PHYSICAL ACTIVITY, SEDENTARY TIME AND SLEEP IN CYSTIC FIBROSIS YOUTH: A BI-DIRECTIONAL RELATIONSHIP?

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Abstract

Purpose: Physical activity (PA) and sleep are highly important for those with Cystic Fibrosis (CF), yet, despite this and suggestions of a bidirectional relationship between these factors in healthy children, their relationship is yet to be investigated.

Methods: PA, sedentary time (SED) and sleep were objectively derived over seven days in 58 youth (11.9±2.7 years; 29 CF). Generalized linear latent and mixed models with a random intercept and slope at child-level were adjusted for age, sex, wear-time, type of day, group and mean PA/SED and sleep.

Results: Every additional 10 mins sedentary was associated with 5.6 and 5.0 mins less sleep and 10.6 and 12.0 mins less wake after sleep onset (WASO) that night, in CF and healthy children, respectively. PA, regardless of intensity, was not associated with total sleep time but every additional 10 mins of light PA (LPA) was associated with 3.0 mins less WASO in healthy participants. Ten mins more sleep was associated with 3.1 and 1.7 mins less SED in CF and healthy children, respectively. In CF, greater sleep time led to less LPA (3.6 mins) the following day, whereas, in healthy children, poor sleep quality (greater WASO) was associated with more LPA (1.4 mins) and moderate-to-vigorous PA (5.2 mins) the following day.

Conclusion: A bidirectional relationship between SED and subsequent total sleep time was evident, irrespective of group, whereas the relationship between sleep and PA was group dependent. These findings have important implications regarding the reciprocal effects of promoting PA or sleep quantity or quality.

Introduction

Cystic fibrosis (CF) is an autosomal recessive disorder that predominantly occurs in individuals of European descent, and affects over 72,000 people worldwide [1]. CF is a multi-system disease caused by mutations in the Cystic Fibrosis Transmembrane Conductance Regulator gene, which leads to abnormally viscous secretions and results in obstruction, inflammation, organ failure and, ultimately, premature mortality [2].

Regular physical activity is integral to the treatment and management of CF [3], irrespective of age or disease severity [3]. Specifically, high levels of physical activity are associated with decelerated lung function decline and improved airway clearance by increasing trans-epithelial fluid transport [4]. Furthermore, increases in physical activity improve cardiorespiratory fitness and lung function in children with CF [5], which is correlated with survival [6] and improved quality of life [7]. However, despite this recognition of the importance of physical activity, it has been reported that they engage in less physical activity than healthy controls by some [8; 9], although not all [10]. A sedentary lifestyle has been suggested to be associated with the progression of both functional and physical impairments in the CF population [4], but there is little consensus regarding sedentary time in those with CF. Specifically, whilst Aznar et al.[8] found those with CF are less sedentary overall and at weekends than their healthy peers, Mackintosh et al. [10] found no difference between groups.

As acknowledged in the recent Canadian 24-hour movement guidelines for youth, physical activity, sedentary time and sleep are inherently inter-related [11]. Indeed, there is growing interest in the potential virtuous/vicious cycle between children's daytime behaviours and night-time sleep. Whilst a recent meta-analysis found higher physical activity levels to be associated with better subjective and objective sleep in healthy pediatric populations [12], evidence regarding the *within* person relationship is considerably more equivocal. Specifically, Pesonen et al. [13] reported increased moderate-to-vigorous physical activity (MVPA) to be associated with poorer subsequent sleep in terms of both duration and efficiency but others found increased MVPA to be related to improved sleep efficiency [14] and duration [15]. Furthermore, Lin et al. [15] reported that sedentary time was associated with decreased sleep whilst, in contrast, Vincent et al. [16] found no association between either physical activity or sedentary time and sleep. Whilst at the between participant level, maintaining recommend sleep throughout the week has been reported to be positively associated with physical activity in children [17], the *within* person influence of sleep on subsequent physical activity and/or sedentary time is similarly lacking in consensus., Specifically, a shorter sleep duration has been reported to be associated with both more [18; 19] or less [15; 20; 21] physical activity the subsequent day, or even not associated at all [14; 16]. The basis for these inter-study discrepancies remains to be elucidated, with further conclusions largely precluded by the use of different methods to assess and quantify physical activity, sedentary time and/or sleep and different statistical approaches to account for *within* and *between* participant variation.

