Aus der
Charité – Universitätsmedizin Berlin
CharitéCentrum 1 für für Human- und Gesundheitswissenschaften
Institut für Medizinische Informatik
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Habilitationsschrift

The Patient-Led Healthcare Revolution: A Hitchhiker's Guide to Diabetes Technology

zur Erlangung der Lehrbefähigung
für das Fach Medizinische Informatik

vorgelegt dem Fakultätsrat der Medizinischen Fakultät
Charité – Universitätsmedizin Berlin

von

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Eingereicht:	Juli 2022
Dekan:	Prof. Dr. Joachim Spranger
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“We are stuck with technology,
when all we really want is just stuff that works.”

Douglas Adams

“Never doubt that a small group of thoughtful, committed citizens can change the world;
indeed, it's the only thing that ever has.”

Margaret Mead

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Abbreviations

ADA	American Diabetes Association
AID	automated insulin delivery
CGM	continuous glucose monitoring
DKA	diabetic ketoacidosis
FDA	Food and Drug Administration
GDP	gross domestic product
GI	glycemic index
HbA1c	hemoglobin A1c
HCPs	healthcare professionals
ISF	insulin sensitivity factor
ISPAD	International Society for Pediatric and Adolescent Diabetes
PwD	people with diabetes
RCT	randomized controlled trial
T1D	type 1 diabetes
US	United States
WHO	World Health Organization

1. Introduction

Traditionally, patients have been considered passive recipients of therapies provided to them. However, under the mantra *"Nothing About Us Without Us"*, there is increasing demand for the patient voice to be included and for patients to be represented as stakeholders in the development of services, products, policies, and educational resources alike. The slogan (Latin: *"Nihil de nobis, sine nobis"*) has its roots in Central European traditions, and over time became a byword for democratic norms. The English term became popular through patient advocates of the disability rights movement in the 1990ies to promote freedom from discrimination, equal opportunities, safety, and accessibility in various aspects of life. [1] Since then, it has moved to other advocacy and interest groups to promote decision-making that includes and welcomes people with lived and learned experiences. [2]

A primary example of patient-led innovation and democratization in healthcare is the *#WeAreNotWaiting* movement, driven by people impacted by diabetes who turn their existing medical devices into so-called "do-it-yourself" or "open-source" artificial pancreas systems for automated, closed-loop insulin delivery. [3,4]

1.1. Managing Type 1 Diabetes: Past and Present

Diabetes mellitus is a chronic health condition characterized by dysregulated production or secretion of, or response to, the peptide hormone insulin. About 537 million adults and 1.2 million children live with diabetes worldwide, and incidences of type 1 and type 2 diabetes continue to increase. [5] Type 1 diabetes (T1D) occurs as an autoimmune-induced loss of pancreatic insulin-producing beta cells, whereby little to no insulin is produced to decrease blood glucose.

The tools and educational resources to manage T1D have continuously evolved over the years: From insulin derived from animals to human and analog insulin, from injections with syringes to pens, smartpens, and continuous administration via insulin pumps; from testing urine samples to capillary blood glucose measurements at home and continuous glucose monitoring (CGM) sensor systems; and from rigid nutrition protocols to flexible therapy plans that take biopsychosocial aspects of patients and their families into consideration. [6–15]

For people living with T1D, insulin administration via subcutaneous injections multiple times per day or continuous delivery via insulin pumps is the primary treatment to maintain glucose levels within the recommended range. Today's insulin therapy management plans usually include the administration of basal and bolus insulins. Basal insulin, typically a long-acting agent injected once or twice per day (e.g. degludec, detemir, neutral protamine hagedorn), or, in insulin pump therapy, a combination of fast-acting insulin doses as different "basal rates" throughout the day, accommodates a person's endogenous glucose production. This endogenous supply derives from gluconeogenesis, where non-carbohydrate substrates are metabolized to glucose, and glycogenolysis, where glucose is generated from the breakdown of glycogen. In addition to basal insulin, short-acting insulin (e.g. aspart, lispro, glulisine, or faster-acting formulas with additives) is administered several times daily to cover the nutritional intake of carbohydrates and include additional correction doses if glucose levels are above target. [7,16]

People with diabetes (PwD) and, for children and adolescents, their caregivers, have to manage their condition day and night. Glycemic levels need to be monitored closely, either via multiple capillary measurements per day or continuous interstitial glucose monitoring via a sensor, to avoid hypo- and hyperglycemia and reduce the risk of developing long-term complications. [17,18] Therefore, comprehensive diabetes education and psychosocial support as parts of diabetes care are just as essential as insulin administration. Empowered by knowledge and experience, PwD and their caregivers learn to “master” all aspects of their own therapy by self-monitoring and adjusting insulin doses according to their day-to-day life. [19,20]

1.2. Living with Type 1 Diabetes as a Life-long Challenge

Despite significant advances in care, pharmaceuticals, and technological developments, T1D remains a challenging chronic condition that impacts life expectancy and diminishes quality of life. [21–24] Only some people with T1D achieve long-term parameter outcomes as recommended by therapeutic guidelines of the International Society for Pediatric and Adolescent Diabetes (ISPAD) and American Diabetes Association (ADA). [25–29] The complexity of diabetes self-management imposes a high cognitive load and can cause distress in daily life, with many PwD reporting disrupted sleep and approximately 40% of them showing symptoms of anxiety or depression. [30–33]

Although diabetes affects people of all ages and genders, there is precedent that people of different ages and genders are affected differently. Managing diabetes is particularly challenging during childhood. Day-to-day tasks often involve the entire family. Children show variability in insulin sensitivity related to physical growth and sexual maturation which require frequent adjustments in insulin dosing. [34,35] With the dynamic physical activity and nutritional intake of young children, their glycemic levels can fluctuate rapidly. [35,36] The transition of responsibility in diabetes management from caregivers to children and their increasing independence during adolescence can often further complicate this difficult dynamic. Adolescents and young adults with diabetes frequently struggle to meet the recommended glycemic targets and are particularly vulnerable to acute complications such as severe hypoglycemia and diabetic ketoacidosis (DKA). [28,37] The psychological burden and potential health implications but also economic impact on caregivers cannot be understated. They frequently report lack of sleep, having quit or changed careers, or reduced work hours to help care for their children and loved ones. [35,38,39] Thus, psychosocial support and individualized treatments play an important role in diabetes care for children with diabetes and their families. [25]

For girls and women, managing diabetes can be particularly challenging throughout different phases of life, particularly during puberty, pregnancy, and menopause. [40–45] Several studies have shown that women with type 1 and type 2 diabetes are less likely to reach targets in hemoglobin A1c (HbA1c), blood pressure, and low-density lipoprotein cholesterol as recommended by therapeutic guidelines [26], compared with men. [45–47]

1.3. Closing the Loop: The Aim for a "Technological Cure"

Technological approaches aim to diminish the decision-making complexity in diabetes self-management and alleviate the cognitive and emotional burden on people with diabetes (PwD), simultaneously improving glycemic levels and variability. As the most recent technological advance in diabetes care, automated insulin delivery (AID) systems, also called "closed-loop insulin delivery systems" or "artificial pancreas", have been developed. These are biotechnological tools that mimic insulin secretion of the human pancreas. As early as 2009 [48–50], stakeholders were conceptualizing the development and engineering, regulation, and clinical trials to eventually bring these devices to commercial market.

In AID systems, insulin dosing is automated based on interstitial glucose levels in a closed-loop system consisting of a (CGM) sensor, an insulin pump for subcutaneous insulin delivery, and a control algorithm operated by a smartphone or small microcontroller. The algorithm uses sensor readings and user-provided data to predict future glucose levels and adjusts insulin dosing accordingly in short intervals, e.g., every five minutes (**Fig. 1**). Current commercially developed AID systems still require the user to deliver bolus insulin for meals, though "fully-closed loop" systems are being developed and tested that may eliminate this task. [51]

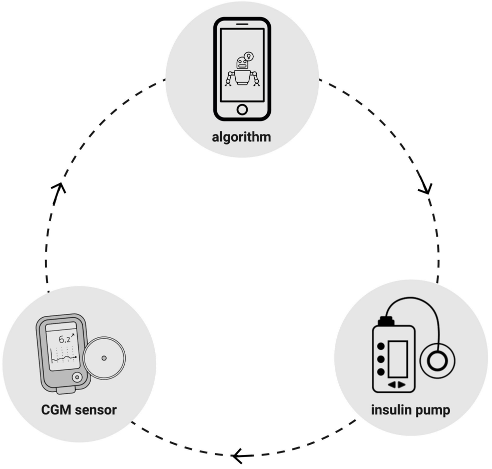

Fig. 1: Components of an automated insulin delivery system. *Image created by the author.*

In current AID systems, three different families of control algorithms are being used to automate dosing decisions:

- **Predictive control** algorithms (e.g., model predictive control) predict the effect of control measures on future outputs, with optimizations performed to select the best set of current and control moves (adaption of insulin infusion) to satisfy the objective (glucose target). Minimum and maximum (constraints) infusion rates can be enforced. The prediction horizon is often larger than the control horizon. [52] Many current AID systems employ predictive control algorithms, including open-source (e.g., Loop [53], FreeAPS [54]) and commercial systems (e.g., Tandem Control IQ [55], OmniPod 5 [56]).
- **Proportional–integral–derivative** control algorithms (e.g., Medtronic 670G SmartGuard [57]) continuously calculate an error value as the difference between set-point and measured process variable and applies a correction based on proportional, integral, and derivative terms.[58]
- **Fuzzy logic** algorithms (e.g., Medtronic's advanced 670G 4.0 algorithm[59]) are based on "degrees of truth" between 0 and 1, rather than a binary "true or false" (0 or 1) logic, and use current glucose level, rate of change, and acceleration to calculate insulin dosage.[60,61]

While the use of CGM sensors and insulin pumps can already significantly improve clinical and quality of life (QoL) outcomes compared to multiple daily injections [62,63], AID systems promise to optimize diabetes management even further. In addition to improvements in clinical outcomes [64–70], such as increased time-in-range (TIR) and lower HbA1c levels, individuals testing AID systems in clinical trials also reported reduced anxiety [71–76], improved quality of sleep [71,74,75,77,78], reduced burden of managing diabetes and distress [73,74,76,79,80], and less fear of hypoglycemia. [71–74,81,82]

Despite significant research and commercial interest, only a limited number of AID systems are currently licensed for use, their regional availability varies, and the parameters of their functionality are limited by regulatory authorities. AID systems are, therefore, not universally available, accessible, affordable, or individually suitable for all PwD. [83–88]

1.4. The Case Study of #WeAreNotWaiting

Given the limitations in availability and access to AID systems, a community of PwD and their families, united under the hashtag *#WeAreNotWaiting*, have created new tools and systems to help PwD better utilize their devices and data. By 2015, the first open-source AID system called "OpenAPS" [3,89,90] was developed by Dana Lewis, a person living with T1D. What initially began as a basic "hack" by users of CGM sensor systems to increase the volume of alarms and enable remote monitoring, has been collaboratively further developed by volunteers of the diabetes online community into open-source AID systems with predictive algorithms, wide device interoperability, and implementation of personalized features.[3,91] Source code and documentation for these systems are shared openly with other people with diabetes and the general public online. [53,54,92–97]

Currently, different open-source AID systems are available, which are based on either the Loop [98] or the OpenAPS [89] algorithm. OpenAPS, as the earliest version of open-source AID, utilizes Raspberry Pi or Intel Edison devices as a micro-controller[93] (**Fig. 2**). AndroidAPS [96] and FreeAPS X [54] use the same codebase as OpenAPS, where either Android (for AndroidAPS) or Apple phones (for FreeAPS X) are used as controllers [99]. Loop and FreeAPS [97] use a different codebase and run on Apple phones (**Fig. 3 and 4**). Depending on the setup, additional hardware may be required for wireless Bluetooth and/or radio signal communication between controller and insulin pump (**Fig. 3**). [100] "Looping" is the generic term used to describe when an individual is using an open-source AID system to manage their diabetes through open-source AID, which works as a "closed-loop" system.

Despite open-source AID systems not being approved by regulatory bodies, the *#WeAreNotWaiting* community is unwilling to settle for the current efforts of medical device manufacturers and is pushing diabetes research forward through patient-driven solutions. Users who build and maintain their individual open-source AID systems use them at their own risk. With code and documentation freely accessible online, the use of such systems continues to increase globally, with an estimated number of well over ten thousand individuals currently using them, including children and adolescents, where caregivers build and maintain these systems on their behalf. [84]

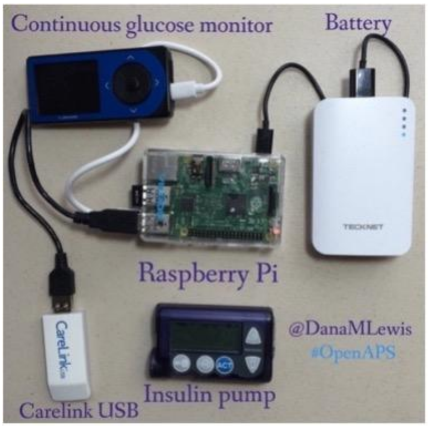

Fig. 2: OpenAPS running on a Raspberry Pi, a Dexcom CGM sensor and out-of-warranty Medtronic insulin pump. First setup in 2015. *Image courtesy of Dana Lewis.* [89]

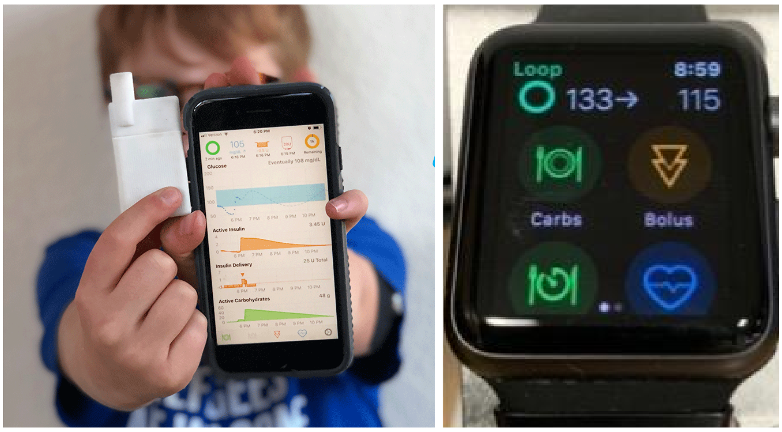

Fig. 3 and 4: "Loop" app running on an iPhone and Apple Watch; "RileyLink" DIY hardware tool (left) communicates with the pump. *Image courtesy of the Facebook peer support group "Looped".* [101]

1.5. Decision Logic of Predictive Control Algorithms

Predictive control algorithms for insulin dosing, such as the Loop and the OpenAPS algorithms, adjust insulin delivery based on a predicted glycemic value. Their logic is similar to the rationale a person with diabetes would apply to make manual dosing decisions. [102] Every five minutes, the algorithm generates a new prediction based on the most recent CGM data and adjusts temporary basal rates, microboli (if enabled), and bolus recommendations accordingly. The Loop algorithm calculates glucose predictions based on insulin activity in the body, amount of absorbed carbohydrates from nutritional intake, retrospective correction, and glucose momentum [103]:

$$BG[t] = Insulin[t] + Carb[t] + RetrospectiveCorrection[t] + Momentum[t]$$

Open-source AID systems enable the user to choose between different types of insulin activity models. The models for rapid-acting insulin for children and adults and faster-acting insulin aspart assume an active insulin time of 6 hours with different peak times, whilst the duration is customizable in the Walsh model. In all models, the remaining active insulin ("insulin on board") is calculated based on dosing data pulled from the insulin pump and an exponential decay curve. [103] The glucose-lowering effect of a single unit of insulin within that timeframe can be specified by the user as the insulin sensitivity factor (ISF). For each administered insulin dose, the Loop algorithm calculates the expected decrease in glucose for each five-minute period of the insulin activity duration.

A multitude of factors, such as physical activity level, stress, medication, hormones, comorbidities, and acute illness, may influence and continuously change an individual's insulin needs, which is why many users create different profiles or regularly update their settings, e.g., by reviewing their own data and/or during endocrinology clinic visits. [103]

The intake of carbohydrates is expected to raise blood glucose, although their absorption and effect duration depends on the complexity and type of carbohydrates. Whilst carbohydrates with a high glycemic index (GI), such as candy or fruit, are expected to raise blood glucose quickly and steeply, the effect of complex carbohydrates with lower GI, such as multigrain or dairy products, will occur over an extended period. Loop and FreeAPS enable the user to indicate the estimated amount of carbohydrates as well as the estimated duration of their absorption time and calculate their absorption rate based on this information ("linear carbohydrate absorption"). The linear model is modulated by "dynamic carbohydrate absorption" based on recently observed changes in glycemic levels.

The retrospective correction enables the Loop algorithm to counter effects other than active insulin and carbohydrates by comparing predicted vs. observed changes in glycemic levels. Observing its own forecast error of the past 30 minutes, the algorithm estimates their magnitude and includes this difference in further predictions. [103] The glucose momentum effect includes a prediction based on the delta in glucose of the past 15 minutes, assuming that the next glycemic level will further follow this trend. Each of the individual factors and their combined effect are illustrated in **Figure 5**.

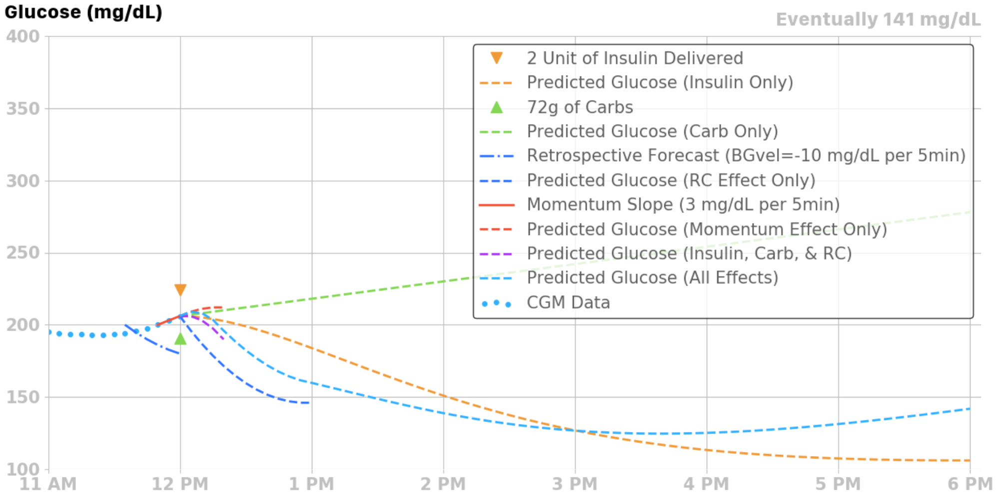

Fig. 5: Glucose predictions of the "Loop" predictive control algorithm based on insulin, carbohydrates, retrospective forecast, and glucose momentum. *Source: loopdocs.org* [103]

Scheduled basal rates that provide an estimate of a user's insulin needs without meal intake are used by the algorithm as a baseline for automated dosing decisions. The algorithm applies relative changes to these doses and applies them either as temporary basal rates or as "microboli" (small amounts of insulin administered as one or multiple bolus doses). Basal rates can either be temporarily decreased, increased, suspended or resumed with their pre-programmed amount. [104]

Dosing decisions are based on the glucose delta, the user's ISF, predicted glucose, and correction target [104]:

$$dose = \frac{delta}{ISF} = \frac{eventual\,BG - correction\,target}{ISF}$$

1.6. Safety Mechanisms of AID Systems

All AID systems, open-source and commercial, have several safety mechanisms in place to avoid potential harm to the user. These include suspension of insulin delivery if glycemic levels are predicted to be below a certain threshold to avoid hypoglycemia [102,104], and maximum delivery limits of basal rate increasements per hour and maximum bolus amounts. [105,106] All current AID systems default to open-loop whenever loss of CGM data occurs. All current systems enable the user to switch off automation and revert to pre-programmed settings in open-loop with no automated dosing features. This can be considered under circumstances with lower or higher insulin needs, e.g., during illness, steroid use, if ketones are present, before, during and after exercise, as the AID system may not be able to respond and readjust quickly enough. [107] When operating in open-loop with CGM signal, some systems (e.g., Medtronic 670G) still provide predictive low glucose suspend features and suspend insulin delivery automatically in case of predicted sensor glucose below a certain threshold, whilst others operate fully manual as “traditional” insulin pumps with no hypoglycemia protection.

In addition, the importance of baseline settings that truly reflect a user’s physiology cannot be understated, as inaccurate therapy parameters may lead to under- or over-delivery of insulin by the dosing algorithm. It is recommended to test and iterate settings in open-loop before automation is enabled. [108,109]

1.7. Addressing the Challenge: the OPEN Project

Social and technical trends are increasingly empowering communities of people with chronic conditions to innovate medical devices and treatments through co-creation and peer support to address their unmet healthcare needs, as is the case with *#WeAreNotWaiting*. These innovations sit outside of clinical trials and the usual commercial and regulatory processes for medical device development and therefore create dilemmas, but also opportunities, for patients and caregivers, healthcare professionals (HCPs) and providers, regulators, and industry. Early on in the development of open-source AID, anecdotal evidence and self-reports from users (**Fig. 6**) have been shared and suggested not only improvements in glycemic outcomes, such as an increase in TIR and decrease in HbA1c levels, lower risk for hypo- and hyperglycemia but also better QoL and sleep. However, it was estimated that there are around 15 million hours of real-world data of open-source AID users, much of which was not fully analyzed and explored by academic research. The rich vein of expertise, knowledge, and experience that existed within the *#WeAreNotWaiting* community was untapped by stakeholders other than the diabetes online community. Further, there were no studies on the impact of using open-source AID on caregivers, partners, and families of PwD.

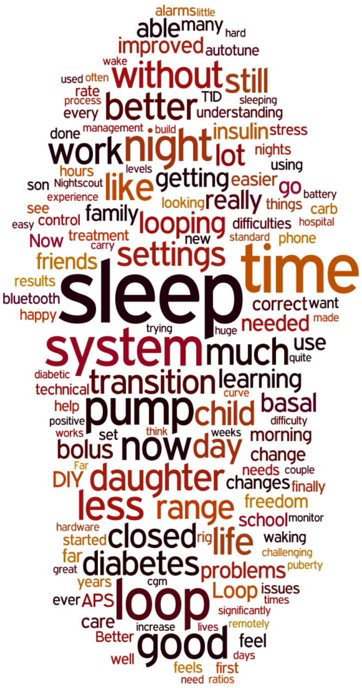

Fig. 6: “Wordle” generated from narratives of caregivers of children using open-source AID. *Image created by the author.*

To address this evidence gap, an international and interdisciplinary group of researchers living with T1D and innovators of the diabetes online community have co-founded the OPEN project [110], which was funded by the European Commission's Horizon 2020 program, the Wellcome Trust, and the Berlin Institute of Health (BIH). Recognizing the need for academia and the patient community to engage on eye level, OPEN has been instrumental in bringing a wide spectrum of stakeholders together and translating experienced-based evidence of the community to academia and industry, and vice versa.

Three years into the project, we have created open-science tools and infrastructure [111,112] (**Figure 7**) and evaluated data regarding self-reported clinical outcomes, QoL and sleep benefits, motivations, and lived experiences of open-source AID users. [35,40,83,113–119] Further, we identified disparities in the access to diabetes technology, the barriers to uptake for aspiring open-source AID users as well as possible solutions to enable their wider diffusion. Based on these insights, we created an international consensus statement to provide guidance for HCPs who seek to support PwD that choose open-source AID. [84]

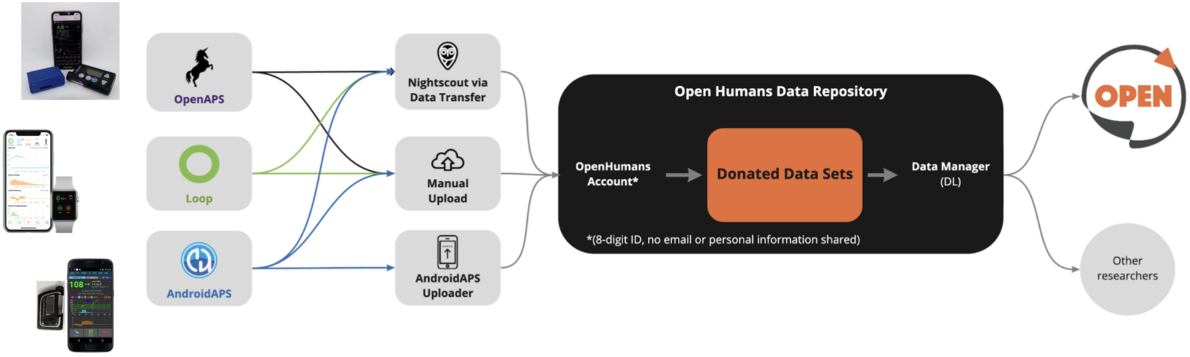

Fig. 7: Open-science infrastructure of the OPEN project for anonymous participation and device data donation to the Open Humans repository. *Image created by the author.* [111]

1.8. Perspectives and Roles

In my scientific work, I combine the perspective of a physician and researcher at Charité and BIH Digital Clinician Scientist with longstanding expertise in diabetes advocacy and strategic consultancy.

As a "doctor/patient hybrid", living with T1D myself for 20+ years, I am passionate about empowering others and strive to raise awareness about innovations emerging from the patient community. As co-chair of the not-for-profit organization "Hacking Health Berlin", I am actively promoting a shift of paradigms in healthcare towards patient-centricity, e.g., through interdisciplinary hackathons. As Head of Medical of Dedoc Labs, a strategic consultancy by, with, and for PwD, I advise and mentor a variety of emerging and leading companies in the field of diabetes technology. My diabetes advocacy activities with several not-for-profit organizations (e.g., as a Young Leader in Diabetes of the International Diabetes Federation, and Global Advocate of T1International) over the past years combined lived experience with learned experience, which complimented the skills I have gained during my residency training in Pediatrics and as a physician in refugee and migrant health in 2015/16.

Over the years, I have listened to the many individual stories and perspectives of PwD around the world, which enabled me to understand the clinical and psychosocial but also economic and cultural aspects of living with diabetes in a variety of countries and healthcare settings. In addition, I had the chance to work with international research teams as a co-lead of OPEN and ISPAD member, and recently as a visiting scholar at the Stanford Diabetes Research Center.

Each of these different professional but also personal perspectives have enhanced my understanding of diabetes as a challenge for the individual but also for our healthcare systems and society as a whole. Therefore, my work aims to change healthcare towards the goal of making personalized and state-of-the-art treatment available to everyone, and redesign the way we support, research, and communicate with and about PwD–an endeavor that can only be achieved collaboratively, with patients as the driving force, healthcare professionals as their advocates and supporters, real-world data as a tool and the spirit of the *#WeAreNotWaiting* community in mind.

1.9. Thesis Aims and Objectives

This thesis provides an overview of recent trends in diabetes technology with special emphasis on open-source, patient-driven approaches, user experience, availability, and access.

First, it presents some of the main research outcomes of the OPEN project with respect to the feasibility of its open-science infrastructure for self-report and real-world data donation, and the consecutive analyses of clinical outcomes, motivations, and lived experiences that were reported by open-source AID users via these tools.

Second, it explores gender-related differences in user experiences with open-source AID based on a qualitative study on a group of women of the *#WeAreNotWaiting* community.

Next, it showcases the professional guidance that has been established based on the available literature and expert consensus.

Finally, it covers a study conducted by the not-for-profit organization T1International in partnership with the OPEN project, with findings on global health disparities in people living with T1D with respect to access and cost of different diabetes treatments, as well as underuse and rationing of insulin and supplies.

2. Original Research

2.1. Open-science Infrastructure for Self-report and Device Data Donation: A Feasibility Analysis.

Most of the data leveraged in OPEN's research relies on an open-science infrastructure that we created with the aim to enable anonymous data sharing and self-report for open-source AID users, the option to make research data openly available to other researchers and to provide the option of re-using this infrastructure and data in follow-up projects. In this feasibility evaluation, we addressed several aspects of open-source AID systems, including challenges related to data management and security across multiple disparate web-based platforms and challenges related to implementing follow-up studies. The following text is reproduced in full from the abstract of the publication:

Cooper D, Ubben T, Knoll C, Ballhausen H, O'Donnell S, **Braune K**, Lewis D. Open-source Web Portal for Managing Self-reported Data and Real-world Data Donation in Diabetes Research: Platform Feasibility Study. *JMIR Diabetes.* 2022 Mar 31;7(1):e33213. https://doi.org/10.2196/33213

In a mixed-methods study (Protocol: doi.org/10.2196/15368; international registered report identifier: PRR1-10.2196/15368), we collected survey responses and anonymized diabetes data donated by participants-of many roles, including adults and children with diabetes and their partners or caregivers. The infrastructure we created helped us manage both front-end participant interactions and back-end data management through a web portal (called the "Gateway"). Participant survey data from electronic data capture (REDCap) and personal device data aggregation on the Open Humans repository were pseudonymously and securely linked and stored within a custom-built database that used both open-source and commercial software. Participants were later given the option to include their healthcare providers in the study to validate their self-reported health data; the database architecture was designed specifically with this kind of extensibility in mind. At the time of the evaluation in 2021, 1,052 visitors had accessed the study landing page of the OPEN project, and 930 of them participated in the study and completed at least one questionnaire. After the implementation of HCP validation of clinical outcomes of the study, an additional 164 individuals visited the landing page, with 142 completing at least one questionnaire. Of the optional study elements, 7 participant-HCP dyads participated in the survey, and 97 participants who completed the survey donated their anonymized medical device data. The uploading methods permitted users to enable real-time data uploads that will continue well beyond OPEN's completion date in 2022. At all times, participants have control over who has access to the data they donate.

In conclusion, this study demonstrated the feasibility of custom software solutions in addressing complex study designs. The gateway was a viable tool for us to conduct research while maintaining compliance with data regulations. We formalized a system of automated data matching between multiple data sets. Scalability of the modular platform was demonstrated with the later addition of self-reported data validation. The underlying source code of the gateway portal has been made available open-source [120], and all cleaned and de-identified data, complete with pre- and post-processing paradigms, can be leveraged by other research groups.

Original Paper

Open-source Web Portal for Managing Self-reported Data and Real-world Data Donation in Diabetes Research: Platform Feasibility Study

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Abstract

Background: People with diabetes and their support networks have developed open-source automated insulin delivery systems to help manage their diabetes therapy, as well as to improve their quality of life and glycemic outcomes. Under the hashtag *#WeAreNotWaiting*, a wealth of knowledge and real-world data have been generated by users of these systems but have been left largely untapped by research; opportunities for such multimodal studies remain open.

Objective: We aimed to evaluate the feasibility of several aspects of open-source automated insulin delivery systems including challenges related to data management and security across multiple disparate web-based platforms and challenges related to implementing follow-up studies.

Methods: We developed a mixed methods study to collect questionnaire responses and anonymized diabetes data donated by participants—which included adults and children with diabetes and their partners or caregivers recruited through multiple diabetes online communities. We managed both front-end participant interactions and back-end data management with our web portal (called *the Gateway*). Participant questionnaire data from electronic data capture (REDCap) and personal device data aggregation (Open Humans) platforms were pseudonymously and securely linked and stored within a custom-built database that used both open-source and commercial software. Participants were later given the option to include their health care providers in the study to validate their questionnaire responses; the database architecture was designed specifically with this kind of extensibility in mind.

Results: Of 1052 visitors to the study landing page, 930 participated and completed at least one questionnaire. After the implementation of health care professional validation of self-reported clinical outcomes to the study, an additional 164 individuals visited the landing page, with 142 completing at least one questionnaire. Of the optional study elements, 7 participant–health care professional dyads participated in the survey, and 97 participants who completed the survey donated their anonymized medical device data.

Conclusions: The platform was accessible to participants while maintaining compliance with data regulations. The Gateway formalized a system of automated data matching between multiple data sets, which was a major benefit to researchers. Scalability of the platform was demonstrated with the later addition of self-reported data validation. This study demonstrated the feasibility of custom software solutions in addressing complex study designs. The Gateway portal code has been made available open-source and can be leveraged by other research groups.

(JMIR Diabetes 2022;7(1):e33213) doi: 10.2196/33213

KEYWORDS

diabetes; type 1 diabetes; automated insulin delivery; diabetes technology; open-source; patient-reported outcomes; real-world data; research methods; mixed methods; insulin; digital health; web portal

Introduction

Under the hashtag *#WeAreNotWaiting*, people with diabetes and their families have come together to develop and support the use of open-source automated insulin delivery systems (also called do-it-yourself artificial pancreas systems). With insulin pumps and data from continuous glucose monitoring, automated insulin delivery systems are able to automate insulin dosing in response to glucose levels through algorithmic prediction [1-4]. With an estimated >10,000 individuals using open-source automated insulin delivery worldwide, there is a wealth of data produced from these systems in real-world settings [5].

