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The Association of Pediatric Psoriasis Severity with Excess and Central Adiposity: An International Cross-sectional Study

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Abstract

Objective—Investigate the relationship of excess and central adiposity with pediatric psoriasis severity.

Design, Setting and Participants—Multi-center, cross-sectional study of 409 psoriatic children. Psoriasis was classified as mild (worst Physician's Global Assessment (PGA) <3 with body surface area (BSA) <10%) or severe (worst PGA >3 with BSA >10%). Children were enrolled from 9 countries July 2009-December 2011.

Main Outcome Measures—Excess adiposity (body mass index (BMI) percentile) and central adiposity (waist circumference (WC) percentile and waist-to-height ratio).

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Results—Excess adiposity (BMI >85th percentile) occurred in 37.8% (n=155) of psoriatics vs. 20.5% (n=42) of controls, but did not differ by severity. The odds of obesity (BMI >95th percentile) overall in psoriatics vs. controls were OR=4.29, 95% CI=1.96-9.39, but were higher with severe (OR=4.92, CI=2.20-10.99) than mild (OR=3.60, CI=1.56-8.30) psoriasis, particularly in the U.S. (OR=7.60, CI=2.47-23.34, and OR=4.72, CI=1.43-15.56, respectively). WC >90th percentile occurred in 9.3% (n=19) of controls, 14.0% (n=27) of mild, and 21.2% (n=43) of severe psoriatics internationally, and especially in the U.S (12.0% of controls, 20.8% of mild, and 31.1% of severe psoriatics). Waist-to-height ratio was significantly higher in psoriatic (0.48) vs. control (0.46) children, but unaffected by psoriasis severity. Children with severe psoriasis at their worst, but mild at enrollment, showed no difference in excess or central adiposity from children who remained severe at enrollment.

Conclusion—Globally, children with psoriasis have both excess adiposity and increased central adiposity, regardless of severity. The increased metabolic risks associated with excess and central adiposity warrant early monitoring and lifestyle modification.

Keywords

adipose tissue; adiposity; adolescent; body mass index; child; metabolic syndrome; obesity; psoriasis; waist circumference; weight

Psoriasis is an immune-mediated inflammatory skin disease that affects 2.5-3.2% of the population.[1,2] Twenty-two to 33% of psoriasis begins during childhood, especially during adolescence[2-5], and the incidence in children has more than doubled since the early 1970's.[3] Adults with psoriasis have an increased risk of obesity, myocardial infarction, stroke, and diabetes.[6-9] Recent studies also suggest the association of psoriasis and obesity in children. Of 211 North American children with moderate-to-severe psoriasis in an etanercept trial, 37% were obese (body mass index (BMI) >95th percentile).[10] Among 96 Italian children with mild to severe psoriasis, 48% were overweight (BMI >85th percentile) vs. 27% of controls.[11] Using a German pediatric registry, obesity (by ICD-10 code) occurred 1.7-fold more often in psoriatic children than controls.[5] In a U.S.-based registry, overweight, moderately obese, and extremely obese children had 1.31-, 1.39-, and 1.78-fold greater odds, respectively, of having psoriasis (by ICD-9 code) than children with normal weight.[12] These investigations provide evidence that children with psoriasis are at increased risk of being overweight or obese. However, ascertainment bias and under-identification are limitations of registry studies, which rely on ICD codes for diagnosis of psoriasis and obesity, rather than direct examination and measurements to calculate BMI. In addition, the risk of excess adiposity relative to psoriasis severity has received little attention. Increased waist circumference (WC) percentile[13-16] and waist-to-height ratio (WHtR)[15-20] are non-invasive surrogates for central adiposity and more sensitive indicators for metabolic disease than BMI percentile, including in children[15, 16, 19, 20]. WC percentile is increased in adults with psoriasis[21], but has never been assessed in psoriatic children. WHtR has more recently been found to be a better predictor of cardiovascular risk than BMI or WC percentiles[17, 19], but has never been assessed in adult or pediatric patients with psoriasis.

Using an international cohort of children with psoriasis, we have further examined the relationship between adiposity and psoriasis in children. Our goals were specifically to: a) evaluate the impact of disease severity on the association of psoriasis with excess adiposity (being overweight or obese); b) assess whether central obesity, as a surrogate for higher cardiovascular risk, was related to psoriasis severity; and c) examine if the association of excess adiposity with psoriasis varied regionally. We hypothesized that both excess adiposity and central adiposity are most highly correlated with psoriasis of greater severity, but that children with mild psoriasis are also at risk. Furthermore, we expected that psoriatic

children in the United States would have a greater risk of excess and central adiposity than children from other countries.

METHODS

Study design and population

A multi-center, international, cross-sectional study was performed to determine the relationship between adiposity and psoriasis severity in children. Subjects were recruited between June, 2009 and December, 2011 from all psoriasis patients who presented to 18 dermatology referral centers with known psoriasis expertise in the Americas (Brazil, Canada, Chile, United States), Europe (Italy, Netherlands, Turkey, United Kingdom), and Asia (Malaysia). Inclusion criteria included age 5-17 years and a >6 month history of plaque psoriasis. Diagnosis was confirmed by a psoriasis specialist. Siblings were excluded in both the psoriatic and control populations. Children of similar age and sex (but not matched for ethnicity) without skin or systemic inflammatory disease (e.g. with nevi, molluscum contagiosum, warts, acne) and without a family history of psoriasis or psoriatic arthritis were also recruited in the United States, Netherlands, Italy, and Malaysia. To minimize ascertainment bias, an attempt was made to recruit all patients serially at presentation, and no potential subject refused. Parents and subjects, as required by each center's Institutional Review Board or Ethics Committee, provided written informed consent. Investigators completed a questionnaire with each patient/parent that addressed patient history, race/ ethnicity, severity of psoriasis at its worst, and history of psoriasis/psoriatic arthritis and metabolic disease in family members. A projected sample of 169/group provided 80% power to detect rates of excess adiposity from 22% among controls to 37% among psoriatics.[10] Subjects who indicated race as "Other" (2 control, 3 MP and 4 SP) were excluded from analysis of impact of race due to their racial heterogeneity. Tanner stage was not examined, but a secondary analysis was performed on subsets of children ages 5 through 7 and 15 through 17 years as representative of prepubertal and postpubertal subjects based on established puberty ranges.[22] De-identified data was compiled centrally by the International Psoriasis Council, and statistical analysis was performed at Northwestern University, Chicago.

