

SDCCAG8 Obesity Alleles and Reduced Weight Loss After a Lifestyle Intervention in Overweight Children and Adolescents

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Genome-wide association analyses (GWAS) contributed to the detection of a number of single-nucleotide polymorphisms (SNPs) associated with obesity. However, little is known about the impact of the obesity-risk alleles on weight loss-related phenotypes after lifestyle interventions. A recent meta-analysis of GWAS reported five genomic loci near or in the genes *FTO*, *MC4R*, *TMEM18*, *SDCCAG8*, *TNKS/MSRA* that were associated with obesity in children and adolescents. Here, we analyzed the effect of the 10 SNPs representative of the five loci on measures of weight loss and cardiometabolic risk after a 1-year lifestyle intervention in 401 children and adolescents (mean age 10.74 years; 55.4% female; mean BMI 27.42 kg/m², mean BMI-standard deviation score (SDS) 2.37). For confirmation of one locus genotyping of three intronic SNPs in *SDCCAG8* was performed in 626 obese adults who completed the 10-week hypoenergetic diet program. Intronic variants of *SDCCAG8*, which are associated with early onset obesity, are associated with reduced weight loss after a 1-year lifestyle intervention in overweight children and adolescents even after adjusting for age, sex, baseline measurement, or multiple testing (all $P < 10^{-6}$). However, our results could not be confirmed in 626 obese adults undertaking a hypoenergetic diet intervention.

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Recent genome-wide association studies (GWAS) conducted in population-based samples assessed for BMI or in case–control samples assessed for extreme obesity led to the discovery of genetic loci relevant for body-weight regulation (reviewed in ref. 1). Taken together variants at 32 loci have been reported to be associated to BMI (ref. 2, $n = 249,796$). In addition, Meyre *et al.* (3) reported five loci to be relevant for extreme obesity ($n = 16,982$). Common to all these studies is their relative focus on adults.

Focusing on children and adolescents, a GWAS meta-analysis (ref. 4; $n = 2,258$) confirmed three known loci for obesity (*FTO*, *MC4R*, and *TMEM18*) and provided evidence for two new loci (*SDCCAG8* and *TNKS/MSRA*) with the latter finding being limited to children and adolescents. A total of 36,468 individuals (8,092 children and adolescents) were genotyped for the confirmation.

Here, we explore the effect of 10 single-nucleotide polymorphisms (SNPs) representative of the five loci on measures of weight loss and cardiometabolic risk profile change after a lifestyle intervention for obese humans. We analyzed the SNPs in 401 overweight children and adolescents completing a 1-year lifestyle intervention. In addition, we investigated the SNPs which were significantly associated with weight loss in an independent sample of 626 adults who completed a 10-week intervention with a focus on a hypoenergetic diet (NUGENOB).

Baseline characteristics and their changes of the overweight children and adolescents who completed the “Obeldicks” intervention are shown in **Table 1**. Associations of the 10 analyzed “obesity-SNPs” to weight loss-related effects are shown in **Table 2**. Genotype-dependent effects on overweight reduction as measured by BMI-standard deviation score (SDS) changes were

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Table 1 Study characteristics of 401 overweight and obese children and adolescents (mean age $\pm$ SD: 10.74 $\pm$ 2.55 years; 55.4% female; 53.9% prepubertal) who completed the obesity lifestyle intervention “Obeldicks”

Outcome	Baseline		Change after intervention (1-year follow-up)	
	Mean $\pm$ SD	1, 2, 3 quartile	Mean $\pm$ SD	1, 2, 3 quartile
BMI $\pm$ SD (kg/m ²)	27.42 $\pm$ 4.46	24.53, 26.85, 29.38	0.60 $\pm$ 1.96	−0.71, 0.48, 1.78
BMI-SDS	2.37 $\pm$ 0.48	2.05, 2.36, 2.65	0.25 $\pm$ 0.31	0.04, 0.22, 0.43
SBP (mm Hg)	116.29 $\pm$ 14.2	110.00, 111.00, 123.50	4.74 $\pm$ 15.37	−3.50, 5.00, 11.00
DBP (mm Hg)	65.94 $\pm$ 11.23	60.00, 64.00, 71.50	1.95 $\pm$ 13.03	−5.00, 0.00, 10.00
Total cholesterol (mg/dl)	171.67 $\pm$ 33.22	152.00, 169.00, 191.00	2.01 $\pm$ 27.74	−10.00, 2.50, 16.25
LDL-cholesterol (mg/dl)	105.34 $\pm$ 31.79	83.00, 101.00, 124.00	5.71 $\pm$ 25	−8.00, 4.00, 21.00
HDL-cholesterol (mg/dl)	50.72 $\pm$ 11.19	43.00, 49.50, 58.00	−0.76 $\pm$ 10.06	−6.00, −0.70, 4.90
Triglycerides (mg/dl)	106.45 $\pm$ 56.56	67.00, 96.00, 130.00	5.27 $\pm$ 53.37	−20.25, 0.00, 30.00
Glucose (mg/dl)	85.91 $\pm$ 7.79	81.00, 86.00, 91.00	−2.16 $\pm$ 29.21	−6.00, −1.00, 4.75
Mean insulin (mU/l)	15.99 $\pm$ 11.26	9.30, 13.40, 19.65	0.97 $\pm$ 11.51	−3.92, 1.00, 5.43
HOMA	3.48 $\pm$ 2.83	1.91, 2.84, 4.14	0.28 $\pm$ 2.92	−0.86, 0.22, 1.10

