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Complications associated with underweight primary immunodeficiency patients: prevalence and associations within the USIDNET Registry

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Abstract

Purpose: The point prevalence of underweight status and obesity in primary immunodeficiency disease (PID) is unknown, despite the described associations between PID and weight loss and failure to thrive. The goal of this study is to estimate the prevalence of underweight status and obesity in PID patients and to investigate the associations between abnormal body weight and complications of PID.

Methods: Using the United States Immunodeficiency Network (USIDNET), we performed a retrospective analysis of 653 pediatric (age 2 to 20 years) and 514 adult (age>20) patient records with information on patient body mass index (BMI). Prevalence of underweight and obese status in PID patients were compared to data from the National Health and Nutrition Examination Survey (NHANES).

Results: After separating BMI data by year of entry to the database, we demonstrated that both adult and pediatric patients with PID had significantly higher prevalence of underweight patients in multiple years of analysis. Further examination of underweight patients by PID diagnosis revealed underweight status in adults with CVID was associated with granulomatous disease as well as earlier age of CVID diagnosis. In the pediatric CVID cohort, underweight status was significantly associated with lymphopenia. Examination of obesity in pediatric and adult PID patients compared to NHANES database revealed only a single year when obesity in PID patients was significantly less prevalent. In other two-year time intervals from 2005–2014, the prevalence of obesity was unchanged in children and adults.

Conclusions: These results quantify the prevalence of underweight status in PID in a North American population and demonstrate that whether as a result of weight loss or poor weight gain, underweight status is more prevalent in the PID population than in the general US population. The

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prevalence of obesity in PID patients was similar to that seen in the general population. This highlights the need for continued education on the association of low weight and PID.

Keywords

primary immunodeficiency; common variable immunodeficiency; failure to thrive; obesity; underweight; National Health and Nutrition Examination Survey (NHANES)

Introduction:

Primary immunodeficiency diseases (PID) are a heterogeneous group of congenital defects in the immune system which lead to susceptibility to infections, as well as autoimmunity, lymphoproliferation, and atopy. Even in monogenic PID, penetrance can be variable resulting in heterogeneity in phenotype. The prevalence of disease-modifying factors are poorly understood in PID patients, which further confounds the ability to understand the prognosis of this population. Thus, the frequency of modifiable risks like underweight or obese body habitus which may alter the risks of complications in PID are important to define across the population of PID patients.

Historically, failure to thrive (FTT) and poor weight gain have been described as a textbook presenting feature of numerous PID. Due to this, FTT has been incorporated in the various "warning signs" systems developed to screen for PID in pediatric patients and weight loss has been incorporated in the adult criteria [1,2]. These criteria were based on expert consensus, however, additional analyses of pediatric patients with PID has supported failure to thrive one of the main clinical predictors of immunodeficiency in children with high specificity and sensitivity [2–4]. FTT and poor weight gain in PID is multifactorial and has been associated with increased metabolic demand, decreased oral intake and poor nutrient absorption due to inflammatory or infectious GI disease [5–7].

Conversely, little is known about the significance of obesity in PID. In western countries over the last decades the rate of obesity has increased significantly over the last half-century [8–11]. Obesity is a recognized worldwide health problem due to increased obesity-associated health risks including diabetes, cardiovascular disease and cancer. However, little is known about the overall prevalence of obesity in the PID population, and how differences in body weight may affect the presentation of PID. In addition to the adverse effects of diabetes on immune function, there have been several demonstrations of subtler immune anomalies due to obesity. Obesity has been associated with decreased natural killer cell numbers and function as well as lymphocyte proliferation in response to mitogens [12–16]. Increased adiposity has been linked to baseline adipocyte dysfunction and immune dysregulation, resulting in higher circulating levels of pro-inflammatory cytokines, such as TNFα, IL-6, and IL-18 [17]. This process is complex and depends upon tissue infiltrating lymphocytes and macrophages [18], and it is unclear to what extent it would be altered in patients with various forms of PID.

Herein we present the first examination of the prevalence of underweight and obese status in adult and pediatric PID populations using data from the US Immunodeficiency Network

(USIDNET) Database. Additionally, we sought to understand the relationship between underweight and obese body weight and disease complications in PID patients.

Methods:

We performed a retrospective analysis of the US Immunodeficiency Network (USIDNET) for all patient records containing complete information on Body Mass Index (BMI) data. The USIDNET is a research consortium that maintains a patient-consented registry of clinical, molecular and laboratory data from primary immunodeficiency patients in North America [19]. Collection of patient data for this database requires Institutional Review Board approval from the patient's home institution, and all patients provided informed consent for inclusion of their clinical data into the database.

Our search resulted in 1,408 records of PID patients with BMI information. Observations which did not contain a valid age, height, weight or gender were censored, leaving 1,167 patient records for analysis. Patient age at data entry was used to categorize patients into adult (age>20) and pediatric (age 2 to 20 years) groups for further analysis. Age cutoffs for inclusion into the pediatric group were chosen based on validation of standard BMI growth chart data for children ages 2 to 20 years old from the Center for Disease Control (CDC) [20,21]. There were 653 pediatric (age 2 to 20 years) and 514 adult (age>20) patient records. Initial visit BMI data was used from the USIDNET database as provided from the clinician for all BMI analyses in this study. For adult patients (age >20 years), body weight category was determined according to standard definitions as follows: underweight (BMI <18.5), normal weight (BMI 18.5 to <25), overweight (BMI 25 to <30) and obese (BMI 30 or higher) [22].

Pediatric BMI standard charts for boys and girls aged two to twenty were downloaded from the United States CDC website [20]. BMI percentiles were interpolated from these standard BMI tables using the gender, age and BMI data provided to USIDNET for each patient. Data for children under the age of two was not analyzed in this study due to uncertainty if recumbent length had been obtained reproducibly for each patient. BMI percentile data for patients 2 to 20 years old were used to determine body weight category according to standard pediatric definitions as follows: underweight (BMI percentile $<5^{th}$), normal weight (BMI percentile 5^{th}-85^{th}), overweight (BMI percentile 85^{th}-95^{th}) and obese (BMI percentile$\geq 95^{th}$) [20,21].

Data received from USIDNET for analysis in this study included diagnosis, age of onset of symptoms, age of diagnosis and age at entry, year of birth, race, gender, details of immunoglobulin replacement therapy if used (age at initiation of therapy, route, and dose) and types of complications reported. Complications examined included infectious outcomes, autoimmune and atopic complications which were analyzed by BMI category within subsets of adult and pediatric patients with the same PID diagnosis to determine if obese or underweight status were associated with increased adverse events. Data were used as entered into USIDNET by investigators, and statistical analyses were performed in Stata (StataCorp, Collegetown, TX) and Graphpad prism (Graphpad Software Inc, La Jolla, CA).