Anthropometric measures

Weight and height were measured and BMI was calculated by dividing subject weight (in kg) by height^2 (in m^2). An age- and sex-adjusted BMI percentile was assigned using the modified LMS estimation procedure from 2000 Center for Disease Control (CDC) growth charts[23] Excess adiposity was defined as being either overweight or obese. Subjects with BMI >85th and <95th percentile were classified as overweight, and those with BMI > 95th percentile as obese.[24, 25] BMI percentile <5 was considered underweight, and 5-<85 healthy weight. WC was measured midway between the most inferior rib and the superior border of the iliac crest with an inelastic measuring tape. WC percentile was determined according to sex, age, and ethnicity-specific cutoffs.[26] WC was classified into six percentile groups with the two highest being the 75th-90th and >90th percentiles. WHtR was considered as a continuous measure of risk, but for estimating odds of excess central adiposity defined by WHtR, cut-offs established by Kahn *et al.* were used to define high (0.539) and intermediate (0.490) levels of cardiovascular risk.[19]

Determination of psoriasis severity

Psoriasis severity was classified as mild or severe was based primarily on Physician Global Assessment (PGA)[27] and secondarily on Body Surface Area (BSA). PGA was scored as 0 (none) to 5 (severe). To establish severity within the pediatric population, PGA of 4-5 was designated as severe psoriasis (SP), and PGA of 1-2 mild psoriasis (MP). A "moderate"

score of PGA 3 was designated MP if the BSA was <10% and SP if the BSA was >10%.[28] Peak severity historically was used to classify patients as mild vs. severe, and severity was also determined at enrollment. For all psoriatics, a current or previous history of treatment with phototherapy and/or systemic medications was recorded. The same physician scored both worst and current severity of subjects at each site to minimize the risk of per subject or per center inter-observer variability.

Statistical analysis

Descriptive statistics are presented as counts and percentages for categorical variables, mean and standard deviations for continuous data, and medians and interquartile range for psoriatic duration. Analyses include generalized linear mixed models for binary (logit link function), categorical (generalized logit link function) and ordinal (gamma link function) outcome data, respectively, and mixed models for outcomes which were normally distributed. All models included a random effect of study center and were adjusted for age, sex, continent or race.

Models comparing MP to SP were also adjusted for systemic medication, phototherapy, and disease duration. Correlation between PGA and BSA severity scales was assessed using a Spearman's rank correlation, as the two measures are not on the same scale. Agreement between BMI categories and WC categories was assessed using a weighted kappa. Interactions between psoriatic groups and age, race (or continent), and sex were assessed to gauge evidence of effect modification; interaction terms were also fit to examine the possibility of a differential effect of race on adiposity levels. When the interaction of race and psoriasis was significant, further analyses were stratified to determine the effect of race within psoriatic groups and *vice versa. A priori* there was interest in comparing psoriatics versus controls and MP versus SP; hence, a significance level of 0.05 was used for all comparisons. While this does increase the chance of a type I error, many comparisons were done to assess if the relationships observed in the primary analyses were seen in subgroups, not to draw specific conclusions about subgroups. All analyses were run in SASv9.2, Cary, NC.

RESULTS

Children with Psoriasis Internationally Have Excess Adiposity, Regardless of Severity

Of 614 subjects enrolled from nine countries, 203 (33.0%) had MP and 206 (33.6%) had SP based on assessment of peak severity; 205 (33.4%) were age- and sex-comparable non-inflammatory controls (Table 1). Age and sex distribution was similar among regions, although ethnicity varied, reflecting different populations regionally. The classification based on PGA severity correlated well with severity based on BSA (r_s=0.763, p=0.001). Severity classification was further validated by use of phototherapy and/or systemic immunosuppressant medications in 56.5% of children internationally and 65.3% of U.S. subjects with SP (vs. 21.8% and 16.8% with MP, respectively) (Tables 1 and 2). Having a history of diabetes, hypertension, hyperlipidemia, obesity, psoriasis or psoriatic arthritis in immediate family members was not significantly different in SP vs. MP children. Categories of adiposity defined by BMI and WC percentiles moderately agreed (weighted kappa (κ_w)=0.55 (95% CI, 0.50-0.61)). The mean age of children with psoriasis was 12.2 years, with no significant difference between MP and SP groups (Table 1). A significantly higher percentage of children with psoriasis than controls showed excess adiposity (37.8% vs. 20.5%) or obesity (20.2% vs. 7.3%) (p<0.001). The odds ratio for excess adiposity in psoriatic children of all severities vs. controls was 2.65 (CI=1.70-4.15) and for obesity was 4.29 (CI=1.96-9.39); similarly in the U.S. the odds ratio for excess adiposity was 4.02 (2.11-7.63) and for obesity was 6.61 (2.16-20.17) (Table 3). There was no modification by

age (p=0.914), pubertal status (p=0.583), or age group (p=0.968). Disease duration did not correlate with excess adiposity (Spearman correlation coefficient 0.008).

The Odds Ratio of Obesity (vs. Overweight) is Highest in Severe Psoriasis Internationally

More SP than MP children were obese (7.3% of controls, 16.8% of MP, and 23.7% of SP, p<0.001) (Table 1); the OR for obesity (vs. healthy weight) was 4.92 (CI-2.20-10.99) for SP and 3.60 (CI-1.56-8.30) for MP (Table 3). In the U.S., obesity was seen in 8.3% of controls and 19.2% of MP children, but occurred in 34.0% of SP children (p=0.013); the OR for being obese (vs. healthy weight) was 4.72 (CI=1.43-15.56) for MP, but 7.60 (CI=2.47-23.34) for SP (Tables 2 and 3). Among children with excess adiposity, SP had the highest odds of obesity (OR=2.85 (CI=1.26-6.42) internationally, whereas the odds of obesity was not increased for MP compared to controls (Table 3).

