

Aerobic Capacity in Children with Hemophilia

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Objective To determine whether aerobic capacity is normal in boys with different types of hemophilia compared with healthy peers and whether the level of aerobic capacity correlates with the amount of physical activity, joint health status, muscle strength, and anthropometrics.

Study design 47 patients (mean [SD] age, 12.9 [3.2] years; age range, 8.2-17.4 years) from the "Van Creveldkliniek" of the University Medical Center Utrecht, participated. Anthropometry, muscle strength, joint impairment, functional ability, and aerobic capacity were measured. The amount of energy expenditure during daily living was assessed.

Results All boys were able to perform at maximal or near-maximal level on exercise tests, and none of them reported bleeds or other adverse events. Relative peak oxygen, peak heart rate, and peak working capacity were significantly lower compared with healthy control subjects. 30% had Z-scores >2 for weight. Total muscle strength was normal, and almost no joint impairment and no decrease in functional ability were found.

Conclusion The aerobic capacity of children with hemophilia is still lower than the normal population, whereas their overall muscle strength is comparable with healthy peers. The functional ability does not differ from healthy peers, and joint health status showed very minor impairments. A substantial proportion of Dutch children with hemophilia was overweight, without showing a reduction in the amount of self-reported physical activities. (*J Pediatr* 2008;xx:xxx)

Hemophilia results from absence or deficiency of factor VIII in hemophilia A or of factor IX in hemophilia B, and both are X-linked recessive disorders with an incidence of approximately 1:10,000 and 1:60,000 people, respectively.¹ Patients with hemophilia often used to have a sedentary lifestyle, because of haemarthroses and subsequent synovitis and arthropathy. With the introduction of prophylactic clotting factor replacement therapy, they had fewer bleeds and were able to participate in physical activities. It is now widely recognized that physical activity and sports are beneficial for patients with hemophilia.²⁻³ Strengthening of muscles may support the joints, thereby decreasing the incidence and severity of injury of the joints.⁴ In this way, physical activity helps prevent joint bleeds and the subsequent development of future arthropathy, and it may speed recovery after joint and muscle bleeds.³ Also some evidence exists that exercise may result in an increase of factor VIII.⁵ Adults with severe hemophilia participate in sport activities at the same level as healthy control subjects, although the type of sport may be different.³ Children with hemophilia are not as physically active as their healthy peers and show a lower level of reported leisure-time activity and lower involvement in intense activity.⁶ Koch et al assessed the physical fitness of children with hemophilia between 8.3 and 15.5 years and reported a significant reduction in exercise capacity (peak work rate), possibly because of insufficient intensity during daily physical activities.⁷ However, they did not measure oxygen uptake, which is regarded as the single best indicator of aerobic capacity during a graded maximal exercise test to exhaustion.⁸ Although motor performance and activity levels of children with hemophilia were comparable with that of healthy peers, Schoenmakers et al reported that

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The cohort of subjects studied is the same for both the Hemophilia Joint Health Score (HJHS) validation study and the aerobic capacity study.

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Σ4SF	Sum of 4 skin-fold measurements	RCHAQ _{3B}	Revised Childhood Health Assessment Questionnaire
BMI	Body mass index	RER	Respiratory exchange ratio
HJHS	Hemophilia Joint Health Score	VO _{2peak}	Peak oxygen consumption
HR	Heart rate	VO _{2peak/kg}	Relative VO _{2peak}
MAQ	Modifiable Activity Questionnaire	W _{max}	Maximal working capacity
MET	Metabolic equivalent score		
MET-h/week	Average MET/ hour per week		

56% of children with hemophilia had parental restrictions, medical restrictions, or both in sports or gymnastics.⁹ Muscle strength and anaerobic power were also significantly reduced in children with hemophilia, especially in the lower limbs.^{6,10} Van der Net et al performed a pilot study in 13 boys with severe hemophilia and found that a maximal exercise test was a safe procedure, and aerobic capacity and functional ability were normal.¹¹ Because they used a small number of participants, it was questioned whether their results are representative.

We studied these question: Is the aerobic capacity normal in boys with different types of hemophilia compared with their healthy peers, and does the level of aerobic capacity correlate with the amount of physical activity, joint health status, muscle strength, and anthropometrics?

