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ORIGINAL ARTICLE

Pediatric Obesity

Who benefits most from outpatient lifestyle intervention? An IMI-SOPHIA study on pediatric individuals living with overweight and obesity

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Abstract

Objective: The first-line approach for childhood obesity is lifestyle intervention (LI); however, success varies. This study aimed first to identify distinct subgroups of response in children living with overweight and obesity and second to elucidate predictors for subclusters.

Methods: Based on the obesity patient follow-up registry the APV (Adipositas-Patienten-Verlaufsdokumentation) initiative, a total of 12,453 children and adolescents (median age: 11.5 [IQR: 9.7–13.2] years; BMI *z* score [BMIz]: 2.06 [IQR: 1.79–2.34]; 52.6% girls) living with overweight/obesity and participating in outpatient LI were studied. Longitudinal k-means clustering was used to identify individual BMIz response curve for up to 2 years after treatment initiation. Multinomial logistic regression was used to elucidate predictors for cluster membership.

Nicole Prinz and Hugo Pomares-Millan contributed equally.

Results: A total of 36.3% of children and adolescents experienced "no BMIz loss." The largest subcluster (44.8%) achieved "moderate BMIz loss," with an average delta-BMIz of −0.23 (IQR: −0.33 to −0.14) at study end. A total of 18.9% had a "pronounced BMIz loss" up to −0.61 (IQR: −0.76 to −0.49). Younger age and lower BMIz at LI initiation, larger initial BMIz loss, and less social deprivation were linked with higher likelihood for moderate or pronounced BMIz loss compared with the no BMIz loss cluster (all $p < 0.05$).

Conclusions: These results support the importance of patient-tailored intervention and earlier treatment escalation in high-risk individuals who have little chance of success.

INTRODUCTION

The Childhood Obesity Task Force of the European Association for the Study of Obesity emphasizes the urgency of acknowledging childhood obesity as a chronic disease [1]. Data from Germany indicate a stabilization of the continuous weight increase among children since the year 2000, although on a high level [2]. For Germany, prevalence of childhood overweight amounts to 15.4% and prevalence of childhood obesity to 5.9%, with increasing prevalence by age and no sex difference [2]. Studies from 2021 and 2022 have pointed to an aggravating effect on childhood obesity by the COVID-19 pandemic, with increased body mass index *z* score (BMIz) change compared with prepandemic years (i.e., 2019 or 2005 through 2019), particularly among the youngest children living with overweight and obesity [3, 4]. Overweight/obesity can impact children's health in terms of cardiovascular risk, glucose derangements, sleep apnea, reduced quality of life, and social stigma throughout the life course [5]. Attempts to sustainably reduce overweight/obesity are urgently needed from health care, as well as policy and society, to assure population health.

In Germany, a variety of standardized lifestyle modification programs encompassing dietary, physical, and behavioral interventions exist, offered either in outpatient or inpatient (rehabilitation) settings. Although they are recommended as first-line treatment prior to pharmaceutical and surgical interventions [6], program quality, reimbursement by health care insurance, and evaluation/certification status differ widely. Because long-term efficacy of lifestyle intervention (LI) is often modest [1, 6], with children and adolescents entering LI programs being more heterogenous in terms of sociodemographic characteristics and presence of obesity-related risk factors [7], it is of major importance to identify individuals who are most likely to reduce BMIz successfully from conservative interventions. This study aimed to evaluate heterogeneous clusters of individual treatment responses for up to 2 years after initiating an outpatient LI. In a large cohort of 12,453 children and adolescents with overweight/obesity, we aimed to identify subgroups who were the most at risk of unfavorable BMIz responses. Furthermore, we evaluated individual features associated with treatment outcomes to aid clinicians in identifying those youths who might benefit most.

Study Importance

What is already known?

- From clinical experience, response to outpatient lifestyle intervention (LI) is known to vary widely among individuals, and long-term success is often modest.

What does this study add?

- In our study, for the first time, to our knowledge, and based on real-world data among a large cohort of children and adolescents living with overweight/obesity, heterogeneity of response to outpatient LI in terms of three distinct subclusters could be shown using an objective algorithm.
- Limited benefit is expected in older children and adolescents (age 11–18 years) living with severe obesity, coming from socioeconomically deprived areas, and having a migration background, as well as a family history of overweight/obesity.

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

- Our results underline the necessity of patient-tailored intervention. In high-risk individuals, intensified obesity treatment and therapy escalation should be offered early.
- Early initiation of outpatient LI at younger ages and in those with less severity of obesity is extremely important among pediatric individuals with overweight/obesity because it is linked with greater success.

METHODS

Adiposity patient registry

Since 2000, a nationwide initiative for standardized documentation of demographic, anthropometric, and metabolic characteristics of children, adolescents, and adults living with overweight/obesity has collected information on LI modality and intensity. Currently, 235 centers that are specialized in obesity care (outpatient or inpatient) from Germany, Austria, and Switzerland participate. Twice yearly, local data are anonymized and transmitted to Ulm, Germany. After validation and corrections (when applicable), data are aggregated into a cumulative database for quality assurance and research [7]. The APV (Adipositas-Patienten-Verlaufsdokumentation) initiative has been approved by the Ethics Committee at the University of Ulm (no. 133/22), and research is performed in accordance with the Declaration of Helsinki.

