

Cross-sectional study of physical activity in adults with achondroplasia

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Abstract

Background: Obesity is a leading cause of cardiovascular disease mortality in the US population, and adequate physical activity has been shown to improve health outcomes for obese patients. The purpose of this study was to demonstrate the utility of accelerometry to quantify physical activity in people with achondroplasia, the most common short stature skeletal dysplasia.

Methods: Twenty subjects with achondroplasia (18-50 years) wore an accelerometer while performing a six-minute walk test (6MWT) under standard conditions in a clinic setting and then nonstop for 7 days at home and also maintained a sleep and activity log. Time spent sleeping and different levels of physical activity were quantified by an accelerometer worn on the wrist based on cut-offs for activity counts per minute (cpm) derived from the 6MWT for moderate and vigorous physical activity. Sleep time was defined as any interval in which 8 of the prior 10 minutes registered zero activity counts, distinguishing it from sedentary activity.

Results: New cutoff points generated for this cohort were 2009 $\leq$ 4607 (moderate activity) and $\geq$ 4608 (vigorous activity) cpm. Participants spent on average 33.4% of their days sleeping, 27.4% of the day in sedentary, 37.4% in light and $<2\%$ moderate and vigorous activity. For comparison, the unadjusted manufacturer activity cut-offs yielded 14.7% sedentary and 10.4% in moderate and vigorous activity.

Conclusions: Accelerometry is an effective tool to assess physical activity in short statured individuals, but modifications are required and further study is needed.

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Introduction

Over recent decades, obesity has become one of the leading causes of preventable death in adults in the United States second only to tobacco smoking [1-3]. The increased morbidity and mortality attributed to obesity is due to its close association with cardiovascular disease, hypertension, diabetes and hypercholesterolemia [4-6]. Societal trends in the U.S. toward increasingly sedentary lifestyles coupled

with increasing caloric intakes and poor quality diets have exacerbated the obesity crisis [7-11].

In individuals with short stature skeletal dysplasia, obesity may be particularly problematic due to the smaller body frame onto which body mass is distributed [12]. In clinical settings, it has become clear that short stature individuals have not escaped the obesity and sedentary lifestyle trends that affect the general U.S. population. Unfortunately, however, there are no published longitudinal studies of body

composition in short stature populations to quantify the problem, and little data is available to define the relationship of mortality to obesity-related conditions among those with skeletal dysplasias. Nonetheless, data have shown a 10-fold greater risk of cardiovascular disease (CVD) mortality and a median 10-year reduction in survival among over 700 patients with achondroplasia, the most common short stature skeletal dysplasia [13], compared to the U.S. population [14]. Further study is clearly needed to ascertain obesity-related risk factors for CVD and all-cause mortality in the short stature population.

Adequate physical activity may improve outcomes related both to obesity and CVD [15, 16], and a variety of physical activity recommendations have been issued over the past decades to try to improve the health of the U.S. population [17, 18]. Most recently, in 2008, the Department of Health and Human Services recommended that all adults participate in 150 minutes of moderate intensity physical activity or 75 minutes of vigorous intensity activity (or a combination of both) every week. Additionally, muscle-strengthening activities were recommended at least 2 times per week [19]. Unfortunately, a large body of medical literature has subsequently indicated that the U.S. population fails to meet these recommendations in virtually every age, ethnicity and U.S. geographic region in both genders [20-25].

Accelerometry has emerged as an important tool for objectively assessing physical activity [26, 27]. Accelerometers can be worn at various body sites (e.g. waist, wrist, and ankle), but placement of the device on the body will affect the total number of counts achieved due to different movement paradigms at different body sites. The devices sense movement in multiple directions as a force applied against them, and they record movement electronically in measures of counts per unit time, with higher counts representative of higher intensity activity levels. Cutoffs for counts per minute (cpm) may be established to characterize time spent in sedentary to vigorous activity in a given population [28]. For some applications, equations to estimate energy expenditure have been derived in adult or pediatric populations undergoing standardized activities against criterion techniques such as calorimetry and doubly labeled water assessment of

total energy expenditure [26, 29]. Accelerometers are typically comfortably worn and have been widely used in average stature, healthy adults as well as populations with a variety of physical disorders including rheumatoid arthritis, acute leukemia, dementia and other disorders [25, 30-32].

