Received: 15 November 2023 | Revised: 14 March 2024 | Accepted: 24 March 2024

DOI: 10.1002/oby.24047

ORIGINAL ARTICLE

Clinical Trials and Investigations

Obesity A Research Journal | THE OBESITY SOCIETY | WILEY

Clinical phenotypes of adults with monogenic and syndromic genetic obesity

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Funding information
Elisabeth Foundation

Abstract

Objective: Considering limited evidence on diagnostics of genetic obesity in adults, we evaluated phenotypes of adults with genetic obesity. Additionally, we assessed the applicability of Endocrine Society (ES) recommendations for genetic testing in pediatric obesity.

Methods: We compared clinical features, including age of onset of obesity and appetite, between adults with non-syndromic monogenic obesity (MO), adults with syndromic obesity (SO), and adults with common obesity (CO) as control patients.

Results: A total of 79 adults with genetic obesity (32 with MO, 47 with SO) were compared with 186 control patients with CO. Median BMI was similar among the groups: 41.2, 39.5, and 38.7 kg/m^2 for patients with MO, SO, and CO, respectively. Median age of onset of obesity was 3 (IQR: 1–6) years in patients with MO, 9 (IQR: 4–13) years in patients with SO, and 21 (IQR: 13–33) years in patients with CO ($p < 0.001$). Patients with genetic obesity more often reported increased appetite: 65.6%, 68.1%, and 33.9% in patients with MO, SO, and CO, respectively ($p < 0.001$). Intellectual deficit and autism spectrum disorder were more prevalent in patients with SO (53.2% and 21.3%) compared with those with MO (3.1% and 6.3%) and CO (both 0.0%). The ES recommendations were fulfilled in 56.3%, 29.8%, and 2.7% of patients with MO, SO, and CO, respectively ($p < 0.001$).

Conclusions: We found distinct phenotypes in adult genetic obesity. Additionally, we demonstrated low sensitivity for detecting genetic obesity in adults using pediatric ES recommendations, necessitating specific genetic testing recommendations in adult obesity care.

INTRODUCTION

Obesity is a global epidemic on the rise, with an increasing prevalence from 4.7% in 1975 to 13.1% in 2016 [1]. This chronic, relapsing disease carries numerous adverse consequences. Genetics play an important role in the development of obesity, as multiple studies have shown high heritability of weight [2,3]. In most cases of obesity, i.e., common obesity (CO), this is likely the combination of many risk

alleles in different genes with cumulative impact on body weight in combination with other individual and environmental factors [3]. In relatively rare cases, obesity is caused by a genetic defect that results in severe early-onset obesity. This can be isolated (non-syndromic monogenic obesity [MO]) or part of a genetic syndrome (syndromic obesity [SO]). Our study in 1230 patients with a suspicion of genetic obesity showed that a single pathogenic genetic variant led to a definitive diagnosis of a genetic obesity disorder in 3.9% and a possible diagnosis in an additional 5.4% of patients [4]. Diagnosing genetic obesity is of paramount importance because it enables personalized treatments, including targeted and nontargeted pharmacotherapy. Also, it may reduce the weight stigma that patients with early-onset severe obesity often suffer from.

Genetic obesity disorders have primarily been described in children exhibiting severe phenotypes such as early onset of obesity and extreme hyperphagia [5]. These features prompted the Endocrine Society (ES)'s recommendations for genetic testing in pediatric obesity, which suggest performing genetic testing in case of onset of obesity before age 5 years together with clinical features of genetic obesity syndromes (particularly extreme hyperphagia) and/or a family history of extreme obesity [5]. Because there are no specific recommendations for genetic screening in adults with obesity, the pediatric ES recommendations are often used. However, in clinical practice, we observed that these recommendations are too strict and sometimes impractical for adults with obesity. For example, determining the age of onset of obesity (AoO) is challenging in adults due to unavailability of objective growth charts, with a reliance instead on patient reports. Additionally, adults with syndromic genetic obesity seen at our obesity center often report AoO later in childhood. Other characteristics such as obesity severity and family history may be less discriminative of genetic obesity in older individuals due to prolonged exposure to obesogenic environments. These experiences suggest that the current pediatric ES recommendations may be less accurate in adults with obesity. In summary, there is a need to evaluate the genetic obesity phenotype in adults because the current phenotype often stems from studies in children with severe phenotypes. This can help clinicians recognize potential genetic obesity in suspected adult patients and guide genetic testing decisions.

Here, we present phenotypic characteristics of adults with genetic obesity and compare these characteristics among adults with MO or SO and adults with CO. In addition, we evaluate the suitability of the pediatric ES recommendations for genetic testing in adult patients.

Study Importance

What is already known?

- Genetic obesity disorders have primarily been described in children exhibiting severe phenotypes such as early onset of obesity before age 5 years and extreme hyperphagia.
- These features prompted the Endocrine Society (ES)'s recommendations for genetic testing in pediatric obesity.
- No specific recommendations for genetic testing are available for adult obesity care.

What does this study add?

- We report distinct phenotypic features concerning age of onset of obesity, appetite characteristics, and specific clinical features in adults with genetic obesity.
- We demonstrate low sensitivity for detecting genetic obesity in adults using the ES recommendations for genetic testing in pediatric obesity.

How might these results change the direction of research or the focus of clinical practice?

- Our findings underscore the urgent need for tailored genetic testing recommendations in adult obesity care.