METHODS

Patients

109 boys from the “Van Creveldkliniek” of the University Medical Center Utrecht, aged between 8 and 18 years, were invited to participate. 48 patients (44%) participated. 1 boy was excluded from analyses *post hoc*, because he had an unknown muscular disorder detected with muscle biopsy. 42 of the participants had hemophilia A, 4 had hemophilia B, and 1 had hemophilia B Leyden. 21 boys had severe hemophilia (<1% of clotting factor activity) and received prophylactic factor replacement therapy; they did not receive an additional dose of factor concentrate before the testing. 7 boys had moderate hemophilia (1%-5% of clotting factor activity), and 19 had mild hemophilia (5%-45% of clotting factor activity). They received on-demand treatment. The participants (48/109) and non-responders (boys who were invited but did not want to participate; 61/109) were compared for type and severity of hemophilia and age. Participants who sustained a joint bleed in either the ankles or knees 2 weeks before testing were excluded.

The study was approved by the institutional medical ethics committee. All participants or parents signed informed consent.

Anthropometry

Weight was measured with an electronic scale; height was measured with a wall-mounted stadiometer. Body mass index (BMI) was calculated ($\text{weight}/\text{height}^2$). The sum of 4 skin-fold measurements ($\Sigma 4\text{SF}$) was used to assess body composition. Measurements were taken with a Harpenden skin fold calliper at the right side of the body at the biceps, triceps, supra iliaca, and at sub scapular sites.

Muscle Strength

Muscle strength was measured during maximal isometric contraction (elbow flexors and extensors, knee flexors and extensors, and foot dorsal flexors bilaterally). These muscle groups were chosen because they are involved in the 3 joints mostly affected in hemophilia (ankles, knees, and elbows).

Approximately 80% of recurrent haemarthroses occur in these diarthrodial joints,¹² most often in the lower limbs.⁶ Measurements were performed in a standardized testing position with a handheld myometer (Citex Groningen, The Netherlands) and performed consecutively 3 times by using the “break” method.¹³ Verbal encouragements were given during the measurements. The highest value was recorded, and values of the left and right side of the same muscle group were averaged. Total muscle strength was calculated by adding up the separate scores.

Aerobic Capacity

A maximal exercise test was performed on an electronically braked cycle ergometer (Lode Corival, Lode BV, Groningen, The Netherlands). After 1 minute of unloaded cycling, the workload (W) was increased according to the Godfrey protocol¹⁴ with 20 watts every minute for participants >1.50 meter and with 15 watts every minute for participants <1.50 meter. Participants stopped cycling when volitional exhaustion was reached.

During the maximal exercise test, participants breathed through a face mask (Hans Rudolph, Kansas City, MO) connected to a calibrated expired gas analysis system (Cortex Metamax, Cortex Medical GmbH, Leipzig, Germany) calculating breath-by-breath minute ventilation, oxygen uptake, carbon dioxide production, and respiratory exchange ratio (RER). Throughout the test, heart rate (HR) was monitored by using a HR monitor (Polar, Kempele, Finland). Absolute peak oxygen uptake ($\text{VO}_{2\text{peak}}$) was calculated as the average value in the last 30 seconds during the test. Relative peak oxygen uptake ($\text{VO}_{2\text{peak}}/\text{kg}$) was calculated by dividing $\text{VO}_{2\text{peak}}$ by body mass.

Hemophilia Joint Health Score

The health status of the joints was assessed by using the Hemophilia Joint Health Score (HJHS), developed by the International Prophylaxis Study Group (Physical Therapy Working Group). The instrument was shown to be reliable, with an interobserver coefficient of 0.83 and a test-retest value of 0.89.^{12,15} In the elbows, knees, and ankles, numeric scores for swelling, duration of swelling, muscle atrophy, axial alignment, crepitus on motion, flexion and extension loss, instability, joint pain, strength, and gait were scored. After adding all scores, raw scores and the percentage of joint impairment were scored (a score of 0% representing no joint impairment). Presented data of the HJHS will also be used in a multicenter validation study.

The amount of bleeds in ankle, knee, and elbow joints per year was scored.

