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Uric acid and gamma-glutamyl-transferase in children and adolescents with obesity: Association to anthropometric measures and cardiometabolic risk markers depending on pubertal stage, sex, degree of weight loss and type of patient care: Evaluation of the adiposity patient follow-up registry

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Summary

Objectives: Associations between body mass index (BMI)- standard deviation score (SDS)/waist-to-height ratio (WHtR) were studied with (i) serum uric acid (sUA)/gamma-glutamyl-transferase (GGT) and (ii) cardiometabolic risk markers in children with obesity, considering sex, pubertal development, and degree of weight loss/type of patient care.

Methods: 102 936 children from the Adiposity-Follow-up registry (APV; 47% boys) were included. Associations were analysed between sUA/GGT and anthropometrics, transaminases, lipids, fasting insulin (FI), homeostasis model assessment of insulin resistance (HOMA-IR), triglycerides to HDL-cholesterol (TG/HDL)-ratio.

Abbreviations: ALAT, Alanine-aminotransferase; APV, Adiposity Patient Follow-up registry; ASAT, Aspartate-aminotransferase; BMI, Body mass index; CI, Confidence interval; FI, Fasting insulin; GGT, Gamma-glutamyl-transferase; HDL-C, High-density lipoprotein-cholesterol; HOMA-IR, Homeostasis model assessment of insulin resistance; LDL-C, Low density lipoprotein–cholesterol; MetS, Metabolic Syndrome; NAFLD, Nonalcoholic fatty liver disease; OGTT, Oral glucose tolerance test; SDS, Standard deviation score; sUA, Serum uric acid; TG/HDL-ratio, Ratio triglycerides to HDL-cholesterol; WC, Waist circumference; WHtR, Waist-to-height ratio.

Follow-up analyses (3–24 months after baseline) considered a BMI-SDS reduction ≥0.2 ($n = 11\,096$) or ≥0.5 ($n = 3728$). Partialized correlation analyses for sex and BMI-SDS were performed, taking pubertal development into consideration.

Results: At baseline, BMI-SDS showed the strongest correlations to sUA ($r = 0.35$; $n = 26\,529$), HOMA-IR/FI ($r = 0.30$; $n = 5513$ /$n = 5880$), TG/HDL-ratio ($r = 0.23$; $n = 24\,501$), and WHtR to sUA ($r = 0.32$; $n = 10\,805$), GGT ($r = 0.34$; $n = 11\,862$) and Alanine-aminotransferase (ALAT) ($r = 0.33$; $n = 11\,821$), with stronger correlations in boys (WHtR and GGT: $r = 0.36$, $n = 5793$) and prepubertal children ($r = 0.36$; $n = 2216$). GGT and sUA (after partializing effects of age, sex, BMI-SDS) showed a correlation to TG/HDL-ratio ($r = 0.27$; $n = 24\,501$).

Following a BMI-SDS reduction ≥0.2 or ≥0.5, GGT was most strongly related to Aspartate-aminotransferase (ASAT)/ ALAT, most evident in prepuberty and with increasing weight loss, and also to TG/HDL-ratio ($r = 0.22$; $n = 1528$). Prepubertal children showed strongest correlations between BMI-SDS/WHtR and GGT. ΔBMI-SDS was strongly correlated to ΔsUA ($r = 0.30$; $n = 4160$) and ΔGGT ($r = 0.28$; $n = 3562$), and ΔWHtR to ΔGGT ($r = 0.28$; $n = 3562$) (all $p < 0.0001$).

Conclusion: Abdominal obesity may trigger hyperuricemia and hepatic involvement already in prepuberty. This may be stronger in infancy than anticipated to date. Even moderate weight loss has favourable effects on cardiometabolic risk profile and glucose homeostasis.

KEYWORDS

APV registry, cardiometabolic risk markers, childhood obesity, pubertal development, serum uric acid; gamma-glutamyl-transferase

1 | INTRODUCTION

Overweight and obesity in children and adolescents are major health problems: In 2016, 50 million girls and 74 million boys were obese worldwide.[1] There is still a significant upward trend in the prevalence of overweight and obesity which can be observed in high-, upper-middle- and lower-middle-income countries around the globe.[2] Children with overweight or obesity have a markedly increased risk to remain obese in adulthood and to develop cardiovascular comorbidities and metabolic disorders of the Metabolic Syndrome (MetS).[3,4] The so-called hepatic manifestation of MetS (elevated liver transaminases, nonalcoholic fatty liver disease [NAFLD]) is often one of the first features that can be diagnosed already during childhood.[5] Increased risk for malignancies later in life is also attributable to obesity during childhood.[6]

According to data from the German KiGGS study as well as results from the Adiposity Patient Follow-up registry (APV) of Germany, Austria, and Switzerland, a total of 30.5% of children with overweight or obesity already present with dyslipidemia, mostly hypertriglyceridemia and/or reduced levels of HDL cholesterol (HDL-C).[7] In addition, there is a clear correlation between BMI-SDS and the prevalence of the MetS, which starts as early as in infancy: With increasing BMI, the threshold values for different features of MetS significantly increase.[7] However, there are no consistent and internationally accepted criteria to define MetS in childhood and adolescence to date. Thus, it is difficult to give exact and comparable prevalence rates for the distinct features.[8]

The development of a certain cardiometabolic risk profile is mediated by a subclinical inflammatory reaction of the adipose tissue, which in turn is initiated by increased secretion and release of proinflammatory cytokines by adipocytes. This process is critically related to cardiovascular risk factors and especially to the development of insulin resistance (IR) and type 2 diabetes.[9,10]

One of the markers that is strongly involved in these proinflammatory processes in children and adolescents with obesity is serum uric acid (sUA). A predictive relationship between hyperuricemia and cardiovascular risk factors as well as an "unhealthy metabolic phenotype" has been shown for children[11–14]: The Bogalusa Heart Study found a strong correlation between hyperuricemia during childhood and arterial hypertension in adulthood,[12] and sUA seems to best predict metabolically unhealthy obesity and increased cardiovascular risk in both children and adults.[13] A potential role of sUA to trigger inflammatory processes has been discussed for decades,[15] and different underlying mechanisms have been suggested (including nitric oxide and interleukins, increased oxidative stress in different tissues[16]). Hyperuricemia is strongly associated not only to cardiovascular disease, but also to hepatic insulin resistance.[17,18] Another marker that plays a significant role in the process of inflammation is γ-glutamyltransferase (GGT). Increased levels of GGT significantly correlate with

the development of cardiovascular disease, arterial hypertension and dyslipidemia.[19,20]

Many children with obesity present with several cardiometabolic risk factors, including hyperuricemia or increased GGT.[21,22] However, the impact of sex, age, pubertal development and degree of weight loss as well as the type of patient care (inpatient/outpatient) is not clearly understood to date. It is well established that the stage of pubertal development plays a crucial role within these processes. Especially during puberty, cardiometabolic risk increases with elevated BMI-SDS or abdominal obesity, measured by increased waist circumference or waist-to-height ratio (WHtR).[23]

The aim of this study is to investigate (a) how sUA and GGT are correlated to the anthropometric measures BMI-SDS and WHtR as well as their correlation to additional cardiometabolic risk markers of MetS (Alanine-aminotransferase [ALAT], Aspartate-aminotransferase [ASAT], triglycerides, HDL-C, LDL-C, fasting insulin (FI), fasting glucose, HOMA-IR, TG/HDL-ratio) and (b) how these associations change after a BMI-SDS reduction of ≥0.2 and ≥0.5, respectively, following outpatient obesity therapy or inpatient treatment. For type of patient care, analyses were repeated for participants with available follow-up data (3–24 months after baseline) who had achieved weight reduction of either ≥0.2 BMI-SDS or ≥0.5 BMI-SDS. Correlation analyses were performed, stratified for sex, age, pubertal development, and BMI-SDS.

2 | MATERIALS AND METHODS

2.1 | APV registry

Pooled data from the standardized multicentre APV registry were analysed (www.a-p-v.de), which has previously been described in more detail.[3] The registry was developed on behalf of the German Working Group of Obesity in Childhood and Adolescence (www.a-g-a.de) in 1999 and collects longitudinal data on children and adolescents with obesity from Germany, Austria, and Switzerland. In all participating APV centres, a standardized electronic health record is used to document both anthropometric and metabolic parameters of the treated children and adolescents. The anonymized data are transferred to Ulm, Germany, twice yearly and compiled in a cumulative database. Participation in this quality control program is the precondition for accreditation of obesity treatment centres by the German Obesity Society (DAG) and for funding of the treatment by health insurance companies. Ethical approval for the APV data collection was obtained by the Ethics Committee of the University of Ulm, and the consortium of the APV registry warrants the integrity of all data. Data protection and ethical guidelines correspond to local standards and all participating institutions confirm adherence to local data protection regulations.

