Universität Bremen

BIPS Leibniz

Augmenting Diabetes Care & Self-Management: What can digital health offer?

A dissertation submitted to the University of Bremen in partial fulfillment of the requirements for the degree of

Doctor of Public Health (Dr. P.H)

by

Mihiretu M. Kebede

Bremen, June 2019

Defended on **30/10/2019**

Reviewers

1. Prof. Dr. Hajo Zeeb
2. Prof. Dr. Sonia Lippke

Supervisors

1. Prof. Dr. Hajo Zeeb
2. Prof. Dr. Claudia R. Piscke

ACKNOWLEDGEMENTS

"And may the Lord reward you for your kindness…."

(Ruth 1:8)

First and foremost, I would like to express my deepest appreciation to my supervisors Prof. Dr. Hajo Zeeb and Prof. Dr. Claudia R. Pischke for providing me unprecedented guidance and support from the very first day until the completion of this dissertation.

I would also like to thank my parents, as well as my sisters and brothers. My father, you are my hero.

I would also like to extend my gratitude to all of my coauthors, Janna Sill and all of my colleagues at the Prevention and Evaluation department. Special thanks to Regine Albrecht and Dirk Gansefort for supporting me to get to know Bremen and quickly feel integrated into the working, academic and social culture of BIPS. I am also very grateful to Dr. Tilman Brand and Dr. Florence Samkange-Zeeb for their support in solving the many questions I had on several occasions. Many thanks to Mariam R. Issak from the Biometry department and Friedrich Boye from the IT for their tremendous help in helping me solve many challenges related with R and R studio. I had a great time with my friend Nickolas Adjei in refreshing my mind with fun discussions (a lot of them were actually science debates), and table football games during lunch breaks at Uni Mensa. Coming back to office after those unforgettable lunch breaks helped me to reboot my mind and sharpen my focus for yet another productive day.

I also would like to thank my former colleagues from the University of Gondar mainly Atinkut A Zeleke and my MPH theses supervisor, Dr Berihun M. Zeleke, who is one of the best epidemiologists that I have ever worked with and have been taught by. Dr Berihun, you are my role model! My heartfelt acknowledgements go to my special colleagues and friends in Gondar: Kiber Temesgen, Birhanu Wubale/Asfaw, and Miteku A Limenih. Chatting with you has a relief to my chronic nostalgia.

This work reached this level because of the great support from the international students' office for facilitating the organizational aspects of my PhD studentship at the University of Bremen. In addition, I am grateful to the Bremen Early Career Researcher Development for supporting my research with an IMPULSE grant that partially covered the cost of my data

collection. I took part in some helpful courses organized by BYRD and I thank the organizers of these courses.

Fortunately, I have met several incredible people in my life. One is a great scientist and the mother of my two sweet daughters (Hilda and Lela). She is Dr. Fleur Fritz-Kebede. Fleur, "where did I get you?" Thanks to Fritz Gruppe (especially Gerlinde Fritz and Norbert Fritz), I found my home away from home!

DEDICATION

I dedicate this dissertation in memory of my late uncle, Molla Tesfahun, who laid the foundations for recognizing the values of education in our family. My uncle started supporting me since the early days: starting from convincing my parents to send me to school instead of farming, and continued with his unprecedented encouragements that empowered me to strive for excellence. I would have had the same fate like many other children in my home village who had no chance for education. Sad that you finally lost your 35 years long battle against Type 1 diabetes. Uncle Molla, I know you will not read this. You will always remain in my heart!

TABLE OF CONTENTS

ACKNOWLEDGEMENTS i

DEDICATION iii

TABLE OF CONTENTS iv

ABBREVIATIONS AND ACRONYMS v

LIST OF FIGURES viii

ABSTRACT ix

ZUSAMMENFASSUNG xiv

PREFACE xiv

1. INTRODUCTION 1

1.1 Historical perspectives of diabetes 1

1.2 Pathophysiology and classifications of diabetes 3

1.3 Diagnosis of diabetes 7

1.4 Epidemiology of diabetes 7

2. DIABETES SELF-MANAGEMENT IN THE DIGITAL AGE 12

2.1 Digitalising diabetes self-management 13

2.2 The role of digital health in artificial pancreas 18

2.3 Patient initiatives in the digitalization of diabetes care and self-management 19

2.4 The role of digital health for improving diabetes patient outcomes 21

3. OBJECTIVES 23

3.1. General objective 23

3.2 Specific objectives 23

4. FRAMEWORK OF THE DISSERTATION 24

5. METHODS 26

5.1. Study I - Effectiveness of Digital Interventions for Improving Glycemic Control in Persons with Poorly Controlled Type 2 Diabetes: A Systematic Review, Meta-analysis, and Meta-regression Analysis 26

5.2. Study II - Comparison of three meta-analytic methods using data from digital interventions on type 2 diabetes 28

5.3. Study III: The Role of Continuous Glucose Monitoring, Diabetes Smartphone Applications, and Self-Care Behavior in Glycemic Control 29