Web-based data repositories, such as Nightscout, allow users to collect, upload, review, analyze, and share data from open-source automated insulin delivery systems with their caregivers and health care teams [6]. Until recently, data uploaded to these sites were rarely used for research, which left an important source of real-world evidence largely untapped. Open-data platforms, such as Open Humans [7], allow users to anonymously donate their data from repository sites for use in research [7-9]. Data from Open Humans have previously been used in research and increasingly to evaluate open-source automated insulin delivery [8].

An international consortium of patient innovators, clinicians, social scientists, computer scientists, and patient advocacy organizations initiated a project called OPEN (Outcomes of Patients' Evidence with Novel, Do-it-Yourself Artificial Pancreas Technology [10,11])) and investigated the *#WeAreNotWaiting* movement and open-source automated insulin delivery use, which led to a web-based survey [12].

It is common practice to use tools such as REDCap for electronic data capture and management in the implementation of web-based surveys. However, it is not possible to achieve required flexibility and user friendliness using such tools alone. The overall aim of this study was to assess the feasibility of developing a platform that would enable participants to share anonymized retrospective diabetes data in addition to completing surveys.

Methods

Study Design

The study design and linkage of multiple elements—including follow-up and satellite projects—is complex. The study concept contained an analysis of real-world diabetes data, and a survey that included questionnaires that collected basic demographic data, self-reported clinical outcomes, and responses to open-ended questions, as well as assessments of quality of life (Pediatric Quality of Life Inventory, World Health Organization-Five Well-Being Index), depression and anxiety (Depression Anxiety Stress Scale), sleep quality (Pittsburgh Sleep Quality Index), problem areas in diabetes (Problem Areas in Diabetes scale), fear of hypoglycemia (Hypoglycemia Fear Survey-II), impact of diabetes (Diabetes Attitudes, Wishes, and Needs), diabetes treatment satisfaction (Diabetes Treatment Satisfaction Questionnaire), diabetes well-being, partner diabetes distress, hesitation around automated insulin delivery systems (DIWHYnot), and the effects of the COVID-19 pandemic on diabetes management and quality of life.

The study included participants who self-identified as an adult or adolescent with diabetes, and caregiver or partner of a person with diabetes. Furthermore, both users and nonusers of open-source automated insulin delivery were included. At a later stage in the study, adult participants were also provided the option to independently validate their self-reported health data and clinical outcomes by their health care professional (endocrinologist, pediatric endocrinologist, diabetes educator or specialist nurse). Thus, the study was made up of 3 major elements: a survey containing questionnaires alone, device data donation on Open Humans, and a linked follow-up study on health care professional–validated health data and clinical outcomes.

Platform Requirements

The nature of this research—a real-world study with human participants—required that data management be compliant with European Union General Data Protection Regulations [13] and that risks related to data sharing for the individual be minimized (pseudonymization, deidentification, informed consent, and right to withdraw). Enabling participants to join follow-up studies without storing their personal information also necessitated a custom solution for pseudonymous data management. Safely and securely managing data from multiple data streams also presented a unique challenge.

Making study participation simple required the development of a web portal for users. Such a web portal needed to also act as a formalized system of automated data matching between multiple data sets. The first objective in creating the platform—the Gateway—was linking questionnaire responses in REDCap to optionally donated device data in Open Humans. The second was for this platform to link data from participants to their partners or health care professionals. The final objective was that the entire process be anonymized and General Data Protection Regulation–compliant.

Front-end Architecture

To users, the Gateway was a landing page (Figure 1) with a simple graphical user interface through which participants selected the profile with the appropriate characteristics (person with diabetes or caregiver of a person with diabetes; user or nonuser of automated insulin delivery) and were provided a unique *Participant ID*. Participants were informed of their rights regarding their survey data and optionally donated diabetes data and could then sign an electronic form if they wished to consent.

Participants responded to a sequence of questionnaires, and upon completion, they were asked if they wished to donate anonymized diabetes data and were provided with a survey link to send to other parties (eg, partners, parents, and health care providers) (Figure 2).

Figure 1. Landing page for the Outcomes of Patients' Evidence with Novel, Do-it-Yourself Artificial Pancreas Technology (OPEN) project.

Welcome to the OPEN project!

Thank you for your interest and willingness to participate in our survey!

OPEN

We are the OPEN project, a European Union-funded international research consortium aiming to study and explore the unique patient innovation of "Do-It-Yourself Artificial Pancreas Systems", or DIYAPS. We are asking **people with diabetes** who are or whose child is using an open-source closed-loop system or who are interested in this technology to help us build evidence on how this technology affects the lives of people with diabetes.

The survey is open again

We have reopened the survey **for new participants**, significantly reducing the number of questionnaires. We now want to focus more on your thoughts about or experiences with DIYAPS.

You can donate your device data, too!

Regardless of if you have participated in our survey last year, or if this is your first time, you still have the option to **anonymously donate your device data** (e.g. from Nightscout) if you have previously registered for a Participant ID. This would **GREATLY HELP** our aim of exploring improvements to the (DIY)APS experience for all, now and in the future.

Further information will be provided on the next pages and here on our website.

Do you already have a Participant ID?

I do not have a Participant ID. →

I already have a Participant ID. →

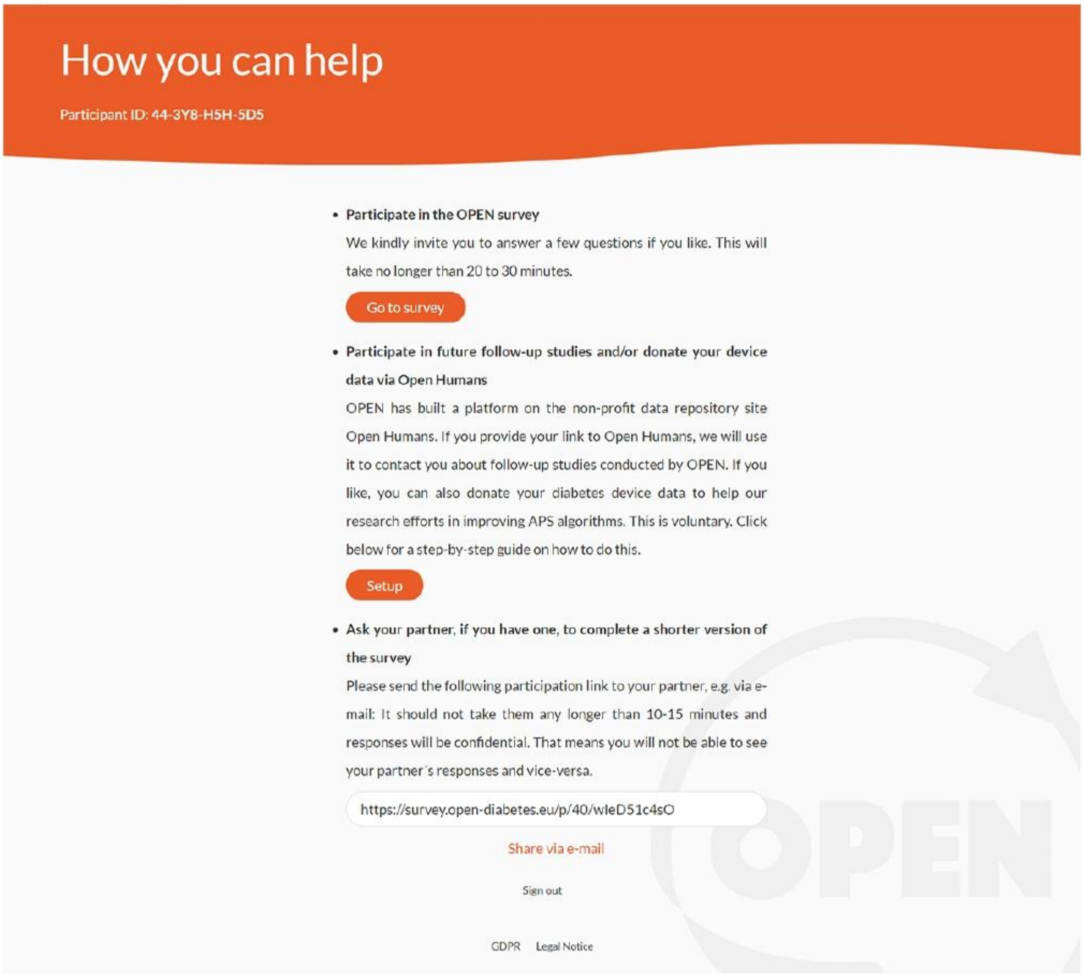
Last but not least: We are very happy to have all of you here! **THANK YOU!**

The OPEN team

This project has received funding from the European Commission's Horizon 2020 Research and Innovation Programme under the Marie Sklodowska-Curie Action Research and Innovation Staff Exchange (RISE) grant agreement number 823902.

GDPR Legal Notice

Figure 2. The Gateway webpage where participants can participate in the survey, donate their medical device data to Open Humans, or ask their partner to participate in the survey.



How you can help

Participant ID: 44-3Y8-H5H-5D5

- **Participate in the OPEN survey**
  We kindly invite you to answer a few questions if you like. This will take no longer than 20 to 30 minutes.
- **Participate in future follow-up studies and/or donate your device data via Open Humans**
  OPEN has built a platform on the non-profit data repository site Open Humans. If you provide your link to Open Humans, we will use it to contact you about follow-up studies conducted by OPEN. If you like, you can also donate your diabetes device data to help our research efforts in improving APS algorithms. This is voluntary. Click below for a step-by-step guide on how to do this.
- **Ask your partner, if you have one, to complete a shorter version of the survey**
  Please send the following participation link to your partner, e.g. via e-mail: It should not take them any longer than 10-15 minutes and responses will be confidential. That means you will not be able to see your partner´s responses and vice-versa.

https://survey.open-diabetes.eu/p/40/wleD51c4sO

Responses to questionnaires were logged using REDCap (Vanderbilt University [14,15]). For privacy reasons, we did not use any device data cloud storage identifiers directly, as personal accounts may not be secure or anonymous. Rather, we managed medical device data donation through Open Humans with a specific project for OPEN [7]. OPEN positively evaluated the ability to communicate anonymously with study participants to notify them about follow-up studies, which is why Open Humans was chosen in addition to its ability to facilitate anonymized data donation. A *record ID* was generated for each participants' survey response in REDCap, and an anonymous *Project Member ID* was generated when they joined the OPEN project on Open Humans. The Participant ID was used to link the record ID and Project Member ID within the Gateway.

Back-end Architecture

The platform was developed using an open-source framework (Ktor, version 1.4.0; JetBrains [16]) in the Kotlin programming language. SQL data were translated (Exposed, version 0.26.1; JetBrains [17]) to Kotlin data types and stored using connection pooling (ie, opening as many database connections as necessary for reliable operation) (HikariCP, version 3.4.5; Brett Wooldridge [18]). Exposed and HikariCP support various databases by using the Java Database Connectivity interface [19], which added additional flexibility to the Gateway; for production, MariaDB [20] was chosen.

The database contained a table with the record ID and the Project Member ID for every survey participant. Application programming interfaces (APIs) were used to interact with these services to access survey and device data; data from these services were not stored in the database itself. In REDCap, each survey had an additional Gateway Instrument variable used to store each Participant ID as a backup measure, as well as additional survey information (eg, participant group, adult or caregiver, user or nonuser), which was used to establish branching logic sequences within specific surveys.

When a participant started the survey for the first time, REDCap's *import record* API was initiated to create a new record containing that participant's information (such as Participant ID and participant group). In that API call, the *Autogenerate record ID* flag was enabled, so that a new record was created instead of an existing record being edited, and the new record ID was returned in the API response. The record ID was then stored in the database; multiple record IDs could be stored for a single Participant ID, allowing for implementation of multiple surveys and follow-up studies. To send the user to the survey, another API call was made to REDCap to export the survey queue link for that given record ID and redirect the user.

Participant ID

The Participant ID was formatted as *1-222-222-222*, where the first number was a consecutive counter (eg, first generated ID: 1, second ID: 2, 100th ID: 100), followed by a 9-digit secret number. The counter was generated by the SQL *auto-increment* feature, and the secret number was randomly generated using a random number generator.

A 9-digit secret number was included to minimize the risk that an unauthorized person could inadvertently or intentionally compromise survey data. For security reasons, the Gateway did not provide any information (questionnaire responses or device data) except for auxiliary status messages (eg, whether the survey has been completed or not), so that no confidential or personal data were exposed in the event that Participant IDs were accidentally made public.

Participants were advised to securely record their Participant ID, because this number allowed participants to start, stop, and resume the survey at any time, and link to the OPEN project on Open Humans.

Authorization

An authorization protocol (OAuth [21]) created for third-party apps to access APIs without requiring app passwords from users—thus creating secure authorization flows—allowed access to and between the Gateway, REDCap, and Open Humans.

The authorization flow was implemented using Ktor's built-in OAuth tool (OAuth, JetBrains [22]). When participants completed the survey, they were invited to donate their diabetes data to the OPEN project on Open Humans. To initiate this process, OAuth first referred participants to a URL on Open Humans where they can register or sign in to Open Humans and join the OPEN project, thereby granting the Gateway access to their data. After this step, the user was redirected back to the Gateway, with a *bearer token* in the URL. The Gateway recognized the token and traded it in at Open Humans for an access token and a refresh token. The access token was used to access the user's data—the refresh token provided a new access token (and refresh token) once the current access token expired. These tokens were stored in the Gateway's database.

Data Set Linkage

Linkage between REDCap records and Open Humans data sets was accomplished by storing the survey record ID and the Project Member ID in the same row as the Participant ID (Table 1) or with a reference using a foreign key. In SQL, every table has a column with a primary key whose values must be unique, which therefore allow a specific row to be referenced without conflict. This is usually just a counter (the first part of the Participant ID), which allows an entry to be referenced from another table. The foreign key is a special constraint that ensures the entry with a given ID exists and that can automatically delete and update an entry if its reference is altered.

Table 1. Data structure of a table of the Gateway database. (Data in the table are an example and not from study participants.)

Consecutive counter, *id*	9-digit secret	Participant group (0–6)[a], *enrollment_type*	REDCap Record ID, *survey_record_id*	Open Humans Project Member ID, *project_member_id*	Access token, *access_token*	Refresh token, *refresh_token*	Unix timestamp (milliseconds), *expires_at*
1	5DBJ4D9R7	2	2	NULL[b]	NULL	NULL	NULL
2	G253LY4VC	1	1	79565297	YmtpPH-HCug8FgVkQBvm-szyP4nmXu6c	ZPhUY2pK85vvYu-vhTr8qbEAtaCGAks	1606799777655
3	290FA1D9B	0	3	NULL	NULL	NULL	NULL

[a] 0 indicates an adult using open-source automated insulin delivery,1 a nonuser adult, 2 a parent of a child user, 3 a parent of a child nonuser, 4 a teenage user, 5 a partner of an adult user, and 6 a partner of an adult nonuser.

[b] NULL indicates that there are no entry data.

Hosting

The Gateway is hosted on a virtual storage server, running CentOS [23] and Docker [24]. The Docker image for the Gateway was created based on the official OpenJDK [25] image published on Docker Hub by including the compiled Gateway executable file and the MariaDB Java Database Connectivity [19] connector, whereas the official MariaDB image was used unmodified. A volume to store the database files was created, and both containers were connected using a bridge network.

The Gateway container exposed the default ports 80 and 443 for HTTP to be accessed publicly by the participants. TLS (Transport Layer Security) certificates were retrieved from Let's Encrypt—a nonprofit certificate authority—using Certbot, which proved domain ownership using the ACME (Automatic Certificate Management Environment) protocol, and were mounted into the container [26,27].

Participant Recruitment

A group of 18 people with, or caregivers and partners of people with, diabetes were recruited to pilot test the platform prior to survey launch. Their responses and data were not included in the final data set.

For the final data set, we sought adults (aged ≥18 years) with diabetes (type 1, 2, or other), caregivers of children and adolescents (aged 3-17 years) with diabetes, and partners or health care professionals of people with diabetes. Participants were recruited via multiple online communities for diabetes, including Facebook groups (such as multinational Looped groups, AndroidAPS users, CGM in the cloud, Nightscout Deutschland), and through the OPEN project website, social media accounts, and Diabetes Daily.

Participant Roles

Upon survey completion, participants were able to send survey links to their partners or caregivers, inviting them to participate in the study. Survey responses from partners or caregivers were linked via the Participant ID to the original participant; partners were linked to adults with diabetes, and caregivers were linked to adolescents with diabetes.

Health care professionals were added at a later stage (while the study was still ongoing). Health care professionals could be invited by people with diabetes to validate their self-reported data by providing information on comorbidities, most recent hemoglobin A_{1c} level, and episodes of severe hypoglycemia and diabetic ketoacidosis based on clinical records. Participants were asked to provide consent for the release of these data by their health care professionals by signing a physical consent form that was given to health care professionals directly and stored in participant health records.

Ethical Approval and Data Privacy

Survey and data donation components of the study were approved by the Life Sciences Human Research Ethics Committee at University College Dublin (LS-20-37).

These study elements are in compliance with data regulation standards of the European Union General Data Protection Regulation. Open Humans is in compliance with regional data privacy laws, particularly those of the United States and European Union. Prior to participation in the study, participants electronically signed an agreement stating that their authorization of data sharing may waive their countries' data privacy laws.

Results

By the survey's close at the end of November 2020, a total of 1052 unique individuals had accessed the Gateway (Figure 3; Table 2), of whom 930 completed at least one questionnaire (users: 696/930, 74.8%; nonusers: 234/930, 25.2%).

Figure 3. Flow diagram of study participation, prior to the addition of health care professional validation. OPEN: Outcomes of Patients' Evidence with Novel, Do-it-Yourself Artificial Pancreas Technology.

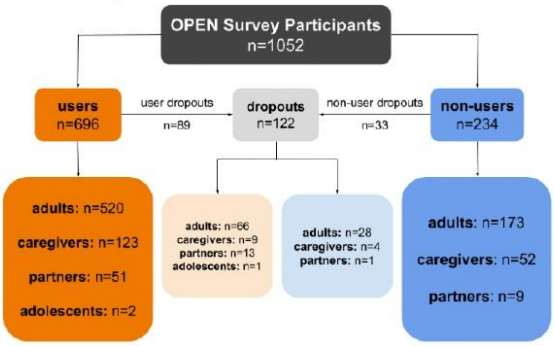


Table 2. Participants who completed at least one questionnaire prior to addition of the health care professional validation element.

Participant type	Users (n=696), n (%)	Nonusers (n=234), n (%)	All (n=930), n (%)
Adults	520 (55.9)	173 (18.6)	693 (74.5)
Adolescents	2 (0.2)	0 (0.0)	2 (0.2)
Caregivers	123 (13.2)	52 (5.6)	175 (18.8)
Partners	51 (5.5)	9 (1.0)	60 (6.5)

After the Gateway was extended to enable health care professional validation of self-reported clinical outcomes, an additional 164 individuals visited the Gateway page, of whom 20 did not proceed to the survey and 2 dropped out during the first questionnaire; therefore, 142 participants (users: 105/142, 73.9%; nonusers: 37/142, 26.1%) completed at least one questionnaire (Figure 4; Table 3). A total of 7 participants allowed their health care professional to validate their clinical data—5 completed the survey before and 2 completed the survey after health care professional validation was added.

Figure 4. Flow diagram of study participation, with the addition of health care professional validation. OPEN: Outcomes of Patients' Evidence with Novel, Do-it-Yourself Artificial Pancreas Technology.

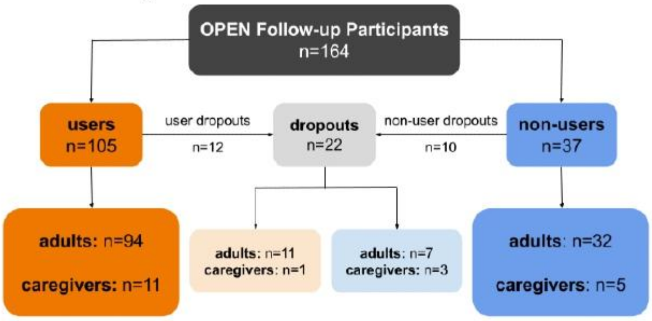


Table 3. Participants who completed at least one questionnaire after the addition of the health care professional validation element.

Participant type	Users (n=105), n (%)	Nonusers (n=37), n (%)	Total (n=142), n (%)
Adults	94 (66.2)	32 (22.5)	126 (88.7)
Caregivers	11 (7.7)	5 (3.5)	16 (11.3)

During the survey period, 137 individuals joined Open Humans. Of those 137 individuals, 97 participated in the survey, uploaded device data, and authorized the OPEN project to access their data on Open Humans; these 97 participants are represented within the larger group of 930 participants who completed at least one survey questionnaire. Open-source automated insulin delivery systems are highly individualized, allowing for a variety of pumps and continuous glucose monitoring systems to be used. Thus, data contained records from multiple different devices, including continuous glucose monitoring data from Dexcom (models G4, G5, or G6), Eversense, Medtronic (Guardian or Enlite models) and Freestyle Libre (model 2), as well as information about insulin delivery provided by pumps—Accu-Chek (Insight or Combo models), older Medtronic pumps, SOOIL Dana Diabecare (R or RS models), and Omnipod (Eros model). Continuous glucose monitoring data included timestamp entries of blood glucose levels, whereas pump data included information about insulin delivery such as extended boluses and temporary basal rates. Nonusers of open-source automated insulin delivery uploaded continuous glucose monitoring and pump data but did not have algorithmic automated insulin delivery data to donate. Individualized profiles from automated insulin delivery systems captured variable and algorithm output data, including changes to blood glucose targets, dosing decisions, carbohydrate entries, and general manual inputs.

Discussion

Principal Results

The Gateway fulfilled 3 main requirements to facilitate anonymous participation in multiple questionnaires and paired diabetes data donation: linking survey records in REDCap to Open Humans Project Member IDs as an optional extension, linking records from partners and health care professionals in addition to open-source automated insulin delivery users and nonusers, and making the entire process anonymized and General Data Protection Regulation–compliant.

Linking, the low cost of services, and familiarity were all related to the central objective of developing a platform for sharing anonymized diabetes data and completing surveys. Linking services improved ease of use for participants; open-source software is free and easier to expand upon (open repositories, direct communication with developers); and familiarity with the services (within research domains) provided a larger body of knowledge to pull from in experimental design, best practices for implementation, and data security. This last element is important—data privacy and security are critical when working with medical data for the protection of participants.

The initial approach was to let participants create an Open Humans account and join the OPEN project (thus generating a Project Member ID), then manually enter their Project Member ID into REDCap and create an identifier on their own with which their partner and health care professional could also join the survey. However, the Project Member ID from Open Humans could not be entered after the REDCap survey was completed, which made setting up data donation on Open Humans before starting the survey necessary. Furthermore, because registering for Open Humans, uploading data, and joining the OPEN project was a multistep process, participants could become fatigued and leave the study before reaching the questionnaires. There was additional concern that participants might accidentally reveal identifying information by creating linking identifiers, hence this approach was abandoned.

Another approach that we considered was requiring that all participants sign up for a personal account on Open Humans, to ensure that every participant had a Project Member ID available when beginning the survey. To minimize the burden of participation, we did not impose this requirement (ie, mandatory registration on a third-party platform), which could have limited the number of potential survey participants.

However, the use of Open Humans as a device data donation platform provided improved security and anonymity. We decided against using Nightscout accounts—or identifiers of any other device data cloud storage—for privacy reasons.

Personal accounts may not be secure or anonymous; whereas, registration through Open Humans provided each participant with a unique anonymous ID and allowed for a standardized process of providing data to the OPEN project.

Existing tools and platforms were used; REDCap and Open Humans are both trusted, well-established, and have proven reliability, which has been demonstrated in previous studies [28-31]. Developing the Gateway was thus a feasible task as it only had to establish a linkage between data sets, whereas implementing questionnaires and data donation were predefined processes in their respective web-based services. Such a design kept overhead costs low relative to development and made use of familiar digital systems.

Completion of an electronic consent form was a prerequisite for participating in the study. While such a consent form was suitable for the bulk of the study—direct participant signatures were not required, only anonymous agreement to the study terms—the release of health care professionals from confidentiality (if participants participated in that component of the study) required a direct signature from the participant. An e-signature stored in the Gateway would have directly tied identifying information to participants' survey responses and medical device data, compromising anonymity.

The decision was made to use physically signed consent forms that were given directly to health care professionals and ultimately stored with participants' health records. These consent records were not available to OPEN—this enabled health care professionals to provide participant information without violating data protection regulations.

With the level of centralization afforded by the Gateway, it was feasible to add health care professional validation at a later stage of the study. It was only necessary to add another record ID from REDCap to the database and link it to the correct Participant ID; REDCap did not directly provide mechanisms for establishing such links; therefore, this would not have been possible without the Gateway.

Data were immediately accessible to the OPEN team at the end of data collection, with conditional access through an internal application process. Questionnaire responses were logged in REDCap and could be downloaded directly; similarly, Open Humans data could be downloaded directly from the OPEN project's profile on Open Humans. The Gateway database—containing all participant IDs, survey record IDs, and Project Member IDs—was shared with OPEN members through a shared cloud drive. The Gateway was designed for adaptation to future studies and remains operational; the late addition of health care professional–validation demonstrated the functionality of linking new elements, allowing for continuous extensibility of the portal.

Limitations

Despite the overall success of the study, there were some drawbacks to the final structure. To donate their diabetes data, participants first had to create Open Humans accounts, upload their data (which may involve first joining and utilizing an *uploader project*), and then join the OPEN Project on Open Humans (ie, authorize the OPEN project to access their device data). All steps had to be completed for the OPEN team to be able to access the anonymous donated diabetes data. The discrepancy between individuals who joined Open Humans and participants who completed the survey and authorized data donation could be attributed to all study elements being optional. Similar to the survey—where individuals across groups left before even completing the baseline demographic information (Figures 3 and 4)—individuals attempting to authorize the OPEN project to access their data may have exited the process before completion. Because all study elements were optional, individuals could choose to complete the survey but not authorize data access, authorize data access but not complete any questionnaires, complete both study elements, or exit before completing anything. The long list of questionnaires and multistep process of data authorization may have been too extensive for some individuals; this may have limited the potential amount of diabetes data captured.

While we thought that ensuring data privacy and anonymity could help to reduce the perceived burden of participation—based on the assumption that people would be more likely to provide detailed information if their identity remains private—there is evidence against this idea [32]. Additionally, the extensiveness of the study may have overpowered any potential reductions in perceived burden of participation due to anonymity; survey fatigue may have negated any retention achieved due to privacy. The presence of dropouts from each participant group is evidence that counters the argument that privacy precipitates participation.

In line with this, the potential risk of participants uploading simulated or falsified data was also considered. On one hand, anonymity theoretically makes tracing these participants more difficult. On the other hand, the number of steps required to produce authentic falsified data would be prohibitively complex. Most falsified automated insulin delivery data can be identified by researchers, as there are a number of elements (such as formatting, quantity and structure, algorithm decisions and variables) within data sets, which would create major barriers to generating authentic falsified data. To date, there are no reported issues of this occurring within research leveraging Open Humans. In general, it has been shown elsewhere [33-35] that real-world data are an important and robust source of information in addition to those from clinical trials. Furthermore, we screened both survey and device data for false entries and removed obvious outliers and erroneous entries where necessary.

While physical signatures were a feasible approach for obtaining consent from participants for their health care professionals to release medical data, the low number of participating health care professionals relative to survey participants may have been a consequence of adding a singular physical element to a study that is largely web-based. Participants may have been less willing to print out and personally send, rather than electronically sign, a form. Health care professional involvement was also the last element to be added to the study; this may have impacted participation. There are many potential factors resulting from the ongoing COVID-19 pandemic (maintaining safety precautions, continued changes to daily life, and carrying out vaccinations) that may have contributed to lower participation rates in the health care professional validation part of the study.

While not necessarily a limitation in this study, future studies may be impacted by tools and frameworks used by this study. Because of the developer's familiarity with Ktor—which did allow for quick prototyping—any future developers working with this codebase that decide to replicate this approach may have to use a completely different toolchain that better fits their needs.

Conclusion

The Gateway, as a portal made OPEN studies [10-12] both accessible for participants and manageable for researchers while maintaining General Data Protection Regulation compliance. Implementation of the disparate study elements was not necessarily complicated; creating the linkages between them required a creative solution, and scalability was also demonstrated with the later addition of health care professional validation of self-reported clinical outcomes. A practical mechanism for matching data sets and establishing links between disparate systems made this study and its extensions possible. In the future, custom software solutions such as the Gateway may become the norm in research with increasingly large data sets across disparate digital services.

Acknowledgments

This work, as part of the Outcomes of Patients' Evidence with Novel, Do-it-Yourself Artificial Pancreas Technology project, has received funding from the European Commission's Horizon 2020 Research and Innovation Program (Marie Skłodowska-Curie Action Research and Innovation Staff Exchange, grant 823902). KB and HB have received funding from the SPOKES Wellcome Trust Translational Partnership Program, and KB has received funding from the German Research Foundation–funded Digital Clinician Scientist Program of the Berlin Institute of Health; both funds are in direct relation to this study. We acknowledge support from the German Research Foundation and the Open Access Publication Fund (*Charité – Universitätsmedizin Berlin*).

Data Availability

After the completion of the OPEN project, requests to access study data can be made to SO. The Gateway codebase [36] is available for use by researchers aiming to implement similar multimodal study designs.

Conflicts of Interest

KB received fees for medical consulting and public speaking from Roche Diabetes Care, Dexcom, Medtronic Diabetes, Diabeloop, Sanofi Diabetes, Novo Nordisk, and BCG Digital Ventures that are not related to this study. DL reports grants from the Robert Wood Johnson Foundation, the Juvenile Diabetes Research Foundation, New Zealand Health Research Council that are not related to this study.

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Abbreviations

API: application programming interface
OPEN: Outcomes of Patients' Evidence with Novel, Do-it-Yourself Artificial Pancreas Technology

2.2. Why #WeAreNotWaiting: Analysis of Motivations and Self-reported Clinical Outcomes of Open-source AID Users.

The “DIWHY” survey was the first cross-sectional and population-based study conducted by OPEN, with the aim to investigate the reasons why PwD or caregivers of children with diabetes initially chose to build and use this technology. The following text is reproduced in full from the abstract of the publication:

Braune K, Gajewska KA, Thieffry A, Lewis DM, Froment T, O'Donnell S, Speight J, Hendrieckx C, Schipp J, Skinner T, Langstrup H, Tappe A, Raile K, Cleal B. Why #WeAreNotWaiting – Motivations and Self-Reported Outcomes Among Users of Open-source Automated Insulin Delivery Systems: Multinational Survey. *J Med Internet Res.* 2021 Jun 7;23(6):e25409. https://doi.org/10.2196/25409

Participants’ characteristics, self-reported clinical outcomes, and motivations to build an open-source AID were assessed with a question and 14 fixed-choice statements followed to conclude the stem “I built an [open-source AID] system ...”. A 5-point Likert-type scale was used to assess their level of agreement.

Of the 897 participants from 35 countries, 80.5% were adults and 19.5% were caregivers of children with diabetes. Primary motivations included improving glycemic outcomes (94% of adults, 95% of caregivers), reducing acute (87% adults, 96% caregivers) and long-term (83% adults, 91% caregivers) complication risks, interacting less frequently with diabetes technology (81% adults, 86% caregivers), improving their or child's sleep quality (72% adults, 80% caregivers), increasing life expectancy (75% adults, 84% caregivers), lack of commercially available AID systems (71% adults, 80% caregivers), and unachieved therapy goals with available therapy options (68% adults, 69% caregivers). Improving their own sleep quality was an almost universal motivator for caregivers (94%).

In addition to the predefined items, participants could indicate further reasons in an open-text field, which were evaluated by content analysis. Most of the indicated responses provided greater details about the predefined statements. Most frequently mentioned were better management and reducing the disease burden, which together with improving sleep quality were understood as the quality of life gains.

Of motivations not previously covered, the most frequently mentioned was autonomy gain in both adults and children or adolescents. All these aspects were associated with improvements in family life. Psychosocial aspects, ranging from diabetes burnout and distress to a desire to improve athletic performance to increasing efficacy at work, were also identified. An important role was also played by the community spirit and peer support in social networks. Not only a “do-it-yourself mindset” and being “early adopters” of technology but also feeling empowered to improve one’s life were highlighted.

Health-related aspects, such as improving the management of diabetes-related complications, increasing safety by avoiding severe hypoglycemia, and living with comorbidities, such as cancer, sexual health difficulties, or conditions requiring cortisone treatment, were also reported. Women and caregivers of girls highlighted hormone-related changes in insulin sensitivity, family planning, and pregnancy. For some, special features were only offered by open-source AID and not by commercial systems, such as customizable targets and smartwatch integration. For caregivers, remote real-time access to their child’s data and the option to remotely control their child’s AID system were of great importance.

