

## Supplemental Material

### Children born SGA receiving growth hormone have similarly impaired glucose-insulin metabolism as children with obesity

Lea Prengemann<sup>1\*</sup>, Robert Stein<sup>1,2,3\*</sup>, Ruth Gausche<sup>1</sup>, Christoph Beger<sup>1</sup>, Mandy Vogel<sup>4</sup>, Eric Wenzel<sup>1,2,3</sup>, Anette Stoltze<sup>1</sup>, Wieland Kiess<sup>1,3,4</sup>, Roland Pfäffle<sup>1,3</sup>, Antje Körner<sup>1,2,3,4</sup>

<sup>1</sup> University of Leipzig, Medical Faculty, University Hospital for Children & Adolescents, Center for Pediatric Research, Leipzig, Germany

<sup>2</sup> Helmholtz Institute for Metabolic, Obesity and Vascular Research (HI-MAG) of the Helmholtz Zentrum München at the University of Leipzig and University Hospital Leipzig, Germany

<sup>3</sup> German Center for Child and Adolescent Health (DZKG), partner site Leipzig/Dresden, Germany

<sup>4</sup> LIFE–Leipzig Research Center for Civilization Diseases, University of Leipzig, Germany

\*Authors contributed equally

Address correspondence to:

Prof. Antje Körner, MD

ORCID: 0000-0001-6001-0356

Helmholtz Institute for Metabolic, Obesity and Vascular Research (HI-MAG)