5.3.1 Questionnaire design, sources of respondents and recruitment....29
5.3.2. Data analysis....30
5.4. Study IV: Popular Diabetes Apps and the Impact of Diabetes App Use on Self-Care Behaviour30
6. SUMMARY OF RESULTS....32
6.1. Results of study I - Effectiveness of Digital Interventions for Improving Glycemic Control in Persons with Poorly Controlled Type 2 Diabetes: A Systematic Review, Meta-analysis, and Meta-regression Analysis....32
6.2. Results of study II - Comparison of three meta-analytic methods using data from digital interventions on type 2 diabetes....33
6.3. Results of study III: The Role of Continuous Glucose Monitoring, Diabetes Smartphone Applications, and Self-Care Behavior in Glycemic Control....33
6.4. Results of study IV: Popular Diabetes Apps and the Impact of Diabetes App Use on Self-Care Behaviour....34
7. DISCUSSION....38
7.1 Principal findings....38
7.2. Interpretations and comparisons with prior work....39
7.3 Strengths and limitations....41
7.3.1 Strengths....41
7.3.2 Limitations....41
7.4 Improving diabetes patient outcomes with digital health: promises and perils....43
7.4.1 Data ownership, protection of privacy and confidentiality....44
7.4.2 Lack of evidence of clinical effectiveness and safety....46
7.4.3. Digital health literacy, digital divide and health inequality....47
7.4.4 Finding an app that perfectly suits the interest of patients is almost impossible....48
7.5 The future of digital health....49
7.5.1 Wearables and the transformation of healthcare and public health....49
7.5.2 Social media and public health....50
8. CONCLUSIONS AND FUTURE DIRECTIONS....53
8.1. Conclusions....53
8.2. Future directions....53
9. REFERENCES....56
10. APPENDIX....76
10.1. Appendix A: Research articles....76
Appendix B: Author's contributions....148

10.2. Appendix C: Declaration 149

Versicherung der eigenständigen Verfassung 149

ABBREVIATIONS AND ACRONYMS

ADA	American Diabetes Association
AADE	American Association of Diabetes Educators
ANCOVA	Analysis of Covariance
BCTs	Behavioural Change Techniques Taxonomy
CCM	Continuous Glucose Monitoring
CDSS	Clinical Decision Support Systems
CGM	Chronic Care Model
DSME	Diabetes Self-Management Education
eCCM	eHealth Enhanced Chronic Care Model
FDA	Food and Drug Administration
GBD	Global Burden of Diseases
GDPR	General Data Protection Regulation
HbA1c	Glycated haemoglobin
HIPPA	Health Insurance Portability and Accountability Act
IDF-Europe	International Diabetes Federation-Europe
IFG	Impaired Fasting Glucose
IGT	Impaired Glucose Tolerance
MEDLINE	Medical Literature Analysis and Retrieval System Online
OGTT	Oral Glucose Tolerance Test
PDA	Personal Digital Assistants
PRISMA	Preferred Reporting Items for Systematic review and Meta-Analysis
RCTs	Randomized Controlled Trials
SACS	Simple Analysis of Change Scores

SAFV	Simple Analysis of Final Values
SDSCA	Summary of Diabetes Self-Care Activities
TES	Technology-enabled Self-management
URL	Universal Ressource Locator
WHO	World Health Organization

LIST OF FIGURES

Figure 1: Global type 1diabetes prevalence across age groups for both sexes (prevalence on the y-axis, and age in years on the x-axis, source: https://vizhub.healthdata.org/gbd-compare/) (51) 6

Figure 2: Global type 2 diabetes prevalence across age groups for both sexes (prevalence on the y-axis, and age in years on the x-axis, source: https://vizhub.healthdata.org/gbd-compare/) (51) 6

Figure 3: Trend of diabetes type 1 diabetes prevalence in all GBD super regions (Source: https://vizhub.healthdata.org/gbd-compare/) (51) 8

Figure 4: Trend of diabetes type 2 prevalence in high burden countries (Source: https://vizhub.healthdata.org/gbd-compare/) (51) 9

Figure 5: Edward H Wagner's Chronic Care Model (120) 13

Figure 6: eHealth Enhanced Chronic Care Model (eCCM) (122) 14

Figure 7: Technology Enabled Framework from the AADE 2016 technology working group (128) ...15

Figure 8: Clinical Decision Support System (CDSS)-based uHealth care system (136) 16

Figure 9: Technology-enabled self-management (TES) feedback loop (141).....17

Figure 10: Framework of dissertation.....25

Figure 11: Popular diabetes apps.....35

Figure 12: Forest plot of the coefficients with 95%CI for factors associated with self-care behaviour in persons with type 1 DM. 36

Figure 13: Forest plot of the coefficients with 95%CI for factors associated with self-care behaviour in persons with type 2 DM. 37

ABSTRACT

Background: The main recommendations for people living with diabetes are: optimally adhere to glucose lowering medications, frequently monitor their blood glucose levels, regularly engage in physical activity, and avoid the consumption of an unhealthy diet. Suboptimal adherence to these recommendations is associated with experiencing poor glycemic control which results in micro- and macro-vascular complications, poor quality of life, and a higher risk of premature death. Therefore, patients with diabetes require an evidence-based medical treatment coupled with effective self-management interventions to maintain a healthy lifestyle and increase disease management capability. Digital health has a strong potential to improve patient outcomes by facilitating diabetes self-management education and personalizing clinical, behavioral, and self-management goals. This dissertation discusses the role of digital health for improving diabetes self-management and outcomes. More broadly, the main aspects of digital health solutions and what it may offer to healthcare and public health, in general, are also discussed.

