

Title: The obesity epidemic in 32,936 youth with type 1 diabetes (T1D) in the German/Austrian DPV and US T1D Exchange (T1DX) registries

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Abbreviations: type 1 diabetes (T1D), Diabetes Control and Complications Trial (DCCT), Epidemiology of Diabetes Interventions and Complications (EDIC), body mass index (BMI), T1D Exchange clinic registry (T1DX), Diabetes Prospective Follow-up registry (DPV), BMI z-scores (BMIz), hemoglobin A1c (HbA1c), severe hypoglycemia (SH), World Health

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Organization (WHO), Centers for Disease Control and Prevention (CDC), German Health Interview and Examination Survey for Children and Adolescents (KiGGS)

Abstract (248/250 words)

Objective: Increased weight gain surfaced as a problem after intensive treatment became the standard of care for youth with type 1 diabetes (T1D). In this study, we examined the current extent of the obesity problem in two large pediatric clinical registries in the US and Europe and examined the hypotheses that increased BMI z-scores would be associated with higher HbA1c and increased frequency of severe hypoglycemia (SH) in youth with T1D.

Study Design: International (WHO) and national (CDC/KiGGS) BMI references were used to calculate BMI z-scores in participants (age 2-<18 years and ≥ 1 year duration of T1D) enrolled in the T1D Exchange (T1DX, n=11,435) and the Diabetes Prospective Follow-up (DPV, n=21,501). Associations between BMI z-scores and HbA1c and SH were assessed.

Results: Participants in both registries had median BMI values that were greater than international and their respective national reference values. BMI z-score was significantly higher in the T1DX versus the DPV ($p<0.001$). After stratification by age-group, no differences in BMI between registries existed for children 2-5 years, but differences were confirmed for 6-9, 10-13 and 14-17 year age-groups (all $p<0.001$). Higher BMI z-scores were significantly related to higher HbA1c levels and more frequent occurrence of SH across the registries, although these associations may not be clinically relevant.

Conclusions: Excessive weight is a common problem in children with T1D in Germany and Austria and, especially, in the US. Our data suggest that obesity contributes to the challenges in achieving optimal glycemic control in children and adolescents with T1D.

Introduction

Historically, obesity was rare in people with type 1 diabetes (T1D) due to ineffective methods to achieve glucose control. In 1993, the Diabetes Control and Complications Trial (DCCT) established the importance of intensive diabetes management in adults and adolescents with T1D (1, 2), but this therapy paradigm was accompanied by increased weight gain in intensively treated participants (3, 4). In the follow up to the DCCT, the Epidemiology of Diabetes Interventions and Complications (EDIC) study, increased body mass index (BMI) was associated with increased cardiovascular disease risk factors and markers of atherosclerosis (coronary artery calcification and carotid intima media thickness) (5). In a similar time period as the transition to intensive therapy for patients with T1D, Western countries have experienced an epidemic of pediatric obesity (6) and youth with T1D are unlikely to have been spared from these effects. Increased BMI in youth with T1D has been reported in clinic based and national cohorts (7-14) and is associated with a more atherogenic cardiovascular disease risk profile (11, 13, 15). Elevated BMI increases insulin resistance; however, the association of BMI, insulin resistance, HbA1c, SH, and daily insulin doses is complex. International data comparing BMI in youth with T1D and the association of BMI with glucose control across countries does not exist.

The T1D Exchange (T1DX) registry in the US and the Diabetes Prospective Follow-up (DPV) registry in Germany and Austria are two large consortia of pediatric diabetes centers that were established with an objective of improving the care of children with T1D through sharing of best practices and the collection of clinical outcome data in large numbers of patients. In this collaborative study, both T1DX and DPV used queries of their databases to describe the prevalence of elevated BMI z-scores (BMIz) in youth with T1D who were 2 to <18 years of age

and had ≥ 1 year duration of diabetes. In addition, we tested the hypothesis that increased BMIz was associated with poorer metabolic control (higher hemoglobin A1c [HbA1c] and increased frequency of severe hypoglycaemia [SH]) in both registries.

Methods

The T1DX Clinic Network includes 70 US based pediatric and adult endocrinology practices in 34 states. A registry of more than 26,000 individuals with T1D commenced enrollment in September 2010 (16). Each clinic received approval from a local institutional review board (IRB). Informed consent was obtained according to IRB requirements. Data were collected for the registry's central database from the participant's medical record and by having the participant or parent complete a comprehensive questionnaire, as previously described (16).