One of the largest research applications of accelerometry was in the U.S. National Health and Nutrition Examination Survey (NHANES), in which accelerometer data were collected from 3522 representative adults ≥ 20 years of age to characterize physical activity of the general U.S. population [25, 33]. A limitation of the U.S. survey data, however, was an inability to accurately characterize time spent during sleep, as the devices used were not worn overnight by participants. Nonetheless, in analyses conducted by Tudor-Locke et al., differences in physical activity levels were noted by the body mass index (BMI) category such that time spent in moderate to vigorous activity declined from normal to overweight to obese groups, supporting the greatest need to enhance physical activity as body mass increases [25].

Just as in average stature U.S. adults, there is a recognized need to address the obesity problem and related medical sequelae in short stature adults, with the intention that quantifying the problem should lead to interventions to improve it. Thus, we embarked upon a cross-sectional assessment of 20 adults with achondroplasia to identify specific cardiovascular disease risk factors while evaluating which research assessment tools could be readily used in this unique population, which tools required modification for successful implementation, and which were inadequate to address a specific research need. Here we present the methods established to quantify time spent in sleep and at various physical activity levels in this cohort using the Actical accelerometer in a two-step process. The first step was a standardized 6-minute walk test (6MWT) performed during an inpatient research encounter from which cutoffs for physical activity levels were established. Then, participants wore the devices for the entire subsequent week under habitual conditions to determine usual physical activity levels.

Methods

Subjects

Subjects were recruited from local community and clinic populations for a comprehensive, cross-sectional pilot assessment of the cardiopulmonary health of adults with achondroplasia. This study was approved by the Johns Hopkins IRB and written informed consent was obtained from all participants. Participants were required to be ambulatory, but a history of prior orthopedic and neurosurgical procedures was allowed. Pre-existing medical conditions were also allowed, but a diagnosis of diabetes or untreated obstructive sleep apnea (i.e. failure to use CPAP/biPAP after prescription by a medical provider) was an exclusion criterion for participation.

Study activities: 6MWT, Actical accelerometry, and activity log

As part of this comprehensive cardiopulmonary assessment of 20 adults (11 male, 9 female) with achondroplasia, subjects were asked to perform a 6-minute walk test (6MWT) under conditions standardized by the American Thoracic Society [34]. This involved walking, not running, as fast as possible along a flat hard flat straight surface 25 m in length for 6 min. Subjects wore an Actical accelerometer (Phillips – Respironics, Oregon, USA) at both the waist and wrist for the 6MWT. Specific verbal instructions were provided to each participant immediately before performing the 6MWT (Supplement, Fig. 1). The wrist device was considered more comfortable by pre-testers and was worn continuously for a total of 7 days while in a natural home setting.

Subjects were required to record periods of sleep and activity over this 7-day interval, while wearing the accelerometer device on the wrist. Activities reported by the participants over the 7-day accelerometry assessment at home were tabulated verbatim from the subjects' activity log. Subjects were instructed verbally by study staff about how to record their daily activities while wearing the accelerometer at home. The following written instructions were also provided: "We would like you to fill out this log

sheet each day, indicating the times that you are least active (i.e. sleeping) and most active (e.g. engaged in walking or running that is beyond your usual level, performing indoor or outdoor chores that are more rigorous than usual, or exercising)."



Figure 1. Participant with achondroplasia participating in the 6MWT

Additionally, the following definitions of activity intensity were discussed and provided in a written form for subjects to reference while he/she recorded physical activity at home: "Please record the type of activity you were engaged in, the time this activity began and ended, and whether you considered the intensity of this activity to be moderate (*increased movement, but normal breathing*), hard (*enough movement to increase rate of breathing*), or strenuous (*intensive movement and greatly increased rate of breathing*).

Each subject self-defined their levels of activity (i.e. moderate, hard, and strenuous) based on this guidance, and their responses were compiled. Subjects were asked to report if a particular day's activity was "typical" for him/her. If not, subjects were asked to describe briefly what made the day atypical (e.g. *Illness, out of town for business, etc.*). Lastly, subjects were asked to record the time he/she fell asleep, awoke and took naps.