Methods: A systematic review and meta-analysis was conducted to determine the effectiveness of digital interventions for improving glycemic control in persons with poorly controlled type 2 diabetes. Multivariable meta-regression was also used to identify the effective components of digital interventions. Three meta-analytic methods, namely, Analysis of Covariance (ANCOVA), Simple Analysis of Change Scores (SACS) and Simple Analysis of Final Values (SAFV) were used to compare the effectiveness of digital interventions. In addition, two empirical studies were conducted to identify popular diabetes application (apps) and investigate the role of diabetes mobile app use for glycemic control and self-care behavior among the digital community of persons with diabetes. Facebook groups, targeted Facebook advertisements (ads) and diabetes-specific patient forums were used to collect data from 1682 respondents.

Results: A statistically significant reduction of glycated haemoglobin (HbA1c) levels favoring participants of digital interventions was found after pooling the effect estimates. This was confirmed by all of the three different meta-analytic methods although there was a slight difference in the estimates and their confidence intervals. Higher baseline HbA1c-levels and Behavior Change Techniques (BCTs), such as ‘problem solving’ and ‘self-monitoring outcomes of behaviour’, were significantly associated with reduced HbA1c-level. More than

half of the respondents with type 1 (n=549, 52.2%) and more than one-third of those with type 2 diabetes (n=210, 33.3%) reported using diabetes apps for self-management. One hundred forty-five different diabetes apps were reported by respondents. Of these apps, “mySugr” was the most popular app. Continuous glucose monitor (CGM) apps, such as “Dexcom”, “Freestyle Libre”, and “Xdrip+”, were also popular, particularly among respondents with type 1 diabetes. The use of diabetes apps for self-management was associated with reduced the odds of experiencing hyperglycaemia in persons with type 2 diabetes (by 37%, AOR = 0.63(95% confidence interval (CI): 0.41 - 0.96)). In both persons with type 1 and type 2 diabetes, the use of diabetes apps for self-management was also independently associated with an increased cumulative self-care behavior scores.

Conclusions: The results of this dissertation indicate that digital health augments diabetes self-management and is associated with improving clinical (HbA1c, hyperglycaemia and hypoglycaemia) and behavioral (self-care behavior) outcomes. Hence, it looks reasonable to endorse the use of diabetes apps for self-management. However, to date, many of these apps are faulty and only a small minority of them meets clinical recommendations for diabetes care. Clinicians should therefore consider prescribing evidence-based and regulatory body-approved diabetes apps. National and international regulatory bodies need to further regulate diabetes apps and ensure clinical safety and effectiveness.

ZUSAMMENFASSUNG

Hintergrund: An Diabetes erkrankten Menschen wird empfohlen blutzuckersenkende Medikamente zu nehmen, ihre Blutzuckerwerte regelmäßig zu kontrollieren, sich ausreichend körperlich zu bewegen und eine ungesunde Ernährung zu vermeiden. Eine ungenügende Einhaltung dieser Empfehlungen ist mit einer schlechten glykämischen Kontrolle verbunden, welche wiederum Probleme am Herz-Kreislaufsystem, verringerte Lebensqualität und das Risiko eines verfrühten Todes mit sich bringt. Um ihre Krankheit bewältigen zu können und eine gesunde Lebensweise aufrecht zu erhalten, benötigen Diabetespatienten daher sowohl evidenzbasierte Behandlungsmethoden als auch Instrumente für ein effektives Selbstmanagement. Digital Health hat das Potential Behandlungsergebnisse zu verbessern, indem es ermöglicht sich über das Selbstmanagement der Diabeteserkrankung zu informieren und sich personalisierte klinische und behaviorale Ziele zu setzen, sowie konkrete Ziele in Bezug auf Selbstmanagement. Diese Dissertation behandelt die Frage, welche Rolle Digital Health in der Verbesserung des Selbstmanagements und der damit verbundenen Behandlungsergebnisse spielt. Im Weiteren werden wichtige Aspekte von Digital Health Anwendungen und ihre Möglichkeiten in Bezug auf Gesundheitsversorgung und Public Health generell diskutiert.

Methoden: Um die Effektivität digitaler Interventionen zur Verbesserung der glykämischen Kontrolle bei Typ 2 Diabetes Patienten mit einem schlecht eingestellten Blutzucker zu bestimmen, wurde eine systematische Übersichtsarbeit und Metaanalyse durchgeführt. Zur Bestimmung der jeweiligen effektiven Komponenten wurde zudem eine multivariable Meta-Regression durchgeführt. Die folgenden drei metaanalytische Methoden wurden angewandt, um die Effektivität der Interventionen zu bestimmen: Analysis of Covariance (ANCOVA), Simple Analysis of Change Scores (SACS) und Simple Analysis of Final Values (SAFV). Darüber hinaus wurde eine Querschnittsstudie unter Menschen mit Diabeteserkrankung durchgeführt, die sich für digitale Interventionen interessieren. Ziel dieser Studie war, beliebte Diabetes Apps zu identifizieren und die Bedeutung von solchen Apps für die glykämische Kontrolle und das Fördern einer gesunden Lebensweise herauszufinden. 1682 Teilnehmer wurden für diese Studie in Facebook Gruppen, speziellen Diabetes-Foren und gezielten Facebook Anzeigen rekrutiert.