Significant clinical outcome improvements, independent of age and gender, were observed in glycated HbA1c: 7.14±1.13% to 6.24±0.64% (P<0.001), and Time-in-Range: 62.96±16.18%, to 80.34±9.41% (P<0.001).

Original Paper

Why #WeAreNotWaiting—Motivations and Self-Reported Outcomes Among Users of Open-source Automated Insulin Delivery Systems: Multinational Survey

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Abstract

Background: Automated insulin delivery (AID) systems have been shown to be safe and effective in reducing hyperglycemia and hypoglycemia but are not universally available, accessible, or affordable. Therefore, user-driven open-source AID systems are becoming increasingly popular.

Objective: This study aims to investigate the motivations for which people with diabetes (types 1, 2, and other) or their caregivers decide to build and use a personalized open-source AID.

Methods: A cross-sectional web-based survey was conducted to assess personal motivations and associated self-reported clinical outcomes.

Results: Of 897 participants from 35 countries, 80.5% (722) were adults with diabetes and 19.5% (175) were caregivers of children with diabetes. Primary motivations to commence open-source AID included improving glycemic outcomes (476/509 adults, 93.5%, and 95/100 caregivers, 95%), reducing acute (443/508 adults, 87.2%, and 96/100 caregivers, 96%) and long-term (421/505 adults, 83.3%, and 91/100 caregivers, 91%) complication risk, interacting less frequently with diabetes technology (413/509 adults, 81.1%; 86/100 caregivers, 86%), improving their or child's sleep quality (364/508 adults, 71.6%, and 80/100 caregivers, 80%), increasing their or child's life expectancy (381/507 adults, 75.1%, and 84/100 caregivers, 84%), lack of commercially available AID systems (359/507 adults, 70.8%, and 79/99 caregivers, 80%), and unachieved therapy goals with available therapy options (348/509 adults, 68.4%, and 69/100 caregivers, 69%). Improving their own sleep quality was an almost universal motivator for caregivers (94/100, 94%). Significant improvements, independent of age and gender, were observed in self-reported glycated hemoglobin (HbA_{1c}), 7.14% (SD 1.13%; 54.5 mmol/mol, SD 12.4) to 6.24% (SD 0.64%; 44.7 mmol/mol, SD 7.0; *P*<.001), and time in range (62.96%, SD 16.18%, to 80.34%, SD 9.41%; *P*<.001).

Conclusions: These results highlight the unmet needs of people with diabetes, provide new insights into the evolving phenomenon of open-source AID technology, and indicate improved clinical outcomes. This study may inform health care professionals and policy makers about the opportunities provided by open-source AID systems.

International Registered Report Identifier (IRRID): RR2-10.2196/15368

(J Med Internet Res 2021;23(6):e25409) doi: 10.2196/25409

KEYWORDS

diabetes; artificial pancreas; automated insulin delivery; open-source; patient-led; user-led; peer support; online communities; diabetes technology; digital health; mobile health; medical device regulation; motivation; sleep quality; do-it-yourself

Introduction

Background

Despite significant advances in health care, pharmaceuticals, and technological developments, type 1 diabetes remains a challenging chronic condition to manage, impacting life expectancy and diminishing quality of life [1-3]. Only a small proportion of people with type 1 diabetes achieve glycated hemoglobin (HbA_{1c}) levels below 7.0% (58 mmol/mol), as recommended by therapeutic guidelines to reduce the risk of long-term diabetes-related complications [4-6]. The complexity of diabetes self-management bears a high cognitive load and can cause distress in everyday life, with approximately 40% of people with type 1 diabetes reporting distress and/or depressive symptoms, particularly prevalent among adolescents and young adults [7-10].

In addition to optimizing glucose levels and variability, diabetes technologies have the potential to ease complex decision making and thereby reduce the cognitive and emotional burden of diabetes self-management. The latest advances in diabetes therapy combine sensors for continuous glucose monitoring and insulin pumps with computerized control algorithms, thereby enabling automated adjustments to insulin delivery in response to the user's changing glucose levels. Automated insulin delivery (AID) systems, also known as *artificial pancreas* or *(hybrid) closed-loop* systems, are in various iterations of development and automaticity. Although a variety of commercial AID systems are under development, and some have recently become available in a limited number of countries, they are not universally available, accessible, or affordable.

To fill in the gap, open-source AID systems, also called *Do-It-Yourself* Artificial Pancreas Systems (DIYAPS), have been created by people with diabetes, in the web-based community behind the hashtag #WeAreNotWaiting, with instructions and codes for these systems available freely and widely via open-source platforms. Although anyone can access this, each user has to take responsibility to build their individual system and use it at their own risk. Initial observational studies have described significant improvements in glycemic outcomes in smaller cohorts of open-source AID users of all age groups, including children and adolescents whose caregivers build and maintain these systems on their behalf [11-15]. Further studies reported improved sleep quality and uninterrupted sleep, in particular, reduced burden of diabetes management, increased confidence in achieving diabetes management goals, increased energy, and reduced mood swings among open-source AID users [15]. An in-silico study of the AndroidAPS algorithm showed similar glycemic improvements and concluded that this algorithm is both safe and effective [16].

Despite the potential benefits of open-source AID systems, little is known about the reasons why people with diabetes initially chose to use this technology. It is important to determine the lessons to be learned from the #WeAreNotWaiting movement, especially for stakeholders involved in research and commercial product development and regulation, such as academia, industry, health care professionals, governance, and regulatory bodies.

Objectives

As part of the OPEN (Outcomes of Patients' Evidence with Novel, Do-it-Yourself Artificial Pancreas Technology) Project, the aim of this study is to investigate motivational factors for building, using, and maintaining an open-source AID system among adults with diabetes (type 1, 2, and others) and caregivers of children and adolescents with diabetes, as well as their self-reported clinical outcomes, through a population-based survey [17].

Methods

Study Design and Participants

From November 2018 to March 2019, we conducted a web-based, cross-sectional survey titled *DIWHY* (Multimedia Appendices 1 and 2). The survey design was created by the patient-led OPEN consortium [17], in collaboration with open-source AID users, and piloted by a small number of them before the final release. The Checklist for Reporting Results of Internet E-Surveys was used to guide survey development [18]. The survey was approved by the Charité–Universitätsmedizin Berlin Ethics Committee (EA2/140/18). Participants were eligible if they were adults (aged >18 years), living with diabetes (type 1, 2, or other), or being caregivers of a child or an adolescent with diabetes using an open-source AID system.

Procedures

Participants were invited through public announcements on the OPEN Project website, in the Facebook groups *Looped* (>6000 members) and *AndroidAPS users* (>1800 members, November 2018), other regional subgroups on Facebook, and by public posts on Twitter using the hashtags #WeAreNotWaiting and #DIYAPS. All posts were organic, meaning there was no paid promotion or targeted advertising of posts on any platform. All participants gave their consent electronically. Participation was anonymous and voluntary; no financial or other compensation was provided. Participants were able to choose between 2 language options (English and German). There was a version for adults with diabetes and one for caregivers. Data were collected and managed using secure Research Electronic Data Capture electronic data capture tools hosted at Charité [19].

Measures

Initial questions focused on demographics, the type of open-source AID systems used, estimated commencement date, and 3 HbA_{1c} values each preinitiation and postinitiation of open-source AID (self-reported for adults; for caregivers, their child's). In addition, participants were asked to provide their or their child's average time in range (TIR; sensor glucose 70 mg/dL/4.0 mmol/L-180 mg/dL/10.0 mmol/L) before and after the commencement of open-source AID.

Subsequently, participants' motivation to build an open-source AID was assessed with a single question: "What motivated you to build a Do-It-Yourself Artificial Pancreas system for yourself? Indicate your level of agreement with each statement." A total of 14 fixed-choice statements followed to conclude the stem "I built a DIYAPS..." (eg, "...to achieve better glycemic control," "...to improve my own sleep quality"). For each statement, a 5-point Likert-type scale was used (*fully applies* to *does not apply at all*). In addition, participants could indicate further motivational factors using free text.

Quantitative Analysis and Statistical Testing

To ensure the reporting of robust parameters regarding HbA_{1c} levels, entries with more than one missing HbA_{1c} value either before or after open-source AID implementation were not considered in the calculation of arithmetic means, SDs, and statistical tests related to HbA_{1c}. The reduction in the average HbA_{1c} levels before and after open-source AID implementation was assessed using the Wilcoxon signed-rank test (*P* value threshold of .05, paired: *TRUE*, and alternative hypothesis: *greater*). Entries not providing TIR values before and after open-source AID implementation were not considered for the computation of TIR-related descriptive statistics and testing for the increased TIR after open-source AID implementation (same statistical test as for HbA_{1c}, with alternative hypothesis set to *lower*). Quantitative analyses were conducted within the R programming framework (v4.0.2; R Core Team), and the ggplot2 package was used to generate figures.

Content Analysis

Content analysis was performed to analyze responses to open-ended questions [20]. A total of 3 researchers coded data and analyzed the responses thematically in 2 rounds. After the first round, which was open, inductive, and independent, 3 lists of codes were merged and combined into a final version. The second round of coding was deductive, and each of the coders assessed the content according to the final list of codes. The interrater reliability (percentage agreement for multiple raters) method was used to calculate the level of agreement between coders, and the final list of the most frequently discussed codes was generated [21]. Codes were then compared with assess the level of similarity, for example, an interrater reliability result of 100% indicated that all codes generated by individual coders matched.

Results

Characteristics of the Study Cohort

A total of 1125 individuals participated in the *DIWHY* survey. After excluding 25.6% (288/1125) incomplete responses, data from 897 individuals over 35 countries were analyzed. Detailed demographic characteristics are shown in Table 1. Participants were mostly from Europe (691/897, 77%), whereas 14% (125/897) were from North America, and 9% (78/897) were from other continents. Most adults (599/722, 82.9%) and caregivers (153/175, 87.4%) had a university degree or higher. Of the respondents, 26% (236/897) had a professional background in information technology and 19% (170/897) in biomedicine or health care. Furthermore, 82% (736/897) of the participants reported out-of-pocket expenses, with an average of US $530 and a maximum of US $1000 per year. In both groups, various types of open-source AID systems were used regularly, with Loop being the most popular system in North America and AndroidAPS being the most frequently used system in Europe. Otherwise, the geographical location and household income did not indicate any specific patterns.

Table 1. Participants' demographic and self-reported clinical characteristics.

Participant demographics	Children and adolescents (n=175)	Adults (n=722)	Total (N=897)
People with diabetes, gender, n (%)			
Female	83 (47.4)	311 (43)	394 (43.8)
Male	92 (52.6)	411 (56.8)	503 (55.9)
Other	0 (0)	2 (0.3)	2 (0.2)
People with diabetes, average age, years (SD)	9.7 (4.0)	41.8 (11.8)	35.6 (16.7)
Type of diabetes, n (%)			
Type 1	174 (99.4)	714 (98.9)	888 (98.9)
Type 2	0 (0)	4 (0.6)	4 (0.4)
Other	1 (0.6)	4 (0.6)	5 (0.6)
Average duration of diabetes, years (SD)	5.1 (3.9)	25.2 (13.3)	21.4 (14.4)
Average duration of open-source AID[a] use, mean (SD)	10.3 (10.0)	10.0 (19.1)	10.1 (17.6)
Type of open-source AID used regularly, n (%)			
OpenAPS	42 (28.4)	104 (16.6)	146 (18.8)
AndroidAPS	71 (48)	380 (60.6)	451 (58.2)
Loop	42 (28.4)	179 (28.5)	221 (28.5)
Other[b]	5 (3.4)	39 (5)	44 (5.7)
Region, country of residence, n (%)			
Europe	130 (74.3)	561 (77.6)	691 (76.9)
Austria	3 (1.7)	23 (3.2)	26 (2.9)
Bulgaria	9 (5.1)	7 (1)	16 (1.8)
Czech Republic	12 (6.9)	9 (1.2)	21 (2.3)
Finland	8 (4.6)	10 (1.4)	18 (2)
Germany	46 (26.3)	363 (50.2)	409 (45.5)
The Netherlands	0 (0)	10 (1.4)	10 (1.1)
Spain	3 (1.7)	11 (1.5)	14 (1.6)
Sweden	8 (4.6)	3 (0.4)	11 (1.2)
The United Kingdom	23 (13.1)	99 (13.7)	122 (13.6)
Other[c]	14 (8)	35 (4.8)	49 (5.5)
North America	21 (12)	104 (13.9)	125 (13.4)
Canada	5 (2.9)	18 (2.5)	23 (2.6)
The United States	16 (9.1)	86 (11.9)	102 (11.3)
Asia	12 (6.9)	14 (2.9)	26 (2.9)
South Korea	12 (6.9)	10 (1.4)	22 (2.4)
Others[d]	0 (0)	4 (0.4)	4 (0.4)
Western Pacific	12 (6.9)	39 (5.4)	51 (5.7)
Australia	12 (6.9)	29 (4)	41 (4.5)
New Zealand	0 (0)	10 (1.4)	10 (1.1)
Africa	0 (0)	1 (0.1)	1 (0.1)
South Africa	0 (0)	1 (0.1)	1 (0.1)
Education: highest completed, n (%)			

Participant demographics	Children and adolescents (n=175)	Adults (n=722)	Total (N=897)
No or some high school	19 (10.9)	54 (7.6)	73 (8.1)
High school	16 (9.2)	67 (9.4)	58 (6.5)
University	111 (64.1)	449 (62.9)	627 (71.1)
Degree or diploma	21 (12.1)	61 (8.5)	82 (9.2)
Doctorate	21 (12.1)	89 (12.4)	110 (12.4)
Occupational status[e], n (%)			
Full time	101 (58.4)	486 (67.6)	587 (65.8)
Part time	55 (31.8)	114 (15.9)	169 (18.9)
Unemployed	10 (5.8)	6 (0.8)	16 (1.8)
Retired	0 (0)	38 (5.3)	38 (4.3)
Student	2 (1.2)	58 (8.1)	60 (6.7)
Other	5 (2.9)	17 (2.4)	22 (2.4)
Professional background[e], n (%)			
Medicine	24 (18.5)	102 (19.5)	126 (19.2)
Tech	35 (26.9)	137 (26.2)	172 (26.3)
Other	71 (54.6)	284 (54.3)	355 (54.4)
Household annual net income[e], US $, n (%)			
<20,000	19 (12)	87 (14.1)	106 (13.6)
20,000 to 34,999	12 (7.6)	60 (9.7)	72 (9.2)
35,000 to 49,999	19 (12)	88 (14.2)	107 (13.7)
50,000 to 74,999	33 (20.9)	138 (22.3)	171 (22.1)
75,000 to 99,999	24 (15.2)	84 (13.6)	108 (13.9)
>100,000	40 (25.9)	124 (20)	165 (21.2)

[a] AID: automated insulin delivery.

[b] xDrip, Nightscout, offline uploader for Medtronic 600 series, HAPP, and custom or own developments.

[c] Belgium, Croatia, Denmark, France, Greece, Hungary, Ireland, Italy, Lithuania, Luxembourg, Norway, Poland, Portugal, Russia, Slovakia, and Switzerland.

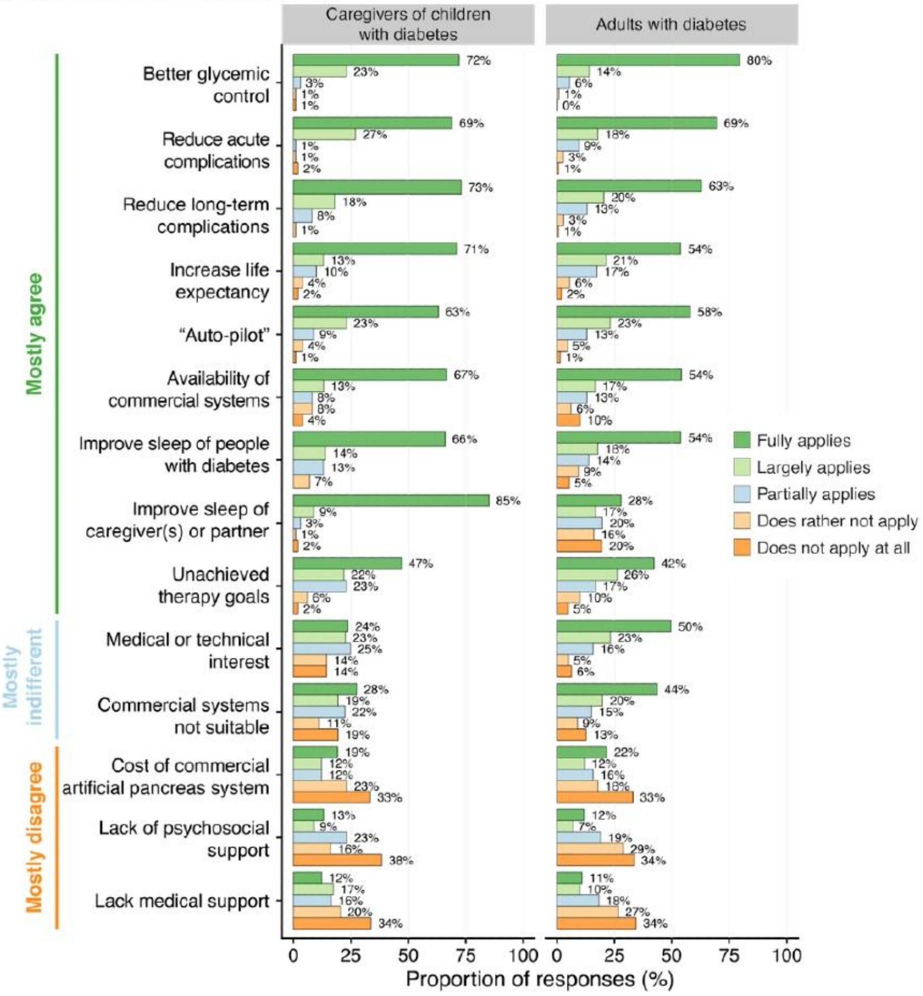
[d] Hong Kong, Kuwait, Palestine, and Singapore.

[e] For adults: own; for caregivers: caregivers.

Motivations to Commence Open-source AID Use

As shown in Figure 1, the most frequently endorsed motivations of adults as well as caregivers (as *fully applies* or *largely applies*) were to improve the overall glycemic control (476/509 adults, 93.5%; 95/100 caregivers, 95%), reduce the risk of acute (443/508 adults, 87.2%; 96/100 caregivers, 96%) and long-term complications (421/505 adults, 83.4%; 91/100 caregivers, 91%), put diabetes on *auto-pilot* mode and interact less frequently with diabetes technology (413/509 adults, 81.1%; 86/100 caregivers, 86%), increase their own or their child's life expectancy (381/507 adults, 75.1%; 84/100 caregivers, 84%), and improve their own or their child's sleep quality (364/508, adults 71.7%; 80/100 caregivers; 80%), because of the lack of commercially available closed-loop systems in their countries (359/507 adults, 70.8%; 79/99 caregivers, 80%) and unachieved therapy goals with the therapy options available to them (348/509 adults, 68.4%; 69/100 caregivers, 69%).

Figure 1. Motivations for building an open-source automated insulin delivery system. The x-axis shows the percentage of responses for each motivation question (y-axis). Bar colors represent the degree of relevance ranging from "does not apply at all" to "fully applies." The left and right columns show the responses of caregivers of children with diabetes and adults with diabetes, respectively. Responses are ranked from the most frequently endorsed motivations (top) to the less frequently endorsed (bottom).



Overall, the motivations of adults and caregivers of children and adolescents with diabetes were largely similar. As the most noticeable difference between the 2 groups, improvement in their own sleep quality (94/100, 94%) was a stronger motivation for caregivers compared with adults with respect to their partners or families (225/505, 44.6%). Curiosity (medical or technical interest) was endorsed more frequently by adults with diabetes (367/503, 73.0%) than by caregivers (45/97, 47%). Some believed that commercial systems did not suit their own or their child's individual needs, more frequently reported by adults (316/498, 63.5%) than by caregivers (46/98, 47%). Out-of-pocket costs related to the use of commercially available systems (166/496 adults, 33.5%; 31/99 caregivers, 31%) played a subordinate role. Lack of adequate medical support (105/501 adults, 21.0%; 29/98 caregivers, 30%) or psychosocial support (94/501 adults, 19.0%; 22/99 caregivers, 22%) were less frequently endorsed as motivating factors, although caregivers more frequently indicated a lack of medical support.

Further Motivations

In addition to the 14 predefined items, participants could indicate further motivation in an open-text field. In total, 127 participants (103 adults and 24 caregivers) provided a free-text response. Textbox 1 provides a list, as well as representative quotes, of the respondents. In the independent coders' selection of first-choice codes, there was an 83% interrater agreement between them (Multimedia Appendix 3).

Textbox 1. Illustrative quotes from adults with diabetes and the caregivers of children or adolescents with diabetes, highlighting additional motivation factors to build an open-source automated insulin delivery system.

Improving Diabetes Management

The psychological benefits of being able to significantly improve active control over diabetes and outcomes, rather than being more passively subjected to it.

Another important reason for me is that I FINALLY have an overview of all data combined for later analysis but also direct decisions (values instead of opinions).

Improving Quality of Life or Reducing the Burden of Diabetes Management

I chose DIY to decrease the demands of living with diabetes every day, around the clock. I also needed help consistently combatting the dawn phenomena, where I would wake up either too high, or too low from overcorrecting.

His quality of life (staying with friends, knowing we can remotely monitor and assist, knowing that loop will help correct if he makes a mistake, attending sports training independently) is vastly improved. We can sleep! A happier, healthier family.

Freedom to participate in normal 8 year old life eg play dates without having to pre-plan everything.

Management of diabetes is helped by support but it is very much a self managed disease and requires 24/7 attention. Closed looping makes it just so much better, much of the time I can leave AAPS to take care of basals by itself. Quality of life is so much better. I can sleep without worrying about not waking up because of a bad hypo.

We only wanted the best for our son. He should get exactly the same chances in life as his friends/children of the same age.

To improve constant feeling of failure.

Diabetes Distress or Burnout

Tired of diabetes after almost 30 years [...] The first real relief for me in my everyday life as a single mom.

To reduce psychological distress, to be able to take responsibility for the course of diabetes, to enjoy life more since you are not torpedoed by Hypos and Hypers. Freedom despite technically higher dependency.

There was no other way. The available treatments just did not control my diabetes sufficiently. The pressure and hopelessness of that scenario caused major mental health problems.

I've lived my whole life [like] this & can't take it anymore. Too hard to do. Worst problem is "brain fog" & lack of energy due to blood sugar swings & hypoglycemic unawareness. I carry guilt for causing my family to lose sleep & carry the burden of diabetes [...]. [The] burden of diabetes is terrible.

Autonomy

I feel so empowered by building my own system and taking control of my T1D. It's an awesome feeling!

Daughter has learning difficulties, to make life easier for her and be less dependent on support, which in turn allows her to live a more independent life.

To regain a sense of control on my diabetes management. I felt I was becoming dependent on my specialist for interpreting the adjustments needed for my insulin regime.

Independent sleepovers with friends (without parents).

To expand our daughter's independence and make her therapy decisions easier.

Dissatisfaction With Available Technology, Choice and Health Care

Out of frustration with the existing designs seeming to have prioritized all stakeholders other than patients.

Commercial closed loop systems do not allow users to specify a custom target BG but instead hard wire an unambitious target more concerned with legal liability that doesn't respect the autonomy, needs and wishes of the user.

Dissatisfied with commercially available options and choice in the market space. No other option is appealing or provides the level of control and true artificial pancreas functions OR user interface.

Doctors and hospitals have been telling me for years that things are simply fluctuating for me (hormones, stress, sensitivity to movement) and that you can't do anything about it. 'Resistant to all treatment options' and well-educated. Unfortunately with no success.

We were desperate for something to use all the CGM data without sending our child crazy with in[sistent] requests for the pump to set low temps etc. We were infuriated by the business based decisions around closed loop in Australia - only the 640G was available and it was the worst decision for management and burden that we ever made. Now (as *in within this fortnight) the 670G is available but still, no one can get training or sensors. We have been looping for nearly 3 years. If we hadn't then we would still be waiting today.*

Improving Sleep Quality

Sleep was the main reason followed by time in range. However, after all these years I still wake up but go back to sleep quickly.

Frequently woke up from sensor alarms, make corrections and still wake up in the morning with a high or low glucose. Since closed looping, I get into bed knowing that Loop will keep me in range and I will wake up with a neat glucose. The only alarms I would ever get during the first period of closed looping were compression lows, and with the experience of loop keeping me in range I am now even confident enough to shut down all CGM alerts. Makes a huge difference for both me and boyfriend now that we start our days well rested. Every single day.

Safety or Reducing Severe Hypoglycemia

Too many overnight hypos that require help.

My child was overdosed on insulin twice by untrained teacher aides at school and if it was not for DIY looping technology- I would not have known about this at all until too late. Seeing the boluses appear on nightscout on real-time allowed me to question the dose and sugar treatment could commence preventatively than child actually going into severe hypo.

"DIY mindset" or Early Adopter of Technology

I was going to build my own and found existing projects.

Early adopter of all diabetes technologies. Turns disadvantage into a challenge.

I love tinkering and making things. I'd always rather DIY, in many aspects of life.

I initially built a closed DIY APS for a hackathon project out of pure tech curiosity. I planned to use the system for only 12 hours and then give a presentation to other employees at our company involved with the hackathon. After 12 hours, I realized I was never going to stop using it. Once on the system, almost every single one of the survey questions above are a "Fully Applies" as to why I decided to stay on the DIY APS.

I'm a doctor and I'd like to test the closed loop first for myself and then use it in the future in my patients' treatment.

Community Spirit

Being part of the community of selfless, generous, caring, and talented people willing to volunteer their time, knowledge, skills and experience to the benefit of the community.

Something that also influenced me to move to a DIY system was the support from the community, and the general feeling that the community gives. It feel like I am part of a big people- powered movement. It feels like a revolution.

I felt a strong moral and ethical imperative that technology should serve people.

Help others to have healthier life.

Comorbidities

I started on AndroidAPS when I was diagnosed with cancer needing chemotherapy. I found it extremely beneficial especially for those times when I was at my lowest and unable to control my BGs in the old way because of insulin resistance. Also when I was admitted to hospital because of infections and sepsis it was a godsend.

More beneficial sexual activity, PDE-5 inhibitors no longer required.

Because of other conditions, I have to take cortisone in different doses on a regular basis. This has made my diabetes management so difficult. The loop absorbs my BG fluctuations much better.

Achalasia (food gets stuck in the esophagus at night), making blood sugar uncontrollable.

I have been on a pump since 1992. I was on the 670G for over a year, and I felt helpless in my efforts to achieve excellent glycemic control while still living my random and not standardized life, where I eat when I am hungry, or forget to eat, and where pre-bolusing is dangerous, because I also have ADHD and I have forgotten to eat many times. My insulin needs vary depending on what I do in terms of activity, but also randomly on the day of the week, the time of the month and many other factors that i don't understand. On the 670G every weekend of high physical activity was followed by a couple of days of high BGs due to the user's inability to interact with the proprietary algorithms (Oh I am so done with Medtronic now).

Diabetes-Related Complications

After 29 years of MDI and [...] retinopathy I decided to improve my health. I've researched several ways to improve control. Ultimately autonomy is the box I needed ticked! AAPS ticks that box 100%.

Gastroparesis, I barely had nights where I wasn't over 200 half the night. With the G5 I was woken up at 170 and was able to intervene. Since the loop and some completed goals, I fall asleep again because the loop prevents the uncontrollable rise!

Heart operation after 30+ years of poorly controlled diabetes.

Female Health

Wanted better control for pregnancy.

As someone whose hormone levels are not considered standard and rapidly change, the ability to [have] a helping hand to smooth out these Diabetes related complications (notably hyperglycemia episodes) was very important to me, as the situation is never the same twice and requires different treatment on a day-to-day basis.

Deteriorating HbA_{1c} *due to puberty and insulin resistance. Massive amounts of insulin needed giving unpredictable blood glucose.*

After manifestation of T1D, we made very high demands on HbA_{1c} *and TiR for the benefit of our daughter...but with the onset of puberty, this led to an almost impossible workload (correcting 10-15 times at night).*

To have more insight as to why my blood glucose was so volatile due to changing hormones (menopause).

Out-of-Pocket Expenses

It was questionable whether I would meet the health insurer's criteria for the Minimed 670 system for reimbursement. I don't have a CGM either, just the Freestyle Libre with an additional transmitter.

Improving Performance

To improve my work at the office.

To improve athletic performance by controlling night time blood sugars.

Curiosity

To learn more about my diabetes in general. You have to acquire a lot of knowledge (technical as well as physiological aspects) before you start looping, and you get excellent support from developers and the community.

The fact alone that you can be curious again about something new to the diabetes field, to see a form of therapy as an exciting challenge, plus the (so far not yet fulfilled hope) to finally better control the hardly controllable variating [postprandial] values.

Most of the indicated *other motivations* provided greater details about the 14 predefined statements. The most frequently mentioned motivations for all—adults and caregivers—were *better management* and *reducing the disease burden*. The first motivation appears consistent with several statements related to hypoglycemia and hyperglycemia and risk reduction, whereas the second motivation may correspond with *to put diabetes management more on auto-pilot and interact less frequently with the therapy system*. This aspect and sleep quality are understood as the quality of life gains. Of motivations not covered by the predefined responses, the most frequently mentioned was *autonomy gain* in both adults and children or adolescents, as indicated by the caregivers. All these aspects were associated with improvements in family life:

> *This is for my wife. She wants me to live forever, this is as close as I can do for her.*

Psychosocial aspects, ranging from diabetes burnout and distress to a desire to improve athletic performance to increasing efficacy at work, were also identified as important motivating factors. The following comments illustrate the wide-ranging benefits experienced by many participants after adopting the technology:

> *Management of diabetes is helped by support, but it is very much a self-managed disease and requires 24/7 attention. Closed looping makes it just so much better, much of the time I can leave [AndroidAPS] to take care of basals by itself. Quality of life is so much better. I can sleep without worrying about not waking up because of a bad hypo. [...] I am so grateful to all the software developers who have freely given their expertise and time to make this possible.*

As highlighted in the example above, an important role was played by the *community spirit* and peer support in social networks:

> *Something that also influenced me [...] was the support from the community, and the general feeling that the community gives. It feels like I am part of a big people-powered movement. It feels like a revolution.*

Not only a *Do-It-Yourself* mindset and being *early adopters* of technology but also being motivated and empowered to improve one's life were frequently mentioned:

> *Because it's the most natural thing to do, after getting to know that it's possible. Because I could.*

Some motivations included other health-related aspects such as improving the management of existing diabetes-related complications and increasing safety by avoiding severe hypoglycemia. Other comorbidities, such as cancer, sexual health difficulties, or conditions requiring cortisone treatment, were also mentioned:

I have to take cortisone in different doses on a regular basis. This has made my diabetes management so difficult. The loop absorbs my BG fluctuations much better.

Women and caregivers of female children highlighted female health aspects such as hormone-related changes in insulin sensitivity, family planning, and pregnancy as reasons to commence open-source AID:

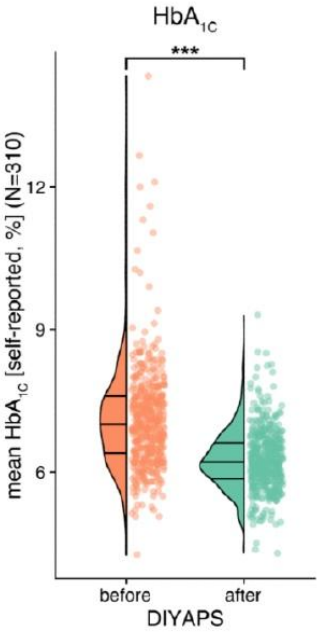
> *To have more insight as to why my BG was so volatile due to changing hormones (menopause).*

For some, special features were only offered by open-source AID and not by commercial systems, that is, customizable targets and the option to bolus from a smartwatch. For caregivers, remote real-time access to their child's data and the option to remotely control their child's AID system have been frequently described.

Improved Glycemic Outcomes Across All Age Groups and Genders

To assess glycemic outcomes, participants were asked to report their or their child's 3 most recent HbA_{1c} results before as well as the first 3 HbA_{1c} results after commencing the open-source AID. HbA_{1c} levels decreased significantly following open-source AID implementation ($P<.001$) from an average of 7.14% (SD 1.13%; mean 54.5 mmol/mol, SD 12.4) to 6.24% (SD 0.64%; mean 44.7 mmol/mol, SD 7.0), with an effect size of −0.9% (Figure 2).