Children with Severe, but not Mild, Psoriasis Have Greater Central Adiposity

Internationally, the odds of a WC percentile >90 was significantly greater for children with psoriasis overall vs. controls (OR=2.52, CI=1.24-5.12) and SP vs. controls (OR=3.06, CI=1.53-6.15), but not MP vs. controls (OR=1.90, CI=0.90-4.01) (Tables 1 and 3). In the U.S. the odds ratio of having a WC percentile >75th or >90th was significantly increased in psoriasis overall vs. controls (OR=1.77, CI=1.03-3.07 and OR=3.47, CI=1.39-8.66, respectively) and SP children vs. controls (OR=2.05, CI=1.12-3.76 and OR=3.85, CI=1.64-9.00, respectively), but not MP children vs. controls (Tables 2 and 3). WHtRs were significantly higher in children with psoriasis vs. controls internationally (p=0.002) and in the U.S. (p=0.010) (Tables 1 and 2). In parallel with WC percentiles, the odds of a WHtR 0.539 was significantly higher for children with psoriasis overall vs. controls (OR=3.10, CI=1.39-6.90) and SP vs. controls (OR=4.10, CI=1.80-9.31), but not MP vs. controls (OR=2.21, CI=0.92-5.32) (Table 3). In the U.S., the odds ratio of having at least a WHtR above the normal range (>.490) was also increased in psoriasis overall (OR=1.77, CI=1.02-3.09) and in SP children (OR=2.06, CI=1.12-3.81), but not in MP children (OR=1.45, CI= 0.75-2.79) (Table 3). Disease duration did not affect central adiposity (Spearman correlation coefficients of −0.008 and −0.010 for WC category and WHtR, respectively).

Among Children Internationally, the Greatest Association of Excess Adiposity and Central Adiposity with Psoriasis is Seen in U.S. Children

The difference in excess adiposity rates between psoriatics and controls was greatest in the Americas vs. other continents (p<0.001, Table 4; Figure 1) and in U.S. vs. non-U.S. sites (p=0.002, Table 5). In addition, differences in central adiposity were greater in the Americas vs other continents (WC%, p = .002; WHtR, p=0.016; Table 4) and in U.S. vs. non-U.S. psoriatics (WC%, p=0.015; WHtR, p=0.048; Table 5). The excess adiposity in psoriatics versus controls was similar across U.S. racial groups (Table 4). However, significantly greater rates for excess adiposity were seen in U.S. Hispanics/African-Americans (59.5%), in comparison with Whites (44.5%) and Asians (40.0%) (p=0.026), and both WC percentiles and WHtRs were higher in African-Americans/Hispanics and Asians than in Whites (p=0.001 and p=0.021, respectively; Table 4).

Clinical Improvement Does not Lower the Odds of Obesity

No difference was noted for SP children who transitioned to MP vs. SP children who remained SP in the odds of having excess adiposity (OR= 1.34 (CI=0.70-2.59)), obesity (OR=0.67 (CI=0.31-1.43)), or central adiposity (OR=0.88 (CI=0.45-1.72)). Internationally, 136 (65.7%) children with SP had transitioned to MP by enrollment, of whom 60% used phototherapy and/or systemic medications (19.2% phototherapy alone, 20.0% systemic

immunosuppressants, and 20.0% both). Sex (p=0.702), age (p=0.280), duration (p=0.279), systemic medication use (p=0.480), or continent (p=0.337) did not predict those who transitioned. By enrollment, 67 (65%) U.S. children with SP had transitioned to MP. Sex (p=0.543), age (p=0.081), duration (p=0.129), systemic medication use (p=0.286), or phototherapy (p=0.118) similarly did not correlate with transition, although Whites were more likely to improve than non-Whites (78.7% vs. 45.2%, p=0.001) and transition was more likely among younger patients (OR=0.82 (CI=0.070-0.97), p=0.019).

DISCUSSION

The prevalence of childhood obesity has increased dramatically worldwide[29-32], although a recent study shows stabilization. Being overweight or obese during childhood is associated with an increased risk of sleep apnea[33], cardiovascular risk factors[34], insulin resistance, orthopedic complications[35, 36], and mortality as an adult from cardiovascular disease.[37] Our large, cross-sectional study overcomes the limitations of registry data and further supports the association of pediatric psoriasis with increased BMI percentile. Importantly, children with psoriasis internationally, regardless of severity, have significantly greater odds than controls of being overweight or obese, and thus are at increased risk of complications related to excess adiposity. Most MP children with excess adiposity were overweight, but not obese, while most SP children with excess adiposity were obese. Consistently, while the odds of obesity were increased in children with MP (OR=3.60), the odds of obesity were much higher for children with SP (OR=4.92), particularly in the U.S. (OR=6.61). These odds ratios are considerably greater than those for adults in the U.K. with SP (OR=1.79) and MP (OR=1.27)[8], and for metabolic syndrome in U.S. adults with psoriasis of all severities (OR=1.96)[38], suggesting a greater association of obesity and psoriasis with childhood-onset vs. adult-onset psoriasis. The particularly high odds of obesity in U.S. children with psoriasis suggest that environment habits (higher caloric diet and less exercise) may impact the risk.

BMI percentile remains the standard method for identifying overweight and obese pediatric patients[39], but WC and particularly WHtR are surrogates for central/visceral adiposity that are considered better indicators than BMI of metabolic risk.[13, 14, 17, 18, 40] Pediatric studies have found WC >90th percentile and, even more so, high WHtRs to correlate better than BMI percentile with a higher risk of hypertension, hypertriglyceridemia, low high density lipoproteins, and fasting insulin levels.[15, 16, 19, 41-45] Our data demonstrate that children with SP (but not MP) have higher odds than controls of having a high WC percentile and WHtR, and thus have additional risks associated with central adiposity.

As a non-blinded cross-sectional study, ascertainment and selection biases are inherent risks. Given that all pediatric psoriasis patients were solicited and agreed to participate, ascertainment bias was limited in MP and SP groups; because measures of disease severity (PGA and BSA) were assessed per standard procedure and by the same physician, disease severity was also measured without bias. Although selection bias for non-inflammatory controls is possible, all eligible children without inflammatory disease were asked to participate; as seen in Figure 2, the distribution of percentiles is approximately uniform, as would be expected in a completely random sample. To establish growth standards for children older than 5 years of age, both the CDC and the World Health Organization (WHO) used to the 1977 National Center for Health Statistics data. The CDC standards were selected for this study because they were the more conservative measure and were more likely to identify subjects who were actually overweight and obese.[46] International growth standards, including distribution for WC and WHtR, should be developed.