Ergebnisse: In dem zusammengefassten Schätzwert zeigte sich eine statistisch signifikante Reduzierung der durchschnittlichen Blutzuckerwerte (HbA1c) unter Patienten, die digitale Interventionen nutzten. Dies wurde durch alle drei verwendeten metaanalytischen Methoden bestätigt. Leichte Abweichungen zeigten sich nur in den Schätzwerten und Konfidenzintervallen. Höhere HbA1c-Werte und Strategien zur Verhaltensänderung (BCT = Behavior Change Techniques), wie z.B. ‚Problemlösen' ('Problem solving') und ‚Monitorierung von Auswirkungen des Verhaltens' ('Self-monitoring outcomes of behaviour') waren signifikant mit einem niedrigeren HbA1c-Wert assoziiert.

Mehr als die Hälfte aller Teilnehmer und Teilnehmerinnen mit Diabetes Typ 1 (n=549, 52.2%) und mehr als ein Drittel derer mit Typ 2 (n=210, 33.3%) berichteten, dass sie Diabetes Apps zum Selbstmanagement nutzen. Es wurden 145 verschiedene Apps angegeben. Die beliebteste darunter war "mySugr". Apps, um die Blutzuckerwerte kontinuierlich zu kontrollieren (CGM = continuous glucose monitoring), waren besonders unter Patienten mit Diabetes Typ 1 beliebt, hier vor allem "Dexcom", "Freestyle Libre" und "Xdrip+". Unter Patienten mit Diabetes Typ 2 war die Nutzung von Apps zum Selbstmanagement assoziiert mit einer reduzierten Chance eine Überzuckerung zu erleiden (37%, AOR = 0.63(95% Konfidenzintervall (KI): 0.41 - 0.96). Unter beiden Patientengruppen war die Nutzung von Apps zum Selbstmanagement unabhängig assoziiert mit einem erhöhten kumulierten Wert für eine Verhaltensänderung.

Schlussfolgerungen: Die Ergebnisse dieser Dissertation weisen darauf hin, dass Digital Health das Selbstmanagement von Diabetikern über verbesserte klinische (HbA1c, Über-/Unterzuckerung) und Verhaltensparameter positiv beeinflussen kann. Daher kann die Nutzung von Diabetes Apps zum Selbstmanagement empfohlen werden. Es gilt allerdings zu beachten, dass derzeit die meisten Apps noch nicht fehlerfrei funktionieren und nur sehr wenige die klinischen Empfehlungen einer Diabetesbehandlung voll berücksichtigen. Es sollten von Ärzten daher nur solche Apps empfohlen oder sogar verschrieben werden, die aufgrund evidenzbasierter Studien zugelassen wurden. Entsprechende nationale und internationale Zulassungsbehörden sollten hier tätig werden, um Patientensicherheit und Behandlungseffektivität zu gewährleisten.

PREFACE

This thesis is organized in several chapters from "Introduction" to "Conclusion". The doctoral thesis is a cumulative summary of four thematically interrelated research papers published in international peer-reviewed journals. The first article determined the effectiveness of digital interventions for improving glycemic control in persons with poorly controlled type 2 diabetes. The second one explored methodological issue for synthesizing the effects of digital interventions. The third and fourth articles investigated the role of diabetes applications use in improving glycemic control and self-care behaviour in both persons with type 1 and type 2 diabetes. In addition to the four core articles, four additional articles were published and seven conference abstracts were produced during the doctoral journey. These conference abstracts were presented at national and international conferences such as the Annual Meeting of the German Society of Epidemiology (DGEPI), American Diabetes Association (ADA), Johanna Briggs Institute conferences, 55th European Association of Studies in Diabetes (EASD) conferences. The core research articles and the additional articles are outlined below.

Core papers

I. **Kebede MM**, Zeeb H, Peters M, Heise TL, Pischke CR. Effectiveness of digital interventions for improving glycemic control in persons with poorly controlled type 2 diabetes: a systematic review, meta-analysis, and meta-regression analysis. Diabetes Technology & Therapeutics, 20(2), 10.1089/dia.2018.0216

II. **Kebede MM,** Peters M, Heise TL, Pischke CR. Comparison of three meta-analytic methods using data from digital interventions on type 2 diabetes. Diabetes Metab Syndr Obes 2019;12:59-73, 10.2147/DMSO.S180106

III. **Kebede MM,** Schuett C, Pischke CR. The role of continuous glucose monitoring, diabetes smartphone applications, and self-care behavior in glycemic control: results of a multi-national online survey. J Clin Med 2019;8(1), 10.3390/jcm8010109

IV. **Kebede MM**, Pischke CR. Popular diabetes apps and the impact of diabetes app use on self-care behaviour: a survey among the digital community of persons with diabetes on social media. Front Endocrinol (Lausanne) 2019;10:135, 10.3389/fendo.2019.00135

Miscellaneous papers

I. **Kebede MM**, Liedtke PT, Möllers T, Pischke RC. Characterizing active ingredients of eHealth interventions targeting persons with poorly controlled type 2 diabetes mellitus using the Behavior Change Techniques Taxonomy: Scoping Review. J Med Internet Res 2017;19(10):e348, 10.2196/jmir.7135.