In the present analysis, APV data until November 2020 were considered applying the following inclusion criteria:

Children aged 8 to18 years with overweight or obesity (BMI ≥90. percentile according to Kromeyer-Hauschild[24]) with at least one complete data set for:

- Body weight, body length, waist circumference.

In addition, at least one of the following parameters of the following list was included:

- sUA, GGT, fasting glucose, FI, HOMA-IR, TG/HDL-ratio, ALAT, ASAT, triglycerides, HDL-C, LDL-C, cholesterol
- Pubertal stage according to Tanner

Patients with syndromic or endocrine obesity and patients on metformin treatment were excluded. The inclusion and exclusion criteria are the same as for the baseline analyses.

For follow-up analyses, patients were selected who had achieved weight reduction 3 to 24 months after the baseline examination. Subgroup analyses were performed, depending on the weight loss achieved (≥0.2 BMI-SDS vs. ≥0.5 BMI-SDS) and the type of patient care (outpatient vs. inpatient). The duration of outpatient programs varied between 3 to 24 months, whereas inpatient obesity treatment in Germany and Austria normally varies between 3 to 6 weeks. Additional analyses were performed considering pubertal stage and sex.

2.2 | Anthropometric and clinical measurements

Measurements were performed by all participating centres following standard procedures. Body mass index (BMI) was calculated by the formula: weight in kilograms divided by the square of the height in meters, and German population–based reference data were used to define the degree of obesity. A cut off ≥1.28 SDS (90th centile) was applied to classify overweight, a cut off ≥1.88 SDS (97th centile) to classify obesity, and a cut off ≥2.58 SDS (99.5th centile) to classify extreme obesity.[24] WHtR was calculated by the formula: waist circumference (WC) in centimetres divided by body height in centimetres. Pubertal stage was assessed according to Tanner stages. For participants with available follow-up data (3–24 months after baseline), analyses were repeated following weight reduction of ≥0.2 BMI-SDS or ≥0.5 BMI-SDS, respectively. Although a child who has achieved a BMI-SDS reduction of ≥0.2 might still be obese, this cutoff has been suggested by the German Association of Childhood Obesity to evaluate the success of obesity therapy programs for children and adolescents in Germany (https://adipositas-gesellschaft.de/aga) and is based on the current German recommendations and S3 guidelines (https://www.awmf.org/uploads/tx_szleitlinien/050-002l_S3_Therapie-Praevention-Adipositas-Kinder-Jugendliche_2019-11.pdf).

To examine the influence of pubertal development on cardiometabolic risk profile, the study cohort was divided into 3 groups according to pubertal stage: group 1 included prepubertal children (Tanner stage 1), group 2 peripubertal children (Tanner stages 2 to 4), and group 3 postpubertal participants (Tanner stages 5 and 6).

2.3 | Statistical analyses

Statistical evaluation was performed using SAS version 9.4 (Statistical Analysis Software SAS Institute, Cary, NC, USA). Data are presented

TABLE 1 Clinical and metabolic characteristics of the entire study cohort (47% boys) at baseline and follow-up (3–24 months after baseline visit)

Variables	Baseline: Mean	Baseline median, [Q1–Q3]	Follow-up (BMI-SDS ≥0.2): Mean	Follow-up (BMI-SDS ≥0.2): Median, [Q1–Q3]	Follow-up (BMI-SDS≥0.5): Mean	Follow-up (BMI-SDS ≥0.5): Median, [Q1–Q3]
Age (years)	12.83	12.88	13.06	12.98	13.68	13.74
n	102 936	[11.1–14.5]	11 993	[11.08–14.82]	4625	[11.76–15.56]
Tanner stage	2.99	3.0	3.15	3	3.36	4
n	32 787	[2–4]	2059	[2–4]	569	[2–5]
BMI (kg/m^2)	30.71	29.8	27.02	26.24	26.34	25.43
n	102 936	[26.6–33.75]	11 096	[23.93–29.28]	3782	[22.98–28,77]
BMI-SDS	2.49	2.47	1.98	1.96	1.78	1.73
n	102 936	[2.11–2.82]	11 096	[1.59–2.36]	3728	[1.34–2.19]
WHtR	0.62	0.61	0.56	0.55	0.55	0.54
n	29 537	[0.56–0.66]	2633	[0.51–0.60]	926	[0.49–0,6]
sUA (mg/dl)	5.96	5.75	5.28	5.15	5.27	5.1
n	36 242	[4.8–6.9]	1689	[4.4–5.97]	708	[4.4–6.0]
GGT (U/l)	20.46	17.0	16.05	14.0	15.30	13.0
n	31 164	[13.0–23.0]	1545	[11.0–18.5]	659	[10.0–17.0]
Chol (mg/dl)	163.91	162.0	159.43	158.0	158.81	151.0
n	63 877	[140–185]	3905	[137.0–179.0]	1607	[131.7–172.0]
LDL (mg/dl)	101.01	98.0	94.68	91.5	89.22	86.23
n	53 219	[79–119]	3630	[75.1–111.37]	1493	[71–104.5]
HDL (mg/dl)	47.79	46.0	49.56	48.0	49.49	48.0
n	55 538	[40–54]	3740	[41.0–56.0]	1548	[41.0–56.0]
TG (mg/dl)	101.47	85.92	101.25	87.0	90.96	80.00
n	63 198	[62–122]	3844	[64.0–120]	1589	[66.0–108.0]
FI (mIU/l)	29.69	16.3	21.89	13.80	18.46	11.8
n	9447	[10.36–27.4]	606	[9.4–21.0]	198	[8.4–23.1]
FG (mg/dl)	84.22	83.0	84.00	83.52	83.24	82.0
n	56 414	[77.0–90.0]	3135	[77.0–90.0]	1307	[76.0–89.0]
HOMA-IR	6.52	3.39	4.43	2.72	3.68	2.21
n	8949	[2.11–5.89]	542	[1.81–3.94]	167	[1.37–3.42-0,6]
TG/HDL ratio	2.35	1.86	2.22	1.81	2.00	1.674
	54 854	[1.23–2.85]	3668	[1.22–2.69]	1529	[1.14–2.42]
ASAT (U/l)	28.98	26.4	23.60	23.0	23.15	23.0
n	39 436	[21.45–33.0]	1952	[18.5–28.0]	780	[18.5–27.0]
ALAT (U/l)	32.41	25.0	22.58	19.0	22.00	19.0
n	39 999	[18.0–36.0]	2000	[15.0–26.0]	796	[14.5–25.0]

Note: Data are presented as mean values as well as median and lower/upper quartile. Follow up data are presented for all participants with BMI-SDS reduction ≥0.2 and ≥0.5, respectively. Available data sets are included for each variable (*n*).
Abbreviations: ALAT, alanine-aminotransferase; ASAT, aspartate-aminotransferase; BMI, body mass index; Chol, Cholesterol; FG, fasting glucose; FI, fasting insulin; GGT, gamma- glutamyltransferase; HDL, high density lipoprotein; HOMA-IR, Homeostasis model assessment of insulin resistance; LDL, low density lipoprotein; sUA, serum uric acid; TG, triglyceride; WHtR, waist-to-height ratio.

as mean values with standard deviation. Nominal data are shown as number (n) and proportion (%). To analyse associations between variables at baseline and following weight loss, Spearman's correlation analyses were performed. As a first step, BMI-SDS or WHtR were correlated with inflammatory markers (sUA, GGT) and with additional cardiometabolic risk markers as well as markers of glucose homeostasis and insulin resistance.

Secondly, sUA or GGT were each correlated with all risk markers (ASAT, ALAT, HDL-C, TG, fasting glucose, FI, HOMA-IR, TG/HDL-ratio). All correlation analyses were performed at baseline and

replicated for participants with BMI-SDS reduction ≥0.2 as well as ≥0.5, respectively, under consideration of the type of patient care (outpatient therapy vs. inpatient treatment). Stratified analyses by sex and pubertal stage were carried out as well. Where applicable, partial Spearman correlation coefficients were calculated and adjusted for age, sex and BMI-SDS. Values were significant at the $p \leq 0.05$ level.

3 | RESULTS

3.1 | Study cohort

As per November 2020, complete data sets from 29 537 children with overweight or obesity (for body weight, body height, BMI-SDS, WHtR, age and sex) were available at the APV registry (47% boys) and were included in the analyses. However, only subgroups which met the inclusion criteria for complete additional data sets for sUA, GGT and cardiometabolic risk markers (transaminases, lipid profile, fasting insulin and glucose, HOMA-IR, TG/HDL-ratio) could be utilized for further analyses. Baseline measurements were included if data records were available up to a maximum of 3 weeks after first presentation. Follow-up data were considered for analyses if participants had presented 3 to 24 months after initial examination. The baseline and follow-up characteristics of the entire study cohort as well as the number of available data sets are presented in Table 1.