The DPV registry is a prospective longitudinal, standardized, and computer-based documentation system for patients with all types of diabetes. Currently, more than 90% of German and more than 70% of Austrian children with diabetes are included in the registry. Data are documented locally by the 391 participating centers in an electronic health record. Twice yearly, anonymized data are exported and transmitted for central analyses. Missing and inconsistent data are reported back to the centers for correction. Data collection is approved by the ethics committee at Ulm University and by the IRBs at the participating centers (17, 18).

This report includes data on 32,936 children 2 to <18 years of age, with T1D duration of at least 1 year and available height and weight data; 11,435 participants enrolled in the T1DX from September 2010 to August 2012 at 59 sites who care for pediatric patients and 21,501 patients

from 262 sites in the DPV who had at least one office visit in either 2011 or 2012. All eligible T1DX and DPV participants were included in this analysis. Median HbA1c over the year prior to the registry assessment, calculated from all available for the prior year but excluding any values obtained within 3 months of diagnosis, was used to represent HbA1c in this analysis. For both the T1DX and DPV, all HbA1c values were DCCT-standardized (19, 20). SH was defined by both registries as a hypoglycemic event in which seizure or loss of consciousness occurred. The numbers given correspond to the percent of patients with at least one SH event during the previous year. BMI percentiles and z-scores were calculated from height and weight and adjusted for age and sex, using both international (WHO) and national (CDC for T1DX and KiGGS for DPV) reference tables (21-26). Extreme BMIZ values <-3 and $>+3$ were truncated. In the WHO and the national reference populations, a BMIZ of 0 represents the mean value of the population; values above the mean are positive and values below the mean are negative. BMI categories were defined using BMIZ according to pediatric standards for each source (22, 26, 27). Underweight individuals were excluded from analyses assessing glucose control, as underweight status in adolescents with T1D is often due to eating disorders and psychiatric disorders have a strong impact on HbA1c and SH.

In the T1DX, data were obtained through a combination of clinic and participant-report. Method of insulin delivery (pump/injection), height, weight, HbA1c values, and frequency of SH were extracted from the medical chart. Rates of self-monitoring of blood glucose and insulin dose were obtained from participant report via completion of a questionnaire. Conversely, all data from the DPV was extracted from the electronic medical record, as documented by members of the local diabetes team during routine patient care. All data from T1DX were obtained at the

enrollment visit through retrospective chart review and data from DPV were collected from office visits that occurred during 2011 or 2012 (a similar time period as T1DX enrollment).

Statistical Methods

To compare BMI between the two registries, a mixed model was performed, using BMI_z calculated from the WHO reference tables. The model accounted for site differences and adjusted for T1D duration, sex, age group, and the interaction between registry and age group. Mixed models also were conducted to assess whether BMI was associated with HbA1c or SH, overall (WHO reference and adjusted for T1D duration, sex, age group, registry, and random site effect) and within each registry (CDC or KiGGS reference and adjusted for T1D duration, sex, age group, and random site effect). Tests of significance were reported from models using BMI_z as a continuous variable; adjusted means were reported from models using BMI as a categorical variable. Underweight individuals (based on corresponding cutoffs for underweight categorization) were excluded from these analyses. While BMI_z adjusts an individual BMI value for age and sex of the reference population, these factors were not fully adjusted for in our population, and thus were included in the statistical models to account for residual confounding that could be present in this analysis cohort. All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC). All p values are two-sided. *A priori*, in view of the large sample size and multiple comparisons, only p values <0.01 were considered statistically significant.

Results

Participant characteristics of children in the T1DX and DPV registries can be found in Table 1. Children in both registries were similar with respect to sex, total daily insulin dose per kg (TDI),

and frequency of SH, but a higher percentage of children in T1DX were using an insulin pump (56% vs 45%). Children in T1DX also had a higher mean HbA1c level (8.5% vs 7.9%) than those in DPV.

Children in both registries had elevated BMI compared to international reference values (unadjusted median BMIz 0.78 for T1DX and 0.65 for DPV) and their respective national reference values (unadjusted median BMIz 0.74 for T1DX and 0.33 for DPV) (Table 1).

Overall, by the WHO, 12% (n=3,977) of children in both registries combined were considered obese, 24% (n=7,825) overweight, 64% (n=20,942) normal weight, and <1% (n=192) underweight (Table 2).

