA and LGA, respectively) have an increased risk for childhood obesity, adverse serum glucose and lipid concentrations, elevated blood pressure, and the metabolic syndrome [2–4]. Furthermore, early growth during the first years of life has been suggested to impact future metabolism and cardiometabolic risk [1, 5, 6].

Chronic low-grade inflammation has a strong relationship with atherogenic changes leading to later cardiovascular disease (CVD) [7]. Interleukin (IL)-1β, one of the proinflammatory cytokines of the IL-1 family, contributes to the risk of atherosclerosis and cardiovascular events [8]. The use of IL-1β analysis in clinical assessment is difficult, as the circulating concentrations of IL-1β are extremely low [9]. Instead, an anti-inflammatory cytokine IL-1 receptor antagonist (IL-1ra), expressed in white adipose tissue [10], is a counterregulator for IL-1β [11], and its circulating concentrations can be measured accurately [9]. Elevated IL-1ra concentrations reflect higher IL-1β secretion [12] and have been suggested for a marker of an inflammatory process [13]. Although IL-1ra is anti-inflammatory by itself, its elevated concentrations are associated with obesity in children [14] and obesity [15], insulin resistance [16], and an increased risk of type 2 diabetes [12] in adults, increasing the overall CVD risk, as reported in a recent meta-analysis [11].

Several studies suggest that low birth size increases low-grade inflammation in children and young adults [17–19], but it has not been examined how birth size affects circulating IL-1ra concentrations in children. Our aim was to investigate if plasma IL-1ra concentrations differ among birth-size groups [SGA, LGA, and appropriate for gestational age (AGA)] and how they associate with other metabolic parameters reflecting later cardiovascular risk in prepubertal children.

1. Methods

We examined a cross-sectional cohort of 128 white children (67 boys), born singleton at term between 2004 and 2007 in Eastern Finland [17]. In brief, the children were enrolled according to their birth size from the Kuopio University Hospital birth registry, and all SGA and LGA children born between those years and randomly selected sex- and age-matched AGA controls were invited to participate. The children were studied at 5.0 to 8.7 years of age [mean (95% confidence interval [CI]), 6.9 (6.8 to 7.1) years; Table 1]. SGA was defined as sex-specific birth weight less than or equal to −2.0 standard deviation score (SDS), LGA as birth weight greater than or equal to +2.0 SDS, and AGA as birth weight and length between −1.0 and +1.0 SDS. Anthropometric data at birth, at the age of 2 years, and at examination were recorded. The enrolled children did not have any chronic diseases, other than atopic eczema, allergic rhinitis, or mild asthma, requiring no continuous medication or systemic medication that might have affected a possible inflammatory state. No child in this study had been previously treated with a growth hormone. Body mass index (BMI) was calculated as the body weight divided by the square of the height (kilograms per square meter). Sex- and age-specific SDS for weight, height, and BMI was calculated according to the recently published Finnish growth reference [20]. Catch-up or catch-down growth was determined as an increase or decrease in weight SDS >0.67 during the first 2 years of life, respectively [21]. Waist circumference was measured midway between the top of the iliac crest and the lowest rib at the end of a normal expiration using a flexible metal tape to the nearest 1 mm. Waist-to-height ratio (WHtR) was calculated as the waist circumference (centimeters) divided by the height (centimeters). Atherogenic index (AI) that has been validated also for use in children [22] was calculated as plasma triglyceride (TG) concentrations, divided by high-density lipoprotein cholesterol (HDL-C) concentrations. Insulin resistance was determined by using the homeostasis model assessment for insulin resistance (HOMA-IR), as (insulin, milliunits per liter × glucose, millimole per liter)/22.5 [23].