With regard to ethnicity, the majority of participating children were of Caucasian origin (69.4%), and most of them were born in Germany (67.2%). For about one third of subjects (29.1%) ethnicity was not indicated and the remaining subjects (1.5%) were mostly of African American or Hispanic origin.

Weight reduction was categorized into BMI-SDS reduction ≥0.2 and ≥0.5, respectively (see above). A total of 11 096 participants achieved a reduction in BMI-SDS ≥0.2 and a total of 3728 participants ≥0.5 BMI-SDS (Table 1), with complete follow- up data sets for body weight, body height, BMI-SDS, age and sex.

A BMI-SDS reduction ≥0.5 corresponded to weight loss of 6.30 kg in outpatient therapy vs. 19.87 kg in inpatient treatment, as initial body weight was markedly higher in patients who had received inpatient therapy compared to patients with outpatient treatment.

Clinical and metabolic characteristics of participants who had achieved a BMI-SDS reduction ≥0.2 or ≥0.5, respectively, under consideration of type of patient care (inpatient vs. outpatient) are presented in Tables 2 and 3.

Baseline levels of sUA and GGT were within the (upper) normal range in the entire study population (sUA: 5.96 mg/dL [reference range: 2,6–6,4 mg/dL]; GGT: 20.46 U/L [children aged 7–12 years: <19 U/L; adolescents: <38 U/L for girls and < 52 U/L for boys]) (Table 1). However, the subgroup of children who had achieved BMI-SDS reduction ≥0.2 and ≥0.5 in inpatient treatment had elevated baseline levels of both markers and markedly higher initial body weight (Tables 2 and 3).

Within all groups with weight reduction ≥0.2 BMI-SDS, data from the groups with BMI-SDS reduction ≥0.5 were also included.

3.2 | Associations between sUA and GGT and anthropometric measures at baseline—Impact of sex and pubertal development

When analysing a potential correlation between serum uric acid (sUA) and gamma-glutamyl-transferase (GGT) as well as a standard deviation score of body-mass index (BMI-SDS) and waist-to-height ratio (WHtR) at baseline, the strongest correlations were found between BMI-SDS and sUA ($r = 0.35$; $n = 26\,529$), between WHtR and sUA ($r = 0.32$; $n = 10\,805$), *as* well as between WHtR and GGT ($r = 0.34$; $n = 11\,862$) (Table 4; all $p < 0.0001$).

These correlations could be confirmed also in sex-specific analyses (Table 4). Most correlations were stronger in boys than in girls (Table 4).

When analysing the influence of pubertal development, the correlation coefficients were strongest between WHtR and GGT in prepubertal children ($r = 0.36$; $n = 2216$; $p < 0.0001$) compared to peripubertal and postpubertal children (Table 4).

tThere were also associations between BMI-SDS and sUA /GGT, albeit weaker than with WHtR. Again, the strongest correlation was found between BMI-SDS and sUA in prepubertal children (Table 4).

3.3 | Associations between sUA, GGT and anthropometric measures with cardiometabolic risk markers and glucose homeostasis at baseline in the entire study cohort

The strongest correlations were found between GGT and ASAT ($r = 0.45$; $n = 30\,705$) as well as ALAT ($r = 0.61$; $n = 30\,805$). In addition, GGT was at baseline correlated to the TG/HDL-ratio as a measure of insulin resistance ($r = 0.27$; $n = 24\,501$).

sUA at baseline, was correlated to ALAT ($r = 0.29$; $n = 26\,336$) and to HDL-C ($r = -0{,}28$; $n = 21\,654$). After partializing for age, sex and BMI-SDS, sUA was correlated to the TG/HDL-ratio ($r = 0{,}29$; $n = 375$).

Regarding anthropometric measures, the best associations were found between BMI-SDS and measures of glucose homeostasis and insulin resistance (HOMA-IR: $r = 0.30$; $n = 5513$; FI: $r = 0.30$; $n = 5880$). WHtR was most strongly correlated to ALAT ($r = 0.33$; $n = 11\,821$). All p-values reached a level <0.0001.

3.4 | Impact of weight loss on the associations between anthropometric measures, sUA and GGT as well as cardiometabolic risk markers and glucose homeostasis in the entire study cohort and depending on pubertal development

In follow-up examinations 3 to 24 months after the first visit, as a first step the impact of weight loss was analysed in all participants, independent of the type of patient care:

TABLE 2 Clinical and metabolic characteristics of participants who had achieved a BMI-SDS reduction ≥0.2, respectively under consideration of treatment regimen

Variables	BMI-SDS ≥0.2/ inpatient: Mean baseline	BMI-SDS ≥0.2/ inpatient baseline median [Q1–Q3]	BMI-SDS ≥0.2 inpatient: Mean Follow-up	BMI-SDS ≥0.2 inpatient: Follow-up median [Q1–Q3]	BMI-SDS ≥0.2 outpatient Mean baseline	BMI-SDS ≥0.2 outpatient: Median baseline [Q1–Q3]	BMI-SDS ≥0.2 outpatient mean follow-up	BMI-SDS ≥0.2 outpatient Follow-up median, [Q1–Q3]
Age (years)	13.94	14.06	14.76	14.85	11.73	11.58	12.55	12.41
n	2759	[12.43–15.72]	2756	[13.33–16.47]	9234	[9.89–13.3]	9234	[10.71–14.13]
Tanner stage	3.36	3	3.52	4	2.68	2	3.08	3
n	14 189	[2–5]	330	[2–5]	10 826	[1–4]	1686	[2–4]
BMI (kg/m^2)	36.05	34.78	30.23	29.4	28.35	27.55	26.16	25.66
n	2354	[30.01–40.74]	2354	[26.2–33.26]	8742	[25.17–30.66]	8742	[23.56–28.22]
BMI-SDS	2,93	2,91	2,27	2254	1.98	1.96	1.78	1.73
n	2354	[2,45-3,37]	2354	[1.79–2.74]	11 096	[1.59–2.36]	3728	[1.34–2.19]
WHtR	0,72	0,7	0.68	0.61	0.60	0.59	0.55	0.55
n	606	[0.63–0.77]	606	[0.55–0.66]	2027	[0.55–0.63]	2027	[0.51–0.59]
sUA (mg/dl)	7.29	7.1	6.06	5.8	5.22	5.1	5.06	5.0
n	371	[6–8.1]	371	[5–7]	1318	[4.3–5.9]	1318	[4.3–5.7]
GGT (U/l)	23.4	19	18.17	14.4	19.0	17.0	15.37	14.0
n	373	[14.0–26.2]	373	[11.0–20.0]	1172	[12.0–21.0]	1172	[10.8–18.0]
Chol (mg/dl)	163.1	162	148.09	145	173.65	171.0	164.14	162.0
n	1147	[39.00–184.4]	1147	[128–165]	2758	[151.0–194.0]	2758	[143.0–182,40]
LDL (mg/dl)	101.54	99.0	86.53	84	106.31	104.0	98.12	94.5
n	1077	[81.2–117.3]	1077	[69.0–101.0]	2553	[85.0–123.74]	2553	[79.0–115.0]
HDL (mg/dl)	43.98	43	45.2	44.0	49.14	47.0	51.42	50.0
n	1118	[36.3–50]	1118	[38.0–51.0]	2622	[41.0–55.0]	2553	[43.0–58.0]
TG (mg/dl)	113.99	101	93.74	85.0	123.93	102.0	104.39	88.0
n	1135	[72–138]	1135	[63.0–112.0]	2709	[73.0–149.69]	2709	[65.0–124.0]
FI (mIU/l)	35.39	32.83	13.83	15.43	29.58	17.75	22.08	13.75
n	14	[11.01–58.6]	14	[5,7–18.92]	592	[11.0–27.65]	592	[9.4–21.3]
FG (mg/dl)	86.78	84	80.96	80.0	86.2	85.86	85.26	85.0
n	916	[77.0–91.0]	916	[74.0–97.0]	2219	[79.0–92.0]	2219	[78.66–90.0]
HOMA-IR	4.38	2.59	2.32	2.44	6.38	3.66	4.46	2.72
n	9	[2.50–7.56]	9	[0.93–2.92]	533	[2.31–5.66]	533	[1.82–3.94]

TABLE 2 (Continued)

Variables	BMI-SDS ≥0.2/ inpatient: Mean baseline	BMI-SDS ≥0.2/ inpatient baseline median [Q1–Q3]	BMI-SDS ≥0.2 inpatient: Mean Follow-up	BMI-SDS ≥0.2 inpatient: Follow-up median [Q1–Q3]	BMI-SDS ≥0.2 outpatient Mean baseline	BMI-SDS ≥0.2 outpatient: Median baseline [Q1–Q3]	BMI-SDS ≥0.2 outpatient mean follow-up	BMI-SDS ≥0.2 outpatient Follow-up median, [Q1–Q3]
TG/HDL ratio	2.83	2.34	2.23	1.90	2.79	2.11	2.22	1.77
	1109	[1.63–3.40]	1109	[1.35–2.74]	2559	[1.41–3.40]	2559	[1.18–2.67]
ASAT (U/l)	29.71	25.0	22.59	14.4	27.78	26.0	23.87	24.0
n	406	[18.0–32.0]	406	[18.0–27.0]	1546	[21.0–33.0]	1546	[18.5–28.8]
ALAT (U/l)	36.06	26.0	22.97	20.0	30.48	23.4	22.49	19.0
n	412	[18.0–43.0]	412	[15.0–29.0]	1588	[17.0–34.0]	1588	[15.0–26.0

Note: Data are presented as mean values as well as median and lower/upper quartile. Available data sets are included for each variable (*n*).