METHODS

Study population

Patients with obesity were referred to the Obesity Center CGG (Dutch: Centrum Gezond Gewicht, Rotterdam, the Netherlands) and (inter) national referral center of expertise for genetic obesity disorders for diagnostic work-up and personalized treatment. Additionally, another group of patients with body mass index (BMI) ≥ 30.0 kg/m^2 was referred to the Obesity Center CGG for participation in an intensive combined lifestyle intervention [6]. This group comprised patients with CO, in whom obesity was attributed to multifactorial causes, including lifestyle and social factors, without suspicion of underlying monogenic cause [7]. Genetic testing was conducted when a combination of clinical features known from literature, such as AoO in childhood, hyperphagia, family history of extreme obesity, and/or specific features of a genetic obesity syndrome such as autism spectrum disorder (ASD), intellectual deficit, or presence of dysmorphic features, was observed [5]. Genetic testing most often entailed diagnostic next-generation sequencing for genetic obesity disorders. The content of the obesity gene panel evolved during the course of this study [4,8]. Additional genetic tests such as array analysis, methylation analysis, or whole exome sequencing were performed when deemed appropriate, for example, in the presence of intellectual disability or short stature. All identified variants were classified according to the guideline of the American College of Medical Genetics and Genomics (ACMG) Laboratory Practice Committee Working Group [9]. When a gene variant of uncertain significance was detected, clinical geneticists conducted additional diagnostics to determine pathogenicity. In several cases, segregation analysis or episignature analysis helped to reclassify a gene variant of uncertain significance to a likely pathogenic variant. Some patients had a prior diagnosis due to a suggestive phenotype or genetic analysis prompted by a family member with genetic obesity; in these cases, only targeted analysis of the familial variant was performed. This study included only patients with molecularly confirmed pathogenic (class V) or likely pathogenic variants (class IV) resulting in MO or SO

who were seen at our outpatient clinic from 2012 until May 2023. Patients with CO served as controls for this study.

The study involving human participants was reviewed and approved by the Ethical Committee of the Erasmus MC, University Medical Center, Rotterdam, the Netherlands. Informed consent of the patients was obtained, when needed, according to the approved protocol.

First visit

Before the first visit to our outpatient clinic, a comprehensive standardized questionnaire, including patients' nationality, educational level, medical history, drug use, AoO, appetite characteristics (including the degree of appetite, satiation, duration of satiety, change in appetite over time, and presence of nightly eating and binge eating), family history, and history of previous obesity treatments, had to be completed by the patient. The exact questions in this questionnaire assessing AoO and appetite are mentioned in the online Supporting Information Methods. All patients completed this questionnaire in their own home environment. If needed, because of intellectual deficit or poor vision, for example, caregivers helped. During the first visit, the patient information collected using this questionnaire was extensively discussed by the patient and physician. AoO was preferably determined using objective growth charts. However, if not available, AoO was self-reported. Patients were asked to show pictures from childhood or adolescence to determine or verify AoO during the first consultation. Additionally, specific questions to evoke certain memories, such as whether they were bullied in kindergarten or elementary school because of having overweight or whether they had visited a dietitian at a young age, provided valuable additional clues to determine AoO. Medical history was obtained via history taking, referral letter, or via other involved caregivers. Weight, height, waist circumference, blood pressure, and heart rate were measured. Height was measured using a wall-mounted calibrated stadiometer. Weight was measured using a calibrated scale while the patient was clothed except for shoes.

Diagnostic work-up

During a later diagnostic work-up visit, a fasting blood sample was taken to evaluate cardiometabolic parameters such as glucose, liver enzymes, and lipid profile, as well as endocrine parameters such as thyroid hormones, insulin, and leptin. When indicated by the treating physician, body composition and resting energy expenditure (REE) were measured. The exact methods of measuring body composition and REE, together with the definitions of the obesity-related comorbidities and endocrine diseases, are mentioned in the online Supporting Information Methods.

Statistical analyses

Data were analyzed using IBM SPSS Statistics version 28.0 (IBM Corp., Armonk, New York). Ethnicity was determined based on the birth country of the parents of the patient [10]. Education level was categorized as low, middle, and high (online Supporting Information Methods) [11]. High birth weight was defined as a birth weight ≥ 4000 g. Post-bariatric weight regain was classified using the Dutch Audit for Treatment of Obesity classification [12]. Fulfilling the ES recommendations was defined as AoO ≤ 5 years together with presence of hyperphagia because these are two major distinctive features of genetic obesity. BMI was calculated by dividing weight in kilograms by height in meters squared. The Harris & Benedict equation was used for calculating predicted REE [13]. The bias in REE (in kilocalories per day) was calculated by subtracting predicted REE from measured REE, and the ratio between measured REE and predicted REE was calculated and multiplied by 100% (%REE). Decreased REE and elevated REE were defined as %REE lower than 90% and 110%, respectively. Data are depicted as mean ± standard deviation (SD) or median (interquartile range [IQR]), depending on the normal distribution. Comparisons were done among groups, i.e., in patients with MO, SO, and CO. We used one-way ANOVA, Kruskal–Wallis tests, and χ^2 tests/Fisher exact tests, as appropriate. Post hoc tests were done to determine significant differences among the groups. Presence of a comorbidity was stepwise-adjusted for age at intake, sex, and underlying cause of the obesity using logistic regression analyses. Afterward, duration of obesity was added to this stepwise logistic regression analyses.

