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CLINICAL RESEARCH

Bone mineral density in Canadian children with severe haemophilia A or B: a cross-sectional study

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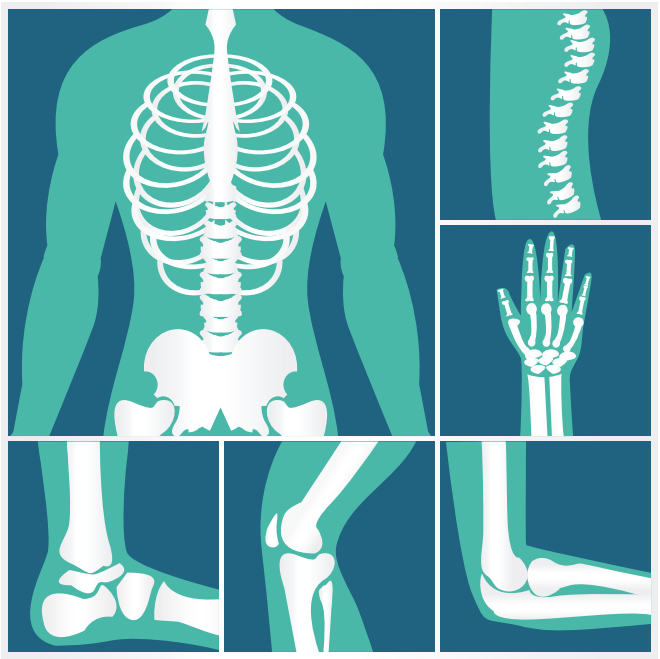
Background: Previous research has shown that bone mineral density (BMD), a measure of bone strength, may be lower among people with haemophilia. However, the majority of this research has been done in adults and in countries where the treatment for haemophilia differs from the standard of care in Canada, and there is a lack of paediatric data. **Aims:** The primary objective of this study was to determine whether Canadian children and youth with severe haemophilia A and B have BMD similar to healthy controls matched for height, age and weight (HAW-score). Secondary objectives included the exploration of any association between BMD and the following variables: factor replacement regimen, Hemophilia Joint Health Score (HJHS), bleeding history, physical activity level, and dietary intake of calcium, vitamin D, vitamin K and protein. **Methods:** A cross-sectional observational study was designed to determine the BMD of children with severe haemophilia A and B in Canada. Ethical approvals were obtained from participating institutions. Thirty-eight participants aged 3–18 with severe haemophilia A and B were



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A study of Canadian children with severe haemophilia A and B shows they demonstrate difference in spine and total body bone mineral density from height-, age-, and weight-matched controls.

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recruited from two treatment centres in Canada. Subjects underwent dual-energy X-ray absorptiometry (DXA) scan, and data was collected from regular clinic visit to identify factor replacement regimen, HJHS, and number of joint bleeds over the lifespan. Physical activity level and dietary intake of calcium, vitamin D, vitamin K and protein were identified using self-report questionnaires. **Results:** Participants showed a mean spine BMD Z-score and HAW-score higher than controls, with no participants showing a spine Z-score or HAW-score of <0. Hip BMD score was within normal range, and 2 participants had a Z-score and HAW-score of <-2. Total body BMD score was lower than controls, with 6 participants having a Z-score of <-2.0, and 3 participants having a HAW-score of <-2.0. Factor replacement regimen, HJHS, calcium intake, and physical activity level had no relationship to BMD Z-score or HAW-score. Low intake of vitamin D was associated with a low hip and spine BMD Z-score and HAW-score. Participants with a HJHS joint score greater than 0 had a higher total body HAW-score than those who had a joint score of 0. **Conclusion:** Canadian children with severe haemophilia A and B demonstrate differences in spine and total body BMD from height-, age-, and weight-matched controls, where spine BMD is higher than controls and total body BMD is lower than controls. Studies with a larger sample size are needed to clarify the status of BMD in children with haemophilia treated with primary prophylaxis.

Keywords: *Bone density, paediatrics, haemophilia, physical activity, vitamin D, height-age-weight-adjusted score*

There is a substantial body of research showing that people with haemophilia (PWH) have decreased bone mineral density (BMD) compared to those in the general population. The first published paper discussing this association was published in 1994 [1], where the researchers of a small case-control study (n=19 people with haemophilia A) concluded that their results suggested significant osteopenia associated with haemophilia A.