of the Helmholtz Zentrum München

at the University of Leipzig and University Hospital Leipzig, Germany

Email: Antje.Koerner@medizin.uni-leipzig.de

Phone: +49-341-9726500

**Table S1: Clinical characteristics of unmatched cohorts**

	SGA	iGHD	lean	obesity	p-value SGA vs. lean	p-value SGA vs. obesity	p-value iGHD vs. lean	p-value iGHD vs. obesity	p-value SGA vs. iGHD	p-value lean vs. obesity
<b>Treatment-naïve</b>										
n subj. (n obs.)	61 (117)	98 (133)	744 (2005)	427 (846)	-	-	-	-	-	-
n subj. male (%)	28 (45.90)	50 (51.02)	375 (50.4)	225 (52.69)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
age in years, mean (SD)	11.54 (±4.19)	8.24 (±3.57)	12.96 (±3.19)	12.26 (±2.87)	<0.001	0.006	<0.001	<0.001	<0.001	<0.001
BMI-SDS, mean (SD)	0.65 (±1.63)	-0.55 (±0.99)	0.79 (±1.41)	2.34 (±0.52)	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Height-SDS, mean (SD)	-0.99 (±1.43)	-2.52 (±0.68)	0.38 (±1.02)	0.73 (±1.02)	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Weight-SDS, mean (SD)	-0.02 (±2.08)	-2.01 (±0.95)	0.86 (±1.42)	2.35 (±0.73)	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
IGF1-SDS, mean (SD)	-0.47 (±1.13)	-1.75 (±1.21)	-0.2 (±1)	-0.2 (±1.03)	<0.001	0.002	<0.001	<0.001	<0.001	n.s.
n obs. pubertal stage 1 (%)	38 (36.89)	68 (81.93)	307 (27.12)	261 (31.56)	<0.001	<0.001	<0.001	<0.001	0.003	n.s.
n obs. pubertal stage 2-4 (%)	40 (38.83)	15 (18.07)	482 (42.57)	353 (42.68)	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
n obs. pubertal stage 5 (%)	25 (24.27)	0	343 (30.3)	213 (25.76)	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
<b>During GH treatment</b>										
n subj. (n obs.)	132 (639)	296 (915)	744 (2005)	427 (846)	-	-	-	-	-	-
n subj. male (%)	68 (51.52)	169 (57.09)	375 (50.4)	225 (52.69)	n.s.	n.s.	0.003	<0.001	0.03	n.s.
age in years, mean (SD)	10.51 (±3.36)	11.69 (±3.38)	12.96 (±3.19)	12.26 (±2.87)	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
BMI-SDS, mean (SD)	-0.83 (±1.24)	-0.43 (±1.17)	0.79 (±1.41)	2.34 (±0.52)	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Height-SDS, mean (SD)	-1.99 (±0.93)	-1.69 (±0.9)	0.38 (±1.02)	0.73 (±1.02)	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Weight-SDS, mean (SD)	-1.84 (±1.43)	-1.3 (±1.26)	0.86 (±1.42)	2.35 (±0.73)	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
IGF1-SDS, mean (SD)	0.48 (±1.62)	0.05 (±1.57)	-0.2 (±1)	-0.2 (±1.03)	<0.001	<0.001	<0.001	<0.001	<0.001	n.s.
GH dose µg/kg, mean (SD)	33.74 (±6.38)	29.57 (±7.15)	-	-	-	-	-	-	<0.001	-
n obs. pubertal stage 1 (%)	227 (43.91)	282 (39.72)	307 (27.12)	261 (31.56)	<0.001	n.s.	n.s.	n.s.	0.01	n.s.
n obs. pubertal stage 2-4 (%)	249 (48.16)	350 (49.30)	482 (42.57)	353 (42.68)	<0.001	<0.001	<0.001	n.s.	<0.001	<0.001
n obs. pubertal stage 5 (%)	41 (7.93)	78 (10.99)	343 (30.3)	213 (25.76)	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
<b>After GH treatment</b>										
n subj. (n obs.)	47 (57)	92 (119)	744 (2005)	427 (846)	-	-	-	-	-	-
n subj. male (%)	20 (42.55)	45 (48.91)	375 (50.4)	225 (52.69)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
age in years, mean (SD)	15.94 (±1.91)	15.64 (±1.99)	12.96 (±3.19)	12.26 (±2.87)	<0.001	<0.001	<0.001	<0.001	n.s.	<0.001
BMI-SDS, mean (SD)	0 (±1.43)	-0.26 (±1.12)	0.79 (±1.41)	2.34 (±0.52)	<0.001	<0.001	<0.001	<0.001	n.s.	<0.001
Height-SDS, mean (SD)	-1.93 (±0.65)	-1.34 (±0.81)	0.38 (±1.02)	0.73 (±1.02)	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Weight-SDS, mean (SD)	-1.08 (±1.43)	-0.98 (±1.18)	0.86 (±1.42)	2.35 (±0.73)	<0.001	<0.001	<0.001	<0.001	n.s.	<0.001
IGF1-SDS, mean (SD)	0.92 (±1.15)	-0.38 (±0.81)	-0.2 (±1)	-0.2 (±1.03)	0.014	0.011	n.s.	n.s.	0.009	n.s.
n obs. pubertal stage 1 (%)	0	3 (3.49)	307 (27.12)	261 (31.56)	<0.001	<0.001	<0.001	<0.001	n.s.	n.s.
n obs. pubertal stage 2-4 (%)	9 (23.68)	38 (44.19)	482 (42.57)	353 (42.68)	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
n obs. pubertal stage 5 (%)	29 (76.32)	45 (52.33)	343 (30.3)	213 (25.76)	<0.001	<0.001	<0.001	<0.001	n.s.	<0.001

Means are weighted for the number of visits if subjects had multiple observations within one time frame. Differences between groups were assessed by linear-mixed-effects regression models for continuous variables and  $\chi^2$ -test for categorical variables. SDS = standard deviation score, SD = standard deviation, BMI = body mass index, IGF1 = insulin-like growth factor 1, GH = growth hormone; n.s. = not significant; lean = lean controls, SGA = children born SGA, obesity = children with obesity, iGHD = isolated growth hormone deficiency, obs. = observations, subj. = subjects