Little is known regarding the potential bidirectional relationship between sleep quality and physical activity in CF. In adults with CF, a secondary analysis of sleep and activity data collected via actigraphy showed that more fragmented sleep was associated with less time spent in MVPA, poorer forced expiratory volume in one second (FEV_1) and reduced exercise capacity [22]. Similarly, Dietz-Terjung et al. [23] reported that time spent in vigorous intensity physical activity was associated with sleep efficiency and the number of awakenings, albeit in a sample of those with CF spanning more than 24 years, and Barbosa et al. [24] found that sedentary time was associated with poorer sleep architecture. This lack of consensus regarding the impact of each component of habitual physical activity and sedentary time on sleep most likely reflects the reliance on participant-level analyses, which are confounded by significant *within*-person variability, and failure to account for the bidirectional nature of movement and sleep behaviours. Given that youth with CF have greater sleep disturbances and a poorer sleep efficiency than their healthy peers [25], with the degree of disturbance associated with lung function [23; 25], mood and quality of life in children with CF [26], further research that considers the bidirectional relationship between physical activity/sedentary time and sleep in youth with CF is warranted. If a bidirectional relationship is evident, it would suggest that interventions that promote either increased physical activity, decreased sedentary time or healthy sleep patterns may have the capacity to elicit reciprocal benefits.

Therefore, the aim of this study was to examine the potential bidirectional relationship between physical activity/sedentary time and sleep among youth with CF compared to their healthy counterparts.

Methods

Participants

In total, fifty-eight participants (11.9 ± 2.7 years; 29 CF; 28 girls) were recruited for the present study. Children and adolescents with CF, confirmed by a sweat chloride >60 mmol·l^{-1} and genotyping, were recruited from CF outpatient clinics in the UK and Canada. Unstable non-pulmonary comorbidities or acute infections warranted exclusion for those with CF; all CF participants continued prescribed medications as usual. A healthy, free from any chronic disease, control group matched for age and sex was used to draw study comparisons. Ethical approval was granted by the Bromley NHS research ethics committee (REC reference: 13/LO/1907) and IWK Health Centre REC (REC reference: 1015217). Written informed consent and assent were obtained from parents/guardians and participants, respectively.

Measures

All data from the CF participants were collected during routine clinical visits from their healthcare centres in both the UK and Canada; data from the control group were collect on separate occasions in a single laboratory visit at Swansea University, UK. Body mass (Seca 875; Hamburg, Germany) and stature (Seca 213; Hamburg, Germany) were measured to the nearest 0.1 kg and 0.01 m, respectively. Forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) were measured using a portable dry spirometer (Alpha, Vitalograph, Buckingham, UK). Each participant was asked to complete three "acceptable" tests, requiring each maximal exhalation to be within 5% of each other. The best of three measurements were taken according to American Thoracic Society guidelines [27] and expressed as a percentage of predicted using appropriate reference data [28].

Participants wore a hip-mounted ActiGraph GT3X+ accelerometer (ActiGraph LLC, Pensacola, FL) sampling at 100 Hz for seven consecutive days and were instructed to only remove the monitor for water-based activities (e.g., bathing, swimming). Data were downloaded using ActiLife software (v6.10.4; ActiGraph LLC), saved in raw format and subsequently converted to .csv format for physical activity, sedentary time and sleep analyses.