RESULTS

General characteristics

The group with SO consisted of significantly fewer female individuals compared with the groups with MO and CO (48.9%, 81.3%, and 76.9%, respectively; $p < 0.05$). Age at intake was significantly lower in the groups with MO and SO compared with the group with CO (25.8, 25.5, and 45.2 years, respectively; $p < 0.05$). Education level was significantly different across all groups, with lower levels of education in the group with SO compared with the other groups ($p < 0.05$). There were no significant differences in anthropometrics, except for the severity of the obesity using the obesity classes. The general characteristics for the three groups are depicted in Table 1. Patients with SO were significantly more often treated with potential weight-inducing antipsychotics compared with the groups with MO and CO (10.6%, 0.0%, and 0.5%, respectively; $p < 0.001$), whereas use of antiepileptics did not differ significantly among the groups (0.0%, 0.0%, and 2.7%, respectively; Table S1). Methylphenidate, an appetite-suppressing drug, was used by one patient in every group. Both the groups with MO and SO still reported an increased appetite even though they were treated with an appetite suppressant. The identified affected genes in our patients with genetic obesity disorders are provided in Table 2. Heterozygous pathogenic melanocortin 4 receptor (*MC4R*) variants were the most common among the group with MO, whereas, in the group with SO, the 16p11.2 deletion syndrome was the most common. The specific genetic variants are shown in Table S2.

Genetic obesity characteristics

Self-reported AoO per subgroups of patients with MO, SO, and CO is depicted in Figure 1. AoO was determined using growth charts in six

TABLE 1 General characteristics in all groups.

	MO ($n = 32$)[a]	SO ($n = 47$)[b]	CO ($n = 186$)[c]	*p* value
Sex, female, *n* (%)	26 (81.3)	23 (48.9)	143 (76.9)	**<0.001**[d]
Age at intake (y)	25.8 (20.3–41.9)	25.5 (21.5–36.4)	45.2 (33.5–55.7)	**<0.001**[e]
Ethnicity, *n* (%)				**0.043**[f]
Dutch	24 (75.0)	43 (91.5)	131 (71.6)	
Western	2 (6.3)	0 (0.0)	20 (10.9)	
Non-Western	6 (18.8)	4 (8.5)	32 (17.5)	
Education level, *n* (%)				**<0.001**[g]
Low	9 (28.1)	30 (63.8)	12 (7.7)	
Middle	14 (43.8)	15 (31.9)	46 (29.7)	
High	9 (28.1)	2 (4.3)	97 (62.6)	
Weight (kg)	119.7 (98.4–150.1)	124.4 (96.0–141.0)	113.7 (101.5–125.7)	0.314
Height (cm)	170.3 ± 10.0	174.3 ± 11.4	171.2 ± 9.0	0.136
BMI ($kg/m^{2)}$	41.2 (36.8–48.3)	39.5 (34.5–45.7)	38.7 (36.0–42.6)	0.248
Obesity class, *n* (%)				**<0.001**[e]
Overweight	3 (9.4)	3 (6.4)	0 (0.0)	
I	3 (9.4)	9 (19.1)	39 (21.0)	
II	7 (21.9)	13 (27.7)	71 (38.4)	
III	19 (59.4)	22 (46.8)	76 (40.9)	
Waist circumference (cm)	113 (90–129)	120 (102–130)	113.0 (103.3–123.3)	0.402
SBP (mm Hg)	143 ± 23	140 ± 15	137 ± 15	0.195
DBP (mm Hg)	86 ± 16	80 ± 11	81 ± 12	0.093
HR	82 ± 23	83 ± 16	79 ± 16	0.179

Note: Data are presented as mean ± SD or median (IQR), depending on the distribution of the data, or *n* (%)
Abbreviations: CO, common obesity; DBP, diastolic blood pressure; HR, heart rate; MO, non-syndromic monogenic obesity; SBP, systolic blood pressure; SO, syndromic obesity.
[a]Data available for waist circumference in $n = 11$, SBP and DBP in $n = 27$, and HR in $n = 23$.
[b]Data available for waist circumference in $n = 20$, SBP and DBP in $n = 42$, and HR in $n = 33$.
[c]Data available for ethnicity in $n = 183$, education level in $n = 155$, waist circumference in $n = 184$, SBP and DBP in $n = 123$, and HR in $n = 105$.
Post hoc pairwise comparisons showed significant differences among the following:
[d]SO vs. MO and SO vs. CO.
[e]MO vs. CO and SO vs. CO.
[f]SO vs. CO.
[g]All subgroups.

out of thirty-two patients with MO and four out of forty-seven patients with SO; in all other patients, including all patients with CO, AoO was self-reported. AoO was significantly lower in the groups with MO and SO compared with the group with CO (3, 9, and 21 years, respectively; $p < 0.05$; Table 3). In addition, AoO in the group with MO was significantly lower compared with the group with SO. The proportion of patients with AoO ≤ 5 years was significantly higher in the groups with MO and SO compared with the group with CO (75.0%, 38.3%, and 4.3%, respectively; $p < 0.05$). This was also significantly different between the groups with MO and SO. The groups with MO and SO more often reported an increased appetite compared with the group with CO (65.6%, 68.1%, and 33.9%, respectively; $p < 0.05$). In 61.3% of patients in the group with MO and 48.9% of patients in the group with SO, impaired satiation was reported. Presence of binge eating episodes did not differ among the three groups. Both the groups with MO and SO reported changes in appetite from childhood to adulthood. In 6.3% of patients in the group with MO and 11.1% of patients in the group with SO, appetite increased with advancing age, whereas, in 43.7% of patients in the group with MO and 35.4% of patients in the group with SO, this decreased. Reasons reported for a decrease in appetite over time were the following: spontaneously; bariatric surgery; or use of appetite-suppressing antiobesity agents. Parental obesity was more often present in the group with MO compared with the group with CO ($p < 0.05$). The group with SO more often reported an intellectual deficit, ASD, or retinal problems compared with the groups with MO and CO (all $p < 0.001$). Self-reported consanguinity was reported by two out of three of the patients with a homozygous gene variant causing MO and two out of five of the patients with recessive SO (1/5 Bardet-Biedl syndrome and 1/5 Alström syndrome). Patients with biallelic MO had a significantly younger AoO compared with those with monoallelic MO (1.0 vs. 4.0 years; $p = 0.023$), whereas

TABLE 2 Included genetic obesity disorders.