**Table S2: Differences of glucose-insulin metabolism by linear mixed model regression**

	SGA vs. lean		SGA vs. obesity		lean vs. iGHD		obesity vs. iGHD		SGA vs. iGHD		obesity vs. lean	
	unadj.	adj.	unadj.	adj.	unadj.	adj.	unadj.	adj.	unadj.	adj.	unadj.	adj.
<b>Treatment-naïve</b>												
<b>fasting glucose level</b>												
beta slope	0.08	0.024	-0.42	-0.375	-0.45	-0.494	0.04	0.067	-0.39	-0.727	0.39	0.378
p-value	n.s.	n.s.	<0.001	<0.001	<0.001	<0.001	n.s.	n.s.	n.s.	<0.05	<0.001	<0.001
<b>2h-glucose level</b>												
beta slope	0.82	0.606	-0.14	-0.099	-1.0	-0.851	-0.06	-0.101	-0.19	-1.292	0.82	0.752
p-value	<0.001	<0.01	n.s.	n.s.	0.014	n.s.	n.s.	n.s.	n.s.	n.s.	<0.001	<0.001
<b>HbA1c</b>												
beta slope	0.08	<0.001	0.05	0.039	0.08	<0.001	0.14	0.159	0.18	0.152	0.03	0.023
p-value	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
<b>glucose AUC</b>												
beta slope	1.66	1.229	0.08	0.002	-2.8	-2.612	-1.25	-1.63	-1.17	-2.113	1.29	1.19
p-value	<0.001	<0.01	n.s.	n.s.	<0.001	<0.01	n.s.	n.s.	n.s.	n.s.	<0.001	<0.001
<b>insulin AUC</b>												
beta slope	0.2	0.087	-0.22	-0.22	1.02	0.811	1.44	1.356	1.19	0.668	0.34	0.358
p-value	0.04	n.s.	0.04	0.03	<0.001	<0.001	<0.001	<0.001	0.002	<0.05	<0.001	<0.001
<b>HOMA-IR</b>												
beta slope	0.07	-0.07	-0.63	-0.582	0.95	0.861	1.64	1.726	0.97	0.093	0.61	0.625
p-value	n.s.	n.s.	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.03	n.s.	<0.001	<0.001
<b>Matsuda index</b>												
beta slope	-0.19	-0.044	0.43	0.405	-0.89	-0.755	-1.5	-1.481	-1.04	-0.322	-0.5	-0.513
p-value	0.04	n.s.	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.01	n.s.	<0.001	<0.001
<b>ODI</b>												
beta slope	-0.1	-0.043	0.22	0.215	0.36	<0.001	0.05	0.06	0.27	0.532	-0.258	-0.258
p-value	n.s.	n.s.	0.03	0.04	0.02	n.s.	n.s.	n.s.	n.s.	<0.05	<0.001	<0.001
<b>During GH treatment</b>												
<b>fasting glucose level</b>												
beta slope	0.336	0.444	-0.13	-0.09	-0.31	-0.268	0.19	0.22	0.08	0.18	0.39	0.37
p-value	<0.001	<0.001	0.02	n.s.	<0.001	<0.001	<0.001	<0.001	n.s.	<0.01	<0.001	<0.001
<b>2h-glucose level</b>												
beta slope	0.947	0.925	0.015	0.03	-0.81	-0.72	0.12	0.11	0.13	0.167	0.82	0.75
p-value	<0.001	<0.001	n.s.	n.s.	<0.001	<0.001	n.s.	n.s.	n.s.	n.s.	<0.001	<0.001
<b>HbA1c</b>												
beta slope	0.08	0.086	0.022	0.02	-0.09	-0.11	-0.04	-0.05	-0.01	-0.03	0.03	0.024
p-value	0.04	0.036	n.s.	n.s.	0.007	<0.01	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
<b>glucose AUC</b>												
beta slope	2.22	2.07	0.67	0.705	-1.66	-1.43	-0.09	-0.08	0.56	0.45	1.3	1.19
p-value	<0.001	<0.001	0.009	<0.01	<0.001	<0.001	n.s.	n.s.	0.03	n.s.	<0.001	<0.001
<b>insulin AUC</b>												
beta slope	-0.16	0.14	-0.574	-0.424	0.149	0.037	0.57	0.53	-0.01	0.22	0.34	0.036
p-value	<0.005	<0.05	<0.001	<0.001	0.005	n.s.	<0.001	<0.001	n.s.	<0.001	<0.001	<0.001
<b>HOMA-IR</b>												
beta slope	-0.06	0.252	-0.743	-0.612	0.12	0.01	0.81	0.776	0.05	0.32	0.61	0.63
p-value	n.s.	<0.001	<0.001	<0.001	0.04	n.s.	<0.001	<0.001	n.s.	<0.001	<0.001	<0.001
<b>Matsuda index</b>												
beta slope	0.038	-0.258	0.637	0.491	-0.08	0.02	-0.68	-0.64	-0.04	-0.28	-0.5	-0.51
p-value	n.s.	<0.001	<0.001	<0.001	n.s.	n.s.	<0.001	<0.001	n.s.	<0.001	<0.001	<0.001
<b>ODI</b>												
beta slope	-0.37	-0.396	-0.057	-0.08	0.18	0.23	-0.11	-0.09	-0.18	-0.16	-0.26	-0.26
p-value	<0.001	<0.001	n.s.	n.s.	<0.001	<0.001	0.03	n.s.	0.007	<0.05	<0.001	<0.001
<b>After GH treatment</b>												
<b>fasting glucose level</b>												
beta slope	0.43	0.438	-0.07	-0.03	-0.29	-0.35	0.203	0.14	0.13	0.06	0.39	0.378
p-value	<0.001	<0.001	n.s.	n.s.	<0.001	<0.001	<0.01	n.s.	n.s.	n.s.	<0.001	<0.001
<b>2h-glucose level</b>												
beta slope	0.707	0.811	-0.24	-0.07	-0.23	-0.33	0.72	0.55	0.46	-0.14	0.82	0.75
p-value	<0.01	<0.01	n.s.	n.s.	n.s.	n.s.	<0.001	<0.01	n.s.	n.s.	<0.001	<0.001
<b>HbA1c</b>												
beta slope	0.06	0.073	0.02	0.02	0.008	0.029	0.05	0.06	0.07	0.11	0.03	0.024
p-value	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
<b>glucose AUC</b>												
beta slope	1.95	2.11	0.37	0.45	-0.59	-0.69	0.98	0.95	1.33	1.33	1.3	1.19
p-value	<0.001	<0.001	n.s.	n.s.	n.s.	n.s.	<0.01	<0.05	<0.01	<0.05	<0.001	<0.001
<b>insulin AUC</b>												
beta slope	0.39	0.357	-0.02	-0.008	-0.04	0.02	0.375	0.44	0.35	0.36	0.34	0.36
p-value	<0.001	<0.001	n.s.	n.s.	n.s.	n.s.	<0.001	<0.001	0.004**	0.02	<0.001	<0.001