Functional Ability

Functional ability was assessed by using the Dutch translation of the Revised Childhood Health Assessment Questionnaire (RCHAQ₃₈). The revised version is a multidimensional questionnaire incorporating 38 questions about

how the child performs on daily activities of different domains (dressing and grooming, arising, eating, walking, hygiene, reach, grip, activities, and school-extracurricular activities). The possible answers range over a wide spectrum, “much worse” than healthy peers to “much better” than healthy peers. This makes it a sensitive, reliable, and valid tool without a ceiling effect.¹⁶

Physical Activities

The amount of energy expenditure during daily living was assessed by using a Modifiable Activity Questionnaire (MAQ¹⁷) and a Bouchard Three-Day Physical Activity Record (Bouchard diary¹⁸). In the MAQ, participants were asked to fill in their sport activities in the previous year. This questionnaire was found to yield a reasonable estimate of habitual physical activity of the past year in adolescents.¹⁷ In younger children, parents assisted with the questionnaire. All activities were assigned an intensity level on the basis of the rate of energy expenditure expressed as metabolic equivalent scores (METs, ratios of activity metabolic rate to standard resting metabolic rate in kJ/kg/hr). 1 MET is considered a resting metabolic rate obtained during quiet sitting. With the given number of months in which a particular sport activity was performed, the days per week, minutes per day, and corresponding MET score, the average MET/hour per week (MET-h/week) was calculated.¹⁹ The Bouchard diary was filled out by the participants on 3 days (2 weekdays and 1 weekend day). Every 15 minutes, they filled out what type of activity they performed and with what intensity, ranging from 1 (sleep, lying in bed) to 9 (competitive sports), corresponding with MET scores of 1.0 to 7.8, respectively. All 9 categories correspond with a median energy cost in Kcal/kg/15min. The sum of all scores gives the average daily expenditure in Kcal/kg, which gives the total amount of Kcal expenditure per day when multiplied by the participant's weight.¹⁸

Statistics

Data were analyzed with SPSS software version 12.0.2 for Microsoft Windows XP (SPSS, Chicago, IL). An independent sample *t* test was used to test for differences in age between participants and non-responders. A χ^2 test was used to test for differences in severity of the hemophilia between participants and non-responders. Normality of the data was assessed by using the Kolmogorov-Smirnov test.

Normal distributed data are described with descriptive statistics (mean, minimum, maximum, range, and SD scores). For non-normal distributions, data are presented with quartiles (median, interquartile range). Independent samples *t* tests and Wilcoxon signed ranks tests, depending on the distribution of the sample, were used to analyze differences between participants and reference values. Pearson and Spearman correlation coefficients were calculated, depending on the distribution of the sample.

The anthropometric data, muscle strength outcomes, and outcomes of the maximal exercise test have been com-

pared with age-related reference values from the Dutch population and transformed to Z-scores.^{13,20-22} Scores were compared between the different severities of the hemophilia (ie, mild, moderate, and severe) and between children with relatively low aerobic capacity (VO_{2peak} Z-score <-2) and children with normal aerobic capacity (VO_{2peak} Z-score ≥-2). For all tests, alpha levels <0.05 (2-tailed) were considered to be statistically significant.

RESULTS

47 patients participated in this study (mean [SD] age, 12.9 [3.2] years; age range, 8.2-17.4 years). None of them reported joint or muscle bleeds or other adverse events because of participation in the study. Participants and non-responders did not differ significantly from each other in age (mean [SD], 12.9 [3.2] versus 13.4 [2.9] years; $P = .44$) or disease severity (Pearson $\chi^2 = 1.3$, $P = .27$).

Children were slightly taller than their healthy peers and had higher weight, BMI, and $\Sigma 4SF$ (Table I; available at www.jpeds.com). 14 boys (30%) had Z-scores >2 for weight and BMI, and 15 boys (32%) had Z-scores >2 for $\Sigma 4SF$. The highest percentage of overweight was found in children with mild hemophilia (Pearson χ^2 , 4.8; $P = .09$). Muscle strength measurements are summarized in Table II. Total muscle strength was normal compared with healthy control subjects. 1 boy (3%) had a Z-score <-2 for total muscle strength. The outcomes of the maximal exercise test are presented in Table III. All boys were able to perform at maximal or near-maximal level, as indicated by the mean HR_{peak} of 190.5 beats/min and a mean RER_{peak} of 1.2 (SD, 0.2). $RER_{peak} >1.0$ and $HR_{peak} >180$ are objective measures to indicate total exhaustion.²² Relative VO_{2peak} , HR_{peak} , and W_{peak} were significantly lower compared with that of healthy control subjects. Only 1 boy scored a $RER_{peak} <1.0$, and 11 boys reached a $HR_{peak} <180$. Two boys showed considerably lower HR_{peak} (ie, both 168; Z-scores, -3.64 and -3.82). 3 boys (6%) scored Z-scores <-2 , and 1 boy (2%) scored a Z-score >2 for absolute VO_{2peak} . 14 boys (30%) scored Z-scores <-2 for relative VO_{2peak} . Children with severe hemophilia had a significantly lower absolute VO_{2peak} , and there was a significant difference between the group with moderate (mean [sd] Z-score, 0.47 [1.1]) and the group with severe hemophilia (mean [sd] Z-score, -0.8 [1.0]). This resulted in a significantly decreased mean Z-score (-0.39 [SD 1.2]) for the total population.