Results

The goal of this study was to determine the prevalence of underweight and obese body weight within the population of patients in the USIDNET. After exclusion for incomplete data, our search returned 653 pediatric (age 2 to 20 years) and 514 adult (age ≥20 years) patient records. Our combined cohort represented 30.6% of the overall USIDNET database which had enrolled 3,808 patients at the time of this study. Tables 1 and 2 compare our pediatric and adult study cohorts to the overall patient population in the USIDNET. In both pediatric and adult study cohorts, there were more male patients. This was more predominant in the pediatric cohort with 67% male patients compared to 58.7% males in the adult patient cohort. This was comparable to the overall USIDNET database, which was comprised of 63.4% male patients (Table 1 & 2). Overall, our cohorts had similar age, gender and race profiles when compared to the overall PID population captured in the USIDNET database. In adult patients (Table 2), common variable immunodeficiency (CVID) affected 67% of patients, representing the majority of the study cohort. An additional 9.3% of adult patients were categorized as having a miscellaneous antibody deficiency, which encompasses humoral defects not meeting criteria for CVID or agammaglobulinemia, including specific antibody deficiency, hypogammaglobulinemia, isolated immunoglobulin G subclass deficiency and selective IgA deficiency. Notably, agammaglobulinemia, chronic granulomatous disease and 22q11.2 were not as well represented within our adult study cohort when compared to proportions of patients in the USIDNET overall. Our pediatric cohort (Table 1), had a lower proportion of patients with humoral diagnoses when compared to the adult study cohort. This reflected more diversity in the cohort's PID diagnoses with higher proportions of patients with 22q11.2 deletion syndrome, agammaglobulinemia, severe combined immunodeficiency (SCID), Wiscott-Aldrich Syndrome, and chronic granulomatous disease (CGD) which more closely mirrored that seen in the overall USIDNET cohort.

We examined the overall prevalence of obesity and underweight status in our adult and pediatric USIDNET body weight study cohorts (Figure 1). In adult patients (Figure 1A), the overall prevalence of obesity was 25.8 (95%CI 22.2–29.8). We observed that 12% of adult patients in our cohort met criteria for class 2 obesity with BMI between 35 and 40. 4.4% of adults in the cohort met criteria for class III obesity with BMI over 40. There were no statistically significant differences seen between men and women (Figure 1A) or between adults with different types of PID diagnoses (Figure 1B). In comparison to national data, BMI-defined obesity for adults has exceeded 30% in the US since 1999, and with disparities across race and gender [23]. During this period of time the prevalence of obesity in the US youths increased steadily from 13.9% in 1999 to 17.2% in 2013 [24]. In our pediatric patients (Figure 1C), we observed a comparable prevalence of obesity to what has been observed in US population data with overall prevalence of 13.2 (95%CI 10.8–15.9). With rising rates of national obesity, the annual prevalence of underweight status in the US adults has steadily declined from 2% in 1999 to 1.4% in 2013; in children the corresponding drop has been from 4.2% to 3.8% across the same time frame [25,26]. We observed an adult rate of 5.6% (95%CI 4.0–8.0) underweight patients (Figure 1A) and pediatric prevalence of 6.6%

(95%CI 4.9–8.8) underweight patients (Figure 1C). This seemed to represent an increase over national rates, therefore we undertook further analysis to verify this.

We therefore analyzed BMI data on a year-by-year basis using the USIDNET BMI entry year, permitting additional specific comparisons to national statistical weight data. USIDNET BMI data results from 2005 through 2014 were compared to National Health and Nutrition Examination Survey (NHANES) BMI Data. NHANES is a cross-sectional, representative survey of the United States non-institutionalized population which involve both survey and examination measures for data collection [27–29]. The NHANES Survey design includes oversampling of some ethnicities. For comparison, from 2011–14, 20,015 total patients were surveyed of which 33.3% were white, 25.0% were black, 11.7% were Asian; of these 25.8% were Hispanic [30]. Despite these variations in demographics from our USIDNET cohort population, NHANES is a reliable source of cross sectional BMI data in the US population as it uses also uses examination-based measures of BMI like the USIDNET. As patient-reported BMI has high levels of error, we felt that this would be the most accurate comparison population for our North-American based PID population. We excluded data from years 1999–2004 in this analysis because there were less than 20 enrolled USIDNET participants in our cohort per year during this time. There were no statistically significant differences in the prevalence of obesity reported in USIDNET compared to NHANES for adults or children, with the exception of adults in year 2009–10 when there was a statistically significant decrease in obese patients in the USIDNET cohort(Figure 2A, C) [31]. However, in adults we observed statistically significant increased underweight prevalence (Figure 2B) in years 2005–06, 2009–10, and 2013–14 [25]. In pediatric patients, we observed a similar increase in the prevalence of underweight patients seen in USIDNET in 2011–12 and 2013–14 when compared to NHANES (Figures 2D) [24,26]. As seen in Figure 1D, underweight pediatric patients were present in all diagnostic categories. In contrast, 79% of underweight adult patients had CVID (Figure 1B) representing 6.6% of the total CVID cohort, which likely reflects that the majority of adult patients in this cohort had CVID.

Given that the majority of underweight patients in the adult cohort had CVID, we next examined complications of CVID across body weight categories (Table 3). We aimed to determine if there were significant associations in underweight or obese body weight with known complications of CVID including sinopulmonary infections, cytopenias, bronchiectasis and interstitial lung disease. In the adult cohort of CVID patients, there was a significant association of underweight status with granulomatous disease (Table 3), with an associated odds ratio of 6.8 (95% CI 1.8–24.7) compared to patients of normal weight. We next examined the pediatric CVID cohort for similar complications of CVID across body weight, using pediatric appropriate body weight percentiles as in previous analyses. Interestingly, in the pediatric CVID population (Table 4), we did not see any significant association of body weight with infectious burden or with granulomatous disease. However, there was a significant association of underweight status with lymphopenia in pediatric patients with CVID with odds ratio of 8.8 (95% CI 2.0–42.6) compared to patients of normal weight. On an exploratory basis, we attempted to analyze infectious and inflammatory complications in the pediatric SCID, agammaglobulinemia, and CGD cohorts by body weight. Unlike in the pediatric CVID cohort, we not find any significant associations.

Additional adult PID subcohorts were not analyzed further due to low numbers of underweight patients in these groups.