BMI percentile distributions showed increased adiposity in both MP and SP American and European subjects, but only in MP children from Asia. While the reason for the lower mean BMI percentile of Asian SP children is currently under investigation, a recent study demonstrated higher proportions of both obese and underweight children in the Chinese population.[47] It is possible that the differences in diet and exercise between the American/European countries and Malaysia as well as genetic variations could also account for regional variations in adiposity. Nevertheless, the small sample size, relatively small Asian control group, and large percentage of underweight SP Asian children (24%) limit our data interpretation. The "ethnicity-adjusted" cutoffs for WC percentile were based on >9,000 U.S. children of African, Mexican, or European, but not Asian descent[26], which could explain the difference in WC percentile distribution in control Asian children vs. other ethnic groups. Indeed, central adiposity varies by ethnic origin among the Malay population[48], and our questionnaire did not distinguish among ethnic subtypes or socio-economic status, both of which can impact the genetic and environmental factors that affect adiposity.

The underlying basis for the relationship between excess adiposity and psoriasis is not well understood. However, overproduction of Th1 and Th17 inflammatory cytokines is associated with both obesity[49] and psoriasis[50] in adults, suggesting that chronic inflammation drives both disorders. Indeed, remission of severe psoriasis has been described in adults after substantial weight loss as a result of gastric bypass surgery.[51, 52] Treatment of psoriatic adults with both cyclosporine and a 24-week weight loss diet (which reduced BMI and waist size) led to a greater reduction in severity than cyclosporine alone[53], further suggesting a relationship between psoriasis and obesity.

Despite the clear association of psoriasis with obesity, an unanswered question is whether high BMI is the precursor of psoriasis in children or whether psoriasis leads to an increased BMI percentile through chronic cytokine release from psoriatic tissue, compounded by a lifestyle that may favor excess adiposity (less physical activity, increased risk of depression).[54, 55] A recent prospective cohort study of 892 affected adult women found that increased adiposity preceded the occurrence of new onset psoriasis[21]; we are currently addressing if increased adiposity precedes psoriasis onset in children.

In our study, SP children who had transitioned to MP at enrollment showed no difference in adiposity from SP children who remained severe, despite controlling for other factors. While not longitudinal, these data suggest that effective intervention for psoriasis may not alter the tendency towards adiposity. A possible confounder for this conclusion is the reported association of use of TNF-α inhibitors and increases in BMI in adults with psoriasis, hypothesized to result primarily from suppression of TNF-α-induced myocyte catabolism.[16, 20, 56, 57] Although the numbers of SP children administered TNF-α inhibitors (etanercept, adalimumab and/or infliximab) by enrollment (23/82 using systemic medications globally and 17/51 in the U.S.) were insufficient for statistical comparison, 52% of SP children globally (59% in the U.S.) administered TNF-α inhibitors remained overweight or obese vs. 41% of SP children globally (52% in the U.S.) administered other systemic immunosuppressants. The possibility that use of TNF-α inhibitors in children leads to weight gain, despite the ameliorative effects on inflammation, deserves further investigation.

In conclusion, children with psoriasis internationally, regardless of severity, are more likely to be overweight or obese and thus at increased risk of complications related to excess adiposity. The association of central adiposity is greatest in children with severe psoriasis, and monitoring of these patients should be especially vigilant. Should future studies show excess adiposity to be a precursor for psoriasis, attempts at early weight loss and lifestyle

modification will be important, not only to decrease the risk of metabolic disease, but also to modulate the course of pediatric psoriasis.

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BMI Percentiles by Continent and Psoriasis Severity

Controls (n=205)
Mild Psoriasis (n=203)
Severe Psoriasis (n=206)
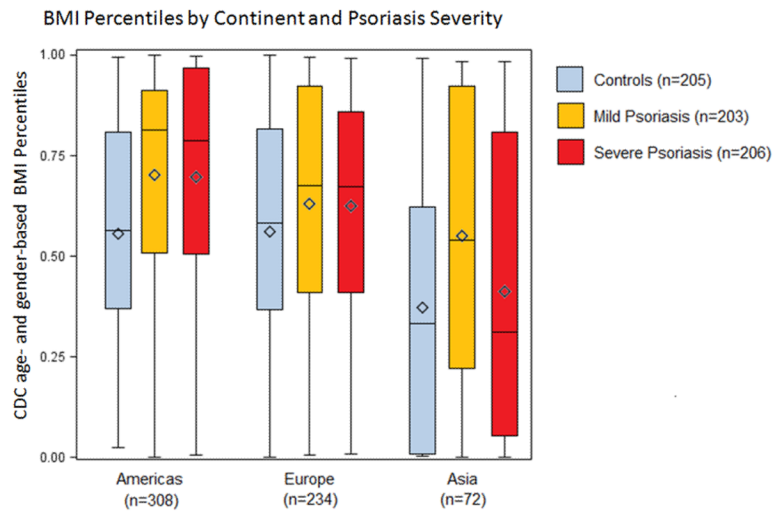
Figure 1.
Box-Plots of BMI percentiles, defined using CDC growth charts, by psoriasis disease severity and continent of study participants. Diamonds within box plots represent group means and horizontals lines medians. Boxes represent interquartile range and whiskers the range.
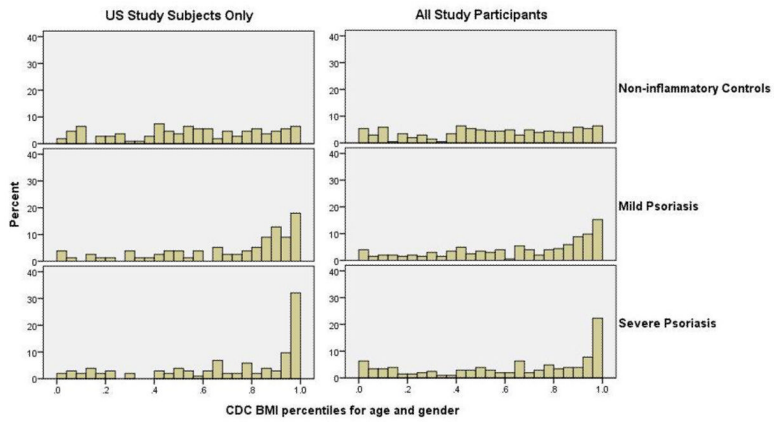
Figure 2.
Histograms of BMI percentiles based on age- and sex-specific CDC growth charts by study groups in the US and International cohorts.