Abbreviations: ALAT, alanine-aminotransferase; ASAT, aspartate-aminotransferase; BMI, body mass index; Chol, Cholesterol; FG, fasting glucose; FI, fasting insulin; GGT, gamma-glutamyltransferase; HDL, high density lipoprotein; HOMA-IR, Homeostasis model assessment of insulin resistance; LDL, low density lipoprotein; sUA, serum uric acid; TG, triglyceride; WHtR, waist-to-height ratio.

3.4.1 | BMI-SDS reduction ≥0.2

A reduction of BMI-SDS ≥0.2 corresponded to a mean weight loss of 4.78 kg and was achieved by a total of 11 096 participants. Additional parameters of this sub-cohort are presented in Table 1. Analyses in this subgroup again revealed positive correlations between BMI-SDS and sUA ($r = 0.25$; $n = 2217$) as well as GGT ($r = 0.24$; $n = 2051$).

When analysing additional cardiometabolic risk markers after BMI-SDS reduction ≥0.2, GGT was most strongly correlated to ASAT ($r = 0.51$; $n = 2159$) and to ALAT ($r = 0.64$; $n = 2184$). These associations were most strongly observable in prepubertal children (ALAT: $r = 0.58$; $n = 467$; ASAT: $r = 0.68$; $n = 474$). In addition, prepubertal children showed a strong correlation between BMI-SDS as well as WHtR and GGT (BMI-SDS and GGT: $r = 0.31$; $n = 450$; WHtR and GGT: $r = 0.35$; $n = 228$). These associations were not or only weakly detectable in peri- and postpubertal children (data not shown). However, in peripubertal (but not pre- or postpubertal) children, GGT was correlated to the TG/HDL-ratio ($r = 0.21$; $n = 1016$).

sUA showed the strongest association to BMI-SDS ($r = 0.25$; $n = 2217$), to HDL-C ($r = -0.29$; $n = 2106$) and to ALAT ($r = 0.23$; $n = 2231$) after BMI-SDS reduction ≥0.2. When considering pubertal development, these associations were most strongly observable in postpubertal participants (for HDL-C: $r = -0{,}36$; $n = 488$; for ASAT: $r = 0.31$; $n = 527$; for ALAT: $r = 0.31$; $n = 530$). All p-values were <0.0001.

Only weak or no correlations were found between GGT and sUA and additional parameters of lipid metabolism or glucose homeostasis (data not shown).

3.4.2 | BMI-SDS reduction of ≥0.5

A reduction of BMI-SDS ≥0.5 corresponded to a mean weight loss of 11.42 kg and was achieved by a total of 3728 participants. Clinical and anthropometric measures of this sub-cohort are presented in Table 1.

Positive and stronger correlations compared to BMI-SDS reduction of ≥0.2 were found between BMI-SDS and sUA ($r = 0.32$; $n = 851$).

When analysing additional cardiometabolic risk markers and markers of glucose homeostasis, GGT was again most strongly correlated to ASAT ($r = 0.47$; $n = 928$) and to ALAT ($r = 0.63$; $n = 940$). This association was again most strongly observable in prepubertal children (ALAT: $r = 0.55$; $n = 149$; ASAT: $r = 0.65$; $n = 156$).

sUA again showed a strong association to HDL-C ($r = -0.35$; $n = 815$), which was stronger than after BMI-SDS reduction ≥0.2. Once again, this correlation was strongest in postpubertal children ($r = -0.31$; $n = 259$) compared to pre- or peripubertal participants. In addition and in line with BMI-SDS reduction ≥0.2, sUA was correlated with ASAT ($r = 0.35$; $n = 292$) and with ALAT ($r = 0.32$; $n = 294$) only in postpubertal children (all p-values <0.0001). Weak or no correlations were found between GGT and sUA and additional parameters of lipid metabolism or glucose homeostasis (data not shown).

TABLE 3 Clinical and metabolic characteristics of participants who had achieved a BMI-SDS reduction ≥0.5, respectively under consideration of treatment regimen

Variables	BMI-SDS≥0.5 inpatient: Mean baseline	BMI-SDS≥0.5 inpatient: Median baseline, [Q1–Q3]	BMI-SDS≥0.5 inpatient: Mean follow-up	BMI-SDS≥0.5 inpatient: Median follow-up, [Q1–Q3]	BMI-SDS≥0.5 outpatient mean baseline	BMI-SDS≥0.5 outpatient: Median baseline, [Q1–Q3]	BMI-SDS≥0.5 outpatient mean follow-up	BMI-SDS≥0.5 outpatient median follow-up [Q1–Q3]
Age (years)	14.1	14.28	14.91	15.02	12.01	11.95	12.87	12.79
n	1835	[12.59–15.91]	1835	[13.48–16.69]	2790	[10.1–13.7]	2790	[10.96–14.54]
Tanner stage	3.36	3	3.5	3	2.74	2	3.29	4
n	13 919	[2–5]	181	[2–5]	8642	[1–4]	388	[2–5]
BMI (kg/m^2)	36.8	35.74	29.38	28.72	28.43	27.45	24.46	24.05
n	1430	[30.85–41.36]	1430	[25.72–32.42]	2298	[25.05–30.61]	2298	[22.11–26.28]
BMI-SDS	2.99	3.01	2.14	2.13	2.31	2.27	1.56	1.55
n	1430	[2.53–3.45]	1,4.30	[1.66–2.61]	2298	[1.97–2.60]	2298	[1.22–1.9]
WHtR	0.71	0.71	0.6	0.6	0.59	0.577	0.52	0.51
n	379	[0.65–0.78]	379	[0.55–0.64]	547	[0.54–0.62]	547	[0.47–0.56]
sUA (mg/dl)	7.31	7.1	5.94	5.7	5.17	5.0	4.86	4.76
n	270	[6.1–8.1]	270	[4.9–6.9]	438	[4.29–5.98]	438	[4.10–5.55]
GGT (U/l)	22.6	19	17.64	14.0	17.9	16.2	13.67	13.0
n	271	[14.0–26.0]	271	[11.0–19.0]	388	[12.0–21.0]	388	[10.0–16.0]
Chol (mg/dl)	164.23	163.0	146.2	143.0	158.89	169.0	158.89	157.0
n	770	[140–185]	770	[126–164]	837	[150.81–193.0]	837	[139.21–177.00]
LDL (mg/dl)	102.79	100.00	85.35	82.0	104.06	102.0	92.84	89.0
n	721	[82.0–119.0]	721	[67.6–100.5]	772	[83.0–121.0]	772	[76.0–107.06]
HDL (mg/dl)	43.8	42.0	45.48	44.0	49.48	47.28	53.32	52.0
n	757	[36.0–50.0]	721	[38.0–51.0]	791	[42.0–55.0]	791	[44.8–60.0]
TG (mg/dl)	116.34	105.0	91.4	61.12	121.63	98.0	90.55	79.72
n	767	[74.0–141.0]	767	[63.0–112.0]	822	[72.0–145.0]	822	[58.46–106.0]
FI (mIU/l)	34.83	36.33	15.03	15.98	28.14	16.35	18.65	11.45
n	10	[11.01–58.6]	10	[5.7–18.92]	188	[10.9–28.64]	188	[8.45–23.6]
FG (mg/dl)	86.72	84.0	80.24	80.0	85.85	86.0	86.03	84.0
n	629	[78.0–91.0]	629	[74.0–86.0]	678	[80.0–92.0]	678	[78.00–90.54]
HOMA-IR	3.99	2.58	2.1	1.88	6.26	3.63	3.74	2.21
n	6	[2.5–7.58]	6	[0.93–2.92]	161	[2.31–5.89]	161	[1.47–3.42]

TABLE 3 (Continued)

Variables	BMI-SDS≥0.5 inpatient: Mean baseline	BMI-SDS≥0.5 inpatient: Median baseline, [Q1–Q3]	BMI-SDS≥0.5 inpatient: Mean follow-up	BMI-SDS≥0.5 inpatient: Median follow-up, [Q1–Q3]	BMI-SDS≥0.5 outpatient mean baseline	BMI-SDS≥0.5 outpatient: Median baseline, [Q1–Q3]	BMI-SDS≥0.5 outpatient mean follow-up	BMI-SDS≥0.5 outpatient median follow-up [Q1–Q3]
TG/HDL ratio	2.91	2.47	2.16	1.84	2.69	2.09	1.83	1.49
	751	[1.68–3.55]	751	[1.33–2.65]	778	[1.36–3.30]	778	[1.04–2.19]
ASAT (U/l)	31.76	26.0	23.51	22.2	27.38	26.0	22.95	23.0
n	277	[20.0–32.0]	277	[19.0–27.0]	503	[20.0–33.0]	503	[18.0–27.5]
ALAT (U/l)	38.0.6	28.05	23.85	20.0	29.94	23.0	21.01	18.0
n	280	[19.0–45.0]	280	[16.0–29.0]	516	[16.0–33.8]	516	[13.5–23.5]

Note: Data are presented as mean values as well as median and lower/upper quartile. Available data sets are included for each variable (*n*).

