Trial@home for children: novel non-invasive methodology for the pediatric clinical trial of the future

Kruizinga, M.D.

CHAPTER 9

Objective home-monitoring of physical activity, cardiovascular parameters and sleep in pediatric obesity patients using digital biomarkers

Accepted by Digital Biomarkers

JM Knijff,[1,2] ECAM Houdijk,[2] DCM van der Kaay,[2,6] Y van Berkel,[2,3] L Filippini,[2,3] FE Stuurman,[1,4] AF Cohen,[1,4] GJA Driessen,[2,5] MD Kruizinga[1,2,4]

1 Centre for Human Drug Research, Leiden, the Netherlands
2 Juliana Children's Hospital, Haga Teaching Hospital, The Hague, the Netherlands
3 Department of pediatrics, Haaglanden Medical Centre, the Hague, the Netherlands
4 Leiden University Medical Centre, Leiden, the Netherlands
5 Department of pediatrics, Maastricht University Medical Centre, Maastricht, the Netherlands
6 Sophia Children's Hospital, Erasmus Medical Centre, Rotterdam, the Netherlands

Abstract

BACKGROUND Clinical research and treatment of childhood obesity is challenging, and objective biomarkers obtained in a home-setting are needed. The aim of this study was to determine the potential of novel digital endpoints gathered by a home-monitoring platform in pediatric obesity.

METHODS In this prospective observational study, 28 children with obesity aged 6-16 years were included and monitored for 28 days. Patients wore a smartwatch, which measured physical activity, heart rate and sleep. Furthermore, daily blood pressure measurements were performed. Data from 128 healthy children were utilized for comparison. Differences between patients and controls were assessed via linear mixed effect models.

RESULTS Median compliance for the measurements ranged from 55%-100%. The highest median compliance was observed for the smartwatch-related measurements (81%-100%). Patients had a lower daily and peak physical activity level, a higher daytime and nighttime heart rate, a higher systolic and diastolic blood pressure and a shorter sleep duration compared to controls.

CONCLUSIONS Remote-monitoring via wearables in pediatric obesity has the potential to objectively measure the disease-burden in the home-setting. Future studies are needed to determine the capacity of the novel digital endpoints to detect effect of interventions.

Introduction

Childhood obesity is a chronic disease with an increasing prevalence worldwide.[1] The disease is associated with a wide spectrum of adverse outcomes, including cardiovascular and metabolic diseases, musculoskeletal problems and psychosocial complications.[2] Treatment, follow-up and clinical research in pediatric obesity is challenging, and logistical problems such as travel distance and scheduling conflicts are mentioned as reasons for non-return to a pediatric weight management program.[3] In addition, patient's and parents' recall of physical activity (PA) and food intake is frequently subjective and suboptimal. Reliable blood pressure (BP) measurements are important in the follow-up of pediatric obesity,[4] but BP measurements during outpatient visits can be distorted by white coat hypertension.[5] These examples indicate that there is a need for objective measurements obtained in a home-setting that can monitor disease activity, and this could be provided via remote monitoring with digital biomarkers.[6]

Previous studies already assessed digital monitoring of PA levels of children with obesity and reported that they are less physically active compared to healthy children.[7] However, wearable devices can also capture other digital biomarkers, such as heart rate (HR) and sleep. Capturing PA, HR and sleep simultaneously via wearable technology has not previously been reported in pediatric obesity. Additionally, home-measured BP could provide a better indication of cardiovascular risk status. The combination of these digital biomarkers could provide an objective overview of the child's health and may lead to early detection of complications of childhood obesity. These digital endpoints could be utilized in clinical care and clinical trials to evaluate the effect of lifestyle interventions in the home-setting and may contribute to a reduction of the burden to visit outpatient clinics. Clinical validation of novel digital endpoints must be performed in the target population before integration in clinical care or clinical trials.[8] This process focuses on the tolerability, the ability to detect a significant difference between patients and controls and the correlation with existing disease metrics of candidate endpoints.

The aim of this study was to determine the clinical potential of novel digital endpoints derived from PA, HR, sleep, and BP gathered via a home-monitoring platform in pediatric obesity.