Table 1. Anthropometric and Biochemical Characteristics of the Study Groups

	LGA	AGA	SGA	*P*
Total number (boys)	49 (25)	56 (29)	23 (13)	
At birth				
Gestational age, wk	39.8 (39.5–40.1)	39.9 (39.6–40.2)	39.7 (39.2–40.3)	0.81
Weight, g	4722 (4631–4812)	3561 (3484–3637)	2476 (2345–2607)	<0.001
Weight, SDS,	2.63 (2.46–2.79)	−0.02 (−0.16 to 0.12)	−2.39 (−2.53 to −2.25)	<0.001
Length, cm	53.0 (52.6–53.4)	50.0 (49.7–50.4)	46.2 (45.5–46.9)	<0.001
Length, SDS	1.58 (1.40–1.76)	−0.11 (−0.24 to 0.03)	−2.16 (−2.43 to −1.88)	<0.001
At the age of 2 y				
Weight, SDS	0.65 (0.41–0.90)	0.16 (−0.14 to 0.45)	−0.95 (−1.37 to −0.53)	<0.001
Height, SDS	0.40 (0.17–0.63)	−0.05 (−0.34 to 0.24)	−0.98 (−1.33 to −0.63)	<0.001
At examination				
Age, y	6.89 (6.62–7.16)	7.09 (6.86–7.33)	6.65 (6.22–7.07)	0.13
Weight, kg	27.6 (26.2–29.0)	27.5 (25.7–29.4)	21.8 (19.8–23.7)	<0.001
Weight, SDS	0.68 (0.38–0.97)	0.39 (0.11–0.67)	−0.80 (−1.26 to −0.33)	<0.001
Height, cm	126.1 (124.0–128.3)	125.7 (123.8–127.7)	119.0 (115.6–122.4)	<0.001
Height, SDS	0.54 (0.30–0.78)	0.20 (−0.07 to 0.46)	−0.64 (−1.01 to −0.27)	<0.001
WHtR	0.46 (0.45–0.47)	0.46 (0.45–0.48)	0.45 (0.43–0.46)	0.469
BMI, SDS	0.56 (0.22–0.89)	0.36 (0.05–0.67)	−0.65 (−1.18 to −0.12)	<0.001
IL-1ra, pg/mL[a]	217.9 (196.3–241.8)	253.3 (229.9–279.2)	290.8 (246.0–343.8)	0.011[b]
IL-1ra, pg/mL[c]	230.5 (209.3–253.9)	252.7 (231.0–276.5)	260.7 (224.8–302.4)	0.257
hs-CRP, mg/L[a]	0.19 (0.14–0.26)	0.22 (0.17–0.30)	0.71 (0.44–1.15)	<0.001[d]

Data are presented as means (95% CI), except geometric means (95% CI) for IL-1ra and high-sensitivity C-reactive protein (hs-CRP).

Analysis of variance among the three study groups, except analysis of covariance for IL-1ra and hs-CRP.

[a]Adjusted for age, sex, and body mass index (BMI) standard deviation score (SDS) at examination.

[b]*Post hoc* test (Sidak correction) between the SGA and LGA groups, $P = 0.015$.

[c]Adjusted for age, sex, and waist-to-height ratio (WHtR).

[d]*Post hoc* test (Sidak correction) between the SGA and LGA/AGA groups, $P < 0.001$.

Fasting blood samples were collected for plasma and serum analyses. Plasma IL-1ra concentrations were analyzed using enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, MN). The intra- and interassay coefficients of variation were 3.59% and 5.68%, respectively. Plasma glucose concentrations were determined by the hexokinase method (Roche Diagnostics GmbH, Mannheim, Germany). Plasma concentrations of total cholesterol and TG were analyzed with colorimetric enzymatic assays and those of HDL-C and low-density lipoprotein cholesterol (LDL-C) with homogeneous colorimetric enzymatic assays (both Roche Diagnostics GmbH). The kinetic method, according to the International Federation of Clinical Chemistry, was used for obtaining plasma alanine transaminase (ALT) concentrations (Roche Diagnostics GmbH). Serum 25-hydroxyvitamin D [25(OH)D] concentrations were assessed using chemiluminescence immunoassay (LIAISON® 25 OH Vitamin D Total Assay; DiaSorin, Stillwater, MN) with an automatic immunoanalyzer (LIAISON®, DiaSorin S.p.A., Saluggia, Italy). Total variation (including intra- and interassay variation) was 8.2% to 11.0% in the concentration range of 21 to 123 nmol/L. Serum high-sensitivity C-reactive protein (hs-CRP) was measured by immunoturbidimetric assay (Roche Diagnostics GmbH).

Blood pressure was measured three times in a supine position using mercury sphygmomanometer and a proper-sized cuff on the right arm after a 15-min rest and with intervals of 1 to 2 minutes between the measurements. The mean of the lowest two values was recorded.

To eliminate the impact of acute infections on hs-CRP concentrations, values exceeding 10 mg/L (one girl) and children reported to have any acute infection, 0 to 14 days before the examination day (n=9; four boys), were excluded from the hs-CRP analysis.

Written, informed consent was obtained from all parents and participating children, aged ≥6 years. The study protocol was approved by the Committee on Research Ethics of the Hospital District of Northern Savo.

A. Statistical Analyses

Data are presented as means (95% CI). Analyses were conducted using SPSS statistical software (version 24; SPSS, IBM, Armonk, NY). A significance level of 0.05 was used in all analyses. Skewed data were either logarithm or square-root transformed before parametric analyses and power transformed to geometric means for presentation. Analysis of variance was used for comparisons among the study groups on anthropometric measures. Analysis of covariance was used for comparisons among the study groups on IL-1ra and hs-CRP concentrations. The obtained estimated means of IL-1ra concentrations are presented in Table 1. Sidak correction was used for *post hoc* tests. General linear model (GLM) was used for estimating associations of IL-1ra concentrations with BMI SDS, WHtR, the weight development before and after 2 years of age, total cholesterol, HDL-C, LDL-C, TG, AI, ALT, glucose, insulin, HOMA-IR, hs-CRP, 25(OH)D, and systolic and diastolic blood pressures. In GLM analyses, the results were reported as standardized risk (β) values, and all P values were corrected using the false discovery rate (FDR) method. The correlation between BMI SDS and WHtR was estimated by the Pearson correlation coefficient.

