Genetic Obesity Disorders: Body Mass Index Trajectories and Age of Onset of Obesity Compared with Children with Obesity from the General Population

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Objective We sought to assess body mass index trajectories of children with genetic obesity to identify optimal early age of onset of obesity (AoO) cut-offs for genetic screening.

Study design This longitudinal, observational study included growth measurements from birth onward of children with nonsyndromic and syndromic genetic obesity and control children with obesity from a population-based cohort. Diagnostic performance of AoO was evaluated.

Results We describe the body mass index trajectories of 62 children with genetic obesity (29 nonsyndromic, 33 syndromic) and 298 controls. Median AoO was 1.2 years in nonsyndromic genetic obesity (0.4 and 0.6 years in biallelic *LEPR* and *MC4R*; 1.7 in heterozygous *MC4R*); 2.0 years in syndromic genetic obesity (0.9, 2.3, 4.3, and 6.8 years in pseudohypoparathyroidism, Bardet-Biedl syndrome, 16p11.2del syndrome, and Temple syndrome, respectively); and 3.8 years in controls. The optimal AoO cut-off was ≤3.9 years (sensitivity, 0.83; specificity, 0.49; area under the curve, 0.79; $P < .001$) for nonsyndromic and ≤4.7 years (sensitivity, 0.82; specificity, 0.37; area under the curve, 0.68; $P = .001$) for syndromic genetic obesity.

Conclusions Optimal AoO cut-off as single parameter to determine which children should undergo genetic testing was ≤3.9 years. In case of older AoO, additional features indicative of genetic obesity should be present to warrant genetic testing. Optimal cut-offs might differ across different races and ethnicities. *(J Pediatr 2023;262:113619)*.

A >10-fold increase in pediatric obesity over the last four decades has resulted in 124 million (7%) children with obesity worldwide.[1] The global prevalence of overweight or obesity in children aged <5 years is predicted to increase to 11% by 2025.[2] In 2%-7% of children with obesity, genetic obesity disorders can be identified.[3-5] Diagnostic yield can increase further by screening high-risk populations using broad genetic tests.[6] Early age of onset of obesity (AoO) is a cardinal feature of genetic obesity.[3,4] Current international guidelines suggests genetic screening in selected cases with an age of onset of severe obesity (AoO_{severe}) of <5 years.[4,7] Clinical practice shows that it can be difficult to distinguish these patients from children with childhood-onset obesity without underlying genetic causes.[8] Prevalence estimations based on population-level genetic data suggest that the majority of patients with genetic obesity are currently not identified.[9] Moreover, only a small minority of children in whom genetic testing is indicated by the guidelines actually undergo testing.[10] Diagnosing patients with genetic obesity is vital for patient-tailored treatment, because novel medications have become available for patients with genetic defects in the leptin-melanocortin pathway, the hypothalamic pathway that regulates satiety and energy expenditure.[11,12]

Genetic obesity comprises a heterogeneous group of rare disorders with 2 distinct subgroups.[4] In nonsyndromic genetic obesity, severe early-onset obesity is the main phenotypic feature. In syndromic obesity, developmental delay, intellectual disability, or multiple congenital anomalies are typically present. For the most common syndromic obesity disorder, Prader-Willi syndrome, it is well-described that the weight increase starts between 2.0 and 4.5 years; therefore, Prader-Willi syndrome will not be further discussed in this article. For other genetic obesity disorders, however, these trajectories are not yet described in detail.[3]

AoO	Age of onset of obesity
AoO_{severe}	Age of onset of severe obesity
BMI	Body mass index
PHP	Pseudohypoparathyroidism
SDS	SD score

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In addition, the guideline cut-off AoO of <5 years does not distinguish between nonsyndromic and syndromic genetic obesity and has not been clinically validated. Several recent pediatric studies report a younger AoO, especially in nonsyndromic genetic obesity.[8,13,14] Moreover, the ideal cut-off might change because early-onset obesity is becoming more prevalent.[15] Therefore, more insight is needed into the body mass index (BMI) trajectories of children with genetic obesity and optimal cut-offs of AoO and obesity severity to determine the indication for genetic testing.

The primary aim of this study was to present BMI trajectories and AoO of children with genetic obesity. The secondary aim was to identify the optimal diagnostic performance cut-off for BMI trajectory characteristics (AoO, AoO_{severe}, and BMI at yearly age bins) by comparing these characteristics between children diagnosed with genetic obesity and controls, ie children from the general population who developed obesity at <10 years of age.

Methods

For this longitudinal, observational study, we used patient data from the Dutch center of expertise for genetic obesity, a collaboration between the departments of Pediatrics and Internal Medicine of Obesity Center CGG (Erasmus MC, Rotterdam, the Netherlands) and the department of Human Genetics (Amsterdam UMC, Amsterdam, the Netherlands). For control comparison, data from The Generation R Study (Rotterdam, the Netherlands) were used.[16] All parents/caretakers of children ≤16 years gave written informed consent; additionally, children ≥12 years gave written informed consent and those <12 years gave verbal consent. Both studies were approved by the medical ethics committee of Erasmus MC.