In Table IV, the outcomes of the HJHS, RCHAQ₃₈, MAQ, and Bouchard diary are presented. In the total group, almost no joint impairment was found (raw scores between 0 and 6, of a maximum of 144; median HJHS % score, 0; interquartile range, 0-0.7). 5 boys (12%) had an impairment of 0.7%, 2 boys (5%) had an impairment of 1.4%, 4 boys (10%) had an impairment of 2.7%, and 1 boy (2%) had an impairment of 4.0 % impairment. Impairment was primarily caused by slight decrease in range of joint motion of knee and ankle joint and the presence of crepitus during movement. In the total population, no decrease in functional ability

Table II. Muscle strength measurements

Mean (SD; min-max)	Total group (n = 47)	Mild (n = 19)	Moderate (n = 7)	Severe (n = 21)
Elbow flexors (N)	201.9 (75.8; 76-396)	219.0 (79.0; 112.5-396.0)	249.6 (59.2; 73.0-359.5)	170.5 (66.6; 76.0-330.0)
Z-score elbow flexors, Mean (SD)	-0.23 (1.3)	0.20 (1.2)	0.05 (0.8)	-0.71* (1.3)
Elbow extensors (N)	155.0† (54.2; 73-294)	165.9* (55.1; 101.0-294.0)	173.5 (40.0; 126.0-230.0)	138.9† (55.0; 73.0-264.5)
Z-score elbow extensors, mean (SD)	0.56† (1.3)	0.93† (1.3)	0.30 (0.6)	0.32 (1.4)
Knee flexors (N)	221.0† (63.1; 108-438)	239.7† (69.0; 159.5-438.0)	254.8* (35.1; 213.0-304.5)	193.0† (53.3; 108.0-305.0)
Z-score knee flexors, mean (SD)	-0.92† (1.0)	†-.53* (1.0)	-0.87* (0.6)	-1.30† (1.0)
Knee extensors (N)	276.3 (80.6; 95-471)	295.1 (77.2; 199.5-470.5)	317.8 (70.9; 240.5-425.0)	246.1 (78.8; 95.0-396.5)
Z-score knee extensors, mean (SD)	-0.14 (1.4)	0.19 (1.4)	-0.50 (1.3)	-0.35 (1.5)
Foot dorsal flexors (N)	227.2† (79.7; 111-402)	243.3 (67.8; 157.0-401.5)	287.8 (78.2; 185.0-400.0)	190.5 (76.1; 111.0-399.5)
Z-score foot dorsal flexors, mean (SD)	0.66† (1.1)	0.99† (0.9)	0.76 (1.1)	0.32 (1.2)
Total muscle strength (N)	1059.0 (310.4; 497.5-1776.5)	1136.2 (287.7; 815.0-1776.5)	1273.7 (260.0; 1008.0-1625.0)	910.5 (288.8; 497.5-1650.5)
Z-score total muscle strength, mean (SD)	-0.03 (0.9)	0.33 (0.9)	-0.05 (0.8)	-0.37 (1.0)

N, Newton.

*Significantly different from reference values with $P < .05$.

†Significantly different from reference values with $P < .01$.