II. **Kebede M**, Christianson L, Khan Z, Heise TL, Pischke CR. Effectiveness of behavioral change techniques employed in eHealth interventions designed to improve glycemic control in persons with poorly controlled type 2 diabetes: a systematic review and meta-analysis protocol. Syst Rev 2017;6(1):21, 10.1186/s13643-017-0609-1.

III. **Kebede M,** Steenbock B, Helmer SM, Sill J, Mollers T, Pischke CR. Identifying evidence-informed physical activity apps: content analysis. JMIR mHealth uHealth 2018;6(12):e10314, 10.2196/10314.

IV. Jemere AT, Yeneneh YE, Tilahun B, Fritz F, Alemu S, **Kebede M**. Access to mobile phone and willingness to receive mHealth services among patients with diabetes in Northwest Ethiopia: a cross-sectional study. BMJ Open 2019;9(1):e021766, 10.1136/bmjopen-2018-021766.

Conference abstracts

I. **Kebede MM**, Liedtke TP, Möllers T, Pischke CR, Characterizing active ingredients of eHealth interventions targeting persons with poorly controlled type 2 diabetes mellitus using the Behavioral Change Technique Taxonomy, ISBNPA 2017 Annual Meeting, Victoria, Canada, June 8-10, poster presentation.

II. **Kebede MM**, Zeeb H, Peters M, Heise TL, Pischke CR**.**, Comparative analysis of ANCOVA, change scores and final values meta-analyses, The 10th Biennial JBI Colloquium, Antwerpen, Belgium, , Oral presentation , (Books of abstracts, page 29, https://www.jbi-colloquium2018.org/upload/docs/antwerp-abstracts-2018.pdf)

III. **Kebede MM**, Zeeb H, Peters M, Heise TL, Pischke CR. Effectiveness of digital interventions for improving glycemic control in persons with poorly controlled type 2 diabetes—a systematic review and meta-regression analysis, 78th American Diabetes Association Conference, Orlando, Florida, poster presentation, abstract available in: Diabetes 2018 Jul; 67(Supplement 1): https://doi.org/10.2337/db18-840-P:

IV. **Kebede MM,** Schütt C, Pischke CR, Diabetes mobile applications use and its association with glycemic control in the digital community of patients with diabetes, 13th Annual Meeting of the German Society of Epidemiology (DGEPI), 2018, in Bremen, poster presentation.

V. **Kebede MM**, Pischke CR, Zeeb H, Investigating the impact of diabetes app use on improving key diabetes self-care components, abstract accepted for poster presentation, 55th Annual Meeting of the European Association for the Study of Diabetes(EASD), September 16-20, 2019, Barcelona, Spain.

VI. **Kebede MM**, Pischke CR, Zeeb H, Self-care practice among the digital community of persons with diabetes in German-speaking countries, accepted for oral presentation at the 14th Annual Meeting of the German Society of Epidemiology (DGEPI), September 11-13, 2019, Ulm, Germany.

VII. **Kebede MM**, Zeeb H, Lessons learned from using innovative methods of recruiting survey participants: the case of Facebook groups and targeted Facebook advertisements, accepted for oral presentation at the 14th Annual Meeting of the German Society of Epidemiology (DGEPI), September 11-13, 2019, Ulm, Germany.

1. INTRODUCTION

1.1 Historical perspectives of diabetes

Diabetes is one of the oldest diseases. Its recognition traced back to the ages of antiquity. In the history of diabetes, there are several milestones that fundamentally changed the clinical picture of diabetes. Ancient Greek physician, Galen, described that he had seen the disease twice and named it "diarrhea urinosa" to mean diarrhea of the urine. Although the history of diabetes dated back to many thousand years, the first accurate description of diabetes was introduced by the "the distinguished physician Aretaeus of Cappadocia" in the second century (150 AD). Aretaeus introduced the term diabetes into medical nomenclature after the Greek verb "diabino", translated as "a condition that fluid runs through" (1-3).

Historically, diabetes was diagnosed by detecting sugar in the urine. Ancient civilizations of the Greeks, Egyptians, Chinese and the Indians diagnosed diabetes by tasting sweet urine or by investigating whether insects are attracted to it (4-6). The word "Mellitus" which means "honey" was added in 1675 by Thomas Willis to recognize the "sweet" taste of urine from persons with diabetes and to distinguish it from the excessive non-sweet polyuria which occurs in diabetes insipidus (7, 8). Until 18th century, diabetes was believed to be "disease of the kidneys" (8, 9). In 1776, Mathew Dobson conducted a diagnostic experiment that led to a conclusion that diabetes is a systemic disorder rather than a disorder of the kidneys (4, 7, 9). Dobson boiled and evaporated urine to detect a brown precipitate tasting like sugar. In addition, he revealed that patients with diabetes have sweet blood (4, 9).