Affected gene	Name of disease	Number of patients (%)
Non-syndromic MO		
Heterozygous *MC4R*		26 (81.3)
Biallelic *MC4R*		3 (9.4)
Biallelic *LEPR*		2 (6.3)
Biallelic *POMC*		1 (3.1)
SO		
16p11.2 deletion	16p11.2 deletion syndrome	29 (61.7)
Distal (including *SH2B1*)		14 (48.3)
Proximal (excluding *SH2B1*)		15 (51.7)
Bardet-Biedl syndrome genes	Bardet-Biedl syndrome	7 (14.9)
GNB1		2 (4.3)
PHIP	Chung-Jansen syndrome	2 (4.3)
ALMS	Alström syndrome	1 (2.1)
MAGEL2	Schaaf-Yang syndrome	1 (2.1)
MYT1L		1 (2.1)
SIM1		1 (2.1)
DNMT3A	Tatton-Brown-Rahman syndrome	1 (2.1)
STX16	Pseudohypoparathyroidism type 1B	1 (2.1)
TRIP12	Clark-Baraitser syndrome	1 (2.1)

Abbreviations: *ALMS1*, ALMS1 centrosome and basal body associated protein; *DNMT3A*, DNA methyltransferase 3 α; *GNB1*, G protein subunit β 1; *LEPR*, leptin receptor; *MAGEL2*, MAGE family member L2; *MC4R*, melanocortin 4 receptor; MO, non-syndromic monogenic obesity; *MYT1L*, myelin transcription factor 1 like; *PHIP*, pleckstrin homology domain interacting protein; *POMC*, pro-opiomelanocortin; *SH2B1*, SH2B adaptor protein 1; *SIM1*, SIM BHLH transcription factor 1; SO, syndromic obesity; *STX6*, syntaxin 6; *TRIP12*, thyroid hormone receptor interactor 12.

appetite characteristics were similar (Table S3). This resulted in a significantly lower proportion of patients with biallelic MO fulfilling the ES criteria for genetic testing compared with patients with monoallelic MO (100% vs. 46.2%; $p = 0.024$).

Previous bariatric surgery and weight regain in patients with genetic obesity

Eight of thirty-two patients with MO had bariatric surgery in the past, of which two out of eight patients had a gastric sleeve, and six out of eight patients had a gastric bypass. This resulted in a median maximum weight loss of −35.0 kg (range: −57.0 to −5.0 kg). In seven out of eight patients, a median weight regain of +19.3 kg (range: 3.5–36.5 kg) was reported after a median follow-up duration of 65.7 months (range: 22.8–198.1 months). The remaining patient did not report weight regain and had the surgery 9.8 months prior. In the group with SO, four patients had undergone bariatric surgery, which resulted in a median maximum weight loss of −39.5 kg (range: −53.5 to −34.3 kg). Two out of these four patients regained 27.9 and 7.1 kg of weight after 22.7 and 39.7 months, respectively. The other two patients did not report weight regain and had their surgery 7.0 and 18.8 months before their intake at our center, respectively.

Body composition and REE

Absolute fat mass and fat-free mass were high in all groups (Table 4; Table S4). Measured REE in kilocalories per day was comparable across all groups. All REE characteristics such as %REE and the proportion of patients with lowered or elevated REE were not significantly different across the groups.

Presence of comorbidities

Table 5 depicts the prevalence of all comorbidities per subgroup. Type 2 diabetes (T2D) was more prevalent in the groups with MO and SO compared with the group with CO ($p = 0.039$). When adjusted for age at intake and sex, patients with MO and SO were 4.1 (95% confidence interval [CI]: 1.4–11.9) and 3.8 (95% CI: 1.4–10.2) times more likely to have T2D compared with patients with CO ($p = 0.01$ and $p = 0.008$). Additional correction for duration of obesity yielded an odds ratio (OR) of 3.1 (95% CI: 0.9–10.2; $p = 0.067$) for MO and 3.2 (95% CI: 1.2–9.1; $p = 0.026$) for SO. Elevated liver enzymes were significantly more often seen in the group with SO compared with the groups with MO and CO (74.4%, 46.4%, and 53.6%, respectively; $p = 0.034$), whereas metabolic syndrome was more often observed in the group with CO compared with the group with MO (73.1% vs. 44.4%, respectively; $p = 0.04$). Separate metabolic and endocrine laboratory parameters are shown in Table S5.

