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Reference Values and Early Determinants of Intra-Abdominal Fat Mass in Primary School Children

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Key Words

Intra-abdominal fat · Reference values · Childhood · Developmental origins of disease · Ultrasonography

Abstract

Background: Intra-abdominal fat (IAF) is a valuable predictor of cardiovascular morbidity. However, neither reference values nor determinants are known in children. ***Methods:*** IAF was assessed as sonographically measured intra-abdominal depth in 1,046 children [median age 7.6 years, interquartile range (IQR) 7.2–7.9; 54% boys] of the URMEL-ICE study. ***Results:*** The intraclass correlation coefficient for intraobserver agreement was 0.93. The median IAF showed a significant gender difference (boys: 54.6 mm, IQR 50.1–59.3, vs. girls: 51.7 mm, IQR 46.3–56.4; $p < 0.001$). Age- and gender-specific centiles were generated. IAF showed a positive correlation to systolic blood pressure [regression coefficient (β) = 0.24 mm Hg/mm; $p < 0.001$] and a negative correlation to HDL cholesterol (β = –0.01 mmol/l/mm; $p < 0.001$). IAF showed a positive association with increased paternal and maternal BMI (β = 0.28 mm/kg/m^2 and 0.27 mm/kg/m^2; $p < 0.001$), increased weight gain in the first 2 years of life (β = 3.04 mm; $p < 0.001$), and maternal smoking during pregnancy (β = 2.4 mm; $p = 0.001$). Increased parental education was negatively associated with IAF (maternal: β = –0.65 mm/degree; $p = 0.004$, and paternal: β = –0.61 mm/degree; $p = 0.002$). ***Conclusion:*** Sonography was a reliable tool to estimate IAF. Factors influencing IAF included rapid infant weight gain, smoking during pregnancy, and parental BMI and education. Since IAF showed an association with cardiovascular risk factors even in prepubertal children, it might become a valuable predictor of cardiovascular vulnerability.

Introduction

Obesity is an ever increasing problem worldwide, especially as it is associated with a high prevalence of morbidity and mortality. Previous studies have shown that risk factors for obesity-related diseases can be tracked

S. Weiland is deceased.

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from childhood into adulthood [1]. In adults, the abdominal distribution of fat rather than obesity as such is of importance for cardiovascular morbidity and mortality [2]. Additional distinction between intra-abdominal (visceral) fat (IAF) and extra-abdominal (subcutaneous) fat reveals a higher morbidity associated with the former [3–5]. In accordance with this observation in adults, studies in children have found a correlation between waist circumference measurements and cardiovascular risk factors [6–10], but direct imaging of IAF has proven to be an even better predictor of cardiovascular risk factors [8, 11, 12]. This is in accordance with the fact that also in childhood visceral fat influences fasting insulin and lipid levels more strongly than subcutaneous fat does [13–15]. Therefore, assessment of IAF might provide a more sufficient estimation of the individual and collective health risk than mere anthropometric measurements can.

The current gold standard for the assessment of IAF is CT or MRI measurement even in children [16–18]. However, their disadvantages such as high costs, radiation exposure (for CT), and limited availability render them impractical for population studies. Therefore, different methods to asses IAF have been explored. In children, there is no good correlation between the waist-hip ratio and visceral fat measured by MRI/CT [16, 17, 19]. Results for waist circumference measurements or skinfold thickness vary as some studies have found a good correlation between waist circumference and IAF [20, 21], some studies have found a good correlation between waist circumference/skinfold thickness and subcutaneous abdominal fat but not IAF [17, 22], and other studies have found no correlation at all [19].

A relatively new method is the assessment of IAF by sonography. Most studies in adults show a good correlation ($r = 0.67–0.91$; $p < 0.001$) for the prediction of IAF mass by sonography compared to CT or MRI [23–26]. Studies in children are scarce; however, a good correlation has also been found ($r = 0.82$) [27]. In addition, abdominal fat measured by sonography shows a positive association to cardiovascular risk factors in adults [5]. In children, very few studies look into this association, most of them using only preperitoneal fat instead of true IAF. However, even here an association has been found [11, 28]. When true IAF was assessed, no correlation between IAF and fasting insulin or HOMA was found, though this might have been due to the small sample size of 51 children [29]. In contrast, visceral fat showed a positive correlation with stiffness of the abdominal aorta [30].

Therefore, since IAF might be a valuable predictor of cardiovascular risk factors and sonography might be an adequate tool to asses IAF, we decided to establish reference values for this method in an age group where hardly any data exist so far.

For adults, some factors influencing IAF are known. Early childhood determinants of IAF, however, remain largely unknown. We presumed that childhood IAF might be influenced by factors similar to those influencing the childhood body mass index (BMI). Hence, we studied the influence of such factors on IAF mass. In addition, we wanted to find out if IAF has an influence on cardiovascular risk factors even in this young and generally healthy cohort.