Positive values of changes indicate a reduction in the respective measurement; except for glucose for all general changes $P < 0.05$ applied using the appropriate statistical test; all variables in the fasting status.

BMI-SDS, BMI as a standard deviation score; DBP, diastolic blood pressure; HOMA, homeostasis model assessment; SBP, systolic blood pressure.

observable for three intronic SNPs of *SDCCAG8* (all corrected $P < 5.4 \times 10^{-5}$) even after adjustment for age, sex, baseline measurements, and multiple testing. Weight reduction was less pronounced the fewer obesity-risk alleles of *SDCCAG8* SNPs were carried (rs10926984: mean Δ BMI-SDS: 0.21 ($n_{TT} = 289$), 0.33 ($n_{GT} = 101$), 0.61 ($n_{GG} = 11$)). This effect was robust under a number of sensitivity analyses (see Methods and Procedures section), present for both sexes but more pronounced in boys (rs10926984: $\beta = 0.23$ BMI-SDS units/G allele (T being the obesity-risk allele); $P = 1.4 \times 10^{-7}$) than in girls ($\beta = 0.09$ BMI-SDS units; $P = 0.02$). Apart from this effect on BMI-SDS changes, another 10 association signals met $P \leq 0.05$ (uncorrected)—all of which were observed for the *SDCCAG8* SNPs. However, no genotype-dependent effect of the *SDCCAG8* variants was observed for the independent NUGENOB sample (all $P > 0.05$; Table 3).

We show that intronic SNPs of the obesity gene *SDCCAG8* are involved in weight loss-related effects after a 1-year lifestyle intervention in overweight children and adolescents. Overweight homozygous carriers of obesity-risk alleles lost less weight than heterozygous carriers or homozygous carriers of the other alleles. However, the effect on weight loss was not observable in a sample of obese adults who completed a 10-week hypoenergetic diet program. Apart from this finding for *SDCCAG8* we observed no weight loss-related effects for the genotypes of SNPs at the other four obesity-risk loci which underlines previous findings (5–7).

The gene *SDCCAG8* is located on the chromosome 1q43–q44 and was represented by three SNPs, which are located in introns 6, 9, and 10. *SDCCAG8* was not among the 32 loci identified in the recent large-scale BMI meta-analysis (2). However, all three SNPs showed P values between 0.034 and 0.073 (minimum $n = 123,844$) with effect alleles consistent to those reported independently from Genetic Investigation of Anthropometric Traits (GIANT) (4). Moreover, mutations in the *SDCCAG8* gene were

shown to be involved in the Bardet–Biedl syndrome (8,9). Trunkal obesity is a cardinal symptom of Bardet–Biedl syndrome. Thus, one may speculate that variants in *SDCCAG8* may have an impact on body-weight regulation in general.

Given the lack of confirmation in NUGENOB, this association—if true—may either be more easily detectable in children or may be triggered by physical activity (as part of “Obeldicks”) as compared to just diet changes (NUGENOB). Furthermore, in “Obeldicks” no hypocaloric diet was recommended in contrast to NUGENOB. Finally, the length of the intervention might also be relevant for the observed association (1 year vs. 10 weeks).