Table III. Maximal exercise test

Mean (SD, min-max)	Total group (n = 47)	Mild (n = 19)	Moderate (n = 7)	Severe (n = 21)
Absolute $\text{VO}_{2\text{peak}}$ (L/min)	2.2 (0.9; 1.1-3.8)	2.3 (0.9; 1.1-3.8)	2.9 (0.6; 2.1-3.8)	1.9* (0.7; 1.1-3.5)
Z-score absolute $\text{VO}_{2\text{peak}}$, mean (SD)	-0.39* (1.2)	-0.26 (1.2)	0.47 (1.1)	-0.80† (1.0)
Relative $\text{VO}_{2\text{peak}}$ (L/min/kg)	42.9† (8.6; 24.4-60.1)	41.0† (10.2; 25.8-60.1)	47.5 (7.6; 31.1-53.6)	43.1† (7.0; 24.4-53.0)
Z-score relative $\text{VO}_{2\text{peak}}$, mean (SD)	-1.33† (1.7)	-1.65† (2.1)	-0.48 (1.6)	-1.34† (1.4)
HR_{peak} (beats/min)	190.5† (11.1; 168-212)	189.0* (11.5; 168.0-211.0)	196.3 (11.7; 178.0-212.0)	189.9† (10.4; 168.0-207.0)
Z-score HR_{peak} , mean (SD)	-0.71† (1.6)	-0.82 (1.7)	0.25 (1.5)	-0.93† (1.3)
RER_{peak}	1.2 (0.2; 1.0-2.0)	1.2 (0.1; 1.0-1.19)	1.2 (0.09; 1.0-1.3)	1.3 (0.2; 1.0-2.0)
Z-score RER_{peak} , mean (SD)	0.53 (2.3)	0.16 (1.9)	-0.11 (1.1)	1.09 (2.8)
W_{peak} (Watt)	182.5† (74.7; 60-340)	191.0 (80.8; 60.0-340.0)	252.7 (58.7; 167.0-325.0)	151.5† (55.8; 75.0-260.0)
Z-score W_{peak} , mean (SD)	-0.47† (1.1)	-0.35 (1.0)	0.03 (1.2)	-0.74† (1.2)

*Significantly different from reference values with $P < .05$.

†Significantly different from reference values with $P < .01$.

Table IV. Descriptive statistics of the Hemophilia Joint Health Score, Revised Childhood Health Assessment, Bouchard diary, and Modifiable Activity Questionnaire

	Total group (n = 47)	Mild (n = 19)	Moderate (n = 7)	Severe (n = 21)
HJHS impairment (%), median (interquartile range)	0.00† (0.00-0.7)	0.00† (0.00-0.7)	0.00 (0.00-0.00)	0.00* (0.00-1.7)
RCHAQ ₃₈ disability score, median (interquartile range)	0.00 (-0.03-0.05)	0.00 (-0.08-0.05)	0.00 (-0.07-0.10)	0.03 (0.00-0.05)
MAQ (MET-h/week)	57.5 (38.1; 58-181.3; n = 34)	53.5 (23.8; 15.0-91.9; n = 16)	65.4 (19.5; 50.3-94.0; n = 4)	59.9 (54.0; 5.8-181.3; n = 14)
Bouchard diary (kCal/day)	2574.3 (790.9; 1438.5-4226.0; n = 37)	2652.8 (756.2; 1438.5-3968.6; n = 17)	3012.8 (866.0; 2161.7-4226.0; n = 5)	2339.2 (777.9; 1538.7-3830.1; n = 15)

*Significantly different from reference values (0) with $P < .05$.

†Significantly different from reference values (0) with $P < .01$.

(RCHAQ₃₈) was found (median score, 0%; interquartile range, -0.03-0.05). In children with mild hemophilia, the mean (SD; range) amount of bleeds per year was 0.26 (0.35; 0-1.2), in moderate hemophilia, it was 1.1 (0.9;0-2.6), and in severe hemophilia, it was 1.45 (1.4; 0-4.5) ($P < .001$).

39 participants returned their Bouchard diary and MAQ (81% response rate). 34 MAQs and 37 Bouchard diaries were properly filled out and used for analysis. The mean MAQ score was 57.5 MET-hour/week (range, 5.8-181.3 MET-hour/week). The mean score on the Bouchard diary was 2574.3 kCal/day (range, 1438.5-4226.0 kCal/day). For all mentioned variables, no significant differences in the severity of the disease (mild, moderate, severe) were found.

Children with relatively low aerobic capacity (absolute VO_{2peak} Z-scores < -2) were compared with normal aerobic capacity (absolute VO_{2peak} Z-scores ≥ -2). 3 participants had a low absolute VO_{2peak} . They had significantly lower Z-scores for W_{peak} and borderline significantly reduced values for relative VO_{2peak} ($P = .08$).

BMI was significantly correlated with total muscle strength (Pearson $r = 0.30$; $P < .05$), relative VO_{2peak} (Pearson $r = -0.77$; $P < .01$), and the HJHS impairment score (Spearman's $\rho = 0.30$; $P < .05$). Absolute VO_{2peak} was significantly correlated with total muscle strength (Pearson $r = 0.30$; $P < .05$) and the outcomes of the Bouchard diary (Pearson correlation coefficient = 0.51; $P < .01$).

DISCUSSION

Aerobic capacity (relative VO_{2peak} , HR_{peak} and W_{peak}) was decreased in 47 boys with hemophilia. VO_{2peak} depends on physical (in)activity and on genetic factors. The observed decrease might be caused by parental overprotection or inactivity, as observed in the healthy population.^{9,23} However, in our population, the MAQ and Bouchard diaries illustrate normal physical activity compared with that of healthy peers.