Subjects and Methods

Study Population

In 2006 the lifestyle intervention study URMEL-ICE was carried out. All 232 second grade classes in 123 primary schools in Ulm and adjacent regions comprising 5,044 children were invited to partake in the study; however, some schools participating in other health programs were retrospectively excluded. In total, 64 classes entered the study. Of these 1,427 pupils 1,119 agreed to participate [median age 7.6 years, interquartile range (IQR) 7.3–7.9; 52% boys]. Parents provided their written informed consent for all clinical assessments and investigations as well as for blood analysis. However, not all children tolerated all examinations nor were all questions in the parental questionnaire answered by all parents. A total of 1,046 children (median age 7.6 years, IQR 7.2–7.9; 54% boys) agreed to have IAF measured by sonography. The number of children who were assessed or the number of answers provided by the parents, respectively, is stated for each parameter (table 1). The study was approved by the ethical committee of Ulm University.

Anthropometric Measurements

In the Endocrine Outpatient Clinic of Ulm Children's Hospital, anthropometric measurements were performed in a standardized manner. Height was measured to the nearest 0.1 cm (Ulm stadiometer; Busse Design, Ulm, Germany) and weight to the nearest 0.1 kg on a calibrated balance beam scale (Seca, Hamburg, Germany) while the children were wearing only underclothes. BMI was calculated as weight (kilograms)/height (meters)^2, and standard deviation scores of BMI were calculated according to the LMS method [31]. In addition, waist circumference was measured to the nearest 0.1 cm at the umbilicus level. Skinfold thickness measurements were performed using a Lange skinfold caliper (Beta Technology, Inc., Santa Cruz, Calif., USA). Subscapular skinfold thickness was measured below the tip of the scapula with the fold running at an angel of 45° downwards from the spine; tricep skinfold thickness was measured on the left arm halfway between the inferior border of the olecranon and the tip of the acromion process. Body fat percentage was calculated using the formula of Slaughter et al. [32]. All anthropometric measurements were taken 3 times by trained personnel.

Table 1. Baseline characteristics of the study group

Characteristics	Whole group			Boys			Girls		
	n	median	IQR	n	median	IQR	n	median	IQR
Age, years	1,042	7.6	7.2–7.9	557	7.6	7.2–7.9	485	7.6	7.2–7.8
Height, cm	1,040	127.2	123.3–130.8	556	127.9	124.1–131.4	484	126.2	122.4–130.0
Weight, kg	1,037	25.4	23.0–28.6	553	25.9	23.5–28.9	484	24.8	22.4–28.2
BMI, kg/m^2	1,030	15.7	14.8–17.2	548	15.8	14.9–17.3	482	15.6	14.6–17.2
Waist circumference, cm	1,036	58.0	55.1–62.3	552	58.3	55.4–62.1	484	57.5	54.8–62.4
Body fat, %	1,040	18.7	15.3–24.4	555	17.8	14.4–23.3	485	19.7	16.4–25.1
IAF, mm	1,043	53.4	48.4–58.0	558	54.6	50.1–59.3	485	51.7	46.3–56.4
Systolic blood pressure, mm Hg	990	108.0	101.5–115.0	530	108.5	102.5–116.0	460	107.5	100.5–113.5
Diastolic blood pressure, mm Hg	990	59.5	55.0–64.5	530	59.5	55.3–65.0	460	59.0	55.0–64.0
Cholesterine, mmol/l	780	4.2	3.8–4.6	427	4.1	3.7–4.5	353	4.3	3.5–4.8
HDL, mmol/l	780	1.4	1.2–1.6	427	1.4	1.2–1.6	353	1.4	1.2–1.6
LDL, mmol/l	780	2.4	2.1–2.8	427	2.3	2.0–2.7	353	2.5	2.2–2.9
Birth weight, g	851	3,410	3,070–3,708	450	3,480	3,090–3,780	401	3,330	3,040–3,630
Weight increase from birth to U7, g/d	797	12.2	11.0–13.6	424	12.5	11.3–13.8	373	11.8	10.6–13.4
BMI (mother), kg/m^2	1,006	23.2	21.1–26.2	540	23.2	21.1–26.0	466	23.3	21.0–26.5
BMI (father), kg/m^2	967	25.7	23.7–27.8	522	25.7	23.8–27.8	445	25.5	23.7–27.8
Exclusive breast-feeding, months	995	3.0	0.0–6.0	537	3.0	0.0–6.0	458	3.0	0.0–6.0

Not all children tolerated all examinations; therefore, the number of participants for every examination is given. HDL = High-density lipoprotein; LDL = low-density lipoprotein; U7 = 7th compulsory German health checkup for children at the age of 20–24 months.

Sonography

Abdominal fat was estimated from the sonographically measured intra-abdominal depth. For this purpose, we used a 3.5-MHz convex transducer and followed a modification of a protocol recommended by Armellini et al. [23] who showed a good correlation between sonography and CT measurements (r = 0.67; $p < 0.001$). All measurements were performed by 1 well-trained investigator. For the examination, the patients lay in a relaxed supine position. Measurements were performed at the end of a quiet expiration, applying minimal pressure without displacement of the intra-abdominal contents. Along the linea alba, at the height of the branching of the arteria mesenterica superior, the distance between the posterior wall of the rectus abdominis muscle and the anterior wall of the aorta was measured (fig. 1). This examination was performed 2 or 3 times, depending on how often it was tolerated by the children. The mean deviation between the mean IAF of a child and each single examination was 3.31 mm (±2.22). In 13 children, 1 of the sonographic measurements differed by more than 3 standard deviations to the mean for IAF for this child. These children were excluded from further analysis if only 2 measurements had been performed (n = 3) or the most discordant measurement was excluded from the calculation of the mean (n = 10).