Figure 2. Positive effects of open-source automated insulin delivery on clinical outcomes: average self-reported glycated hemoglobin (%; y-axis) for all 310 respondents, before and after open-source automated insulin delivery (x-axis) distinguished by orange and green colors, respectively. The left side is displayed as a density plot, with horizontal lines indicating quartiles. The right side depicts the data as a scatter plot. DIYAPS: Do-it-Yourself Artificial Pancreas System; HbA_{1c}: glycated hemoglobin.



The average self-reported TIR across adults and children with diabetes significantly increased by +17.4%, from 62.96% (SD 16.18%) to 80.34% (SD 9.41%; $P<.001$; Figure 3). Similar outcomes were observed separately for adults and children with diabetes (Multimedia Appendix 3) and were independent of age and sex (Figure 4). Overall, 92.3% (286/310) of the respondents reported a decreased average HbA_{1c} level (Figure 5).

Figure 3. Self-reported time in range (%; x-axis) of adults and children with diabetes, before and after implementing an open-source automated insulin delivery system. The left side is displayed as a density plot, with horizontal lines indicating quartiles. The right side depicts the data as a scatter plot.

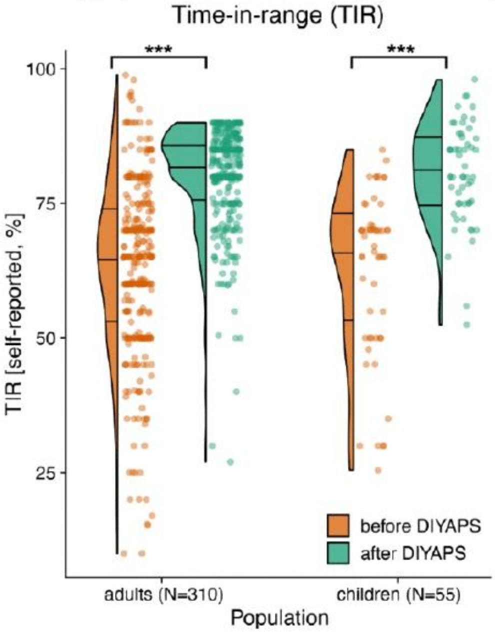


Figure 4. Improvements in self-reported glycated hemoglobin levels associated with open-source automated insulin delivery, independent of age or gender: relation between average glycated hemoglobin levels (%; y-axis) and age (x-axis), shown separately for female and male respondents (top and bottom rows, respectively). Colors separate average glycated levels before (orange) and after (green) open-source automated insulin delivery implementation. Each point represents one respondent after filtering of responses (the Methods section). Solid lines and their gray areas represent the trend and standard error for the respective groups. AID: automated insulin delivery; HbA$_{1c}$: glycated hemoglobin.

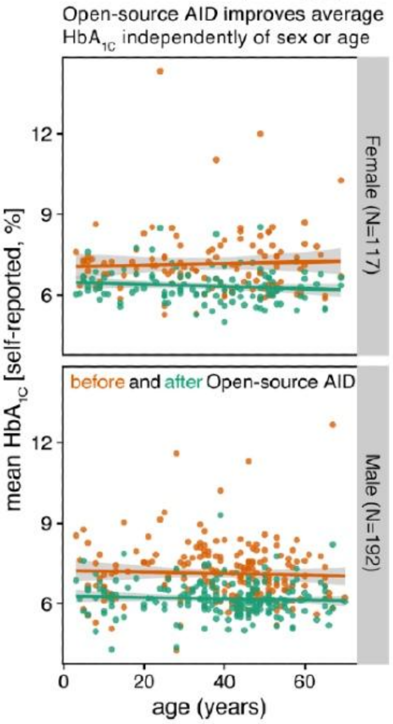
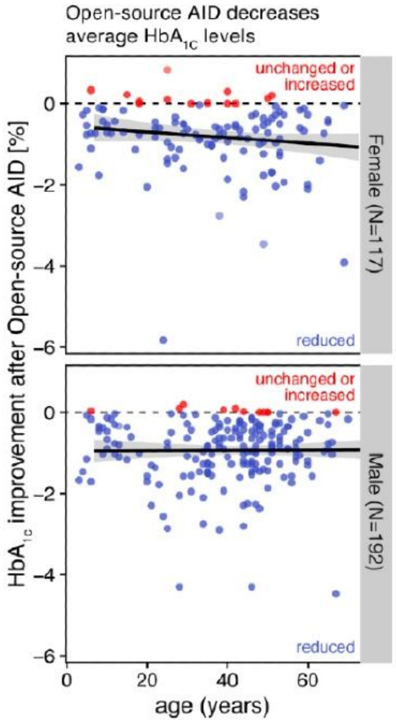


Figure 5. Improvements in self-reported glycated hemoglobin levels associated with open-source automated insulin delivery, independent of age or gender: the y-axis shows the difference of average glycated hemoglobin levels after open-source automated insulin delivery, compared with before its implementation. Colors distinguish respondents with reduced average glycated hemoglobin (blue) from those with unchanged or increased glycated hemoglobin (red). AID: automated insulin delivery; HbA_{1c}: glycated hemoglobin.



Discussion

Principal Findings

This study is the first to systematically analyze the motivations found within the #WeAreNotWaiting movement of people with diabetes, who have built and maintained their open-source AID systems and created their own ecosystem of international self-support networks. To the best of the authors' knowledge, this is also the largest study reporting the self-reported clinical outcomes of open-source AID users across several continents. We found large effect sizes for self-reported improvements in HbA_{1c} (−0.9% on average) and TIR (+17.4% on average), indicating considerable biomedical benefits associated with open-source AID, which were independent of sex and age.

Why #WeAreNotWaiting: Main Motivators to Choose an Open-source AID

The main motivators for adults were improvements in overall glycemic and long-term outcomes and quality of life, whereas the strongest motivation for caregivers was improvement of their own sleep, followed by improved glycemia of the child and possibility of remotely controlling glycemia and insulin delivery via the internet. The results indicate that motivations are configured differently among caregivers and that other motivations also scored a high level of consensus among the respondents. These findings suggest that motivation to transition toward open-source AID is multifaceted and complex, with reasoning and decision making bound up with the psychological and social intricacies of individuals' lives.

Improvement in Sleep Quality

Caregivers experience reduced sleep quality because of fear of hypoglycemia, which often requires them to regularly check their child's glucose levels overnight [22]. In our study, caregivers reported experiencing fewer demands and less apprehensiveness regarding their child's glucose levels at nighttime. As shown in the free-text responses, open-source AID also appears to offer caregivers with the reassurance necessary to provide their child more autonomy and engage in activities that might otherwise present a risk, such as having *a sleepover* with friends. Previous studies in adults using open-source AID have shown self-reported improvement in sleep quality [23,24]. These initial findings indicate a substantial benefit for users and caregivers for sleep and most likely for their psychological and physical well-being. Poor quality of sleep negatively affects the psychological well-being, cognitive functioning, and a diverse range of hormones that affect the regulation of appetite and our homeostatic systems as well as the immune system [25-34]. Recent research also points to sleep as impacting the actual maintenance of the brain and our DNA regenerative systems [35]. Thus, AID may play an important role in improving the psychological and physical health of people with diabetes and their family members. However, it has been noted elsewhere that the potential discomfort or inconvenience of wearing devices and overnight alarms may also hamper the benefits for some users [36].

The Importance of Customizability: One Size Does Not Fit All

The majority of participants reported that currently approved and available commercial therapy options may not be sufficiently flexible or customizable to fulfill their or their children's individual needs. Among caregivers, features only available in open-source AID, in particular, the possibility of remote management was the main additional motivation. A wider range of features and adjustable settings to improve user experience may be beneficial for people with diabetes of all ages, which mirrors a recent study in very young children using a commercial AID [36]. Interestingly, for many adult respondents, *curiosity* was cited as an important motivation. In contrast, curiosity was a much lower motivating factor for caregivers who chose to build a system for more practical or psychosocial reasons.

Do-it-Yourself Is Not Do-it-Alone: The Impact of Peer Support

The ability to receive and provide support within the do-it-yourself (DIY) community and observe the success of others was an important motivating factor associated with opting to use open-source AID for some. Obtaining and exchanging information and advice from open forums limits the spread of misinformation because other users constitute a community of inquirers ready to challenge and correct spurious or misleading information [37]. Although open-source AID is individualized and patient focused, it is also a grassroots community-driven movement. The number of responses to our survey reflects the enthusiasm and importance of open-source AID. In challenging traditional top-down hierarchies in medicine, open-source AID presents a patient-focused initiative that serves to empower people with diabetes through personalized technology. Because of the availability of current technology and individualized innovations, open-source AID has previously been described as having the potential to democratize health care, revolutionizing treatment and the way people with diabetes as well as other stakeholders such as care teams, researchers, and device manufacturers view chronic conditions such as diabetes [38]. The importance of peer support in the context of open-source AID use has recently been highlighted elsewhere, and a sense of community underpinning the development and diffusion of open-source AID has been emphasized by individual users [39]. Further research should consider community phenomena as an integral part of the DIY experience.

Strengths and Limitations

This study is the first to investigate motivations of users and caregivers to build and use open-source AID. In addition, this is the largest study that reports self-reported clinical outcomes of open-source AID users globally and adds to the existing evidence base around glycemic outcomes in smaller cohorts [11-15]. At the time of data collection, it surveyed the majority of open-source AID users worldwide, with 897 respondents of a population estimated in 2018 (N=1500). The sample is impressive not only in size but also because people with diabetes from various continents and regions of the world are represented. Of other strengths, this study has been conducted by an interdisciplinary consortium, with members of the diabetes community directly involved. However, this firsthand experience should be acknowledged as a potential bias. In addition, a key limitation of the study is the fact that self-reported outcomes have not been corroborated by clinical records. Some may consider this has potential for inaccuracy, that is, by lacking precision as witnessed by the overaccumulation of rounded TIR values or to be biased by the specificity of the population that participated. However, other studies have found that real-world data are robust and reliable [40]. We acknowledge that open-source AID users constitute a specific group of people with diabetes who may be highly motivated, engaged, and willing to improve the quality of their diabetes care and life, limiting the scope of our findings to this group. However, a recent study of newly available commercial AID systems indicates that users are similarly motivated to achieve the best possible outcomes but are dissatisfied with postprandial glycemic outcomes under commercial AID systems [41]. The earliest adopters of available commercial AID technology may be more similar to the group of people with diabetes choosing open-source AID in terms of motivation and engagement than expected. The lack of widespread availability of AID technology in general, including commercial systems with regulatory approval, at the time of the study likely influenced the perspectives of people with diabetes choosing open-source systems. In the future, wider availability—and, importantly, better funding or insurance coverage of commercial AID systems—may further influence this cohort. Similarly, it remains to be seen if the predicted *second generation* of commercial systems—with a hypothesis of increased sophistication or improvements on the first-generation devices and algorithms—will enable people with diabetes to achieve results similar to those they are currently achieving with their chosen open-source AID system.

It should also be noted that those who benefit from and continue to use open-source AID may be motivated to share their positive experiences. Although the survey was open to people with type 2 and gestational diabetes, it was completed almost exclusively by adults and caregivers of children with type 1 diabetes. This is likely a reasonable reflection of the DIY community, but efforts need to be made in the future to encourage participation of those with other types of diabetes. The high percentage of respondents from Europe may be influenced by the fact that the majority of the research team is EU based, which may be another bias. This may also be explained by the characteristics of the European health services provision and reimbursement of diabetes-related technology, which may provide a greater degree of accessibility of the underlying components needed (eg, pumps and continuous glucose monitors). Language barriers may have limited responses from other parts of the world as the survey was only available in 2 languages. Finally, the majority of participants had a university degree, suggesting that open-source AID uptake is more common among people of higher socioeconomic status. Increasing socioeconomic inequalities in access to the underlying technologies needed to build an open-source AID system may help to explain some of these variations. Thus, further investigation into how the wider diffusion of open-source AID is conditioned by factors such as social class, gender, age, and geographic location is required.

Conclusions

This study provides new insights into the factors that motivate people to adopt *DIY* solutions in relation to their diabetes and beyond. Our findings contribute to a better understanding of the unmet needs of people with diabetes and some of the current challenges in the uptake of AID technology. This study, alongside other efforts in the DIY community space, can help key stakeholders, including academia, the medical device industry, regulators, health care providers, and care teams, to better address some of the fundamental gaps and needs that still exist for people with diabetes worldwide, even with the advent of first-generation commercial AID systems. The DIY movement has resulted in impactful solutions addressing the unmet needs of people with diabetes and represents an exemplary case of how informed and connected patients are shaping the direction of technological innovation in diabetes care and potentially for other areas of health care in the future.

Acknowledgments

The authors would like to thank the #WeAreNotWaiting and DIY community that supported and greatly contributed to this study. The OPEN project has received funding from the European Commission's Horizon 2020 Research and Innovation Program under the Marie Skłodowska-Curie Action Research and Innovation Staff Exchange grant agreement number 823902. J Speight and CH were supported by the core funding to the Australian Center for Behavioral Research in Diabetes provided by the collaboration between Diabetes Victoria and Deakin University. KB received the funding from the Berlin Institute of Health Digital Clinician Scientist Program and the SPOKES Wellcome Trust Translational Partnership Program. The funding sources had no involvement in the study.

Authors' Contributions

KB was the guarantor of this study. KB, DL, TS, HL, KR, J Schipp, KAG, CH, and BC performed the literature search. KB, SO, BC, A Tappe, DL, and KR designed the survey. KB collected the data. KB, DL, SO, TF, KAG, and BC analyzed and interpreted the data. A Thieffry conducted quantitative analyses and produced the associated figures. KB, DL, SO, and BC prepared the initial draft. All authors reviewed the manuscript, contributed revisions, and approved the final version.

Conflicts of Interest

All authors have completed the Unified Competing Interest form and declare the following: KB has received research grants from the Berlin Institute of Health, SPOKES Wellcome Trust, Stiftung Charité, and the German Diabetes Association (Deutsche Diabetes Gesellschaft). She has served as a speaker and advisory board member for Medtronic Diabetes and Hi.Health and received fees for medical consulting and public speaking from Roche Diabetes Care, Dexcom, Medtronic Diabetes, Diabeloop, BCG Digital Ventures, and Bertelsmann Stiftung, outside the submitted work. DL reports grants from the Robert Wood Johnson Foundation, JDRF, personal fees from Lilly, Diabeloop, Roche Diabetes Care, and Novo Nordisk and Tandem, outside the submitted work. J Speight has served on advisory boards for Janssen, Medtronic, Roche Diabetes Care, and Sanofi Diabetes; her research group (Australian Centre for Behavioural Research in Diabetes) has received honoraria for this advisory board participation and has also received unrestricted educational grants and in-kind support from Abbott Diabetes Care, AstraZeneca, Medtronic, Roche Diabetes Care, and Sanofi Diabetes. J Speight has also received sponsorship to attend educational meetings from Medtronic, Roche Diabetes Care, and Sanofi Diabetes and consultancy income or speaker fees from Abbott Diabetes Care, AstraZeneca, Medtronic, Novo Nordisk, Roche Diabetes Care, and Sanofi Diabetes, all outside the submitted work. KR is an advisory board member of Lilly Diabetes Care and Abbott Diabetes Care outside the submitted work. KB, DL, SO, A Tappe, and KAG are members of the open-source AID web-based community. All other authors have no conflict of interest to declare.

Multimedia Appendix 1

Questionnaire for people with diabetes.
[PDF File (Adobe PDF File), 92 KB-Multimedia Appendix 1]

Multimedia Appendix 2

Questionnaire for caregivers of children and adolescents with diabetes.
[PDF File (Adobe PDF File), 92 KB-Multimedia Appendix 2]

Multimedia Appendix 3

Supplementary tables 1 (codes and frequency of mentioned additional motivations as responses to the open-ended question) and 2 (detail of time-in-range improvements following open-source AID implementation).
[DOCX File , 16 KB-Multimedia Appendix 3]

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Abbreviations

AID: automated insulin delivery
DIY: do-it-yourself
DIYAPS: Do-It-Yourself Artificial Pancreas Systems
HbA_{1c}: glycated hemoglobin
OPEN: Outcomes of Patients' Evidence with Novel, Do-it-Yourself Artificial Pancreas Technology
TIR: time in range

2.3. Emotional and Physical Health Impact of Open-source AID: Qualitative Analysis of Lived Experiences.

In addition to the previously presented set of questions, the DIWHY survey further included two sets of open-ended questions at the end, which sought to capture lived experiences with open-source AID in the form of narratives. The richness and quality of the data prompted us to perform a separate qualitative analysis using a template codebook. Narratives from adults[119] and caregivers of children and adolescents were analyzed separately. [121] The following text is reproduced in full from the abstract of the publication:

Braune K, Krug N, Knoll C, Ballhausen H, Thieffry A, Chen Y, O'Donnell S, Raile K, Cleal B. Emotional and Physical Health Impact in Children and Adolescents and Their Caregivers Using Open-source Automated Insulin Delivery: Qualitative Analysis of Lived Experiences. *J Med Internet Res.* 2022 Jul 14;24(7):e37120. https://doi.org/10.2196/37120

Narratives of 60 caregivers from 15 countries were analyzed. There were a combined 107 responses to both questions. Four topics, “Emotional and Quality of Life Impact,” “Physical Health Impact,” “Challenges,” and “Support” were used to organize the qualitative data, recognizing the fact that participants’ responses were partially primed by the framing of the open-ended questions.

A range of emotions as well as improvements in quality of life and physical health were reported by the participants. Their experiences with the initiation of open-source AID were associated with a range of emotions, from worry, despair, and great hopes before use, to excitement, relief, and a feeling of empowerment when they had implemented the system. Participants expressed concerns associated with opting for open-source AID, but they also highlighted the deep-rooted frustration and dissatisfaction with commercially available therapy options. Therefore, using open-source AID was never a decision taken lightly but at the point when all other options appeared inadequate and insufficient.

Once the choice was made, improvements in quality of life, and reduced burden of diabetes management were frequently mentioned. The use of open-source AID systems enabled families to shift their focus away from diabetes therapy. Caregivers were less worried about nocturnal hypoglycemia and the occurrence of hypoglycemia outside their family homes. This led to increased autonomy for the child. Simultaneously, the glycemic outcomes and sleep quality of both the children and caregivers improved. Nonetheless, the acquisition of suitable hardware and technical setup could sometimes be challenging. The *#WeAreNotWaiting* community was reported as the primary source of practical but also emotional support.

These findings highlight the benefits and transformative impact of open-source AID and peer-support on children with diabetes and their caregivers and families, where commercial AID systems were not available or suitable, and add new evidence to quantitative studies on psychosocial outcomes of open-source AID users.

Original Paper

Emotional and Physical Health Impact in Children and Adolescents and Their Caregivers Using Open-source Automated Insulin Delivery: Qualitative Analysis of Lived Experiences

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Abstract

Background: Given the limitations in the access and license status of commercially developed automated insulin delivery (AID) systems, open-source AID systems are becoming increasingly popular among people with diabetes, including children and adolescents.

Objective: This study aimed to investigate the lived experiences and physical and emotional health implications of children and their caregivers following the initiation of open-source AID, their perceived challenges, and sources of support, which have not been explored in the existing literature.

Methods: Data were collected through 2 sets of open-ended questions from a web-based multinational survey of 60 families from 16 countries. The narratives were thematically analyzed, and a coding framework was identified through iterative alignment.

Results: A range of emotions and improvements in quality of life and physical health were reported, as open-source AID enabled families to shift their focus away from diabetes therapy. Caregivers were less worried about hypoglycemia at night and outside their family homes, leading to increased autonomy for the child. Simultaneously, the glycemic outcomes and sleep quality of both the children and caregivers improved. Nonetheless, the acquisition of suitable hardware and technical setup could be challenging. The #WeAreNotWaiting community was the primary source of practical and emotional support.

Conclusions: Our findings show the benefits and transformative impact of open-source AID and peer support on children with diabetes and their caregivers and families, where commercial AID systems are not available or suitable. Further efforts are required to improve the effectiveness and usability and facilitate access for children with diabetes, worldwide, to benefit from this innovative treatment.

International Registered Report Identifier (IRRID): RR2-10.2196/15368

(J Med Internet Res 2022;24(7):e37120) doi: 10.2196/37120

KEYWORDS

automated insulin delivery; closed-loop; do-it-yourself; open source; peer support; patient-reported outcomes; lived experiences; qualitative analysis; mobile phone

Introduction

Background

Type 1 diabetes (T1D) is a challenging chronic condition for children, adolescents, and their caregivers and is associated with long-term macro- and microvascular complications and the consequent risk of increased morbidity and mortality. Therapeutic guidelines of the International Society for Pediatric and Adolescent Diabetes recommend a target hemoglobin A_{1c} (HbA_{1c}) level of <7% for children and adolescents with T1D, albeit a target that must be balanced with the individual disease burden and risk of hypoglycemia [1].

The management of diabetes is particularly challenging during childhood and adolescence. Day-to-day tasks often involve an entire family. Children show variability in insulin sensitivity related to physical growth and sexual maturation, which requires frequent adjustments in insulin dosing [2]. With the dynamic physical activity and nutritional intake of young children, their glycemic levels can fluctuate rapidly [3]. In addition, the transition of responsibility for diabetes management from caregivers to children and their increasing independence during adolescence can often further complicate this difficult dynamic. Adolescents and young adults with diabetes frequently struggle to meet the recommended glycemic targets and are particularly vulnerable to acute complications, such as severe hypoglycemia and diabetic ketoacidosis [4,5]. Living with T1D also impacts the quality of life and mental health [6]. Thus, psychosocial support and individualized treatment play an important role in diabetes care in this age group [1].

Recent advances in diabetes technology have led to the development of automated insulin delivery (AID) systems, also known as hybrid closed-loop, closed-loop, or artificial pancreas systems. In AID, a control algorithm automatically adjusts the insulin delivery of an insulin pump in response to readings from a continuous glucose monitor (CGM) to help improve glycemic levels and variability and reduce the day-to-day burden in diabetes management [7-10].

Although commercially developed AID systems have recently become available in select countries, not all are licensed for use by children. Currently, CamAPS FX (CamDiab Ltd) is the only AID system that has received regulatory approval for children aged ≤7 years but is restricted in interoperability and only compatible with one specific CGM and pump model, only available in select European countries, and must be individually purchased on a subscription basis. Young children are often the last cohort to be included in a clinical trial. Off-label use of commercial AID in this group shows only minor time in range (TIR) and HbA_{1c} improvements compared with older individuals, indicating a higher hypoglycemia risk for this age group [11,12].

Parents and caregivers of children with diabetes have been in the vanguard of the drive toward AID systems. Under the hashtag *#WeAreNotWaiting*, a web-based patient community has sought to create resources and tools for diabetes management since 2013. The movement began with the "Nightscout" project, where caregivers created a cloud-based platform for alerts and remote glucose monitoring for their children. Eventually, the community developed control algorithms for the AID. In these "do-it-yourself" or "open-source" AID systems, commercially available sensors for CGM and insulin pumps are linked to a microcontroller or an app on a smartphone. The source code and documentation of these systems were shared freely on the web. In addition, the community provides both practical and emotional peer support with setup and maintenance. To date, open-source AID systems have not been approved by regulatory bodies and must be built and used at an individual risk. An estimated number of >10,000 individuals, worldwide, use open-source AID. Approximately 20% of these users are children and adolescents, where their caregivers are building and maintaining the systems on their behalf [13,14].

Although evidence based on the clinical outcomes of open-source AID is growing, there are relatively few published studies on the lived experiences of people with diabetes using this technology and fewer still, concerning children and adolescents with diabetes and their caregivers. Previous studies have found improvements in HbA_{1c} and percentage TIR in various age groups, including children and adolescents [13-16]. As part of the Outcomes of Patients' Evidence with Novel, Do-it-Yourself Artificial Pancreas Technology (OPEN) [17] project, we previously assessed self- or caregiver-reported clinical outcomes [14,15] and motivations [14] to build open-source AID. Improved sleep quality was a primary reason for caregivers to use AID, followed by improved glycemia and reduced complication risk for the child, and the option of remote monitoring and control via the internet, thus reducing disease burden and enabling more independence for children. A recently published international consensus statement on open-source AID supported its use for children and adolescents, as long as the child's welfare is being considered by health care professionals (HCPs) and caregivers who are setting up open-source AID systems for their children, with the child's assent and engagement [18].

Objectives

This study aimed to examine four specific, albeit interrelated, aspects of the lived experiences of children and adolescents with diabetes and their caregivers on their journey to becoming open-source AID users: (1) the emotional health implications of open-source AID, (2) the experience of changes to physical health using open-source AID, (3) perceived challenges with the implementation and maintenance of open-source AID, and (4) sources of support during the implementation and maintenance of open-source AID. Self-reported glycemic outcomes and sleep have also been reported to provide further context for lived experience data.

Methods

The results were obtained from answers to 2 open-ended questions included in a cross-sectional web-based survey examining the use of open-source AID. The survey titled "DIWHY" was conducted between November 2018 and March 2019 [17].

Ethics Approval

Ethics approval was provided by Charité—Universitätsmedizin Berlin (EA2/140/18).

Survey Design

The survey (Multimedia Appendix 1) was created by the patient-led OPEN consortium in collaboration with further users of open-source AID and was piloted with a small group before the final release. The Checklist for Reporting Results of Internet E-Surveys (CHERRIES) guideline was used to guide the survey development [19]. The survey included 39 items in total, including questions on the child's demographic information, the open-source AID system in use, HbA_{1c}, and TIR before and after initiation, and 2 composite open-ended questions, which sought to capture lived experiences with open-source AID in the form of narratives. Participants could enter a free-text answer with up to 1000 words for each of the 2 questions.

The first question inquired about the individual journey of the caregiver and child toward setting up and using an open-source AID system, including sources of information, support, motivation, and emotional impact:

> *If you would like, please share your personal story about why you decided to build your own artificial pancreas system and how you got started. Feel free to share any experiences that had a significant impact on how you manage your diabetes as well. This story can be as short or as long as you wish.*

The second question addressed the perceived changes following the initiation of open-source AID and the challenges experienced:

> *When reflecting on your personal DIY closed-loop story, you may want to consider the following: When did you first hear about DIY closed-loop systems and how did you look for further information? Were there any key events or experiences that were a factor in your decision to begin closed looping? Was there anyone else involved in helping you come to decision to begin DIY closed-looping? For example a friend, family member or an online support group? What were your emotions in the lead-up to building your DIY closed-loop system? For example, had you any major hopes or fears?*

Participants and Recruitment

Participants were eligible if they were caregivers of a child or adolescent with diabetes (type 1, 2, or other), using an open-source AID. There were no restrictions on age, time since diagnosis, or commencement of open-source AID. Participants were recruited using public announcements on the OPEN project website and social media channels, such as the Facebook groups "Looped" (>6000 members) and "AndroidAPS Users" (>1800 members as of November 2018), regional subgroups, and tweets under the hashtags *#WeAreNotWaiting* and *#DIYAPS*. All posts were organic, meaning that their web-based reach was not affected by any monetary influence. Participants consented electronically and joined voluntarily and anonymously with the children's assent. The survey was available in German and English.

Data Collection and Analysis

Data were collected and managed using the REDCap (Research Electronic Data Capture; Vanderbilt University) electronic data capture tools hosted at Charité. Following deidentification of the data set, qualitative analysis was performed using NVivo 12 (QSR International, 2018) software. The narratives were analyzed using an approach based on the principles of Template Analysis [20]. Acknowledging the response priming included in the framing of the open-ended questions, initial coding (by KB, CK, and NK) sorted the data in accordance with 4 predefined topics: physical health impact, emotional impact, sources of support, and perceived challenges. To establish alignment, all 3 coders analyzed and sorted the first 30 narratives into 4 topics. Using the "coding comparison" function in NVivo, it was established that there was a high level of agreement among the coders. Level of agreement was defined as the number of units of agreement divided by the total units of measure within the data item, as a percentage. In the next phase of data analysis, all data extracts sorted into the 4 topics were coded inductively and independently by the 3 coders, which led to an extensive set of descriptive codes. Finally, codes were collaboratively collated and used to establish a set of higher-level codes, each of which was described in detail in a codebook. The template codebook was refined and modified in discussions between the 3 coders and the project group.

To test the utility and resonance of the themes as captured in the template, 2 coders (HB and BC) further used the template to analyze the narratives independently of one another. The initial group of coders (KB, CK, and NK) then refined the template based on the coding and feedback provided during this process. A third independent coder (SO) then analyzed the data using the refined template. After this final review of coded responses and the template, it was agreed that code saturation had been achieved, and all major themes were identified.

Retrospective and caregiver-reported clinical outcome data were analyzed within the R (R Foundation for Statistical Computing) programming framework. Only respondents who reported at least one value before and after open-source AID commencement were considered, leading to sample sizes of N=52 and N=36 for HbA_{1c} and TIR, respectively. The HbA_{1c} values were averaged. Moreover, 1-tailed Student *t* tests were conducted with the parameter *paired=TRUE*. Figures were produced using the ggplot2 package.

Results

Participant Characteristics

In total, 60 caregivers (35.7% of all 168 participants in the DIWHY study) from 16 countries responded to the open-ended questions on behalf of their children, and there were combined 107 responses to both questions. All children and adolescents were diagnosed with T1D, aged between 3 and 20 years, and using an open-source AID for a duration of <1 month and up to 3 years. The caregiver and child demographics as well as the clinical features of the 60 participants who responded to the open-ended questions are summarized in Table 1, whereas the characteristics of the other 108 participants of the DIWHY study are included in Table S1 in Multimedia Appendix 2.

Of the 60 children and adolescents, the average HbA_{1c} levels (of participants with reported measures both before and after AID commencement, see Methods section) decreased from 7.0% (SD 0.8; 53 mmol/mol) to 6.3% (SD 0.7; 45 mmol/mol; 1-tailed paired *t* test; $P<.001$; Figure 1), and TIR increased from 60.7% (SD 15.1) to 80.4% (SD 9.1; 1-tailed paired *t* test; $P<.001$) following the initiation of open-source AID (Figure 2).

Table 1. Children’s and caregivers’ demographic and self-reported clinical characteristics (N=60).

	Children and adolescents
Child’s gender, n (%)	
Female	26 (43)
Male	34 (57)
Other	0 (0)
Child’s age (years), mean (SD)	10.0 (4.5)
Type of diabetes, n (%)	
Type 1	60 (100)
Type 2	0 (0)
Other	0 (0)
Duration of diabetes (years), mean (SD)	5.3 (4.3)
Duration of open-source AID[a] use (months), mean (SD)	10.9 (9.2)
Type of open-source AID, n (%)	
AndroidAPS	28 (47)
OpenAPS	21 (35)
Loop	17 (28)
Other[b]	2 (3)
Region and country of residence, n (%)	
Europe	47 (78)
Germany	12 (20)
United Kingdom	9 (15)
Finland	7 (12)
Sweden	5 (8)
Czech Republic	3 (5)
Spain	3 (5)
Slovakia	3 (5)
Others[c]	14 (12)
North America	6 (10)
United States	4 (7)
Canada	2 (3)
Asia	
South Korea	3 (5)
Western Pacific	
Australia	5 (8)
Caregiver’s education: highest completed, n (%)	
University degree or diploma	38 (63)
Doctorate	9 (15)
High school	8 (13)
Other	5 (8)
Caregiver’s occupational status, n (%)	
Full-time	39 (65)
Part-time	15 (25)

	Children and adolescents
Unemployed	3 (5)
Other	3 (5)
Annual household income (US $), n (%)	
<20,000	4 (7)
20,000 to 34,999	5 (8)
35,000 to 49,999	4 (7)
50,000 to 74,999	11 (18)
75,000 to 99,999	10 (17)
>100,000	16 (27)
I would rather not say	3 (3)
Not stated	7 (12)

[a] AID: automated insulin delivery.

[b] "Open loop with AndroidAPS" and "custom development."

[c] Austria, Bulgaria, Croatia, and Greece.

Figure 1. Outcomes of open-source automated insulin delivery (AID) implementation. Density distributions of hemoglobin A1c (HbA1c) before and after commencement of open-source AID (line colors); n=52.