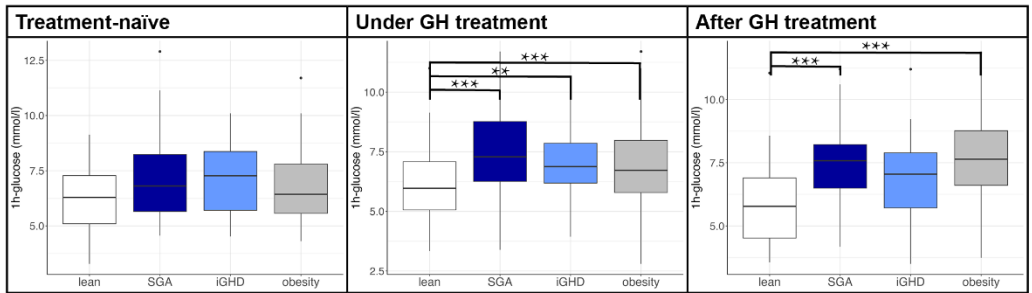
	SGA vs. lean		SGA vs. obesity		lean vs. iGHD		obesity vs. iGHD		SGA vs. iGHD		obesity vs. lean	
	unadj.	adj.	unadj.	adj.	unadj.	adj.	unadj.	adj.	unadj.	adj.	unadj.	adj.
<b>Matsuda index</b>												
beta slope	-0.44	-0.40	0.16	0.16	0.02	-0.01	-0.57	-0.65	-0.41	-0.38	-0.5	-0.52
p-value	<0.001	<0.001	n.s.	n.s.	n.s.	n.s.	<0.001	<0.001	<0.001	<0.01	<0.001	<0.001
<b>ODI</b>												
beta slope	-0.37	-0.34	-0.05	0.005	0.09	0.09	-0.21	-0.26	-0.26	-0.22	-0.26	-0.26
p-value	<0.001	<0.001	n.s.	n.s.	n.s.	n.s.	<0.01	<0.01	0.02	n.s.	<0.001	<0.001

Coefficients estimate fixed effects of a linear mixed model with the respective glucose-insulin index as dependent variable and either the treatment group alone (unadj. = unadjusted) or the treatment group, as well as age, sex, pubertal stage and BMI-SDS (adj. = adjusted) as independent variables. A mixed model with the subject ID as random effect was applied to take repeated measurements of the same participant into account. \* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$