When comparing BMIz between the registries using WHO reference tables, BMI was significantly higher in T1DX than in DPV ($p < 0.001$, Table 1). Differences in least squares mean BMIz by age group are shown in Figure 1, adjusted for T1D duration, sex, age group, and the interaction between registry and age group. No significant difference in BMIz was found in the 2 to <6 year old group ($p = 0.10$), but children in T1DX had higher BMIz than DPV children in all other age groups ($p < 0.001$ for all).

Overall, higher BMIz (WHO) was associated with higher HbA1c, adjusted for T1D duration, sex, age group, and registry (Figure 2a, $p < 0.001$). When we looked at the registry-specific BMIz (CDC or KiGGS), higher BMI was also associated with higher HbA1c within each registry ($p < 0.001$ for both, adjusted for T1D duration, sex, and age group). Similarly, higher BMIz (WHO) was associated with increased frequency of at least one SH event in the past year,

adjusted for T1D duration, sex, age group, and registry (Figure 2b, $p < 0.001$). However, when looking at registry-specific BMIz (CDC or KiGGS), higher BMIz was significantly associated with SH within DPV ($p = 0.004$) but only marginally within T1DX ($p = 0.05$).

Discussion

In contrast to historic experience, our data demonstrate that youth with T1D have elevated BMIz compared to the international norms developed by the WHO and the respective national norms for youth in the US and in Germany/Austria. These data extend the findings of recent reports from the DCCT/EDIC study to highlight the consistency of elevated BMI in Western countries in which intensive management of T1D is standard of care (5). Of particular concern, our cross-sectional data also demonstrate that higher weight in youth with T1D may be inversely associated with achieving the goals of intensive treatment, since increased BMIz was associated with higher HbA1c in both registries. This relationship between HbA1c and BMI was not found in a recent paper by Redondo et al, but that study assessed a cohort of newly diagnosed patients with T1D, whereas our report was limited to participants with at least 1 year T1D duration (mean duration 4.8 ± 3.5 years) (28). Increased BMIz was associated with a greater risk of SH in the DPV cohort, but an association between BMI and SH was not found in the T1DX registry. However, these differences in HbA1c and SH between BMI groups were small and may not be clinically relevant. Further, the cause-effect relationship of the association between SH and BMI is uncertain.

When comparing to international WHO BMI standards, youth in the T1DX were more obese than youth in the DPV, except in the 2-<6 year old group. It is likely that the differences in

lifestyle and nutrition that contribute to increased rates of obesity in non-diabetic children in the US compared to Europe also contribute to the different prevalence of overweight and obesity in youth with T1D. Whether differences in nutritional counseling and carbohydrate counting recommendations for patients with T1D between US and Europe also contribute to these trans-Atlantic differences in BMI remains to be determined.

Healthy weight is an important component of care for youth with T1D but how to achieve this goal while maintaining glucose and HbA1c levels as close to normal as possible with intensive insulin therapy has not been established. Greater attention to avoidance of excessive caloric intake and better food choices early in the treatment of T1D, encouragement of regular physical activity, reduced screen time, and the elimination of unnecessary snacks are among the factors that could play roles in achieving and maintaining healthy weights in this population. Given the challenges of preventing and treating obesity in youth with T1D who receive intensive treatment, adjunctive therapies to insulin, like metformin, GLP1 agonists and SGLT2 inhibitors that have been shown to lower HbA1c and body weight in adults with T2D, could be important additions to current options for care in youth with T1D (29, 30).

Recent studies indicate that the benefits of limiting excessive weight gain in children and adolescents with T1D extend beyond improvements in body image and psychosocial well-being to include a reduction in insulin resistance and cardiovascular risk factors. Insulin resistance is increased in youth with T1D compared to non-diabetic youth of similar age, sex, and BMIz, especially in children who fail to achieve target HbA1c levels (31, 32). As insulin resistance increases so do cardiovascular disease risk factors (33). Similarly, data from the DCCT/EDIC

study in adults with T1D indicate that excessive weight gain is associated with insulin resistance, hypertension, dyslipidemia, central obesity, and more extensive atherosclerosis (as assessed by coronary artery calcium and carotid intima media thickness) (5). Further studies on the magnitude of the association of obesity with vascular disease risk factors in youth with T1D are needed (34).