Physical activity, sedentary time and sleep analyses were performed in R (http://cran.r-project.org) using the GGIR package (version 1.9-1), which autocalibrated the raw triaxial accelerometer signals and converted them into gravity-corrected vector magnitude units the Euclidean norm minus one; ENMO; [29]. To be included in the analyses, data had to be available for a minimum of 10 hours per day of wake wear time on any three days [30] and daily sleep time had to be ≥ 160 mins per night with >90% estimated wear-time [15]. Non-wear was estimated according to the standard deviation and value range of each accelerometer axis using a 60-minute window moving in 15-minute increments [29]. For each 15-minute period identified as non-wear on otherwise valid days, missing data were imputed from the mean value of the same time period of different measurement days. Overall, six children (five controls, one CF) did not meet the wear-time criteria and were excluded from further analyses. The prediction equations of Hildebrand et al. [31] were used to determine intensity-specific cut-points. Specifically, the Hildebrand equations were solved for 2 Metabolic equivalents (METs) and 4 METs to identify the LPA and MPA thresholds, respectively [32; 33]. Sleep was estimated within GGIR according to the angle method using a 5° sensitivity. Although polysomnography is the gold-standard for sleep measurement, actigraphy is commonly used as an objective, non-invasive and cost-effective alternative [34]. Sleep measures examined were: (i) wake after sleep onset (WASO) - total minutes of wakefulness during sleep; (ii) total sleep time – total minutes of sleep during night (i.e. sleep duration minus WASO); and (iii) sleep efficiency – total sleep time as a percentage of sleep duration.

Statistical Analyses

All statistical analyses were conducted using Stata MP v13 (StataCorp, Texas, USA). Independent t-tests were conducted to examine differences between participants who were included and excluded from the analyses and between the CF and healthy groups for all descriptive variables (mean ± SD). Given the hierarchical, nested nature of the data, generalized linear latent and mixed models were used to examine the temporal relationship between physical activity/sedentary time and sleep using a two-level model (day and child). In all models, a random intercept and slope were used at the child-level and analyses were adjusted for age, sex, wear-time, type of day and group, as well as average daily physical activity/sedentary time and sleep. The first set of analyses examined whether physical activity/sedentary time on any given day was associated with sleep outcomes that night. The second considered whether sleep on any given night was associated with physical activity/sedentary time the following day. Separate analyses were conducted for each physical activity intensity, sedentary time and sleep outcome for each group. Analyses were conducted using both MPA and VPA separately, but no significant associations were observed, so combined MVPA is reported. Pearson correlation coefficients were used to assess the relationship between average variables across the week with key descriptive characteristics. Statistical significance was set at $P < 0.05$.

Results

As shown in Table 1, there was no significant difference in the anthropometrical characteristics of those with CF or their healthy counterparts. However, those with CF had a lower percentage predicted FEV_1 and FVC than their peers ($P < 0.05$). The healthy control children accumulated significantly more LPA and MVPA and had a shorter total sleep time than those with CF (Table 2; $P < 0.05$). There were no significant differences in descriptive characteristics, physical activity or sleep between those who were included and excluded from the final analyses.

In terms of physical activity/sedentary time predicting sleep, sedentary time on any given day was significantly associated with total sleep time and WASO that night, irrespective of group (Table 3). Specifically, 10 mins more sedentary time was associated with 5.6 mins less sleep and 10.6 mins less WASO in those with CF, and 5.0 and 12.0 mins, respectively, in healthy controls. In contrast, there were no associations between physical activity of any intensity and total sleep time, regardless of group. In the healthy controls, 10 mins more LPA during the day was associated with 3.0 mins less WASO that night, respectively.

With regards to the influence of sleep on physical activity/sedentary time the following day, total sleep time predicted sedentary time, irrespective of group (Table 4), with 10 mins more sleep associated with 3.1 mins and 1.7 less sedentary time in those with CF and healthy controls, respectively. In those with CF, total sleep time was also associated with LPA, with 10 mins more sleep leading to 3.6 mins less LPA the following day (Table 4). In the healthy group, every 10 min increase in WASO was further associated with a 1.4 and 5.2 min increase in LPA and MVPA, respectively.