The strengths of this study are its longitudinal design, its focus on the analysis of variants previously detected by GWAS meta-analysis in (extremely) obese children and adolescents, as well as the parallel assessment of 10 variables of weight loss and cardiometabolic risk change. However, due to the relatively small sample size the findings have to be interpreted cautiously. Our sample was too small to detect moderate influences of SNP genotypes on intervention outcomes. Conversely, studies on lifestyle interventions in pediatric obesity are difficult to perform and genetic data with long-term follow-up is lacking. Acknowledging these caveats, our finding should be regarded as pilot evidence for an involvement of the *SDCCAG8* SNPs in weight loss of overweight children and adolescents. Additional studies with comparable interventions are warranted as such findings may be of greater clinical relevance than obesity-risk associations (10,11).

In summary, we found an impact of SNP genotypes of the recently identified obesity gene *SDCCAG8* on the outcome of a lifestyle intervention for overweight children and adolescents supporting the role of this gene region on body-weight regulation. With regard to the validity of our findings and the moderate study sample, subsequent replication studies in a similar setting are necessary.

Table 2 Genetic effect on weight loss and cardiometabolic risk changes in 401 overweight and obese children and adolescents who completed the obesity lifestyle intervention "Obeldicks"

	1q43-q44 (SDCCAG8)			2p25.3 (TMEM18)		8p23.1 (TNKS/MSRA)			16q12.2 (FTO)			18q21.32 (MC4R)
	rs10926984 (β ; 95% CI; P for G)	rs12145833 (β ; 95% CI; P for G)	rs2783963 (β ; 95% CI; P for T)	rs11127485 (β ; 95% CI; P for C)	rs17150703 (β ; 95% CI; P for A)	rs13278851 (β ; 95% CI; P for A)	rs516175 (β ; 95% CI; P for T)	rs1558902 (β ; 95% CI; P for A)	rs9935401 (β ; 95% CI; P for A)	rs17700144 (β ; 95% CI; P for A)		
Δ BMI-SDS	0.148 (0.091, 0.205) 5.4×10^{-7}	0.152 (0.095, 0.209) 2.9×10^{-7}	0.155 (0.098, 0.213) 1.7×10^{-7}	0.023 (-0.038, 0.084) 0.457	-0.006 (-0.071, 0.059) 0.853	-0.01 (-0.074, 0.054) 0.758	0.006 (-0.054, 0.066) 0.844	-0.017 (-0.059, 0.025) 0.428	-0.012 (-0.055, 0.03) 0.569	0.036 (-0.012, 0.084) 0.145		
Δ SBP (mm Hg)	1.619 (-0.74, 3.977) 0.178	1.719 (-0.65, 4.087) 0.154	1.738 (-0.639, 4.116) 0.151	0.952 (-1.49, 3.395) 0.444	-1.283 (-3.846, 1.28) 0.326	-1.292 (-3.808, 1.224) 0.313	-1.387 (-3.791, 1.017) 0.257	-0.57 (-2.26, 1.121) 0.508	-0.133 (-1.84, 1.573) 0.878	-0.945 (-2.881, 0.992) 0.338		
Δ DBP (mm Hg)	0.905 (-1.166, 2.975) 0.391	0.827 (-1.253, 2.907) 0.435	0.745 (-1.34, 2.83) 0.483	0.849 (-1.292, 2.991) 0.436	-0.189 (-2.439, 2.06) 0.869	-0.199 (-2.41, 2.012) 0.86	0.127 (-1.987, 2.241) 0.906	-0.181 (-1.661, 1.3) 0.811	0.18 (-1.314, 1.674) 0.813	1.368 (-0.322, 3.059) 0.112		
Δ Total cholesterol (mg/dl)	3.856 (-1.069, 8.781) 0.125	3.885 (-1.066, 8.836) 0.124	3.357 (-1.617, 8.331) 0.185	-1.875 (-7.092, 3.342) 0.48	-2.122 (-7.555, 3.31) 0.443	-2.215 (-7.549, 3.119) 0.415	-1.49 (-6.536, 3.557) 0.562	1.206 (-2.386, 4.799) 0.509	1.354 (-2.266, 4.973) 0.462	0.632 (-3.486, 4.75) 0.763		
Δ LDL- cholesterol (mg/dl)	3.534 (-0.821, 7.889) 0.111	3.588 (-0.783, 7.958) 0.107	3.345 (-1.041, 7.73) 0.134	-0.336 (-4.99, 4.319) 0.887	-1.747 (-6.587, 3.094) 0.478	-1.511 (-6.26, 3.238) 0.532	-1.056 (-5.522, 3.41) 0.709	0.893 (-2.322, 4.109) 0.585	1.185 (-2.059, 4.429) 0.697	-0.514 (-4.18, 3.151) 0.783		
Δ HDL- cholesterol (mg/dl)	-1.855 (-3.661, -0.05) 0.044	-1.813 (-3.628, 0.002) 0.05	-2.189 (-4.005, -0.373) 0.018	0.173 (-1.748, 2.093) 0.86	0.477 (-1.529, 2.482) 0.641	0.192 (-1.775, 2.159) 0.848	0.709 (-1.153, 2.571) 0.454	0.697 (-0.632, 2.026) 0.303	0.445 (-0.895, 1.785) 0.514	-0.273 (-1.789, 1.244) 0.724		
Δ Triglycerides (mg/dl)	9.357 (0.675, 18.039) 0.035	9.155 (0.443, 17.866) 0.039	8.042 (-0.718, 16.802) 0.072	-0.436 (-9.637, 8.765) 0.926	-5.801 (-15.395, 3.797) 0.235	-5.092 (-14.522, 4.337) 0.289	-3.907 (-12.863, 5.049) 0.392	-0.817 (-7.146, 5.512) 0.8	-0.409 (-6.792, 5.974) 0.9	0.621 (-6.648, 7.889) 0.867		
Δ Glucose (mg/dl)	0.455 (-5.303, 6.213) 0.877	0.463 (-5.332, 6.257) 0.875	0.349 (-5.467, 6.164) 0.906	-3.367 (-9.272, 2.538) 0.263	0.959 (-5.239, 7.156) 0.761	1.178 (-4.9, 7.257) 0.703	1.612 (-4.213, 7.438) 0.587	-1.139 (-5.217, 2.939) 0.583	-1.251 (-5.364, 2.863) 0.55	-2.107 (-6.749, 2.535) 0.373		
Δ Insulin (mU/l)	2.112 (0.144, 4.081) 0.036	2.649 (0.676, 4.622) 0.009	2.387 (0.409, 4.366) 0.018	0.927 (-1.07, 2.924) 0.362	-0.806 (-2.884, 1.273) 0.446	-0.737 (-2.774, 1.3) 0.477	-0.58 (-2.507, 1.347) 0.554	-0.407 (-1.822, 1.008) 0.611	-0.417 (-1.992, 1.158) 0.603			
Δ HOMA	0.449 (-0.011, 0.909) 0.056	0.572 (0.11, 1.033) 0.015	0.513 (0.05, 0.976) 0.03	0.081 (-0.379, 0.54) 0.731	-0.217 (-0.695, 0.261) 0.372	-0.19 (-0.658, 0.278) 0.425	-0.149 (-0.597, 0.299) 0.513	-0.038 (-0.357, 0.291) 0.842	-0.099 (-0.46, 0.262) 0.591			