Lastly, we analyzed the age of symptom onset and diagnosis in CVID patients to determine if abnormal body weight affected disease presentation. As shown in Figure 3A, in the adult CVID cohort there was an association of obese patients developing symptoms later than underweight ($p<0.001$), normal weight ($p<0.05$) and overweight ($p<0.05$) patients with CVID. Similarly, linear regression models demonstrated that underweight BMI in adults with CVID was associated with significantly earlier age at diagnosis compared to normal weight, overweight or obese patients (Figure 3B). For adult CVID patients, the mean age of diagnosis was 11.1 years (95%CI 3.0, 19.3) later in the normal group than in the underweight group, 12.6 years (95%CI 4.3, 20.8) later in the overweight group and 16.0 years (95%CI 7.6, 24.4) later in the obese group. This trend was specific to adults with CVID and was not seen in other subgroups of pediatric or adult PID patients, including pediatric patients with CVID.

Discussion:

To our knowledge, there have been no previous studies to examine the overall prevalence of abnormal body weight in large cohorts of PID patients. Using USIDNET data from 514 adults and 653 children with PID, we have examined the overall prevalence of underweight and obese status in PID patients. For the first time, we demonstrate a significantly higher prevalence of both adult and pediatric PID patients with underweight status when compared with a compared to nationally representative data from the NHANES database (Figure 2B & 2D). Underweight patients were distributed throughout the different types of PID diagnoses equally (Figure 1D), whereas in adults the primary diagnosis category with underweight patients was CVID (Figure 1B). This latter finding is perhaps not surprising as CVID was the most frequent diagnosis seen in adult patients in this study, representing 66.9% of the overall cohort. One potential confounding effect within our data is that the distribution of PID diagnoses within our cohorts vary from the USIDNET population. However, as we do not have any BMI data available on the remainder of patients in the USIDNET it is not possible to determine what effect this selection could have on our BMI analysis. Additionally, our study does not include longitudinal data and may have unintentionally excluded patients with significant weight changes over the course of disease.

Many previous case reports and case series have described the association of failure to thrive with primary immunodeficiency. Larger analyses of PID referral criteria support FTT as one of the signs with high specificity and sensitivity [2–4], and in a population of Kuwati PID patients, FTT was one of several clinical variables found to be associated with death years after the onset of symptoms [32]. Of importance, we found significant associations with underweight status with granulomas in adults with CVID (Table 3), and that underweight patients were diagnosed with CVID significantly earlier in life (Figure 3). These findings suggest that in adults with CVID, underweight status may be a marker of more severe disease or a trigger for an evaluation. Alternatively, it is possible that preexisting poor nutritional status could modify disease outcome in persons predisposed to development of CVID. We observe a significant association of lymphopenia with the underweight category

of children with CVID (Table 4). T cell lymphopenia has been described in a subset of patients with CVID, and has been correlated with lower immunoglobulin G levels as well as more autoimmune complications [33–35]. Children meeting criteria for CVID presenting with lymphopenia and weight loss or FTT warrant careful screening with lymphocyte enumeration and mitogen stimulation assay to exclude combined immunodeficiency, which may present similarly.

Interestingly, as shown in Figures 2B and 2D, with the exceptions of adults in 2009, we do not see a statistically significant decrease in the prevalence of obese pediatric or adult PID patients when compared to national data. There has been little focus on the effects of obesity on immune function in PID. However, studies in immunocompetent persons suggests that obesity modifies immune function as evidenced by reducing T cell proliferation in response to mitogens [36,37], and decreased response to Hepatitis B and influenza vaccines [38,39]. Although we did not find any association between obesity and increased rate of infectious or inflammatory complications in PID patients, which may be attributable to the cross-sectional design of our study. It is possible that with longitudinal followup it would be possible to capture differences in patient outcome attributable to obesity, however additional studies are required to examine these outcomes in PID patients.

This study has several limitations. The PID patient data are limited to data from the USIDNET registry. Although the USIDNET registry collects data longitudinally when possible, this followup data is not available at this time for the majority of patients. Therefore, we employed a cross-sectional approach in this study using only the data point at the time of USIDNET entry for patients in the database without following changes in body weight or associated complications over time in this study. Additional detail regarding the timing of complications and longitudinal consequences is limited because the database is dependent on physician reporting of patient illnesses and may be subject to some error. Although this is the largest study of body weight in PID patients to date, it is possible that the smaller groups of PID patients within our study were not powered to find significant associations and this is why we did not find any association with abnormal body weight and PID in these analyses. Further, some groups, including adults with 22q11.2 as well as both children and adults with NEMO deficiency, complement deficiency or leukocyte adhesion disorders were not well represented for subgroup analysis by BMI in this study. Analysis of larger cohorts of PID patients could provide additional power to determine if there are interactions of body weight with disease-specific outcomes. This could also potentially permit testing of race as a co-variate with body weight to determine if there is any bias of race on the impact of body weight on PID outcomes. This is significant as previous studies have demonstrated significant impact of race on obesity as well as access to medical care in the US. However, one major strength of our approach is the ability to directly compare BMI data collected by physical examinations from PID patients in the USIDNET to the US population within NHANES. This permitted objective comparison of the BMI from patients with PID to a cross sectional control population within the US.

Conclusion:

We identified that the prevalence of underweight patients is increased in both adult and pediatric PID populations compared to national background rates, whereas the prevalence of obesity is equivalent. In the underweight cohort of adults with CVID, we find a significant association with granulomas. Additionally, body weight had significant effects on the timing of CVID presentation and diagnosis in adults but not in children. Underweight pediatric patients with CVID were significantly more likely to have lymphopenia than normal weight counterparts. Further longitudinal studies of body weight and nutrition in PID are warranted to predict disease modifying effects of both underweight status and obesity on PID.

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Abbreviations:

(PID)	Primary immunodeficiency diseases
(FTT)	Failure to thrive
(BMI)	Body Mass Index
(USIDNET)	United States Immunodeficiency Network
(CDC)	Center for Disease Control
(CVID)	common variable immunodeficiency
(SCID)	severe combined immunodeficiency
(CGD)	chronic granulomatous disease
(NHANES)	National Health and Nutrition Examination Survey

References:

1. Foundation TJM. 10 Warning Signs [Internet]. [cited 2017 Jan 1]. Available from: http://www.info4pi.org/library/educational-materials/10-warning-signs
2. Lankisch P, Schiffner J, Ghosh S, Babor F, Borkhardt A, Laws HJ. The Duesseldorf Warning Signs for Primary Immunodeficiency: Is it Time to Change the Rules? J. Clin. Immunol 2015;35:273–9. [PubMed: 25749910]
3. Subbarayan A, Colarusso G, Hughes MS, Gennery RA, Slatter M, Cant JA, et al. Clinical Features That Identify Children With Primary Immunodeficiency Diseases. Pediatrics. 2011;127:810–6. [PubMed: 21482601]
4. Reda SM, El-Ghoneimy DH, Afifi HM. Clinical predictors of primary immunodeficiency diseases in children. Allergy. Asthma Immunol. Res 2013;5:88–95. [PubMed: 23450209]
5. Guerrerio AL, Frischmeyer-Guerrerio P a, Lederman HM, Oliva-Hemker M. Recognizing gastrointestinal and hepatic manifestations of primary immunodeficiency diseases. J. Pediatr. Gastroenterol. Nutr 2010;51:548–55. [PubMed: 20871412]
6. Patel NC, Hertel PM, Estes MK, de la Morena M, Petru AM, Noroski LM, et al. Vaccine-Acquired Rotavirus in Infants with Severe Combined Immunodeficiency. N. Engl. J. Med. Massachusetts Medical Society; 2010;362:314–9.
7. Barron MA, Makhija M, Hagen LE, Pencharz P, Grunebaum E, Roifman CM. Increased Resting Energy Expenditure is Associated with Failure to Thrive in Infants with Severe Combined Immunodeficiency. J. Pediatr 2011;159:628–632.e1. [PubMed: 21592502]
8. Ogden CL, Carroll MD, Curtin LR, McDowell MA, Tabak CJ, Flegal KM. Prevalence of Overweight and Obesity in the United States, 1999–2004. JAMA. American Medical Association; 2006;295:1549.
9. Ogden CL, Troiano RP, Briefel RR, Kuczmarski RJ, Flegal KM, Johnson CL. Prevalence of Overweight Among Preschool Children in the United States, 1971 Through 1994.
10. Troiano RP, Flegal KM, Kuczmarski RJ, Campbell SM, Johnson CL. Overweight Prevalence and Trends for Children and Adolescents Arch. Pediatr. Adolesc. Med American Medical Association; 1995;149:1085. [PubMed: 7550810]
11. Troiano RP, Flegal KM. Overweight Children and Adolescents: Description, Epidemiology, and Demographics. Pediatrics. 1998;101.
12. Jahn J, Spielau M, Brandsch C, Stangl GI, Delank KS, Bähr I, et al. Decreased NK cell functions in obesity can be reactivated by fat mass reduction. Obesity. 2015;23:2233–41. [PubMed: 26390898]
13. Laue T, Wrann CD, Hoffmann-Castendiek B, Pietsch D, Hübner L, Kielstein H. Altered NK cell function in obese healthy humans. BMC Obes. 2015;2:1. [PubMed: 26217516]
14. Nieman DC, Nehlsen-Cannarella SI, Henson DA, Butterworth DE, Fagoaga OR, Warren BJ, et al. Immune response to obesity and moderate weight loss. Int. J. Obes. Relat. Metab. Disord 1996;20:353–60. [PubMed: 8680463]
15. Tanaka S, Inoue S, Isoda F, Waseda M, Ishihara M, Yamakawa T, et al. Impaired immunity in obesity: suppressed but reversible lymphocyte responsiveness. Int. J. Obes. Relat. Metab. Disord 1993;17:631–6. [PubMed: 8281221]
16. Han SN, Jeon KJ, Kim MS, Kim H-K, Lee AJ. Obesity with a body mass index under 30 does not significantly impair the immune response in young adults. Nutr. Res 2011;31:362–9. [PubMed: 21636014]
17. Ouchi N, Parker JL, Lugus JJ, Walsh K. Adipokines in inflammation and metabolic disease. Nat. Rev. Immunol 2011;11:85–97. [PubMed: 21252989]
18. Lee B-C, Lee J. Cellular and molecular players in adipose tissue inflammation in the development of obesity-induced insulin resistance ☆. 2014;
19. Sullivan KE, Puck JM, Notarangelo LD, Fuleihan R, Caulder T, Wang C, et al. USIDNET: A strategy to build a community of clinical immunologists. J. Clin. Immunol 2014;34:428–35. [PubMed: 24711005]
20. Centers for Disease Control and Prevention NC for HS. Data Table of BMI-for-age Charts. August 24, 2001. p. https://www.cdc.gov/growthcharts/html_charts/bmiag.

21. Kuczmarski RJ, Ogden CL, Guo SS, Grummer-Strawn LM, Flegal KM, Mei Z, et al. 2000 CDC Growth Charts for the United States: methods and development. Vital Health Stat. 11 2002;1–190.
22. Garrow JS, Webster J. Quetelet's index (W/H2) as a measure of fatness. Int. J. Obes 1985;9:147–53.
23. Flegal KM, Carroll MD, Kit BK, Ogden CL. Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999–2010. JAMA. 2012;307:491–7. [PubMed: 22253363]
24. Ogden C, Carroll M, Lawman H, Fryar C, Kruszon-Moran D, Kit B, et al. Trends in obesity prevalence among children and adolescents in the united states, 1988–1994 through 2013–2014 Jama. American Medical Association; 2016 p. 2292–9.
25. Fryar CD, Carroll MD, Ogden CL. Prevalence of Underweight Among Adults Aged 20 and Over: United States, 1960–1962 Through 2013–2014 [Internet]. 2016 p. 2 Available from: https://www.cdc.gov/nchs/data/hestat/underweight_adult_13_14/underweight_adult_13_14.pdf
26. Fryar CD, Carroll MD, Ogden CL. Prevalence of Underweight Among Children and Adolescents Aged 2–19 Years: United States, 1963–1965 Through 2013–2014 [Internet]. 2016 Available from: https://www.cdc.gov/nchs/data/hestat/underweight_child_13_14/underweight_child_13_14.pdf
27. Johnson CL, Dohrmann SM, Burt VL, Mohadjer LK. National Health and Nutrition Examination Survey: Sample Design, 2011 – 2014. Vital Heal. Stat 2014;2:1–33.
28. Curtin LR, Mohadjer LK, Dohrmann SM. National Health and Nutrition Examination Survey: Sample Design, 2007 – 2010. Vital Heal. Stat 2010;160:1–32.
29. Curtin LR, Mohadjer LK, Dohrmann SM, Montaquila JM, Kruszan-Moran D, Mirel LB, et al. The National Health and Nutrition Examination Survey: Sample Design, 1999–2006. Vital Health Stat. 2 2012;1–39.
30. National Health and Nutrition Examination Survey. 2013–2014 Data Documentation, Codebook, and Frequencies, Demographic Variables and Sample Weights [Internet]. 10 2015 Available from: https://wwwn.cdc.gov/Nchs/Nhanes/2013-2014/DEMO_H.htm
31. Flegal KM, Kruszon-Moran D, Carroll MD, Fryar CD, Ogden CL. Trends in Obesity Among Adults in the United States, 2005 to 2014. JAMA. 2016;315:2284. [PubMed: 27272580]
32. Al-Herz W, Moussa MAA. Survival and predictors of death among primary immunodeficient patients: A registry-based study. J. Clin. Immunol 2012;32:467–73. [PubMed: 22205205]
33. Cunningham-Rundles C, Bodian C. Common Variable Immunodeficiency: Clinical and Immunological Features of 248 Patients. Clin. Immunol 1999;92:34–48. [PubMed: 10413651]
34. Boileau J, Mouillot G, Gérard L, Carmagnat M, Rabian C, Oksenhendler E, et al. Autoimmunity in common variable immunodeficiency: Correlation with lymphocyte phenotype in the French DEFI study. J. Autoimmun 2011;36:25–32. [PubMed: 21075598]
35. Wong GK, Huissoon AP. T-cell abnormalities in common variable immunodeficiency: the hidden defect. J. Clin. Pathol 2016;69:672–6. [PubMed: 27153873]
36. Tanaka S, Inoue S, Isoda F, Waseda M, Ishihara M, Yamakawa T, et al. Impaired immunity in obesity: suppressed but reversible lymphocyte responsiveness. Int J Obes Relat Metab Disord. 1993;17:631–6. [PubMed: 8281221]
37. Nieman DC, Henson D a, Nehlsen-Cannarella SL, Ekkens M, Utter a C, Butterworth DE, et al. Influence of obesity on immune function. J. Am. Diet. Assoc 1999 p. 294–9. [PubMed: 10076580]
38. Weber DJ, Rutala WA, Samsa GP, Santimaw JE, Lemon SM. Obesity as a Predictor of Poor Antibody Response to Hepatitis B Plasma Vaccine JAMA. American Medical Association; 1985;254:3187–9. [PubMed: 2933532]
39. Sheridan PA, Paich HA, Handy J, Karlsson EA, Hudgens MG, Sammon AB, et al. Obesity is associated with impaired immune response to influenza vaccination in humans Int. J. Obes Nature Publishing Group; 2012;36:1072–7.