Study cohort

As of October 2022, a total of 132,578 individuals have been documented in the registry. For the study, patients aged 5 to ≤18 years with BMIz ≥ 1.28 (equals BMI ≥ 25 kg/m^2 in adults) [2] at the start of outpatient LI were analyzed. Longitudinal data on BMIz up to 2 years after LI initiation have been acquired. The follow-up was subdivided into four intervals: 3 months (T3); 6 months (T6); 1 year (T12); and 2 years (T24), representing the usual structure of follow-up visits after LI initiation. In the case of multiple BMIz values per individual, data were aggregated for the respective interval. For each individual, at least one BMIz at three of the four intervals was required. Individuals with syndromic, drug-induced, or endocrine causes of overweight/obesity were excluded, as well as individuals undergoing bariatric surgery or using metformin, orlistat, and/or glucagon-like peptide-1 receptor agonists owing to their potential effects on weight.

The final cohort comprised 12,453 children and adolescents with overweight/obesity from 148 centers specializing in obesity from Germany, Austria, or Switzerland.

Clustering variable

Because BMI varies with age and sex in children, BMI was age- and sex-standardized using national data as reference [8]. *Z* scores were calculated using Cole's Box-Cox transformation [9].

To evaluate treatment outcome, BMIz change is given as the difference (delta) between BMIz values at each time point and BMIz baseline. Delta-BMIz was used as the clustering target variable, with time since LI start as the underlying time scale. A BMIz reduction < 0.2 within 1 year was considered as "no success" [10].

Although concerns have been raised regarding the use of BMIz in youths with severe obesity, we decided to stick with BMIz as the clustering variable owing to comparability with other studies.

Covariates

Migration background was defined as the individual or at least one parent having been born outside Germany, Austria, or Switzerland. The German Index of Socioeconomic Deprivation (GISD) of the year 2012 was applied as an indicator for regional socioeconomic differences among individuals [11]. This version was selected because the time period of the assessment of GISD data lies within the treatment year of individuals studied. The index summarizes education, occupation, and income at the regional level and assigns individuals to GISD_{2012} quintiles by using the five-digit postcode of the residence. Quintile Q1 is linked with the lowest deprivation (privileged), whereas quintile Q5 is considered to be the highest deprivation (most disadvantaged).

Tanner stages (breast, genital, pubic hair) were used to assign individuals to pubertal stages. Prepuberty was defined as Tanner 1, puberty as Tanner 2 through 4, and postpuberty as Tanner 5. The presence of hypertension, dyslipidemia, and/or glucose derangement at baseline was summarized as existing obesity-related comorbidities. Hypertension was defined as blood pressure > 95th age-, sex- and height-specific percentile of the representative population-based German study KiGGS (German Health Interview and Examination Survey for Children and Adolescents) [12]. At least one abnormal lipid value (total cholesterol ≥ 200 mg/dL, low-density lipoprotein cholesterol ≥ 130 mg/dL, high-density lipoprotein cholesterol ≤ 35 mg/dL, or triglycerides ≥ 130 mg/dL) was defined as dyslipidemia [13]. Glucose derangement was defined as fasting blood glucose ≥110 mg/dL and/or hemoglobin A_{1c} ≥ 5.7% [14, 15]. In line with the World Health Organization (WHO) cutoff, a parent's BMI ≥ 25 kg/m^2 was considered as the presence of overweight/obesity.

Intensity of LI treatment was reflected by the duration of the program and by the number of therapy units (one unit equals 45 minutes) on nutrition, exercise, psychological counseling, and medical advice for the individual/parent. In a subgroup of individuals ($n = 8100$), additional information on treatment intensity and duration was available. Duration of LI was grouped by < 12 months or ≥ 12 months. Therapy units were added up over the 2-year follow-up. The beeline distance between home of residence and treatment facility was analyzed and grouped by < 25 km or ≥ 25 km.

Statistical methods

Descriptives are given as median with quartile or proportion. For the description of treatment intensity, mean with standard deviation is provided.

We employed the longitudinal k-means clustering algorithm (KmL) [16] to identify distinct clusters of individuals' trajectories according to their BMIz change (delta-BMIz) from baseline after LI initiation. Briefly, the KmL algorithm is an extension of the known k-means clustering technique, which iteratively aggregates observations into centroids according to the (dis)similarities among them, without supervision. Because KmL does not assume any trajectory distribution or form a priori [17], we chose this nonparametric approach to adequately handle anticipated fluctuations of BMI change in pediatric populations. The optimal number of clusters was determined using the Calinski and Harabatz [18] and the Ray and Turi [19]