Materials and Methods

Location and ethics

This study was conducted at the Haga Teaching Hospital, Juliana Children's Hospital (The Hague, the Netherlands) and at the Centre for Human Drug Research (Leiden, the Netherlands). The study protocol was approved by the Medical Ethics Committee Zuid West Holland (The Hague, the Netherlands), and was conducted according to the Dutch Act on Medical Research Involving Human Subjects (WMO) and Good Clinical Practice Guideline. Written informed consent was obtained from all parents. Verbal consent was obtained from children aged younger than 12 years and written consent was obtained from children aged 12 years and older. The trial was registered at the Dutch Trial Registry (NTR, Trial NL7611, registered 18-Mar-2019).

Subjects and study design

During this prospective observational case-control study 28 patients, aged between 6-16 years old, were recruited via the outpatient clinic between November 2018 and April 2020. Patients diagnosed with obesity grade 1, 2 or 3 were included.[9] Children diagnosed with a chronic condition, other than obesity, that might impair PA levels were excluded. Data from 128 healthy controls, children aged between 6-16 years, were collected via a separate study.[6] The control group had a similar age and sex distribution as the patient group. Before the start of the study an informative session was planned for education on the study devices. Afterwards, patients were monitored in the home-setting during 28 consecutive days and used a smartphone that connected to other study devices. Patients were expected to wear a Steel HR smartwatch (Withings, Issy-les-Molineux, France) 24 hours per day, which measured PA in step count and several sleep-related parameters via a built-in accelerometer and registered HR through a photoplethysmography (PPG) sensor every 10 minutes. Data were directly uploaded to the server via the CHDR MORE application. Daily BP measurements were performed by a wireless upper arm cuff and oscillometric determination of pressure (Withings BPM) each evening at approximately the same clock time. Patients were instructed not to physically exert themselves just before the measurement. Weekly weight assessments were conducted with Withings Body+Scales. A daily questionnaire was completed on the smartphone regarding the daily screen time of the patient.

Baseline characteristics and environmental data

At the start of the study, baseline characteristics were collected, and the Children's Somatization Inventory (CSI) questionnaire and Pediatric Quality of Life Inventory (PedsQL) 4.0 questionnaire were completed.[10,11] The calculated Body Mass Index Standard Deviation Score (BMI SDS) was adjusted for age and sex at baseline. Data regarding the population density of the child's city of residence were obtained via the Dutch Central Office of Statistics (CBS). Weather data during the study period were collected from the Royal Dutch Meteorological Institute (KNMI) at the weather station located in Hoek van Holland.

Analysis

COMPLIANCE The tolerability of the novel endpoints was assessed by determining the compliance for each measurement type. The compliance was calculated for each participant individually by dividing the amount of completed measurements by the amount of expected measurements. When the weight assessment deviated more than two days from the protocolized time point, this assessment was counted as not completed. The watch wear time between 6AM-10PM was calculated to include as a covariate for the analysis of PA data. Calculation of the watch wear time was based on hourly data of PA and HR. When there was no registration of both HR and PA in a particular hour, it was concluded that the watch was not worn by the subject.

CANDIDATE BIOMARKERS Multiple candidate endpoints based on PA, HR, sleep and BP were defined prior to the analysis. First, proposed PA derived candidate biomarkers consisted of the daily PA, average PA per hour of the day and PA during the most active hour per day (peak physical activity). HR data between 6AM-10PM were summarized as average daytime HR and HR data between 0-5AM were summarized as average nighttime HR. In addition, the average HR per hour of the day was calculated. Moreover, systolic and diastolic BP were considered as candidate biomarkers. Lastly, sleep-related candidate endpoints consisted of the average sleep duration, sleep depth (average proportion light sleep) and the amount of wake-ups per night.