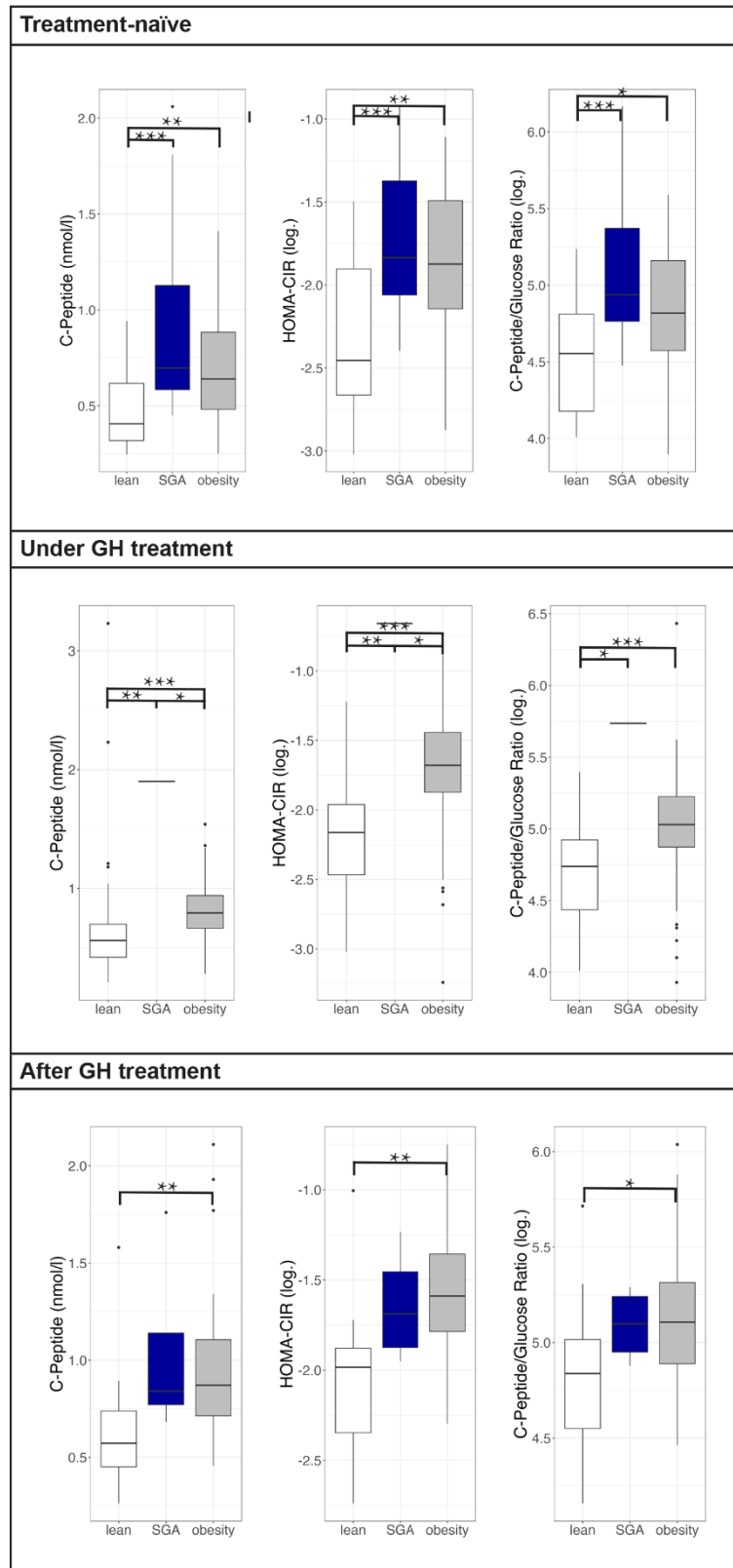
**Table S3: Longitudinal dynamics of BMI, growth factors and glucose-insulin metabolism**