TABLE 1 Cohort description at baseline (start of LI) overall and per cluster

Variable	All	Cluster: No BMIz loss (reference)	Cluster: Moderate BMIz loss	Cluster: Pronounced BMIz loss
N	12,453	4526	5574	2353
Age (y)	11.5 (9.7; 13.2)	12.3 (10.8; 13.8)	**11.1 (9.4; 12.9)**	**10.6 (8.5; 12.7)**
Migration background, %	24.2	26.3	25.3	**17.5**
Boys, %	47.4	48.3	47.7	**45.1**
BMIz	2.06 (1.79; 2.34)	2.07 (1.77; 2.33)	**2.08 (1.82; 2.35)***	2.02 (1.74; 2.35)
≥95th BMI percentile, %	85.3	84.3	**87.0**	83.2
Weight-z	2.05 (1.68; 2.41)	2.04 (1.65; 2.40)	**2.07 (1.71; 2.42)**	2.00 (1.65; 2.41)
Height-z	0.71 (0.03; 1.43)	0.62 (−0.07; 1.32)	**0.76 (0.09; 1.47)**	**0.77 (0.09; 1.49)**
$GISD_{2012}$, %				
Q1 (privileged)	14.6	12.4	**15.6**	**16.6**
Q2	19.8	17.0	**20.8**	**22.8**
Q3	17.8	17.8	18.1	17.1
Q4	26.8	30.6	**25.4**	**22.5**
Q5 (most deprived)	16.1	16.5	15.5	16.5
N/A	4.9	5.7	4.6	4.5
Developmental stages, %				
Prepuberty	39.6 (*n* = 5198)	30.5 (*n* = 2067)	**43.8** (*n* = 2301)	**50.7** (*n* = 830)
Puberty	48.7	53.9	**46.3**	**42.7**
Postpuberty	11.7	15.6	**9.9**	**6.6**
Parental overweight, %	33.3 (*n* = 7313)	35.4 (*n* = 2627)	33.7 (*n* = 3305)	**28.5** (*n* = 1381)
Obesity-related comorbidities[a], %	59.0 (*n* = 10,241)	60.8 (*n* = 3735)	58.7 (*n* = 4575)	**56.1** (*n* = 1931)
Distance to treatment center ≥25 km, %	14.3 (*n* = 10,215)	13.5 (*n* = 3703)	14.9 (*n* = 4630)	14.6 (*n* = 1882)

Note: Median with Q_1; Q_3, or proportion. *P* values are given for the comparison with the no BMIz loss cluster. Bold type indicates $p < 0.05$ compared with reference group (no BMIz loss).

Abbreviations: BMIz, body mass index *z* score; GISD, German Index of Socioeconomic Deprivation; height-z, height *z* score; LI, lifestyle intervention; N/A, not available; weight-z, weight *z* score.

[a]Hypertension and/or dyslipidemia and/or glucose derangement.

*Clinically not relevant; significance presumably owing to the high number of individuals studied.

criteria. To investigate any sex-specific trajectories, the approach was applied for boys and girls separately.

To validate our findings, we applied group-based trajectory modeling using SAS PROC TRAJ (SAS Institute Inc., Cary, North Carolina) [20, 21], in addition to KmL.

To identify sociodemographic and additional features linked with KmL cluster membership, multinomial logistic regression was used with cluster group as outcome. We started with a simple model, including sex as sole covariate, and added, in separate models, the following: age at LI start; BMIz at LI start; and migration background, respectively. A full model, including all of the aforementioned variables as covariates, was created. To this main model, additional covariates such as BMIz change within the first 3 months (</≥5%), pubertal stage (prepuberty, puberty, and postpuberty), socioeconomic deprivation (GISD quintile Q1–Q5), presence of obesity-related comorbidities (yes/no), parental overweight/obesity (yes/no), therapy duration (</≥12 months), or distance to treatment center (</≥25 km) were added. In all models, the "no BMIz loss" cluster was used as reference.

The KmL package (version 2.4.1) [17] was applied for clustering within the statistics software R (version no. 4.0.2; R, Vienna, Austria). All other statistics were carried out using SAS version 9.4 (TS1M7, SAS Institute). A two-tailed $p < 0.05$ was considered significant. Owing to multiple comparisons, *p* values were adjusted using false discovery rate.

RESULTS

Baseline characteristics of the study cohort are summarized in Table 1. Slightly more girls entered outpatient LI, and a migration background was documented in nearly one-quarter of enrolled individuals.

Three heterogeneous clusters of treatment response

Applying KmL, three distinct clusters of treatment response were identified (Figure 1). Children and adolescents belonging to the cluster that experienced, on average, a slight BMIz increase were labeled "no

TABLE 2 Type and intensity of treatment over a 2-year follow-up period per cluster