STATISTICAL ANALYSIS OF THE CANDIDATE ENDPOINTS Days with watch wear time <50% between 6AM-10PM were excluded from the analysis. Differences between the two groups were assessed for each candidate endpoint via linear mixed effect models with condition (healthy or obesity) as fixed effect and subject as random effect. Residual plots were inspected, and logarithmic and square root transformations were applied in the case of heteroscedasticity. The following parameters were tested as additional fixed effect in a model when expected to explain additional variance: age, sex, watch wear time, day of the week, type of day (school day/weekend/holiday), population density, rain duration, temperature, sunshine duration, and step count.[6] Polynomial regression with 3 degrees of freedom was utilized when exploratory plots suggested a nonlinear relationship. Inclusion of a covariate or factor and determining the best model fit were based on Akaike's information criterion, Bayesian information criterion and likelihood ratio tests. Interactions between included covariates and factors were tested and considered to be included in the model if the interaction was biologically plausible. Estimated marginal means were calculated for both study groups and plotted with a 95% confidence interval. For all estimated means, fixed effects were held constant to their population average. Models including watch wear time were visualized with a watch wear time of 100%. A p-value smaller than 0.05 was considered statistically significant. Within the patient group, correlations between BMI SDS, quality of life and daily PA were assessed by calculating Pearson's correlation coefficient or Spearman's correlation coefficient.

SOFTWARE Promasys® 7.3 (Anju Software, Fort Lauderdale, Texas, USA) was used for data management of the baseline characteristics. Statistical analysis was performed with R version 3.6.2 with utilization of the lme4, emmeans and ggeffects packages.[12-15]

Results

Baseline characteristics

Baseline characteristics of the children with obesity (n=28) and the healthy children (n=128) are presented in *Table 1.* The mean age was 11 years and 46% of the participants was male in both study groups. The mean BMI SDS of patients was 3.6, versus 0.3 of controls. The average quality of life score measured by the PedsQL questionnaire was 78.6 out of 100 in the patient group versus 90.7 out of 100 in the control group.

Table 1. Baseline characteristics

	Children with obesity (n=28)	Healthy children (n=128)6
Age (years) (Mean (SD))	11.6 (3.1)	11.1 (3.1)
Sex, male (n (%))	13 (46%)	59 (46%)
Weight (kg) (Mean (SD))	77.7 (24.6)	42.7 (15.7)
Height (cm) (Mean (SD))	156.3 (15.5)	151.3 (17.7)
BMI (Mean (SD))	30.9 (5.2)	18.0 (3.1)
BMI SDS (Mean (SD))	3.6 (0.4)	0.3 (1.2)
PedsQL score (Mean (SD))	78.6 (14.2)	90.7 (7.4)
CSI score (Mean(SD))	12.3 (11.4)	-
Obesity Grade (n (%)) Grade 1 Grade 2 Grade 3	 10 (36%) 10 (36%) 8 (29%)	-
Plays sports (n (%))	18 (64%)	117 (91%)
Ethnicity (n (%)) Caucasian Asian/Hindi Other/Mixed	 20 (71%) 3 (11%) 5 (18%)	 122 (95%) 2 (2%) 4 (3%)
Extremely urbanized area (n (%))	25 (89%)	97 (76%)

Compliance

The median compliance of each measurement type is listed in *Table 2*. The median overall compliance was 74% (IQR 55%-85%). The median wear time of the smartwatch was 22.0 hours per day. The lowest median compliance was observed for the daily questionnaire (55%), while the highest median compliance was observed for two smartwatch-related measurements, HR (100%) and step count (100%). Two patients did not complete any BP measurements and two patients did not wear the smartwatch at night.

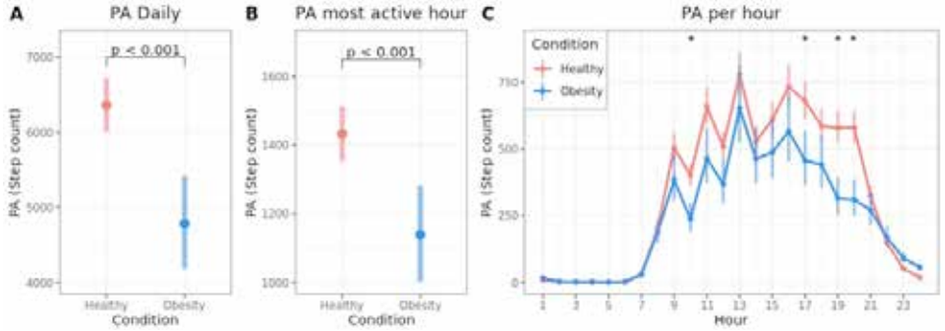
Table 2. Compliance of children with obesity during the study period