	SGA						IGHD					
	during vs. before GH therapy		end vs. beginning of GH therapy		after vs. during GH therapy		during vs. before GH therapy		end vs. beginning of GH therapy		after vs. during GH therapy	
<b>Δ BMI SDS</b>												
n	33		110		40		95		219		63	
mean	-0.05		0.53		0.196		-0.016		0.299		0.08	
p-value	n.s.		<0.001		0.008		n.s.		n.s.		n.s.	
<b>Δ insulin AUC</b>												
n	2		26		14		4		33		17	
mean	0.14		0.51		-0.32		0.89		0.24		-0.21	
p-value	n.s.		<0.001		0.02		n.s.		0.03		n.s.	
<b>Δ HOMA-IR</b>												
n	3		35		17		5		39		24	
mean	0.86		0.57		-0.46		0.55		0.35		-0.43	
p-value	n.s.		<0.001		0.012		n.s.		0.02		0.01	
<b>Δ Matsuda index</b>												
n	2		26		13		4		31		16	
mean	-0.36		-0.57		0.41		-0.63		-0.33		0.27	
p-value	n.s.		<0.001		0.02		n.s.		0.02		n.s.	
<b>Δ ODI</b>												
n	2		26		13		4		31		16	
mean	-0.84		-0.29		0.12		0.66		-0.19		0.1	
p-value	n.s.		n.s.		n.s.		n.s.		n.s.		n.s.	
<b>Δ IGF1-SDS</b>												
n	12		33		5		32		76		18	
mean	1.17		-0.31		-0.87		0.614		0.132		-0.81	
p-value	0.01		n.s.		n.s.		<0.001		n.s.		<0.001	
<b>Δ IGFBP3-SDS</b>												
n	11		31		5		32		78		20	
mean	0.92		0.008		0.374		0.183		-0.264		-0.44	
p-value	0.004		n.s.		n.s.		n.s.		n.s.		n.s.	
<b>Association with change in BMI-SDS</b>												
	unadj.	adj.	unadj.	adj.	unadj.	adj.	unadj.	adj.	unadj.	adj.	unadj.	adj.
<b>Δ Insulin AUC</b>												
beta slope	0.27	0.27	0.36	-0.09	-0.33	3.59	0.36	7.4	0.155	0.21	-0.31	1.77
p-value	n.s.	n.s.	0.02	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	0.03	n.s.
<b>Δ HOMA-IR</b>												
beta slope	0.92	0.16	0.36	0.78	-0.48	2.46	0.43	0.17	0.13	1.61	-0.49	1.45
p-value	n.s.	n.s.	0.04	n.s.	0.01	n.s.	n.s.	n.s.	n.s.	n.s.	<0.001	n.s.
<b>Δ Matsuda index</b>												
beta slope	-0.84	-0.84	-0.39	-0.39	0.42	-3.91	-0.34	-6.1	-0.17	-0.85	0.43	-1.43
p-value	n.s.	n.s.	0.009	n.s.	0.02	n.s.	n.s.	n.s.	n.s.	n.s.	0.01	n.s.
<b>Δ ODI</b>												
beta slope	-1.87	-1.87	0.04	-0.86	0.12	-2.33	0.48	-2.86	-0.08	0.03	0.24	0.65
p-value	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
<b>Association with change in IGF1-SDS</b>												
<b>Δ Insulin AUC</b>												
beta slope	3.35	3.35	0.29	-0.14	-0.23	-3.45	-1.54	-1.54	-0.02	3.31	-0.05	4.02
p-value	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
<b>Δ HOMA-IR</b>												
beta slope	-2.7	-1.79	0.57	0.68	-0.48	-3.74	0.69	0.69	0.11	2.47	0.09	2.18
p-value	n.s.	n.s.	0.001	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
<b>Δ Matsuda index</b>												
beta slope	-12.02	-12.02	-0.44	-0.62	0.75	0.75	0.97	0.96	0.05	-3.25	-0.08	-4.2
p-value	n.s.	n.s.	0.013	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
<b>Δ ODI</b>												
beta slope	-25.7	-25.7	-0.19	0.74	1.03	1.03	2.75	2.75	0.03	0.31	-0.27	-2.25
p-value	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.