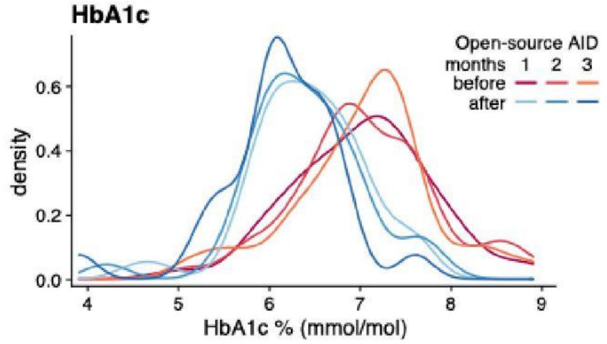
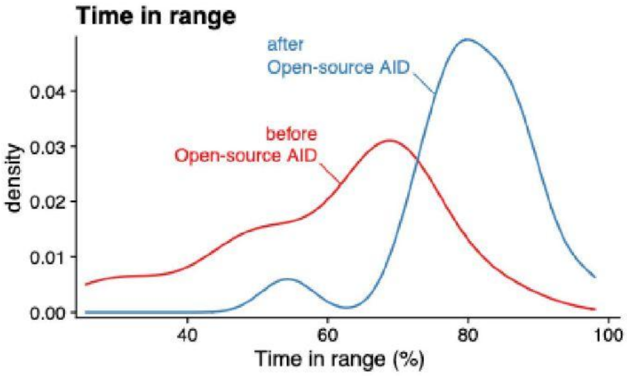


Figure 2. Outcomes of open-source automated insulin delivery (AID) implementation. Density distributions of time in range (70-180 mg/dL/3.9-10.0 mmol/L) before and after commencement of open-source AID (line colors); n=36.



Template Analysis

Overview

A total of 4 topics, "Emotional and Quality of Life Impact," "Physical Health Impact," "Challenges," and "Support" were used to organize the qualitative data, recognizing the fact that participants' responses were partially primed by the framing of the open-ended questions. The data were subsequently analyzed to generate codes within these topics to expand and illustrate them. The codes are described with examples of illustrative quotes, the number of occurrences, and the respondents' profiles, as shown in Table 2.

Table 2. Final codebook template including deductively (A-D) and inductively (A1-D2) developed codes.

Topic	Occurrences[a], n	Illustrative quote	Respondent profile
Emotional and quality of life impact (A)			
Worry and fear (A1): describes difficult emotions such as worry and fear of caregivers related to living with and managing diabetes, experiencing hypoglycemia, and developing long-term complications. It also refers to the concern of not being able to build and maintain the open-source AID[b].	16	"I was very skeptical and scared. Over time more information became available and the safety became clear and compelling. We realized we would be safer with a Loop than without. I was scared that others would not be able to comprehend this (because even endocrinologists fail to understand fully the burden and dynamism of type 1) and that they would question whether we were putting our child at risk and make a report about us to child well-being authorities."	Caregiver of a boy aged 13 years, from Australia; aged 6 years at diagnosis; using Loop for 2.5 years
Desperation and frustration (A2): describes feelings of desperation and frustration of caregivers related to living with diabetes and caring for a child with diabetes, diabetes management, and the implementation of the open-source AID.	14	"As a mom I was desperate, I was tired from being up all night, I was getting frustrated from teen hormones and I was willing to try almost anything to help both of us."	Caregiver of a girl aged 17 years, from the United States; aged 2 years at diagnosis; using Loop for 33 months
Uncertainty (A3): describes uncertainty and insecurities of caregivers regarding legal grounds, missing regulatory guidelines, and the trust of reliability in an open-source AID system.	6	"Nevertheless, there is still a legal uncertainty and at the moment we just dare to use the loop in our own four walls. In the morning we switch to the normal Any-Dana A app, in the evening back to AndroidAPS."	Caregiver of a boy aged 12 years, from Germany; aged 11 years at diagnosis; using OpenAPS for 2 weeks
Anticipation, hope, and wishes (A4): describes positive and hopeful emotional states of anticipation and great expectations of caregivers that lie on the AID for improved diabetes management and hope for improved quality of life. Also includes wishes for access to an AID system for everyone.	24	"Major driver for the project was to give my son more years without complications by lowering the HbA_{1c}[c]."	Caregiver of a boy aged 18 years, from Finland; aged 1 year at diagnosis; using OpenAPS for 1 year
Excitement, appreciation, and satisfaction (A5): describes all positive emotions of caregivers and children related to the experience with the open-source AID in daily use including excitement, happiness, satisfaction with the results, and appreciation.	51	"I remember the exact place I stood watching the [OpenAPS] log [roll] and seeing the [preflight] was successful and then that the loop was complete. I was in shock that we could do this and that I could afford it and that my child was going to [be] better off because of this. It was a defining moment in my life as a parent. No one could stop me giving my child the care they needed anymore. Especially not a company who places shareholders above clients (which legally they must do). I was no longer at the mercy of markets, profits, politics and whims, I had the capacity to provide for my child again."	Caregiver of a boy aged 13 years, from Australia; aged 6 years at diagnosis; using Loop for 2.5 years
Security and reassurance (A6): relates to caregivers feeling more empowered, more secure, and reassured owing to the use of an open-source AID system, through automation, remote monitoring, and control, as well as experiencing success and observing the success of others using an open-source AID.	45	"Our child never woke up if she had a low even though her pump was sounding a very loud alarm. And because she slept in her own room we were afraid of sometimes not hearing the pump alarm either. So Nightscout sounded like the perfect solution, as we could then be woken up by any mobile phone or iPad. This added a lot to our feeling of security."	Caregiver of a girl aged 10 years, from Finland; aged 7 years at diagnosis; using OpenAPS for 3 months

Topic	Occurrences[a], n	Illustrative quote	Respondent profile
Child empowerment and independence (A7): describes the degree of independence, autonomy, and self-determination in children and adolescents using the open-source AID, enabling them to participate in daily life and social activities in a responsible and self-determined way.	25	"Daughter can work without having to phone me for advice. She has been on holiday [for the] first time without parents. She[...] now feels confident to consider leaving home."	Caregiver of a girl aged 20 years, from Croatia; aged 10 years at diagnosis; using OpenAPS for 3 months
Physical health impact (B)			
Glycemic outcome improvement (B1): refers to improved time in range and HbA_{1c} levels, less glucose variability, fewer hypo- and hyperglycemic events, and reduced long-term complication risk.	36	"Every single morning she's in range. If at night she's not, we know that by the morning she will be, and she [will get] there safely. It's really good."	Caregiver of a girl aged 18 years, from the United Kingdom; aged 11 years at diagnosis; using AndroidAPS for 8 months
Quality of life improvement (B2): refers to the mentioned improvements of quality of life and describes the degree to which an individual is healthy, comfortable, and able to participate in or enjoy life events.	14	"I keep a continuous discussion with my twins that both use DIY closed loops, through texting. I use this way to share my remote observations on their status, while they concentrate on their university studies, or simply enjoy their lives. I inform them this way about a failing connection, a reservoir getting empty, a battery needing charging, or to drink some juice to avoid a coming low."	Caregiver of a boy, aged 20 years, from Greece; aged 2 years at diagnosis; using OpenAPS for 1 year
Improved sleep (B3): denotes all aspects of improved sleep quality for either caregivers or children such as increased sleep duration, fewer sleep interruptions, and feeling better rested in the morning.	40	"It's been as good as expected, and better still as now we sleep. You forget how much sleep deprivation clouds your judgment."	Caregiver of a boy aged 8 years, from the United Kingdom; aged 7 years at diagnosis; using AndroidAPS for 3 months
Facilitated diabetes management (B4): relates to the simplifications of the individual diabetes management due to the open-source AID, such as fewer interactions with the technology or between caregiver and child; for example, through remote control and automation. It also includes the age-appropriate transfer of responsibilities from caregivers to adolescents to self-manage diabetes therapy.	42	"There is no comparison with earlier. There used to be 5-6 blood measurements per child per day, and that was all. With or without a pump, every meal was a challenge. For 1.5 years, the APS has been adjusting the blood sugar value after the bolus, adding more insulin if the value increases, or adjusting the delivery if the value drops."	Caregiver of a boy aged 20 years, from Greece; aged 1 year at diagnosis; using OpenAPS for 17 months
Challenges (C)			
Access to technology (C1): relates to the issue concerning obtaining access to the component parts of an open-source AID system, such as loopable pumps and supplies, CGM[d], and additional required hardware.	27	"Getting the hardware was most frustrating. I tried to buy the hardware from the manufacturer but in Sweden you could not do that without a subscription from your doctor. I ended up getting a second hand Dana R pump from another patient who upgraded to a newer pump."	Caregiver of a boy aged 3.5 years, from Sweden; aged 2 years at diagnosis; using AndroidAPS for 4 months
Out-of-pocket expenses (C2): describes barriers regarding out-of-pocket expenses and cost for the hardware and supplies related to insurance coverage, household income, and other financial challenges in access.	6	"We were concerned about the cost of sensors. They are not covered by private health here and it cost approximately US $5000 a year when we started. Now kids are covered, but when they turn 21 that ends. We are still worried about covering that bill in the future."	Caregiver of a boy aged 13 years, from Australia; aged 6 years at diagnosis; using Loop for 2.5 years
Self-perceived lack of technical skills (C3): denotes the issue of yet self-perceived limited knowledge and missing technical skills caregivers are experiencing to set up open-source AID initially.	9	"Major fears I wouldn't be able to understand the technology."	Caregiver of a girl aged 12 years, from Australia; aged 11 years at diagnosis; using Loop for 1 month

Topic	Occurrences[a], n	Illustrative quote	Respondent profile
Lacking health care provider support (C4): relates to instances where caregivers reflect upon their children's health care providers' lack of support and negative attitudes.	14	"Fight with our own diabetologist to get a DANA RS prescribed. Although we didn't talk openly about looping, she has repeatedly emphasized that we only want the DANA RS pump for looping, which is not allowed. We have won, but now hide the loop, which cannot be a permanent state. We need medical care in which we can communicate openly."	Caregiver of a boy aged 12 years, from Germany; aged 11 years at diagnosis; using AndroidAPS for 2 weeks
Impracticability of carrying additional devices (C5): relates to the necessity for children and adolescents having to carry additional devices for open-source AID and protect them from breaking.	9	"It also meant that our daughter had to carry an extra item, i.e. the mini-computer, with her during the day."	Caregiver of a girl aged 10 years, from Finland; aged 4 years at diagnosis; using OpenAPS for 2 months
Transition from childhood to adulthood (C6): describes challenges associated with the transition from childhood to adulthood, regarding physical and hormone-related changes during puberty and psychosocial challenges in adolescents living with T1D[e] and taking over responsibility for their own therapy with an open-source AID.	10	"While our control has improved, it is still significantly more variable than I would expect based on the results I see from others in the community. My son is highly insulin sensitive [...], variable in his activity level and intensity [...], and experiencing substantial swings in carb ratios, basal rates, and insulin sensitivities as he is going through great physiological changes in puberty."	Caregiver of a boy aged 11 years, from the United States; aged 8 years at diagnosis; using OpenAPS for 1 year
Setup and maintenance effort (C7): relates to difficulties caregivers experience while setting up open-source AID. This includes an unexpected high time effort and multiple throwbacks while initially setting up the system, technical difficulties with running and maintaining the system, and fine-tuning to find the right settings and parameters to accomplish desired results.	54	"As a family, we feel very happy that we can finally control the blood sugar levels of our children in the desired area, even if it takes great care to do everything right. Batteries (pump, CGM, mobile phone, OpenAPS computer) must be regularly charged or exchanged, the CGM must be continuously calibrated, insulin must be refilled, every 3 days you exchange the catheter, every 14 days the CGM, etc. With such a result, no problem. The hundreds of hours I've spent on it are worth it."	Caregiver of a boy aged 20 years, from Greece; aged 1 year at diagnosis; using OpenAPS for 17 months
Support (D)			
Community peer support (D1): includes actively received or provided community peer support. This support could either be provided on the web through social media groups and communities or in person through life events, individual people, or meet-ups. Does not include individual key people or role models.	45	"So in that same Facebook group I started to learn about DIY artificial pa[n]creases and I joined another, international group called Looped to learn more. I then asked around and I was told that OpenAPS was the most advanced of the three options and decided to go for that."	Caregiver of a girl aged 10 years, from Finland; aged 7 years at diagnosis; using OpenAPS for 9 months
Individuals as role models (D2): describes one or multiple key people, often members of the #WeAreNotWaiting community, who inspired or directly supported caregivers and children in building an open-source AID.	15	"I found Tim Street's Diabettech website and started following him on twitter/blog at [the] same time. He was coming to speak at a medical conference in Edinburgh and was going to a [type 1] meet up. I gate-crashed the meet in the pub and had to wait until the end[...] I asked him to show me his pancreas! [...] Tim organized the first U.K. meet up in London and offered me an old transmitter which would complete my build. My son and I flew to London and we got going that evening."	Caregiver of a boy aged 12 years, from the United Kingdom; aged 8 years at diagnosis; using OpenAPS
Web-based resources (D3): describes web-based resources such as wiki blogs, tutorials, websites, webinars, and other documentation.	19	"Once I had the equipment, I set the system up in two nights, the instructions available on the web are very clear and I found it easier tha[n] expected."	Caregiver of a girl aged 10 years, from Finland aged 6 years at diagnosis; using OpenAPS for 3 months

Topic	Occurrences[a], n	Illustrative quote	Respondent profile
Health care professionals (D4): this code refers to the support provided by health care professionals, such as pediatricians, endocrinologists, and other members of the diabetes teams, including help with setup, access to components, and fine-tuning of settings.	8	"Endocrinologist was supportive even though legally couldn't recommend it."	Caregiver of a girl aged 12 years, from Australia; aged 11 years at diagnosis; using Loop for 1 month

[a] Defined by the number of codes assigned to a text segment.

[b] AID: automated insulin delivery.

[c] HbA_{1c}: hemoglobin A_{1c}.

[d] CGM: continuous glucose monitor.

[e] T1D: type 1 diabetes.

Topic 1: Emotional and Quality of Life Impact

For respondents, experiences with the initiation of open-source AID were associated with a range of emotions, from worry, despair, and great hopes before use, to excitement, relief, and a feeling of empowerment after implementing the system. Caregivers in the sample expressed concerns when opting to choose an open-source AID, but it also highlights the deep-rooted frustration and dissatisfaction with commercially available solutions for diabetes management. Therefore, choosing to opt for an open-source AID was never a decision taken lightly but at the point when all other options appeared inadequate and insufficient.

Once the choice was made, quality of life improvements and reductions in the burden of diabetes management were frequently mentioned. With the automation of insulin delivery, families could reboot everyday life without diabetes management being constantly the center of attention, empowering children and caregivers to experience more freedom and flexibility:

> *Now we plan for things in our lives. We have been thinking of getting a pet, [and have] started to remodel our house. [We] made sure both kids have passports because now it feels like we actually can travel and show them the world.* [Caregiver of boy aged 8 years, from Sweden; aged 1 year at diagnosis; using OpenAPS and AndroidAPS for 1.5 years]

The option to remotely follow and control glycemic levels, treatments, and insulin delivery via Nightscout reassured caregivers was specifically mentioned as a reason to choose open-source AID. Caregivers experienced fewer worries about their children experiencing hypoglycemia at night or away from home, which led to greater independence, empowerment, and age-appropriate participation of children in their own treatment.

The complexity of the implementation process of open-source AID raised concerns among some of the respondents, who were initially worried about not being able to manage the technical setup on their own. Uncertainties regarding the safety of new and unfamiliar therapies have also been mentioned. Furthermore, they were unsure whether the new treatment would be accepted by their children's health care team as well as their wider social environment. In addition, some expressed the need for regulatory approval and improved access to AID for everyone:

> *I wonder how it can be that such a development is not already established? Why does it take so long? Do the old systems have to be remunerated? The loopers show how it works, how can it be that with so much added value, the professional institutions are still so lethargic?* [Caregiver of a boy, from Germany, aged 1 year at diagnosis; using Loop for 3 months]

Overall, caregivers described the transition to open-source AID as a predominantly positive experience for the entire family. They were highly satisfied with the outcomes and benefits for their children's emotional and physical health and perceived open-source AID as the best therapy option available:

> *If I could give my pancreas to my son, I would. This is the next best available option.* [Caregiver of a boy aged 12 years, from the United Kingdom; aged 3 years at diagnosis; using Loop for 1 month]

Topic 2: Physical Health Impact

Improvements in glycemia, such as improvements in HbA_{1c} and TIR levels, as well as less hypoglycemia and fewer glucose fluctuations, have been extensively described:

> *Every single morning she's in range. If at night she's not we know that by the morning she will be, and she [will get] there safely.* [Caregiver of a girl aged 18 years, from the United Kingdom; aged 11 years at diagnosis; using AndroidAPS for 8 months]

In addition to diabetes-related health improvements, better sleep quality was frequently highlighted by the respondents. Before using an open-source AID, many caregivers were not able to sleep through the night as they were concerned with nighttime hypoglycemia or the administration of correction doses of insulin, poor sleep, and reduced quality of life. With an open-source AID, they were released from frequent check-ups and the associated emotional pressure:

> *We were waking at 11 pm, 2 am, 5 am, 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 [of] hours at [a] time. Now, we all sleep all night.* [Caregiver of a girl aged 8 years, from the United States; aged 4 years at diagnosis; using Loop]

Even in cases with little improvement in glycemic outcomes, where HbA_{1c} and TIR levels were in or close to the recommended targets before the initiation of open-source AID, caregivers noted that the amount of effort required to achieve these results was significantly diminished. As this point highlights, the data repeatedly pointed to the ways in which physical outcomes are inextricably intertwined with emotional outcomes when considering diabetes management.

Topic 3: Challenges

Difficulties in accessing compatible hardware have frequently been reported. This was mainly associated with differences in the availability of insulin pumps and sensors and reimbursement policies among countries and also with out-of-pocket expenses. Some participants raised concerns regarding access to components and financial aspects of maintaining their open-source AID system in the future:

> *We were concerned about the cost of sensors. They are not covered by private health here and it cost approximately US[D] 5000 a year when we started. Now, kids are covered, but when they turn 21 that ends. We are still worried about covering that bill in the future.* [Caregiver of a boy aged 13 years, from Australia; aged 6 years at diagnosis; using Loop for 2.5 years]

Understanding the documentation and initial setup process is time consuming and challenging, especially for caregivers with little pre-existing knowledge in technology. Ultimately, the complex setup procedure led to a better understanding of the functionalities of open-source AID, enabling caregivers to better respond to technical issues when they occurred. Being part of the *#WeAreNotWaiting* community, caregivers felt gratitude for the available peer support and resources to help with the technical and practical aspects.

Once the setup was successfully managed, the next perceived challenge was the iterative determination of the appropriate settings and therapy parameters to generate satisfactory results. This “fine-tuning” was described as requiring considerable time and endurance. The need to carry around additional devices (eg, a microcontroller or bridge device to remotely communicate between the phone and insulin pump) poses further practical challenges for children in daily life.

The attitudes of HCPs involved in diabetes care of children were described as mixed, ranging from proactive support to refusal:

> *After detailed research, the reserved position of our center could not stop us either. In the past year, I have repeatedly had the impression of knowing more about the disease and the possible forms of therapy than the doctors at our center.* [Caregivers of a girl aged 10 years, from Germany; aged 6 years at diagnosis; using Loop for 1 year]

Despite these reported clinical and quality of life improvements, some expressed uncertainty arising from a lack of support from health care providers. Consequently, a family decided not to disclose the use of open-source AID to their health care team, which caused feelings of isolation, disappointment, and misunderstanding:

> *Although we didn't talk openly about looping, [our diabetologist] has repeatedly emphasized that we only want the DANA RS pump for looping. [...] We[...] now hide the loop, which cannot be a permanent state. We need medical care in which we can communicate openly.* [Caregiver of a boy aged 12 years, from Germany; aged 11 years of age at diagnosis; using AndroidAPS for 2 weeks]

Topic 4: Sources of Support

Participants frequently approached the *#WeAreNotWaiting* community for their support. Social media groups play a key role, where many users share their experiences, respond to questions, discuss related topics, and provide peer support. These were also sources of reassurance in cases of concerns or uncertainties. The extent and quality of peer support available was often a key factor in their decision-making, establishing a sense of trust in the systems, even in the absence of health care provider support or regulatory approval:

> *So in that same Facebook group I started to learn about DIY artificial pa[n]creases and I joined another, international group called Looped to learn more. I then asked around and I was told that OpenAPS was the most advanced of the 3 options and decided to go for that.* [Caregiver of a girl aged 10 years, from Finland; aged 7 years at diagnosis; using OpenAPS for 9 months]

Besides the peer support caregivers found on the web, they attended in-person meetings and local meet-ups with members of the community. Lectures, workshops, and public presentations of open-source AID developers, researchers, and other users and parents enhanced their motivation to start their own journey toward open-source AID. Key individuals who were integral in the development of open-source AID are personally named on a number of occasions. The perceived integrity and altruism of these individuals were also key in creating a sense of confidence and trust in the systems:

> *I found Tim Street's Diabettech website and started following him on Twitter [...]. He was coming to speak at a medical conference in Edinburgh and was going to a [type 1] meet up. I gate-crashed the meet in the pub and had to wait until the end[...] I asked him to show me his pancreas! [...] My son and I flew to London and we got going that evening.* [Caregiver of a boy aged 12 years, from the United Kingdom; aged 8 years at diagnosis; using OpenAPS]

Although HCPs could not prescribe open-source AID systems owing to the absence of regulatory approvals, some were very supportive of the children's and caregivers' decision to use open-source AID. Support by HCPs has mostly been reported regarding access to compatible components, such as specific insulin pumps and CGM types that are prescriptible. In a small number of cases, individual caregivers reported that their health care provider initiated a discussion about open-source AID and directed them to relevant sources of information. Conversely, a lack of support from HCPs was also articulated in a number of accounts, although this usually took the form of "turning a blind eye" and passivity, and very few reported being actively opposed by their health care provider. Where such cases did occur, it usually took the form of preventing caregivers from acquiring the hardware needed to set up an open-source AID system.

Discussion

Principal Findings

In this qualitative analysis, we described the emotional and physical health impact of open-source AID use in children or adolescents and their caregivers, as well as their perceived challenges and sources of support.

Overall, caregivers reported a range of emotions before and after the initiation of open-source AID use. Before initiation, for example, participants reported frustration and dissatisfaction with their existing diabetes management solutions and anticipation and excitement—sometimes marked with anxiety and trepidation—at the prospect of using an open-source AID. Likewise, the experience of using open-source AID evoked both great joy and relief, but this was also tinged, for some, with frustration and worry. Improvements in children's diabetes management, glycemic outcomes, physical health beyond diabetes, and emotional well-being were highlighted in the narratives. Furthermore, sleep quality and quality of life improved for both children and caregivers. The initial challenges were difficulties in accessing the required components, lack of confidence in technical skills for setup and maintenance, concerns about the response from health care teams, and the wider social environment of the family. Later, finding and "fine-tuning" of the right therapy settings, as well as the impracticality of carrying additional devices for the children, were described. The *#WeAreNotWaiting* web-based community was frequently approached as the primary source of information as well as emotional and practical support.

This study can inform stakeholders regarding the unmet needs of children and adolescents with T1D regarding the therapeutic options available to them. Furthermore, our findings highlight how children might benefit from customizable open-source AID systems where commercial options are not accessible, approved for certain age groups, or limited in their functionality to cover the lower and variable insulin requirements of children.

Comparison With Prior Work

The ethical and legal aspects of the off-label use of unregulated medical devices in children and adolescents are multifaceted and complex. Although the off-label use of pharmaceuticals is both common practice and a necessity in pediatrics, it is still uncommon in medical devices. HCPs were sometimes perceived to be reticent in their support of the decision to use open-source AID. This reticence is understandable given that many HCPs, as indicated by the caregivers in this study, had very little knowledge of the systems and uncertainty regarding what legal ramifications there might be in providing support for a system not approved by regulatory bodies. Following a number of position papers from several local diabetes organizations, a group of international HCPs recently provided an international consensus statement for practical guidance on the safe and ethical use of open-source in clinical settings [18]. The consensus encourages colleagues to learn about all treatment options that could help people with diabetes, including open-source AID, and to support individual decisions to use open-source AID for treatment, as long as benefits and risks are understood. In addition, children's welfare must always be considered by caregivers and HCPs, with their assent and engagement [18].

Although there are numerous studies about the clinical outcomes of the use of open-source and commercially available AID systems in adults and children [13-15,22-24], there is yet very limited knowledge about the lived experiences and psychological antecedents or consequences leading to the use of and with AID. To the best of our knowledge, this is the most extensive study on lived experiences in children and adolescents using open-source AID, and their caregivers and families, conducted at a multinational level. Our findings are in line with other studies that indicated a reduced burden of diabetes in users of commercial and open-source AID [8,25-31]. Caregivers' sleep and mental and physical health in the context of their children's diabetes remains an underresearched area. A reduced burden on caregivers of young children was previously identified as the main outcome of the use of a commercial AID system [8]. The DIWHY survey was conducted between 2018 and 2019. At the time, only one commercially developed AID system was approved and made available in the United States. We did not explicitly ask for this information, although with only 4 participants from the United States, it can be assumed that most of the participants did not have access to commercial AID. Furthermore, open-source AID systems have continuously improved over time with respect to usability and device interoperability. For example, the need to carry around additional hardware may no longer be applied in the recent versions of AndroidAPS, FreeAPS, and Loop. We suggest further research in this field to provide a better understanding of the full psychosocial and economic impact of any kind of AID, as well as the challenges in the access and use of these systems.

Strengths and Limitations

This study has several strengths and limitations. Of particular strength is its patient and public involvement in the study design process and its multinational scope. Limitations include that the anonymous study design did not allow participants to follow up for clarification or further questions, to strictly follow the General Data Protection Regulation guidelines. A selection bias may be present with the survey only being available in German and English, which may have excluded users not proficient in these languages in the first place. Furthermore, those within the sample might not have responded in detail, or not at all, to the open-ended questions owing to language barriers among other factors. In addition, a significant proportion of the OPEN team was German, with strong links to the German diabetes community; therefore, the teams' ability to reach people was particularly high in that country. Finally, the challenges in building and setting up an open-source AID had to be overcome by caregivers with perseverance and self-motivation in the first place, potentially resulting in a selected population that limits broad generalizations to all people with diabetes.

Conclusions

With frequent changes in insulin requirements, glycemic variability due to counterregulatory hormones, and physical activity, children are ideal candidates for AID. Although the uptake of insulin pumps and CGM is high among children in countries where access to diabetes technology is facilitated, the uptake of AID in children is protracted owing to the license status of commercially available AID systems. However, their efficacy in young children and those with low insulin requirements remains limited. Furthermore, glycemic outcome improvements in the off-label use of commercial AID systems by very young children are suboptimal, although they experience similar glycemic improvements as older children, adolescents, and adults with commercial systems approved for their age [7] and with open-source AID [13-16]. Our findings indicate a transformative impact of open-source AID in children and adolescents of various ages on their emotional and physical health, as well as their and their caregivers' sleep and quality of life. They further highlight how remote monitoring and control are perceived by parents to be safe and how the children are provided with greater autonomy.

Similar to commercial AID systems, there remains much room for improvement in open-source AID systems, and further research is needed to improve the effectiveness of algorithms and usability of AID systems in general, particularly in young children where approved therapy options remain limited. To achieve this, concerted efforts are required using a multi-stakeholder approach, an approach in which the diverse and valuable experiences of caregivers and children who have opted to move into the vanguard of AID need to be heard and appreciated.

Acknowledgments

The authors would like to thank the members of the *#WeAreNotWaiting* community and their families for their collaboration and support in cocreating and disseminating this study.

The authors acknowledge the support of Dana Lewis, developer of OpenAPS, and Adrian Tappe, developer of AndroidAPS, for the study design. We further acknowledge the support of Dr Henriette Langstrup as mentor for the interpretation and discussion of the findings of this study.

The authors acknowledge support from the German Research Foundation and the Open Access Publication Fund of Charité—Universitätsmedizin Berlin.

Conflicts of Interest

KB received fees for medical consulting and public speaking from Roche Diabetes Care, Dexcom, Medtronic Diabetes, Diabeloop, Novo Nordisk, Sanofi Diabetes, Diabetes Center Berne, Abbott and BCG Digital Ventures; outside the submitted work. KR received fees for medical consulting and public speaking from Dexcom, Abbott, Lilly Diabetes Care, Novo Nordisk (Germany), and Springer Healthcare United Kingdom; outside the submitted work.
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Multimedia Appendix 1

Questionnaires for caregivers of children and adolescents with diabetes, using open-source automated insulin delivery.
[PDF File (Adobe PDF File), 92 KB-Multimedia Appendix 1]

Multimedia Appendix 2

Demographic and clinical characteristics of participants of the DIWHY study who have not responded to any of the open-ended questions.
[DOCX File , 16 KB-Multimedia Appendix 2]

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Abbreviations

AID: automated insulin delivery
CGM: continuous glucose monitor
CHERRIES: Checklist for Reporting Results of Internet E-Surveys
HbA1c: hemoglobin A1c
HCP: health care professional
OPEN: Outcomes of Patients' Evidence with Novel, Do-it-Yourself Artificial Pancreas Technology
REDCap: Research Electronic Data Capture
T1D: type 1 diabetes
TIR: time in range

Edited by R Kukafka, G Eysenbach; submitted 07.02.22; peer-reviewed by S Hussain, R Lal, C Campos-Castillo, L Laestadius; comments to author 29.03.22; revised version received 21.04.22; accepted 29.05.22; published 14.07.22

Please cite as:
Braune K, Krug N, Knoll C, Ballhausen H, Thieffry A, Chen Y, O'Donnell S, Raile K, Cleal B
Emotional and Physical Health Impact in Children and Adolescents and Their Caregivers Using Open-source Automated Insulin Delivery: Qualitative Analysis of Lived Experiences
J Med Internet Res 2022;24(7):e37120
URL: https://www.jmir.org/2022/7/e37120
doi: 10.2196/37120
PMID:

2.4. Impact of the Menstrual Cycle on Glycemic Outcomes and Insulin Requirements in Women Using Open-Source AID: Qualitative Analysis.

The many female health-related testimonials of participants of the DIWHY survey [35,83,119] prompted us to perform further research in this area. The following text is reproduced in full from the abstract of the publication:

Mewes D, Wäldchen M, Knoll C, Raile K, **Braune K**. Variability of Glycemic Outcomes and Insulin Requirements Throughout the Menstrual Cycle: A Qualitative Study on Women With Type 1 Diabetes Using an Open-Source Automated Insulin Delivery System. *J Diabetes Sci Technol*. 2022 Mar 7:19322968221080199. https://doi.org/10.1177/19322968221080199

The impact of sex hormone dynamics on insulin sensitivity and glucose metabolism is subject of constant scientific debate and generally represents an under-represented and under-researched area. Despite therapeutic and technological advances, diabetes management remains challenging for women with T1D and leads to differences in a variety of their health outcomes.

With an open and explorative study design in mind, we performed semi-structured interviews with 12 women using open-source AID and explored their perceived changes in glycemic levels and insulin requirements throughout the menstrual cycle and different phases of life. Transcripts of the interviews were analyzed using thematic analysis with an inductive, hypothesis-generating approach.

Participants reported significant differences in glycemic levels and insulin requirements between the follicular phase, ovulation, and luteal phase of their cycles and also during puberty, pregnancy, and menopause. They reported increased comfort and felt safer since they started using open-source AID but were still required to frequently manually adjust their therapy settings, which was perceived as an additional burden. Mostly, they were unaware of cycle-related fluctuations before they started using open-source AID. Workaround strategies to respond to changing insulin requirements included the use of “Override Presets” (Loop) and “Profile Switches” (AndroidAPS), manual changes of single parameters such as basal rates, insulin sensitivity factor (ISF), and carb ratio (CR), and the intentional overestimation of carbohydrate intake–referred to as “fake carbs”–before or between meals. Features such as ‘Autosens’ were used for fine-tuning their ISF. Other strategies unrelated to insulin delivery were performing more exercise in phases with increased insulin resistance.

As for perceived challenges, the scarcity of information and research in the field was acknowledged by many interviewees. Healthcare provider awareness and knowledge, as well as publicly available information on menstrual cycles and diabetes, were perceived as very limited.

Several ideas on how to further improve diabetes management for women using AID were shared. Besides hardware improvements (louder alarms, smaller dosage settings), participants expressed that the connection of AID to the phases of their menstrual cycle would be beneficial and already feasible. Suggestions included the option to specify insulin dosage settings for individual cycle phases, and pattern recognition for personalized profiles, e.g. by Apple Health. The implementation of self-learning machine learning algorithms was also envisioned. A significant concern was increasing insulin delivery too early and provoking hypoglycemia in return. Therefore, many described their management strategies as reactive rather than preventative.

Our findings provide valuable insights into the challenges women face in managing T1D throughout life, and yield suggestions to further improve future generations of AID systems for women, contributing to gender equality and improved quality of care.

Original Article

Journal of Diabetes Science and Technology
1–13

DOI: 10.1177/19322968221080199
journals.sagepub.com/home/dst
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Variability of Glycemic Outcomes and Insulin Requirements Throughout the Menstrual Cycle: A Qualitative Study on Women With Type 1 Diabetes Using an Open-Source Automated Insulin Delivery System

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Abstract

Background: The impact of hormone dynamics throughout the menstrual cycle on insulin sensitivity represents a currently under-researched area. Despite therapeutic and technological advances, self-managing insulin therapy remains challenging for women with type 1 diabetes (T1D).