Measurement	Median compliance (IQR)
Smartwatch	
Step count	100% (93%-100%)
Heart rate	100% (93%-100%)
Sleep	81% (62%-89%)
Wear time watch per day	22.0h (18.0h-23.3h)
Blood pressure	59% (32%-79%)
Weight	75% (25%-100%)
Daily questionnaire	55% (20%-79%)
Overall compliance	74% (55%-85%)

Difference patients and controls

PHYSICAL ACTIVITY The average daily step count was 4528 for patients versus 6066 for controls (difference 1538 steps, 95% confidence interval (CI) 919–2157, *Figure 1A*). For patients, PA during the most active hour was lower compared to controls with a difference of 289 steps (1099 steps vs 1388 steps, 95% CI 149–428, *Figure 1B*). A separate analysis was performed to calculate the average PA per hour of the day, which was significantly lower for the patient group compared to the control group with a difference of more than 50 steps per hour at 10AM, 5PM, 7PM and 8PM, after controlling for age and sex (*Figure 1C*). The 10TH and 90TH percentile of the daily PA within a week, which were both lower for patients compared to controls. An overview of all analyses with adjusted and unadjusted differences are listed in *Supplementary Table S1.* The relationship between daily PA and daily screen time for both study groups is visualized in *Figure S1*. Daily PA decreased with an increase in screen time for both the patient group and the control group. Patients performed less PA compared with controls with a similar screen time duration.

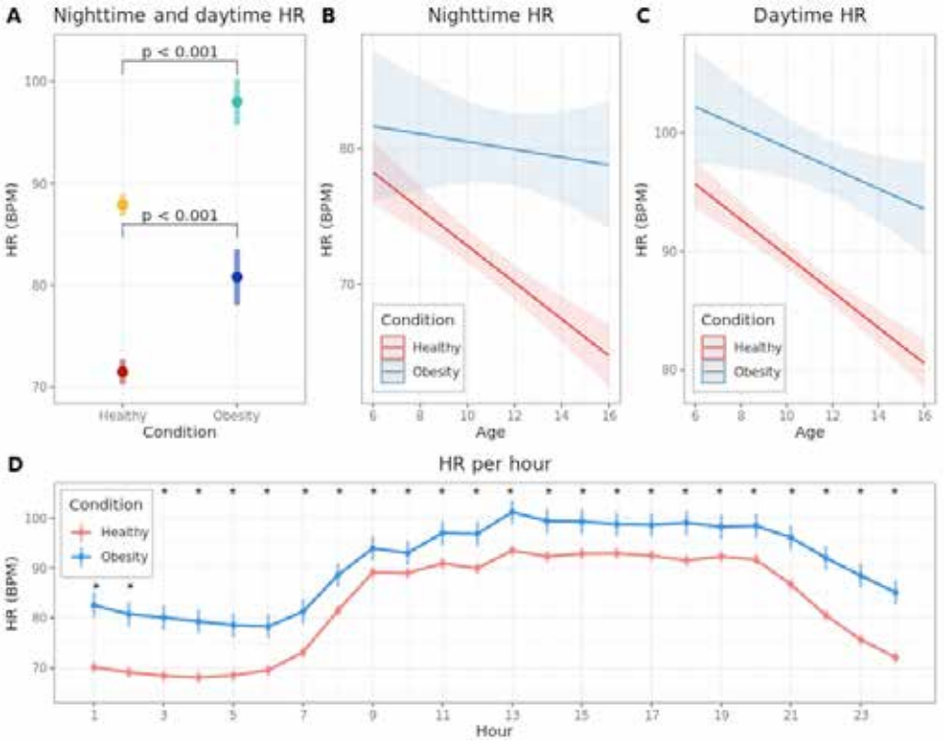
Figure 1. Differences in PA between children with obesity and healthy children. A–B. Estimated marginal mean (95% CI) daily step count (A) and step count during the most active hour per day (B) for children with obesity and healthy children. Age (11 years), rain duration (1.87h), weekday, degree of urbanization and sex were fixed to their population average. Plots are visualized with watch wear time 100% C. Estimated marginal mean (95% CI) PA per hour during the day for children with obesity and healthy children. Age (11 years) and sex are fixed to their population average.



* Indicate hours with a p-value <0.05 for the difference (>50 steps per hour) after Holm's correction for multiple tests.