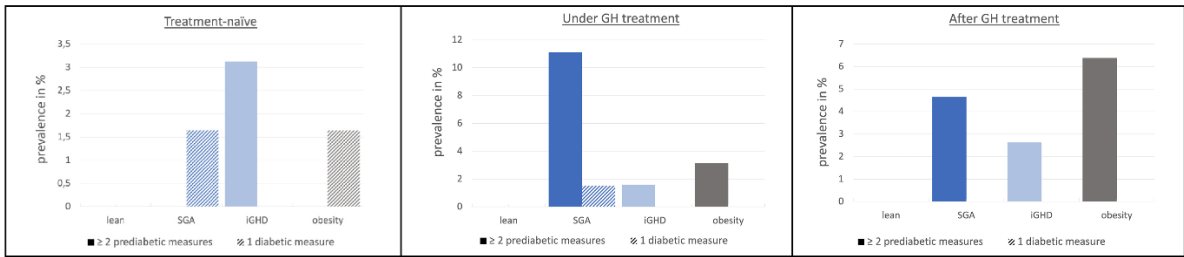
The upper part of the table summarizes changes of body composition, glucose-insulin metabolism and growth factors between different timepoints. P-values estimate whether the changes were significantly different from 0 through one-sample t-test. The lower part of the table summarizes the association of change in BMI-SDS or change in IGF1-SDS with measures of glucose-insulin metabolism. We therefore used univariate (unadj.) or multivariate (adj.) linear regression with the respective glucose-insulin index as dependent variable and BMI-SDS / IGF1-SDS as independent variables. Results were adjusted (adj.) for sex and age where indicated. Δ = delta/ difference, BMI = body mass index, IGF1 = insulin-like growth factor 1, IGHD = isolated growth hormone deficiency, n.s. = not significant, ODI = oral disposition index, SDS = standard deviation score, SGA = children born SGA



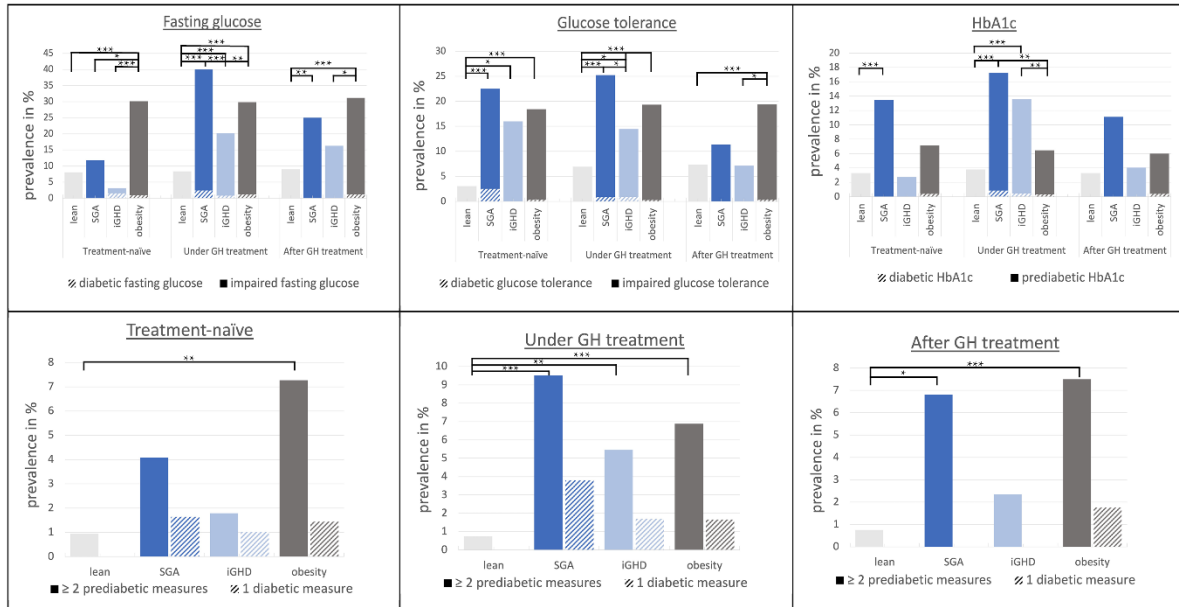
**Figure S1: 1-hour glucose at different time points in the matched cohort. \*p<0.05, \*\*p<0.01, \*\*\*p<0.001**