Patients and Control Sample

Patients (0-18 years of age), referred to Obesity Center CGG for diagnostic evaluation and/or multidisciplinary treatment advice, underwent an extensive diagnostic work-up as described in detail previously (https://doi.org/10.1371/journal.pone.0232990.s001).[6] This work-up included extensive genetic testing (gene panel analysis or whole exome sequencing) by ISO15189-accredited academic genetic diagnostics laboratories for the clinically most important genetic obesity disorders as mentioned in the guideline, such as *LEP*, *LEPR*, *POMC*, *PCSK1*, *MC4R*, *SIM1*, *ALMS1*, and *GNAS*.[5] Variants were classified following the American College of Medical Genetics and Genomics guideline.[17] Genetic obesity was diagnosed when a pathogenic or likely pathogenic variant or copy number variation was identified that matched the patient's clinical phenotype. The genetic diagnosis was confirmed by a clinical geneticist. For this report, we included patients with diagnosed genetic obesity referred from February 2015 to March 2020. Exclusion criteria were declining informed consent or genetic testing, or lack of growth measurements (<2 weight/height measurements) (**Supplementary Figure S1**). Patients were subclassified into nonsyndromic (including biallelic or heterozygous pathogenic variants) and syndromic genetic obesity. To compare BMI trajectories with a control sample of children with multifactorial obesity unlikely to have genetic obesity, we included children from the Generation R Study, a population-based study in the Rotterdam area with follow-up from fetal life onwards.[16] For this report, we selected children who had sustained obesity (≥2 consecutive measurements) to avoid including children in whom obesity was present due to measurement errors as an example. We also excluded control children with a BMI SD score (SDS) of >4 SDS (n = 25), because these children might have other specific underlying causes for their obesity. This yielded 298 of 8896 control children (3.3%) with obesity (**Figure 1**), which is in line with obesity prevalence between age 2 and 12 years in the Dutch general population (2.9%).[18]

Assessment of Obesity and AoO

For all children, we asked for consent to retrieve anthropometric measurements of the Dutch nationwide screening program which all children visit at ages 0.75, 2, 3, 5, 8, 11, 14, months, and 3 years of age. Additionally, for patients with genetic obesity, we collected measurements of all previous contacts with healthcare professionals before referral, including general practitioners, pediatricians, dieticians, and physical therapists. During follow-up at our center, weight and height were measured in 0.1-cm increments while lightly clothed and standing without shoes. Control subjects were measured similarly at ages 6 and 10 years. We calculated BMI and age- and sex-specific SDS using Dutch references.[19] We used International Obesity Task Force cut-offs to define obesity and severe obesity (BMI above the age- and sex-specific cut-offs corresponding with an adult BMI of ≥30 and ≥35 kg/m^2, respectively).[20] Because these cut-offs are only validated for children ≥2 years of age, we used the World Health Organization definition of obesity (weight-for-height SDS of ≥3.0) for children <2 years of age; for this age group, there is no accepted definition of severe obesity.[2] We defined AoO as the age at which the obesity cut-off was first crossed. This metric was calculated by linear interpolation between the last measurement at which the child did not have obesity and the first measurement at which the child had obesity. We adopted this strategy to mimic daily clinical practice wherein individual growth measurements are plotted over reference charts and subsequently connected to yield an individual trajectory.

Statistical Analyses

Data are presented as mean ± SD or median (IQR). Differences in baseline characteristics and AoO between patients and controls were analyzed using independent sample *t* tests, Mann-Whitney *U* tests, and χ^2 tests. We used receiver operating characteristics curve analysis to investigate diagnostic performance (sensitivity, specificity, positive likelihood ratio) of AoO and AoO_{severe}. We defined optimal cut-off based