Abbreviations: ALAT, alanine-aminotransferase; ASAT, aspartate-aminotransferase;BMI, body mass index; Chol, Cholesterol; FI, fasting insulin; FG, fasting glucose; GGT, gamma-glutamyltransferase; HDL, high density lipoprotein; HOMA-IR, Homeostasis model assessment of insulin resistance; LDL, low density lipoprotein; sUA, serum uric acid; TG, triglyceride; WHtR, waist-to-height ratio.

3.5 | Impact of weight loss on the associations between anthropometric measures, sUA and GGT as well as cardiometabolic risk markers and glucose homeostasis depending on the type of patient care

In the next step, the impact of weight loss was analysed in subgroups, depending on achieved weight loss and inpatient/outpatient care. Clinical and anthropometric measures of these sub-cohorts are presented in Tables 2 and 3.

3.5.1 | BMI-SDS reduction of ≥0.2 / outpatient therapy

A reduction of BMI-SDS ≥0.2 in obesity outpatient therapy was achieved by 8742 participants. GGT showed a correlation to BMI-SDS ($r = 0.24$; $n = 1629$), ASAT ($r = 0.53$; $n = 1639$), ALAT ($r = 0.64$; $n = 1654$) and also to the TG/HDL-ratio as a marker of insulin resistance ($r = 0.22$; $n = 1528$). Additional analyses in this subgroup revealed only weak associations ($r < 0.20$).

3.5.2 | BMI-SDS reduction of ≥0.2 / inpatient therapy

A reduction of BMI-SDS ≥0.2 was achieved by 2354 participants. GGT again showed strong correlations to ASAT ($r = 0.44$; $n = 520$) and to ALAT ($r = 0.62$; $n = 528$). sUA was associated to ASAT ($r = 0.29$; $n = 475$) and to ALAT ($r = 0.33$; $n = 480$) as well as to HDL-C ($r = -0.30$; $n = 382$) (all *p*-values <0.0001).

3.5.3 | BMI-SDS reduction of ≥0.5 / outpatient therapy

This was achieved by 2298 participants. GGT again showed strong correlations to ASAT ($r = 0.49$; $n = 535$) and to ALAT ($r = 0.65$; $n = 542$). In addition and in contrast to BMI-SDS reduction ≥0.2, a strong correlation could also be observed between GGT and FI ($r = 0.33$; $n = 190$) as well as with HOMA-IR ($r = 0.26$; $n = 160$). sUA was most strongly associated to HDL-C ($r = -0.27$; $n = 545$). All p-values reached a level <0.0001. Additional analyses in this subgroup revealed only weak associations ($r < 0.20$).

3.5.4 | BMI-SDS reduction of ≥0.5 / inpatient therapy

This was achieved by 1430 participants. There were again strong correlations between GGT and ASAT ($r = 0.44$; $n = 393$) and ALAT ($r = 0.60$; $n = 398$). sUA was associated to ASAT ($r = 0.33$; $n = 353$), ALAT ($r = 0.33$; $n = 358$) and to HDL-C ($r = -0.25$; $n = 270$). All p-values reached a level <0.0001. Additional analyses in this subgroup

TABLE 4 Associations between proinflammatory markers sUA and GGT with anthropometric measures in the entire study cohort and separated by sex as well as pubertal stage at baseline (Spearman Correlation Coefficients; all *p*-values <0.0001)

	sUA	GGT
BMI-SDS	$n = 26\,529$	$n = 31\,164$
all	$r = 0.35$	$r = 0.27$
WHtR	$n = 10\,805$	$n = 11\,862$
all	$r = 0.32$	$r = 0.34$
BMI-SDS	$n = 13\,872$	$n = 16\,244$
Girls only	$r = 0.37$	$r = 0.28$
BMI-SDS	$n = 12\,657$	$n = 14\,920$
Boys only	$r = 0.37$	$r = 0.33$
WHtR	$n = 5541$	$n = 6069$
Girls only	$r = 0.29$	$r = 0.30$
WHtR	$n = 5264$	$n = 5793$
Boys only	$r = 0.33$	$r = 0.36$
BMI-SDS	$n = 4343$	$n = 5096$
Prepubertal	$r = 0.29$	$r = 0.26$
WHtR	$n = 1998$	$n = 2216$
Prepubertal	$r = 0.31$	$r = 0.36$
BMI-SDS	$n = 15\,317$	$n = 18\,071$
Peripubertal	$r = 0.32$	$r = 0.24$
WHtR	$n = 6344$	$n = 6987$
Peripubertal	$r = 0.28$	$r = 0.32$
BMI-SDS	$n = 6869$	$n = 7997$
Postpubertal	$r = 0.25$	$r = 0.27$
WHtR	$n = 2463$	$n = 2659$
Postpubertal	$r = 0.27$	$r = 0.33$

revealed only weak associations ($r < 0.20$) or could not be interpreted due to a high loss in follow-up.

3.6 | Associations between ΔBMI-SDS and ΔWHtR with ΔsUA and ΔGGT respectively

Analyses of the differences (Δ) between BMI-SDS and WHtR with differences in sUA and GGT (Spearman Correlation) respectively, showed the best correlations between ΔBMI-SDS and ΔsUA ($r = 0.30$; $n = 4160$) and between ΔBMI-SDS and ΔGGT ($r = 0.28$; $n = 3562$; $p < 0.0001$). ΔWHtR was neither strongly correlated with ΔsUA nor with ΔGGT.

When considering a BMI-SDS reduction of ≥0.2 and calculating partial Spearman correlation coefficients, adjusted for age, sex and BMI-SDS, the above correlations between ΔBMI-SDS and ΔsUA/ΔGGT remained, albeit weaker (for ΔsUA: $r = 0.26$; for ΔGGT: $r = 0.25$; $n = 520$).

With a BMI-SDS reduction ≥0.5 and calculating partial Spearman correlation coefficients, adjusted for age, sex and BMI-SDS, all correlations between both anthropometric measures and ΔsUA / ΔGGT became markedly weaker (all $r \leq 0.20$; data not shown).

4 | DISCUSSION

This study aimed to investigate (a) the associations between sUA and GGT and (b) anthropometric measures of obesity (BMI-SDS) and body fat distribution (WHtR) as well as (c) cardiometabolic risk markers (liver enzymes, lipid profile, measures of glucose homeostasis) in children and adolescents with obesity before and after weight loss. Sex, pubertal development and the degree of weight loss and type of patient care was taken into account. For this purpose, a large cohort of children and adolescents from the German/Austrian/Swiss APV registry were analysed. WHtR is an incomplete measure of body fat distribution since it may reflect accumulation of fat in both subcutaneous as well as visceral fat stores. Despite this, we decided to include the WHtR ratio in our analyses as it represents a clinically useful measure in daily routine to define increased abdominal obesity (WHtR ≥0.5) as a risk factor for MetS.

The main findings of this study are as follows:

First, at baseline, BMI-SDS is most strongly associated with sUA in all groups studied, and associations are stronger in boys than in girls. WHtR as a marker of abdominal obesity is most strongly correlated to sUA and GGT. Associations are strongest in prepubertal compared with peri- and postpubertal children. This may suggest that abdominal obesity (defined as increased WHtR) is a risk factor towards the development of hyperuricemia and hepatic involvement, already in prepubertal children. Boys seem to be at higher risk than girls.

Second, with regard to additional cardiometabolic risk markers and measures of glucose homeostasis/insulin resistance at baseline, BMI-SDS shows the strongest associations with markers of glucose homeostasis (HOMA-IR, FI, TG/HDL-ratio), and WHtR is most strongly correlated to the liver enzymes. Both sUA and GGT are also strongly associated to liver enzymes in all subgroups investigated. The results suggest that a hepatic manifestation may be one of the first (preclinical) features of obesity in childhood that might occur even before other cardiometabolic complications can be found. NAFLD—in accordance with what is known so far—was suggested to be related to the onset of puberty, and elevated liver enzymes before puberty were often thought to be temporary.[25] In addition, the prevalence of NAFLD and hyperuricemia has been shown to be up to 5 fold higher in boys than in girls.[25,26] As we found the strongest correlations between sUA and GGT as well as measures of obesity and liver enzymes in prepubertal children, our results suggest that a hepatic involvement of childhood obesity may be stronger in early childhood than anticipated to date.