Covariates

Since URMEL-ICE is a school-based study, the children attended the study with their teachers but without their parents. Therefore, a standardized parental questionnaire was used to collect parental data and information on early childhood. The current parental height and weight were used to calculate BMI. Migration background was defined as the child's father or mother having been born abroad or as the father or mother having spoken a foreign language during the child's first years of life. Parental education was evaluated according to the highest educational level achieved throughout life (none, 9 years of schooling completed, 11 years of schooling completed, highschool graduation, or university degree) coded from 0 to 4.

Information on maternal smoking during pregnancy (yes or no) was collected. Information on breast-feeding was analyzed for breast-feeding in general (yes or no) and for a dosage effect of 0–9 months of exclusive breast-feeding. Data on birth weight and weight development during early childhood were extracted from the children's screening books. Early childhood weight gain between birth and 2 years of age (7th compulsory childhood health check in Germany; 'U7') was analyzed [33]. Rapid weight gain was defined as a weight gain above the 75th percentile of the whole group. The group of children who were born small for their gestational age was defined by comparing the birth weight to the reference data of Voigt et al. [34] with a cutoff at the 3rd percentile (n = 103).

Cardiovascular Risk Factors

Blood samples were obtained by venous puncture and processed shortly after withdrawal. Routine chemical analyses were performed by standard methods. Age-related reference values were obtained from the instructions of the commercial analysis.

Blood pressure was measured 2 times with cuff sizes fitting the different arm circumferences while the children were sitting.

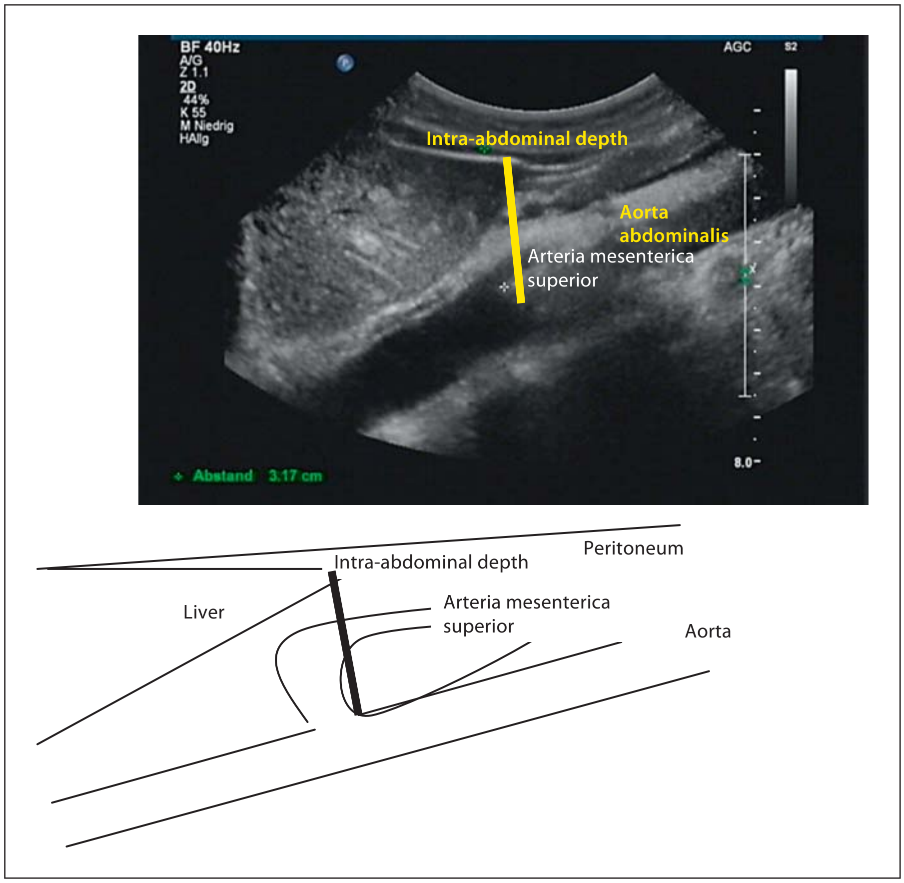

Fig. 1. Depiction of a sonography examination. The intra-abdominal depth was measured between the posterior wall of the musculus rectus abdominis and the anterior wall of the aorta at the branching of the arteria mesenterica superior.

Statistical Analysis

Descriptive statistics summarizing the characteristics of the study population and IAF values according to BMI percentiles are presented as medians and IQR. Furthermore, the association between IAF and BMI, IAF and waist circumference, and IAF and body fat percentage are presented as scatter plots. IAF percentiles stratified for age and gender were calculated via an empirical distribution function with averaging. Intraobserver agreement was examined using the intraclass correlation coefficient (ICC). An ICC of 1 would indicate that the whole variation observed is caused by between-subject variations. The difference in median IAF values between the 2 genders was analyzed using the Wilcoxon test.