Activity ‘counts’ (i.e. discrete registered movements in X-Y plane over an ‘epoch’ or defined period of time) from the Actical equipment were examined from the 6MWT for the entire cohort. The intensity level during the 6MWT was defined as ‘moderate’, as exemplified by increased physical effort following the standardized instructions to perform this test. Based on the 10th and 90th percentiles of counts per minute (i.e. total counts during the 6MWT divided by 6), cutoffs between ‘vigorous’ and ‘moderate’ activity were assigned at the 90th percentile, and between ‘moderate’ and ‘light’ activity at the 10th percentile. These values expressed per minute were ultimately applied to the home accelerometry data to determine the percentage of time (i.e. total minutes in a day) spent at each of these activity levels.

In addition to these study activities, subjects also underwent procedures for anthropometry and body composition, dietary assessment, resting energy expenditure, and a blood draw. The anthropometry included basic height, weight and head circumference as well as skin folds. Dual energy x-ray absorptiometry (DXA) was performed on each subject to quantify body composition of lean mass, fat mass and bone; body fat from DXA are not presented.

Analysis

Activity counts recorded during the 6MWT via the accelerometer devices at the wrist and waist (simultaneous data available for 16 subjects when multiple devices were available) were downloaded using the manufacturer’s software, which recorded data using 30 second recording intervals (epochs). A comparison of total activity counts at the wrist and waist for the 6MWT activity is presented. Data from the 7-day home study were collected in 1-minute epochs from wrist measurements and downloaded upon return of the devices. Since the device recorded one day as midnight to midnight, the first and last days of home data collection did not represent a complete 24 h period. Days 1 and 7 were therefore dropped from the study, leaving 5 complete days to assess usual physical activity. Study data were collected and managed using research electronic data capture (REDCap) tools hosted at Johns Hopkins University [35] and ultimately transferred to

Microsoft Excel and Stata 13 [36] for subsequent analysis.

There were cutoffs for counts per unit time pre-programmed in the software to define low, moderate, and vigorous activity levels. We present a comparison of the time spent at the different activity levels between the manufacturer’s analysis and the population-specific cutoffs that we derived from the 6MWT standardization activity. As described, our cutoffs for moderate activity were derived from the 10th (minimum) and 90th (maximum) percentiles of cpm from the study population during the 6MWT.

A definition of “sleep” was also established based on data collected over the 7-day period. By default, any activity that did not meet the minimum cut off of ‘light’ activity (100 to < 2009 activity cpm) was considered sedentary (therefore <100 activity cpm). The sedentary category included sleep, as well as inactive awake periods. The time intervals categorized specifically as sleep was generated from the Actical minute-by-minute epoch data in which a participant is classified as sleeping at any given time if 8 or more of the last 10 time points (the point being considered and the previous nine) have activity counts of 0.

With these definitions in place, the average percentage of total time spent in each activity category (i.e. sleeping, sedentary, light/low, moderate, vigorous) for each subject over the 5-day home physical activity analysis period was recorded to establish typical sleep and activity patterns in this patient population for each minute in the 24 h period. Comparisons are shown between data derived from cutoffs provided by the manufacturer and our own cutoffs.

Results

Twenty participants were recruited into this study with an average age of 36.6± 8.7 years. Table 1 shows that 11 (55%) of the study were males but there were no statistically significant gender differences in age, weight or height; however, this may be because of the small sample size. However, the percentage body fat assessed by DXA was 17.5% higher in females compared to males (p=0.003) in this cohort.

Table 1. Demographics of the adult achondroplasia population

	Female	Male	p-value
n	9	11	
Age (y)	38.5 ± 6.3	35.1 ± 10.4	0.4
Body Weight (kg)	60.0 ± 11.2	51.1 ± 11.6	0.1
Height (cm)	123.5 ± 4.7	125.9 ± 5.2	0.3
BMI	39.0 ± 5.1	32.4 ± 8.1	0.05
% Fat (DXA)	42.7 ± 5.2	25.2 ± 10.5	0.003

Abbreviations: BMI, body mass index; DXA, Dual energy x-ray absorptiometry

6-minute walk test

Fig. 2 shows the activity counts recorded by the Actical accelerometer worn on the wrist by each participant plotted against the distance covered by the participants during the 6MWT. Greater distance walked was linearly correlated with activity counts ($r=0.7$, $p<0.001$). Based on the distribution of counts recorded by the accelerometer over the 6MWT, moderate activity was defined as 2009 up to and including 4607 activity cpm, while vigorous activity was defined as including and over 4608 cpm.