Several studies have been published since then, many of which have been included in two meta-analyses. Published in 2010, a meta-analysis by Iorio et al.[2] included three paediatric studies [3-5] with a total of 111 paediatric cases and 307 age-matched controls. Two of the three studies were performed in subjects with no access to prophylaxis; the third involved subjects who underwent prophylaxis but did not describe the frequency of infusions. The pooled standardised mean difference of BMD Z-score for the comparison between PWH and controls in the paediatric population was -0.636 (95% confidence interval [CI] -0.933 to -0.340, p<0.001), and the authors concluded there was an association between severe haemophilia and low BMD. A second meta-analysis by Paschou et al. published in 2014 [6] included one additional paediatric study for which details of prophylaxis were unavailable [7]. In this meta-analysis, the random effects' standardised mean difference for lumbar spine in children was 0.92 (95% CIs: 0.07-1.77), with the authors concluding that men with haemophilia present a significant reduction in both lumbar spine and hip BMD which appears to begin in childhood.

The gold standard for quantification of BMD is dual energy X-ray absorptiometry (DXA) scanning, reported as g/cm2. In the paediatric population, the DXA-obtained bone density score is described as a Z-score. The Z-score is the number of standard deviations above or below the mean BMD for age- and sex-matched controls. The Z-score does not account for deviations in body size and can influence the interpretation of results to such an extent that there is the risk of an over-diagnosis of osteoporosis [8]. For example, a child who is small for their chronological age is likely to have a measured BMD less than the expected-for-age BMD, hence a negative Z-score; however, their bone strength may be adequate to support the lower-than-average mechanical burdens due to a smaller body size. This is a major limitation in all previous studies evaluating the BMD of children with severe haemophilia A [3-5,7]. Webber et al. developed a height-age-weight-adjusted score (HAW-score) to account for these deviations [8,9], demonstrating that body size deviations affected the interpretation of measured BMD in approximately 17.5% of children. The calculation of HAW-scores accounts for body size deviations and provides a more accurate assessment of bone integrity. These scores were developed for children aged 3–18 years using the Hologic or Discovery DXA scanner.

The primary objective of this study was to determine whether Canadian children and youth with severe haemophilia A and B have BMD similar to healthy controls. Secondary objectives include exploring any association between BMD and the following variables: factor replacement regimen, joint score, bleeding history, physical activity level, and dietary intake. This study also aimed to identify the need for further investigation of the mechanism behind differences in BMD and to identify whether BMD assessment should be standard of care for Canadian children with severe haemophilia A and B.

METHODS

Study design

The study was cross-sectional and observational. Patients with severe haemophilia A or B were identified through the paediatric haemophilia services at participating institutions. Study staff reviewed patients' records to determine eligibility for the proposed study. Eligible patients were telephoned at home to obtain initial verbal consent in order for a DXA scan to be booked to coincide with their scheduled clinic appointment. At the clinic appointment, patients and/or parents were approached by the research coordinator at each site for written informed consent.

Inclusion and exclusion criteria

Patients with severe haemophilia A or B undergoing primary prophylactic FVIII or FIX replacement ages 3–18 years from Hamilton and Vancouver haemophilia treatment centres were included. Patients were excluded if they had a history of inhibitors to FVIII or FIX, were non-English speaking, or had another diagnosis associated with significant morbidity (i.e. Hepatitis C).

Methods of measurement

Subjects underwent DXA scan using a Hologic QDR-Discovery A densitometer (Hologic Inc., Waltham, MA). HAW-score was devised using a standardised method described elsewhere [8,9]. Data was collected from the clinic visit to identify prophylaxis regimen, Hemophilia Joint Health Score (HJHS), and number of lifetime joint bleeds. The HJHS was assessed according to standard procedure [10] by clinic physiotherapists. Physical activity level was measured using the Habitual Activity Estimation Scale (HAES) [11]. Dietary intake of calcium, vitamin D, vitamin K and protein was measured using a food frequency questionnaire (FFQ) [12].