The association between IAF and other measurements was assessed via bivariate linear regression. The association between IAF and factors possibly influencing IAF development was further assessed by multivariate analysis. For this analysis, all parameters which were significantly associated with IAF in the bivariate analysis were included. However, when 2 factors were closely correlated (maternal and paternal BMI and maternal and paternal education) only 1 factor was included. Data are shown as regression coefficients, standard deviations, and p values. The unit of each regression coefficient explains the relationship between the tested measurements; for example, mm Hg/mm (IAF) means that each millimeter of IAF is associated with an increase in millimeters of mercury in blood pressure.

$p < 0.05$ was considered statistically significant. All analyses were carried out using the statistical software package SAS release 9.1 (SAS Institute, Cary, N.C., USA).

Results

Baseline Characteristics of the Study Group

1,046 children (median age 7.6 years, IQR 7.2–7.9; 54% boys) agreed to be examined by sonography. As described above, 3 children were excluded from analysis due to increased intraindividual variability between the sonographic measurements. For further details of the group analyzed see table 1.

Reference Values for IAF and Correlation to BMI

Intraobserver agreement assessed by the ICC for IAF estimated from the intra-abdominal depth was 0.93. The median IAF showed a significant gender difference (boys: 54.6 mm, IQR 50.1–59.3, vs. girls: 51.7 mm, IQR 46.3–56.4; $p < 0.001$).

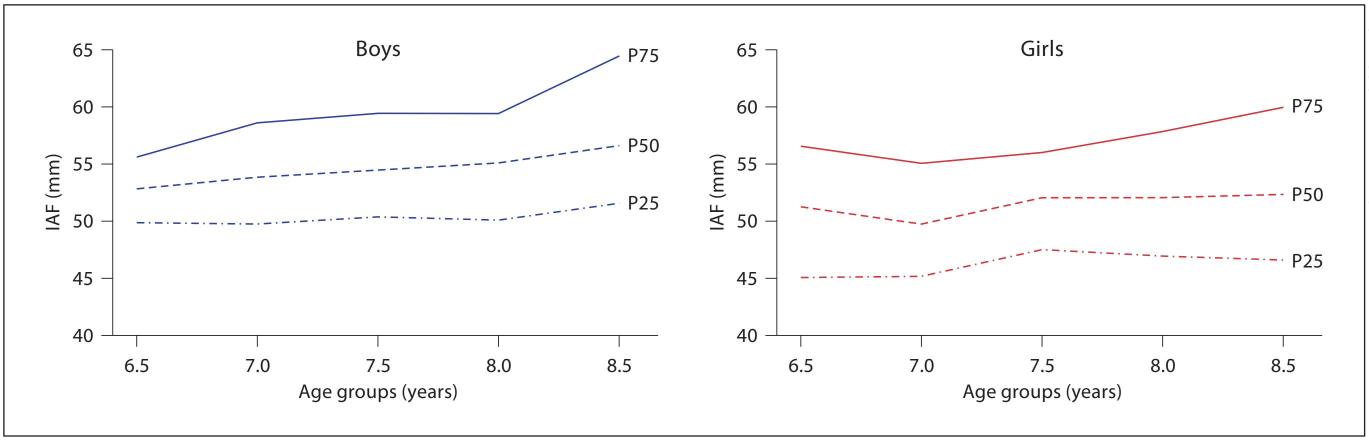

Fig. 2. Centiles for IAF. The 25th, 50th, and 75th centiles were generated from values for IAF estimated from intra-abdominal depth stratified according to age and gender. The sample sizes in the different age groups were as follows: 6.5 years: boys n = 7, girls n = 13; 7 years: boys n = 142, girls n = 114; 7.5 years: boys n = 229, girls n = 223; 8 years: boys n = 177, girls n = 149; 8.5 years: boys n = 39, girls n = 26.

To demonstrate the interaction between IAF, gender, and age we generated centiles for IAF stratified for gender and age (6.5–8.5 years; fig. 2).

A positive correlation existed between IAF and BMI, IAF and waist circumference, and IAF and body fat percentage (whole group: β = 1.8 mm/kg/m^2, β = 0.6 mm/cm, and β = 0.4 mm/%, respectively; $p < 0.001$, data not shown). To assess the shape of these associations, figure 3 shows the respective scatter plots. All 3 graphs show a fairly good linear relationship. Because of the close correlation between BMI and IAF we generated a table showing the mean IAF stratified not only according to age and gender but also according to BMI centiles (table 2). Thereby, we provide a means of estimating IAF in children with known BMI.

Association between IAF and Birth Weight, Early Childhood Weight Gain, and Breast-Feeding

For boys, a distinct weight increase between birth and 2 years of age was associated with increased IAF (β = 0.5 mm/g/d; $p < 0.001$). After dichotomization into rapid and slow weight gainers this relationship could also be seen for the whole group (β = 3.0 mm; $p < 0.001$) and for girls alone (β = 3.4 mm; p = 0.001). No correlation between IAF and birth weight as such could be found, even after excluding children small for their gestational age; no correlation between being small for the gestational age and IAF could be found. Breast-feeding (yes or no) or exclusive breast-feeding in months showed no significant correlation with IAF either (table 3a).