ES recommendations for genetic testing

The proportion of patients fulfilling the pediatric ES recommendations for genetic testing is depicted in Figure 2. These were fulfilled in 56.3% of the group with MO and 29.8% of the group with SO. Five out of one hundred and eighty-six (2.7%) patients with CO fulfilled the pediatric ES criteria. Among these five patients, the first patient reported lifelong use of corticosteroids due to asthma and eczema and had consequently gained +27 kg in 1.5 years. The second patient also used inhalation corticosteroids for 20 years due to asthma. She also used dermal and systemic corticosteroids in the past. The third patient reported binge eating, a history of alcohol addiction, and use of several potential weight-inducing medications. The fourth patient

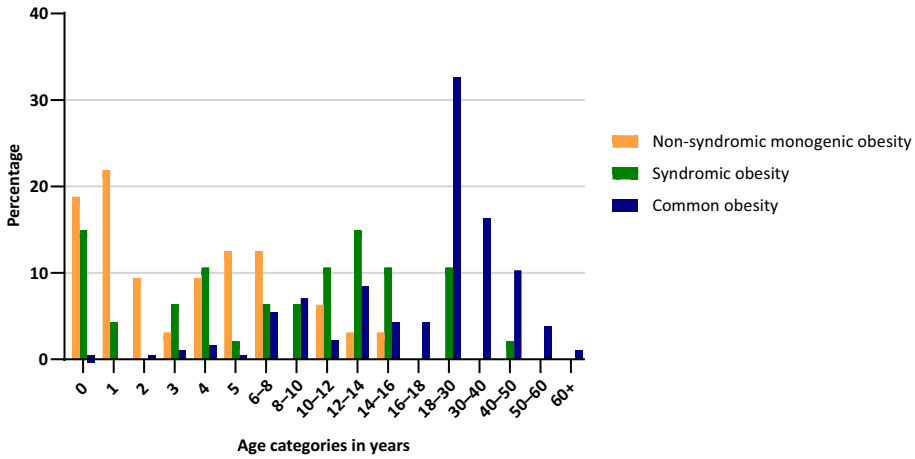

FIGURE 1 Age of onset of obesity (AoO), categorized per type of obesity.

reported binge and emotional eating, multiple family members with obesity on her mothers' side, and a clinical picture of polycystic ovary syndrome (PCOS). The fifth patient reported use of several potential weight-inducing medications due to hay fever and a confirmed diagnosis of PCOS. Genetic analysis of 14 obesity-associated genes was offered to all five patients. In patient 1, 3, 4, and 5, genetic screening did not show abnormalities. Patient 2 decided to refrain from genetic testing.

DISCUSSION

In this study, we show evident differences in phenotypic features among adults with genetic obesity (MO and SO) and adults with CO. More specifically, adults with genetic obesity had a significantly lower age of onset of their obesity and more often reported an increased appetite. Other characteristics of an impaired appetite regulation, such as lower satiation or shorter duration of satiation, were also present in adults with genetic obesity. Adults with MO reported a significantly lower median AoO (3 years) compared with those with SO (9 years), which is also reflected in a higher proportion of patients with MO reporting an early onset of obesity at age 5 years or younger. Body composition and REE characteristics did not differ among all groups. T2D and elevated liver enzymes were more prevalent among patients with genetic obesity. Furthermore, we show that the ES recommendations for genetic testing in children with a genetic obesity phenotype were fulfilled in less than half of our adult populations with confirmed genetic obesity. Particularly, most adult patients with SO did not fulfill these criteria.

Comparing our results regarding AoO in patients with MO to existing literature is challenging due to varying reporting of AoO and age cutoffs for early-onset obesity. For example, a study on MC4R deficiency (proportion of children and adults is unreported) showed AoO before 10 years in all patients with homozygous *MC4R* gene variants and in 68% of those with pathogenic heterozygous *MC4R* gene variants [14]. Other studies in children and adults with biallelic leptin receptor (*LEPR*) or pro-opiomelanocortin (*POMC*) variants reported AoO in early childhood, without reporting exact AoO in most studies [15–18]. Another complexity in comparing literature is that most studies have been performed in children exhibiting severe phenotypes. For example, studies on children with MO due to MC4R or LEPR deficiency reported AoO ≤5 years in 93% of the children and median AoO of 1.2 years [8,19]. Both studies showed younger AoO in children compared with adults with MO [8,19]. Also, for SO, AoO is often unreported in the literature. A study on 16p11.2 deletion syndrome reported AoO in early adolescence through adulthood [20]. This finding is strengthened by a study on children with SO reporting AoO ≤ 5 -years in only 66.7% of patients [8]. In contrast, a study on Bardet-Biedl syndrome showed that 70.9% of the patients developed obesity at age 5 years or younger, which is significantly higher than the 38.3% in our group with SO [21]. Additionally, a study in children with SO reported median AoO of 2.0 years [19].

In this study, 65.6% of adults with MO reported increased appetite, which was lower than the 100% reported in a study of patients with MC4R deficiency [14]. This difference may be due to a smaller number of adults in the previous study, although exact numbers were not reported. A study in children with MC4R or LEPR deficiency reported hyperphagia in 87% of patients, which is significantly higher than in our study including only adults [8]. Moreover, in adults with heterozygous MC4R deficiency, lower prevalence rates of impaired appetite regulation were observed, i.e., 31.0% for increased hunger, 10.6% for binge eating, and 31.6% for hyperphagia [22,23]. Studies in patients with biallelic *LEPR* or *POMC* variants have shown that most patients had hyperphagia [15–18]. Among our patients with SO, 68.1% reported increased appetite. Studies in 16p.112 deletion syndrome and Bardet-Biedl syndrome have mentioned disinhibited eating behaviors and hyperphagia but did not provide specific prevalence numbers [24,25]. Interestingly, a study in children with SO reported a lower hyperphagia prevalence of only 50.0%, possibly due to their younger age at assessment.

In our study, T2D was reported twice as often in patients with MO (21.9%) compared with patients with CO (10.8%), despite

TABLE 3 AoO, appetite characteristics, and other genetic characteristics in all groups.