Statistics

Statistics were analysed using SAS version 9.4 software. Descriptive statistics, single-sample T-tests, and univariate and multivariate regression analyses were performed.

Ethics

Ethics approval was obtained through the Research Ethics Board of each participating site.

RESULTS

Demographics

Thirty-eight subjects were recruited. Five had severe haemophilia B, and 33 had severe haemophilia A (Table 1). All participants underwent primary prophylaxis at individualised levels of frequency.

Table 1. Participant characteristics

CLINICAL CHARACTERISTICS	HAEMOPHILIA A MEAN +/- SD	HAEMOPHILIA B MEAN +/- SD
N	33	5
Age (years, months)	10.2 +/- 4.8	9.5 +/- 3.8
Height (cm)	140.1 +/- 25.2	142.6 +/-23.5
Weight (kg)	37.9 +/- 21.2	39.3 +/- 19.1
BMI (kg/m^2)	17.9 +/- 4.7	18.8 +/- 2.8
Lifetime joint bleeds	31.0 +/- 21.6	35.2 +/- 27.9
Hemophilia Joint Health Score	2.6 +/- 3.4	4.4 +/- 3.5
Whole body bone mineral content (kg)	1.2 +/- 0.7	1.25 +/- 0.7
Lean body mass (kg)	26.5 +/- 15.9	26.9 +/- 15.2
Fat mass (kg)	10.2 +/- 6.3	25.4 +/- 18.2
Prophylaxis starting age (years, months)	2.4 +/- 1.8	2.7 +/- 2.1
Prophylaxis frequency (days/week)	2.9 +/- 1.3	2.0 +/- 1
Adequate intake calcium (% of subjects)	75	100
Adequate intake vitamin D (% of subjects)	46	40
Adequate intake vitamin K (% of subjects)	28	40
Adequate intake protein (% of subjects)	91	100
Physical Activity Score (out of 10)	6.6 +/- 1.1	6.3 +/- 0.4

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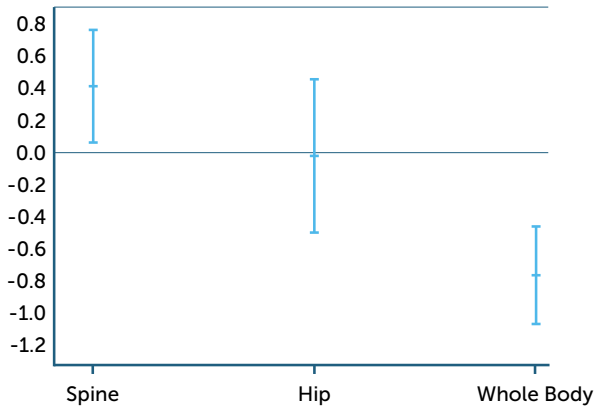
Figure 1. Bone mineral density height-age-weight-adjusted (HAW) score in Canadian children with severe haemophilia A or B: mean with 95% confidence interval



Bone mineral density

Spine BMD was increased in participants compared to height-age-weight-matched controls (mean difference: 0.4189; 95% CIs: 0.0680-0.7698; p-value: 0.206). No participants demonstrated a spine Z-score or HAW-score of <0 (Figures 1-2).

Study participants did not differ from normal scores on hip HAW (mean difference: -0.0171; 95% CIs: -0.4977-0.4634; p-value: 0.9426). Two participants (0.5%) had a hip Z-score and HAW-score of <-2 (Figure 3).

Study participants had lower total body BMD than height-age-weight-matched controls (mean difference: -0.7647; 95% CIs: -1.06909, -0.4604; p-value: <0.001). Twenty-seven participants (79%) had lower total BMD than the controls. Six participants (18%) demonstrated a Z-score of <-2.0, and 3 participants (9%) demonstrated a HAW-score of <-2 (Figure 4).

Prophylaxis regimen

Prophylaxis regimen is described in Table 1. After adjusting for the other variables, prophylaxis regimen was not associated with BMD.

Lifetime joint bleeds

Lifetime joint bleeds are described in Table 1. Whole-body BMD was increased in participants with a lifetime number of joint bleeds greater than 0 (mean difference: 0.62; 95% CIs: -0.5405-1.7805; p-value: 0.2846).