Association between IAF and Parental Factors

Both the BMI of the father and the BMI of the mother were positively associated with IAF (whole group: β = 0.3 mm/kg/m^2; $p < 0.001$). Boys also showed an increase in IAF if at least one parent had a migration background (β = 1.5 mm; p = 0.04). For the whole group and for the girls when analyzed separately, a positive correlation for IAF was found for maternal smoking during pregnancy (whole group: β = 2.4 mm; p = 0.001, and girls: β = 3.5 mm; p = 0.001). Boys showed a tendency towards the same association (β = 1.5 mm; p = 0.116).

Increased parental education, on the other hand, had a small yet significant negative association with IAF in the whole group (maternal education: β = – 0.7 mm/degree; p = 0.004, and paternal education: β = –0.6 mm/degree; p = 0.002). Among the boys, the influence of maternal education showed only a tendency towards significance (table 3a).

Multivariate Analysis of Early Childhood and Parental Factors

In multivariate analysis, rapid weight gain in infancy (whole group, boys, and girls) and maternal BMI (whole group and boys) were significantly associated with IAF. Smoking during pregnancy showed a tendency towards significance for girls, migration background a tendency towards significance for boys, and the educational level of the mother a tendency towards significance for the whole group (table 3b).

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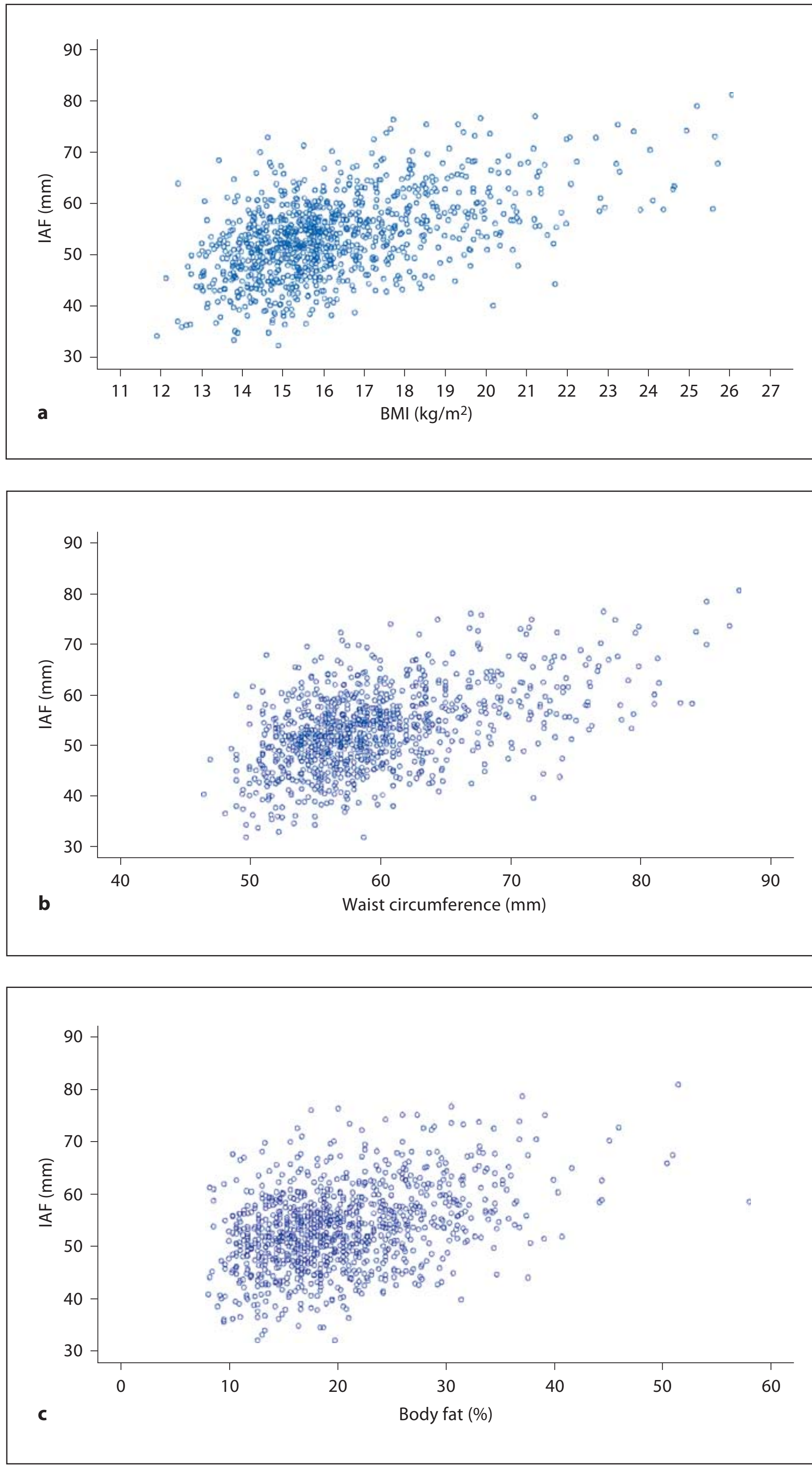

Fig. 3. a Correlation between IAF and BMI. **b** Correlation between IAF and waist circumference. **c** Correlation between IAF and body fat percentage. The values for IAF estimated from sonographically measured intra-abdominal depths were correlated with BMI, waist circumferences, and body fat percentages, respectively. The results are shown as scatter plots.