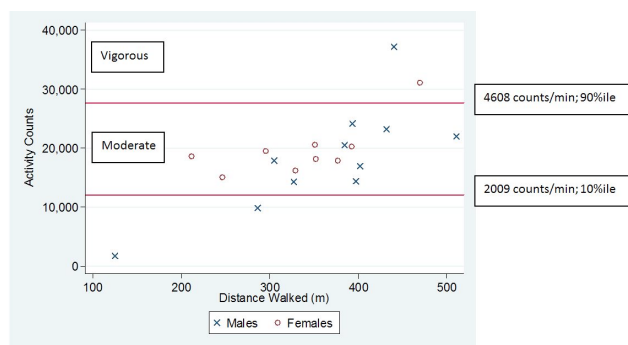


Figure 2. Activity counts versus distance traveled in the 6-minute walk test (6MWT)

Greater distance walked was linearly correlated with activity counts ($r=0.7$, $p<0.001$). Activity intensity during the 6MWT was defined as 'moderate' for this patient population. The minimum and maximum activity count for 'moderate' activity was established from the 10th and 90th percentiles of the population activity counts. Vigorous activity was defined as over 4608 counts per minute and light as less than 2009 counts per minute.

Fig. 3 compares the activity counts recorded during the 6MWT when participants wore an Actical accelerometer on their hip and wrist simultaneously. The correlation coefficient was 0.8 ($p<0.001$) with the wrist counts consistently higher in 15 of 16 participants.

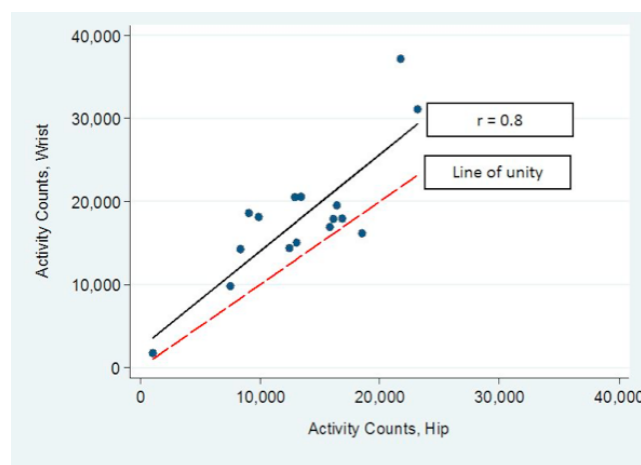


Figure 3. Activity counts during the 6MWT estimated by an Actical accelerometer placed on the hip versus the wrist.

Activity counts registered at wrist were higher than at waist in 15/16 subjects.

Physical Activity

Information from the home-based activity logs is shown in Table 2. Self-reported moderate, hard, or strenuous activities did not indicate participants were engaged in high levels of physical activity. The accelerometry data in Fig. 4 compares activity levels as originally characterized by cpm cutoffs programmed in the accelerometer software versus those derived from the standardized 6MWT activity in males and females, respectively. Based on our data, participants spent ~28% of the time in sedentary activities, compared to the manufacturers estimated ~15%. Overall moderate activity was <2% in the corrected result compared to 10% ascertained by the manufacturer. Low levels of vigorous activity were recorded in both. There were no differences in male and female activity levels.

Table 2. Self-report of activity intensity for moderate, hard and strenuous over the 5 day Actical trial

Moderate (increased movement but normal breathing)	Walking; vacuuming, cleaning, laundry; dancing, watching TV, eating; getting ready for work, work; climbing ladders, sanding drywall; washing car; shopping; using computer; relaxing; getting dressed; sledding; removing Christmas tree; playing guitar
Hard (enough movement to increase rate of breathing)	Carrying tools; walking; moving luggage; biking; picking up mother who fell; playing guitar
Strenuous (intense movement and greatly increased rate of breathing)	Biking

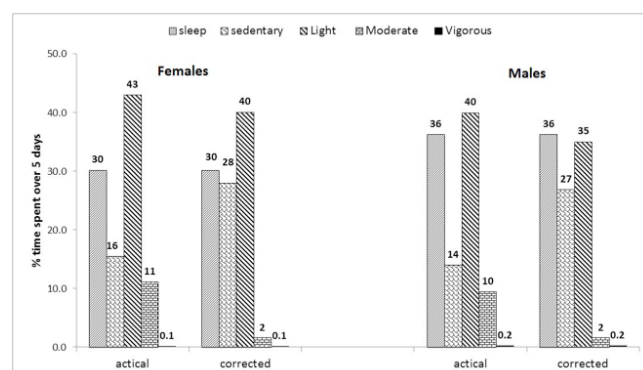


Figure 4. Average percentage of time spent in sedentary, light, moderate and vigorous activity

Calculated over a 7-day period estimated from Actical movement counts (left) versus the corrected average percentage time spent in these same activity categories, modified based on the activity counts registered in the 6MWT as moderate activity for this physical task.