Variable	Cluster: No BMIz loss (reference)	Cluster: Moderate BMIz loss	Cluster: Pronounced BMIz loss
Medical advice (units)	7.7 (8.0) (*n* = 2518)	**6.8 (6.9)** (*n* = 3255)	**6.6 (6.3)** (*n* = 1348)
Nutritional advice (units)	20.3 (21.7) (*n* = 2687)	**21.3 (21.9)** (*n* = 3545)	21.9 (26.2) (*n* = 1573)
Psychological counseling (units)	18.2 (20.2) (*n* = 2186)	18.9 (19.5) (*n* = 2862)	19.3 (21.1) (*n* = 1218)
Physical advice (units)	58.3 (60.8) (*n* = 2151)	59.1 (59.7) (*n* = 2896)	58.0 (64.2) (*n* = 1263)
Patient advice[a] (units)	85.9 (91.6) (*n* = 2783)	87.6 (92.0) (*n* = 3680)	85.7 (97.4) (*n* = 1634)
Parental advice[b] (units)	34.7 (35.2) (*n* = 2639)	35.2 (36.1) (*n* = 3472)	**33.4 (36.3)** (*n* = 1483)
Overall advice[c] (units)	118.7 (121.7) (*n* = 2785)	120.9 (124.1) (*n* = 3681)	**116.0 (127.2) (*n* = 1634)**
Therapy duration ≥1 y, %	41.8 (*n* = 1105)	42.2 (*n* = 1520)	**48.9** (*n* = 610)

Note: Mean with SD or proportion. One unit equals 45 minutes; all units documented over the follow-up period (2 years) were summed per treatment category. Bold type indicates $p < 0.05$ compared with reference group (no BMIz loss).
Abbreviation: BMIz, body mass index *z* score.
[a]Sum of all education units provided to the patient, independent of type.
[b]Education units focused on parents (usually without child present).
[c]Overall units of patient/parent education, independent of type.

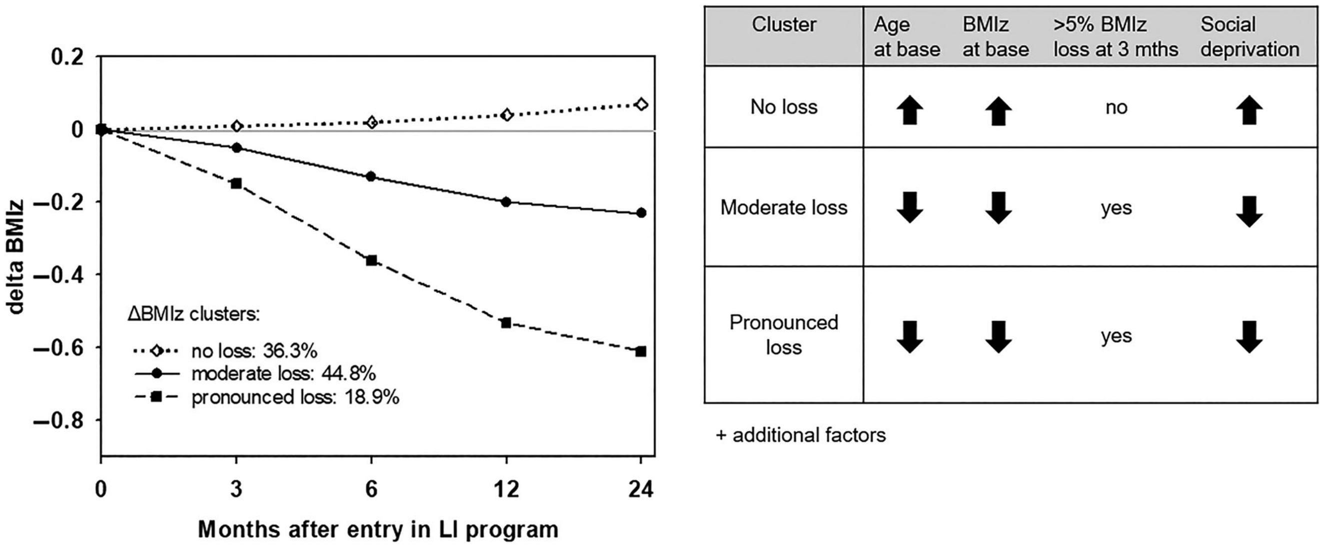

FIGURE 1 Three heterogeneous clusters of treatment response (BMI *z* score [BMIz] change) up to 2 years after initiation of outpatient lifestyle intervention (LI) in children and adolescents with overweight/obesity (*n* = 12,453). BMIz change is given as difference (delta) between quarterly/semiannually aggregated BMIz values at each time point (i) and the baseline value, for example, delta-BMIz (i) = BMIz (i) – (baseline BMIz). Negative values indicate a BMIz loss at the specific follow-up interval compared with baseline. Table indicates covariates linked with cluster membership based on multinomial logistic regression.

BMIz loss" (36.3%). Most individuals (44.8%) reached an average BMIz reduction of 0.2 at 1 year after LI start, with a continuous decrease thereafter, up to an average delta-BMIz of −0.23 (interquartile range [IQR]: −0.33 to −0.14) at 2 years of follow-up. This cluster was named "moderate BMIz loss." The smallest cluster comprised 18.9% of children and adolescents experiencing a "pronounced BMIz loss" up to an average of −0.61 (IQR: −0.76 to −0.49) at study end. Table 1 presents baseline features of the three subclusters identified.