HEART RATE The average nighttime HR was 81 BPM for patients versus 71 BPM for controls (difference 9.3 BPM, 95% CI 6.3–12.3, *Figure 2A*). In addition, the average daytime HR was also higher for patients compared to controls (98 BPM vs 88 BPM, difference 10.1 BPM, 95% CI 7.6–12.6, *Figure 2A*). The difference in average nighttime HR between patients and controls increased as a function of age by a difference of 1.1 BPM/age year (95% CI 0.1–2.0, *Figure 2B*). This age-related effect was not observed for the daytime HR (*Figure 2C*). A separate analysis per hour showed that patients had a significantly higher average hourly HR compared to controls for every hour of the day, after controlling for age and sex (*Figure 2D*).

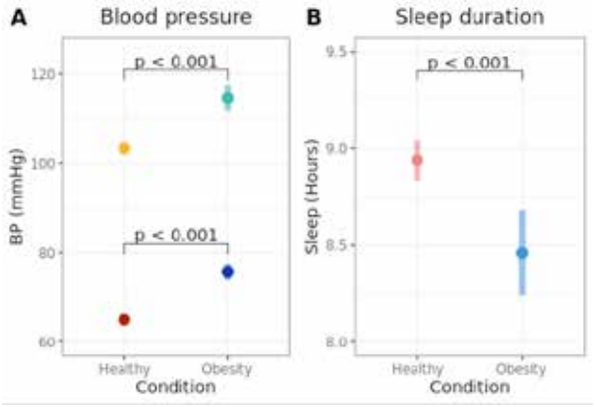
Figure 2. Differences in HR between children with obesity and healthy children. A. Estimated marginal mean (95% CI) nighttime and daytime HR for children with obesity and healthy children. Light colors represent daytime HR, dark colors represent nighttime HR. Age (11 years) and sex for both nighttime and daytime HR and daily step count (7000 steps) for daytime HR only, were fixed to their population average. B. Relationship between age and nighttime HR (difference of 1.1 BPM/age year, 95% CI 0.1–2.0, p = 0.029). C. Relationship between age and daytime HR (difference of 0.6 BPM/age year, 95% CI -0.2 to 1.5, p = 0.119). B–C. Bold lines represent the estimated marginal means, shaded areas indicate the 95% CI of the estimated mean. D. Estimated marginal mean (95% CI) HR per hour of the day for children with obesity and healthy children. Age (11 years) and sex were fixed to their population average.



*Indicate hours with a p-value <0.05 for the difference after Holm's correction for multiple tests.

BLOOD PRESSURE Patients had a higher systolic BP (115 mmHg vs 104 mmHg, difference 11.3 mmHg, 95% CI 8.1–14.5, *Figure 3A*) as well as a higher diastolic BP (76 mmHg vs 65 mmHg, difference 10.7 mmHg, 95% CI 8.7–12.7, *Figure 3A*) compared to controls. The difference in diastolic BP between patients and controls increased significantly as a function of age (difference 0.9 mmHg/age year, 95% CI 0.3–1.5, *Supplementary Figure S2A*). This age-related effect was not observed for the systolic BP (*Supplementary Figure S2B*).

Figure 3. Difference in BP and sleep duration between children with obesity and healthy children.
A. Estimated marginal mean (95% CI) systolic BP and diastolic BP for children with obesity and healthy children. Light colors represent systolic BP, dark colors represent diastolic BP. Age (11 years) was fixed to their population average. B. Estimated marginal mean (95% CI) sleep duration for children with obesity and healthy children. Age (11 years), sex and type of day were fixed to their population average.



SLEEP The adjusted average sleep duration per night was shorter for patients compared to controls (8.5h vs 8.9h, difference 0.5h, 95% CI 0.2–0.7, *Figure 3B*). The average proportion of light sleep per night was 52.6% for the patient group versus 56.9% for the control group (difference 4.3%, 95% CI 1.8–6.8). There was no significant difference found in the average number of wakeups per night between patients and controls.

Correlations in the patient group

No significant correlation was found between daily PA and BMI SDS as well as between daily PA and quality of life in the patient group. Since a period of 28 days was too short to observe evident differences in weight, no further analyses were performed with the weight data obtained by the weekly weight assessments.