Total muscle strength was normal compared with that of healthy control subjects. This is in contrast with Falk et al, who reported a significant strength reduction in the knee extensors, which was explained by less spontaneous activity.¹⁰

Our study population is representative of the total population of the "Van Creveldkliniek," a national referral center in the Netherlands; no significant differences were found in severity or age between participants and non-participants.

30% of the study population had Z-scores > 2 for weight, BMI, and $\Sigma 4SF$ scores indicating overweight, whereas relative VO_{2peak} , HR_{peak} and W_{peak} were significantly lower. Our results are in concordance with the studies by Falk et al who also found higher $\Sigma 4SF$ scores in boys with hemophilia compared with their healthy peers.⁵ The reason for the group with mild hemophilia to be more overweight than the group with severe hemophilia is hard to explain.

A potential weakness of using the RCHAQ to assess functional ability lies in the appearance of an emphasis on upper extremity and fine motor activities. Because knees and ankles are more frequently involved in bleeding and development of joint arthropathy, especially in children, the

RCHAQ may not be sensitive enough to demonstrate functional limitations. However, children with hemophilia scored normal on the domain of school and extracurricular activities (eg, running, participating in sport activities).

No participants in our study mentioned pain as a reason to stop the test, which eliminates pain as a possible reason for showing a lower aerobic capacity. Severe joint impairment was not observed, illustrated by a mean HJHS score of 0.5% (range, 0%-4.0%). 71% of our participants did not show any impairment on the HJHS scores, and only 1 boy showed an impairment of 4.0%. He was an immigrant and did not have primary prophylaxis. This is in concordance with the results of Schoenmakers et al, who showed a normal radiological Petterson score and an orthopedic joint score in 71% of their participants.⁹ Overall, the HJHS scores illustrate that our patients have minimal joint impairment. The question remains whether joint impairment is present but so subtle that the HJHS is not sensitive enough to detect it. Outcomes of the validation study of the HJHS might clarify these issues. However, if the HJHS scores illustrate no to minimal joint impairment, this might indicate that prophylactic and on-demand treatment is very successful in reducing bleeds and in preventing subsequent arthropathy.

The aerobic capacity of children with hemophilia is still lower than that of the normal population, whereas their overall muscle strength is comparable with that of healthy peers. The functional ability does not differ from healthy peers and the joint health showed very minor impairments. A substantial proportion of children with hemophilia was overweight, without showing a reduction in the amount of self-reported physical activities.

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Table I. Clinical characteristics

Mean (SD; min-max)	Total group (n = 47)	Mild (n = 19)	Moderate (n = 7)	Severe (n = 21)
Age (years)	12.9 (3.2; 8.2-17.4)	12.7 (2.7; 9.3-17.2)	14.7 (2.1; 11.2-17.4)	11.7 (2.9; 8.2-17.1)
Height (m)	1.59* (0.17; 1.27-1.86)	1.62† (0.15; 1.41-1.85)	1.72 (0.11; 1.58-1.86)	1.52 (0.2; 1.27-1.85)
Z-score height mean (SD)	0.37† (0.9)	0.58† (0.8)	0.39 (1.2)	0.18 (1.0)
Weight (kg)	50.8† (15.8; 25.1-92.5)	54.5† (14.0; 36.2-92.5)	61.3 (10.8; 45.0-71.7)	44.1* (16.3; 25.1-75.3)
Z-score weight mean (SD)	1.30† (1.9)	1.88† (1.9)	1.23 (2.5)	0.79* (1.6)
BMI (kg/m ²)	19.6† (3.2; 14.6-27.0)	20.6† (2.9; 16.4-27.0)	20.6 (3.0; 7.5-26.4)	18.3* (3.1; 14.6-24.3)
Z-score BMI mean (SD)	1.58† (2.2)	2.32† (2.3)	1.43 (2.6)	0.97* (1.7)
Σ4SF (mm), median (interquartile range)	33.6† (24.5-54.5)	43.4† (26.1-79.6)	33.6 (24.3-38.7)	31.5* (24.2-38.75)
Z-score Σ4SF mean (SD)	2.07† (3.4)	3.04† (3.6)	1.23 (2.9)	1.48 (3.4)

*Significantly different from reference values with $P < .05$.

†Significantly different from reference values with $P < .01$.