HJHS

Participants with a joint score >0 had higher mean total body HAW-score than those who had a joint score =0 (effect estimate: 0.6312; 95% CIs: 0.0632-1.1992; p-value: 0.0294), (Table 2).

HAES

The average level of self-reported overall physical activity was 4 (moderately active), with a range from 1 (very inactive) to 6 (very active), (Figure 5). After adjusting for other variables, physical activity was not associated with BMD.

Table 2. Multivariate analysis total body HAW

PARAMETER	LEVEL	ESTIMATE (95% CI)	PR>CHISQ
Regimen (vs. 1x week)	2x week	-0.0813 (-1.1006,0.9379)	0.8757
Regimen (vs. 1x week)	3x week	0.3864 (-0.6681,1.4410)	0.4726
Joint score > 0	1	0.6312 (0.0632,1.1992)	0.0294
Physical activity: overall		-0.3563 (-0.8913,0.1786)	0.1917
Calcium	1	-0.4021 (-1.375,0.5707)	0.4179
Vitamin D	1	0.6189 (-0.0676,1.3054)	0.0772
Lifetime joint bleeds		-0.0110 (-0.0261,0.0041)	0.1528

Table 3. Univariate analysis hip HAW

PARAMETER	LEVEL	ESTIMATE (95% CI)	PR>CHISQ
Regimen (vs. 1x week)	2x week	-0.6333 (-2.2199,0.9532)	0.4340
Regimen (vs. 1x week)	3x week	-0.0467 (-1.5201,1.4268)	0.9505
Joint score > 0	1	-0.3531 (-1.3340,0.6278)	0.4805
Physical activity: overall		0.3024 (-0.1655,0.7703)	0.2052
Calcium	1	0.7993 (-0.4363,2.0350)	0.2048
Vitamin D	1	1.0996 (0.1709,2.0282)	0.0203
Lifetime joint bleeds		0.0023 (-0.0169,0.0216)	0.8144

Table 4: Univariate analysis spine HAW

PARAMETER	LEVEL	ESTIMATE (95% CI)	PR>CHISQ
Regimen (vs. 1x week)	2x week	-0.4000 (-1.6579,0.8579)	0.5331
Regimen (vs. 1x week)	3x week	-0.1182 (-1.2795,1.0431)	0.8419
Joint score > 0	1	0.1095 (-0.6067,0.8257)	0.7644
Physical activity: overall		0.1256 (-0.2229,0.4741)	0.4801
Calcium	1	0.5588 (-0.3073,1.4249)	0.2060
Vitamin D	1	0.7800 (0.1023,1.4577)	0.0241
Lifetime joint bleeds		0.0095 (-0.0048,0.0238)	0.1916

FFQ

For participants taking appropriate doses of vitamin D, the mean spine and hip HAW was significantly higher than those not taking vitamin D. The effect estimate for hip HAW was 1.0996 (95% CIs: 0.1709-2.0282; p-value: 0.0203), (Table 3). The effect estimate for spine HAW was 0.7800 (95% CIs: 0.1023-1.4577; p-value: 0.0241), (Table 4). From the univariate results for total body HAW, none of the variables reached statistical significance.

DISCUSSION

The data presented in this study demonstrates that, in our subjects, whole body BMD was lower than height-age-weight-matched controls. This is in line with the current literature on BMD in children with haemophilia. To our knowledge, this study is the first to demonstrate a low whole-body BMD Z-score and HAW-score in children with severe haemophilia treated with primary prophylaxis. Interestingly, our study found spine BMD was higher than height-age-weight-matched controls with none showing a score of <0. This is in contrast to a publication by Soucek et al. who reported that children with haemophilia had lower trabecular, and by consequence, low spine BMD [13]. Participants in the aforementioned study were either treated on-demand or with prophylaxis, however no details were provided regarding the frequency or dosage. In addition, levels of physical activity and nutritional intake were not measured. Another study by Christoforidis et al. found that lumbar spine BMD in children with moderate and severe haemophilia A was comparable to controls [14]. This study evaluated children on primary or secondary prophylaxis, however frequency of infusions was not described.