Discussion

This novel study examined whether physical activity levels and/or sedentary time on any given day were associated with sleep parameters the previous or subsequent night in children and adolescents with CF and age- and sex-matched healthy controls. Overall, the greater the time spent sedentary, the shorter the total sleep time that night. Moreover, a longer total sleep time was associated with less sedentary time the following day. Importantly, this bidirectional relationship was manifest irrespective of group, whereas, in contrast, the relationship between sleep and physical activity was dependent on group. Specifically, in those with CF, an increased total sleep time was associated with decreased LPA the following day. In the healthy children, a poorer sleep quality, as indicated by WASO, was associated with greater LPA and MVPA the following day. These findings have important implications regarding the reciprocal effects of promoting physical activity or sleep quantity or quality in future interventions.

Despite recognition of the potential influence of declining total sleep time and increasing sedentary time over recent decades on both mental and physical health outcomes, evidence regarding the potential temporal and bidirectional associations between these parameters remains relatively sparse. The current findings of a bidirectional relationship between sleep and sedentary time are largely in agreement with those of Lin et al. [15] and Nixon et al. [35] in healthy pre-pubertal children, extending these studies to demonstrate a similar relationship is evident in healthy pubertal adolescents and in CF populations. This growing body of evidence supporting a bidirectional relationship is especially relevant in identifying potential targets for future interventions that seek to promote a healthy body mass as both sleep and sedentary time have been independently associated with obesity [36]. The mechanisms underpinning these relationships are likely to be multi-factorial and are largely beyond the scope of this study. It is, however, pertinent to note the contradiction of the present and earlier findings with the commonly cited notion that a lower quantity and/or quality of sleep is associated with inactivity due to sleepiness and fatigue [37], at least in the terms of sedentary time.

Little consensus is currently available regarding the relationship between MVPA and total sleep time. Specifically, increased MVPA has been reported to be associated with poorer [13], improved [14; 15] or, as in the current study, unaltered subsequent sleep [16]. Similarly equivocal results have been reported regarding the relationship between total sleep time and MVPA the subsequent day [13; 14; 16; 18; 20; 35]. These equivocal findings are likely to reflect numerous methodological inconsistencies that limit inter-study comparisons, such as in the device type and wear location and the period over which this measurement was conducted [16], as well as the data reduction techniques applied to derive these parameters. Furthermore, there has been considerable heterogeneity in the treatment of data and control of confounding factors. Indeed, the majority of studies have relied on count-based estimates of physical activity [13; 14; 20], the limitations of which are well-established, and few have appropriately accounted for age and sex, both of which significantly affect both physical activity and total sleep time during childhood [38]. It is also important to distinguish studies that have considered the bidirectional and temporal associations at the participant- rather than population-level from those that have used experimental manipulations from observational studies, as these are likely to provide different insights and should not be considered inter-changeable. The current findings therefore provide further clarity to the bidirectional relationship in healthy children and extend these findings to those with CF.

The health benefits associated with LPA are increasingly recognized, not least because it accounts for a greater proportion of daily physical activity than MVPA [39]. Indeed, LPA may represent an appropriate conduit by which to encourage previously sedentary individuals to increase daily physical activity towards achieving the physical activity recommendations [40]. It is therefore particularly of interest to note that, in the current study, LPA was the most widely associated intensity of physical activity with sleep, irrespective of direction. Specifically, 10 mins greater LPA on any given day was associated with 3.0 mins less WASO that night, and 10 mins more WASO was reciprocally associated with 1.4 mins more LPA the following day, in healthy children. This relationship between LPA and sleep quality may be attributable to numerous factors, with several hypotheses relating to thermoregulatory effects, body restoration and energy conservation requirements, all previously suggested to explain the positive effects of physical activity on sleep in adults [41]. However, the applicability of such explanations to children, or LPA, let alone specific diseases, is yet to be established. It is also pertinent to note that increased total sleep time was associated with a lower sedentary time in both groups and a lower LPA in those with CF the following day. It could be speculated that this may reflect a shift in activity behaviors towards greater time spent in higher physical activity intensities but as this was not observed in the present study this may rather reflect the finite, time-constrained nature of daily physical activity and sleep [42].