Table 1

Demographic and Characteristics of All Subjects by Severity

Demographic	Non-Inflammatory Control (C)	Psoriatic (P)	Mild Psoriasis At Peak (MP)	Severe Psoriasis At Peak (SP)	[a] p-value for C vs. P	[b] p-value for MP vs. SP
N	205	409	203	206		
Age, yr. mean (SD)	11.5 (3.8)	12.2 (3.6)	11.8 (3.6)	12.5 (3.6)	0.974	0.862
Male, No. (%)	96 (46.8)	178 (43.5)	84 (41.4)	94 (45.9)	0.218	0.771
Duration of psoriasis, year median (interquartile range)		4 (2,8)	4 (2,7)	5 (2,8)		0.780
Race, No. (%)					0.477	0.528
White (non Hispanic)	156 (76.1)	247 (60.5)	134 (66.0)	113 (55.1)		
Asian	18 (8.8)	84 (20.5)	33 (16.3)	51 (24.6)		
Hispanic or Latino	19 (9.3)	46 (11.2)	20 (9.9)	26 (12.3)		
Black/AA	8 (3.9)	13 (3.2)	5 (2.5)	8 (3.9)		
Other	4 (2.0)	19 (4.6)	11 (5.4)	8 (3.9)		
Continent, No. (%)					0.979	0.892
Americas	108 (52.7)	200 (48.8)	89 (43.8)	111 (53.6)		
Europe	87 (42.4)	148 (36.1)	90 (44.3)	58 (28.0)		
Asia	10 (4.9)	62 (15.1)	24 (11.8)	38 (18.4)		
Other Characteristics, No. (%)						
Psoriatic arthritis	--	23 (5.6)	7 (3.5)	16 (7.7)	--	0.722
Phototherapy [c]	--	88 (21.8)	18 (8.9)	70 (34.8)	--	**<0.001**
Systemic medications [c]	--	104 (25.7)	22 (10.8)	82 (40.8)	--	**<0.001**
Family History, No. (%)						
Diabetes	66 (41.8)	153 (48.1)	66 (44.0)	87 (51.8)	0.249	0.716
Hypertension	83 (52.5)	165 (52.2)	77 (51.3)	88 (53.0)	0.952	0.188
Hyperlipidemia	77 (48.7)	115 (36.2)	53 (35.3)	62 (36.9)	0.656	0.684
Obesity	48 (30.4)	94 (29.6)	37 (24.7)	57 (33.9)	0.610	0.705
Psoriatic arthritis	--	21 (6.6)	5 (3.3)	16 (9.5)	--	0.757

Demographic	Non-Inflammatory Control (C)	Psoriatic (P)	Mild Psoriasis At Peak (MP)	Severe Psoriasis At Peak (SP)	a p-value for C vs. P	b p-value for MP vs. SP
Psoriasis, extended family	--	213 (52.0)	97 (47.8)	116 (56.0)	--	0.167
Psoriasis, immediate family	--	118 (28.9)	56 (27.6)	62 (30.1)	--	0.890
Metabolic Characteristics						
SBP, mm/Hg mean (SD)	114 (11)	110 (12)	111(12)	110 (12)	**0.008**	0.553
DBP, mm/Hg mean (SD)	66 (9)	67 (8)	68 (8)	66 (8)	0.803	**0.049**
Height Percentile, mean (SD)	59.7 (30.9)	52.7 (32.2)	52.6 (33.4)	52.9 (31.2)	0.505	0.927
Weight Percentile, mean (SD)	59.7 (29.1)	62.6 (31.7)	62.7 (31.0)	62.6 (32.4)	**0.029**	0.804
BMI Percentile, mean (SD)	54.9 (29.6)	63.8 (31.8)	65.3 (30.0)	62.3 (33.4)	**<0.001**	0.294
BMI Percentile, median (interquartile range)	56.4 (36.5, 80.8)	71.6 (40.8, 93.4)	73.3 (41.6, 92.3)	69.6 (34.6, 94.7)	**<0.001**	0.275
BMI Category, No. (%)					**<0.001**	0.098
Underweight	13 (6.3)	25 (6.1)	10 (4.9)	15 (7.3)		
Healthy weight	150 (73.2)	229 (56.1)	115 (56.6)	114 (55.6)		
Overweight	27 (13.2)	72 (17.6)	44 (21.7)	28 (13.5)		
Obese	15 (7.3)	83 (20.2)	34 (16.8)	49 (23.7)		
Waist Circumference, No. (%)					**0.050**	0.280
<10th percentile	15 (7.4)	44 (11.1)	15 (7.8)	29 (14.3)		
10-25th	36 (17.7)	50 (12.6)	21 (10.9)	29 (14.3)		
25-50th	41 (20.1)	65 (16.4)	35 (18.1)	30 (14.8)		
50-75th	55 (27.0)	102 (26.0)	59 (30.6)	43 (21.7)		
75-90th	38 (18.6)	64 (16.2)	36 (18.7)	28 (13.8)		
>90th	19 (9.3)	70 (17.7)	27 (14.0)	43 (21.2)		
Waist to Height Ratio, mean(SD)	0.46 (0.05)	0.48 (0.08)	0.48 (0.07)	0.48 (0.09)	**0.002**	0.378

AA=African-American; BMI=body mass index; C=control; DBP=diastolic blood pressure; MP= mild psoriasis; N=number; P=psoriasis; SBP= systolic blood pressure; SD=standard deviation; SP=severe psoriasis

[a] Adjusted for fixed effects of age, sex, and continent, and random effect of center.

[b] Adjusted for fixed effects of age, sex, continent, phototherapy, systemic medications, and psoriasis duration, and random effects of center.

[c] Some patients had used both phototherapy and systemic immunosuppressant medications