As with any comparison between two large clinical registries, differences in the data collection methods are a potential limitation. SH events were clinic-reported for both registries; however, the type of data extraction—manual for T1DX and automatic for DPV—may have led to underreporting of events within T1DX. For this report, while there may be some differences in the collection of height and weight measurements across the clinics, it is highly unlikely that all errors are in the same direction, thus reducing the possibility of systematic bias. Additionally, standardized measurements of height and weight using calibrated devices and trained personnel is standard in pediatric endocrine /diabetes clinics taking care of children with T1D. Regarding possible differences in HbA1c measurements, we have previously reported that in both registries HbA1c methods are DCCT standardized and three different sensitivity analyses did not change results in a comparison focused on between-registry HbA1c differences in children <6 years of age (19). However, it is possible that assay variation may mask relationships with HbA1c. As noted above, the very large sample sizes of the two registries may result in associations that are statistically significant but not clinically important. It also should be noted that the reference tables used to calculate BMIz are somewhat outdated, particularly CDC data, which dates prior to 2000. The KiGGS reference tables are also somewhat dated, as the normative data was collected from 2003-2006. However, for the aim of comparing BMI between the registries, the

potentially outdated reference tables are not a limitation. Finally, the DPV registry is a population-based sample that included 70-90% of all potential patients in Germany and Austria whereas the T1DX registry is a sample of patients from participating pediatric diabetes centers staffed by pediatric endocrinologists and only includes the children of families who volunteered to participate. The T1DX registry participants represent about one fourth of the patients with T1D who are followed at a T1D Exchange Clinic Network site (16), thus the T1DX data may not be representative of all youth with T1D in the US. While it is difficult to compare socioeconomic status between the two registries, the proportion of minorities was similar for each group—21% of T1DX participants were not non-Hispanic white and 20% of DPV participants had a history of migration (defined as at least one parent born outside of Germany or Austria).

In conclusion, the obesity epidemic has not spared youth with T1D, as youth in both the T1DX and DPV registries have elevated BMIz, with youth in the T1DX being more obese than those in DPV. Increased obesity in youth with T1D has negative implications for glucose control, vascular disease risk factors, and future health outcomes. Data from large registries such as the T1DX and the DPV allow for comparison of diabetes care and the opportunity to focus clinical care to improve outcomes for people with T1D. An important future direction is to further delve into how practices differ between countries in an effort to discover which diabetes care strategies are most effective for youth with T1D.

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A listing of the T1D Exchange Clinic Network and DPV sites and investigators is available in the online supplemental file.

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Figure 1. Mean BMI Z-Score in T1DXvs. DPV by Age*

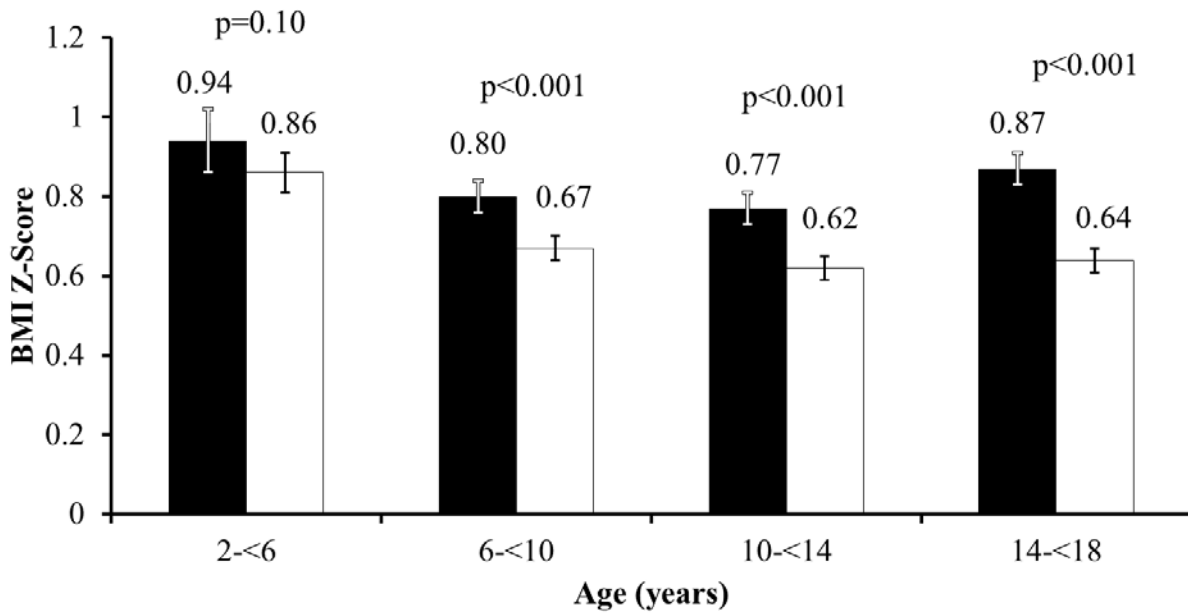


Figure Legend

Solid black bar= T1D Exchange

Solid white bar= DPV

Error bars show 95% CI.