The first clinical test for glycosuria was introduced in 1841 by Karl Trommer. He treated urine samples with strong acid and hydrolysed disaccharides into monosaccharides. He then neutralized the acid with alkali, copper sulphate, and boiled it to detect if brick-red cuprous oxide precipitate is formed that indicates the presence of glucose in the urine (6). In 1850, Herman von Fehling who was inspired by Trommer's experiment developed the first test to quantify glucose in the urine and established the degree of hyperglycaemia and glycosuria (6). These historical glycosuria diagnosis milestones were important for the development of "stick" or "strip" tests, as well as enzymatic approaches to detect and quantify glycosuria (10). Glycated haemoglobin (HbA1c), the now surrogate marker and the standard of diabetes care, was first isolated by Huisman and colleagues (11). It was later characterised as a glycoprotein (12). However, its link with diabetes was unclear until Samuel Rahbar revealed

the unusually elevated levels of HbA1c in patients with diabetes (13, 14). In 1976, Koenig and colleagues introduced HbA1c as a key biomarker for monitoring blood glucose levels in patients with diabetes (15).

In 1910, Sharpey-Schafer revealed that people with diabetes have a deficiency of a substance produced by the islets of the pancreas (now called Islets of the Langerhans after their discovery by Langerhans in 1869). Sharpey-Schafer called the substance "insulin" (8). More than a century after Dobson's experiment on glycosuria, Minkowski and von Mering (in 1889) demonstrated the causal link between pancreatomised dogs and the development of the symptoms of diabetes (16). That led to the link between diabetes and a specific organ for the first time (8, 17). With that, the causal link between insulin deficiency and diabetes was revealed for the first time. Frederick Banting and John Macleod, the winners of the 1923 Nobel Prize, discovered insulin in the early 1920s. In 1922, Banting, Best and Macleod extracted purified substance from the islets (insulin) of a healthy dog and intravenously administered it to the pancreatomised dogs which resulted in the reduction of glucose levels and glycosuria (16). The first insulin dose which was administered to a 14-year-old boy Leonard Thompson is hailed as one of the most dramatic events in the history of treatment of diseases (18). The discovery of insulin remains one of the most important events in the history of diabetes. It is certainly one of the most notable achievements of modern medicine (2) which significantly changed our knowledge of diabetes (19). Few years after the discovery of insulin, the first commercial production of insulin was started.

After John Rollo discovered the relationship between the foods eaten and the quantity of sugar excreted in the urine, diabetes treatment was mainly through diet support. He advocated consuming low carbohydrate, and high protein foods and foods that are rich in fat. Albeit unsuccessful, low carbohydrate diet was the only treatment available for nearly two thousand years, until the discovery of insulin in 1922 (4, 6, 20).

In 1936, Himsworth differentiated insulin-sensitive and insulin-insensitive types of diabetes (21). This became more evident during the 1950s after a reliable radioimmunoassay insulin measurement technique helped distinguishing insulin-dependent and non-insulin dependent types of diabetes (22). Only few decades later (1979), the American National Diabetes Group developed a new classification system for diabetes in 1979: type 1, type 2, gestational diabetes and diabetes associated with other syndromes or conditions. In 1995, the first drug, metformin, became available in the United States. Another important event in the history of

diabetes was the recognition of prediabetes. In 1995, the American Diabetes Association (ADA) defined prediabetes as "as impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT)" (23).

Recent research revealed that type 2 diabetes could be a potentially reversible condition (24, 25). Todate, technological advancements for the prevention, diagnosis and treatment of diabetes continues to progress (26-28). However, the causes of diabetes are yet to be further explored and, of course, the cure for diabetes remains the most important question in diabetes research and once discovered, it will be one of the greatest achievements in the history of medicine.

1.2 Pathophysiology and classifications of diabetes

"I'm not ill, my pancreas is just lazy"

Anonymous (Source: Healthline)

Diabetes mellitus is a group of chronic metabolic diseases which affect beta-cells of the pancreas resulting in impaired carbohydrate, lipid and protein metabolism (29-31). In 1999, the World Health Organization (WHO) defined diabetes as "a metabolic disorder of multiple etiology characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both" (32). Insulin and glucagon are two very important antagonistic hormones for carbohydrate metabolism (33). These hormones, produced by the alpha- and beta-cells of the pancreas, regulate glucose levels circulating in the blood. The circulating glucose is from three main sources: intestinal absorption during the fed state, glycogenolysis (formation of glucose from glycogen during short fasting), and gluconeogenesis (formation of glucose from fats and protein during starvation). Both gluconeogenesis and glycogenolysis are hepatic processes which are mainly regulated by glucagon. Following ingestion of a meal, insulin is secreted by beta-cells of the pancreas to regulate glucose metabolism. Insulin facilitates glucose metabolism by binding with its specific receptors in cells of the body and helps glucose to enter the cells (19). When insulin secretion, action or both are impaired, circulating glucose levels will be high (32). For this reason, diabetes is characterized by consistent high glucose levels in the circulatory system: a characteristic known as hyperglycemia. Consistent hyperglycemia is associated with macrovascular and microvascular complications and organ failures affecting the eyes, kidneys, nerves, blood vessels, and the heart (29-31).

Although insulin is the most important agent in glucose metabolism, recent discoveries indicate that additional hormones such as incretin and glucocorticoid steroid hormones also play a role in glucose homeostasis (19). The interplay among additional hormones, such as incretin, amylin, and glucagon governing glucose metabolism has led to the understanding of diabetes as a multi-hormonal disorder of glucose metabolism (19, 34).