2. Results

The SGA children had the highest and the LGA children the lowest age-, sex-, and BMI SDS-adjusted plasma IL-1ra concentrations, but when adjusted for age, sex, and WHtR, the differences turned nonsignificant (Table 1). The correlation coefficients between BMI SDS and WHtR ($P < 0.001$) were 0.81 in all children, 0.83 in LGA, 0.85 in AGA, and 0.84 in SGA children. When adjusted for age and sex, IL-1ra concentrations had strong associations with BMI SDS and hs-CRP concentrations, and the association with hs-CRP concentrations remained strong after further adjustment for BMI SDS (Table 2). Age- and sex-adjusted IL-1ra concentrations associated positively with the weight development (changes in weight SDS), both before and after 2 years of age. IL-1ra concentrations adjusted for age and sex had

Table 2. Associations Between Plasma IL-1ra Concentrations and Metabolic Variables

	n	β^a	P^b	β^c	P^d
BMI SDS	126	0.50	<0.001[e,f]	n/a	n/a
WHtR	125	0.63	<0.001[e,f]	n/a	n/a
Δ Weight SDS, 0–2 y	124	0.19	0.047	n/a	n/a
Δ Weight SDS, after 2 y	124	0.23	0.024	n/a	n/a
Cholesterol	126	0.08	0.466	0.14	0.413
HDL-C	126	−0.23	0.022[f]	−0.12	0.447
LDL-C	126	0.18	0.066[f]	0.20	0.197
TG	126	0.25	0.018[f]	0.19	0.181
AI	126	0.28	0.007[f]	0.19	0.257
ALT	126	0.14	0.167	0.05	0.840
Glucose	125	−0.04	0.678	0.02	0.857
Insulin	126	0.24	0.019[f]	0.04	0.769
HOMA-IR	125	0.22	0.022[f]	0.04	0.706
hs-CRP	116	0.51	<0.001[e,f]	0.43	<0.001
25(OH)D	120	−0.24	0.021	−0.24	0.135
Systolic blood pressure	124	−0.01	0.869	−0.09	0.591
Diastolic blood pressure	124	−0.03	0.433	−0.04	0.516

Abbreviations: n/a, not applicable; Δ Weight SDS, change in weight SDS.
[a]GLM adjusted for sex and age.
[b]FDR-corrected P values for GLM adjusted for sex and age.
[c]GLM adjusted for sex, age, and BMI SDS at examination.
[d]FDR-corrected P values for GLM adjusted for sex, age, and BMI SDS at examination.
[e]The association is significant in the LGA group.
[f]The association is significant in the AGA group.

negative associations with HDL-C and 25(OH)D concentrations and positive associations with TG and insulin concentrations, but these associations turned nonsignificant when adjusted also for BMI SDS (Table 2). Both AI and HOMA-IR associated positively with IL-1ra concentrations when adjusted for age and sex but not when adjusted further for BMI SDS (Table 2). The other measured biochemical parameters or blood pressure did not associate with IL-1ra concentrations.

We also looked at associations of IL-1ra with metabolic risk factors separately in three birth weight groups. In the SGA group, no significant associations were found. In the AGA and LGA groups, age- and sex-adjusted IL-1ra concentrations were associated with BMI SDS (LGA: $\beta = 0.49$, $P = 0.004$; AGA: $\beta = 0.71$, $P < 0.001$), WHtR (LGA: $\beta = 0.68$, $P < 0.001$; AGA: $\beta = 0.69$, $P < 0.001$), and hs-CRP (LGA: $\beta = 0.58$, $P = 0.003$; AGA: $\beta =$, $P < 0.001$). The association of IL-1ra with hs-CRP was not significant in any separate birth-size group when adjusted further for BMI SDS (Table 2).

GLM analyses were also conducted among the groups formed by early weight development [catch-up n = 34 (19 boys), no-change n = 28 (18 boys), and catch-down n = 62 (28 boys)]. IL-1ra concentrations associated with hs-CRP concentrations when adjusted for both age and sex and further, for BMI SDS in the catch-up and catch-down groups ($\beta = 0.59/0.54$, $P < 0.001$; $\beta = 0.55/0.40$, $P < 0.001/P = 0.015$, respectively) but not in the no-change group. IL-1ra concentrations had a significant association with BMI SDS ($\beta = 0.45$ to 0.57) and WHtR ($\beta = 0.60$ to 0.71) in all of these groups.