Methods: To investigate perceived changes in glycemic levels and insulin requirements throughout the menstrual cycle and different phases of life, we performed semi-structured interviews with 12 women with T1D who are using personalized open-source automated insulin delivery (AID) systems. Transcripts were analyzed using thematic analysis with an inductive, hypothesis-generating approach.

Results: Participants reported significant differences between the follicular phase, ovulation, and luteal phase of the menstrual cycle and also during puberty, pregnancy, and menopause. All participants reported increased comfort and safety since using AID, but were still required to manually adjust their therapy according to their cycle. A lack of information and awareness and limited guidance by health care providers were frequently mentioned. Although individual adjustment strategies exist, achieving optimum outcomes was still perceived as challenging.

Conclusions: This study highlights that scientific evidence, therapeutic options, and professional guidance on female health-related aspects in T1D are insufficient to date. Further efforts are required to better inform people with T1D, as well as for health care professionals, researchers, medical device manufacturers, and regulatory bodies to better address female health needs in therapeutic advances.

Keywords

glycemic variability, insulin sensitivity, sex hormones, menstrual cycle, automated insulin delivery, open-source

Introduction

Diabetes is one of the most common chronic conditions in women, and the global incidence of type 1 diabetes (T1D) and type 2 diabetes (T2D) has been on the rise for multiple decades.[1] Recently, therapeutic and technological advances in diabetes care such as continuous glucose monitoring (CGM) systems and continuous subcutaneous insulin infusion (CSII) have facilitated the development of automated insulin delivery (AID) systems—also called "(Hybrid-) Closed-Loop Systems" or an "Artificial Pancreas." The control algorithms used in AID systems automate and continuously adjust insulin dosage based on changes in glycemic levels and other factors such as carbohydrate intake. Randomized controlled trials and observational studies have

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supported the ability of these systems to improve glycemic outcomes, decrease hypoglycemic events, and improve quality of life in people with diabetes (PwD) of various age groups[2-4] and in women with T1D during pregnancy.[5-7]

Prior to the availability of commercially developed AID systems, a community of people affected by T1D behind the hashtag #WeAreNotWaiting have collaboratively developed open-source AID algorithms and openly shared their source code and documentation online. In these systems, existing medical devices are connected with an app running an open-source control algorithm on their smartphones (AndroidAPS for Android phones, Loop for Apple iPhones) or on a small microcontroller (OpenAPS). Worldwide, an estimated number of several thousand PwD[8,9] are currently using open-source AID, of which approximately 44% are women.[9-11] Observational studies[9,11,12] have shown safety and efficacy for open-source AID for PwD of various age groups and genders alike. User experiences reflect quality-of-life improvements and describe the customizability and range of personalized features of these systems as important characteristics.[13-17]

For women living with T1D, managing diabetes can be particularly challenging throughout different phases of life. Several studies have shown that women with T1D and T2D are less likely to reach targets in hemoglobin A1c, blood pressure, and low-density lipoprotein cholesterol as recommended by therapeutic guidelines,[18] compared with men, with possible explanations for these disparities remaining unclear.[19,20]

The impact of sex hormone dynamics on insulin sensitivity and glucose metabolism is subject of constant scientific debate.[21-23] Variations in insulin sensitivity throughout the menstrual cycle have been previously studied in women without diabetes. However, the underlying molecular mechanisms are complex, and variable correlations of female sex hormones and insulin sensitivity were observed. Several studies that examined intravenous glucose tolerance in smaller cohorts found either increased insulin resistance[24-26] or no significant differences in insulin sensitivity[27] during the luteal phase of the menstrual cycle. A euglycemic, hyperinsulinemic clamp study found no insulin sensitivity differences in relation to menstrual cycle phases.[28] A longitudinal study that investigated fasting glucose and insulin concentrations in a larger cohort of 257 women without diabetes showed significant changes in insulin resistance associated with estradiol and progesterone concentrations and higher insulin resistance during the luteal phase,[22] in line with observational studies that found significant correlations of estradiol concentrations in saliva and insulin levels in 204 women regardless of their current menstrual cycle phase,[29] and between estradiol and insulin concentration in 845 postmenopausal women.[30]

Despite the available evidence on the influence of sex hormones on glycemic levels in individuals without diabetes, research on women with diabetes is sparse but equally controversial. First observations suggesting an association of diabetes and the menstrual cycle were made early in the history of insulin therapy in the 1940s, where cyclic changes in blood glucose concentrations were observed in seven girls with T1D prior to their menarche.[31] Further studies from the 1990s and the early 2000s have found menstrual irregularities to occur more frequently in adolescents[32] and adults with T1D.[33,34] Insulin sensitivity in relation to the menstrual cycle was first investigated by hyperglycemic, hyperinsulinemic clamp studies in the 1990s. A clamp study of 16 women reported marked heterogeneity in glucose metabolism in all and lower insulin sensitivity during the luteal phase in some of the participants.[35] These findings could not be confirmed by others.[36,37] A population-based study from 1996 on 124 women with T1D first highlighted self-reported changes in glycemic levels around menstruation in 61% of the participants.[38] Data throughout several complete menstrual cycles were first assessed in 2004 by a pilot study of four women with T1D using CGM,[39] where different interindividual sensor glucose patterns were found; however, these patterns were consistent over several cycles of the same person.[39] An observational study of 12 women using CSII and CGM combined found hyperglycemia to occur more frequently around ovulation and the early luteal phase compared with the early follicular phase.[40] Controversially, a recent study of seven participants found postexercise hyperglycemia to be more prominent during the follicular phase.[41]

Despite these implications, sex hormone–related aspects are—except for pregnant women with diabetes[42]—not sufficiently considered in therapeutic guidelines, medical device development, and clinical trials to date. The use of AID systems, and customizable open-source AID systems in particular, could facilitate the investigation of insulin needs and glycemic patterns in relation to the menstrual cycle, and thus contribute to the evidence base of this under-researched area. Therefore, this explorative study aimed to investigate user experiences of women living with T1D and using open-source AID systems in relation to their menstrual cycles, thereby leveraging experienced-based evidence and ideas for further improvement of AID systems from the #WeAreNotWaiting community and enabling further research in the field of T1D and women's health.

Methods

Study Design

As part of the patient-led OPEN project,[43] a questionnaire for the assessment of participant demographics and a schedule for semi-structured interviews were created by the OPEN team. Interview questions were designed based on previous reports of open-source AID users in response to the DIWHY survey,[14,44] on discussions related to the study topic between open-source AID users in online peer-support groups of the #WeAreNotWaiting community and on the research team's

(KB, MW, KR) personal experience with T1D and using open-source AID. The interview framework was pilot-tested with two women using open-source AID before further participants were enrolled.

Inclusion Criteria

Participants were eligible if they met the following inclusion criteria: >18 years of age, biological sex was female, living with T1D, using an open-source AID system for at least six months, and were proficient in either English or German at conversation level. No specific exclusion criteria applied.

Recruitment

To specifically target open-source AID users of different ages and internationally, recruitment was carried out through social media. Announcements were posted both publicly (eg, on Twitter using the hashtag #WeAreNotWaiting) and in online peer-support groups for open-source AID (eg, the Facebook groups "Looped," approximately 23 000 members, and "Looped-DE," approximately 2000 members in July 2020). Participation was entirely voluntary with no financial compensation provided. The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board (or Ethics Committee) of Charité—Universitätsmedizin Berlin (protocol code EA2/122/20, July 7, 2020). Prior to the interviews, participants were informed about the professional background and characteristics of the researchers performing the interviews and their interests and aims in pursuing this research. In addition, a detailed information sheet was provided to all participants and their electronic consent was obtained. Participants were recruited from July 2020 to January 2021. With a target sample size of 10 to 15, participants were purposively sampled until data saturation occurred.[45-49]

Procedures

Semi-structured interviews with 12 participants were conducted via secure online video calls in either German or English. Online interviews were conducted by DM and CK with the use of encrypted online video chat services Zoom (Zoom Video Communications, San Jose, California) and Google Meet (Google Inc., Mountain View, California). The calls lasted 45 to 60 minutes each. The questionnaire assessing demographics and personal female health and diabetes-related history (Supplemental Material) was sent to the participants prior to the video call. During the interviews, the researcher asked the participants to share their observations and perceived challenges related to their diabetes during different phases of life (eg, puberty, menopause, pregnancy) and throughout the menstrual cycle (eg, if they had noticed variability in glycemic outcomes and an estimate of the relative changes in overall insulin requirements throughout the menstrual cycle in percentage). Next, the interviewer assessed participants' individual solution strategies and manual "workarounds" with their open-source AID system and otherwise to address these challenges. Interviews finished with discussions on users' ideas of how to better automate control algorithms and further improve future generations of AID systems for women.

Data Collection and Analysis

Data collection was carried out in accordance with national data protection regulations. The interviews were audio and video recorded, transcribed, and de-identified. Transcribed texts were imported into the MAXQDA Plus 2020 software (VERBI GmbH Berlin, Germany).[50] Given the scarcity of existing qualitative research on the topic of women's health and T1D, an explorative and inductive approach was chosen to generate new hypotheses and remain open to unexpected findings. The analysis and generation of themes were carried out by the research team collaboratively (DM, MW, CK, KB). It should be noted that "themes" refer to interpretive stories about particular patterns of shared meaning in the data. These were developed in interaction with the researchers' theoretical assumptions, their analytic skill, and the collected data. Thematic analysis was used to analyze the data, including data familiarization, coding, generation of themes, theme review, theme definition, and naming.[50] The thematic analysis did not strictly follow procedures such as coding or achieving inter-rater reliability between researchers, and instead enabled reflection and engagement by the researchers throughout the analytic process.[50] Iterative discussion rounds were held until consensus between researchers was achieved. The COREQ (COnsolidated criteria for REporting Qualitative research) checklist was used to guide reporting.[51]

Results

Of the 28 women who expressed their interest in participating, 12 participants based in four different countries were recruited, meeting our target sample with no dropouts. Participants had a median age of 39 years, ranging from 24 to 56 years, and a median experience of using an open-source AID system (OpenAPS, Loop, or AndroidAPS) of 21 months, ranging from 12 to 48 months. Further demographics and health characteristics are presented in Table 1. Content analysis of the data provided six themes with several subthemes, as presented in Table 2.

Theme A: Improvements Through Open-Source AID

All participants expressed high satisfaction with open-source AID as their treatment option of choice, noting that it increased their quality of life (subtheme A1). One participant

Table 1. Participant Demographics, Diabetes-Related and Gynecological History.

No.	Age (years)	Country of residence	AID system(s)	AID experience (mo)	No. of pregnancies	Contraceptive method(s)	Mean cycle length (d)	Years since T1D diagnosis (y)
1	56	Germany	AndroidAPS, OpenAPS	48	2	Nonhormonal	In menopause	21
2	31	Germany	AndroidAPS, Loop	31	None	Barrier and sympto-thermal methods	34	19
3	33	Germany	AndroidAPS	13	2	Hormonal IUD	26	28
4	46	Germany	AndroidAPS	25	1	None	28	29
5	26	United States	Loop	31	None	Hormonal IUD	Not menstruating	24
6	49	Germany	AndroidAPS	16	3	Barrier methods	29	27
7	47	Australia	AndroidAPS, Loop	22	None	Hormonal IUD	In menopause	42
8	31	United States	Loop	20	1	Copper IUD	36	20
9	26	Germany	AndroidAPS	16	None	Barrier methods	30	23
10	24	Germany	AndroidAPS	12	None	Nonhormonal	29	17
11	45	France	Loop	17	2	None	26	23
12	52	Germany	AndroidAPS	31	4	Barrier methods	In menopause	43

Abbreviations: AID, automated insulin delivery; IUD: intrauterine device; T1D, type 1 diabetes.

called it a “huge relief for life in comparison to the past” (33-year-old German woman, using AndroidAPS for one year); another described it as “the easiest and safest my care has ever been” (26-year-old American woman, using Loop for 2.5 years).

Improved clinical outcomes were also reported (subtheme A2). This was mostly associated with the availability of fast, predictive, and automated dosing of.

correction insulin in response to changes in sensor glucose, which to a large degree did not require frequent manual intervention. Decreases in hemoglobin A1c, increases in time-in-range, and fewer hypoglycemic events, especially at nighttime, were described frequently:

> I can tell: June 13th, 2018. First time I slept through the first night, with Loop. [Previously], I was [. . .] very often woken up either by my own hypoglycemia, by noticing [the symptoms] myself, or by an alarm. The loop has made it: It was really the first night I didn’t wake up to some stupid alarms. [. . .] And I am no longer afraid that it will happen. Because I know someone will take care of it. My app. (52-year-old German woman, using AndroidAPS for 2.5 years)

Theme B: Variations in Glycemia and Insulin Requirements

All participants reported having experienced changes in glycemic levels and insulin requirements associated with different phases of their menstrual cycle (subtheme B1), which required most of them (n = 10) to adjust their insulin therapy. Most participants (n = 10) reported experiencing regular fluctuations in glucose levels and insulin needs throughout the menstrual cycle, requiring them to change their settings. An overview of the interindividual differences throughout the follicular phase, around ovulation, and the luteal phase is summarized in Figure 1 and Table 3 based on the data reported by the participants (Supplementary Table 1).

This was often associated with frustration:

> It’s like a major frustration for me because the first couple weeks of my cycle are so nice and then the last half is kind of a disaster zone. (31-year-old American woman, using Loop for 1.5 years)

Theme C: Additional Effort to Achieve Therapy Outcomes

All participants stated that even with using AID, manual therapy adjustments and “workarounds” related to the menstrual cycle were still necessary on a regular level, which caused them a constant time effort, cognitive load, and distress (subtheme C2), especially when compared with men (subtheme C1):

> I always find it so inequitable when men [. . .] brag about their great blood sugar levels. I would wish them a month in the life of a woman and then see how they deal with it. That is, I would wish them humility. I think if you never experienced it yourself, you can’t imagine what it’s like. (49-year-old German woman, using AndroidAPS for 16 months)

Women of a younger age who managed multiple responsibilities such as work and childcare especially mentioned a lack of time to keep track of the changes and react to them. Even those participants with professional backgrounds in health care and personal interest in the topic of women’s health, as well as active members of the open-source online

Table 2. Content Analysis: Theme Structure, Definition, Example Quotes, and Respondent Profiles.

Theme	Definition	Example quote(s)	Respondent profile
(A) Improvements through open-source AID			
(A1) Increased quality of life	Refers to perceived improvements in everyday life and reduced diabetes-related distress following the implementation of open-source AID	"This is the easiest and safest my care has ever been."	26-year-old American woman, using Loop for 2.5 years
(A2) Improved clinical outcomes	Refers to the perceived changes in clinical outcomes (eg, fewer hypoglycemia and hyperglycemia, more time-in-range) and perceived increases in safety following the implementation of open-source AID	"I can tell: June 13th, 2018. First time I slept through the first night, with Loop. [$^{\text{Previously}}$,] I was [. . .] very often woken up either by my own hypoglycemia, by noticing [the symptoms] myself, or by an alarm. The loop has made it: It was really the first night I didn't wake up to some stupid alarms. [. . .] And I am no longer afraid that it will happen. Because I know someone will take care of it. My app."	52-year-old German woman, using AndroidAPS for 2.5 years
(B) Variations in glycemia and insulin requirements			
(B1) Intraindividual differences	Refers to variability in glycemic outcomes and insulin requirements throughout the menstrual cycle and different life stages observed by the women	"It's like a major frustration for me because the first couple weeks of my cycle are so nice and then the last half is kind of a disaster zone."	31-year-old American woman, using Loop for 1.5 years
(C) Additional effort to achieve therapy outcomes			
(C1) Gender inequality	Refers to the perceived differences between men and women in therapy effort needed to achieve the desired outcomes	"I always find it so inequitable when men [. . .] brag about their great blood sugar levels. I would wish them a month in the life of a woman and then see how they deal with it. That is, I would wish them humility. I think if you never experienced it yourself, you can't imagine what it's like."	49-year-old German woman, using AndroidAPS for 16 months
(C2) Causing distress	Refers to the additional burden perceived by the women related to female health–related challenges in managing diabetes	"You know, you can do your best, but it won't be good enough."	31-year-old American woman, using Loop for 1.5 years
(D) Limited awareness and support			
(D1) Limited awareness pre-AID	Refers to the novelty of the observations since using open-source AID and the participants' unawareness of a possible correlation between menstrual cycle and diabetes prior to using an AID system	"I notice the [correlation] very prominently. I also noticed it with MDI, but I could not attribute it that way." "I would say that you can see a tendency that in the second half of the cycle the levels and the insulin requirements are higher. Before Loop, I didn't even notice anything. With the closed-loop, you notice it way more when something is off."	56-year-old German woman, using OpenAPS and AndroidAPS for four years 31-year-old German woman, using Loop for 2.5 years
(D2) Limited HCP support	Refers to therapy adjustments that were often attempted "trial and error" with limited professional medical guidance and the perceived lack of awareness toward sex- and gender-specific aspects in diabetes care among physicians and other HCPs, in the fields of both endocrinology/diabetes care and obstetrics/gynecology	"At a time when it would have been very important for me, for example, when I had children, my endocrinologist never pointed out to me that we had to adjust anything. I've only just noticed now that there is a women's area in the Loop [groups]. Makes sense, that [the therapy] is specifically adjusted during pregnancy. But to take a closer look at the cycle? [. . .] No one said '[. . .] please increase your basal rates every 26 days.' That was just not a discussion to have with the endocrinologist. [. . .] Now I am with a woman [endocrinologist] and I asked her about menopause. She said yes, she didn't know either, she'd have to read up on it. [. . .] I asked her: 'How is it now with [diabetes], menopause, what to expect?' And then she started [telling me] about night sweats. And I said, 'No, that's not the question at all. I would like to know how the blood glucose reacts to it?' And then she did not know the answer."	52-year-old German woman, using AndroidAPS for 2.5 years
(E) Solution strategies			
(E1) Peer-support	Refers to support provided by other people with diabetes, often online in social media groups	"I am on a lot of Facebook groups including a 'Looping in Pregnancy' one and a 'Breastfeeding and Type 1 Diabetes' one. Those are particular groups I'd be sooner to ask sort of women-specific or hormonal questions on."	31-year-old American woman, using Loop for 1.5 years
(E2) Cycle documentation	Refers to ways of documenting the menstrual cycle	"I used to document the first day of my period in my phone. And in my paper calendar. Then I have discovered the insulin age [field] in AndroidAPS which I am using now. Practically I do not enter my insulin age in the app, but [use if for] the first day of my period. [. . .] That is actually perfectly suited to get a bit of an overview, how far along [in the cycle] I am right now."	49-year-old German woman, using AndroidAPS for one year

(continued)

Table 2. (continued)

Theme	Definition	Example quote(s)	Respondent profile
(E3) Open-source AID features	Refers to the use of already existing features in open-source AID (eg temporary overrides, profile switches)	"When I encounter higher levels, I switch to a temporary override relatively quickly. [. . .] You can set [all parameters] to 110%, 120% and so on."	31-year-old German woman, using Loop for 2.5 years
(E4) Fake carbs	Refers to carbohydrate entries in the AID system without actually consuming them	"I tried changing my profile, it really means everything ISF and everything changed and that did not work. [Now I am] only changing the basal rate and then possibly correct again if I notice it is not working. Then I add a few more fake carbs. [. . .] The Loop thinks I still have carbohydrates [on board], but there aren't any. And [. . .] then, the Loop reacts a little more aggressively."	46-year-old German woman, using AndroidAPS for two years
(E5) Manual changes of settings	Refers to manual adjustments of AID settings (eg, ISF, carb ratio, targets)	"The ISF. It's not the case for older big ladies, like really big ladies. I think because they still have a lot of estrogen anyway because they are big. But for average size ladies, and there are some quite thin ladies I know, they are very very sensitive using ISFs of nine, ten, ten and a half. Which is about what toddlers use. And I did not change my ISF from five until I talked to some of these ladies and they're like: 'Yeah, I've had to put mine up to nine.' And so, I tried that, and I got a flat line."	47-year-old Australian woman, using Loop and AndroidAPS for 1.5 years
(E6) Exercise	Refers to intentional exercise in phases with high insulin resistance	"Before my period, for at least a week, I need a lot more insulin, so my insulin sensitivity is a lot lower. [. . .] I guess I exercise on purpose just to try to not increase the insulin by so much."	31-year-old American woman, using Loop for 1.5 years
(F) Ideas for further improvements			
(F1) Further research and education	Refers to the perceived scarcity of the available literature and education on the topic of female health and diabetes	"I think we absolutely all need to learn about this. It's probably only been in the last five or six, maybe ten, years that women had the chance to reflect on continuous glucose monitoring during their cycles. Before that it was just, you know, whatever. And I think also we—Because, I mean, everything is tested on men, generally white men, we do miss out on a lot of research. And this stuff is so important. I think this is something little girls need to know about. It's not just the birds and the bees, it's: 'Hey, your insulin is going to need to do some weird stuff. It's all going to be different'. Because none of us had any idea, right? Just wasn't talked about. Wasn't a thing."	47-year-old Australian woman, using Loop and AndroidAPS for 1.5 years
(F2) Menstrual cycle-related automation	Refers to the ideas and suggestions for further automation and additional features to better cater to the users' unmet needs	"It would help anticipate a little bit more in terms of, you know, I'm on day 20 and so this is where things are starting to be a little more resistant, but I don't realize that. [. . .] Loop already talks to Apple Health, and I use the Apple Health app to track my cycle, so it doesn't seem very far to take that information from Apple Health. [. . .] If Loop could already take into account when was the cycle 'day one' it would probably be helpful already."	45-year-old French woman, using AndroidAPS for 1.5 years
(F3) Machine learning	Refers to the implementation of self-learning algorithms based on user data	"If it was learning from the data—I love the idea of Autotune but I don't think it's necessarily accurate for Loop specifically—if there was something like 'I've noticed that it seems you really need, [. . .] my need seems to ramp up over time and then ramp down as opposed to being from day to day normal and then all of the sudden 20% more. [. . .] Your period is predicted to start in 12 days so I'm going to go up by 5 percent. And now 10. And now 15'. [. . .] If [the algorithm] learned based on experience—you know: 'Your last three cycles your insulin needs were like this so I'm going to mimic that'."	31-year-old American woman, using Loop for 1.5 years

Abbreviations: AID, automated insulin delivery; HCP, heath care professional; ISF, insulin sensitivity factor; MDI, multiple daily injections.

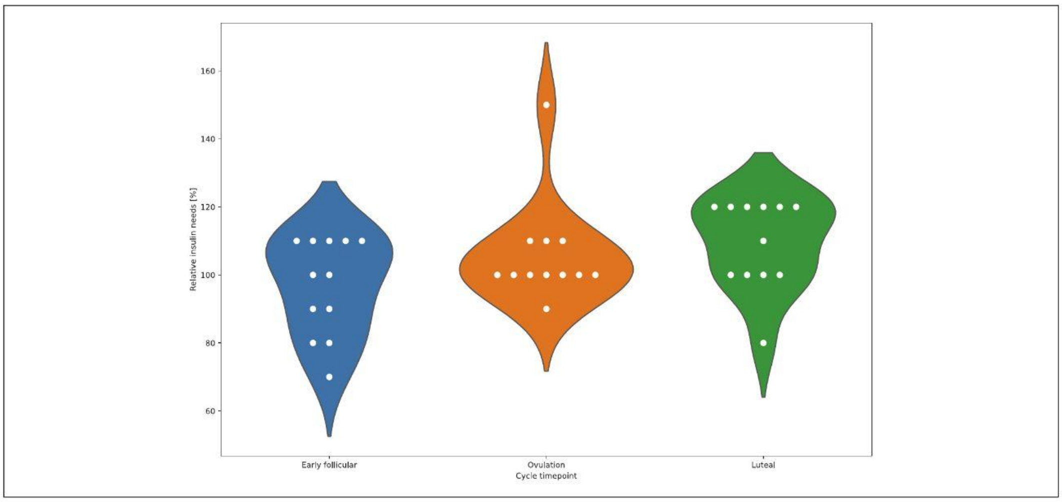

Figure 1. Relative changes (%) in self-reported insulin requirements of female open-source AID users during different menstrual cycle phases (blue: early follicular phase, orange: around ovulation, green: luteal phase). Abbreviation: AID, automated insulin delivery.

community who are in frequent exchange with other women with T1D, expressed that they rarely felt they were "in control" of their diabetes at all times. Even though the participants reported that switching to open-source AID had increased their knowledge about menstrual cycle effects on glucose levels and made diabetes management easier and safer, many expressed that certain challenges remain:

> I'd say it's still a major problem for me. I just remember being, just a few weeks ago, so frustrated. I just kept spiking high after meals, staying high overnight and stuff. So, I changed my settings and then in that instance, for whatever reason, I needed more than I thought, I guess. Or I would spike high after meals but then I would be low otherwise, so my basal was too strong but my carb ratio wasn't good, or maybe I needed to pre-bolus longer than usual. (31-year-old American woman, using Loop for 1.5 years)

The frequent need for manual adjusting of settings and fine-tuning was also seen as straining:

> Because anything that keeps me from having to constantly wonder about, you know: "Oh, okay. I'm getting a result I didn't expect so now I have to do this whole troubleshooting in my head." If the system just knew it's the week before the period then that would save me some manual troubleshooting, I guess. (31-year-old American woman, using Loop for 1.5 years)

Theme D: Limited Awareness and Support

The effect of the menstrual cycle on glucose levels and insulin requirements was first noticeably observed by the participants following the initiation of open-source AID use (subtheme D1):

> I notice the [correlation] very prominently. I also noticed it with MDI, but I could not attribute it that way. (56-year-old German woman, using OpenAPS and AndroidAPS for four years)

Furthermore, support and awareness of women's health and diabetes from endocrinologists and obstetricians/gynecologists were perceived to be limited (subtheme D2) by all of the participating women:

> But I had a conversation with him about what sort of problems I could expect for menopause. And he said "Oh, should be a breeze." [. . .] Yeah, so they're clueless. Completely clueless. (47-year-old Australian woman, using Loop and AndroidAPS for 1.5 years)

If valuable suggestions regarding insulin therapy were brought up by health care providers, they were highly appreciated:

> Usually she at least comes up with one helpful thing each time I go. I do a lot of research myself, a lot of thinking and testing myself. For her to come up with any additional thoughts, I think is pretty good. (31-year-old American woman, using Loop for 1.5 years)

Theme E: Solution Strategies

Peer-support (subtheme E1) via online communities such as the "Looped" Facebook groups was common among

Table 3. Self-Reported Perceived Changes in Glycemic Levels and Insulin Needs of Open-Source AID Users Throughout Different Phases of the Menstrual Cycle and Special Situations (Pregnancy, Menopause).

Menstrual cycle phase or special situation	Perceived changes in insulin needs
Follicular phase	With the onset of menses and the following two to three days, some (n = 5) women reported a sudden increase in insulin requirements and therefore the necessity to decrease their insulin delivery by 10% to 30%, while some (n = 4) needed to increase their dose by 10% to 20%. One woman reported a small decrease in insulin needs but does not regularly adapt settings accordingly. During menses, correlations between changing insulin needs and the occurrence and intensity of menstrual pain and other related symptoms, level of physical activity, and comorbidities were suspected. The late follicular phase up to the suspected day of ovulation was considered as the most "stable" and "easy to manage" in relation to glycemic levels. Insulin needs during that phase were considered as "normal" or "average."
Around ovulation	Participants identified their ovulation to take place between cycle day 13 and day 21, depending on their cycle length. Some either reported to perceive specific physical symptoms (n = 6) such as one-sided abdominal pain or a "pulling sensation", and increased libido, or used menstrual cycle tracking apps to identify their fertile window. A sudden increase in insulin requirements on ovulation day and the following one to two days of the cycle was reported by three participants, whereas one woman explained to experience decreased insulin needs, which has been more prominent after her first pregnancy but has become less noticeable since then.
Luteal phase	Post-ovulation, insulin needs were reported to be increased by up to 35% until the next cycle. Participants performed several different therapy adjustment strategies: two of the three women who experienced higher insulin needs during ovulation kept their more aggressive settings until the end of the cycle. One participant decreased her insulin "back to normal" (100%) temporarily after ovulation and then increased her insulin dose again for the last cycle week. One woman reported perceiving a small decrease in insulin demand for the last days of the cycle, whereas another woman explained being able to keep her settings on "default" (100%) throughout ovulation and until the next cycle begins. Of the five women who did not change settings during ovulation regularly, four reported to have a steady increase in insulin needs leading up to the next cycle. One woman reported being slightly more sensitive to insulin during that time and therefore decreased her intake to 80%.
Pregnancy	Different life phases and events, such as puberty, pregnancy, and menopause, were perceived as particularly challenging with respect to managing diabetes. Participants who had been pregnant in the past (n = 7) reported a constant effort of adapting their insulin requirements to the dynamic hormonal situation. Following pregnancies, participants reported that their insulin requirements needed to be reevaluated, rather than returning to their prepregnancy profiles. Furthermore, cycle length and strength of menstrual bleeding were perceived differently compared to before pregnancy.
Menopause	The transition into menopause was associated with decreased overall insulin requirements, changes in the length of the menstrual cycle, a decrease in menstrual bleeding, and ovulation frequency.

Abbreviation: AID, automated insulin delivery.

interviewees. As an example, group video calls for setting optimizations were mentioned, and one woman reported that a friend with T1D regularly reminded her to consider the current cycle phase in relation to glycemic outcomes outside target range.

Except for three women who used a hormonal intrauterine device (IUD), are in menopause, or both, all participants stated that they regularly document their cycle and associated symptoms (subtheme E2). Methods of cycle tracking included apps such as "Clue," "myNFP," "Mein Kalender Flo," "Period Tracker," or default calendar apps on Android and Apple smartphones. Some (n = 3) also used paper calendars. Documented attributes were the beginning of menses, duration, intensity of bleeding, and suspected or calculated day of ovulation, and the fertile window. One woman explained how she used the "insulin age" field of AndroidAPS to document her cycle. She expressed not necessarily needing this field for its intended purpose as she generally replaces her insulin every few days. Instead, having her cycle documented "at a glance" together with sensor glucose levels and insulin delivery was described as helpful.

A significant concern among participants was increasing their insulin delivery too early and provoking hypoglycemia in return, which a participant described as at "minimum annoying, maximum dangerous" (31-year-old American woman, using Loop for 1.5 years). Therefore, many described their management strategies as reactive rather than preventative, and changes were not being made until a significant upward trend in glucose levels was witnessed after a few days. The most commonly ($n = 9$) used features of open-source AID (subtheme E3) were "Override Presets" (in Loop) and "Profile Switches" (in AndroidAPS). Both features enable the user to automatically apply relative changes of all parameters affecting dosage calculation, including basal rate (BR), insulin sensitivity factor (ISF), and carb ratio (CR). Both AID systems allow for the saving and naming of profiles:

> In Loop there's the "Override Presets" so I'll do one at 80 or 90 percent of total insulin needs, and I'll just put it on until I eventually am running high because of the changes. But then I put on the 120 percent preset to increase my insulin. (26-year-old American woman, using Loop for 2.5 years)

Another mentioned strategy (n = 2) was the intentional overestimation of carbohydrate intake—referred to as "fake carbs" (subtheme E4)—before or between meals. The participants explained they used this method in addition to using override presets or profile switches as described above, if necessary. Some (n = 2) explained that a relative change of BR, ISF, and CR combined does not work sufficiently for them. Instead, through personal experience, they have found that manually changing the settings one by one (subtheme E5) gives them better results. Features such as "Autosens," an algorithm in AndroidAPS that estimates insulin sensitivity based on the user's glucose deviations,[52] were used for fine-tuning their ISF. Other strategies unrelated to insulin delivery were performing exercise (subtheme E6) in phases with increased insulin resistance.

Theme F: Ideas for Further Improvements

Several ideas on how to further improve diabetes management for women using an open-source AID system were shared. First, the scarcity of information and research in the field (subtheme F1) was acknowledged by many interviewees:

> I think we absolutely all need to learn about this. It's probably only been in the last five or six, maybe ten, years that women had the chance to reflect on continuous glucose monitoring during their cycles. Before that it was just, you know, whatever. And I think also we—Because, I mean, everything is tested on men, generally white men, we do miss out on a lot of research. And this stuff is so important. I think this is something little girls need to know about. It's not just the birds and the bees, it's: "Hey, your insulin is going to need to do some weird stuff. It's all going to be different." Because none of us had any idea, right? Just wasn't talked about. Wasn't a thing. (47-year-old Australian woman, using Loop and AndroidAPS for 1.5 years)

The required technical skills and levels of digital literacy required to set up and use open-source AID systems were also acknowledged (n = 3). Therefore, the desire to have a better understanding of the automated decisions, for example, rationales for temporary BR adjustments, was expressed.