Table 2. Median IAF stratified according to age and gender and BMI centile groups

BMI centile	>6.75–7.25 years				>7.25–7.75 years				>7.75–8.25 years			
	n	BMI	IAF	IQR	n	BMI	IAF	IQR	n	BMI	IAF	IQR
Boys												
0–10	7	≤13.88	51.5	46.7–56.6	18	≤13.96	48.8	45.6–56.2	16	≤14.07	50.5	46.7–54.6
>10–25	16	>13.88–14.64	52.9	49–57.9	25	>13.96–14.76	50.3	47.1–53.5	21	>14.07–14.90	54.8	50.2–57.2
>25–50	37	>14.64–15.66	51.0	45.6–56.1	71	>14.76–15.82	52.9	50.6–57.5	48	>14.90–16.01	52.3	48.9–56.7
>50–75	35	>15.66–16.92	52.0	50.1–58.8	40	>15.82–17.14	54.1	49.2–57.0	41	>16.01–17.40	56.2	49.2–59.8
>75–90	16	>16.92–18.34	58.0	53.8–62.0	30	>17.14–18.65	57.7	55.2–62.6	22	>17.40–19.01	58.7	54.7–66.6
>90	20	>18.34	57.8	53.7–62.7	30	>18.65	62.0	58.0–65.0	16	>19.01	59.3	54.7–67.7
Girls												
0–10	7	≤13.69	46.5	43.4–51.6	27	≤13.8	46.2	42.0–48.8	10	≤13.92	44.6	41.8–48.2
>10–25	18	>13.69–14.52	45.9	44.0–50.1	27	>13.8–14.66	48.5	43.4–52.0	25	>13.92–14.82	50.6	44.8–53.5
>25–50	32	>14.52–15.62	48.2	44.7–52.2	63	>14.66–15.81	51.8	48.2–54.5	44	>14.82–16.03	51.3	46.4–55.3
>50–75	20	>15.62–16.98	51.5	47.4–55.3	43	>15.81–17.24	53.7	50.5–6.7	22	>16.03–17.53	54.2	50.7–56.6
>75–90	19	>16.98–18.51	53.2	54.5–57.7	20	>17.24–18.86	55.3	51.9–64.4	20	>17.53–19.25	55.2	50.4–60.5
>90	13	>18.51	61.1	58.2–65.3	22	>18.86	57.6	55.4–66.3	15	>19.25	58.6	55.4–67.8

The median IAF and the IQR are presented in millimeters. They are estimated from the sonographically measured intra-abdominal depth and are categorized according to gender, age groups, and BMI centile groups using normative values from Kromeyer-Hauschild et al. [49].

IAF and Cardiovascular Risk Factors

IAF showed a very small yet significant correlation with the mean systolic blood pressure ($\beta = 0.24$ mm Hg/mm; $p < 0.001$) and HDL cholesterol ($\beta = -0.01$ mmol/l/mm; $p < 0.001$), whereas no correlation could be found for the mean diastolic blood pressure, total cholesterol, or LDL cholesterol (table 3c). A similar correlation was found for BMI with systolic blood pressure and HDL cholesterol ($\beta = 1.54$ mm Hg/kg/m^2 and $\beta = -0.02$ mmol/l/kg/m^2, respectively; $p < 0.001$, data not shown), as well as for the percentage body fat with systolic blood pressure and HDL cholesterol ($\beta = 0.42$ mm Hg/% and $\beta = -0.6$ mmol/l/%; $p < 0.001$, data not shown). In contrast to IAF, BMI and body fat percentage also showed a significant correlation with diastolic blood pressure ($\beta = 0.39$ mm Hg/kg/m^2 and $\beta = 0.13$ mm Hg/%, respectively; $p < 0.001$, data not shown) and LDL cholesterol ($\beta = 0.03$ mmol/l/kg/m^2; $p = 0.005$, and $\beta = 0.01$ mmol/l/%; $p < 0.001$, respectively; data not shown).

Discussion

Increased IAF has been associated with an increased risk of cardiovascular morbidity. Assessment of IAF has so far been performed mainly by CT or MRI, limiting the number of subjects eligible for studies. Previous studies have shown that sonographically assessed IAF values correlate well with measurements by CT or MRI ($r = 0.67–0.91$; $p < 0.001$). In the sonographic analysis performed in this study, we used a modification of a protocol established by Armellini et al. [23], which showed a good correlation between the IAF estimated from the sonographically measured intra-abdominal depth and the IAF measured by CT ($r = 0.67$; $p < 0.001$). It must be pointed out, however, that the sonographic measurement of intra-abdominal depth for the estimation of IAF has some drawbacks. Values depend on the pressure the investigator makes on the abdomen as well as on respiration. Since all of the measurements in this study were taken by only 1 experienced investigator, these differences are likely to be very small. This was highlighted by good intraobserver agreement with an ICC of 0.93.