Table 2

Demographic and Characteristics of U.S. Subjects by Severity

Characteristic Demographic	Non-Inflammatory Control (C)	Psoriatic (P)	Mild Psoriasis At Peak (MP)	Severe Psoriasis At Peak (SP)	[a] p-value for C vs. P	[b] p-value for MP vs. SP
N (% of total)	108 (37.4)	181 (62.6)	78 (27.0)	103 (35.6)		
Age, yr. mean (SD)	11.3 (4.0)	12.6 (3.6)	12.3 (3.6)	12.8 (3.6)	0.161	0.596
Male, No. (%)	43 (39.8)	73 (40.3)	27 (34.6)	46 (44.7)	0.831	0.530
Duration of psoriasis, years, median (interquartile range)	--	5 (2.9)	4 (2.8)	5 (2.9)	--	0.992
Race, No. (%)					0.138	0.964
White (non Hispanic)	73 (67.6)	110 (60.8)	49 (62.8)	61 (59.2)		
Asian	8 (7.4)	22 (12.2)	9 (11.5)	13 (12.6)		
Hispanic or Latino	17 (15.7)	33 (18.2)	14 (18.0)	19 (18.5)		
Black/AA	8 (7.4)	9 (5.0)	3 (3.9)	6 (5.8)		
Other	2 (1.9)	7 (3.9)	3 (3.9)	4 (3.9)		
Other Characteristics, No. (%)						
Psoriatic arthritis	--	19 (10.5)	7 (9.0)	12 (11.7)	--	0.588
Phototherapy [c]	--	40 (22.1)	6 (7.7)	34 (33.0)	--	**0.001**
Systemic medications [c]	--	65 (35.9)	14 (17.9)	51 (49.5)	--	**0.001**
Family History, No. (%)						
Diabetes	53 (49.1)	103 (56.9)	44 (56.4)	59 (57.3)	0.165	0.636
Hypertension	61 (56.5)	101 (55.8)	48 (61.5)	53 (51.5)	0.315	0.061
Hyperlipidemia	64 (59.3)	83 (45.9)	37 (47.4)	46 (44.7)	0.955	0.607
Obesity	41 (38.0)	62 (34.3)	23 (29.5)	39 (37.9)	0.662	0.659
Psoriatic arthritis	--	17 (9.4)	3 (3.9)	14 (13.6)	--	0.157
Psoriasis, extended family	--	93 (51.4)	35 (44.9)	58 (56.3)	--	0.275
Psoriasis, immediate family	--	55 (30.4)	20 (25.6)	35 (34.0)	--	0.990
Metabolic Characteristics						
SBP, mm/Hg mean(SD)	110 (12)	110 (12)	109 (11)	111 (12)	0.740	0.525

Characteristic Demographic	Non-Inflammatory Control (C)	Psoriatic (P)	Mild Psoriasis At Peak (MP)	Severe Psoriasis At Peak (SP)	[a] p-value for C vs. P	[b] p-value for MP vs. SP
DBP, mm/Hg mean(SD)	64 (10)	67 (8)	67 (8)	67 (8)	0.458	0.479
Height Percentile, mean(SD)	59.9 (28.6)	54.4 (31.9)	52.3 (33.2)	56.1 (30.9)	0.558	0.431
Weight Percentile, mean(SD)	59.8 (28.0)	68.0 (31.2)	65.2 (31.9)	70.2 (30.7)	**0.035**	0.660
BMI Percentile, mean(SD)	55.6 (28.8)	70.4 (30.1)	70.5 (28.9)	70.4 (31.1)	**<0.001**	0.538
BMI Percentile, median (interquartile range)	56.4 (37.0, 80.9)	82.7 (50.8, 96.1)	83.0 (50.8, 93.4)	80.8 (50.7, 96.7)	**<0.001**	0.652
BMI Category, No. (%)					**<0.001**	0.216
Underweight	4 (3.7)	7 (3.9)	4 (5.1)	3 (2.9)		
Healthy weight	83 (76.9)	88 (48.6)	37 (47.4)	51 (49.5)		
Overweight	12 (11.1)	36 (19.9)	22 (28.2)	14 (13.6)		
Obese	9 (8.3)	50 (27.6)	15 (19.2)	35 (34.0)		
Waist Circumference, No. (%)					0.129	0.782
<10th percentile	9 (8.3)	17 (9.4)	6 (7.8)	11 (10.7)		
10-25th	15 (13.9)	21 (11.7)	8 (10.4)	13 (12.6)		
25-50th	22 (20.4)	27 (15.0)	11 (14.3)	16 (15.5)		
50-75th	31 (28.7)	42 (23.3)	24 (31.2)	18 (17.5)		
75-90th	18 (16.7)	25 (13.9)	12 (15.6)	13 (12.6)		
>90th	13 (12.0)	48 (26.7)	16 (20.8)	32 (31.1)		
Waist to Height Ratio, mean (SD)	0.46 (0.05)	0.49 (0.08)	0.49 (0.06)	0.49 (0.10)	**0.010**	0.970

AA=African-American; BMI=body mass index; C=control; DBP=diastolic blood pressure; MP= mild psoriasis; N=number; P=psoriasis; SBP= systolic blood pressure; SD=standard deviation; SP=severe psoriasis

[a] Adjusted for fixed effects of age, sex, and race ethnicity and random effect of center.

[b] Adjusted for fixed effects of age, sex, race ethnicity, phototherapy, systemic medications, and psoriasis duration and random effect of center.

[c] Some patients had used both phototherapy and systemic immunosuppressant medications

Table 3

Age, Sex, Race/Continent, and Center Adjusted Odds Ratios

Predicting	Referent Control	Comparison	BMI% Threshold[a] OR(95% CI)	WC % threshold[b] OR (95% CI)	WHtR Threshold[c]
All Subjects Internationally					
Overweight weight +Obesity (Excess adiposity)	Healthy	Psoriasis vs. Control	2.65 (1.70, 4.15)	1.42 (0.96, 2.10)	1.45 (0.96, 2.19)
		Mild vs. Control	2.76 (1.69, 4.50)	1.30 (0.83, 2.04)	1.35 (0.85, 2.15)
		Severe vs. Control	2.56 (1.57, 4.17)	1.54 (0.99, 2.41)	1.56 (0.98, 2.48)
Obesity weight	Healthy	Psoriasis vs. Control	4.29 (1.96, 9.39)	2.52 (1.24, 5.12)	3.10 (1.39, 6.90)
		Mild vs. Control	3.60 (1.56, 8.30)	1.90 (0.90, 4.01)	2.21 (0.92, 5.32)
		Severe vs. Control	4.92 (2.20, 10.99)	3.06 (1.53, 6.15)	4.10 (1.80, 9.31)
Obesity	Overweight	Psoriasis vs. Control	1.93 (0.89, 4.15)	1.77 (0.85, 3.67)	2.88 (1.19, 6.99)
		Mild vs. Control	1.38 (0.63, 3.05)	1.37 (0.62, 3.06)	1.67 (0.64, 4.38)
		Severe vs. Control	2.85 (1.26, 6.42)	2.36 (1.04, 5.39)	5.11 (1.96, 13.34)
U.S. Subjects					
Overweight weight +Obesity (Excess adiposity)	Healthy	Psoriasis vs. Control	4.02 (2.11, 7.63)	1.77 (1.03, 3.07)	1.77 (1.02, 3.09)
		Mild vs. Control	4.22 (2.05, 8.67)	1.44 (0.75, 2.78)	1.45 (0.75, 2.79)
		Severe vs. Control	3.87 (1.95, 7.70)	2.05 (1.12, 3.76)	2.06 (1.12, 3.81)
Obesity weight	Healthy	Psoriasis vs. Control	6.61 (2.16, 20.17)	3.47 (1.39, 8.66)	4.87 (1.51, 15.76)
		Mild vs. Control	4.72 (1.43, 15.56)	2.05 (0.80, 5.25)	2.49, (0.71, 8.74)
		Severe vs. Control	7.60 (2.47, 23.34)	3.85 (1.64, 9.00)	6.62 (2.11, 20.76)
Obesity	Overweight	Psoriasis vs. Control	1.61 (0.51, 5.06)	3.29 (1.22, 8.87)	4.28 (1.33, 13.75)
		Mild vs. Control	0.93 (0.31, 2.84)	2.51 (0.84, 7.48)	1.41 (0.48, 4.12)
		Severe vs. Control	2.96 (0.99, 8.86)	4.24 (1.33, 13.46)	7.53 (2.29, 24.78)