There are two main types of diabetes: type1and type 2 diabetes. Type 1 diabetes is mainly due to an absolute insulin secretion deficiency caused by autoimmune disease damaging the beta-cells of the pancreatic islets (29-31) whereas type 2 diabetes is due to resistance to insulin action and an inadequate compensatory insulin secretory response (29-31).

Type 1 diabetes is now considered a T-cell mediated autoimmune disorder characterized by destruction of insulin producing cells of the pancreas (β-cells) (35-37). The level of autoimmune destruction of β-cells and the onset of the type 1 diabetes is not yet clear. Literature suggests that after the destruction of 85-90% of the β-cells, the symptoms of the disease start to manifest and with complete destruction of these cells, the process of the autoimmunity is considered completed and from the point onwards, insulin medication is an absolute necessity for survival (37). There was a general long-standing dogma of type 1 diabetes: β-cells are eventually eliminated in patients who have type 1 diabetes for long time. However, recent discoveries suggest that subjects with long standing diabetes actually have β-cells. The reason for this is unknown but the hypotheses are that some of the β-cells may escape the autoimmune attack or that there is a process during which these cells are and subsequently destroyed again (36). These conditions partly justify the period which is commonly referred to as “honeymoon period” or the extremely rare remission of Type 1 diabetes (38-41). However, efforts to delay the progression of type 1 diabetes or remission have failed to a large extent (36). Very recently (June, 2019), Herold KC and colleagues demonstrated Teplizumab (antibody) for reducing the actions of CD8+ T lymphocytes cells in β-cells destruction (42). This is by far one of the very few encouraging developments to delay the progression of type 1 diabetes in high-risk persons.

What triggers the autoimmune destruction of β-cells is unknown, but, may include environmental determinants, both in-utero and during the first decades of life (36, 43). There are heterogeneities within type 1 diabetes in terms of onset, autoimmune reaction and treatment efficacy. Two main subtypes of type 1 diabetes are known: type A and type B. Type A accounts for more than 90% of type 1 diabetes and the autoimmune nature of the disease is serologically detectable. Type B is rather idiopathic and the hormonal autoimmunity remains

unclear (8, 44, 45). However, there is no clear-cut demarcation between the two subtypes of type 1 diabetes (8).

As mentioned earlier, type 2 diabetes results from insulin resistance and/or an inadequate compensatory insulin secretory response (29-31). Several risk factors playing a significant role in insulin resistance have been extensively investigated. These risk factors include unhealthy lifestyles, such as a high calorie intake and sedentary lifestyles, genetic predispositions and other factors affecting incretin hormones (8, 46, 47). People with obesity and their first-degree relatives are at an increased risk for insulin resistance. The initial stages of insulin resistance are compensated by hyper secretion of insulin by β-cells of the pancreas that leads to hyperinsulinemia (8). Over a period of time, this increased compensatory production of insulin by β–cells to maintain glucose homoeostasis declines. This eventually leads to a β–cell dysfunction and the body is no longer able to produce enough insulin, resulting in the onset of type 2 diabetes (8, 48). This period of abnormal insulin sensitivity until the onset of type 2 diabetes may take up to 15 years (49). This might explain why type 2 diabetes is not common during adulthood. However, the traditional thought that type 2 diabetes occurs at a later stage of life and type 1 diabetes during childhood is no longer accurate because both forms of diabetes have occurred in both stages of life (50). Using the Global Burden of Diseases (GBD) data visualization tool and displaying the relationship between the age and the onset of diabetes shows a bell-shaped relationship between age and the onset of diabetes, i.e., an increasing level of type 1 diabetes prevalence among the younger age groups until it peaks in the age group of 40-49 years (Fig 1)(51). For type 2 diabetes, however; the increase in prevalence reaches its maximum at an older age group, displaying a J-shaped relationship (85-89) (Fig 2).