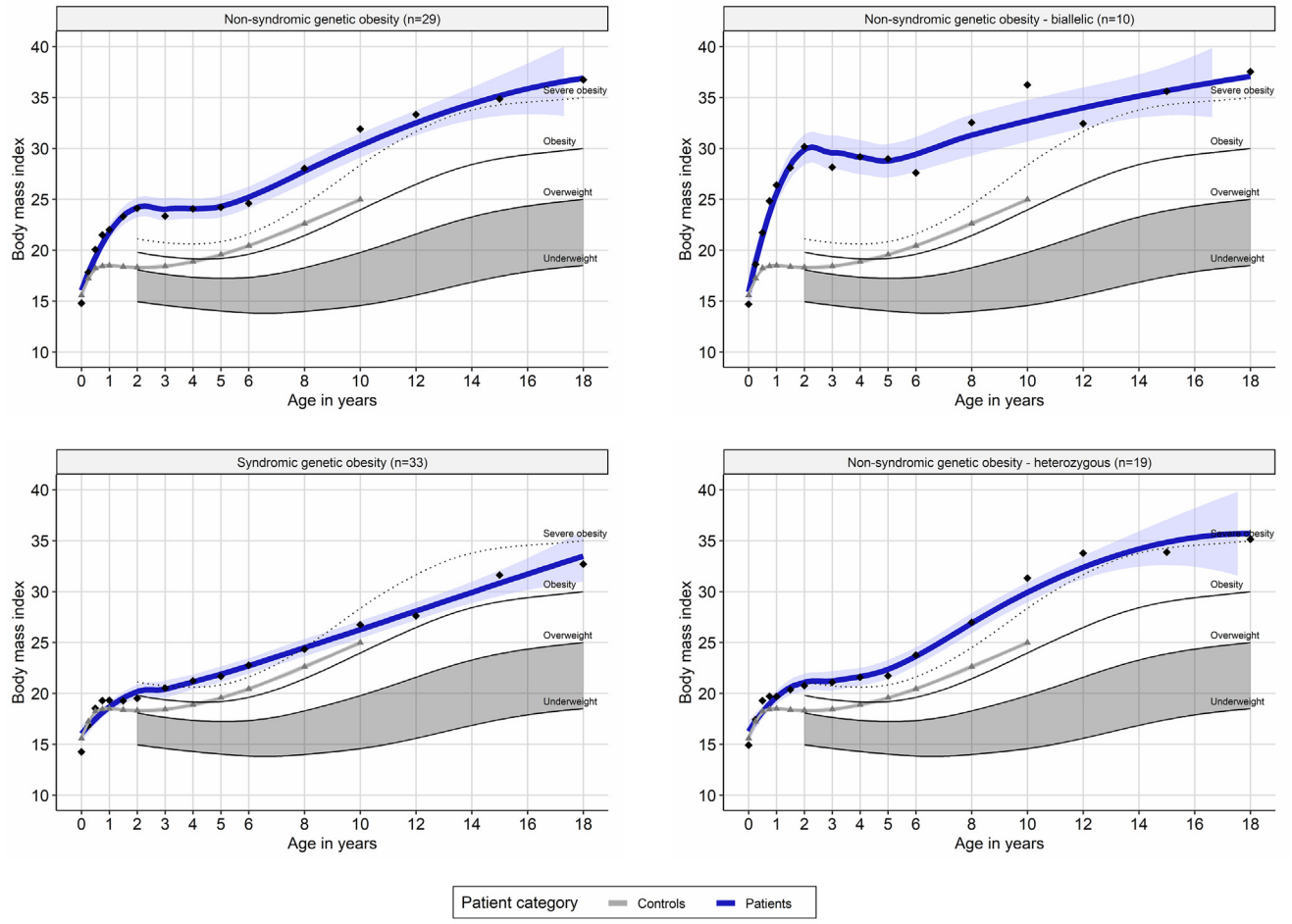

Figure 1. BMI trajectories in patients with and without genetic obesity disorders. Childhood BMI are presented for patients with nonsyndromic (top left) and syndromic (bottom left) genetic obesity disorders, and for biallelic (top right) and heterozygous (bottom right) nonsyndromic genetic obesity separately. The dots indicate the mean values per age bin; the line indicates the locally estimated scatterplot smoothing regression line; the shaded areas around the regression line indicate the 95% CI. The female International Obesity Task Force cut-offs are presented as reference, with the grey shaded area indicating normal weight.

on Youden's *J*. Because the aim of using AoO as diagnostic screening tool would be to minimize the number of patients with genetic obesity who would erroneously not be genetically screened (false negatives), we defined optimal cut-off as the value with a sensitivity of ≥0.80 with the highest Youden's *J*. We calculated posttest probability of genetic obesity and number needed to test to identify one diagnosis based on a pretest genetic obesity prevalence of 2%-7%.[3-5] To visualize BMI and BMI SDS trajectories, we categorized measurements analogous to previous studies into age bins: 0 years (range 0.000-0.125), 0.25 years (range 0.125-0.375), 0.5 years (range 0.375-0.625), 1 year (range 0.625-1.250), 1.5 years (range 1.25-1.75), 2 years (range 1.75-2.50), 3 years (range 2.5-3.5), 4 years (range 3.5-4.5), 5 years (range 4.5-5.5), 6 years (range 5.5-7.0), 8 years (range 7.0-9.0), 10 years (range 9.0-11.0), 12 years (range 11.0-13.5), 15 years (range 13.5-16.5), and 18 years (range 16.5-18.5).[8,21] Furthermore, we calculated ΔBMI and ΔBMI SDS expressed as yearly changes. When a child had multiple measurements available, we calculated the mean for that bin. If a child did not have a measurement available for a given age bin, but had measurements available for the previous and following age bin, we calculated the missing data point by linear interpolation. For each age bin, a receiver operating characteristics curve analysis was performed on raw BMI values to evaluate the diagnostic performance of obesity severity. We used R version 4.0.0 (R Core Team, Vienna, Austria) and SPSS version 28 (IBM, Armonk, NY) with a 2-sided α of 0.05.

Results

Characteristics of the Study Samples

We included 62 patients with genetic obesity: 29 nonsyndromic (of whom 10 had biallelic and 19 heterozygous variants) and 33 syndromic, and 298 controls with obesity (**Supplementary Figure S1**). Individual-level clinical and genetic data are presented in **Supplementary Table S1**. Baseline characteristics are summarized in **Table I**. For

Table I. Group characteristics, anthropometrics, and AoO of the study populations