In addition to being associated with greater LPA, poorer sleep quality was also associated with decreased sedentary time and increased time spent in MVPA in healthy children. These findings may simply reflect that children who do not sleep well consciously move more during the day to fight fatigue [21], although this explanation is unlikely in our modern environment that enables and even encourages sedentary behaviours. Alternatively, it has been suggested that a greater WASO and daytime physical activity may be related to an individual’s innate physical activity level [13]. Specifically, given the relatively high hereditability estimate of physical activity [43], it has been suggested that an individual’s physical activity traits may determine their physical activity level irrespective of the time of day [13].

This is the first study to consider the potential bidirectional relationship between sleep and physical activity in those with CF, despite both of these parameters being cornerstones in the treatment strategy of CF. In general, the present study revealed fewer associations between sleep and physical activity, or vice versa, in those with CF than their healthy counterparts. However, the study did reveal an important relationship between time spent sedentary and subsequent sleep in CF patients. Specifically, in those with CF, 10 mins greater sedentary time was associated with 5.6 mins less sleep that night. This highlights the importance of minimising time spent sedentary in those with CF in order to avoid detrimental consequences for sleep duration, a conclusion largely in agreement with those of Barbosa et al. [24]. The explanation for the somewhat contradictory relationship also observed between increased sedentary time and improved sleep quality (reflected by decreased WASO) is currently unclear but reinforces the complex relationship between physical activity, sedentary time and sleep components. In those with CF, 10 mins more sleep was associated with 3.1 and 3.6 mins less sedentary time and LPA, respectively, the following day. These findings, which agree with McNeil et al. [21], are most likely to reflect a compensatory response due to less waking time available and the prioritization of MVPA, possibly due to strictly controlled treatment strategies, which limit flexibility and, potentially, opportunities for physical activity. Indeed, it has previously been suggested that MVPA may not be as susceptible to variation according to sleep quality and quantity in healthy children because MVPA is more dependent on motivation and scheduled time than on sleep *per se* [14]. The lack of association observed in the present study between MVPA and sleep, or the reciprocal, may be related to the very low MVPA levels found in those with CF (9.6 ± 11.1 mins). Indeed, the current MVPA levels were considerably lower than reported by Dietz-Terjung et al. [23], who, in contrast to the present findings, reported a significant association between vigorous and very vigorous activity and sleep efficiency and number of awakenings. The *within* vs *between* participant approaches utilised in these studies limit inter-study comparisons but it should also be noted that physical activity in both studies was derived using activity thresholds developed for healthy children and which therefore cannot account for disease-specific factors that may alter the energy expenditure associated with daily movement [44]. This may have resulted in the misclassification of sedentary time and activity intensities, influencing the current findings.

Several limitations should be acknowledged within the present study design. These include the lack of child or parental reported sleep onset and offset times to corroborate those identified through GGIR. Furthermore, whilst the type of day was accounted for, the sample size did not allow us to investigate the associations on weekdays or weekend days separately, nor the influence of when physical activity occurred relative to subsequent sleep. Future studies should consider a compositional approach, which more appropriately accounts for the co-dependency, co-linearity and finite nature of 24-hour behavioural data [42]. Finally, the participants with CF were characterized by relatively mild disease; further investigation of the bidirectional relationship is warranted in a more diverse range of disease severities where greater divergences from healthy children may be evident.

In conclusion, the present study revealed a bidirectional relationship between sleep and sedentary time, irrespective of group. In contrast, whilst there was no relationship between physical activity and the subsequent night's total sleep time in either group, in healthy children, a poorer sleep quality was associated with more time spent in LPA and MVPA and less sedentary time the following day. In those with CF, fewer associations were observed between variations in sleep and physical activity, possibly due to strictly controlled treatment strategies, which limit flexibility and, potentially, opportunities for physical activity. These findings warrant further investigation into the relationship between physical activity/sedentary time and sleep in children with CF and other respiratory diseases to better elucidate the optimal approach to promoting both physical activity and sleep quantity and quality in future interventions.

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Competing Interests

The authors have no competing interests to declare.

Authorship Contributions

MAM and KAM conceived and designed the research. MAM, KAM, DS and MS collected the data which was analysed by MAM, SH and SR. MAM wrote the manuscript which was subsequently read and approved by all authors.

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