Sex-specific analyses again revealed three distinct clusters. Visual inspection indicated similar patterns between boys and girls and almost comparable group sizes between sexes (Supporting Information Figure S1).

Group-based trajectory modeling by Nagin et al. [20], with three groups prespecified, indicated similar cluster patterns compared with KmL (Supporting Information Figure S2). The proportion of individuals allocated to the respective clusters was similar for the moderate BMIz loss cluster, slightly higher in the no BMIz loss cluster, and lower in the pronounced BMIz loss cluster. A total of 88.8% (11,056 out of 12,453) of children and adolescents were allocated to the same cluster by both approaches.

Predictors of treatment response group

Multinomial logistic regression was used to identify predictors of cluster membership. The first simple model, with sex as covariate and cluster group as outcome variable, yielded an Akaike information criterion (AIC; the lower the better) for goodness of fit of 25,966.

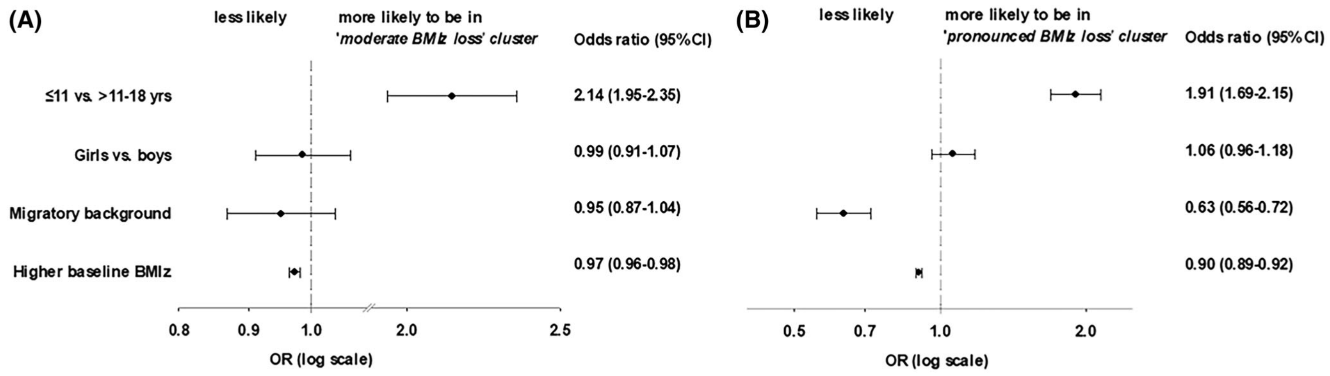

FIGURE 2 Odds (95% CI) of membership in (A) "moderate BMIz loss" cluster and (B) "pronounced BMIz loss" cluster by demographics and baseline BMI z score (BMIz) from multinomial logistic regression (reference is the "no BMIz loss" cluster). Odds ratios with 95% CI were estimated from multinomial logistic regression, including baseline age, sex, migration background, and baseline BMIz as covariates. For BMIz, data are given per 0.2-unit increase. For dichotomous variables, data are always given for "yes vs. no" if not otherwise stated.