	Patients with genetic obesity			Control population
	All patients (n = 62)	Nonsyndromic genetic obesity (n = 29)	Syndromic genetic obesity (n = 33)	Children with obesity before age 11 years from the general population (n = 298)
Characteristics at first visit to Obesity Center CGG (patients)/last Generation R Study visit (controls)				
Sex, female	39 (63)	18 (62)	21 (64)	173 (58)
Age, years	10.5 (6.9 to 14.8)	11.5 (6.8 to 14.3)	9.3 (6.4 to 14.8)	10.5 (9.5 to 13.6)
Socioeconomic status z-score	0.0 (–1.0 to 0.6)*	−0.0 (–1.8 to 0.6)†	0.2 (–0.5 to 0.7)*	−1.2 (–2.5 to −0.7)‡
Height SDS	0.55 ± 1.46	1.26 ± 1.30	−0.07 ± 1.32	0.52 ± 1.01
Weight SDS	3.17 ± 1.49	4.05 ± 1.16	2.40 ± 1.32	2.42 ± 1.35
BMI SDS	3.13 ± 1.16	3.66 ± 1.13	2.68 ± 0.98	2.36 ± 0.51
AoO and AoO_{severe}				
AoO, years	1.5 (0.7 to 3.9)*	1.2 (0.6 to 3.8)*	2.0 (0.9 to 4.2)*	3.8 (2.3 to 6.2)
AoO_{severe}, years	1.4 (0.6 to 4.4)	1.1 (0.6 to 4.9)	1.6 (0.8 to 3.0)	2.6 (1.0 to 4.1)

NA, not applicable.
Values are number (%), median (IQR), or mean ± SD.
AoO_{severe} was available for n = 28 patients with nonsyndromic genetic obesity, n = 25 patients with syndromic genetic obesity and n = 157 control subjects without genetic obesity.
*$P < .001$ compared with control population.
†$P < .01$ compared with control population.
‡Unknown in n = 16 control children.

patients with genetic obesity, the mean BMI SDS was 3.1 ± 1.2, indicating severe obesity. A median of 21 BMI measurements (IQR, 18-27) per patient were available. For controls, a median of 9 BMI measurements (IQR, 7-11) per child were available.

BMI Trajectories

BMI trajectories are presented in Figure 1. Patients with nonsyndromic genetic obesity had similar weight-for height SDS at birth compared with controls, followed by rapidly increasing BMI within the first 2 years of life and significantly higher mean BMI SDS from age 0.5 year onward. The rapid increase of BMI was more pronounced in patients with biallelic than heterozygous variants (Figure 1). Patients with syndromic genetic obesity had a lower mean weight-for height SDS at birth compared with controls, followed by gradually increasing BMI until 5-6 years of age. Their mean BMI SDS was significantly higher than controls between ages 3-5 years only. Disorder-specific BMI trajectories are presented in Figure 2. Notably, a distinction was seen between syndromic genetic obesity disorders with rapid increase in BMI within the first 2 years of life similar to nonsyndromic genetic obesity (eg, Bardet-Biedl syndrome, pseudohypoparathyroidism [PHP] types 1a and 1b), and syndromes with low weight-for height SDS at birth and gradual BMI increase during childhood (eg, 16p11.2 deletion syndrome, Temple syndrome).

AoO

The AoO was significantly lower in both nonsyndromic and syndromic genetic obesity vs controls (both $P < .01$) and was below the guideline cut-off of <5 years in all subgroups, including controls (Table I). Patients with nonsyndromic genetic obesity with biallelic variants had a lower AoO compared with patients with heterozygous variants (median, 0.6 years [IQR, 0.4-0.7 years] vs 2.3 years [IQR, 1.1-4.3 years]; $P < .001$). Both subgroups had a younger AoO compared with controls (both $P < .01$). Disorder-specific AoO is presented in Figure 3. The youngest AoO was found in patients with biallelic nonsyndromic genetic obesity and PHP. Patients with other syndromic genetic obesity disorders had variable AoO ranging from 1 to 14 years of age.

Predictive Value of BMI Trajectory Characteristics

Using AoO as a single predictor to discriminate between patients vs controls yielded an AUC of 0.79 for nonsyndromic (95% CI, 0.69-0.88; $P < .001$) and 0.68 for syndromic genetic obesity (95% CI, 0.56.79; $P = .001$). The optimal AoO cut-off for nonsyndromic genetic obesity was ≤3.9 years of age. Compared with the guideline cut-off (<5 years), this yielded lower sensitivity, but higher specificity and positive likelihood ratio (Table II). The optimal AoO cut-off for syndromic genetic obesity was ≤4.7 years of age. Compared with the guideline cut-off (<5 years), this yielded the same sensitivity and slightly higher specificity (and positive likelihood ratio (Table II). AoO_{severe} showed worse performance (Supplementary Results). The severity of obesity using BMI as single predictor yielded a good diagnostic performance for nonsyndromic genetic obesity from age 0.5 year upward (AUCs, 0.73-0.90; all $P < .001$) and moderate performance for syndromic genetic obesity between ages 1 and 6 years (AUC, 0.61-0.72; $P < .001$-0.046) (Table III). Corresponding optimal BMI cut-offs per age bin are presented in Table III. Changes in growth charts characteristics (ΔBMI, ΔBMI SDS, Δweight-for-height SDS) showed worse performance (data not shown).