Discussion

This study evaluated digital endpoints derived from PA, HR, BP and sleep in pediatric obesity through wearable devices at home. These multiple digital endpoints gathered by a home-monitoring platform show potential for future use in clinical trials and clinical care because of the high tolerability and ability to differentiate patients from controls, which are prerequisites for implementation.[8] Adequate validation must be performed before implementation of the ubiquitous digital devices and applications in clinical research and ultimately in clinical practice. A previously proposed stepwise approach to fit-for-purpose validation of (digital) biomarkers was applied in this study.[8]

One of the most important characteristics of digital biomarkers is the tolerability in the target population.[8] Non-compliance will lead to incomplete datasets and biased results. The smartwatch-related measurements showed the highest tolerability (median compliance 81%–100%). Gathering data via a smartwatch appeared to be superior to gathering data via a questionnaire (median compliance 55%) in children with obesity. Compared to a previous study in healthy children, the overall compliance was lower for children with obesity (94% vs 74%). This difference is predominantly caused by the difference in median compliance for the daily BP measurements (95% for healthy children vs 59% for patients) and daily questionnaire (90% for healthy children vs 55% for patients).[6] Childhood obesity is associated with a less structured home environment.[16] In contrast to the smartwatch related measurements, the daily BP measurements and questionnaire need to be planned and performed actively by the child or parents which might be more difficult in a less structured home environment.

Another important validation criterion for biomarkers is the ability to discriminate healthy children from patients, which was assessed for all candidate biomarkers. The average daily PA was lower for patients compared to controls, which has been cited in numerous previous studies with comparable differences.[7] However, the reported differences in step count throughout the literature vary due to, inter alia, the utilization of a wide selection of pedometers and differences in age of the study populations. There is conflicting evidence whether the awareness of wearing an accelerometer is affecting the level of PA in healthy youth.[17] The majority of studies examining differences in step count between children with obesity and healthy children monitored for a maximum of 8 days.[7] In this study patients were monitored for 28 days. We did not find a decrease in PA levels comparing the first and last week in either study group. As reported by past studies patients

had a lower peak PA compared to controls.[18] We demonstrated a difference in peak PA between the two groups not only by analyzing PA levels during the most active hour per day, but also by calculating the 90TH percentile of the daily PA within a week. The latter endpoint is less variable and could be a useful biomarker for long-term monitoring.[6] Based on the data presented here, interventions focused on PA after school time seem most appropriate, since the biggest differences in PA between the two groups were observed in the after-school period. The combination of PA derived biomarkers provides a wide-ranging and objective overview of the PA level of the patient and can be utilized to promote PA and to provide personal advice.

Multiple candidate biomarkers based on HR were examined in this study. HR was registered through a PPG sensor, which has shown an acceptable validity in adults and has demonstrated to be accurate in measuring HR in children undergoing elective surgery.[19,20] Patients had a higher average nighttime HR compared to controls, with similar absolute differences compared to previous research with other methods of heart rate monitoring.[21] Additionally, children with obesity had a higher daytime HR compared to controls, which also has been reported in the past.[22,23] Analysis of HR per hour clearly displayed the difference in daily HR pattern for patients compared to controls. The higher HR in the patient group can be explained by sympathetic nervous system overactivation,[22,24,25] caused by dysregulation of the release of multiple adipokines (leptin, free fatty acids, TNF-α, IL-6, adiponectin) and baroreflex dysfunction.[26,27] In this study the difference in average nighttime HR between patients and controls increased as a function of age (while no correlation between BMI SDS and age was found). This is a novel observation, possibly explained by the fact that in healthy children a progressive increase in cardiac parasympathetic activity relative to sympathetic activity occurs with an increase in age, while for children with obesity this process is disrupted.[28] This age-related effect was not observed for the average daytime HR, most likely due to the higher proportion of unexplained variability in this data. Weight loss is associated with a decrease in HR, which may suggest that the lower parasympathetic activity is reversible.[29,30] It has been reported that a higher resting HR leads to a higher risk of cardiovascular disease and (non)-cardiovascular death in adults and is associated with dyslipidemia in children.[31–34] Consequently, nighttime HR might be an attractive surrogate biomarker to assess the risk for cardiovascular disease in children with obesity.

