ISPAD-JDRF FELLOWSHIP AWARD PROGRESS REPORT

Title: Synergies in Sleep, Software and Diabetes Management (SIESTA)

Subtitle: Characterizing sleep of caregivers of people with type 1 diabetes: a cross-sectional analysis of subjective sleep measures and real-world diabetes data

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1. Introduction

1.1 Background and Relevance

Sleep quality and diabetes management have a complicated, synergistic relationship. Both adults and children with type 1 diabetes have been shown to have shorter measured sleep duration than their peers without the condition[1]. This can translate directly into negative outcomes in diabetes management; short sleep duration, poor sleep quality and reduced light sleep have been associated with higher than ideal HbA1c values[1]. Social jetlag—recurrent circadian rhythm disruption—is also associated with higher Hb1Ac in people with diabetes[2]. Additionally, sleep duration and self-monitored sensor glucose checks are significantly positively correlated, while they are inversely correlated with HbA1c[3].

We can see that less sleep and poorer sleep quality leads to challenges in diabetes management and worse glycemic outcomes, wherein a vicious cycle may continue indefinitely without intervention. Thankfully, there are research groups investigating how improving sleep may influence glycemic outcomes; thus far there have been improvements in sleep regularity and time-in-range, and reductions in glycemic variability for adults with type 1 diabetes following a sleep-specific intervention[4].

While the importance of sleep is being addressed for those living with type 1 diabetes, rarely is that consideration extended to *caregivers* of people with diabetes. Chronic sleep debt—regardless of the presence of a chronic disease like diabetes mellitus—can significantly lower glucose tolerance, and increase nighttime cortisol levels and sympathetic nervous system activity[5]. More worrisome: even a single night of partial sleep deprivation is capable of inducing both central and peripheral insulin resistance[6]. Thus there exists a bilateral relationship between glycemic outcomes of the child and sleep debt of their caregiver; caregiver physical and mental health is at risk, potentially up to the level of developing diabetes themselves.

The OPEN project is one such group that has taken notice of this underrepresented caregivers group within the #WeAreNotWaiting community[7]. In an international survey concerning the use of do-it-yourself artificial pancreas systems (DIYAPS)—now more broadly referred to as automated insulin delivery (AID) systems—the caregiver of a 8-year-old girl living with diabetes for four years had this to say on how AID had impacted their quality of life[8]:

> *"We were waking at 11pm, 2am, 5am, etc. to manually blood glucose check our daughter. We haven't done that in years. I was having seizures from almost 5 years of not sleeping more than a couple hours at [a] time. Now, we all sleep all night."*

Given the risks posed by chronically poor sleep on both developing and worsening symptoms of diabetes[1,5], this is a relevant research topic.

1.2 OPEN Surveys

The aforementioned OPEN project is a consortium concerned with the "Outcomes of Patients' Evidence With Novel, Do-It-Yourself Artificial Pancreas Technology"[7]. DIYAPS/AID combine readily available continuous glucose monitors, insulin pumps, and open-source software to manage insulin dosing in a "closed-loop" where people with diabetes and their caregivers can rely on medical technology to manage their diabetes overnight, optimizing their time-in-range of normoglycemia[9,10]. Both open-source (OS-) and commercial (C-) AID systems exist and are in use by people living with type 1 diabetes, however OPEN is primarily concerned with individuals using open-source systems.

OPEN's latest study recruited adults, children, and caregivers of those living with type 1 diabetes to respond to a series of questionnaires concerning their clinical outcomes and quality of life living with diabetes, and to donate their AID data and more generally medical device data. Of the questionnaires implemented, the Pittsburgh Sleep Quality Index (PSQI) provided insight into participants' subjective experience of their sleep quality within the past two weeks[11]. Adults with T1D using OS-AID reported better sleep outcomes compared to those not using an automated system[12].

Our project titled "Synergies in Sleep, Software and Diabetes Management" (SIESTA) aims to extend analysis of OPEN's survey to parent-child dyads—including their medical device data—and see if a similar pattern of improved subjective sleep holds true for parents of children with diabetes using AID.

1.3 Aims

Our primary aim is to analyze for correlations between real-world night-time sensor glucose values of children with T1D, and subjective sleep quality of their caregivers. This is in pursuit of establishing if improved clinical outcomes in children—mediated by AID—translate to improved sleep quality in caregivers. This

Our secondary aim is to investigate differences in AID system settings between parent-child dyads; if caregivers have better sleep resulting from AID-mediated management of their child's diabetes, are there specific system settings that lead to these positive outcomes?