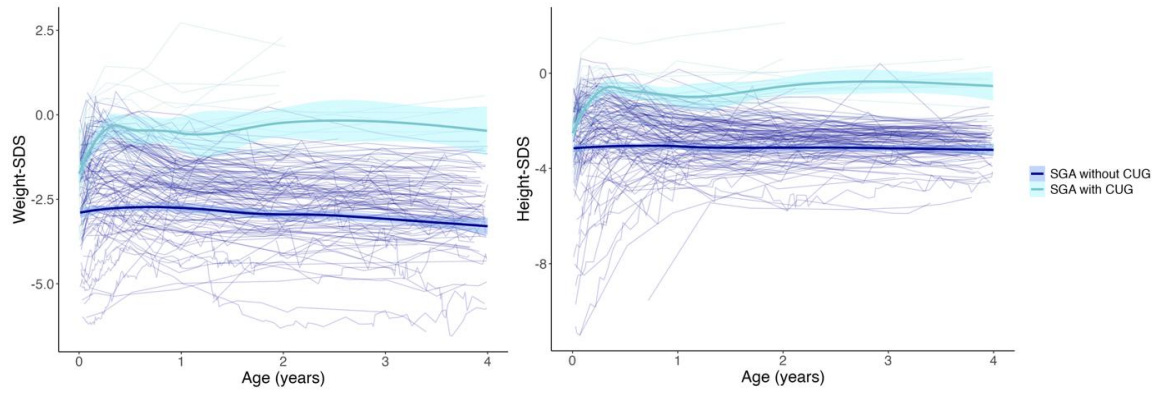
**Figure S2: Fasting C-peptide indices at different time points in the matched cohort.** Statistical differences were determined by ANOVA with Tukey post-hoc test. Of note, there was only one patient with c-peptide measures during treatment in the SGA-cohort. \* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$ .



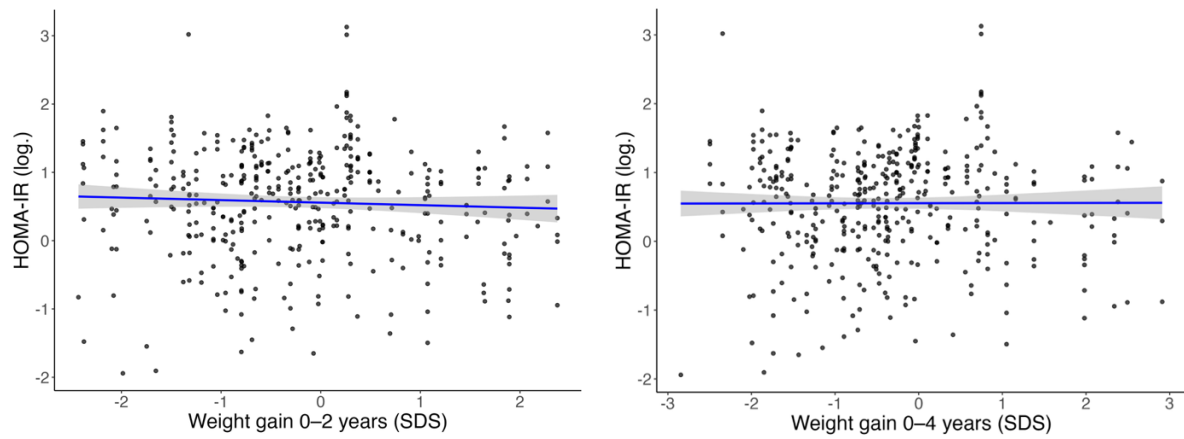
**Figure S3: Prevalence of (pre-) diabetic measures in the matched cohort.** Of note, there was no occurrence of overt diabetes (more than one diabetic measure at the same time) in any subject; no statistical differences were determined by  $\chi^2$ -test.



**Figure S4: Prevalence of (pre-) diabetic measures in the unmatched dataset.** Of note, there was no occurrence of overt diabetes (more than one diabetic measure at the same time) in any subject; Statistical differences were determined by  $\chi^2$ -test. \* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$ .



**Figure S5: Progress of weight-SDS and height-SDS of SGA patients with or without CUG in the first 4 years of life. SGA n=125, SGA-CUG n=27.**



**Figure S6: HOMA-IR of treatment-naïve SGA patients related to weight gain at 0-4 years.**  
 Linear regression analysis. Weight gain measured between weight-SDS at birth and weight-SDS of the visit closest to the age of 2 or 4 years.  
 Weight gain 0-2 years: N=115, beta-slope= -0.069, p-value= 0.31, correlation-coefficient= -0.05.  
 Weight gain 0-4 years: N=115, beta-slope= 0.004, p-value= 0.96, correlation-coefficient= 0.003.