For each SNP effect sizes (β estimators), their 95% confidence intervals and the P values are listed. The β estimators were derived from linear regression models (additive mode of inheritance adjustment for age (linear), sex, and the respective baseline measurement). Results that were significant after multiple testing corrections are highlighted in bold. Positive values the effect sized for the changes (Δ) indicate a reduction in the respective measurement; all variables in the fasting status.

BMI-SDS, BMI as a standard deviation score; CI, confidence interval; DBP, diastolic blood pressure; HOMA, homeostasis model assessment; HDL, high-density lipoprotein; LDL, high-density lipoprotein; SBP, systolic blood pressure.

Table 3 Genotype-specific effects of SDCCAG8 SNP genotypes on response to the obesity lifestyle intervention “Obeldicks” in 401 overweight and obese children and adolescents as compared to the response to the 10-week dietary weight loss intervention NUGENOB in 626 obese adults

Study	Outcome (changes)	rs10926984			rs12145833			rs2783963		
		GT	GG	P value	GT	GG	P value	CT	TT	P value
		β_{GT} (95% CI)	β_{GG} (95% CI)		β_{GT} (95% CI)	β_{GG} (95% CI)		β_{CT} (95% CI)	β_{TT} (95% CI)	
“Obeldicks”	Δ BMI-SDS ^{a,b}	0.12 (0.05,0.19)	0.40 (0.22,0.58)	1.01×10^{-6}	0.13 (0.06,0.19)	0.40 (0.22,0.58)	7.49×10^{-7}	0.13 (0.05,0.19)	0.39 (0.25,0.61)	2.95×10^{-7}
NUGENOB	Δ BMI ^a (kg/m ²)	0.09 (-0.12,0.29)	-0.05 (-0.67,0.57)	0.68	0.09 (-0.11,0.30)	-0.06 (-0.68,0.56)	0.66	0.06 (-0.14,0.26)	0.03 (-0.65,0.71)	0.83

BMI-SDS, BMI as a standard deviation score; CI, confidence interval.