	MO ($n = 32$)[b]	SO ($n = 47$)[c]	CO ($n = 186$)[d]	*p* value
AoO				
AoO (y)	3 (1–6)	9 (4–13)	21 (13–33)	**<0.001**[e]
AoO ≤ 5 y, *n* (%)	24 (75.0)	18 (38.3)	8 (4.3)	**<0.001**[f]
Appetite characteristics				
Appetite, *n* (%)				**<0.001**[e]
Increased	21 (65.6)	32 (68.1)	62 (33.9)	
Normal	9 (28.1)	12 (25.5)	117 (63.9)	
Decreased	2 (6.3)	3 (6.4)	4 (2.2)	
Satiation, *n* (%)	19 (61.3)	22 (48.9)	NA	0.286
Duration satiety, *n* (%)			NA	0.699
<1 h	10 (32.3)	10 (22.7)		
1–2 h	10 (32.3)	17 (38.6)		
2–4 h	8 (25.8)	10 (22.7)		
>4 h	3 (9.7)	7 (15.9)		
Change of appetite over time, *n* (%)			NA	0.855
Unchanged	16 (50.0)	23 (51.1)		
Increased	2 (6.3)	5 (11.1)		
Decreased	14 (43.7)	17 (35.4)		
Spontaneously	5 (35.7)	6 (35.3)		
Bariatric surgery	2 (14.3)	1 (5.8)		
Antiobesity agents	7 (50.0)	10 (58.8)		
Nocturnal eating, *n* (%)	5 (15.6)	7 (15.9)	NA	0.438
Binge eating, *n* (%)	17 (53.1)	30 (63.8)	95 (54.9)	0.509
Other specific traits				
Only person with obesity within family household, *n* (%)[a]	6 (20.0)	16 (36.4)	57 (33.7)	0.279
Parental obesity, *n* (%)[a]				**0.003**[g]
None	6 (25.0)	20 (52.6)	77 (46.4)	
Only 1 parent	7 (29.2)	8 (21.1)	64 (38.6)	
Both parents	11 (45.8)	10 (26.3)	25 (15.1)	
Age of menarche (y)	13 (12–14)	12 (11–13)	12 (12–13)	0.173
High birth weight, *n* (%)	4 (14.3)	11 (24.4)	25 (18.8)	0.540
Intellectual deficit, *n* (%)	1 (3.1)	25 (53.2)	0 (0)	**<0.001**[f]
ASD, *n* (%)	2 (6.3)	10 (21.3)	0 (0)	**<0.001**[e]
Retinal problems, *n* (%)	0 (0)	8 (17.0)	0 (0)	**<0.001**[h]
ES criteria				
Fulfilling ES criteria for genetic testing, *n* (%)	18 (56.3)	14 (29.8)	5 (2.7)	**<0.001**[e]

Note: Data are presented as median (IQR) or *n* (%).

Abbreviations: AoO, age of onset of obesity; ASD, autism spectrum disorder; CO, common obesity; ES, Endocrine Society; MO, non-syndromic monogenic obesity; SO, syndromic obesity.

[a]Obesity was defined as BMI ≥ 30 kg/m^2.

[b]Data available for satiation and duration satiety in $n = 31$, parental obesity and birth weight in $n = 28$, obesity within family in $n = 30$, and age menarche in $n = 24$.

[c]Data available for satiation and change in appetite over time in $n = 45$, duration satiety and nightly eating in $n = 44$, parental obesity in $n = 38$, obesity within family in $n = 44$, age menarche in $n = 22$, and birth weight in $n = 45$.

[d]Data available for age of onset obesity in $n = 184$, appetite in $n = 183$, binge eating in $n = 173$, obesity within family in $n = 169$, birth weight in $n = 133$, and fulfilling ES criteria for genetic testing in $n = 184$.

Post hoc pairwise comparisons showed significant differences among the following:

[e]MO vs. CO and SO vs. CO.

[f]All subgroups.

[g]MO vs. CO.

[h]SO vs. MO and SO vs. CO.

TABLE 4 Body composition and resting energy expenditure characteristics in all groups.

	MO ($n = 32$)[a]	SO ($n = 47$)[b]	CO ($n = 186$)[c]	*p* value
Body composition				
Fat mass				
kg	57.2 (38.5–84.4)	57.4 (43.5–73.7)	47.8 (38.0–57.9)	0.065
%	46.6 ± 11.0	47.1 ± 7.7	43.9 ± 6.9	0.237
Fat-free mass				
kg	63.3 ± 11.6	65.5 ± 15.3	61.9 ± 11.8	0.513
%	53.4 ± 11.0	52.9 ± 7.7	56.1 ± 6.9	0.237
Resting energy expenditure				
Weight (kg)	112.6 (84.4–145.3)	127 (97.8–139.4)	107.3 (96.4–126.6)	0.138
Height (cm)	169.8 ± 8.9	172.0 ± 12.5	169.2 ± 8.3	0.710
mREE (kcal/d)	1724 (1548–2282)	1976 (1725–2433)	1710 (1580–2215)	0.058
pREE (kcal/d)	1915 ± 294	2259 ± 488	1815 ± 258	0.003[d]
Mean bias (mREE–pREE) (kcal/d)	−64 (−196–71)	−159 (−339–120)	−9 (−108–160)	0.294
REE%	96.5 (89.8–103.1)	93.3 (86.8–105.9)	99.7 (93.7–108.9)	0.349
Lowered REE, *n* (%)	3 (25.0)	8 (38.1)	3 (18.8)	0.414
Elevated REE, *n* (%)	1 (8.3)	2 (9.5)	2 (12.5)	0.928

Note: Data are presented as mean ± SD or median (IQR), depending on the distribution of the data, or *n* (%).
Abbreviations: CO, common obesity; MO, non-syndromic monogenic obesity; mREE, measured resting energy expenditure; pREE, predicted resting energy expenditure; REE%, ratio between mREE and pREE was calculated and multiplied by 100%; SO, syndromic obesity.
[a]Data available for body composition in $n = 20$ and resting energy expenditure characteristics in $n = 12$
[b]Data available for body composition in $n = 28$ and resting energy expenditure characteristics in $n = 21$
[c]Data available for body composition in $n = 42$ and resting energy expenditure characteristics in $n = 16$.
Post hoc pairwise comparisons showed significant differences between:
[d]SO vs. MO and SO vs. CO.