Finally, our tertiary aim is to commit to an open-source philosophy in the dissemination of our work; this includes standardizing our data analysis protocols and publishing our research results—including data and data processing strategies—open access.

2. Methods

The OPEN Project is a Horizon 2020-funded Research and Innovation Staff Exchange (RISE) that was established to investigate—and share with the public—outcomes in patient evidence of open-source automated insulin delivery system use. Unfortunately, many commercial manufacturers do not allow users full access to their system data (basal rates, carb corrections, temporary basals, etc.), making meaningful analysis of commercial-AID (C-AID) data impossible. As such, all data donated to the OPEN project concerning AID systems is from open-source systems only.

2.1 Data Structure

2.1.1 Survey Data

OPEN ran two surveys during which participants pseudonymously donated medical device data and responded to survey questionnaires; these were internally titled the "Big OPEN Survey" and "OPEN Light", with the former being a general survey for people with diabetes both using and not using OS-AID, and the latter specifically recruiting those who were willing to involve their personal healthcare providers (HCPs) as clinical validators of their self-reported clinical outcomes.

In the Big OPEN Survey, all questionnaires were responded to on a voluntary basis—study participants were thus counted as having responded to at least the first questionnaire concerning baseline demographics. The following table shows a breakdown of the various participant groups for this cohort.

	Total (–Dropouts)				
Big OPEN	Adults	Caregivers	Partners	Teenagers	Totals (dropouts removed)
Users	586 (–66)	132 (–9)	64 (–13)	3 (–1)	696
Non-users	201 (–28)	56 (–4)	10 (–1)	0 (–0)	234
BIG OPEN Total completed at least baseline demographics:					**930**

Table 1: table detailing the breakdown of participant subgroups from the Big OPEN survey, including both total number of "participants" (those who initiated the survey) and dropouts (those who did not complete at least the first questionnaire).

Participants in Big OPEN had the opportunity to respond to the Pittsburgh Sleep Quality Index (PSQI), a questionnaire assessing individuals' subjective sleep quality within the previous two weeks[11]. After responding to a series of questions, scores are calculated from the aggregate responses and scaled from 0–21; those scoring up to a 5 are considered as having good sleep quality, whereas those above have increasingly severe instances of sleep disturbances resulting in poor sleep quality[13]. In the case of parent-child dyads, parents responded to the PSQI concerning their own sleep quality, whereas any donated medical device data was from their children with T1D. Individuals from this cohort who completed both the PSQI and donated medical device data will be included in our assessment of parent-child dyad sleep quality.

In OPEN Light participants were recruited to again respond to a series of questionnaires and donate data, but with a streamlined questionnaire list focusing more on dynamics and interactions with the healthcare providers (HCPs). Partners of people with T1D and teenagers living with T1D were ineligible from participating in this survey. As shown in the following table, fewer individuals participants in this survey compared to the Big OPEN Survey, which is similarly reflected in how many more individuals from this cohort may have donated medical device data to our online repository.

	Total (–Dropouts)				
OPEN Light	Adults	Caregivers	Partners	Teenagers	Totals (dropouts removed)
Users	105 (–11)	12 (–1)	N/A	N/A	105
Non-users	39 (–7)	8 (–3)	N/A	N/A	37
OPEN Light Total completed at least baseline demographics:					**142**

Table 2: table showing participants and dropouts from the OPEN Light HCP-focused survey. Participants and dropouts are defined the same as for the Big OPEN survey.

As OPEN Light participants did not complete the PSQI, they are unfortunately not eligible to be included in the analysis of parent-child dyad sleep. However, for those from OPEN Light that did donate medical device data, their contributions will be considered in identifying which system settings contribute to attaining normoglycemia.

Survey data were recorded using REDCap and exported as .csv files[14].

2.1.2 Medical Device Data

Medical device data were donated to the Open Humans open-source data repository[15]. Participants uploaded their data using either Nightscout (NS) or AndroidAPS (AAPS), which use different file system hierarchies for organizing AID data.

Nightscout segregates data into four distinct file types: Profile (user-defined variables for visualizing basal rates), Entries (sensor glucose readings recorded every five minutes), DeviceStatus (insulin pump information, glucose predictions, etc.) and Treatments (user-entered log info for meal announcements, carbohydrate corrections, insulin boli, injuection site changes, temporary basal rates, etc.)[16,17]. All data for a single participant is usually collected in single folders of each data type but may be split into multiple folders if participants have exceedingly large amounts of data.