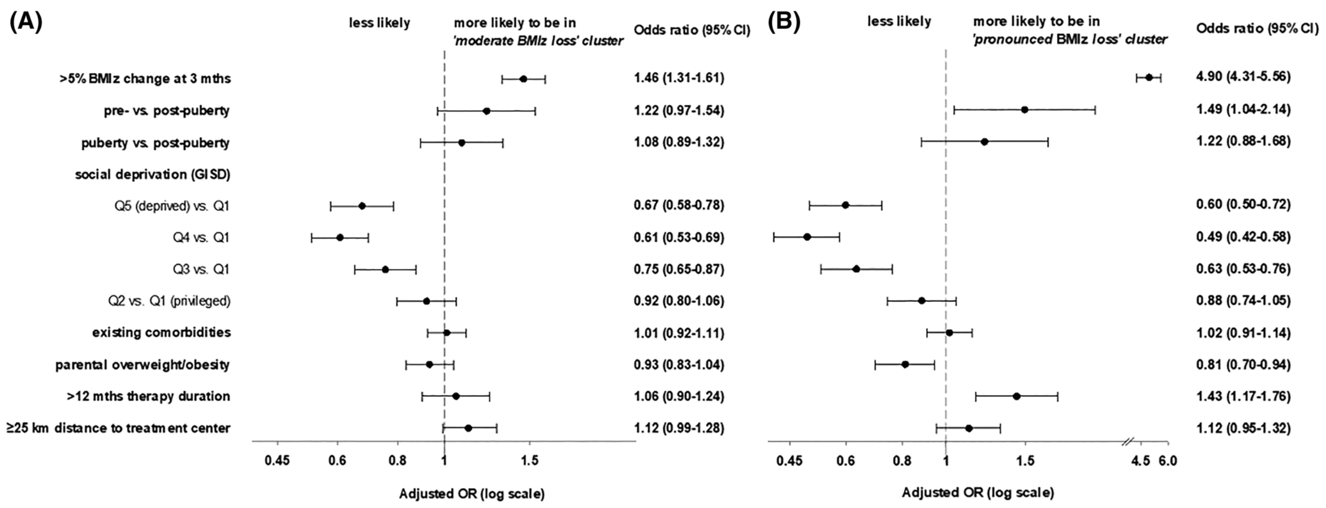

FIGURE 3 Adjusted odds (95% CI) of membership in (A) "moderate BMIz loss" cluster and (B) "pronounced BMIz loss" cluster by initial BMI *z* score (BMIz) reduction, pubertal status, socioeconomic deprivation, either parent having overweight/obesity, therapy duration, and distance to treatment center from multinomial logistic regression (reference is the "no BMIz loss" cluster). Odds ratios with 95% CI were estimated from multinomial logistic regression, adjusted for baseline age, sex, migration background, and baseline BMIz. All covariates were added each in a separate model adjusted for baseline age, sex, migration background, and baseline BMIz. For dichotomous variables, data are given for "yes vs. no" if not otherwise stated.

Adding age at LI initiation as covariate improved prediction capability. The further addition of baseline BMIz and migration background again lowered the AIC. The final main model yielded an AIC of 25,034.

What characterizes a "good responder?"

Figure 2B summarizes the odds for being in the cluster with pronounced BMIz loss, depending on demographics and baseline BMIz. Compared with the no BMIz loss cluster, the likelihood of belonging to the pronounced BMIz loss cluster was higher if the child was aged ≤11 years at LI initiation and had no migration background. Moreover, with each 0.2-unit increase in BMIz at LI initiation, the child was less likely to belong to the pronounced BMIz loss cluster. Figure 3B indicates additional markers linked with cluster membership. An initial BMIz reduction of more than 5% within the first 3 months and being prepubertal at LI entry were additional features linked with higher odds of pronounced BMIz loss, whereas living in socioeconomically deprived areas and having at least one parent with overweight/obesity were associated with a lower likelihood of being a "good responder" to LI. Regarding treatment intensity, a therapy duration of at least 12 months was linked with higher odds of belonging to the pronounced BMIz loss cluster (Figure 3B).

What characterizes a "moderate responder?"

Figures 2A and 3A summarize the odds of being in the moderate BMIz loss cluster, depending on demographics and other biomarkers. Again, the no BMIz loss cluster was used as reference. Similar to the pronounced BMIz loss cluster, a younger age and a lower BMIz at LI initiation were associated with a higher likelihood for moderate BMIz loss. In contrast, the presence of a migration background was no longer relevant for cluster membership. Furthermore, an initial BMI reduction of less than 5% within the first 3 months and living in socioeconomically deprived areas while starting LI lowered the odds for moderate BMIz loss.

Impact of type and intensity of treatment

Table 2 summarizes type and intensity of treatment for the subgroup with available details ($n = 8{,}100$). Documented lessons on dietary education, psychological counseling, physical activity reinforcement, medical advice, and parents' training varied widely among individuals. Overall, small differences among clusters could be observed.

DISCUSSION

To the best of our knowledge, this is the first real-world study aiming to longitudinally cluster heterogeneity of BMIz change among a large national sample of children and adolescents living with overweight/obesity and participating in outpatient LI. We aimed to identify subgroups with a high chance of successful BMIz reduction. We identified three distinct clusters, with almost half of pediatric individuals (45%) reaching a moderate BMIz reduction, on average, of −0.2 after 2 years. Only a small cluster of nearly 19% was identified with a pronounced BMIz reduction of more than −0.6 after 2 years. The remaining 36% of children and adolescents with overweight/obesity experienced, on average, no BMIz loss or even a slight increase.

Compared with previous cross-sectional studies focusing on average weight loss, the achievable BMIz reduction with LI has been shown to fall within a range of −0.15 to −0.3 after 1 year [22, 23] or −0.25 to −0.6 after 2 years [10, 22, 24]. Systematic reviews have reported BMIz reductions by LI of various length and intensity between −0.06 (95% CI: −0.10 to −0.02) [25] and −0.34 (95% CI: −0.66 to −0.02) [26]. Unfortunately, the heterogeneity of treatment settings, among and within countries, with various durations, different combinations of therapy components (physical/behavior/dietary intervention, parental involvement), program availability, reimbursement, and largely heterogeneous age ranges of children investigated, impedes valid comparisons. However, even a moderate loss of ≥0.2 BMIz units has favorable effects on the cardiometabolic risk profile in children and adolescents with overweight/obesity, independent of type of patient care. This underlines the importance of early identification and treatment of children at risk, as well as the beneficial effects of even moderate BMIz loss in the pediatric population [27].