Discussion

This study presents childhood BMI trajectories and AoO in 62 pediatric patients with nonsyndromic and syndromic genetic obesity disorders compared with 298 children with childhood-onset obesity sampled from the general

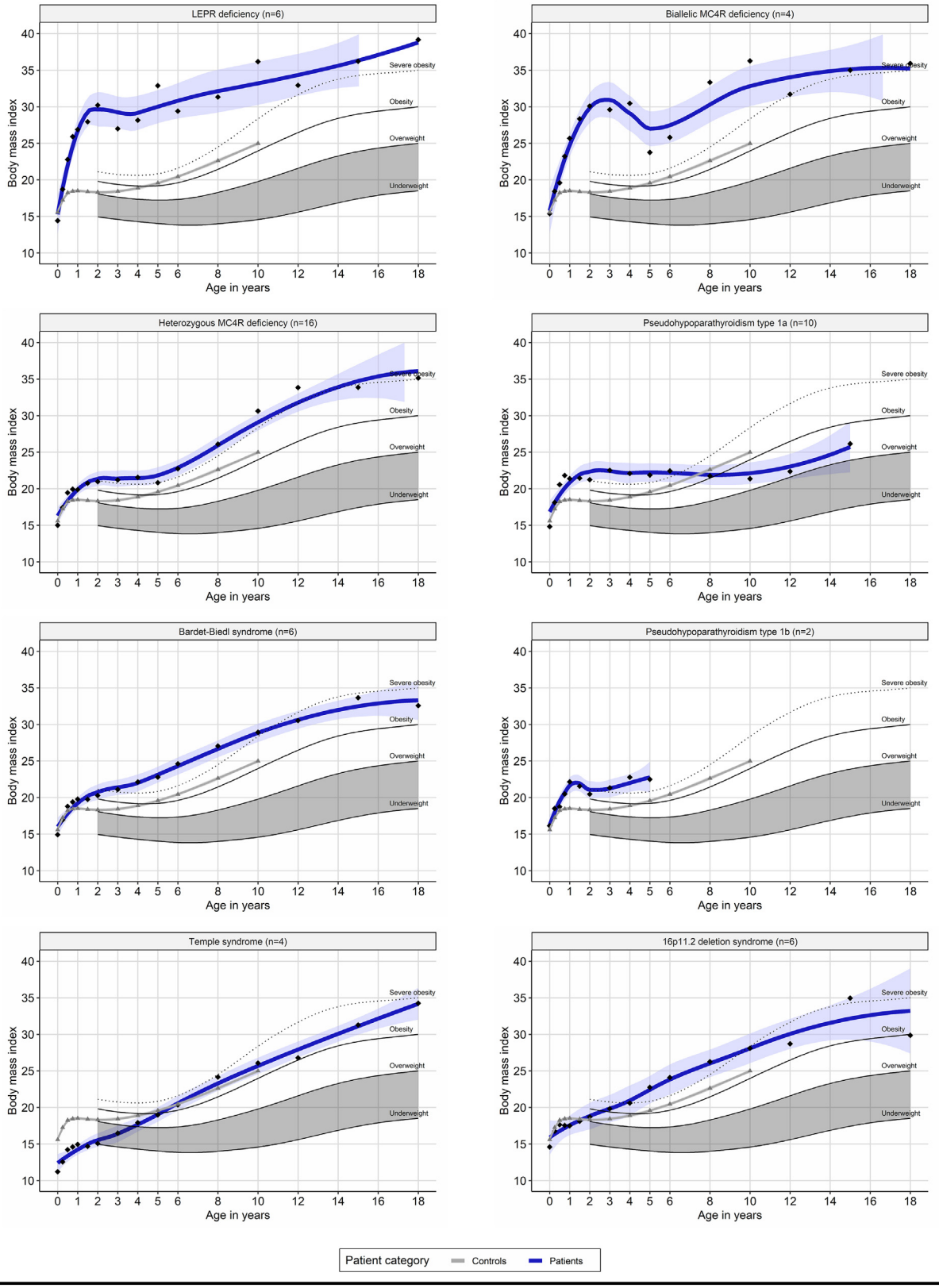

Figure 2. BMI trajectories in specific genetic obesity disorders. Childhood BMI trajectories are presented for patients specific genetic obesity disorders. The dots indicate the mean values per age bin; the line indicates the locally estimated scatterplot smoothing regression line; the shaded areas around the regression line indicate the 95% CI. The female International Obesity Task Force cut-offs are presented as reference, with the grey shaded area indicating normal weight.