Discussion

This is the first study to document the use of accelerometry to objectively quantify physical activity in adults with achondroplasia, a skeletal dysplasia with a demonstrated risk for obesity and cardiovascular disease. There are over 250 short stature skeletal dysplasias recognized in the current

bone disorder nosology [37]. Though quite diverse in terms of body proportion, disease manifestations and genetic etiology, an accepted definition of a short stature skeletal dysplasia is a generalized bone disorder resulting in final adult height of less than 4'10" (and typically over 2'). Since there is no universal registry of short stature skeletal dysplasia patients, it is difficult to ascertain the diagnosis distribution over these 250+ skeletal dysplasias. However, 3 recent convenience samples of Little People of America members (both online and in person) for different research projects revealed that achondroplasia constitutes ~50-60% of the total short stature skeletal dysplasia population, followed by ~10 additional diagnoses making up an additional 30-40% of the total population [38]. Thus, the remaining 10-20% of the short stature skeletal dysplasia population is composed of the other ~240 diagnoses. Based on diagnosis distribution and evidence of obesity and cardiovascular risk, we targeted adults with achondroplasia for this first ever study to objectively quantify physical activity with an accelerometer in a short stature skeletal dysplasia population. We expect that implementation of the methods developed in this pilot study would be successful in other short stature diagnoses.

We quantified the percentage of time our achondroplasia cohort spent in sedentary, light, moderate and vigorous physical activity over 5 complete consecutive days with an accelerometer secured at the wrist. We utilized the accelerometer on the wrist because of evidence that an accelerometer on the foot or hip does not detect movement as well as the upper extremity [29, 39]. We found a similar difference within our achondroplasia population with the registered movement at the wrist nearly always higher than that at the hip. Additionally, the device was particularly well-tolerated in that position compared to when worn at the waist. The wrist would be our preferred site for future, long-term studies in larger populations.

It was clear that the device had to be calibrated for the population under study to appropriately interpret physical activity levels defined by activity cpm. Activity cpm assessed against the manufacturer's software cutoffs suggested participation in physical activity at levels far above what was realistic for this population, particularly given self-reported activities

and comparisons with the general population. For example, participants reported watching TV, eating and playing guitar as activities of moderate intensity, requiring “increased movement but normal breathing”. Compared to the guidelines provided by study personnel to participants to estimate physical activity intensity, these study subjects were strikingly less “active” than they perceived. This further supported the concept that we were likely overestimating their physical activity in the analysis using the preprogrammed cutoff. This perception of activity level also demonstrates the need for objective, validated measures of physical activity in free-living situations to appropriately characterize actual activity levels.

A question remains as to why cutoffs for various activity levels established in other populations by the accelerometer manufacturer were not applicable in this population. It is likely that the habits of individuals with achondroplasia contributed to a movement style that exaggerated the number of activity counts at both the waist and wrist relative to actual physical activity. For example, with shorter extremities, individuals with achondroplasia rotate their hips more than average stature individuals during locomotion, and may swing their arms more to enhance speed and balance. These suppositions have yet to be proven with rigorous gait analysis. Nonetheless, our findings support the importance of establishing the utility of accelerometry devices for use in unique populations. In this case, we were able to use the standardized activity of the 6MWT as a basis for characterizing light, moderate, and vigorous activity levels. It should be noted that our modified cut-off points based on cpm in the 6MWT were similar to NHANES accelerometry results which quantified physical activity in over 3,000 US average stature adults. In that cohort, time in moderate and vigorous activity were defined as 2,020-5,999 and >5,999 activity cpm, respectively [25, 28].