^aEstimates for BMI-SDS and BMI change are derived from a linear regression model including genotype, age (linear), and sex; P values are based on a χ^2 test for genotypic both being equal to 0.

^bFor the comparability to the NUGENOB data where BMI changes in adults were reported it is important to know that the standard deviation in NUGENOB BMI changes was -1 (thus BMI-SDS changes and BMI changes are roughly comparable).

METHODS AND PROCEDURES

Study subjects and lifestyle intervention

A total of 401 unrelated overweight children and adolescents (mean age $\pm$ SD: 10.74 ± 2.55 years; 55.4% female; 53.9% prepubertal) were ascertained. None of the children suffered from endocrine disorders including type 2 diabetes mellitus, familial hyperlipidemia, syndromal disorders, and none were on medications. All completed consecutively in the 1-year outpatient lifestyle intervention “Obeldicks” (see details in refs. (12,13)). Briefly, “Obeldicks” is based on physical exercise, nutrition education, and behavior therapy including individual psychological care of the child and his or her family. The nutritional course was based on a fat- and sugar-reduced diet as compared to the every-day nutrition of German children: The diet contained 30E% fat, 15E% proteins, and 55E% carbohydrates including 5E% sugar.

The association of SDCCAG8 SNPs to weight loss was followed-up in up to 626 obese (BMI ≥ 30 kg/m²) adults who completed the 10-week hypoenergetic diet program NUGENOB (see details in refs. 6,14,15); Nutrient-gene interaction in human obesity: implication for dietary guidelines; www.nugenob.org). Briefly, the diet consistent of either a low- or high-fat content. Common to both diets was that daily energy intake should equal the estimated daily energy requirement (measured basal metabolic rate multiplied by 1.3) minus 600 kcal.

Both studies including their protocols for subject recruitment and assessment and the informed consent for participants were reviewed and approved by ethics committees or local institutional review boards and conducted in accordance with The Declaration of Helsinki. Written informed consent was obtained from all subjects and, in case of minors, their parents.

Anthropometric and cardiometabolic measures

Overweight in children and adolescents was defined by a BMI >90th percentile for German children (16) according to the definition of International Task Force of childhood obesity. The degree of overweight was quantified as BMI-SDS (17). Systolic and diastolic blood pressure was measured using a validated protocol (12,13). Cardiometabolic risk measures were assessed in the fasting state commercially available test kits (Roche Diagnostics, Mannheim, Germany; Boehringer, Mannheim, Germany; Ortho Clinical Diagnostics, Neckargemuend, Germany; Abbott, Wiesbaden, Germany). Intra- and interassay variations were <5%. Homeostasis model assessment was used to describe the degree of insulin resistance (18).

Details on anthropometric and cardiometabolic measures in NUGENOB are described in refs. (6,14,15). In NUGENOB, we focused on BMI changes only to replicate the SDCCAG8 findings for Δ BMI-SDS in children and adolescents.

For both samples changes of measurements (Δ) were defined as differences from baseline such that positive values indicate a reduction in the respective outcome.

SNP selection and genetic analyses

We selected all 10 SNP from ref. (4). SNP genotyping in “Obeldicks” was performed by the MALDI-TOF mass spectrometry-based iPLEX Gold assay (4) with a well-established assay with a discordance rate <0.5% in routine duplicates whereas in NUGENOB TaqMan SNP Assays were used (Applied Biosystems, Foster City, CA). Further details on genotyping quality control measures were previously provided (4,6,14,15); for example, we observed no evidence for departure from Hardy-Weinberg equilibrium (all $P > 0.01$).