A study from our group in 2014, including 3135 children with overweight/obesity undergoing a structured multidimensional LI, assessed treatment response cross-sectionally by grouping individuals into predefined subgroups due to their BMIz change at respective time points [10]. Interestingly, five distinct weight curves were reported. The most successful group had a similar BMIz reduction of approximately −0.6 within the first 2 years, which could be compared with our "pronounced BMIz loss" cluster. The different numbers of subgroups between these two studies can be explained by the distinctly different statistical approaches used. In this study, we used an unsupervised longitudinal technique that clusters individual BMIz change over time into subgroups, which are not defined a priori. This approach is superior in describing the real-life situation and, as such, it could help identify determinants of different trajectories. To validate our approach, we used an alternative methodology (group-based trajectory modeling by Nagin et al. [20]); again, we observed three subgroups of diverse treatment responses, with very similar BMIz trajectories over time compared with the KmL clustering and with a high proportion of individuals allocated to the same cluster in both approaches.

The proportion of children achieving successful BMIz reduction of at least ≥0.2 after 2 years with LI has been reported to be between 25% and 51% (with 10%–25% reaching a BMIz reduction > 0.5) [28, 29]. This underlines the success of outpatient LI in childhood obesity over at least 2 years observed in our study, with a success rate of more than 60%. However, this also indicates the need for intensified or alternative strategies for approximately one-third of individuals with minor or no response. Identifying pretreatment markers characterizing high-risk individuals will offer clinicians an opportunity to adapt treatment strategy and escalate treatment earlier by combining LI with pharmaceutical intervention or bariatric surgery where appropriate. For example, our study indicated that a child with treatment duration of more than 12 months had a higher likelihood of being in the pronounced BMIz loss cluster, emphasizing the permanent change of lifestyle as a key challenge. Previously, a treatment duration of at least 6 months has been linked with greater BMIz reduction [5, 29–31]. Moreover, the use of once-weekly semaglutide, a glucagon-like peptide-1 receptor agonist, in addition to LI among adolescents with obesity indicated a greater BMI reduction over 68 weeks compared with LI alone [32]. Although liraglutide is the only approved drug by the European Medicines Agency for adolescents aged 12 years or older with obesity [33], additional promising weight reduction drugs might be approved for this age group in the near future. However, treatment response to semaglutide in Weghuber et al. [32] was also highly heterogeneous, and this warrants a better understanding of the underlying mechanisms.

Contrary to previous studies evaluating few covariates, we analyzed a comprehensive set of variables potentially associated with cluster membership. In particular, a lower age and BMIz at LI initiation and at least 5% BMIz loss within the first 3 months were highly linked with pronounced or moderate BMIz loss. Conversely, individuals living in socioeconomically deprived areas were less likely to be successful in outpatient LI. For a pronounced BMIz loss, being native, being prepubertal, neither parent having overweight/obesity, and participation in LI for at least 1 year were additional relevant indicators. According to guidelines, multidisciplinary LI should be offered to children and adolescents with overweight plus relevant comorbidities or with a family risk constellation [6]. However, our data underline the relevance of early intervention because these children may have the greatest chance for successful long-term weight loss. Many previous studies have identified a link between younger age or lower degree of overweight at LI initiation with greater weight reduction [10, 29, 34–36]. Among a Dutch cohort, age ≤11 years also was linked with significantly higher BMIz loss compared with those aged 12 to 18 years [22]. Some aspect of BMIz reduction, particularly in those aged <12 years, may be attributable to spontaneous resolution of overweight (up to −0.18 BMIz within 1 year), albeit the chance decreases with severity of obesity and age [37]. Moreover, in younger children, parental involvement has been linked with better outcomes, particularly if lifestyle changes have been implemented early [25, 36, 38]. Age-specific physiologic development may additionally contribute to weight reduction. Adolescence and puberty have been shown to be a challenging period, with increasing autonomy, conflicts with parents, stress, less physical activity, and diminished parental but increasing peer-group influence all contributing to the often unfavorable weight course during this period of life [10, 22, 36]. Nevertheless, in successful adolescents, a greater responsibility for weight loss and weight loss maintenance compared with younger adolescents (aged <16 years) was reported, which underlines the importance of an individual's age and ability to take responsibility for his/her health [38].

Whereas the BMIz change within the first year of intervention was reported to be a strong predictor for BMIz reduction up to 5 years after LI [36], we observed that BMIz change within the first 3 months was highly predictive. An early BMIz reduction can enhance patient motivation by motivating patients to continue with improved lifestyle long term.

Furthermore, a high impact of privileged versus deprived families was demonstrated in our study because individuals living in privileged areas had higher odds of belonging to the pronounced or moderate BMIz loss classes. In contrast, a migration background seemed not to impede moderate BMIz loss, although, for pronounced loss, a migration background was unfavorable. Having a migration background and lower socioeconomic status has been related to lower odds for long-term weight loss [5, 10, 29], attributed to factors such as language and cultural barriers. Programs specifically tailored to the needs and abilities of families with lower socioeconomic status were shown to be effective at least in preventing weight gain [39], underlining the value of individualized LI programs adapted to the family situation.

Aside from family situation, family history impacts success. Whereas having a mother with obesity has been linked with reduced weight loss or with increasing BMIz in childhood in smaller studies [40, 41], we observed parental overweight/obesity as a proxy that hampers pronounced BMIz loss.