Third, following weight loss, BMI-SDS shows the strongest correlation to sUA, which is stronger after BMI-SDS reduction ≥0.5 compared to ≥0.2. In addition, sUA shows a strong association to HDL-C, which is again stronger following higher weight loss and is most evident in postpubertal children.

GGT shows the best correlation to ALAT und ASAT, which is highest in prepubertal children and stronger after higher weight loss.

With BMI-SDS reduction ≥0.5, there is also a close relation between GGT and FI as well as between sUA and HDL-C, independent of the treatment regime, both of which are not seen after smaller weight loss (BMI-SDS reduction ≥0.2).

In addition, close relations can be found between sUA and transaminases after both BMI-SDS-reduction ≥0.2 as well as ≥0.5, but only as a result of inpatient therapy. These results suggest that even moderate weight loss may have favourable effects on sUA and GGT as potential triggers of subclinical inflammation and the development of MetS later on. In addition, even moderate weight loss may improve cardiometabolic risk profile in all children with obesity, and this is most evident in prepubertal children. As expected, higher weight loss is associated with even better improvement of cardiometabolic risk including glucose homeostasis, independent of the therapy applied (in- vs. outpatient).

As already known from other studies, GGT seems to be a strong predictor for NAFLD, and ALAT as well as ASAT are highly correlated to this parameter.[25] GGT is a good marker for subclinical inflammation and a good predictor towards the development of NAFLD. Increased GGT levels in childhood are associated with increased cardiometabolic disease and increased mortality in adulthood.[20] In addition and in line with our results, a previous analysis of the APV registry could demonstrate a strong association between GGT and the degree of obesity, with strongest correlations in extreme obesity. In addition, associations were more significantly observed in boys with obesity than in girls with obesity.[27]

As shown in a recent study, obesity in children with NAFLD is not only associated with increased accumulation of hepatic fat but also of pancreatic fat: Whereas hepatic fat fraction was closest associated to sex, age and body fat in children with NAFLD, pancreatic fat fraction was closest associated with arterial hypertension and increased fasting glucose, suggesting that the pathophysiology of ectopic fat accumulation varies across organs in children with NAFLD.[28]

Thus, the early detection and management of children or adolescents with obesity and metabolic associated fatty liver disease is challenging, and a non-invasive prediction protocol has recently been suggested.[29]

There is strong evidence for an association between sUA and obesity to trigger proinflammatory processes and the development of MetS already in childhood[26]: Children and adolescents with extreme obesity have significantly higher levels of sUA compared to their peers of normal weight, and this early hyperuricemia is suggested to trigger cardiovascular disease at a young age.[26] In addition, sUA seems to be a risk factor linking obesity to associated cardiovascular disease such as arterial hypertension. Elevated sUA levels can be observed in nearly 90% of adolescents with essential hypertension.[21] It is therefore important to identify and treat children at risk, that is, with hyperuricemia, as early as possible: Feig et al. could demonstrate that allopurinol medication is able to reduce blood pressure in adolescents with newly diagnosed arterial hypertension,[30] and a meta-analysis could confirm a potential impact of allopurinol therapy on blood pressure in several studies.[31] Besides pharmacotherapy, significant weight loss has also been shown to improve pre-existing hyperuricemia and cardiovascular risk factors. A recent study in adolescents with obesity before and after 6 months of lifestyle intervention could show that weight reduction was associated with reductions in branched-chain amino acids (BCAAs), glutamate and C3/C5 acylcarnitines, as well as increases in urea cycle, implicating an increase in BCAA catabolism. In addition, increases in urea cycle during weight reduction were associated with increases in adiponectin, a marker of insulin sensitivity. The authors concluded that weight reduction in adolescents might be associated with increases in BCAA catabolism and improvements in insulin sensitivity, which is of clinical importance towards the prevention of insulin resistance and progression to T2DM in adolescents with obesity.[32] In addition, sUA, glutamate and BCAAs as well as other markers form a sex-dependent metabolic signature which is associated with various markers of IR in adolescents[33]: A higher impact of GGT on cardiometabolic risk in boys compared to girls has been previously shown.[27] In the present study, we can extend these findings by showing that GGT is more strongly associated to body fat content (BMI-SDS) as well as body fat contribution (WHtR) in boys than in girls. In contrast, sUA is stronger associated to WHtR in boys than in girls compared to BMI-SDS. In addition, GGT showed a moderately stronger correlation to WHtR in prepubertal children compared to peripubertal and postpubertal children and also compared to BMI-SDS. These associations could be confirmed after BMI-SDS reduction of ≥0.2 (strong positive correlations between GGT and WHtR as well as BMI-SDS, but not between sUA and the other measures).

Lifestyle modification interventions are the cornerstones of treatment of paediatric obesity but in general the efficacy in reducing weight and BMI is low.[34–37] Most of the programs only achieve modest success with a BMI-SDS reduction ranging from 0.05–0.39.[37] It is well proven that different intervention regimens and obesity therapy programs may improve BMI-SDS and cardiometabolic risk markers in the short term.[36,37] A BMI-SDS reduction of 0.13 in children with pre-existing disturbed glucose tolerance could normalize glucose tolerance 1 year later. This underlines the beneficial effects of only moderate weight loss in children with obesity on risk makers for the MetS.[38] In addition, the NHANES study which investigated the impact of dietary patterns in adolescents aged 12 to18 years, could show that consuming a pro-inflammatory diet is associated with alterations in cardiometabolic risk such as albuminuria, lipid homeostasis and blood pressure.[39]

Our results strengthen the understanding of the association between body weight, sUA, GGT, and additional cardiometabolic risk markers and insulin-resistance, depending on sex and pubertal development: In more detail we show that there is already a strong association between (abdominal) obesity, hepatic involvement, hyperuricemia and cardiometabolic risk as early as in prepubertal children.

Our results are in line with previous studies, such as the HELENA study and studies from other groups,[23,40–44] which have also shown that obesity related inflammation may occur long before the onset of puberty. The fact that some of the observed associations were

strongest in prepubertal children underlines and confirms the importance of identifying children at risk and initiating therapy as early as possible.

There is a physiological insulin resistance (IR) during puberty, putting adolescents with pre-existing obesity at an even higher risk[45–48]: As shown by Allard et colleagues, the marked increase in insulin concentrations and in HOMA-IR in adolescents compared to younger children is attributable to the lowering in insulin sensitivity associated with the onset of puberty. Additional factors that may influence the degree of IR include sex, ethnicity, the stage of pubertal development, total degree of obesity as well as body fat distribution.[47] One explanation of the gender differences in metabolic risk during puberty might be the fact that various hormones associated to IR are differently regulated during puberty. Metabolic health defined by HOMA-IR is predicted by various hormones, and some of them are gender specific: In a predictive model of HOMA-IR, thyroid function tests, adiponectin, ghrelin and leptin concentrations played an important role in both genders. However, prolactin, testosterone and glucagon contributed to the model only in boys, while progesterone and dehydroepiandrosterone sulfate levels contributed only in girls. After Bonferroni correction, levels of leptin, adiponectin, the leptin/adiponectin ratio, SHBG and the fT4/TSH ratio were related to insulin sensitivity in both genders, whereas testosterone and glucagon levels were only associated in boys and levels of TSH and free triiodthyronine (fT3) only in girls. In general, boys with obesity seem to be more insulin resistant than girl with obesity during puberty, which is probably - at least partly-attributable to higher androgen levels as well as lower SHGB levels in boys than in girls which are associated with lower insulin sensitivity.