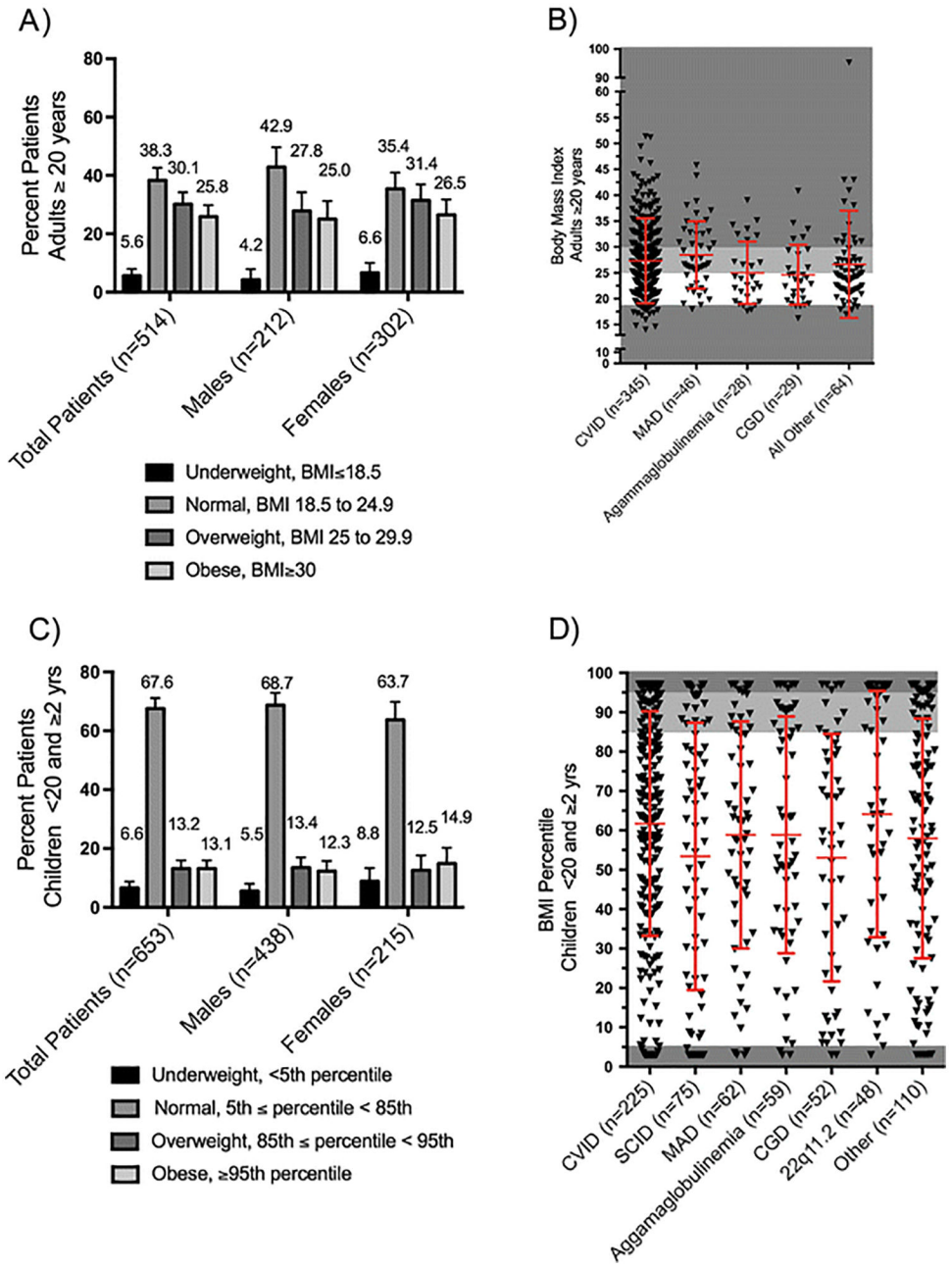

Figure 1: BMI analysis by age, gender and immunodeficiency diagnosis.

A. Adult patients were grouped as a whole or by gender using standard BMI category definitions as shown in the figure legend. Data are presented as overall prevalence across all data entry years (percent ± 95%CI). **B.** BMI by PID diagnosis in adults, with median ± interquartile range displayed in red. BMI ranges are shaded on graph. White = normal range, lower dark gray range = underweight, light gray range = overweight, upper dark gray range = obese. **C.** Pediatric BMI percentile was calculated for each patient and used to determine underweight, overweight or obese status per CDC definitions as shown in the figure legend. Data are presented as overall prevalence across all data entry years (percent ± 95%CI). **D.** Breakdown of pediatric BMI in PID patients, by diagnosis. Median ± interquartile range

displayed in red. Bottom dark gray shading = underweight (BMI percentile <5th), white = normal weight, light gray = overweight (BMI percentile 85th-95th) and top gray portion = obese (BMI percentile≥95th).