*Means and p values obtained from a mixed model comparing BMI z-score (WHO reference) between the two registries, adjusted for T1D duration, sex, age group, random site effect, and the interaction between registry and age group. BMI z-score of 0 is equivalent to the mean value of the WHO reference population.

Figure 2a. Mean HbA1c by BMI Category*

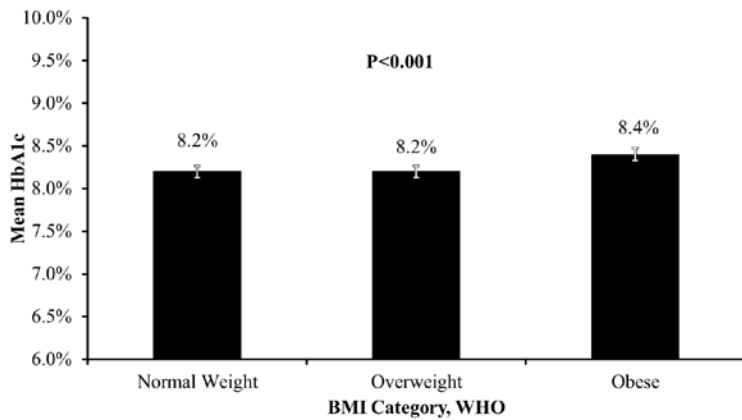


Figure Legend

Black bar= Mean HbA1c. Error bars show 95% CI.

*P value obtained from a mixed model adjusted for T1D duration, sex, age group, registry, and random site effect, with BMI z-score as a continuous variable. Means obtained from a mixed model adjusted for T1D duration, sex, age group, registry, and random site effect, with BMI as a categorical variable. Underweight individuals were excluded.

Figure 2b. Percent with Severe Hypoglycemic Event in Past Year by BMI Category*

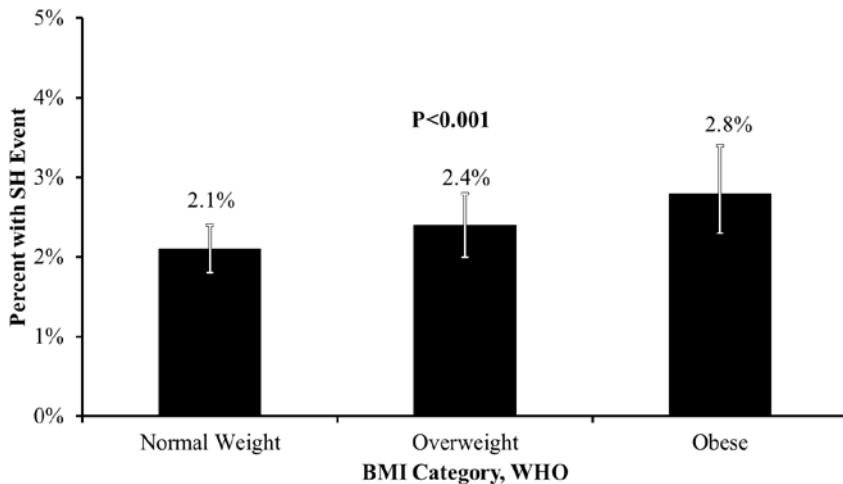


Figure Legend

Black bar= Percent with ≥ 1 severe hypoglycemia event (seizure/loss of consciousness) in the past year. Error bars show 95% CI.

*P value obtained from a mixed model adjusted for T1D duration, sex, age group, registry, and random site effect, with BMI z-score as a continuous variable. Means obtained from a mixed model adjusted for T1D duration, sex, age group, registry, and random site effect, with BMI as a categorical variable. Underweight individuals were excluded.