We established reference values for IAF in 7- to 8-year-old children based on a large population-based cohort. In addition, we provide mean IAF values for every 10th BMI percentile (table 2), thereby offering clinicians the possibility to roughly estimate the IAF of their patients if the BMI is known. Furthermore, if both IAF and BMI have been measured in a patient, the clinician can assess to what extent these values show a physiological ratio. One restriction, however, is that for the youngest and slimmest children the groups assessed became quite small, so data here should be used cautiously.

Table 3. Results of statistical analysis

a Linear regression analysis of parameters associated with the development of IAF

Parameter	Whole group				Boys				Girls			
	n	β	SD	p	n	β	SD	p	n	β	SD	p
Birth weight (g)	851	0.0	0.0	0.125	450	0.0	0.0	0.484	401	0.0	0.0	0.502
Birth weight (without SGA children; g)	774	0.0	0.0	0.259	403	0.0	0.0	0.799	371	0.0	0.0	0.861
SGA (yes/no)	851	–0.7	0.9	0.426	450	–0.5	1.2	0.640	401	–1.8	1.5	0.221
Weight increase from birth to U7 (g/d)	797	0.1	0.0	0.117	424	0.5	0.1	<0.001	373	0.0	0.0	0.704
Rapid weight gain from birth to U7 (yes/no)	797	3.0	0.6	<0.001	424	2.4	0.8	0.003	373	3.4	1.0	0.001
Breast-feeding (yes/no)	1,021	0.2	0.6	0.724	551	1.2	0.8	0.142	470	–1.1	0.9	0.200
Exclusive breast-feeding (months)	995	0.0	0.0	0.995	537	0.0	0.1	0.898	458	–0.0	0.1	0.836
Smoking during pregnancy (yes/no)	1,030	2.4	0.7	0.001	552	1.5	0.9	0.116	478	3.5	1.0	0.001
Educational achievement of the mother (degree)	1,022	–0.7	0.2	0.004	549	–0.4	0.3	0.165	473	–0.9	0.3	0.005
Educational achievement of the father (degree)	987	–0.6	0.2	0.002	531	–0.7	0.3	0.008	456	–0.7	0.3	0.018
BMI of the mother (kg/m^2)	1,006	0.3	0.1	<0.001	540	0.4	0.1	<0.001	466	0.2	0.1	0.049
BMI of the father (kg/m^2)	967	0.3	0.1	<0.001	522	0.3	0.1	0.001	445	0.2	0.1	0.032
Migration BG from at least 1 parent (yes/no)	951	0.9	0.5	0.084	501	1.5	0.7	0.040	450	0.5	0.8	0.559

b Multivariate linear regression analysis of IAF and selected parameters

Parameter	Whole group				Boys				Girls			
	n	β	SD	p	n	β	SD	p	n	β	SD	p
Rapid weight gain from birth to U7 (yes/no)	706	3.0	0.7	<0.001	372	2.4	0.8	<0.001	334	3.2	1.0	<0.001
Smoking during pregnancy (yes/no)	706	1.3	0.9	0.134	372	0.5	1.1	0.634	334	2.4	1.3	0.064
Educational achievement of the mother (degree)	706	–0.5	0.3	0.071	372	–0.2	0.4	0.502	334	–0.9	0.4	0.053
BMI of the mother (kg/m^2)	706	0.2	0.1	<0.001	372	0.3	0.1	<0.001	334	0.1	0.1	0.160
Migration BG from at least 1 parent (yes/no)	706	0.2	0.7	0.795	372	1.7	0.9	0.064	334	–1.0	1.0	0.341

c Association between IAF and the development of cardiovascular risk factors

Parameter	Whole group				Boys				Girls			
	n	β	SD	p	n	β	SD	p	n	β	SD	p
Systolic blood pressure (mm Hg)	990	0.24	0.04	<0.001	530	0.21	0.06	<0.001	460	0.24	0.06	<0.001
Diastolic blood pressure (mm Hg)	990	0.02	0.03	0.506	530	0.05	0.05	0.314	460	–0.03	0.05	0.606
Cholesterol (mmol/l)	780	0.00	0.00	0.238	427	0.00	0.00	0.636	353	0.00	0.00	0.851
HDL (mmol/l)	780	–0.01	0.00	<0.001	427	–0.01	0.00	<0.001	353	–0.01	0.00	<0.001
LDL (mmol/l)	780	0.00	0.00	0.823	427	0.00	0.00	0.576	353	0.00	0.00	0.200

IAF was assessed as the sonographically measured intra-abdominal depth in millimeters. Not all children tolerated all examinations; therefore, the number of participants for every examination is given. In tables 3a, c variables were assessed in a bivariate linear regression analysis. In table 3b variables were assessed in a multivariate linear regression. In this model, the significant factors of table 3a were used; however, when 2 factors were closely correlated (maternal and paternal BMI, maternal and paternal education) only 1 factor was included.