BMI=body mass index; CI=confidence interval; OR=odds ratio; WC=waist circumference; WHtR=Waist to Height Ratio.

[a] Overweight and obesity defined as >85 percentile or >95 percentile, respectively, of BMI for age and sex; healthy weight defined as between the 5th-85th percentiles.

[b] Overweight and obesity defined as >75th or >90th percentile, respectively, of waist circumference for age, sex, and race; healthy weight defined as between the 10-75th percentiles.

[c] Overweight and obesity defined as WHtR>4.90 or >0.539, respectively. WHtR<0.377 (the lower 5% of our cohort) were eliminated from analysis, as they may be considered underweight, although conclusions remained consistent when they were inclued as normal/healthy.

Table 4

Comparison of Demographic and Metabolic Features by Continent (International) and Race (U.S.)[a]

All by Continent	Non-inflammatory (control)			Psoriasis			p-values	
	Americas	Europe	Asia	Americas	Europe	Asia	Interaction p-value	Race/Continent p-value
N	108	87	10	200	148	62		
Age, yr. mean (SD)	11.3 (4.0)	11.5 (3.6)	13.0 (4.1)	12.6 (3.6)	11.5 (3.5)	12.4 (3.7)	0.408	0.152
Male, No. (%)	43 (39.8)	46 (52.9)	7 (70.0)	84 (42.0)	63 (42.6)	32 (51.6)	0.723	0.616
Duration of psoriasis, yrs Median (interquartile range)				5 (2,9)	3 (1,6)	5 (2,9)		0.816
Weight percentile, mean (SD)	59.8 (28.0)	62.6 (27.8)	32.1 (39.5)	67.5 (30.6)	65.7 (25.9)	39.7 (37.5)	0.751	**<0.001**
BMI Percentile, mean (SD)	55.6 (28.8)	56.0 (29.3)	37.3 (37.9)	69.9 (29.9)	62.8 (29.1)	46.6 (37.1)	0.693	**0.001**
BMI Category (%)							0.211	0.088
Underweight	4 (3.7)	6 (6.9)	3 (30.0)	7 (3.5)	6 (4.1)	12 (19.4)		
Healthy weight	83 (76.8)	62 (71.3)	5 (50.0)	101 (50.5)	97 (65.5)	32 (51.6)		
Overweight	12 (11.1)	15 (17.2)	0 (0)	40 (20.0)	22 (14.9)	10 (16.1)		
Obese	9 (8.3)	4 (4.6)	2 (20.0)	52 (26.0)	23 (15.5)	8 (12.9)		
Waist Circumference %							0.892	**0.002**
<10th	9 (8.3)	3 (3.5)	3 (30.0)	18 (9.1)	13 (9.6)	13 (21.3)		
10-25th	15 (13.9)	19 (22.1)	2 (20.0)	22 (11.1)	17 (12.5)	11 (18.0)		
25-50th	22 (20.4)	17 (19.8)	2 (20.0)	29 (14.6)	24 (17.7)	12 (19.7)		
50-75th	31 (28.7)	23 (26.7)	1 (10.0)	51 (25.6)	46 (33.8)	6 (9.8)		
75-90th	18 (16.7)	20 (23.3)	0 (0)	29 (14.6)	24 (17.7)	11 (18.0)		
>90th	13 (12.0)	4 (4.7)	2 (20.0)	50 (25.1)	12 (8.8)	8 (13.1)		
Waist to Height Ratio	0.46 (0.05)	0.45 (0.05)	0.46 (0.07)	0.49 (0.08)	0.46 (0.07)	0.47 (0.07)	0.660	**0.016**

U.S. by Race	White	Hispanic/ Black	Asian	White	Hispanic/ Black	Asian	Interaction P-value	Race/ Continent p-value
N	73	25	8	110	42	22		

U.S. by Race	White	Hispanic/ Black	Asian	White	Hispanic/ Black	Asian	Interaction P-value	Race/ Continent p-value
Age (year), mean (SD)	11.6 (4.1)	10.2 (4.1)	11.9 (3.0)	12.6 (3.5)	12.6 (3.7)	13.0 (4.0)	0.434	0.521
Male, n (%)	29 (39.7)	10 (40.0)	4 (50.0)	48 (43.6)	12 (28.6)	11 (50.0)	0.514	0.272
Duration of psoriasis, years Median (interquartile)				2 (2, 10)	4 (2, 8)	6 (4, 8)	--	0.096
Weight percentile, mean (SD)	59.6 (27.2)	62.0 (28.2)	54.6 (38.2)	68.0 (29.3)	77.3 (27.0)	52.4 (40.7)	0.489	**0.006**
BMI Percentile, mean (SD)	53.4 (28.1)	63.0 (26.8)	54.1 (40.4)	68.9 (29.2)	81.8 (22.4)	57.9 (38.0)	0.572	**0.002**
BMI Category							0.613	**0.026**
Underweight	2 (2.7)	1 (4.0)	1 (12.5)	2 (1.8)	1 (2.4)	3 (13.6)		
Healthy weight	59 (80.8)	18 (72.0)	4 (50.0)	59 (53.6)	16 (38.1)	10 (45.5)		
Overweight	7 (9.6)	3 (12.0)	2 (25.0)	25 (22.7)	9 (21.4)	1 (4.6)		
Obese	5 (6.9)	3 (12.0)	1 (12.5)	24 (21.8)	16 (38.1)	8 (36.4)		
Waist Circumference %							0.761	0.001
<10th	8 (11.0)	1 (4.0)	0 (0.0)	8 (7.3)	1 (2.4)	7 (31.8)		
10-25th	10 (13.7)	2 (8.0)	2 (25.0)	17 (15.6)	2 (4.8)	2 (9.1)		
25-50th	10 (13.7)	10 (40.0)	2 (25.0)	13 (11.9)	12 (28.6)	1 (4.6)		
50-75th	22 (30.1)	7 (28.0)	1 (12.5)	32 (29.4)	5 (11.9)	3 (13.6)		
75-90th	14 (19.2)	3 (12.0)	1 (12.5)	15 (13.8)	10 (23.8)	0 (0.0)		
>90th	9 (12.3)	2 (8.0)	2 (25.0)	24 (22.0)	12 (28.6)	9 (40.9)		
Waist to Height Ratio	0.46 (0.05)	0.47 (0.06)	0.47 (0.06)	0.47 (0.08)	0.51 (0.08)	0.50 (0.10)	0.818	**0.021**