Table 1. Participant Characteristics of T1DX and DPV

| | Overall N=32,936 | T1DX N=11,435 | DPV N=21,501 |
|---|-----------------------------------|-----------------------------------|-----------------------------------|
| Male - (%) | 52% | 51% | 52% |
| Age - median (25th, 75th percentile) | 12.6 (9.5, 15.1) | 12.8 (9.9, 15.3) | 12.4 (9.2, 15.0) |
| T1D Duration - median (25th, 75th percentile) | 4.0 (1.9, 7.0) | 4.0 (2.0, 7.0) | 3.6 (1.4, 6.7) |
| BMI Z-score (WHO) - median (25th, 75th percentile) | 0.70 (0.07, 1.36) | 0.78 (0.16, 1.47) | 0.65 (0.02, 1.30) |
| BMI Z-score (CDC and KiGGS) - median (25th, 75th percentile) | N/A | 0.74 (0.18, 1.30) | 0.33 (-0.24, 0.89) |
| Insulin Pump Use - (%) | 49% | 56% | 45% |
| HbA1c (%) - mean\pmSD mmol/mol | 8.1 \pm 1.4% 65.1 \pm 15.2 | 8.5 \pm 1.4% 68.9 \pm 15.1 | 7.9 \pm 1.4% 63.1 \pm 14.9 |
| Frequency of Self-Monitoring of Blood Glucose - median (25th, 75th percentile) | 6 (5, 8) | 6 (4, 7) | 6 (5, 8) |
| Total Daily Insulin Dose (units/kg body weight) - median (25th, 75th percentile) | 0.82 (0.65, 1.02) | 0.82 (0.64, 1.03) | 0.82 (0.66, 1.02) |
| Percent Prandial Insulin - median (25th, 75th percentile) | 57% (48%, 65%) | 56% (47%, 65%) | 57% (48%, 65%) |
| ≥ 1 Severe Hypoglycemic Event[∞] in Past 12 Months - (%) | 2.5% | 2.4% | 2.5% |

Data shown are unadjusted percentages, mean \pm SD, or median and inter-quartiles (25th, 75th percentile).

[∞]Resulting in seizure/loss of consciousness

Table 2. BMI Categories* Overall and by Registry, according to each Reference Table

| | Overall N=32,936 | T1DX N=11,435 | DPV N=21,501 |
|------------------------|-----------------------------------|--------------------------------|-------------------------------|
| WHO Reference | | | |
| Underweight - N (%) | 192 (<1%) | 61 (<1%) | 131 (<1%) |
| Normal weight - N (%) | 20,942 (64%) | 6,844 (60%) | 14,098 (66%) |
| Overweight - N (%) | 7,825 (24%) | 2,791 (24%) | 5,034 (23%) |
| Obese - N (%) | 3,977 (12%) | 1,739 (15%) | 2,238 (10%) |
| CDC Reference | | | |
| Underweight - N (%) | 317 (1%) | 86 (<1%) | 231 (1%) |
| Normal weight - N (%) | 22,629 (69%) | 7,228 (63%) | 15,401 (72%) |
| Overweight - N (%) | 6,599 (20%) | 2,547 (22%) | 4,052 (19%) |
| Obese - N (%) | 3,391 (10%) | 1,574 (14%) | 1,817 (8%) |
| KiGGS Reference | | | |
| Underweight - N (%) | 988 (3%) | 311 (3%) | 677 (3%) |
| Normal weight - N (%) | 27,178 (83%) | 9,142 (80%) | 18,036 (84%) |
| Overweight - N (%) | 3,507 (11%) | 1,392 (12%) | 2,115 (10%) |
| Obese - N (%) | 1,263 (4%) | 590 (5%) | 673 (3%) |

*BMI categories defined as follows:

- WHO: Underweight: Z-score < -1.881 (<3rd percentile)
Normal weight: $-1.881 \leq Z\text{-score} \leq 1.036$ (3rd-85th percentile)
Overweight: $1.036 < Z\text{-score} \leq 1.881$ (>85th-97th percentile)
Obesity: Z-score > 1.881 (>97th percentile)
- CDC: Underweight: Z-score < -1.645 (<5th percentile)
Normal weight: $-1.645 \leq Z\text{-score} < 1.036$ (5th-<85th percentile)
Overweight: $1.036 \leq Z\text{-score} < 1.645$ (85th-<95th percentile)
Obesity: Z-score ≥ 1.645 (\geq 95th percentile)
- KIGGS: Underweight: Z-score < -1.282 (<10th percentile)
Normal weight: $-1.282 \leq Z\text{-score} \leq 1.282$ (10th-90th percentile)
Overweight: $1.282 < Z\text{-score} \leq 1.881$ (>90th-97th percentile)
Obesity: Z-score > 1.881 (>97th percentile)