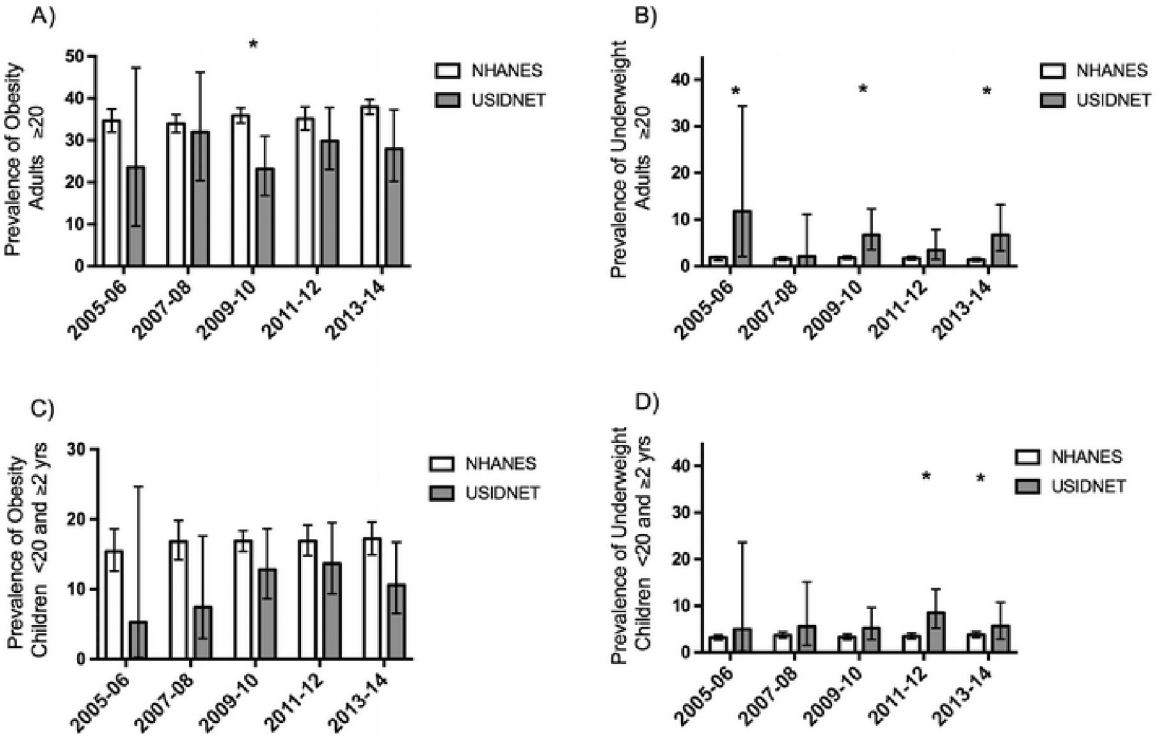

Figure 2: Analysis of USIDNET data by year and comparison with National Health and Nutrition Examination Survey (NHANES) Data.

USIDNET patient data was categorized by year of visit and BMI category for comparison to NHANES [25,31] data for adults for A) obesity and B) underweight are represented as prevalence±95%CI. Pediatric USIDNET body weight status by two-year intervals compared to NHANES [24,26] data for C) obesity and D) underweight are also shown. (*p≤0.05)

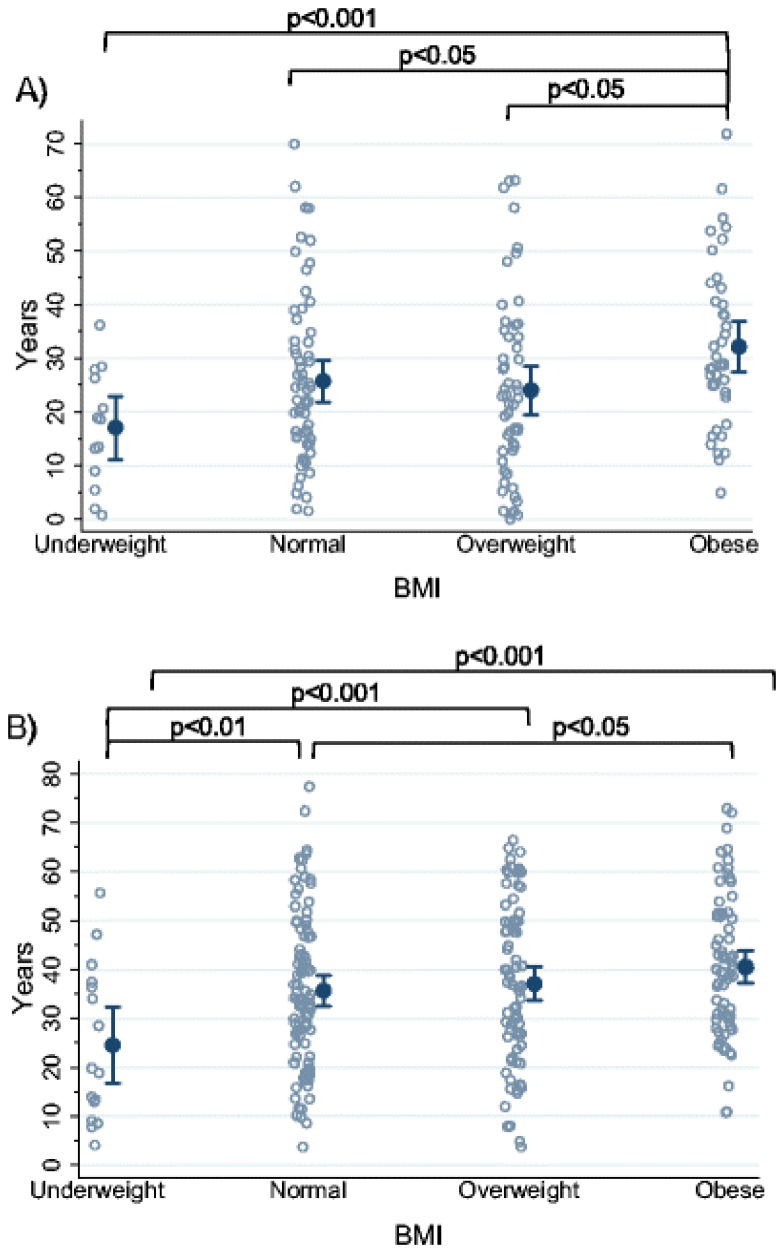

Figure 3: Underweight adults with CVID have earlier onset of symptoms and present earlier.
Adults with CVID were grouped by BMI into groups by body weight category. Physician-reported age of A) symptom onset (n=171) and B) age of diagnosis (n=260) are graphed individually and as mean±SEM. Between group differences were analyzed by linear regression with multiple comparisons with between group significance as noted.