Systolic and diastolic BP were also proposed as candidate endpoints, and both were elevated in patients compared to controls. The differences in BP reported here are slightly larger compared to the differences mentioned in previous research but are within the ranges reported in the literature.[4] This relatively large difference between patients and controls could be explained by our study population, which consists of a high percentage of children diagnosed with grade 2 and 3 obesity (65%) compared with other studies. This might have led to a high proportion of patients at risk for cardiovascular problems in our cohort, since an increase in BMI is associated with an increase in BP.[35] Another explanation is the BP cuff used in this study, which was identical for healthy children and children with obesity. This could have resulted in an overestimation of the BP in patients due to a bigger arm circumference, though the observed differences in BP appear too large to be entirely attributed to the utilization of the single sized cuff.[36] Moreover, the Withings device has been validated in accordance with the ESH International Protocol Revision 2010.[37] The pathophysiological mechanism of hypertension in children with obesity is multifactorial and complex. Suggested contributing factors are increased sympathetic nervous system activation, dysfunction of the endocrine system, disturbed sodium homeostasis and vascular damage.[38] The difference in diastolic BP, but not systolic BP, between patients and controls increased as a function of age. Presently, a pathophysiologic explanation for this observation is lacking, and more research regarding hypertension subtypes in children with obesity may elucidate the underlying mechanism.[39] Childhood hypertension has multiple adverse consequences, such as an increased carotid intima-media thickness and left ventricular hypertrophy,[40,41] both precursors to adverse cardiovascular outcomes in adulthood.[42,43] Literature regarding the reversibility of the adverse cardiovascular effects of childhood obesity states that lifestyle interventions improve early markers of atherosclerosis and reduce the BP.[44] Hence, the combination of HR registration and BP measurements appear a valid option to monitor the cardiovascular status of the patient non-invasively.

Multiple sleep parameters were tested as candidate endpoints. Patients had a significantly shorter sleep duration than healthy children, an observation supported by previous studies.[45] Data regarding sleep quality and sleep efficiency in children with obesity compared with healthy children are inconsistent partly due to different measurement methods and definitions.[45] Since sleep parameters were measured via accelerometry, the lower proportion of light sleep for children with obesity compared to the healthy children could be caused by less movement at night due to the habitus of the patients. Also, it must be considered that when interpreting accelerometry-derived sleep measurements, accelerometry has shown to be less accurate compared to polysomnography.[46] On the other hand, sleep registration via accelerometry is less invasive and can be performed multiple

nights in a natural setting in contrast to polysomnography. Furthermore, accelerometry-derived sleep recording has shown to be more reliable than sleep registration via maternal sleep reports and avoids the recall bias related to sleep diaries.[47] In the future, with further improvement of the underlying algorithms, accelerometer-derived parameters might be useful to detect sleep related breathing disorders, such as obstructive sleep apnea, or to monitor children non-invasively after treatment.[48,49]

This study has several limitations. The sample size was limited to 28 patients. Nevertheless, important baseline characteristics (age, sex, and obesity grade), were well distributed in the patient group. The median compliance for the smartwatch-related measurements was high in this study. However, further studies are needed to examine the long-term compliance, which is very important in monitoring treatment effects. If the long-term compliance is sufficient, home-monitoring via wearables could reduce outpatient visits. Moreover, a disadvantage of gathering data in a home-setting is missing data due to non-compliance. Although the amount of missing data was low and therefore unlikely to impact the overall results, watch wear time was included as covariate in the PA models. Finally, when appraising PA-related endpoints, it must be considered that PA has been measured in step count and that activities like cycling and swimming were not registered. Strengths of this study consisted of the utilization of a structured validation process of the candidate endpoints, the inclusion of a large control group, with a similar distribution of age and sex compared to the patient group and the relatively long-term monitoring period of 28 days. Additionally, the linear mixed effect models utilized for the analysis of the candidate endpoints can handle small sample sizes and missing data points. The defined endpoints based on PA, HR, BP and sleep could be utilized to promote and track PA, to assess the risk for cardiovascular disease and to detect sleep-related alterations of childhood obesity.