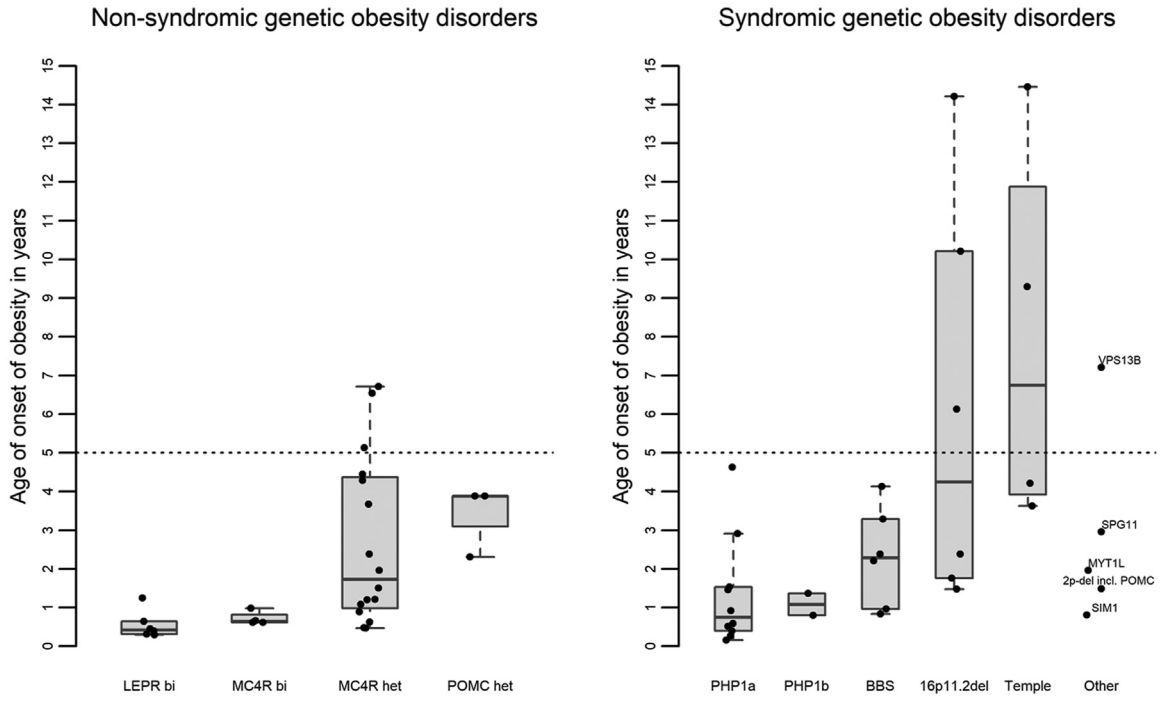

Figure 3. Individual ages of onset of obesity in genetic obesity disorders. Individual AoO of obesity are summarized on individual patient and disorder level. The dots represent the exact AoO of obesity of each patient. The box plot indicates the median and IQR of AoO of obesity for the specific genetic obesity disorder. The dotted horizontal line represent the Endocrine Society guideline's cut-off age of 5 years. *bi*, biallelic; het, heterozygous; *LEPR*, leptin receptor; *MC4R*, melanocortin 4 receptor; *POMC*, pro-opiomelanocortin; *PCSK1*, proprotein convertase subtilisin/kexin type 1; *PHP1a*, pseudohypoparathyroidism type 1a; *BBS*, Bardet-Biedl syndrome; *16p11.2del*, 16p11.2 deletion syndrome; *Temple*, Temple syndrome; *VPS13 B*, vacuolar protein sorting 13 homolog b (leading to Cohen syndrome); *SPG11*, spastic paraplegia 11; *MYT1L*, myelin transcription factor 1 like; *2p-del incl*., deletion of the short arm of chromosome 2 including; *SIM1*, single-minded homolog 1; *PHP1b*, pseudohypoparathyroidism type 1b.

population. The BMI trajectories show a clear distinction between patients subgroups and controls. Children with biallelic nonsyndromic genetic obesity showed a rapid increase in BMI and development of severe obesity in the first year of life, whereas children with heterozygous obesity-associated variants developed obesity after age 1 year, but well before age 5 years. In syndromic genetic obesity, BMI trajectories were more variable and disorder-specific. In children with obesity from the general population, BMI trajectories showed gradually increasing BMI throughout childhood starting from normal birth weight. Our results are in line with recent reports of case series and small patient groups with specific genetic obesity disorders and their BMI trajectories.[8,14,22-24] The median AoO in our study was well before the guideline cut-off <5 years in both nonsyndromic (1.2 years) and syndromic genetic obesity (2.0 years), and even in the controls (3.8 years).[4] A decreasing AoO in children with obesity is observed worldwide, reflecting the secular trend of increasing obesity prevalence in early childhood.[2,15] Recent longitudinal population-based studies

Table II. Overview of diagnostic performance of AoO for nonsyndromic and syndromic genetic obesity disorders in patients visiting a pediatric obesity center

Characteristics	AoO cut-off value, years	Sensitivity	Specificity	LR+	PostTP	NNT
Nonsyndromic genetic obesity disorders (AUC 0.79; $P < .001$)						
Optimal cut-off value (highest Youden index and sensitivity ≥0.80)	≤3.9	0.83	0.49	1.63	3.2%-11.0%	9-31
ES guideline cut-off	≤5	0.90	0.35	1.37	2.7%-9.4%	11-37
Highest Youden index (point of least misclassification)	≤1.25	0.59	0.93	7.94	14.0%-37.4%	3-7
Syndromic genetic obesity disorders (AUC 0.68; $P = .001$)						
Optimal cut-off value (highest Youden index and sensitivity ≥0.80)	≤4.7	0.82	0.37	1.30	2.6%-8.9%	11-39
ES guideline cut-off	≤5	0.82	0.35	1.25	2.5%-8.6%	12-40
Highest Youden index (point of least misclassification)	≤3.0	0.67	0.67	2.03	4.0%-13.2%	8-25

ES, Endocrine Society; *LR+*, positive likelihood ratio; *NNT*, number needed to test to diagnose 1 genetic obesity disorder; *PostTP*, post-test probability (based on a pretest probability of 2%-7%).