TABLE 5 Presence of obesity–related comorbidities and associated endocrine diseases in all groups.

	MO ($n = 32$)[a]	SO ($n = 47$)[b]	CO ($n = 186$)[c]	*p* value
Type 2 diabetes, *n* (%)	7 (21.9)	11 (23.4)	20 (10.8)	0.039[d]
Dyslipidemia, *n* (%)	12 (42.9)	22 (52.4)	79 (42.7)	0.515
Elevated liver enzymes, *n* (%)	13 (46.4)	29 (74.4)	96 (53.6)	0.034[e]
Metabolic syndrome, *n* (%)	8 (44.4)	21 (72.4)	122 (73.1)	0.040[f]
OSAS, *n* (%)	5 (15.6)	18 (38.3)	58 (33.9)	0.081
PCOS, *n* (%)	1 (3.8)	1 (4.5)	12 (10.2)	0.449
Male hypogonadism, *n* (%)	0 (0.0)	0 (0.0)	10 (24.4)	0.395
Thyroid status, *n* (%)				0.976
Euthyroid	26 (81.3)	40 (85.1)	155 (83.3)	
Hypothyroid	4 (12.5)	4 (8.5)	21 (11.3)	
Subclinical hypothyroid	2 (6.3)	3 (6.4)	10 (5.4)	

Abbreviations: CO, common obesity; MO, non-syndromic monogenic obesity; OSAS, obstructive sleep apnea syndrome; PCOS, polycystic ovary syndrome; SO, syndromic obesity.
[a]Data available for type 2 diabetes, OSAS, and thyroid status in $n = 32$, dyslipidemia and elevated liver enzymes in $n = 28$, metabolic syndrome in $n = 18$, PCOS in $n = 26$, and male hypogonadism in $n = 1$.
[b]Data available for type 2 diabetes, OSAS and thyroid status in $n = 47$, dyslipidemia in $n = 42$, elevated liver enzymes in $n = 39$, metabolic syndrome in $n = 29$, PCOS in $n = 22$, and male hypogonadism in $n = 5$.
[c]Data available for type 2 diabetes and dyslipidemia in $n = 185$, elevated liver enzymes in $n = 179$, metabolic syndrome in $n = 167$, OSAS in $n = 171$, PCOS in $n = 118$, and male hypogonadism in $n = 41$.
Post hoc pairwise comparisons showed significant differences between:
[d]SO vs. CO.
[e]MO vs. SO.
[f]MO vs. CO.

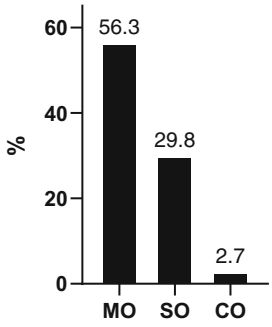

FIGURE 2 The proportion of adult patients fulfilling the pediatric Endocrine Society (ES) recommendations for genetic testing, categorized per type of obesity. CO, common obesity; MO, non-syndromic monogenic obesity; SO, syndromic obesity.

patients with MO being significantly younger. This T2D prevalence aligns with other studies reporting 20% to 25% prevalence in obesity caused by biallelic *LEPR*, leptin (*LEP*), *POMC*, and proprotein convertase subtilisin/kexin type 1 (*PCSK1*) gene variants [15,17]. However, this is significantly higher compared with studies in patients with obesity caused by heterozygous *MC4R* gene variants showing a prevalence of 10.1% to 11.8% [23,26]. Recent research has highlighted the role of leptin, its receptor, POMC neurons, and MC4R in glucose metabolism, suggesting that defects in this pathway may elevate the risk of T2D [27]. This emphasizes the importance of regular screening for obesity-related comorbidities, especially in patients with genetic obesity because their obesity may manifest earlier. Detecting and treating these comorbidities promptly is essential to prevent complications, highlighting the need for proper guidelines to screen for genetic obesity in adults.

Because our study raises awareness that recommendations for genetic testing in adult obesity care are needed, we advocate international collaboration among specialized centers in adult genetic obesity to develop these recommendations. By assembling a larger and diverse cohort of patients from different countries with a variety of genetic obesity disorders, an international consensus can be achieved by proposing more robust criteria for genetic testing in adults with obesity. Several considerations when developing these new recommendations should be noted (Table 6). First, hyperphagia is a complex concept that entails several components of impaired appetite regulation, including increased appetite, decreased satiation and/or satiety, shortened duration of satiety, binge eating, and nocturnal eating. Evaluating hyperphagia should cover different life stages, from childhood to adulthood, allowing patients to compare their eating behavior with peers and siblings. Future studies are needed to understand the natural history of appetite in these patients. Second, we suggest different age cutoffs for early-onset obesity than the recommended age cutoff of ≤5 years for early-onset obesity in children. Our data suggest that, in the current adult population suspected of having genetic obesity, AoO ≤7 years for MO and ≤15 years for SO would be an appropriate cutoff. However, it is essential to also include the presence of hyperphagia now or during childhood, specific genetic obesity features, striking weight differences with first-degree family members, or family history of extreme and early-onset obesity in the diagnostic work-up [5]. Last, specific syndromic genetic obesity features such as intellectual deficit, ASD, organ-specific congenital malformations, and dysmorphic features should be considered when assessing patients for SO.