According to the most recent International Society for Clinical Densitometry paediatric guidelines, the use of hip measurements in DXA is discouraged due to the large variation in skeletal development between children [15]. Our study found no difference between the hip BMD of children with haemophilia and controls. Therefore, we suggest that regular hip measurements in DXA evaluation is not appropriate for Canadian children with severe haemophilia A or B.

Another interesting finding of our study is an association between a HJHS joint score greater than 0 with higher total body HAW-score. In addition, whole-body BMD was increased in the cohort with a lifetime number of joint bleeds greater than 0, although the relationship is not statistically significant. This is counter-intuitive, as we expect that a higher joint bleed count would lead to decreased activity and therefore sarcopenic changes to bone. In fact, we found a higher lifetime joint bleed count to be negatively correlated with physical activity, although the result was not significant (Pearson's correlation: -0.19; p-value: 0.31). Those with a higher lifetime bleed count had a significantly higher frequency of infusion (Pearson's correlation: 0.38; p-value: 0.03). We found no relationship between physical activity level and BMD for the entire study population.

Our study also found an association between inadequate intake of vitamin D and low hip and spine BMD. Data on vitamin D intake was collected through a food frequency questionnaire. The prevalence of inadequate intake of vitamin D was 54% and 60% for participants with haemophilia A and B, respectively. Hypovitaminosis D is known to be a worldwide problem in children and adolescents, and vitamin D deficiency and insufficiency has been associated with low BMD in children [16]. A study by Albayrak and Albayrak found 96% of children with severe haemophilia A to have vitamin D deficiency or insufficiency [17]. The role of vitamin D therapy in children with haemophilia and low BMD has yet to be elucidated. Routine checking of vitamin D level and vitamin D supplements to maintain its level between 30 and 100 ng/ml has been recommended [17].

Limitations

We originally planned a sample size of 80 patients; however, we fell short of this goal by recruiting 38 subjects. Another limitation of our study is the use of a food frequency questionnaire, which was prone to recall bias and had not been validated in our study population.

CONCLUSION

This is the first multi-centre, comprehensive evaluation of the BMD of children and youth with severe haemophilia A or B that addresses the limitation of using a Z-score. Canadian children with severe haemophilia A and B demonstrate differences in spine and total body BMD from height-, age-, and weight-matched controls, where spine BMD is higher than controls and total body BMD is lower than controls, HJHS joint score greater than 0 was associated with a higher whole-body BMD, and low intake of vitamin D was associated with lower spine and hip BMD.

Future study with a larger sample size is warranted with an aim to further clarify the status of BMD in children with haemophilia who undergo primary prophylaxis, as there remains conflict in the current literature.