Conclusion

Remote-monitoring via wearable technology has the potential to objectively measure the disease-burden in the home-setting in pediatric obesity. The digital biomarkers based on PA, HR, BP and sleep have a high tolerability and can demonstrate differences between patients and controls, in line with previous studies gathering the endpoints via conventional clinic-based methods. Future studies are needed to determine the capacity of these novel digital endpoints to detect effect of interventions.

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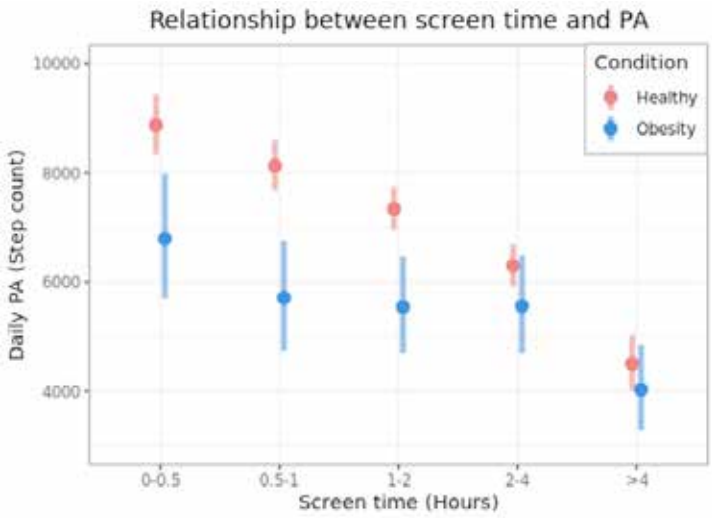
Sup. Table S1. Unadjusted and adjusted differences between children with obesity and healthy children.

Candidate Endpoints	Unadjusted		Adjusted		Adjusted for
	Difference* (95% CI)	p-value	Difference* (95% CI)	p-value	
Daily step count	2143(1318-2968)	<0.001	1538 (919-2157)	<0.001	Age, sex, wear time watch, weekday, rain duration, degree of urbanization
Step count during most active hour	368(194-542)	<0.001	289 (149-428)	<0.001	Age, sex, wear time watch, weekday, rain duration, degree of urbanization
10TH percentile daily step count	1574(891-2256)	<0.001	948 (325-1571)	0.003	Age, sex, wear time watch, rain duration
90TH percentile daily step count	2878(1880-3877)	<0.001	2257 (1315-3199)	<0.001	Age, sex, wear time watch, rain duration
Nighttime heart rate	-8.7(-12.1 to -5.3)	<0.001	-9.3(-12.3 to -6.3)	<0.001	Age, sex
Daytime heart rate	-7.0(-10.2 to -3.7)	<0.001	-10.1(-12.6 to -7.6)	<0.001	Age, sex, daily step count**
Systolic blood pressure	-11.9(-16.1 to -7.8)	<0.001	-11.3 (-14.5 to -8.1)	<0.001	Age
Diastolic blood pressure	-10.8(-13.0 to -8.7)	<0.001	-10.7(-12.7 to -8.7)	<0.001	Age
Sleep duration	0.5(0.2-0.8)	<0.001	0.5(0.2-0.7)	<0.001	Age, sex, type of day
Sleep depth (% light sleep)	4.2(1.6-6.8)	0.002	4.3(1.8-6.8)	0.001	Age, sex
Number of wake-ups	-0.3(-0.8 to 0.3)	0.326	-0.3(-0.8 to 0.3)	0.326	-

* Differences presented are 'estimated mean healthy controls'-'estimated mean children with obesity'
** 3RD degree polynomial.

Sup. Figure S1. Relationship between screen time and daily step count for children with obesity and healthy children. Relationship between screen time and daily PA for healthy children and children with obesity. Estimated marginal means are plotted (95% CI) for both study groups. Age (11 years) and sex were fixed to their population average.



Sup. Figure S2. Relationship between BP and age for children with obesity and healthy children. A. Relationship between age and diastolic BP (difference of 0.9 mmHg/age year, 95% CI 0.3–1.5, p = 0.005). B. Relationship between age and systolic BP (difference of 0.2 mmHg/age year, 95% CI -0.8 to 1.2, p = 0.693). A–B. Bold lines represent the estimated marginal means, shaded areas indicate the 95% CI of the estimated mean.