TABLE 6 Key considerations for developing recommendations regarding genetic testing in adults with obesity.

Considerations before performing genetic testing in an adult with obesity when a combination is present of the following signs and symptoms
1. Different aspects of hyperphagia should be assessed across different life stages, spanning from childhood to adulthood, including the following: • Increased appetite • Decreased satiation and/or satiety • Shortened duration of satiety • Presence of binge eating • Presence of nocturnal eating
2. The recommended age cutoff for early-onset obesity in children is ≤5 years of age. For adults who are suspected of having genetic obesity, our data suggest age cutoffs for early-onset obesity of the following: • ≤7 years of age for MO • ≤15 years of age for SO
3. In addition to hyperphagia and early-onset obesity, it is essential to also evaluate other specific genetic obesity features and/or striking weight differences with first-degree family members and family history of extreme and early-onset obesity[a].
4. In case of suspicion of SO, specific syndromic genetic obesity features such as intellectual deficit, ASD, organ-specific congenital malformations, and dysmorphic features should be considered.

Abbreviations: ASD, autism spectrum disorder; MO, non-syndromic monogenic obesity; SO, syndromic obesity.
[a]Examples are endocrinopathies (e.g., hypogonadotropic hypogonadism, adrenocorticotropic hormone [ACTH] deficiency, mild hypothyroidism), intellectual deficit, retinal dystrophy, congenital deafness, dysmorphic extremities (i.e., syndactyly, brachydactyly, or polydactyly), neurobehavioral problems.

Strengths of this study include a large sample size of patients with confirmed pathogenic genetic obesity, categorized as MO and SO. We carefully conducted systematic phenotyping with a focus on AoO and hyperphagia, comparing it with a valid control group of patients with CO. Additionally, four out of five patients with CO who fulfilled the pediatric ES recommendations were genetically screened. However, our study is limited by its observational design. Selection bias may be present because patients with severe therapy-resistant obesity may be more frequently referred to our specialized tertiary obesity center. Use of clinical features of genetic obesity based on literature and clinical experience and partially driven by the knowledge of the ES recommendations for genetic screening by the physicians could also introduce selection bias. However, we also offered genetic testing to patients with milder genetic obesity phenotypes who did not fulfill these recommendations based on our clinical experience. Moreover, our lifestyle program allowed the inclusion of patients with CO without a priori suspicion of genetic obesity. Additionally, current obesity gene panels

focus on genes causing early-onset obesity, whereas new literature has suggested that genes such as bassoon presynaptic cytomatrix protein (*BSN*), which is associated with adult-onset obesity, may play a role as well [28]. Choices had to be made by clinical geneticists with extensive knowledge on genetic obesity regarding which genes to include in the obesity gene panel. In addition, not all genes causing early-onset obesity have been discovered yet. It is therefore likely that the number of patients with one or multiple genetic defects and copy number variants is underestimated. Nevertheless, our obesity gene panel is capable of detecting copy number variants, i.e., deletions, within the 16p11.2 region. Last, we assessed self-reported consanguinity and appetite. The genetic tests that we performed were not designed to assess consanguinity; therefore, we could not formally confirm consanguinity. Additionally, there are no questionnaires available and validated to assess hyperphagia in patients with genetic obesity disorders. Recall bias may be present because patients had to self-report their AoO in the absence of growth charts. However, this method aligns with current clinical practice in adult obesity care. Prospective studies using objective measures for AoO and appetite regulation, such as validated questionnaires, are needed.

In conclusion, our study highlights distinct phenotypic features concerning AoO, appetite characteristics, and specific clinical features in adults with genetic obesity. We also demonstrate low sensitivity for detecting genetic obesity in adults using the ES recommendations for genetic testing in pediatric obesity. Our findings underscore the urgent need for tailored genetic testing recommendations in adult obesity care.O

AUTHOR CONTRIBUTIONS

Mila S. Welling was involved in the conception and design of the work and the acquisition, analysis, and interpretation of the data and drafted the work. Mostafa Mohseni and Renate E. H. Meeusen made substantial contributions to the acquisition and interpretation of the data and critically revised the work. Cornelis J. de Groot, Mariëtte R. Boon, Lotte Kleinendorst, Jenny A. Visser, Mieke M. van Haelst, and Erica L. T. van den Akker made substantial contributions to the interpretation of the data and critically revised the work. Elisabeth F. C. van Rossum was involved in the conception and design of the work and the acquisition, analysis, and interpretation of the data and critically revised the work. All authors gave final approval for the version to be published.

CONFLICT OF INTEREST STATEMENT

The authors declared no conflict of interest.

FUNDING INFOMATION

Mariëtte R. Boon, Erica L. T. van den Akker, and Elisabeth F. C. van Rossum are supported by the Elisabeth Foundation, a nonprofit foundation supporting academic obesity research.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Welling MS, Mohseni M, Meeusen REH, et al. Clinical phenotypes of adults with monogenic and syndromic genetic obesity. *Obesity (Silver Spring)*. 2024;32(7):1257-1267. doi:10.1002/oby.24047