In addition, the ratio of fT3 to free thyroxine, GGT activity and levels of triglycerides and sex hormone-binding globulin have also been shown to be higher in boys than in girls, contributing to higher IR during puberty in boys.[49,50] In accordance with these findings, most of the correlations in our study cohort were stronger in boys than in girls. We also found strong associations between body fat content and measures of glucose homeostasis and IR (FI and HOMA-IR). However, results should be interpreted with caution due to the small numbers of participants (e.g. for FI) who could be included in the follow-up analyses due to a high loss in follow-up. Additional measures of glucose homeostasis or insulin sensitivity, such as HbA1c or adiponectin, could not be applied for analyses, as HbA1c is only routinely measured in a small number of participating centres and adiponectin is not routinely measured at all. Thus, we included the TG/HDL-ratio as an additional surrogate marker of IR in our analyses.[33,51,52] At baseline, BMI-SDS and GGT were both strongly correlated to the TG/HDL-ratio, and the latter was most evident in peripubertal children, reflecting IR during puberty. After partializing age, sex and BMI-SDS, we also observed a strong correlation between sUA and the TG/HDL-ratio. A cutoff for the TG/HDL-ratio of 2.27 has been suggested to reflect IR in Caucasian girls and boys, whereas for both Hispanics and African Americans an optimal cutoff could not be calculated.[51] In our study cohort, the mean baseline TG/HDL-ratio was 2.35, suggesting IR. Following weight loss, the TG/HDL-ratio could be decreased to below the suggested cutoff of 2.27 in all subcohorts, independent of the degree of weight loss and the type of patient care. The decline to below the suggested threshold was most obvious after a BMI-SDS reduction of ≥0.5 (Tables 1–3). Thus, the TG/HDL- ratio is a simple measure to identify children or adolescents with obesity and increased risk of IR that may be applied in daily clinical practice.

There is a profound genetic predisposition of hyperuricemia, as metabolism of uric acid is controlled by at least 28 genes—as shown by an international genome-wide association study of more than 140 000 participants—and familiar predisposition for hyperuricemia is as high as 40–70%.[50] In addition, hyperuricemia may also derive from renal tubular resistance to insulin and/or excess fructose ingestion.[53]

In contrast, elevated levels of GGT are most frequently attributable to toxic influences such as obesity but also viral infections, autoimmune disease or others. The British Health Survey could show that serum activity of GGT is strongly associated to cancer- and diabetes-related mortality, and an isolated increase of GGT is a significant marker of cardiovascular risk.[54] It has previously been shown that sUA and GGT may have combined effects in association with obesity and other cardiovascular risk factors also in children and adolescents.[55] A correlation between sUA and liver enzymes was only observable after a BMI-SDS reduction ≥0.5 in inpatient therapy, which was the group with the highest weight loss due to the most intense therapy. However, this group had the highest baseline levels of both sUA and GGT compared to the other groups and the highest improvement following therapy (Tables 2 and 3), which might explain why associations could only be seen in this group.

One of the strengths of this study is the large dataset analysed: Comprehensive data from more than 10 obesity centres from Germany and Austria that provide data for the APV registry were utilized. All data (anthropometric, clinical, biochemical) were obtained following standard procedures to allow comparison of results and analysing data in combined data sets. Thus, our comprehensive data analyses of the APV registry represents "data from real life" of obesity therapy in children and adolescents, that is, a trend surveillance. We have also included different degrees of weight loss (reduction of ≥0.2 vs. ≥ 0.5 BMI-SDS) and different types of patient care (outpatient obesity therapy vs. inpatient treatment) to strengthen the conclusions of our study.

There are also some limitations: There was a massive loss of follow-up in the APV registry, which is also well known from other APV-analyses and from other studies. At baseline, complete data sets of body weight, body height, BMI-SDS, age and sex were available from 102 936 children and adolescents within the APV registry, from which only a small proportion remained for follow-up analyses (Tables 2 and 3). Especially in the group of postpubertal children (Tanner stages 5 and 6), only small numbers were available at follow up for correlation analyses, which may have led to some bias. We may not rule out that loss in follow-up was higher in children who were not successful in decreasing body weight and did therefore not show up again, and this may represent another bias of our results. Another limitation might have been the rather large time span of 3 to 24 months for follow up. However, each individual was included with

only two measurements (one at baseline and one at follow up), meaning that we had no additional measurements for individuals who presented for follow up only 24 months after baseline. Thus, by choosing a smaller time span, we would have had to face an even higher rate of loss in follow-up. Finally, we also regard it as a limitation of our study that we could only include sUA and GGT as potential risk markers of proinflammation in our analyses: As in the large multicentre cohort of the APV registry only certain parameters are routinely measured by all participating centres, we had to adhere to these available parameters. However, we believe that the comprehensive data set of our analyses is powerful enough to draw the conclusions made in this study.

The present study underlines the importance of early identification of children with obesity with increased cardiometabolic risk, ideally in prepubertal stage. This is especially the case for markers of liver function as early surrogates of the hepatic manifestation of MetS, as NAFLD may trigger IR and subsequent disturbed glucose metabolism and the progression to type 2 diabetes later in life.[32] The TG/HDL-ratio as a simple measure that may be applied in daily clinical practice—in addition to markers of glucose homeostasis and IR—can identify children or adolescents with obesity and increased risk of IR.

4.1 | Summary and conclusion

BMI-SDS and WHtR are strongly associated to sUA and GGT already in early childhood, and the associations are stronger for boys than for girls. (Abdominal) obesity may trigger hyperuricemia and hepatic involvement as the earliest clinical features associated with childhood obesity already before the onset of puberty. In addition, hepatic involvement may be stronger in early childhood than anticipated to date. Even moderate weight loss may have favourable effects on sUA and GGT as triggers for subclinical inflammation as well as on the cardiometabolic risk profile. Higher weight loss (BMI-SDS reduction ≥0.5) leads to stronger improvement of cardiometabolic risk factors, independent of the type of patient care and duration of therapy.

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CONFLICT OF INTEREST

The authors disclose any potential conflict of interest.

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REFERENCES

1. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 1289 million children, adolescents, and adults. *Lancet*. 2017; 390(10113):2627-2642.
2. Fan H, Zhang X. Recent trends in overweight and obesity in adilescents aged 12 to 15 Years across 21 countries. *Pediatr Obes*. 2022; 17(1):e12839. doi:10.1111/ijpo.12839
3. Holl RW, Hoffmeister U, Thamm M, et al. Does obesity lead to a specific lipid disorder? Analysis from the German/Austrian/Swiss APV registry. *Int J Pediatr Obes*. 2011;6(Suppl 1):53-58.
4. Reilly JJ, Kelly J. Long-term impact of overweight and obesity in childhood and adolescence on morbidity and premature mortality in adulthood: systematic review. *Int J Obes (Lond)*. 2011;35(7):891-898.
5. Zimmet P, Alberti KG, Kaufman F, et al. The metabolic syndrome in children and adolescents—an IDF consensus report. *Pediatr Diabetes*. 2007;8(5):299-306.
6. Weihe P, Spielmann J, Kielstein H, Henning-Klusmann J, Weihrauch-Blüher S. Childhood obesity and cancer risk in adulthood. *Curr Obes Rep*. 2020;9(3):204-212.
7. Flechtner-Mors M, Thamm M, Wiegand S, et al. Comorbidities related to BMI category in children and adolescents: German/Austrian/Swiss obesity register APV compared to the German KiGGS study. *Horm Res Paediatr*. 2012;77(1):19-26.
8. Weihe P, Weihrauch-Bluher S. Metabolic syndrome in children and adolescents: diagnostic criteria, therapeutic options and perspectives. *Curr Obes Rep*. 2019;8(4):472-479.
9. Hivert MF, Sullivan LM, Shrader P, et al. The association of tumor necrosis factor alpha receptor 2 and tumor necrosis factor alpha with insulin resistance and the influence of adipose tissue biomarkers in humans. *Metabolism*. 2010;59(4):540-546.
10. Reinehr T. Inflammatory markers in children and adolescents with type 2 diabetes mellitus. *Clin Chim Acta*. 2019;496: 100-107.
11. Weghuber D, Zelzer S, Stelzer I, et al. High risk vs. "metabolically healthy" phenotype in juvenile obesity - neck subcutaneous adipose tissue and serum uric acid are clinically relevant. *Exp Clin Endocrinol Diabetes*. 2013;121(7):384-390.
12. Alper AB Jr, Chen W, Yau L, Srinivasan SR, Berenson GS, Hamm LL. Childhood uric acid predicts adult blood pressure: the Bogalusa heart study. *Hypertension*. 2005;45(1):34-38.
13. Mangge H, Zelzer S, Puerstner P, et al. Uric acid best predicts metabolically unhealthy obesity with increased cardiovascular risk in youth and adults. *Obesity (Silver Spring)*. 2013;21(1):E71-E77.
14. Mărginean CO, Meliț LE, Ghiga DV, Mărginean MO. Early inflammatory status related to pediatric obesity. *Front Pediatr*. 2019; 7:241.