AndroidAPS also segregates data based on type; these are ApplicationInfo, DeviceInfo, DisplayInfo, GlucoseValues and UploadInfo. However, it continuously splits the data into chunks, producing many files of the same file type. For example: while an NS user may only have four total files (one of each file type), AAPS users will have hundreds of files for each file type that have to be "stitched" back together when preparing the dataset for analysis[18].

2.2 Data Pre-processing

Survey data from REDCap does not require an extensive pre-processing methodology; REDCap natively exports data subsets as .csv files with pre-determined parameters (participant subgroups, specific questionnaires, etc.), so most data manipulation can be done within the graphical user interface before export.

Pre-processing of device data from Open Humans is a laborious process due to the differences between the two uploaders used. This is in addition to the fact that this is a donated "real-world" dataset, where participants may have uploaded incomplete or corrupted historical data. Our group is actively contributing to the existing OPEN project repository developing data tools—the "Open Humans Data Tools"—for working with data from Open Humans[19].

3. Current status of first six months (January–June 2023)

Ethical clearance was obtained for working with our dataset from the Charité Ethikkommision with the corresponding application number EA2/206/21.

In total 727 participants responded fully to the PSQI, including 129 caregivers. A further breakdown of their responses is included in a table below.

PSQI	Adults	Caregivers	Total
Users ≤5	284	54	338
Users >5	169	39	208
Non-users ≤5	49	10	59
Non-users >5	96	26	122
Total	598	129	727

Table 3: breakdown of participant results to the Pittsburgh Sleep Quality Index as part of the Big OPEN Survey. Questionnaire aggregate results equal to or below 5 (≤5) are considered "good sleep quality" and results above 5 (>5) are considered "poor sleep quality". Values indicate the number of participants within a participant sub-group who received the indicated aggregate score.

The OPEN project officially closed donation to its repository on Open Humans in April 2023. In total we were able to recruit 147 participants to the data donation platform, of which 134 donated medical device data. The latest version of the dataset was downloaded from Open Humans on 23 May 2023, following updates to Open Humans' API—updates to the API were necessary due to the size of our dataset compared to other Open Humans projects. We are actively working to match PSQI responses to medical device datasets using OPEN's bespoke data management platform[20].

We have continued development of the Open Humans Data Tools scripts, specifically the latest fork connected to our team within the Institute of Medical Informatics. Previous versions of our pre- and post-processing pipeline for working with Open Humans data only worked with each of the data types in isolation; we had not developed a way of aggregating the myriad variables in a meaningful way.

	A	B	C
1	memberID	data_file	
2	12345678	profile.json.gz	
3	12345678	entries.json.gz	
4	12345678	treatments.json.gz	
5	12345678	devicestatus.json.gz	
6	22345678	profile.json.gz	
7	22345678	entries.json.gz	
8	22345678	treatments.json.gz	
9	22345678	devicestatus.json.gz	
10	32345678	profile.json.gz	

Figure 1: The "date_file" column contains variables for all file types including Entries, Profile, DeviceStatus, and Treatments for Nightscout, and ApplicationInfo, DeviceInfo, DisplayInfo, GlucoseValues and UploadInfo for AndroidAPS. By iterating variable names within a single column, we can contain multiple data types within a much smaller footprint, while standardising timestamp information, values associated with each variable, and containing the units for each value in an adjacent column. This vastly reduces the number of separate "master" spreadsheets needed for containing participant data and allows for more easy data manipulation across file types.

With our new format, we are able to aggregate data from all file types for all participants in a single spreadsheet, allowing us to more easily unify timestamps and provide a more standardised database for future analyses to work from. Script development began in January 2023 and is still ongoing[21].

4. Next steps

Our immediate next steps are to complete our version of the updated Open Humans Data Tools; the final scripts should process and output the dataset in a way that is compliant with HL7 FHIR standards[22]. We will then analyze for correlations between child AID system data with parent responses to the Pittsburgh Sleep Quality Index and investigate which medical device settings are most frequently associated with positive sleep outcomes. Data analysis will be carried out using R Studio, with data visualization using both the Tidyverse and ggplot2 packages[23]. All analysis scripts will be stored using GitHub.

Additionally, we intend to investigate causal inference methods to establish a causal relationship between child diabetes outcomes and parent sleep. Assad et al. address various methods of causal discovery for time series data[24], as do Haufe et al.[25]. Based on the

complexity inherent in multivariate time series analysis—especially when applied to causal frameworks—we will continue our literature search to see if this is a viable path forward.

Finally, we will assess the OPEN dataset with how it adheres to FHIR standards before and after processing. This will lead into establishing a truly “final” iteration with necessary documentation for other researchers to work with the dataset now that the OPEN project has reached its conclusion.

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