Besides hardware improvements such as devices with louder alarms and smaller dosage settings for the insulin pump, all participants expressed that the linkage of AID to the phases of their menstrual cycle (subtheme F2) would be beneficial and already feasible. Suggestions included the option to specify insulin dosage settings for individual cycle phases ($n = 7$) and pattern recognition ($n = 6$) for personalized profiles, for example, by the combination of different information in Apple Health:

> It would help anticipate a little bit more in terms of, you know, I'm on day 20 and so this is where things are starting to be a little more resistant, but I don't realize that. [. . .] Loop already talks to Apple Health, and I use the Apple Health app to track my cycle, so it doesn't seem very far to take that information from Apple Health. [. . .] If Loop could already take into account when was the cycle "day one" it would probably be helpful already. (45-year-old French woman, using AndroidAPS for 1.5 years)

The implementation of self-learning machine learning algorithms (subtheme F3) was also envisioned:

> If it was learning from the data—I love the idea of Autotune but I don't think it's necessarily accurate for Loop specifically—if there was something like "I've noticed that it seems you really need, [. . .] my need seems to ramp up over time and then ramp down as opposed to being from day to day normal and then all of the sudden 20% more. [. . .] Your period is predicted to start in 12 days so I'm going to go up by 5 percent. And now 10. And now 15." . . . If [the algorithm] learned based on experience—you know: "Your last three cycles your insulin needs were like this so I'm going to mimic that." (31-year-old American woman, using Loop for 1.5 years)

In this context, concerns regarding the ability of algorithms to cater to individual constellations and needs were raised:

> I think you would have to have an absolutely regular cycle. And certainly, I had that as a young woman. But teenagers aren't necessarily regular. Menopausal ladies aren't necessarily regular. In the middle women are often having babies and then breastfeeding and having their cycles when breastfeeding. So, there's a lot, awful lot, of potential for irregularity which is normal. It's not abnormal to be irregular. And I think for the very young women who are just starting their cycles, they've got all

> sorts of stuff going on and I think manual control of that would be better, maybe. But I can see maybe for a few people yes. At certain stages of their life. Nice regular cycles. A bit busy with work and things to stop and think about it. Yeah, maybe it could work. (47-year-old Australian woman, using Loop and AndroidAPS for 1.5 years)

Discussion

This study reports that women with T1D using an open-source AID system perceived a significant impact of changes in insulin needs throughout their menstrual cycle and throughout different events and phases of life, such as puberty, pregnancy, and menopause. The influencing factors were mostly unknown to them before they started using open-source AID systems and caused them to perform several workarounds to manually adjust their therapy. Although using open-source AID had an overall positive effect on glycemic outcomes and quality of life, the requirement to respond to variability in insulin needs was perceived as an individual burden. Health care provider awareness and knowledge, as well as publicly available information on menstrual cycles and diabetes, were perceived as limited. Our findings provide valuable insights into the challenges women face in managing T1D throughout life and yield suggestions to further improve future generations of AID systems for women, contributing to gender equality and improved quality of care.

Although qualitative studies on lived experiences with AID systems among adults, teenagers,[10] and younger children[53] exist, this is the first qualitative study focusing specifically on women as a user group outside the context of pregnancy. The literature describes similar improvements of clinical and patient-reported outcomes for PwD of various ages and genders since commencing open-source AID.[9-11,17] However, our findings suggest that women with T1D have to undertake extra efforts to achieve these results. These findings align with others that have highlighted where currently available commercial AID systems do not meet their users' expectations and either terminate use or come up with unexpected solutions.[54] Findings like these should be a call to action for academia, developers and manufacturers of diabetes technology to closely work together with PwD in their research and product development at an early level, to generate research questions that matter to them and improve the products' usability and efficacy.

Our findings on self-reported variable insulin requirements in relation to the menstrual cycle are in-line with the few previous studies on women with T1D using therapies other than AID[40,55] and mirror the correlation of increased insulin resistance in the luteal phase observed in women without diabetes.[22,24-26] However, this is the first qualitative study to report how women's health-related challenges were experienced by and reacted to by women with T1D. Furthermore, this is the first study to report on what strategies and "workarounds" AID users perform to respond to dynamic changes in insulin demands. Although it was already self-reported by women in the 1990s that most perceive differences in glycemia around their menstruation and some adjust their therapy,[38] there is still no therapeutic guidance on the topic.

It is acknowledged that several strengths and limitations apply to our study. Of particular strength is the multinational character and wide age range despite the small sample size, and the stakeholder engagement strategy directly including the experience and ideas of people with T1D and the open-source AID community during the study design.

For the purpose of this study, ethics approval was only provided for adult participants. While we could identify similarities between participants of different ages, women under the age of 24, with a diabetes duration shorter than 17 years, women with less than 12 months experience in using open-source AID, and women using hormonal contraception methods with higher systemic impact than in hormonal IUDs, such as oral contraception or hormonal implants, are not represented in our study. The likelihood of selection bias when recruiting participants via social media further limits broad generalizations to all women using open-source AID. Further investigations on larger cohorts, including adolescents and young adults <24 years of age and shorter diabetes duration, and women using different methods of hormonal contraception are necessary. With the increasing availability of commercial AID options, it would also be of interest if similar experiences were being made by women using commercially developed AID systems.

In addition to our findings from this explorative study and qualitative analysis, future studies should focus on the analysis of diabetes device data from the AID systems in context with documentation of menstrual cycle data to provide a better understanding of the correlations that we found, identify patterns, investigate the efficacy and actual benefit of using workaround strategies compared to using an AID system with fixed settings, and set the stage for further automation tools and/or machine learning-supported AID for girls and women with menstrual cycles.

Conclusions

Sex hormones are likely to directly or indirectly influence insulin requirements in women with and without T1D, although these correlations have so far not been sufficiently researched. In this study, we generated experience-based evidence of women of the #WeAreNotWaiting community which provides an overview on current challenges to address in future research and by developers of commercial and open-source AID. Due to the automation of insulin dosing and data tracking in AID, it should be possible to quantify recurring patterns in glycemic outcomes and insulin needs throughout the menstrual cycle.

Furthermore, the "workaround strategies" the women created provide useful information for potential further usability improvements and automation of control algorithms. As an example, the integration of menstrual cycle tracking data into AID systems could further improve safety and efficacy in users with menstrual cycles.

Last, awareness, existing scientific evidence, and professional guidance on the topic of female health in diabetes management are still insufficient. Therefore, we encourage an open dialogue on women's health between women with T1D and health care professionals, and to consider cycle-related changes in insulin sensitivity when reviewing data and adjusting insulin dosage as part of their contacts. Moreover, further education and advocacy efforts are required to better inform PwD, health care professionals, and device manufacturers, and more research is required to better address the needs of women with T1D in therapeutic advances.

Abbreviations

AID, automated insulin delivery; CGM, continuous glucose monitoring; CSII, continuous subcutaneous insulin infusion; PwD, people with diabetes; T1D, type 1 diabetes; T2D, type 2 diabetes.

Acknowledgements

The authors would like to thank the members of the #WeAreNotWaiting community for their time and trust and for sharing their valuable insights with the study team, and Jasmine Schipp and Drew Cooper for critically proofreading the article.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Mandy Wäldchen was employed by Medtronic Diabetes Germany until 2018. Katarina Braune received fees for medical consulting and public speaking from Roche Diabetes Care, Dexcom, Medtronic Diabetes, Diabeloop, BCG Digital Ventures, Novo Nordisk, Abbott, Sanofi Diabetes, and Diabetes Center Berne, outside the submitted work. Klemens Raile is an advisory board member at Lilly Diabetes Care and Abbott Diabetes Care; he received fees for public speaking from Abbott Diabetes Care, Novo Nordisk, Sanofi, and Springer Healthcare IME. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work is part of the OPEN project (www.open-diabetes.eu). OPEN has received funding from the European Commission's Horizon 2020 Research and Innovation Program under the Marie Skłodowska-Curie Action Research and Innovation Staff Exchange (RISE) grant agreement number (823902). KB received funding from the DFG-funded Berlin Institute of Health (BIH) Digital Clinician Scientist Program and the BIH/Wellcome Trust SPOKES Translational Partnership program.

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Supplemental Material

Supplemental material for this article is available online.

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2.5. Practical Guidance on Open-Source AID for Healthcare Professionals: An International Consensus Statement.

The following text is reproduced in full from the abstract and full text of the publication:

Braune K#, Lal RA#, Petruželková L, Scheiner G, Winterdijk P, Schmidt S, Raimond L, Hood KK, Riddell MC, Skinner TC, Raile K, Hussain S; OPEN International Healthcare Professional Network and OPEN Legal Advisory Group. Open-source automated insulin delivery: international consensus statement and practical guidance for health-care professionals. *Lancet Diabetes Endocrinol.* 2022 Jan;10(1):58-74. # equal contributions, https://doi.org/10.1016/s2213-8587(21)00267-9

The uptake of open-source AID continues to increase globally. Despite these trends, there was no professional guidance for HCPs to support PwD and caretakers using these systems. Therefore, we formed a multi-professional steering committee to develop this consensus statement and invited 44 medical and 4 legal experts from >20 countries across several global regions to contribute. Appraisal was also provided by 9 professional diabetes organizations. The consensus provided a review of current evidence, description of the technologies, discussed ethics and legal considerations from an international perspective and provided much-needed clinical guidance and recommendations for key stakeholders.

The consensus statements are summarized as follows:

We concluded that scientific evidence exists from real-world and in-silico data to suggest that open-source AID systems are safe and effective treatment options. They have the potential to help a wide population of PwD alongside commercial AID, including individuals with suboptimal or optimal glycemic control and people who are looking to ease their day-to-day burden.

We agreed that respect for autonomy, as one of the fundamental practical, legal, and ethical tenets of medicine, includes supporting the right of PwD or their caregiver's informed decisions about their own medical care.

We recommend that HCPs attempt to learn about all treatment options that might benefit PwD, including open-source AID. It is reasonable to provide a comprehensive overview of all available options and educate on the availability and existing evidence if risks and benefits are clearly explained. HCPs who are unfamiliar with the specifics, do not have resources or have legal/regulatory concerns should consider cooperation with or a referral to other HCPs.

The benefits of open-source AID may include wide availability and access, device and platform interoperability, and customizability. However, it is important to note that these systems have not undergone the same regulatory evaluations as commercially available technologies. There is no commercial technical support, but extensive community support.

Clarifying the user's goals and setting realistic expectations are crucial to the success of using AID. To ensure maximum safety, users should be guided to optimize their systems for hypoglycemia prevention before pursuing tight glycemic targets.

Whilst our consensus does not universally recommend the use of open-source over available and accessible commercial AID systems, we propose that the best interest of the individual must be balanced against risks.

We also do not recommend that HCPs violate local law or organizational governance. However, if ethical and effective treatment is either deemed unlawful or occupies an uncertain and problematic regulatory position, regional policies should be clarified. We encourage authorities and representative organizations to help to apply professional consensus and evidence to update legal interpretations and frameworks.

We stated that all manufacturers of AID, including commercial systems, should fully disclose how their systems operate to enable HCPs, PwD, and caregivers to make informed decisions. Additionally, users should have real-time access to their own health data at all times.

Lastly, in view of the challenges of randomized controlled trials and the value of true user experience, real-world evidence should be considered by device regulators. Streamlined regulatory processes to evaluate and test algorithm updates should be adopted.

2.6. Uncovering Global Health Disparities in Type 1 Diabetes: Cross-Sectional Study on Costs and Underuse of Insulin and Diabetes Supplies.

The following text is reproduced in full from the abstract and full text of the publication:

Pfiester E#, **Braune K**#, Thieffry A, Ballhausen H, Gajewska KA, O'Donnell S. Costs and underuse of insulin and diabetes supplies: Findings from the 2020 T1International cross-sectional web-based survey. Diabetes Res Clin Pract. 2021 Sep;179:108996. # equal contributions, https://doi.org/10.1016/j.diabres.2021.108996

Despite the centennial of insulin's discovery by Banting and colleagues at the University of Toronto in 1921, half of the people living with diabetes worldwide cannot access or afford it. Since the discoverers sold the patent for 1 Dollar, and Banting famously said "Insulin does not belong to me, it belongs to the world", the cost of insulin has dramatically increased globally. Despite efforts of the World Health Organization (WHO) to encourage manufacturers to lower costs, together with the inclusion of insulin analoga and their biosimilars on the WHO Essential Medicines List, it remains unaffordable for many. Insulin rationing is a leading cause of DKA admissions in PwD from minority populations. Furthermore, differences in household income were found to be relevant for access to home refrigeration, usage of insulin pens, insulin pumps, glucagon (as emergency medication for severe hypoglycemia) and ketone strips, HbA1c testing, and complications screening in children and adolescents with T1D.

While a significant body of literature highlighted the prevalence and impact of cost-related insulin underuse in the United States (US), there was little research on how this practice varies across countries globally. While the cost of insulin may be as much as four times higher in the US compared to other high-income countries, access to insulin varies worldwide, with many lower and middle-income countries lacking universal coverage of diabetes medications. Additionally, there was a pressing need to investigate these disparities in the context of the COVID-19 pandemic, where disruptions of supply chains have led to further precarity in access to insulin in some regions.

This was the first study to investigate self-reported out-of-pocket expenses and their effects on rationing of insulin and blood glucose testing in context of health coverage, country, and gross domestic product (GDP) of the country. We conducted a web-based, cross-sectional, population-based survey. The analysis included comparisons between responses from countries with no, partial, and full healthcare coverage. Quantitative analyses were conducted within the R statistical framework. The original survey dataset and associated R scripts are publicly available on a GitHub repository. [122,123]

Of the 1,066 participants from 64 countries who took part in the study, 41% reported having rationed test strips, and 25% have underused insulin at least once within the last year due to cost. In low- and middle-income countries, out-of-pocket expenses posed a significant share of household income and per capita GDP, and in some countries even exceed it.

Rationing and underuse were virtually absent in countries with universal healthcare coverage, and a significant correlation was observed between rationing, out-of-pocket expenses, and reported household income for respondents with partial healthcare coverage. Medical devices (CGM, insulin pumps) were the leading category of expenses, followed by insulin, test strips, and glucagon. In countries with no healthcare coverage, such as Ghana and the Philippines, priority was given to acquiring insulin and test strips over glucagon and devices. 63% of participants reported disruption of insulin supplies and 25% reported an increase in prices related to the COVID-19 pandemic.

DIABETES RESEARCH AND CLINICAL PRACTICE 179 (2021) 108996

Contents available at ScienceDirect

Diabetes Research
and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

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Costs and underuse of insulin and diabetes supplies: Findings from the 2020 T1International cross-sectional web-based survey

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ARTICLE INFO

Article history:
Received 13 July 2021
Received in revised form
23 July 2021
Accepted 2 August 2021
Available online 4 August 2021

Keywords:
Costs
Out-of-pocket expenses
Rationing
Underuse
Type 1 diabetes
Insulin

ABSTRACT

Aims: To investigate self-reported out-of-pocket expenses (OoPE) associated with insulin and diabetes supplies for people living with type 1 diabetes (T1D) worldwide.

Methods: A web-based, cross-sectional survey was conducted from August to December 2020. The analysis included comparisons between responses from countries with no, partial, and full healthcare coverage.

Results: 1,066 participants from 64 countries took part in the study. ~25% of respondents reported having underused insulin at least once within the last year due to perceived cost. A significant correlation was observed between OoPEs and reported household income for respondents with partial healthcare coverage. 63.2% of participants reported disruption of insulin supplies and 25.3% reported an increase of prices related to the COVID-19 pandemic.

Conclusions: This study confirms previous reports of ~25% of people in the United States with T1D using less insulin and/or fewer supplies at least once in the last year due to cost, a trend associated with the extent of healthcare coverage. Similar trends were observed in some middle/low income countries. Moreover, patients reported an increase in insulin prices and disruption of supplies during the COVID-19 pandemic. This study highlights the importance of self-reported OoPEs and its association with underuse/rationing of insulin.

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https://doi.org/10.1016/j.diabres.2021.108996
0168-8227/© 2021 The Authors. Published by Elsevier B.V.

1. Introduction

Despite the centennial of insulin's discovery by Frederick Banting, Charles Best, and colleagues at the University of Toronto in 1921 [1,2], half of the people living with diabetes worldwide cannot access or afford it [3]. Since the discoverers sold the patent for 1 USD each, and Banting famously said "Insulin does not belong to me, it belongs to the world" (https://insulin100.utoronto.ca/about), the cost of insulin has dramatically increased globally: For example, since the 1990s, the cost of analog insulin in the United States (US) has increased by well over 1000% [4]. High out-of-pocket expenses (OoPEs) and restricted access have been associated with insulin underuse, which in turn can lead to clinical outcomes associated with increased risks for long-term complications and premature death [5,6]. Insulin underuse is a leading cause of diabetes ketoacidosis (DKA) admissions in people with diabetes from minority populations [7]. Furthermore, differences in household income were found to be relevant for access to home refrigeration, usage of insulin pens, insulin pumps, glucagon and ketone strips, hemoglobin A1c (HbA1c) testing, and complications screening in children and adolescents with type 1 diabetes (T1D) [6,8]. However, while the cost of insulin may be as much as four times higher in the US compared to other OECD countries [9], access to insulin also varies worldwide, with many lower/middle-income countries (LMICs) lacking universal coverage of diabetes medications [10]. While a significant body of literature highlights the prevalence and impact of cost-related insulin underuse in the US [11–15], further research is needed at a global level with an emphasis on how this practice varies across countries with differing healthcare coverage types. Particularly, there is a pressing need in the context of the SARS-CoV-2 (COVID-19) pandemic, where disruptions of supply chains may have led to further precarity in access to insulin in some regions [16–18]. To our knowledge, this is the first study investigating self-reported out-of-pocket expenses and its effects on rationing of insulin and blood glucose testing in context with health coverage, country, and country income level.

Self-reported access to insulin and other diabetes supplies, as well as OoPE associated with the use of diabetes treatment, has been monitored by T1International in the last decade. T1International is a United Kingdom (UK) registered Charity (T1International.com) that advocates for people with type 1 diabetes around the world. It is a patient-led not-for-profit organization that receives no funding from pharmaceutical or industry donors. In both 2016 and 2018, T1International completed a web-based survey on access to insulin and diabetes supplies. The results are freely available on the T1International website (www.t1international.com/access-survey), but have not previously been published. The aim of this study is to present contemporary data concerning OoPEs, the extent of insulin and supply underuse, and the degree of financial coverage people with T1D are experiencing across the world. The study focuses primarily on the US rationing and healthcare coverage results as they compare to those of other countries.

2. Material & methods

2.1. Survey design

A web-based, cross-sectional, anonymous survey (**Supplementary Data 1**), titled "Type 1 Diabetes Access to Insulin and Supplies Survey", was conducted from August to December 2020 using the Research Electronic Data Capture (REDCap) platform [19]. The survey was co-developed by four people, three of whom are living with T1D, ensuring that questions were relevant and easy to understand for the participants. The questionnaire comprised items about healthcare coverage (e.g. health insurance, types of insulin and supplies, and associated costs). OoPEs were defined at the beginning of the survey and local currencies were converted to USD using the online XE Currency Converter tool (www.xe.com). Prior to launching the survey, T1International utilized a pilot group of N = 10 volunteers from North America, South America, Europe, Asia, and Africa. Based on their feedback on readability, usability, and clarity of the survey questions, alterations were made to improve the survey tool before sharing it with the wider T1D community.

2.2. Participants and procedures

The survey was open to people diagnosed with T1D aged 18 years and above, their partners, caregivers of children and adolescents with T1D, as well as healthcare professionals (HCP) responding on behalf of their patients. Informed consent to participate was required to proceed to the survey questions. Respondents were informed that no identifiable information would be collected and that no compensation or other financial reward for participating would be received. All work was carried out in an ethical manner and in accordance with the Declaration of Helsinki. The survey was linked from the T1International website and disseminated using online newsletters, emails, and social media platforms (including Facebook, Instagram, LinkedIn, and Twitter). It was also shared by local partner organizations where T1International advocates are active as well as global partners of T1International.

2.3. Data analysis and statistical tests

Quantitative analyses were conducted within the R statistical framework (www.r-project.org) and figures were produced using the ggplot2 package (https://ggplot2.tidyverse.org). The analysis included comparisons between countries with full, partial or no healthcare coverage. The underuse analysis of insulin and diabetes supplies frequencies were conducted on the basis of two groups with, on the one side, *Never*, and on the other side all other frequencies (*Once per year or more*, *Once per month or more*, *Once per week or more*, and *Every day*). The base R function *chisq.test()* was used and resulting *P* values were corrected with the Bonferroni method [20]. The *cramerV()* function from the rcompanion package (www.rcompanion.org) was then used with bias correction to measure the degree of association. All statistical significance thresholds were set to 0.05. When indicated in the axis legend of the relevant figures, a pseudocount of 1 USD was added to all declared OoPEs in order to retain the null values (0 USD) during the log-transformation necessary to facilitate visualization. The original survey dataset and associated R scripts are publicly available on the Github repository: https://github.com/athieffry/T1International-OoPE-survey-2020.

3. Results

3.1. Represented countries and healthcare coverage landscape

Responses from a total of 1,080 participants were recorded over a total duration of 5 months. Fourteen participants did not indicate their consent and were subsequently removed. Of the 1,066 responses that were included in the analysis, 671 (62.9%) were female, 789 (74.2%) were adults living with T1D, 117 (10.9%) were caregivers, 12 (1%) were partners and 4 (0.4%) were HCPs providing care to people with T1D. Participants were based in 64 different countries (Fig. 1**A**). The majority of responses originated from the United States (US, N = 542, 50.8%), followed by Ghana (GH, N = 46, 4.3%), and Canada (CA, N = 35, 3.3%). To mitigate the rapidly decreasing sample size while still allowing insightful comparisons by considering diverse geographic locations and country income levels, most of the downstream analyses were focused on the five most represented countries. This subset consists of the US, GH, CA, Philippines (PH, N = 28, 2.6%), and the United Kingdom (UK, N = 26, 2.4%). Overall, three groups could be distinguished on the basis of healthcare coverage distribution in the top five most represented countries, with i) mostly *full* healthcare coverage (UK), ii) mostly *partial* coverage (US, GH, and CA), and iii) mostly no coverage (PH) (Fig. 1**B**).

3.2. Out-of-pocket expenses in the five most represented countries

To identify the main drivers of OoPEs, participants were asked to report their monthly expenditures in USD (see Methods) for the following categories: insulin (short- and long-acting, mixed, and other types), devices (insulin pumps and continuous glucose monitors), glucagon kits, and testing strips for blood glucose and ketone levels (**Supplementary Data 1**). A significant but weakly positive correlation was observed between OoPEs and reported household income (Table 1) for respondents with *partial* healthcare coverage (r_s: 0.27, P = 4.3e-6, N = 565). Devices were the leading category of OoPEs (276.8 USD; 95% CI [236.2, 317.3]) followed by insulin (155.3 USD; 95% CI [128.0, 182.5]), glucagon (61.1 USD; 95% CI [50.1, 72.1]), and test strips (45.1 USD; 95% CI [39.1, 51.1]) (Fig. 2**A**). Participants with *full* healthcare coverage had the lowest self-reported OoPEs with virtually all respondents reporting 0 USD (Fig. 2**B, D**). However, monthly expenses were similar overall between *none* and *partial* healthcare coverage (Fig. 2**B**). Countries could clearly be distinguished into three categories with regards to expenses: i) the UK showing low OoPE amounts, ii) Ghana, Philippines, and the US grouping towards the highest OoPE amounts, and iii) Canada occupying a relatively uniform OoPE distribution (Fig. 2**C**).

To minimise the risks of univariate analysis and gain a more granular understanding of OoPEs, we broke down

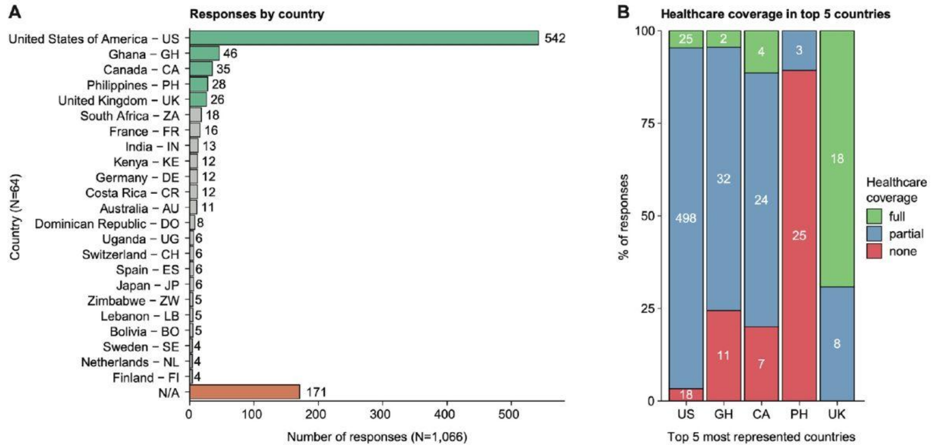

Fig. 1 – Response by country and healthcare coverage in top 5 countries. (A) **Ordering of countries (Y-axis) per number of responses (X-axis). Countries are indicated by full name followed by the alpha-2 code. Top 5 most represented countries are indicated in green, others in grey. N/A: not attributed. Only countries with more than 3 respondents are shown.** (B) **Ratio of reported healthcare coverage types (Y-axis, percent) in top 5 most represented countries (X-axis). Colors indicate the type of healthcare coverage, ranging from none (red) and partial (blue) to full coverage (green). White numbers denote the number of responses. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)**

Table 1 – Demographic characteristics of the study cohort.

Characteristic	Answers	Worldwide (N = 1,066)	Top 5 most represented countries (N = 677)
Gender	Female	671 (62.9%)	509 (75.2%)
	Male	233 (21.9%)	151 (22.3%)
	Transgender	2 (0.2%)	2 (0.3%)
	Other	7 (0.6%)	7 (1%)
	Prefer not to answer	8 (0.7%)	7 (1%)
	NA	145 (13.6%)	1 (0.1%)
Connection to T1 diabetes	Person with diabetes	789 (74.2%)	574 (84.7%)
	Caregiver	117 (10.9%)	92 (13.5%)
	Partner	12 (1%)	11 (1.6%)
	Healthcare professional of a person with diabetes	4 (0.4%)	0 (0%)
	NA	144 (13.5%)	0 (0%)
Monthly household income (USD)	< 1,000	115 (10.8%)	65 (9.6%)
	1,000–1,499	37 (3.5%)	31 (4.6%)
	1,500–2,999	149 (14%)	127 (18.8%)
	3,000–4,999	98 (9.2%)	85 (12.5%)
	greater than 5,000	36 (3.4%)	31 (4.6%)
	NA	631 (59.1%)	338 (49.9%)
Country income level	Low	11 (1%)	0 (0%)
	Middle	181 (17%)	74 (11%)
	High	703 (66%)	603 (89%)
	NA	171 (16%)	0 (0%)

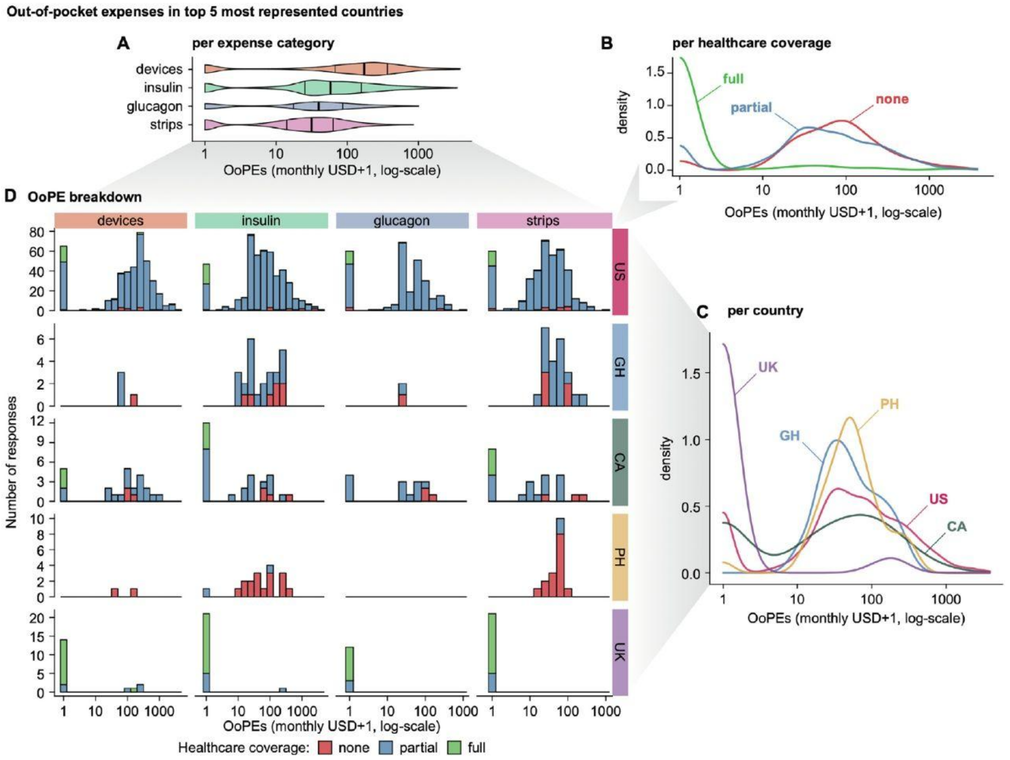

Fig. 2 – Overview of Out-of-Pocket Expenses in the top 5 most represented countries. **(A) Violin plot of self-reported Out-of-Pocket Expenses (X-axis) indicated in USD (pseudocount: +1, log-scale), for testing strips, glucagon kit, devices and insulin (Y-axis). The strips category (pink) includes both blood glucose testing strips and ketone testing strips. The devices category (orange) comprises insulin pumps and continuous glucose monitors. The insulin category (green) encompasses short-acting, long-acting, mixed-types, and other types of insulins. Violin ticks indicate quantiles and areas are proportional to the number of responses. (B) Density distribution of Out-of-Pocket Expenses (X-axis, organized as in A) per healthcare coverage type (colors) in the top 5 most represented countries (rows). (C) Density distribution of Out-of-Pocket Expenses (X-axis, organized as in A) per country (colors). (D) Breakdown of Out-of-Pocket Expenses (organized as in A) per expense category (columns), country (rows), and healthcare coverage (bar colors). Y-axis indicates the number of respondents. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)**

expenses by all factors considered above (country, healthcare coverage, and category of expenditure) (Fig. 2D). This led to the confirmation that most participants with *full* healthcare coverage originated from the UK and reported virtually no OoPEs (Fig. 2D). While most respondents with *partial* healthcare coverage reported OoPEs in the vicinity of 100 USD per month, a considerable number also reported 0 USD in the US and Canada. We note that insulin and test strips were the two categories for which the highest number of reported OoPEs were incurred, independently of healthcare coverage and country of origin. The great majority of participants reporting to be without any healthcare coverage were based in the Philippines and Ghana.

3.3. *Impact of the COVID-19 pandemic*

Participants were asked whether their access to insulin and diabetes supplies was affected by the COVID-19 pandemic. All five aforementioned countries had at least half of the participants reporting an impact of the COVID-19 pandemic, a proportion even higher in Ghana and Philippines (Fig. 3A). Specifically, the most reported COVID-19 impact was a disruption of supply (63.2%, N = 203), and a considerable fraction of participants reporting disruption to their insulin supplies also reported an increase of insulin price (25.3%, N = 203), most frequently in Ghana. Insulin access issues as a consequence of COVID-19 were mostly observed in Ghana and the Philippines (Fig. 3B).

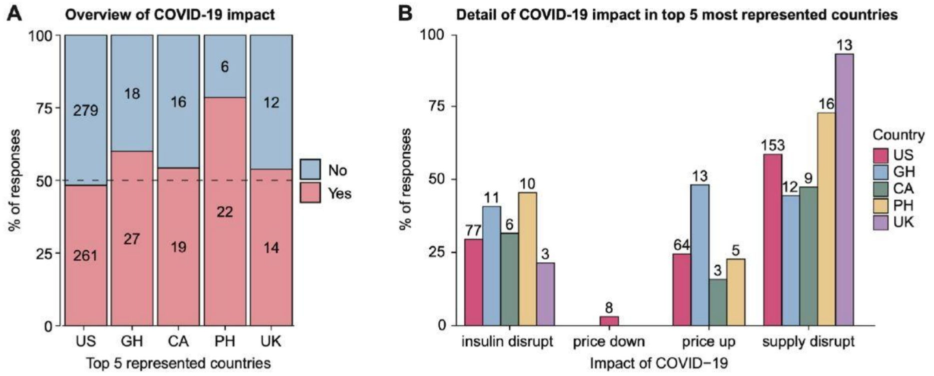

Fig. 3 – Impact of the COVID-19 pandemic in the top 5 most represented countries. (A) Overview of respondents (Y-axis, percent) in the top 5 most represented countries (X-axis) reporting an impact of the COVID-19 pandemic. (B) Detail of COVID-19 pandemic impact categories ('Yes' answer in A) in the top 5 most represented countries (bar colors). Y-axis shows the percentage of responses.