Figure 2. Spine HAW-score distribution and spine HAW plot

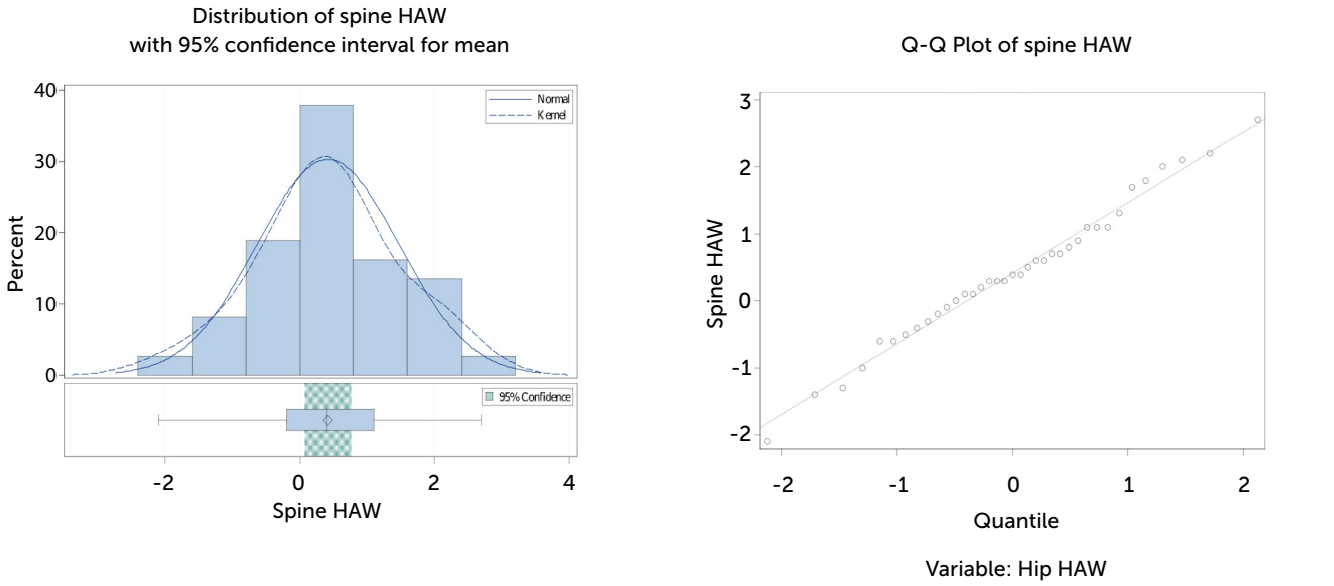


Figure 3. Hip HAW-score distribution and hip HAW plot

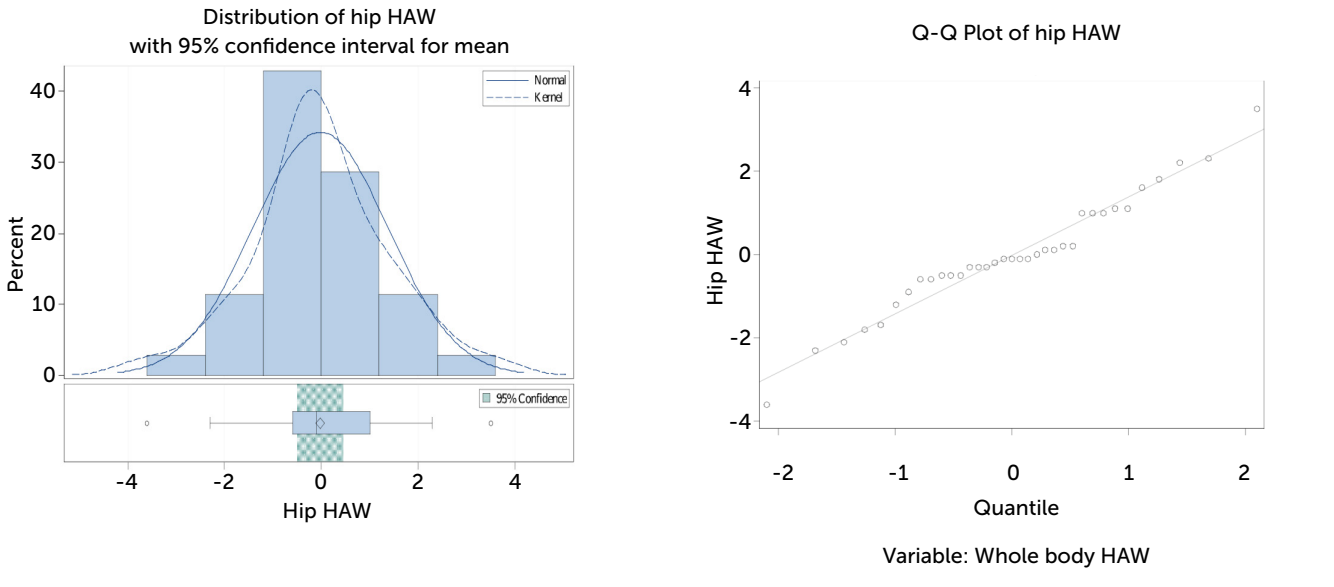


Figure 4. Whole body HAW-score distribution and whole body HAW plot

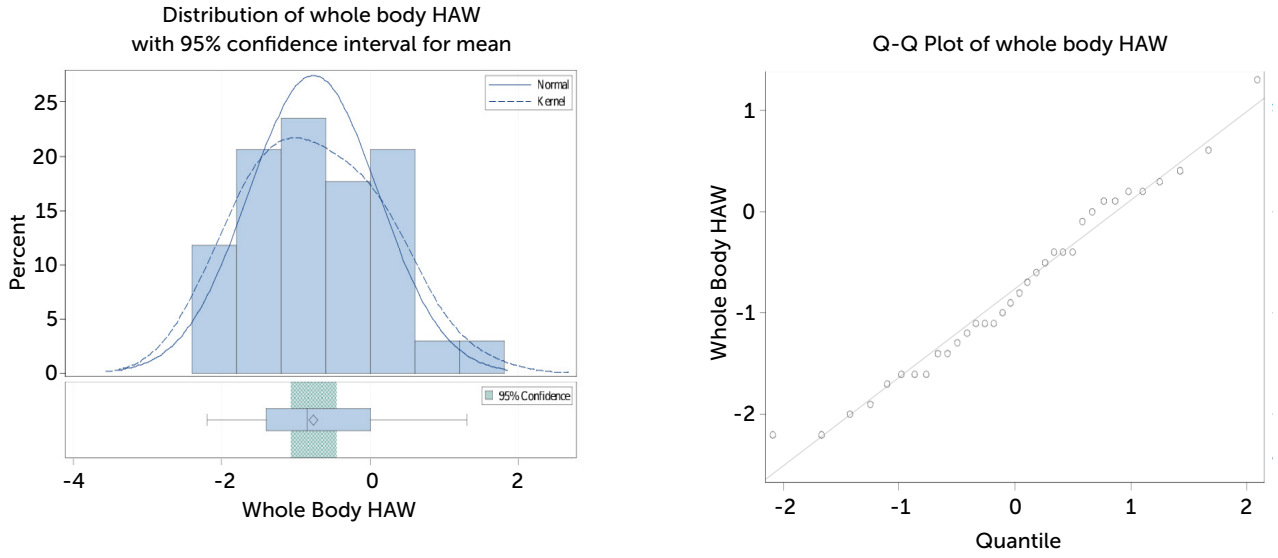