BMI=body mass index; C=control; DBP=diastolic blood pressure; MP= mild psoriasis; N=number; P=psoriasis; SBP= systolic blood pressure; SD=standard deviation; SP=severe psoriasis.

[a]Hispanic and Black/African-American children were combined because of their lower sample size and similar metabolic characteristics. Due to small sample sizes and heterogeneity of the group, those who indicated race as "Other" were excluded from this analysis.

Table 5

U.S/non-U.S. Comparison of Demographic and Metabolic Characteristics

Demographic	Non-Inflammatory Control			Psoriatic			Group by U.S. interaction p-value[a]
	U.S.	Non-U.S.	p-value[a]	U.S.	Non-U.S.	p-value[b]	
N	108	97		181	228		
Age, yr. mean (SD)	11.3 (4.0)	11.6 (3.6)	0.506	12.6 (3.6)	11.9 (3.6)	0.295	0.304
Male, No. (%)	43 (39.8)	53 (54.6)	0.498	73 (40.3)	105 (46.1)	0.483	0.740
Duration of psoriasis, yr. median (interquartile range)				5 (2,9)	4 (2, 7)		--
Race, No. (%)			0.004			0.599	0.043
White (non Hispanic)	73 (67.6)	83 (85.6)		110 (60.8)	137 (60.1)		
Asian	8 (7.4)	10 (10.3)		22 (12.2)	62 (27.2)		
Hispanic or Latino	17 (15.7)	2 (2.1)		33 (18.2)	13 (5.7)		
Black/AA	8 (7.4)	0 (0)		9 (5.0)	4 (1.8)		
Other	2 (1.9)	2 (2.1)		7 (3.9)	12 (5.3)		
Other Characteristics, No. (%)							
Psoriatic arthritis	--	--	--	19 (10.5)	4 (1.8)	**0.029**	--
Phototherapy	--	--	--	40 (22.7)	48 (21.2)	0.405	--
Systemic medications	--	--	--	65 (36.9)	39 (17.2)	0.182	--
Family History, No. (%)							
Diabetes	53 (49.1)	13 (26.0)	0.186	103 (56.9)	50 (36.8)	0.080	0.559
Hypertension	61 (56.5)	22 (44.0)	0.866	101 (55.8)	64 (47.1)	0.378	0.181
Hyperlipidemia	64 (59.3)	13 (26.0)	0.152	83 (45.9)	32 (23.5)	0.055	0.541
Obesity	41 (38.0)	7 (14.0)	0.602	62 (34.3)	32 (23.5)	0.568	0.904
Psoriatic arthritis	--	--	--	17 (9.4)	4 (2.9)	0.755	--
Psoriasis, extended family	--	--	--	93 (51.4)	120 (52.6)	0.510	--
Psoriasis, immediate family	--	--	--	55 (30.4)	63 (27.6)	0.418	--
Metabolic Characteristics							
SBP, mm/Hg mean (SD)	110 (12)	118 (10)	0.085	110 (12)	111 (12)	0.829	0.165

Demographic	Non-Inflammatory Control			Psoriatic			Group by U.S. interaction p-value[a]
	U.S.	Non-U.S.	p-value[a]	U.S.	Non-U.S.	p-value[b]	
DBP, mm/Hg mean (SD)	64 (10)	69 (7)	0.089	67 (8)	67 (9)	0.928	0.254
Height Percentile, mean (SD)	59.9 (28.6)	59.6 (33.4)	0.863	54.4 (31.9)	51.3 (32.5)	0.556	0.869
Weight Percentile, mean (SD)	59.8 (28.0)	59.5 (30.4)	0.925	68.0 (31.2)	58.4 (31.5)	0.127	0.388
BMI Percentile, mean (SD)	55.6 (28.8)	54.1 (30.6)	0.817	70.4 (30.1)	58.6 (32.2)	0.061	0.303
BMI Percentile, median (interquartile range)	56.4 (37.0, 80.9)	56.4 (29.3, 78.9)	0.998	82.7 (50.8, 96.1)	64.7 (33.7, 89.1)	**0.035**	0.444
BMI Category, No. (%)			0.729			**0.019**	0.238
Underweight	4 (3.7)	9 (9.2)		7 (3.9)	18 (7.9)		
Healthy weight	83 (76.9)	67 (69.1)		88 (48.6)	141 (61.8)		
Overweight	12 (11.1)	15 (15.5)		36 (19.9)	36 (15.8)		
Obese	9 (8.3)	6 (6.2)		50 (27.6)	33 (14.5)		
Waist Circumference, No. (%)			0.485			**0.015**	0.557
<10th percentile							
10-25th	9 (8.3)	6 (6.3)		17 (9.4)	27 (12.6)		
25-50th	15 (13.9)	21 (21.9)		21 (11.7)	29 (13.5)		
50-75th	22 (20.4)	19 (19.8)		27 (15.0)	38 (17.7)		
75-90th	31 (28.7)	24 (25.0)		42 (23.3)	60 (27.9)		
>90th	18 (16.7)	20 (20.8)		25 (13.9)	39 (18.4)		
	13 (12.0)	6 (6.3)		48 (26.7)	22 (10.2)		
Waist to Height Ratio	0.46 (0.05)	0.45 (0.05)	0.625	0.49 (0.08)	0.47 (0.07)	**0.048**	0.206

[a] Adjusted for fixed effects of age, and sex, and random effect of center.

[b] Adjusted for age, sex, race, systemic medication, phototherapy, and psoriasis duration.