3.4. *Rationing of insulin and blood glucose testing*

To examine cost-related underuse of medication, we then analyzed the extent of rationing of insulin and blood glucose testing strips. All countries considered, rationing of blood glucose testing strips (41.3%, N = 721) was higher than rationing of insulin (25.9%, N = 779). A significant increase of underuse frequency was associated with lower healthcare coverage for both insulin intake (χ^2 [df = 2, N = 776] = 29.0, adjusted P = 4.8e-7) and blood glucose testing alike (χ^2 [df = 2, N = 716] = 54.9, adjusted P = 1.16e-12), with moderate effect sizes as indicated by Cramer's V coefficients of 0.19 and 0.27, respectively (Fig. 4**A**). A similar trend was observed in relation to country income-level (categorized as *low*, *middle*, or *high*) with the underuse frequency of blood glucose testing (χ^2 [df = 2, N = 704] = 62.87, adjusted P = 2.22e-14, Cramer's V: 0.29) and, though to a much lower extent, insulin intake (χ^2 [df = 2, N = 756] = 11.17, adjusted P = 0.037, Cramer's V: 0.11) (Fig. 4**B**).

In the five most represented countries (Fig. 4**C**), responses from the UK demonstrated no insulin underuse (0%, N = 24) and the lowest rationing of testing strips (13%, N = 23), closely followed by Canada with 11.5% (N = 26) and 25% (N = 24), respectively. In contrast, rationing in the US was well above 25% for both insulin intake (29.8%, N = 483) and blood glucose testing (39.8%, N = 447), a situation only met in the Philippines (29.4% and 70.6% respectively, both N = 17) and Ghana otherwise (51.6%, N = 31; and 90.9%, N = 33). Philippines and Ghana were the countries with the most reported insulin or blood glucose testing underuse, with Ghana being the sole country reporting a majority of respondents underusing both insulin and blood glucose testing.

4. Discussion

The main strengths of this study resides in its international breadth and its focus on costs associated with T1D management: To the best of our knowledge, this is the first study to cross-nationally compare OoPEs associated with diabetes medications and how costs impact self-management behaviours. Notably, the design of the survey was patient-led and the majority of people involved in the creation and analysis of the study are living with diabetes. The self-reported nature of the survey also brings insights into how these perceptions of incurred costs impacts on self management practices, both through the quantitative data and also through qualitative data gathered in an open text box (**Supplementary Data 2**). Generally, the greater the extent of coverage of diabetes-related expenses by the state or health insurance, the less likely insulin rationing and underuse was reported. This study highlights the importance of healthcare coverage and its direct effect on unhealthy and dangerous behaviors associated with insulin rationing.

This study reports unequal access to insulin and other diabetes-related supplies by people living with type 1 diabetes worldwide. 1,066 participants from 64 countries took part in the study, and one out of every four respondents reported having underused or rationed their insulin at least once within the last year due to high cost. The large differences between the US and other high-income countries, in terms of insulin and blood glucose testing rationing, as well as overall costs, were particularly striking. This may be partly explained by the fact that the majority (92.1%) of US respondents had access to partial coverage of their healthcare costs. Findings for the number of people with T1D in the US who had rationed insulin in the past year (29.8%) aligns with findings from previous studies on insulin underuse [12]. Indeed, the circumstances for US people living with T1D appeared to be on par with most lower-middle income countries in the extent to which cost related insulin underuse was reported by participants. In contrast, insulin underuse is virtually non-existent in the UK.

In terms of the global south, the majority of respondents from the Philippines and Ghana reported to be without any

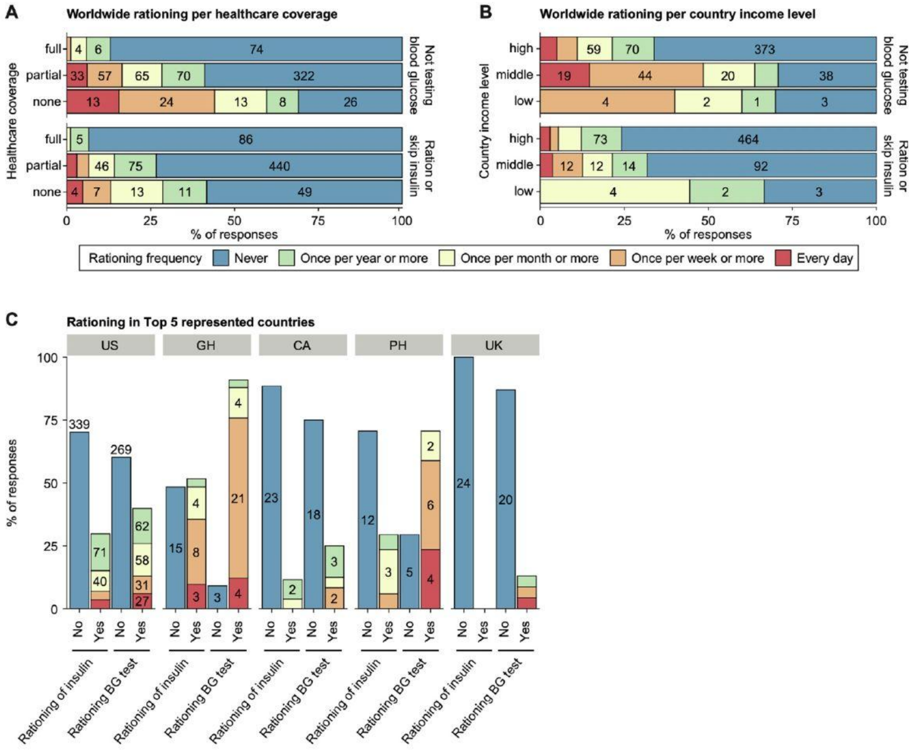

Fig. 4 – Underuse of insulin and blood glucose testing. (A) **Worldwide overview of rationing frequencies (bar colors) for i) not testing blood glucose levels (top), and ii) rationing/skipping insulin due to cost (bottom), divided by healthcare coverage types (Y-axis). X-axis indicates the percentage of responses.** (B) **Organized as in A but with Y-axis denoting country income level.** (C) **Detail of rationing frequencies (bar colors) in the top 5 most represented countries (columns). Y-axis indicates the percentages of responses. X-axis shows the categories of rationing as in A, but grouped into 'No' (Never) and 'Yes' (any positive frequency).**

healthcare coverage. From this observation naturally results a lower priority of glucagon kits, pumps, and Continuous Glucose Monitoring (CGM) devices for diabetes management, a priority that might be confounded with difficulty of access, as recently reported [21]. The impact of COVID-19 on access to insulin and supplies was also prevalent. Across the five most represented countries in this survey, approximately half of respondents noted the impact of the pandemic on their supply access, with most (63.2%) noting that access had become more difficult. This perceived insulin supply disruption and increased cost might be in part related to difficulty accessing medical personnel during the pandemic.

Unmistakable trends were observed in the relationship between underuse, healthcare coverage, and to some extent country income-level. In the UK, a high-income country, instances of insulin underuse were virtually nonexistent. This may be partly explained by the universal healthcare coverage model of the National Health Service (NHS) whereby medication costs incurred by patients are largely reimbursed by the state, thus for the most part eliminating the need for any (cost-related) underuse of insulin. By contrast, insulin underuse was common in most low-income countries and many middle-income countries alike, in addition to the unique situation of the United States which was an outlier among high income countries. The paradoxical situation of the US could be linked with the lack of Universal Health Coverage and that healthcare delivery is predominantly based on private insurance, or tied to employment. This generates an insulin underuse tendency among those who are unemployed (or employed without an adequate insurance package). Consequently, this contributes to socioeconomic inequalities in diabetes outcomes, as evidenced by the large number of people with diabetes who are uninsured in the US [22] and several deaths due to unaffordable insulin [23]. Among the US participants who reported having adequate health insurance in this study, many expressed feeling trapped within their current employment and unable to move on to a new role, fearing the loss of health insurance plan (see **Supplementary Data 2**). How the imperative to secure adequate health insurance affects career and life trajectories of those living with diabetes in the US, and other countries with only partial health coverage, is worthy of future inquiries.

Importantly, we note that, even within the NHS, recent restrictions around access to test strips introduced as part of government cost-containment measures are giving rise to rationing among people living with diabetes [24]. The consequences in terms of ability to successfully manage diabetes is unknown. Furthermore, there is also evidence of growing inequalities in access to state-of-the-art technologies such as CGM and insulin pumps, even within countries with universal systems of healthcare provision, which may lead to the exacerbation of inequalities in diabetes outcomes in the future [25,26].

We note that this survey encountered several limitations, the most prominent of which was the low number of respondents outside the US. Also, marginalized individuals and communities are likely under-represented due to Internet access requirements to complete this survey. Similarly, respondents must have been engaged with online activities or organizations focusing on diabetes care and probably demonstrate a proactive attitude in diabetes self-management practices. The survey was only disseminated in English. We acknowledge the existence of reasons for insulin underuse other than access and costs, such as allergic reactions [27], insulin purging [28], hypoglycemia anxiety [29], and mental health-related aspects, which have not been captured in this study. Additionally, precise standards of care vary widely across nations and specificities are beyond the scope of this study. Future research should more deeply explore OoPEs for people with diabetes in low-income countries, rural areas, and communities without internet access or high literacy or English language rates. It should also address access to diabetes education, specialty care, HbA1c testing, screening for diabetes-related complications, and psychosocial support, in addition to access to medication and tools.

In conclusion, insulin and supply underuse are issues of global concern. These issues have only been exacerbated by the global COVID-19 pandemic. The cost of insulin and other necessities for people with T1D should be reduced to ensure standard of care, minimize disease burden, and meet health needs. This study highlights that while there are many factors that impact physical and mental health of people with T1D, reducing the cost of insulin and supplies would decrease instances of insulin and supply underuse, and therefore diabetes-related health complications and mortality. Finally, this study adds to limited international evidence on OoPEs of people living with T1D, and its effect on diabetes management practices. These findings will help to inform and remind healthcare providers, policymakers, politicians and health service planners of the importance of equal access to this life-saving medicine.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: EP is employed as Executive Director of T1International. KB received funding from the European Commission Horizon 2020 program, the DFG-funded Berlin Institute of Health (BIH) Digital Clinician Scientist program, the BIH Junior Clinician Scientist program, the BIH QUEST center, the German Diabetes Association (DDG) and Wellcome Trust; and fees for medical consulting and public speaking from Roche Diabetes Care, Dexcom, Medtronic Diabetes, Diabeloop, Sanofi Diabetes, BCG Digital Ventures and Novo Nordisk; all outside the submitted work. AT analyzed the data in quality of consultant for T1International. KG received fees for public speaking from Novo Nordisk and is an employee of Diabetes Ireland, an organization cooperating with companies producing insulin and supplies. All other authors declare no conflict of interest.

Acknowledgements

We thank Sharon Sauter, James Elliott, and Kristi Sidney Annerstedt for their support with survey design, as well as Sharon Sauter, Timothée Froment, and Bryan Cleal for critical review of the manuscript.

Funding

This work was supported by a grant to T1International USA from Arnold Ventures [20–05146]. The use of REDCap was sponsored through the Center for Translational Science and Training Grant Support [1UL1TR001425-01].

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2021.108996.

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3. Discussion

This thesis provided an overview of user-driven innovation in diabetes technologies and their clinical and quality of life benefits. Specifically, it included new evidence on the effectiveness of open-source AID systems in the real world [83], lived experiences of users of open-source AID and their caregivers [121], based on qualitative analyses of their narratives, demonstrated the feasibility of the implementation of open-science infrastructure for real-world data sharing [84,111], and provided guidance to healthcare professionals and other important stakeholders in the form of an international consensus statement. Further, we looked into health disparities and access-related barriers to uptake of diabetes treatments and technology with an international scope.[123] In addition to the selection of articles for this thesis, we have also extensively studied user characteristics, time-in-range and glucose variability in time series data [115], barriers to uptake of non-users of open-source AID[124], QoL and sleep using validated measures [35,113,115–117,119,125], as well as on the barriers and enablers of the transition from traditional to digital care.[126]

3.1. Evidence on Open-Source AID: What Do We Know?

This work carried out by the OPEN project, but also findings from others that were in line with ours—based on *in silico*, self-/caregiver-reported, physician-reported, and device data—concluded that open-source AID systems are safe and effective treatment options for PwD, including very young children, adolescents, and elderly people.

The OpenAPS algorithm has been tested *in silico* [127] using the UVA/Padova simulator in a variety of scenarios (e.g., with bolus over- and underestimation, anticipated and late mealtime bolus) and with different glycemic targets and algorithm features enabled (e.g., advanced meal assist and administration of microboli in addition to temporary basal rate changes). The Loop and OpenAPS algorithms have also been tested head-to-head in swine with unannounced meals, which found slightly superior TIR with a comparable % of time in hypoglycemia for OpenAPS with microboli and the unannounced meal feature enabled over the Loop algorithm with integral retrospective correction. [128]

Real-world studies have shown that open-source AID systems are being widely used by PwD in various regions of the world, including countries where commercial AID systems are not available or are limited by cost and/or policy. [84] In these studies, glycemic outcomes improved significantly with decreased and near-physiological HbA1c levels and increased TIR well above recommended therapy targets, while hypoglycemia and glycemic variability were reduced at the same time. [90,99,113,129–138] With the CREATE trial conducted in New Zealand, the safety and efficacy of the OpenAPS algorithm could first be demonstrated by a randomized controlled trial (RCT). [139]

In addition to clinical outcome improvements, several studies from various regions of the world reported improved psychosocial health outcomes of open-source AID users and caregivers, with significant QoL improvements, better sleep quality, less fear of hypoglycemia, less diabetes distress, and reduced disease burden in day-to-day life. [118,130,131,133,140,141]

In summary, the clinical and patient-reported outcome changes for open-source AID appear at least comparable to commercially developed AID systems with respect to clinical and QoL benefits [134]; however, no direct head-to-head comparison with standardized protocols has so far been conducted. [84]

3.2. Strengths and Limitations of Current Evidence on Open-Source AID

Several strengths and limitations may apply to our but also others' work on open-source AID. Of particular strength are the multi-stakeholder approach, engagement and close collaboration with the patient innovators of the *#WeAreNotWaiting* community, the representative sample size in some of the studies, policies for anonymous participation and open-data donation, the development and establishment of standardized protocols for data cleaning and analysis, and exclusively independent funding mechanisms. [111,115,120,142–144]

Of further strengths, the open-science infrastructure of all OPEN studies enables anonymous participation for open-source AID users whilst the richness of the data is not compromised. In our investigation of non-users of open-source AID and their perceived barriers to uptake, fear of losing their healthcare provider's support or their health insurance if they started using open-source AID were significant concerns, which might cause participants to worry about identification based on their shared data. [124,145] In addition to the introduction of a stricter General Data Protection Regulation (GDPR) in 2016, privacy and cybersecurity aspects of personal health data are now more relevant than ever. As an example, the Supreme Court's decision to overturn abortion rights ("Roe v. Wade" [146]) led to concerns about how data collected from period-tracking apps, among other health-related data, could potentially be used to penalize anyone seeking or considering abortion in the United States. There were public announcements encouraging women to uninstall their period-tracking apps, and manufacturers of such apps have rapidly introduced additional privacy features in response. [147,148] This underlines the importance of secure and anonymous ways for users to participate in open-science that prevents potential harm to the participant when sharing their health data with various researchers. It also supports the importance of how science should always remain independent of political and/or public opinion.

As for limitations, there currently is only one RCT that demonstrated the safety and efficacy of the OpenAPS algorithm. [139,149] Some of the observational studies on open-source AID may be limited by the lack of a control group and a possible self-selection bias of PwD opting to use open-source AID (e.g., potentially more tech-savvy, with higher educational attainment and lower baseline HbA1c levels prior to AID use compared to the average population of PwD). [84,114,134] Living with diabetes and self-managing insulin therapy inherently carries risk, with both under- and over-delivery of insulin posing potentially significant health consequences. [84] Regulatory approval is a label that is legally required for companies to sell devices. However, safety and efficacy can be determined in a variety of ways, and researchers but also individual PwD and HCPs can assess that for themselves if they so choose and, for example, compare risks posed by algorithm-controlled insulin delivery and human error. [150] Acknowledging the importance of RCTs in biomedical research, particularly in the evaluation of medical devices, the relevance of, and interest of regulatory bodies in, real-world evidence are increasing. The approval process usually requires clinical trials that cost millions of dollars. Conducting RCTs is not only complex and time-consuming but also creates significant barriers to entry. Hence, the same research institutions and companies are frequently involved, further contributing to inequalities in access that are already ubiquitous. Indeed, it is open to question whether the

RCTs framework still represents an appropriate standard in relation to rapidly evolving medical devices (e.g., digital apps) in general, and user-driven technologies in particular. Commercial funding–acknowledged or otherwise–is one aspect; an equally relevant challenge is the long duration of RCTs, including preparatory and follow-up work and the documentation associated with them. The timeframe required to conduct clinical trials is at odds with the rate at which users of user-driven open-source solutions are dynamically evolving and iteratively improving.

3.3. Next Steps in AID Research

With the implications outlined above, it can be argued that real-world evidence is not only more practical but also more indicative of the actual performance of an AID system than safety and efficacy results obtained via RCTs. With the Tidepool Loop project [151] in the US, efforts are underway to obtain regulatory approval for AID systems based on open-source AID algorithms. In these projects, industry partnerships with creators and patient innovators of the *#WeAreNotWaiting* community have been established. For the safety and effectiveness evaluation of Tidepool Loop, observational real-world evidence will already be considered by the US Food and Drug Administration (FDA) for its regulatory approval. [152] The generation of real-world evidence from independent sources comparing multiple AID systems head-to-head in similar clinical settings would therefore reflect AID performance under real-world conditions most accurately, which will be subject of one of our follow-up projects.

Approaches for further advances in AID development include the use of faster and shorter-acting insulin, the development of bi-hormonal systems using insulin and its counterregulatory hormone glucagon, fully automated systems without the necessity to administer mealtime insulin manually, and the application of artificial intelligence to further improve usability and dosing algorithms. [100] Further analysis of device data in context with self-reported data will provide us an informative basis to help us identify improvement potential of AID algorithms and features (e.g., pattern recognition of the circadian rhythm and menstrual cycle [153], dynamics in insulin requirements during pregnancy and throughout childhood and adolescence). Further, we will look into the importance of therapy settings and their relevance to the performance of open-source AID systems. This information will help update and complement clinical guidance on the use of AID in a variety of PwD in different settings, and of different genders and age groups.

3.4. A Multi-Stakeholder Ethicolegal Dilemma

In addition to providing much-needed recommendations and guidance for the safe and ethical use of open-source AID in clinical settings through our consensus statement [84], a handful of healthcare providers and diabetes advocacy organizations have released position statements and legal expert opinions. [154–158]

Research specifically examining the legal, ethical, and policy implications of open-source AID is scarce. Despite the publication of these position statements and opinion pieces, important questions remain, which have not yet been adequately examined, let alone resolved; for instance, who is liable in case of safety issues and device malfunctions that could harm users; if open-source AID systems are adequately captured by the architecture of existing regulatory structures today; and the impact of open-source AID on the ethical and legal responsibilities of clinicians towards those who choose to use such systems in their respective legislations. [145]

Furthermore, humanities and social science have only begun to tease out the implications of the emergence of peer production in healthcare as a new system of value creation alongside commercial and publicly funded institutions. There are numerous ways in which peer production breaks with current paradigms of medical innovation and regulation. Firstly, peer production tends to be driven primarily by collaboration and diverse personal and prosocial interests (e.g., self-interest, altruism, solidarity, affection, care, curiosity) towards the goal of addressing a specific need [159]; i.e., reducing the physical and emotional burden and cognitive load of living with diabetes. Profit and monetary interests may still exist, but are peripheral and not the core of activities. Secondly, in peer production, there is no separation between the traditional "producer" and "consumer". Innovators within the community are typically either the end-users themselves or care for someone who is an end-user. Thus, from the developers' point of view, the safety of the systems is more than just a requirement to be met in order to obtain regulatory approval; they are a matter of their own or their loved ones' life and death. Thirdly, open sharing of information and data are tenets of the philosophy behind *#WeAreNotWaiting*. The source code of the different open-source AID apps operating the algorithms is shared on open-source repositories online and extensively documented so that others can not only compile such systems for themselves but also check the integrity of the code. There is a clear explanation of the logic underpinning the calculations and decisions of the dosing algorithms that are used as part of the automation process (i.e., no "black box"). This allows PwD, alongside real-world evidence produced by academia in collaboration with the community, to make informed decisions as to the relative risk and merits of building a system for themselves. [4,150] All of these conditions have created a situation in which patients have built a high level of trust in a technology that has been developed entirely outside of existing regulatory frameworks. [150]

3.5. The Digital Divide

While PwD generally report positive experiences with diabetes technologies, the complexity of accessing and maintaining them currently remains challenging for some. [160] Significant health disparities in access to diabetes care exist between countries and regions, but even within the same country. [123] Market availability of a medical device per se does not automatically imply universal access for patients. [161]

Our analysis of barriers to uptake for open-source AID has shown that sourcing the necessary components (CGM, insulin pump) is the most significant challenge for building an AID system. [124,125] In low-and-middle-income countries with no or partial insurance coverage, diabetes technologies are almost universally inaccessible and unaffordable for most households. [123,162] In developing countries and/or countries with no healthcare coverage, access to a qualified HCP, a specialized hospital, appropriate medication, and technology often depends on what household a person is born into, or on their biological sex. [163,164] This issue has been extensively studied in India where girls with T1D are significantly disadvantaged in access to diabetes care compared to boys [163,164], and those with lower socioeconomic status and living in poorer neighborhoods not only have a higher prevalence of type 2 diabetes but also in diabetes related-complications. [165,166] In countries that are supported by the "Life for a Child" program of the International Diabetes Federation [167], only 0.2% of young PwD are using insulin pumps. Diabetes care, as it is recommended by the ISPAD guidelines is prohibitively expensive for PwD in lower resource countries.[168] Very little care is provided by government health systems, resulting in high mortality, and high complication rates in those who do survive. [169,170] In the lowest resourced countries, even minimal care with insulin injections and capillary blood glucose monitoring is beyond many families' means so they depend on additional support. [169–172]

Even in high-income countries where diabetes technologies are largely covered by the healthcare system, that does not guarantee access and availability to the individual PwD. Limitations in license status may apply, and reimbursement policies vary between regions and insurance plans. [84] For example, in Germany, Ireland, and the US, children, adolescents, and young adults with T1D are less likely to meet therapeutic target recommendations for HbA1c and be prescribed a CGM or an insulin pump if they belong to an ethnic group other than Non-Hispanic White or are socially deprived. [86,173–179] This particularly applies to PwD from indigenous communities in North America and the Western Pacific region. [180–183] Similar patterns as in access to insulin and supplies apply for access for PwD to diabetes education. [184–189]

In addition to structural barriers impacting universal access to advanced diabetes technologies, there are also behavioral barriers, founded on the attitudes and beliefs of HCPs, also referred to as "implicit bias" and "clinical inertia". [190–192] Recommendations for the transition to technologically mediated treatment may be influenced by clinicians' limited resources in time and education, lack of familiarity with the efficacy and safety of therapeutic regimens, or their assessment of whether PwD are genuinely committed to reaching optimal glycemic targets and their intellectual capacity to do so. [177,192,193] Such assumptions may systematically exclude certain population groups, even though there is evidence that initiation of technologically mediated treatment can serve as a catalyst for some PwD to truly engage with their diabetes management, even though they have not previously shown any inclination to do so. [194–196]

The "digital divide" might further increase these disparities between PwD if access and availability of digital innovations are not taken into consideration and given a priority early on in planning their distribution. [197] Although advances in safety, efficacy, and usability of technologically mediated treatments promise much, there remain significant concerns with respect to social inequality and the challenge of ensuring that the benefits of diabetes technologies, and AID in particular, are widely diffused across the population. Globally, around 80% of PwD live in low-income and middle-income countries, yet most interested parties continue to pursue a research agenda driven by high-income needs. [198,199] The challenges around the access and adoption of diabetes technology are, therefore, not exclusively medical or technical. They are also profoundly ethical, sociological, and political in nature and require an interdisciplinary and intersectoral approach to be addressed effectively. As questioned by medical anthropologist Paul Farmer: "If healthcare is [...] a human right, who is considered human enough to have [it]?" [200] – or is it just a privilege?

3.6. Industrial Healthcare fails Patients–and Clinicians

Structures and workflows in healthcare have evolved over the last decades, to a large part towards industrially-oriented models. In his book "Why we revolt: A patient revolution for careful and kind care", endocrinologist Victor Montori argues that industrial healthcare "fails to notice patients". [201] In such healthcare systems, rigid protocols and fear of deviating from them miss the individual person. Encounters that are enforced to be brief and shallow speed patients through consultations in which HCPs cannot appreciate their situation. "Failure to notice" is also related to encounters bloated with industrial agendas, such as documentation and billing. [201] "The harm is not only to patients", he concludes, "industrial healthcare is killing the healer's soul. Enforced productivity depletes clinicians. Industrial healthcare has stopped caring for [...] everyone at the frontline". Clinicians have described their experience with seeing patients in such a series of short-term encounters as a "blur" in which they can barely remember the individual and their history at the end of the day.[201] This stress and mental health burden on HCPs has only increased for practicing and aspiring doctors given the challenges of the Covid-19 pandemic. [202–204]

Industrial healthcare not only fails to notice patients as part of encounters in clinical care, but also fails to make essential tools, medication, and education accessible to a vast majority of the population. In the "100 years of insulin" special issue of The Lancet, the editors described the centennial of insulin as a "technical success, but an access failure". [198] Similarly, it was stated in the New England Journal of Medicine that the anniversary of the discovery of insulin celebrates "100 years of insulin for some". [205] This is not only prevalent in low-and-middle-income countries but also in the US, where skyrocketing prices for insulin significantly contribute to disparities in healthcare within the American population. [206,207] *#WeAreNotWaiting* has not been the only precedent where the public and patient community have been approached for help by PwD. As described in the study "GoFundMe as a medical plan" by Litchman et al., individuals turning to crowdfunding websites for financial support of their healthcare-related costs is becoming more and more popular. [208,209] Other approaches for Americans who cannot afford to buy insulin include medical tourism to border states (i.e., Canada and Mexico); however, due to the FDA, it is generally illegal for Americans to import drugs into the US for personal use and has provided border inspectors expanded authority to destroy imported drugs at their point of entry. [210,211]

The case of *#WeAreNotWaiting* highlights how informed and connected people already disrupt the medical device industry and its regulatory landscape, simply because patients and their families did not accept the limitations in availability and access to advanced treatments but also the slow speed of development and regulatory processes. As one of our study participants described: *"It was a defining moment in my life as a parent. [...] I was no longer at the mercy of markets, profits, politics and whims. I had the capacity to provide for my own child again."* [121]

3.7. "Do-it-Yourself" is not "Do-it-Alone": The Impact of Community

With implications of availability and access to diabetes care as outlined above, involving peers in their own or a child's diabetes care is gaining momentum. For some, this is a proactive choice; for some, it is a necessity. [208,212,213] In today's digital world, PwD are using a variety of text, pictures, audio, and video to express their needs, wishes, failures, frustrations, and successes; to provide companionship and mentoring, and to share their experience and advice in an unprecedented 24/7 stream of consciousness. [213] A recent study by Tendrich et al. has highlighted how online peer support groups "fill critical gaps in the healthcare system" by providing real-time support and education to PwD "anywhere, anytime".[213] These resources of social, emotional, and experiential support generally have a positive impact on diabetes management. [214] This is in line with our findings on the motivation to engage with the *#WeAreNotWaiting* community, where a sense of community and helping others "#PayItForward" was frequently mentioned. As stated by one of our study participants: *"It feels like I am part of a big people-powered movement. It feels like a revolution."*

The aspect of "patient centricity" in research and clinical care is gaining importance but, in reality, is oftentimes poorly executed. Whilst many concepts promise to be "patient-centric" or "-oriented", actual patients who can speak for themselves have only marginally been involved, e.g. as research participants or in minor advisory roles. As patient and caregiver perspectives can provide meaningful information that is critical for an intervention's success, their impact should not be underestimated. With the uptake of collaborations between research institutions and patient innovators, recommendations for diabetes advocacy being considered in the latest version of the ADA guidelines, the ISPAD's plans to involve PwD in their next iteration of clinical guidelines, and the launch of the #dedoc° voices program–a scholarship program that brings diabetes advocates to scientific conferences–efforts are underway to increase public and patient involvement in diabetes research and care. [215,216]

4. Summary and Conclusion

While the search for a biological cure for T1D continues, AID systems remain at the forefront of technologies and treatments for optimal diabetes management as a new state-of-the-art therapy option or so-called “technological cure”.

While current studies, our own and others’, have shown that users of AID systems (commercial and open-source) achieve positive outcomes with respect to clinical parameters and QoL, there are still areas for improvement and further iteration in terms of interoperability, user experience, education for PwD and HCPs, personalization, suitability for different gender and age groups, and especially wider access for PwD. Medical devices should no longer be manufactured and marketed as “one size fits all”. Manufacturers should therefore no longer continue to develop products and services in isolation. Instead, users from many backgrounds should be involved as early as possible. Their wishes and needs should be identified and understood, and challenges as the basis for developing effective and marketable solutions that meet their expectations and are accessible and applicable for a variety of different groups throughout the social gradient. *#WeAreNotWaiting* is unlikely to be the last bottom-up initiative in the field of medicine and healthcare. Taking matters into their own hands, this unique community and its bottom-up approach is a novelty, and a primary example of impact by peer support, where intelligent computing, open sharing of data and information, community support, and direct user feedback combine to push innovation while striving to ensure that privacy, security, and safety are not compromised.[4] It is important to determine the lessons to be learned from this movement, especially for stakeholders involved in research and medical device development but also regulatory affairs, governance, and policymaking. Mutual efforts will help us to finally fully “close the loop”.

“If I could give my pancreas to my son, I would. This is the next best available option.”

(Caregiver of a 12-year-old boy, UK, using OpenAPS since 2018) [121]

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Acknowledgments

I thank my amazing scientific and clinical co-mentorship team Klemens Raile of the Department of Pediatric Endocrinology and Felix Balzer of the Institute of Medical Informatics at Charité–Universitätsmedizin Berlin, Bryan Cleal of Steno Diabetes Center Copenhagen, Sufyan Hussain of King’s College London, and Rayhan Lal, Korey Hood, David Maahs and Bruce Buckingham of the Stanford Diabetes Research Center: Your expertise, advice, approachability and support helped me grow as a person, but also medical professional and researcher.

I am grateful to Nathalie Huber, Iwan Meij, Katharina Walentin, Beatrice Sobek, Nele Mohr, Igor Sauer and Sarah Weschke of the Berlin Institute of Health for supporting us (Digital) Clinician Scientists on our mission to translational and impactful research. My gratitude goes to Duška Dragun who initiated this initiative and will always be a role model.

In addition to the Berlin Institute of Health, I would like to acknowledge the European Commission, Wellcome Trust, Deutsche Forschungsgesellschaft, Nightscout Foundation, DesignIt and Stiftung Charité for having funded or otherwise supported our projects.

My gratitude goes to the organizers and other members of the Falling Walls Foundation Intensive Track for Female Science Talents for their mentorship, support, and inspiration.

I thank the entire *#WeAreNotWaiting* community and the OPEN consortium for their curiosity and team spirit, and for making the past few years so special. Further, I thank the many people who contributed to our OPEN international healthcare professional network and legal advisory group, and to all people with diabetes and their families who joined our studies and shared their experiences and data. I thank the professional diabetes organizations for their endorsement of our consensus statement and trust in our work.

Special thanks to my friends and family, Claudia, Ralf and Fox, for always having my back.

I thank my global diabetes family for their courage and kindness:
You showed me how to never give up, and how to #PayItForward.

Erklärung
§ 4 Abs. 3 (k) der HabOMed der Charité

Hiermit erkläre ich, dass

- weder früher noch gleichzeitig ein Habilitationsverfahren durchgeführt oder angemeldet wurde,
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- mir die geltende Habilitationsordnung bekannt ist.

Ich erkläre ferner, dass mir die Satzung der Charité – Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis bekannt ist und ich mich zur Einhaltung dieser Satzung verpflichte.

Berlin, den 19.10.2022