Table 1:

Pediatric Patient Cohort Characteristics

Demographic data and primary immunodeficiency diagnoses of cohort patients compared to all USIDNET patients in database from ages 2 to 20 years at the time of entry into the USIDNET database.

	Pediatric Patients, ages 2 to 20 years (n=653)	All USIDNET Pediatric Patients ages 2 to 20 years (n=1,460)
Age (years)		
Mean ± SD	10.1 ± 4.9	11.9 ± 4.7
Median (IQ range)	10.5 (6.6, 14.4)	12.2 (8.8, 15.75)
Gender		
Male	438 (67%)	889 (70.9%)
Female	215 (33%)	364 (29.1%)
Race		
Caucasian	430 (65.8%)	799 (54.7%)
African American	50 (7.6%)	103 (7.1%)
Asian	16 (2.5%)	37 (2.5%)
Native American	4 (0.6%)	21 (1.4%)
Unknown	153 (23.4%)	500 (34.3%)
Primary Immunodeficiency		
Common Variable Immunodeficiency	224 (34.3)	329 (22.5%)
Miscellaneous Antibody Deficiency	61 (9.3%)	91 (6.2%)
Agammaglobulinemia	59 (9.0%)	150 (10.3%)
Chronic Granulomatous Disease	54 (8.3%)	134 (9.2%)
Hyper-IgM Disease	20 (3.1%)	72 (4.9%)
Severe Combined Immunodeficiency	75 (11.5%)	173 (11.8%)
Wiscott-Aldrich Syndrome	19 (2.9%)	59 (4.0%)
Other	58 (8.9%)	82 (5.6%)
22q11.2 deficiency	48 (7.4%)	333 (22.8%)
NEMO	12 (1.8%)	12 (0.8%)
Complement Deficiency	16 (2.5%)	20 (1.4%)
Leukocyte Adhesion Disorder	5 (0.8%)	5 (0.3%)

Data are presented as counts (percentages) unless indicated.

Table 2:

Adult Cohort Patient Characteristics

Demographic data and primary immunodeficiency diagnoses of adult cohort patients compared to all USIDNET patients over 20 in database at the time of study.

	Adult Patients, ages 20–84 (n=514)	All Adult USIDNET Patients >20 yrs (n=1,982)
Age (years)		
Mean ± SD	41.8 ± 15.7	41.3 ± 15.8
Median (IQ Range)	41 (28.5, 55.3)	39.5 (27.3, 52.6)
Gender		
Male	302 (58.7%)	1,615 (58.8%)
Female	212 (41.3%)	817 (41.2%)
Race		
Caucasian	385 (74.9%)	1,410 (71.1%)
African American	23 (4.5%)	79 (4.0%)
Asian	7 (1.4%)	22 (1.1%)
Native American	---	15 (0.8%)
Unknown	100 (19.4%)	456 (23.0%)
Primary Immunodeficiency		
Common Variable Immunodeficiency	344 (66.9%)	956 (48.2%)
Miscellaneous Antibody Deficiency	47 (9.1%)	93 (4.7%)
Agammaglobulinemia	28 (5.4%)	220 (11.1%)
Chronic Granulomatous Disease	29 (5.6%)	312 (15.7%)
Hyper-IgM Disease	11 (2.1%)	65 (3.3%)
Severe Combined Immunodeficiency	10 (1.9%)	53 (2.7%)
Wiscott-Aldrich Syndrome	10 (1.9%)	143 (7.2%)
Other	29 (5.6%)	61 (3.1%)
22q11.2 deficiency	---	75 (3.8%)
NEMO	2 (0.4%)	2 (0.1%)
Complement Deficiency	2 (0.4%)	1 (0.05%)
Leukocyte Adhesion Disorder	---	1 (0.05%)

Data are presented as counts (percentages) unless indicated.

Table 3.

Analysis of Complications in Adult CVID patients by BMI Group

Analysis of complications reported in adult CVID subcohort by body weight. Data are presented as numbers of patients with frequency percentages in parentheses. Chi-squared test was performed, excepting where marked with $^{+}$, indicating that Fisher's exact test was performed due to lower numbers patient observations in some body weight groups. *p* values are reported in the right-most column.* denotes p<0.05

	Present?	Total	Underweight	Normal	Overweight	Obese	P value
Sepsis	No	317 (92.2%)	19 (90.5%)	113 (94.2%)	107 (93.9%)	78 (87.6%)	0.2934
	Yes	27 (7.8%)	2 (9.5%)	7 (5.8%)	7 (6.1%)	11 (12.4%)	
Pneumonia	No	151 (43.9%)	8 (38.1%)	56 (46.7%)	52 (45.6%)	35 (39.3%)	0.6702
	Yes	193 (56.1%)	13 (61.9%)	64 (53.3%)	62 (54.4%)	54 (60.7%)	
Sinusitis	No	80 (23.3%)	6 (28.6%)	26 (21.7%)	27 (23.7%)	21 (23.6%)	0.9145
	Yes	264 (76.7%)	15 (71.4%)	94 (78.3%)	87 (76.3%)	68 (76.4%)	
Abscess^{+}	No	333 (96.8%)	20 (95.2%)	114 (95.0%)	110 (96.5%)	89 (100.0%)	0.1194
	Yes	11 (3.2%)	1 (4.8%)	6 (5.0%)	4 (3.5%)	0 (0.0%)	
Otitis media	No	239 (69.5%)	14 (66.7%)	77 (64.2%)	87 (76.3%)	61 (68.5%)	0.2382
	Yes	105 (30.5%)	7 (33.3%)	43 (35.8%)	27 (23.7%)	28 (31.5%)	
Asthma	No	214 (62.2%)	13 (61.9%)	81 (67.5%)	69 (60.5%)	51 (57.3%)	0.4793
	Yes	130 (37.8%)	8 (38.1%)	39 (32.5%)	45 (39.5%)	38 (42.7%)	
Lymphopenia	No	318 (92.4%)	20 (95.2%)	110 (91.7%)	105 (92.1%)	83 (93.3%)	0.9315
	Yes	26 (7.6%)	1 (4.8%)	10 (8.3%)	9 (7.9%)	6 (6.7%)	
Neutropenia	No	323 (93.9%)	21 (100.0%)	109 (90.8%)	110 (96.5%)	83 (93.3%)	0.1926
	Yes	21 (6.1%)	0 (0.0%)	11 (9.2%)	4 (3.5%)	6 (6.7%)	
Thrombocytopenia	No	283 (82.5%)	20 (95.2%)	96 (80.0%)	97 (85.8%)	70 (78.7%)	0.1978
	Yes	60 (17.5%)	1 (4.8%)	24 (20.0%)	16 (14.2%)	19 (21.3%)	
Hemolytic Anemia^{+}	No	337 (98.0%)	21 (100.0%)	115 (95.8%)	113 (99.1%)	88 (98.9%)	0.3514
	Yes	7 (2.0%)	0 (0.0%)	5 (4.2%)	1 (0.9%)	1 (1.1%)	
Granuloma^{+}	No	321 (93.3%)	***17 (81.0%)***	116 (96.7%)	107 (93.9%)	81 (91.0%)	***0.0482****
	Yes	23 (6.7%)	***4 (19.0%)***	4 (3.3%)	7 (6.1%)	8 (9.0%)	
Lymphadenopathy	No	298 (86.6%)	20 (95.2%)	103 (85.8%)	99 (86.8%)	76 (85.4%)	0.6751
	Yes	46 (13.4%)	1 (4.8%)	17 (14.2%)	15 (13.2%)	13 (14.6%)	
Splenomegaly	No	296 (86.0%)	18 (85.7%)	99 (82.5%)	104 (91.2%)	75 (84.3%)	0.2569