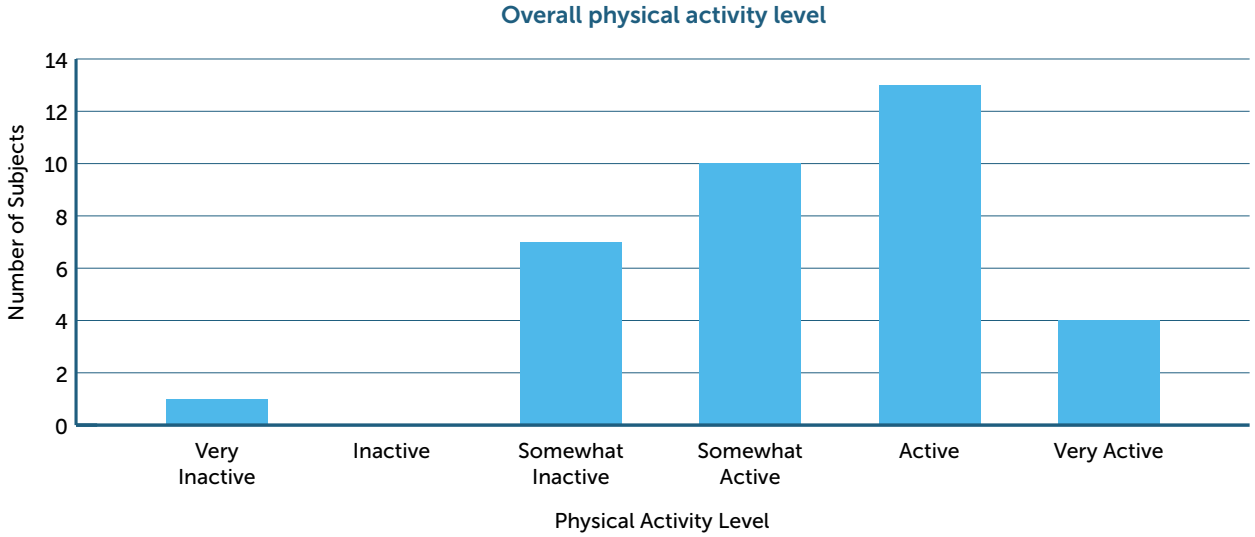


Figure 5. Physical activity levels



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Informed consent has been obtained from the participants in the study reported in this paper.

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