The association between sex and BMIz loss is complex. Although we and others have observed no differences between sexes [24, 29, 36], boys were reported to be more likely to reduce and maintain BMIz following LI [10].

Furthermore, program design seems to play a minor role, at least in our study, even though a recent review indicated the impact of diet and physical activity on BMIz decreases in LI programs for children [30]. The landscape of programs offered is large and depends on the treatment center. The high variability in the numbers and types of treatment units administered in our study might, to some extent, contribute to the lack of association between treatment intensity and cluster membership. Moreover, reverse causality could influence results, for example, because of escalating treatment for those struggling with BMIz decrease. Owing to the complexity of obesity/overweight, there are numerous other (modifiable) factors influencing BMIz beyond aspects addressed in this study. A biological barrier to long-term weight loss is the homeostatic model regulating body weight, food intake, and energy balance in order to keep the individual set point [42]. Contrary to former reports [5], genetic predisposition appears to play a minor role in weight reduction through LI in children [43, 44]. Patient and family adherence to behavioral recommendations is highly important for long-term outcome [45]. Moreover, the occurrence of COVID-19 was shown to negatively impact LI success [40]. Conflicting priorities (family interests, leisure time with friends) and less time for physical activities, as well as financial aspects (e.g., fresh food being more expensive), might hamper success, especially after the end of LI.

A limitation of many single-center studies is the high dropout rate or the lack of documentation of follow-up visits. Loss to follow-up may bias the results because successful children are more likely to attend follow-up visits. With the multicenter data collection, a large number of pediatric individuals with overweight/obesity from Germany, Austria, and Switzerland with longitudinal follow-up after outpatient LI is available in the APV registry, although, owing to the inclusion criteria (three of four time points), families with the best adherence might be selected. Another strength is the wide age range of the participants (5–18 years), enabling us to study the effect of age on treatment response. Moreover, the study describes the effect of LI under real-world conditions in contrast to randomized-controlled trials with preselected participants.

One limitation is that only individuals participating in outpatient LI have been considered. Individuals undergoing LI in a rehabilitation clinic ($n = 532$) with documented control visits during follow-up were excluded owing to different treatment intensity and structure of care. Second, treatment center and health care team composition might bias success rate, even though treatment center has not been predictive in one study [36]. Third, the APV registry covers more than 130,000 individuals with overweight/obesity from more than 230 centers, although the database is likely not representative for all children and adolescents with overweight/obesity in Germany, Austria, and Switzerland. Nevertheless, the most specialized treatment clinics are likely to be included because, at least in Germany, participation in the APV initiative is necessary for accreditation of obesity treatment centers and sometimes for cost reimbursement of the intervention. Fourth, individual socioeconomic status was not available. To capture individuals' socioeconomic situation, we used the GISD based on a regional level as a proxy.

CONCLUSION

Our study underscores the large heterogeneity of the effect of outpatient LI among young people living with overweight/obesity, with only a small proportion achieving good BMIz loss, whereas the majority had a moderate or no response. Limited benefit is expected in older children and adolescents (aged >11–18 years) with severe obesity who are coming from socioeconomically deprived areas and have a migration background, as well as a family history of overweight/obesity. For these high-risk individuals, other obesity treatment options such as medication or surgery might be offered early on to support BMIz loss. Moreover, early initiation of outpatient LI at younger ages and less severity of obesity is extremely important because it is linked with greater success. In general, patient-tailored intervention programs should be developed considering an individual's chance for success and with related predictors disclosed.O

AUTHOR CONTRIBUTIONS

Nicole Prinz contributed to conception and design of the study and the statistical analysis, drafted the manuscript, and created figures and tables. Hugo Pomares-Millan and Stefanie Lanzinger performed the statistical analysis, reviewed and edited the manuscript, and contributed to interpretation of results. Almut Dannemann, Christine Joisten, Antje Körner, Daniel Weghuber, Susann Weihrauch-Blüher, and Susanna Wiegand collected data and reviewed and edited the manuscript. Giuseppe N. Giordano and Reinhard W. Holl contributed to conception and design of the study and reviewed and edited the manuscript. All authors have given final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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CONFLICT OF INTEREST STATEMENT

Christine Joisten received honoraries for lectures by Berlin-Chemie AG; MSD Sharpe & Dohme GmbH; Novartis AG; AbbVie Inc.; Pfizer; Janssen Pharmaceuticals; Eli Lilly and Company; Chiesi Farmaceutici S.p.A; Chugai Pharmaceutical Co., Ltd.; Novo Nordisk A/S, Daiichi-Sankyo; Sanofi S.A.; and Pharmacosmos A/S. Moreover, Christine Joisten is part of an advisory board for Novo Nordisk A/S. Susann Weihrauch-Blüher received honoraries for lectures by Novo Nordisk A/S, Rhythm Pharmaceuticals, Merck Healthcare GmbH, and AstraZeneca and travel support by Merck Healthcare GmbH. Susann Weihrauch-Blüher is part of the advisory board "Obesity in Childhood" for Novo Nordisk A/S. The other authors declared no conflict of interest.

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SUPPORTING INFORMATION

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

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