In the analysis of the association between IAF and possible influencing parameters, IAF was the dependent variable (tables 3a, b). In the analysis of the association between IAF and cardiovascular risk factors, IAF was the independent variable (table 3c). SD = Standard deviation; U7 = 7th compulsory German health checkup for children at the age of 20–24 months; rapid weight gain = weight gain above the 75th percentile of the whole group, SGA = small for gestational age (birth weight below the 3rd percentile according to Voigt et al. [34]); BG = background; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

Since we studied only primary school children, all of the information on IAF provided here is only applicable to this age group. So far, however, no normative values exist for this age group; therefore, this study provides a valuable contribution to this topic.

Childhood determinants of IAF are largely unknown. In contrast, quite a few early childhood factors influencing BMI have already been established. Since we found a correlation between BMI and IAF, it seems likely that IAF might be influenced by similar factors.

Intrauterine growth retardation is associated with an increased BMI, especially when the intrauterine growth retardation can be attributed to a reduced maternal calorie intake during early pregnancy, for example during war times [35]. When children are born small for their gestational age today, the causes differ widely (including infections, caloric restriction, or smoking) and the insult might have occurred at any time during pregnancy, leading to a controversial influence on BMI and fat accumulation [35]. This might explain why neither being small for the gestational age nor birth weight as such showed a significant influence on IAF in our cohort. In contrast, assessment of an isolated risk factor for reduced fetal nourishment – maternal smoking during pregnancy – showed a strong positive correlation for increased IAF in childhood, especially in girls, in bivariate linear regression.

One explanation for the accumulation of increased weight or body fat after restricted fetal nourishment is a compensatory rapid weight gain in early infancy ('catch-up growth') [33, 36]. Several birth cohort studies show that early infancy weight gain (during the first 1–2 years of life) is positively associated with a subsequent increased risk of obesity [37] and cardiovascular complications in adulthood [38, 39]. In our study, we found that an increased weight gain in the first 2 years of life was also associated with an increased accumulation of IAF. When rapid infant weight gain was included in multivariate analysis, smoking during pregnancy was no longer significantly associated with IAF. This could be due to a decreased number of available subjects for multivariate analysis, or it could indicate that rapid infant weight gain might be at least in part a link between smoking during pregnancy and increased IAF.

One dietary factor which has been shown to be protective against early weight gain is exclusive breast-feeding during the first months of life [40, 41]. However, we did not find an association between IAF and breast-feeding, though breast-feeding did show a negative correlation with childhood BMI (data not shown).

Childhood BMI is also known to be influenced by a variety of parental factors including parental education, migration background, and parental BMI. We showed that increased parental BMI is associated with increased childhood IAF, whereas improved parental education showed a negative correlation with IAF. Parental migration background was associated with increased IAF, but only among boys. When maternal BMI was included in multivariate analysis, migration background and maternal education were no longer significantly associated with IAF. Again, this might be due to a decreased number of subjects available for multivariate analysis. However, it could also indicate that one of the links between those factors and an increased IAF accumulation might in fact be maternal BMI.

When assessing the covariates, a few restrictions have to be mentioned. Since this was a school-based study, parental information could only be gathered via a questionnaire. Here, some bias, for example in answers concerning smoking during pregnancy or parental BMI, might have occurred. In addition, answers to retrospective questions like the duration of breast-feeding might not have been remembered correctly. A further limitation of our study is its cross-sectional design. Because of this design we can only examine associations and not conclude on causes. Nevertheless, since this study is the first to examine early determinants of childhood IAF in a large cohort it provides valuable information on this topic which might be consolidated by further studies.

Despite of the young ages in our cohort, we found an association between increased IAF and cardiovascular risk factors.

A correlation between IAF and parameters of glucose homeostasis has already been proven even among children [7, 8, 11, 12, 42, 43]; however, all of these children were either pubertal or at least overweight. For parameters of fat metabolism some studies were also able to prove a correlation with IAF [8, 15, 44, 45], even among normal-weight prepubertal children [44], while others found no such correlation [7]. This may be because of a small sample size. Since our participants were not fasted, neither glucose homeostasis nor triacylglycerol could be examined. However, it is of special interest that because of our large cohort we were able to prove a correlation between systolic blood pressure and HDL cholesterol even among normal-weight prepubertal children.

Since central obesity assessed by waist circumference [46] or skinfold measurements [47] is known to be tracked from childhood to adolescence, it seems reasonable to assume that positive tracking can also be found for IAF.

The association between IAF and cardiovascular risk factors becomes even stronger among adolescents and adults [12, 15, 48], and this indicates that sonographically estimated IAF might be an important assessment parameter for obesity-associated comorbidity.

In conclusion, sonography proved to be a valuable clinical tool to estimate IAF. We established the first normative values for IAF assessed by sonography for children aged 7–8 years. Furthermore, we identified early childhood factors influencing IAF development such as rapid infant weight gain and parental BMI and education as well as smoking during pregnancy. Even at this young age, IAF showed a very small yet significant association with increased cardiovascular risk factors.

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