Statistical analyses

In “Obeldicks,” we measured 10 variables of weight loss and cardiometabolic risk change (Table 2). As primary analysis, we performed standard linear regression analyses for each variable (changes after the intervention) with genotype (under an additive mode of inheritance) as predictor while adjusting for age (linear), sex, and the respective baseline measurement. To address multiple testing, we

applied a Bonferroni-corrected $\alpha_{BF} = 0.05/100 = 5 \times 10^{-4}$ (10 variables and 10 SNPs). This procedure is conservative as both the variables and the SNPs at the same locus are correlated (for *SDCCAG8* pairwise r^2 ranged between 0.93 and 0.99). As sensitivity analyses, we checked the robustness of the association of the *SDCCAG8* SNPs by performing sex-stratified analyses, analyses with two estimators for genotypic effects, robust linear regression to check the outliers impact and analyses altering the adjustment set (data not shown). In NUGENOB, we focused on BMI changes for the *SDCCAG8* SNPs. Unless stated otherwise, all reported *P* values are nominal, two-sided, and not adjusted for multiple testing. We report β effect size estimators with 95% confidence intervals.

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DISCLOSURE

The authors declared no conflict of interest.

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REFERENCES

- Hebebrand J, Volckmar AL, Knoll N, Hinney A. Chipping away the ‘missing heritability’: GIANT steps forward in the molecular elucidation of obesity - but still lots to go. *Obes Facts* 2010;3:294–303.
- Speliotes EK, Willer CJ, Berndt SI *et al.*; MAGIC; Procardis Consortium. Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. *Nat Genet* 2010;42:937–948.
- Meyre D, Delplanque J, Chèvre JC *et al.* Genome-wide association study for early-onset and morbid adult obesity identifies three new risk loci in European populations. *Nat Genet* 2009;41:157–159.
- Scherag A, Dina C, Hinney A *et al.* Two new Loci for body-weight regulation identified in a joint analysis of genome-wide association studies for early-onset extreme obesity in French and German study groups. *PLoS Genet* 2010;6:e1000916.
- Müller TD, Hinney A, Scherag A *et al.* Fat mass and obesity associated gene (FTO): no significant association of variant rs9939609 with weight loss in a lifestyle intervention and lipid metabolism markers in German obese children and adolescents. *BMC Med Genet* 2008;9:85.
- Sørensen TI, Boutin P, Taylor MA *et al.*; NUGENOB Consortium. Genetic polymorphisms and weight loss in obesity: a randomised trial of hypo-energetic high-versus low-fat diets. *PLoS Clin Trials* 2006;1:e12.
- Vogel CI, Boes T, Reinehr T *et al.* Common variants near MC4R: exploring gender effects in overweight and obese children and adolescents participating in a lifestyle intervention. *Obes Facts* 2011;4:67–75.
- Janssen S, Ramaswami G, Davis EE *et al.* Mutation analysis in Bardet-Biedl syndrome by DNA pooling and massively parallel resequencing in 105 individuals. *Hum Genet* 2011;129:79–90.
- Otto EA, Hurd TW, Airik R *et al.* Candidate exome capture identifies mutation of *SDCCAG8* as the cause of a retinal-renal ciliopathy. *Nat Genet* 2010;42:840–850.
- McCarthy MI. Genomics, type 2 diabetes, and obesity. *N Engl J Med* 2010;363:2339–2350.
- Reinehr T, Hebebrand J, Friedel S *et al.* Lifestyle intervention in obese children with variations in the melanocortin 4 receptor gene. *Obesity (Silver Spring)* 2009;17:382–389.
- Reinehr T, de Sousa G, Toschke AM, Andler W. Long-term follow-up of cardiovascular disease risk factors in children after an obesity intervention. *Am J Clin Nutr* 2006;84:490–496.
- Reinehr T, Temmesfeld M, Kersting M, de Sousa G, Toschke AM. Four-year follow-up of children and adolescents participating in an obesity intervention program. *Int J Obes (Lond)* 2007;31:1074–1077.
- Grau K, Hansen T, Holst C *et al.* Macronutrient-specific effect of FTO rs9939609 in response to a 10-week randomized hypo-energetic diet among obese Europeans. *Int J Obes (Lond)* 2009;33:1227–1234.
- Grau K, Cauchi S, Holst C *et al.* TCF7L2 rs7903146-macronutrient interaction in obese individuals’ responses to a 10-wk randomized hypoenergetic diet. *Am J Clin Nutr* 2010;91:472–479.
- Kromeyer-Hauschild K, Wabitsch M, Kunze D *et al.* Perzentilen für den Body Mass Index für das Kinder- und Jugendalter unter Heranziehung verschiedener deutscher Stichproben. *Monatsschr Kinderheilkd* 2001;149:807–818.
- Cole TJ, Bellizzi MC, Flegal KM, Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: international survey. *BMJ* 2000;320:1240–1243.
- Matthews DR, Hosker JP, Rudenski AS *et al.* Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985;28:412–419.