15. Kannel WB, Castelli WP, McNamara PM. The coronary profile: 12-year follow-up in the Framingham study. *J Occup Med*. 1967; 9(12):611-619.
16. Ndrepepa G. Uric acid and cardiovascular disease. *Clin Chim Acta*. 2018;484:150-163.
17. Cicerchi C, Li N, Kratzer J, et al. Uric acid-dependent inhibition of AMP kinase induces hepatic glucose production in diabetes and starvation: evolutionary implications of the uricase loss in hominids. *FASEB J*. 2014;28(8):3339-3350.
18. Di Bonito P, Valerio G, Licenziati MR, et al. Uric acid, impaired fasting glucose and impaired glucose tolerance in youth with overweight and obesity. *Nutr Metab Cardiovasc Dis*. 2021;31(2): 675-680.
19. Rantala AO, Lilja M, Kauma H, Savolainen MJ, Reunanen A, Kesäniemi YA. Gamma-glutamyl transpeptidase and the metabolic syndrome. *J Intern Med*. 2000;248(3):230-238.
20. Lee DS, Evans JC, Robins SJ, et al. Gamma glutamyl transferase and metabolic syndrome, cardiovascular disease, and mortality risk: the Framingham heart study. *Arterioscler Thromb Vasc Biol*. 2007;27(1): 127-133.
21. Feig DI, Kang DH, Johnson RJ. Uric acid and cardiovascular risk. *N Engl J Med*. 2008;359(17):1811-1821.
22. Ndrepepa G, Colleran R, Kastrati A. Gamma-glutamyl transferase and the risk of atherosclerosis and coronary heart disease. *Clin Chim Acta*. 2018;476:130-138.
23. Bluher S, Molz E, Wiegand S, et al. Body mass index, waist circumference, and waist-to-height ratio as predictors of cardiometabolic risk in childhood obesity depending on pubertal development. *J Clin Endocrinol Metab*. 2013;98(8):3384-3393.
24. Kromeyer-Hauschild K, Wabitsch M, Kunze D, et al. Perzentile für den Body-mass-Index für das Kindes- und Jugendalter unter Heranziehung verschiedener deutscher Stichproben. *Monatsschr Kinderheilkd*. 2001;149(8):807-818.
25. Newton KP, Lavine JE, Wilson L, et al. Alanine aminotransferase and gamma-Glutamyl Transpeptidase predict histologic improvement in pediatric nonalcoholic steatohepatitis. *Hepatology*. 2020;73(3): 937-951.
26. Ford ES, Li C, Cook S, Choi HK. Serum concentrations of uric acid and the metabolic syndrome among US children and adolescents. *Circulation*. 2007;115(19):2526-2532.
27. Wiegand S, Thamm M, Kiess W, et al. German competence network Adipositas. Gamma-glutamyl transferase is strongly associated with degree of overweight and sex. *J Pediatr Gastroenterol Nutr*. 2011; 52(5):635-638.
28. Lee EH, Kim JY, Yang HR. Association between ectopic pancreatic and hepatic fat and metabolic risk factors in children with non-alcoholic fatty liver disease. *Pediatr Obes*. 2021;16(10):e12793.
29. Oses M, Cadenas-Sanchez C, Medrano M, et al. Development of a prediction protocol for the screening of metabolic associated fatty liver disease in children with overweight or obesity. *Pediatr Obes*. 2022;17(9):e12917.
30. Feig DI, Soletsky B, Johnson RJ. Effect of allopurinol on blood pressure of adolescents with newly diagnosed essential hypertension: a randomized trial. *JAMA*. 2008;300(8):924-932.
31. Agarwal V, Hans N, Messerli FH. Effect of allopurinol on blood pressure: a systematic review and meta-analysis. *J Clin Hypertens (Greenwich)*. 2013;15(6):435-442.
32. Jachthuber Trub C, Balikcioglu M, Freemark M, et al. Impact of lifestyle intervention on branched-chain amino acid catabolism and insulin sensitivity in adolescents with obesity. *Endocrinol Diabetes Metab*. 2021;4(3):e00250.
33. Newbern D, Gumus Balikcioglu P, Balikcioglu M, et al. Sex differences in biomarkers associated with insulin resistance in adolescents with obesity: metabolomic profiling and principal components analysis. *J Clin Endocrinol Metab*. 2014;99(12):4730-4739.
34. Koutny F, Stein R, Kiess W, Weghuber D, Körner A. Elevated transaminases potentiate the risk for emerging dysglycemia in children with overweight and obesity. *Pediatr Obes*. 2021;16(12):e12822. doi: 10.1111/ijpo.12822
35. Mead E, Brown T, Rees K, et al. Diet, physical activity and behavioural interventions for the treatment of overweight or obese children from the age of 6 to 11 years. *Cochrane Database Syst Rev*. 2017;6(6):6. doi:10.1002/14651858.CD012651
36. Al-Khudairy L, Loveman E, Colquitt JL, et al. Diet, physical activity and behavioural interventions for the treatment of overweight or adolescents with obesity aged 12 to 17 years. *Cochrane Database Syst Rev*. 2017;6(6):6.
37. Muhlig Y, Wabitsch M, Moss A, Hebebrand J. Weight loss in children and adolescents. *Deutsches Arzteblatt International*. 2014;111(48):818-824.
38. Kleber M, Lass N, Papcke S, Wabitsch M, Reinehr T. One-year follow-up of untreated obese white children and adolescents with impaired glucose tolerance: high conversion rate to normal glucose tolerance. *Diabet Med*. 2010;27(5):516-521.
39. Sethna CB, Alanko D, Wirth MD, et al. Dietary inflammation and cardiometabolic health in adolescents. *Pediatr Obes*. 2021;16(2):e12706.
40. Huang T, Larsen KT, Møller NC, Ried-Larsen M, Frandsen U, Andersen LB. Effects of a multi-component camp-based intervention on inflammatory markers and adipokines in children: a randomized controlled trial. *Prev Med*. 2015;81:367-372.
41. Robertson W, Fleming J, Kamal A, et al. Randomised controlled trial evaluating the effectiveness and cost-effectiveness of 'Families for Health', a family-based childhood obesity treatment intervention delivered in a community setting for ages 6 to 11 years. *Health Technol Assess*. 2017;21(1):1-180.
42. Makni E, Moalla W, Benezzeddine-Boussaidi L, Lac G, Tabka Z, Elloumi M. Correlation of resistin with inflammatory and cardiometabolic markers in adolescents with obesity with and without metabolic syndrome. *Obes Facts*. 2013;6(4):393-404.
43. Loureiro C, Godoy A, Martínez A, et al. Metabolic syndrome and its components are strongly associated with an inflammatory state and insulin resistance in the pediatric population. *Nutr Hosp*. 2015;31(4): 1513-1518.
44. González-Gil EM, Cadenas-Sanchez C, Santabárbara J, et al. Inflammation in metabolically healthy and metabolically abnormal adolescents: the HELENA study. *Nutr Metab Cardiovasc Dis*. 2018;28(1):77-83.
45. Marín-Echeverri C, Aristizábal JC, Gallego-Lopera N, et al. Cardiometabolic risk factors in preschool children with abdominal obesity from Medellín. *Colombia J Pediatr Endocrinol Metab*. 2018;31(11):1179-1189.
46. Higgins V, Omidi A, Tahmasebi H, et al. Marked influence of adiposity on laboratory biomarkers in a healthy cohort of children and adolescents. *J Clin Endocrinol Metab*. 2020;105(4):e1781-e1797.
47. Allard P, Delvin EE, Paradis G, et al. Distribution of fasting plasma insulin, free fatty acids, and glucose concentrations and of homeostasis model assessment of insulin resistance in a representative sample of Quebec children and adolescents. *Clin Chem*. 2003; 49(4):644-649.
48. Peplies J, Jiménez-Pavón D, Savva SC, et al. Percentiles of fasting serum insulin, glucose, HbA1c and HOMA-IR in pre-pubertal normal weight European children from the IDEFICS cohort. *Int J Obes (Lond)*. 2014;38(Suppl 2):S39-S47.
49. Aldhoon-Hainerová I, Zamrazilová H, Dušátková L, et al. Glucose homeostasis and insulin resistance: prevalence, gender differences and predictors in adolescents. *Diabetol Metab Syndr*. 2014; 16(1):100.
50. Aldhoon-Hainerová I, Zamrazilová H, Hill M, Hainer V. Insulin sensitivity and its relation to hormones in adolescent boys and girls. *Metabolism*. 2017;67:90-98.
51. Giannini C, Santoro N, Caprio S, et al. The triglyceride-to-HDL cholesterol ratio: association with insulin resistance in obese youths of different ethnic backgrounds. *Diabetes Care*. 2011;34(8):1869-1874.

52. Köttgen A, Albrecht E, Teumer A, et al. Genome-wide association analyses identify 18 new loci associated with serum urate concentrations. *Nat Genet*. 2013;45(2):145-154.
53. Menè P, Punzo G. Uric acid: bystander or culprit in hypertension and progressive renal disease? *J Hypertens*. 2008;26(11):2085-2092.
54. Unalp-Arida A, Ruhl CE. Noninvasive fatty liver markers predict liver disease mortality in the U.S. population. *Hepatology*. 2016;63(4):1170-1183.
55. Kong AP, Choi KC, Ho CS, et al. Associations of uric acid and gamma-glutamyltransferase (GGT) with obesity and components of metabolic syndrome in children and adolescents. *Pediatr Obes*. 2013;8(5):351-357.

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