	Present?	Total	Underweight	Normal	Overweight	Obese	P value
Bronchiectasis	Yes	48 (14.0%)	3 (14.3%)	21 (17.5%)	10 (8.8%)	14 (15.7%)	0.1267
	No	281 (81.7%)	14 (66.7%)	95 (79.2%)	99 (86.8%)	73 (82.0%)	
Interstitial Lung Disease[+]	Yes	63 (18.3%)	7 (33.3%)	25 (20.8%)	15 (13.2%)	16 (18.0%)	0.6107
	No	317 (92.2%)	19 (90.5%)	109 (90.8%)	108 (94.7%)	81 (91.0%)	
Hypertension	Yes	27 (7.8%)	2 (9.5%)	11 (9.2%)	6 (5.3%)	8 (9.0%)	0.1071
	No	270 (78.5%)	20 (95.2%)	98 (81.7%)	87 (76.3%)	65 (73.0%)	
	Yes	74 (21.5%)	1 (4.8%)	22 (18.3%)	27 (23.7%)	24 (27.0%)	

Table 4:

Analysis of Complications in Pediatric CVID patients by BMI Group

Analysis of complications reported in pediatric CVID subcohort by body weight. Data are presented as numbers of patients with percentages in parentheses. Fisher's exact test was performed, and *p* values are reported in the right-most column. * denotes p<0.05

		Total	Underweight	Normal	Overweight	Obese	P value
Sepsis	No	214 (95.5%)	12 (92.3%)	145 (95.4%)	27 (93.1%)	30 (100.0%)	0.3969
	Yes	10 (4.5%)	1 (7.7%)	7 (4.6%)	2 (6.9%)	0 (0.0%)	
Pneumonia	No	133 (59.4%)	8 (61.5%)	89 (58.6%)	20 (69.0%)	16 (53.3%)	0.6661
	Yes	91 (40.6%)	5 (38.5%)	63 (41.4%)	9 (31.0%)	14 (46.7%)	
Sinusitis	No	82 (36.6%)	3 (23.1%)	55 (36.2%)	13 (44.8%)	11 (36.7%)	0.6218
	Yes	142 (63.4%)	10 (76.9%)	97 (63.8%)	16 (55.2%)	19 (63.3%)	
Abscess	No	223 (99.6%)	12 (92.3%)	152 (100.0%)	29 (100.0%)	30 (100.0%)	0.0580
	Yes	1 (0.4%)	1 (7.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Otitis media	No	102 (45.5%)	5 (38.5%)	69 (45.4%)	14 (48.3%)	14 (46.7%)	0.9588
	Yes	122 (54.5%)	8 (61.5%)	83 (54.6%)	15 (51.7%)	16 (53.3%)	
Asthma	No	122 (54.5%)	7 (53.8%)	83 (54.6%)	18 (62.1%)	14 (46.7%)	0.7154
	Yes	102 (45.5%)	6 (46.2%)	69 (45.4%)	11 (37.9%)	16 (53.3%)	
Lymphopenia	No	213 (95.1%)	***10 (76.9%)***	147 (96.7%)	28 (96.6%)	28 (93.3%)	***0.0349****
	Yes	11 (4.9%)	***3 (23.1%)***	5 (3.3%)	1 (3.4%)	2 (6.7%)	
Neutropenia	No	206 (92.0%)	11 (84.6%)	139 (91.4%)	28 (96.6%)	28 (93.3%)	0.5603
	Yes	18 (8.0%)	2 (15.4%)	13 (8.6%)	1 (3.4%)	2 (6.7%)	
Thrombocytopenia	No	201 (89.7%)	11 (84.6%)	138 (90.8%)	25 (86.2%)	27 (90.0%)	0.6909
	Yes	23 (10.3%)	2 (15.4%)	14 (9.2%)	4 (13.8%)	3 (10.0%)	
Granulomas	No	218 (97.3%)	13 (100.0%)	149 (98.0%)	28 (96.6%)	28 (93.3%)	0.3048
	Yes	6 (2.7%)	0 (0.0%)	3 (2.0%)	1 (3.4%)	2 (6.7%)	
Lymphadenopathy	No	207 (92.4%)	12 (92.3%)	142 (93.4%)	25 (86.2%)	28 (93.3%)	0.5312
	Yes	17 (7.6%)	1 (7.7%)	10 (6.6%)	4 (13.8%)	2 (6.7%)	
Splenomegaly	No	209 (93.3%)	13 (100.0%)	142 (93.4%)	27 (93.1%)	27 (90.0%)	0.7757
	Yes	15 (6.7%)	0 (0.0%)	10 (6.6%)	2 (6.9%)	3 (10.0%)	
Bronchiectasis	No	199 (88.8%)	9 (69.2%)	134 (88.2%)	28 (96.6%)	28 (93.3%)	0.0783
	Yes	25 (11.2%)	4 (30.8%)	18 (11.8%)	1 (3.4%)	2 (6.7%)	

		Total	Underweight	Normal	Overweight	Obese	P value
	No	219 (97.8%)	12 (92.3%)	150 (98.7%)	28 (96.6%)	29 (96.7%)	0.1369
Interstitial Lung Disease	Yes	5 (2.2%)	1 (7.7%)	2 (1.3%)	1 (3.4%)	1 (3.3%)	
	No	219 (97.8%)	13 (100.0%)	150 (98.7%)	27 (93.1%)	29 (96.7%)	0.168
Hypertension	Yes	5 (2.2%)	0 (0.0%)	2 (1.3%)	2 (6.9%)	1 (3.3%)	