Table III. Overview of ROC analysis of BMI stratified on age bins

	Nonsyndromic genetic obesity						Syndromic genetic obesity					
Age bin, years	AUC (95% CI)	*P* value	Optimal BMI cut-off, kg/m^2	Sens	Spec	LR+	AUC (95% CI)	*P* value	Optimal BMI cut-off, kg/m^2	Sens	Spec	LR+
0	0.35 (0.21-0.49)	.019	N/A	N/A	N/A	N/A	0.30 (0.19-0.40)	.001	N/A	N/A	N/A	N/A
0.5	0.73 (0.62-0.84)	<.001	18.3	0.82	0.45	1.82	0.57 (0.43-0.68)	.317	N/A	N/A	N/A	N/A
1.0	0.77 (0.66-0.89)	<.001	18.8	0.82	0.59	1.99	0.61 (0.48-0.74)	.046	16.6	0.81	0.11	0.90
1.5	0.80 (0.69-0.92)	<.001	18.9	0.81	0.63	2.21	0.63 (0.50-0.76)	.017	17.3	0.81	0.21	1.02
2.0	0.83 (0.72-0.94)	<.001	19.1	0.82	0.68	2.52	0.66 (0.53-0.79)	.005	16.2	0.81	0.08	0.88
3.0	0.81 (0.71-0.91)	<.001	18.9	0.82	0.61	2.09	0.72 (0.60-0.85)	<.001	17.1	0.83	0.26	1.12
4.0	0.77 (0.65-0.89)	<.001	18.5	0.92	0.39	1.51	0.68 (0.56-0.81)	.001	18.2	0.83	0.36	1.30
5.0	0.78 (0.64-0.91)	<.001	19.5	0.90	0.45	1.64	0.65 (0.52-0.79)	.012	17.9	0.82	0.17	0.98
6.0	0.80 (0.68-0.91)	<.001	20.4	0.85	0.52	1.76	0.65 (0.51-0.79)	.016	18.4	0.88	0.19	1.09
8.0	0.88 (0.79-0.96)	<.001	25.3	0.80	0.90	7.92	0.59 (0.42-0.77)	.148	N/A	N/A	N/A	N/A
10.0	0.90 (0.80-1.00)	<.001	27.7	0.87	0.88	7.16	0.63 (0.46-0.79)	.061	N/A	N/A	N/A	N/A

LR+, positive likelihood ratio; *Sens*, sensitivity; *spec*, specificity; *N/A*, optimal cut-off not applicable owing to nonsignificant or inversely significant AUC; *ROC*, receiver operating characteristic. Optimal cut-off values defined as cut-offs with highest Youden's index with sensitivity of ≥0.80.

indeed show that the deviation from normal BMI of adolescents with overweight or obesity starts around 2-3 years of age, with BMI acceleration occurring between ages 2 and 6 years.[21,25] When focusing on children with severe obesity at 6 years of age, deviation from normal BMI starts as early as age 6 months.[26] Interaction with the obesogenic environment has been hypothesized to shift AoO further downward, even in patients with genetic obesity.[27,28] Therefore, it is logical that the guideline cut-off of <5 years needs shifting toward a younger age in the current generation.

Our second aim was to evaluate whether BMI trajectory characteristics can aid clinical decision-making regarding which children should be genetically screened, and what the ideal cut-offs would be. We found between-disorder and interindividual variation of AoO in genetic obesity as well as overlap with controls. The earliest AoO (<1 year) was found in biallelic nonsyndromic genetic obesity and PHP, in line with a recent study in which 21 of 22 patients with PHP had an AoO of <1 year of age.[13] In heterozygous nonsyndromic and syndromic genetic obesity disorders, AoO variation between individuals and disorders was large, ranging from <1 to 14 years of age. Optimal cut-offs were ≤3.9 years of age for nonsyndromic and ≤4.7 years of age for syndromic genetic obesity. Moreover, AoO as a single screening parameter performed better for nonsyndromic than for syndromic genetic obesity. AoO_{severe} showed worse diagnostic performance than AoO. The current guideline suggests that genetic screening is indicated in cases with an AoO_{severe} of <5 years with additional clinical features suggestive of genetic obesity disorders.[4] However, 10% of patients with nonsyndromic genetic obesity and 18% of patients with syndromic genetic obesity developed obesity after age 5 years. Moreover, 24% of patients with syndromic genetic obesity never developed severe obesity and would therefore be missed when using AoO_{severe}. Additionally, we and others found that patients with and without diagnosed underlying causes did not differ in obesity severity, and no accepted definition of severe obesity exists at an age of <2 years.[29] Therefore, AoO seems to be a more suitable genetic screening parameter than AoO_{severe}. Absolute BMI at prespecified age bins showed good performance for nonsyndromic genetic obesity from age 0.5 years onward, but less so for syndromic genetic obesity. In 2018, a study suggested absolute BMI cut-offs of >27 kg/m^2 at 2 years of age or >33 kg/m^2 at 5 years of age to distinguish between biallelic nonsyndromic genetic obesity (caused by *LEP* or *LEPR* mutations) and controls with severe obesity.[8] In our cohort, these cut-offs would correctly identify 3 of 6 patients with biallelic LEPR mutations.