In this study, we also established a definition for time spent in sleep. We defined sleep as 10 minutes or more of continuous zero activity intensity counts. This represents an improvement over accelerometry data collected in the U.S. population during the NHANES study, where an accelerometer was worn on the waist and removed for sleep each night. Using NHANES data, time that the device was not worn had

to be estimated by minutes absent of any activity counts. For example, in the study by Troiano, non-wear time inclusive of sleep was simply defined as an interval of 60 consecutive minutes of zero activity intensity counts with allowance for 1-2 min of counts between 0 and 100 [33]. Tudor-Locke’s definition was the difference of wear time from 1440 minutes with no concise definition of sleep [25]. Thus, while sleep would be assumed to occur during the absence of counts, the absence of counts could also exist during waking and active states when the accelerometer was not being worn, leading to compromised accuracy of the data. Our study better characterizes true sleep time as there was no non-wear time over the course of the home activity.

This population of individuals with achondroplasia spent 33.4% of time sleeping, 27.4% in sedentary, 37.4% light, 1.6% moderate and less than 1% in vigorous activity compared to approximately 57% in sedentary, 23.7 % low, 16.7% light, 2.6% moderate and 0.2% vigorous activity in the general US population [25]. It should be noted that we allowed any duration of increased physical activity in the light, moderate or vigorous categories in our achondroplasia study cohort to contribute to time spent in each category. This was far more lenient than the requirements in NHANES for participants to sustain a level of physical activity for 10 minutes or more (with only 1 minute of decreased intensity) to get ‘credit’ for that activity level [33]. Despite our leniency, the percentage of time in moderate or vigorous activity of our cohort was similar to that of the average stature population and, significantly, both were far below the recommended activity levels of two and a half hours (150 minutes) per week of moderate intensity physical activity [19].

In the US population, the distribution of activity was shifted to less moderate and vigorous activity and increasing “non-wear”, sedentary, or light activity with increasing BMI. Our small sample size would not allow us to look for patterns of activity with BMI or body composition. We did not show differences in activity level or BMI between men and women, although women had significantly higher percentage body fat. We have previously suggested caution in interpreting BMI in those with achondroplasia relative to cutoffs established in average stature adults due to the unique body proportions of this group [40].

However, obtaining data on the association of body composition, physical activity, and health outcomes is critical for optimizing health care and health recommendations among those with skeletal dysplasias.

Obesity is a problem in this population [12] and will not change quickly without aggressive healthcare intervention. More study is needed to understand the components of energy balance (i.e. basal metabolic rate, energy expenditure, and dietary intake) specifically in short stature skeletal dysplasia patients in order to formulate a plan to manage body weight and obesity in this population. Conventional health recommendations for preferred BMI, body fat composition [41], and energy expenditure estimates from accelerometry, are all based on height, weight, body habits, exercise and medical history in average stature adults [29, 39, 42]. Clearly specific norms are needed for short stature individuals [40]. This study offers a reasonable method to quantify activity in short stature adults. More importantly, this study offers strong evidence that physical activity is at minimal level in this population and must be increased to start tackling the obesity problem in short stature adults.

This study is limited in that our accelerometry definitions were based on a single 6MWT rather than a more extensive battery of standardized activities. Nonetheless the 6MWT was a reasonable tool for characterizing activity levels by accelerometry in this patient group in whom somatic movement may be compromised. We offer that this methodology may be applicable to other unique ambulatory study populations. We were able to establish a valid approach for objectively characterizing physical activity levels in this unique population, inviting future research in larger populations inclusive of other skeletal dysplasias, in whom these types of studies are sorely lacking. Additionally, the sample size was small, but this was a pilot study to evaluate the functionality of the accelerometer in a unique population. Our study showed that the accelerometer devices were well-tolerated by participants, easy to use and most importantly, were able to detect physical activity based on raw activity counts. Finally, we were dependent on self-report in order to assess the type of activities carried out by our study participants. Though real-time self-reports cannot

account for participant errors or selective reporting, it is superior to any type of retrospective recall or frequency questionnaires in terms of accuracy [43]. Additionally, the self-reported activity data were critical for establishing that the pre-programmed cutoffs overestimated activity levels and our adult achondroplasia cohort had significant misperception of activity, which is an excellent target for future clinical intervention.

Conclusions

Accelerometry may prove to be an effective objective tool for assessing physical activity levels in individuals with skeletal dysplasia, assuming appropriate population-specific validation of its use. This may become an important tool for monitoring and encouraging activity that may help stem the increase in obesity in these unique populations.

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