3. Discussion

We found a clear association between birth size and plasma IL-1ra concentrations in prepubertal children: the children born SGA had the highest and the children born LGA the lowest BMI SDS-adjusted concentrations. IL-1ra concentrations associated strongest with BMI SDS and hs-CRP.

Previous studies have shown the association between elevated IL-1ra concentrations and childhood obesity [14]. This study confirms this, as BMI SDS had a strong positive association with IL-1ra concentrations. To our knowledge, this is the first study to compare birth size and plasma IL-1ra concentrations in midchildhood. Interestingly, the children born SGA had the highest and the children born LGA the lowest IL-1ra concentrations, even though BMI SDS appeared the opposite. This suggests that prepubertal SGA children have low-grade inflammation, independent of their current weight. Other associations of IL-1ra concentrations were also strongly weight related; hence, the majority of these turned nonsignificant after further adjustment for BMI SDS. When IL-1ra concentrations were adjusted for WHtR, the differences among the study groups were nonsignificant. WHtR is age dependent in prepubertal children, which could explain partly the differences in results after BMI SDS and WHtR adjustments [24].

Chronic low-grade inflammation is associated with obesity and CVD risk factors in youth [25]. Although anti-inflammatory itself, endogenous IL-1ra concentrations reflect an ongoing inflammatory state [26]. The association between plasma IL-1ra concentrations and hs-CRP was clear in our current study. In a recent study, Bugge *et al.* [25] did not find any correlation between CRP and IL-1ra concentrations in adolescents, but in adults, the positive correlation has been reported [27]. Furthermore, the correlation between IL-1ra concentrations and the CVD risk factor profile remained nonsignificant in Danish adolescents, even though other inflammation markers had important associations with the profile [25].

It is unclear if elevated IL-1ra concentrations only indicate higher IL-1 activity or if they also suppress the inflammatory response by reducing IL-1 signaling [26]. Increased IL-1ra concentrations have been suggested to precede type 2 diabetes [12], even if the experimental use of recombinant IL-1ra to block IL-1 receptor type 1 and decrease IL-1 bioactivity has been shown to protect β cells from glucose-induced apoptosis and improve IL-1β-mediated, impaired β cell function in human cells [28]. Both HOMA-IR and insulin concentrations had positive associations with IL-1ra concentrations in our study when adjusted for age and sex but not when further adjusted for BMI SDS.

An adverse lipid profile is a risk factor for future CVD [29]. AI is a simple tool for detecting the risk of the metabolic syndrome and CVD in adults [30] and children [22, 31]. In a previous study, nonobese, LGA-born children had higher AIs compared with nonobese, AGA-born children [32]. In this study, we demonstrated a positive but weight-related association between IL-1ra and AI. Furthermore, TG associated positively and HDL-C negatively with IL-1ra concentrations when examined independently. These findings may suggest a relationship between an adverse lipid profile and low-grade inflammation, as reviewed previously [33].

The strengths of this study include detailed anthropometric data since birth, allowing determination of early weight development. The study participants were enrolled strictly according to birth size and examined thoroughly before puberty. The major weakness is the relatively small sample size affecting the power in the analyses; we have adjusted the analyses for the most important confounding factors to reduce that effect. Another limitation of this study is that the nutritional status of the children was not described. There is a possibility of some bias in the study population, which we tried to minimize by recruiting only children who were not followed or did not require any special medical attention at the hospital. Accordingly, the invitations were sent to home, not given at the hospital.

Even though IL-1ra is only one indicator of low-grade inflammation and future CVD risk, our findings suggest that the relationship between birth size and CVD risk would be rather linear than U-shaped, as previously suggested [34]. Accordingly, we have also demonstrated in this study population that LGA children had lower serum dehydroepiandrosterone sulfate concentrations than SGA and AGA children [35], and along with body weight, dehydroepiandrosterone sulfate was positively associated with bone mineral density [36]. Fetal metabolic programming has been hypothesized to contribute to the increased CVD risk in SGA children. The adverse effects of large birth size in later life could be partly mediated by being overweight, to which LGA children are predisposed, rather than by the birth size itself. LGA children may have a combined environmental and genetic susceptibility to metabolic disturbances that do not emerge if the children do not become significantly overweight. Our finding is preliminary and warrants additional studies in larger study populations to confirm the significance of IL-1ra as a CVD risk marker in children.

In conclusion, the children born SGA had the highest and those born LGA the lowest IL-1ra concentrations in this study cohort. Most associations found between IL-1ra and the studied metabolic parameters were weight related, but the relationship between IL-1ra and hs-CRP remained strong after adjustment for BMI SDS. Our results indicate that at prepuberty, SGA-born children have a stronger inflammatory state than LGA-born ones and may thus be at a greater risk for later metabolic disturbances.

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