As long as genetic testing remains too expensive and challenging to perform in all children with early-onset obesity, clinical criteria are necessary to determine who should be screened. The presented BMI trajectories can aid clinical decision-making. Our data suggest that nonsyndromic and syndromic genetic obesity disorders should be viewed separately. AoO can be used as single parameter, even without involving obesity severity or other features like hyperphagia. A cut-off of ≤3.9 years of age performed best in the setting of a pediatric obesity center outpatient clinic. This cut-off identifies most children with nonsyndromic genetic obesity (eg, *LEPR*, *MC4R*), Bardet-Biedl syndrome, and PHP. In case of AoO of >3.9 years of age, additional features indicative of genetic obesity disorders, such as severe obesity, hyperphagia, or a family history of severe obesity, should be present to warrant genetic testing to increase specificity owing to the overlap with children with obesity in the general population.[4] Moreover, the large AoO variation in syndromic genetic obesity disorders indicates that AoO should not be the main driver for genetic screening. For example, these patients often present with developmental problems at a younger age than their severe obesity, providing an opportunity for earlier diagnosis. If optimal specificity and number needed to screen are required, a more stringent AoO cut-off of ≤1.25 years showed the best results. Because most genetic obesity disorders are rare, except heterozygous MC4R deficiency, future studies should aim at increasing diagnostic yield by developing evidence-based diagnostic algorithms and disease-specific growth charts by combining data of all known patients with genetic obesity through international collaboration networks.[22] Moreover, our proposed cut-offs should

be validated prospectively in unselected cohorts of children referred to pediatricians and in diverse populations as optimal cut-offs might differ across races and ethnicities.

Early identification of patients with genetic obesity is crucial for patient-tailored treatment.[6,11,12] Establishing a diagnosis gives the opportunity for genetic counselling, tailored lifestyle interventions and decreases social stigmatization and health risks later in life.[3,8,11] Moreover, effective pharmacological treatments are available for genetic obesity patients with variants in *LEP*, *LEPR*, *POMC*, *PCSK1*, and Bardet-Biedl syndrome, or show promising results (*MC4R*).[12,30,31]

A strength of our study is our unique cohort comprising 13 rare genetic obesity disorders owing to extensive genetic testing in our highly experienced center. Another strength was the large amount of growth measurements per patient, enabling precise estimations of AoO. Previous studies show that it is difficult to find an appropriate control group with childhood-onset obesity for comparing BMI trajectories.[8] In this study, we included controls from a population-based study of children who grew up in the same geographic region and time frame as our patients. Growth data in the controls were available during a long follow-up duration of 10 years, and their median AoO is in line with other recent population-based studies with complete follow-up until adulthood, increasing the generalizability of our results.[21] Our study also has its limitations. We did not perform genetic testing in the controls. However, the expected prevalence of mutations is low, at 0.3% for pathogenic heterozygous *MC4R* variants, whereas other genetic obesity disorders are rare to ultrarare.[22] Furthermore, we excluded controls with a BMI SDS of >4. Therefore, we do not expect genetic obesity in the controls. Another limitation is the difference in study design between patients and controls. However, for all participants, early childhood growth measurements were used from the Dutch nationwide screening program, thereby minimizing between-group heterogeneity. Furthermore, we cannot rule out referral bias; we are a national obesity expertise center. An inherent limitation of childhood obesity research is the lack of a universal obesity definition across childhood: BMI-based definitions are available from age ≥2 years, whereas severe obesity is not defined at <2 years of age.[2,20] Because current guidelines focus on severe obesity and many children with genetic obesity have an AoO of <2 years of age, a universally accepted definition of severe obesity at <2 years of age is needed.

In conclusion, we present childhood BMI trajectories of patients with nonsyndromic and syndromic genetic obesity disorders compared with children with childhood-onset obesity from the general population. We show that AoO can be useful as single parameter to determine which children with early-onset obesity should undergo genetic testing, especially for nonsyndromic genetic obesity with an optimal cut-off AoO of ≤3.9 years. In case of older AoO, the decision to perform genetic screening when suspecting syndromic genetic obesity should be guided by the additional clinical features. Identifying genetic obesity is important because new disease-specific treatment modalities are available for specific genetic obesity disorders. ■

CRediT Authorship Contribution Statement

Ozair Abawi: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Visualization, Writing – original draft. **Rama J. Wahab:** Data curation, Formal analysis, Investigation, Methodology, Project administration, Validation, Visualization, Writing – review & editing. **Lotte Kleinendorst:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Writing – original draft, Writing – review & editing. **Lizette A. Blankers:** Data curation, Investigation, Methodology, Writing – review & editing. **Ammelies E. Brandsma:** Data curation, Funding acquisition, Investigation, Project administration, Resources, Software, Writing – review & editing. **Elisabeth F.C. van Rossum:** Formal analysis, Funding acquisition, Investigation, Resources, Software, Supervision, Validation, Writing – review & editing. **Bibian van der Voorn:** Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Writing – review & editing. **Mieke M. van Haelst:** Data curation, Formal analysis, Investigation, Resources, Validation, Writing – review & editing. **Romy Gaillard:** Formal analysis, Funding acquisition, Investigation, Methodology, Resources, Supervision, Validation, Writing – review & editing. **Erica L.T. van den Akker:** Conceptualization, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Writing – review & editing.

Declaration of Competing Interest

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The authors declare no conflicts of interest.

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Data Statement

Data sharing statement available at www.jpeds.com.

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