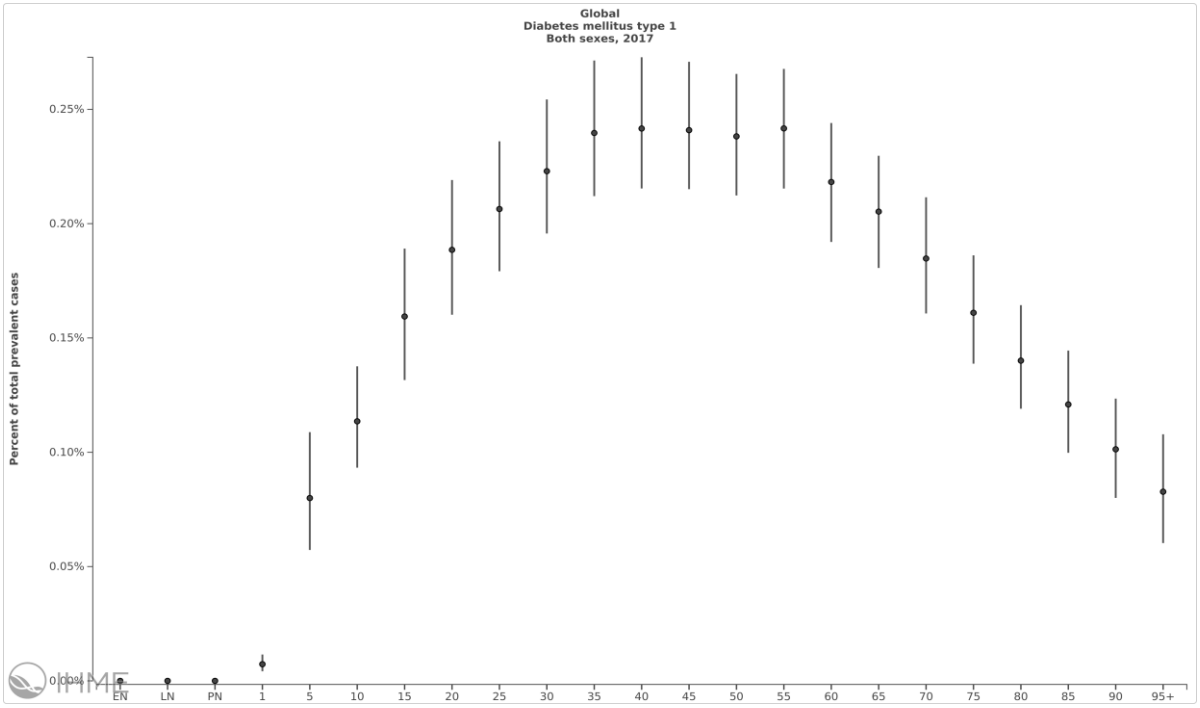


Figure 1: Global type 1diabetes prevalence across age groups for both sexes (prevalence on the y-axis, and age in years on the x-axis, source: https://vizhub.healthdata.org/gbd-compare/) (51)

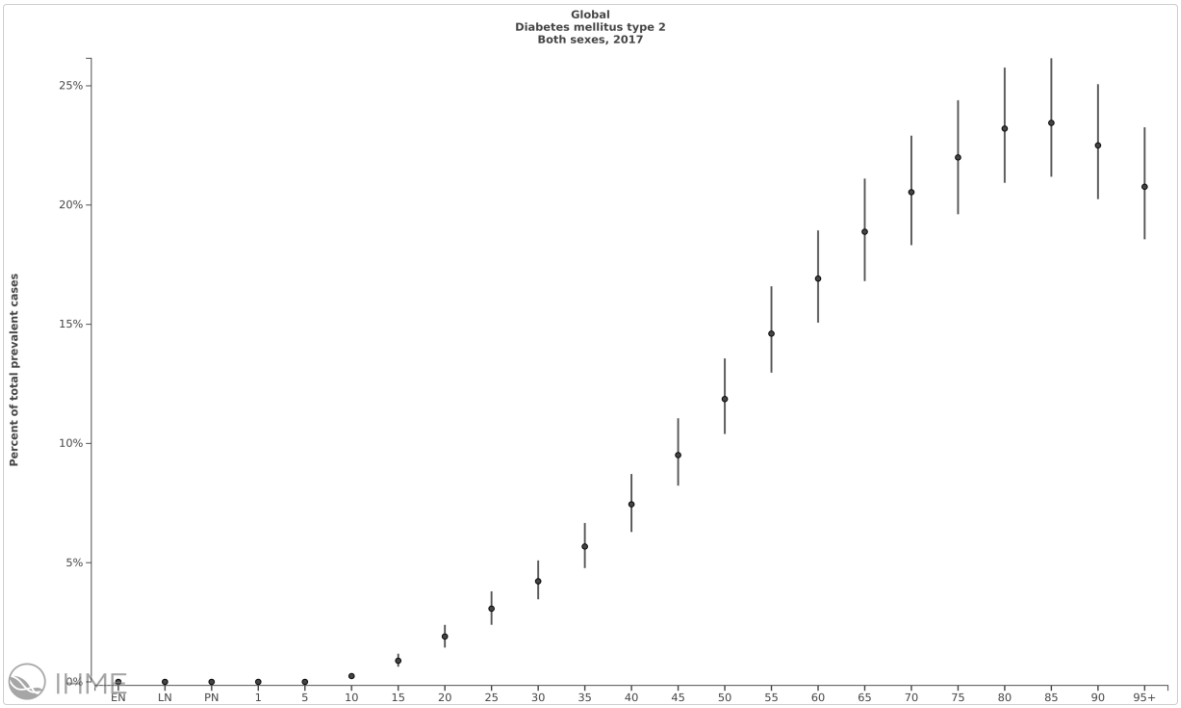


Figure 2: Global type 2 diabetes prevalence across age groups for both sexes (prevalence on the y-axis, and age in years on the x-axis, source: https://vizhub.healthdata.org/gbd-compare/) (51)

1.3 Diagnosis of diabetes

Diabetes can be diagnosed by using HbA1c criteria or by determining levels of plasma glucose using fasting glucose or oral glucose tolerance test (OGTT) (50). The criteria for diabetes diagnosis are an HbA1c level above 6.5% performed by a certified laboratory, or a fasting plasma glucose level above 126 mg/dl or a 2-hour plasma glucose value of more than 200 g/dl during the OGTT. In the absence of any unambiguous hyperglycaemia, the tests should be repeated to confirm the results (50). The HbA1c test may be more advantageous because fasting is not needed, has greater pre-analytical stability and it is less susceptible to day-to-day glycemic fluctuations that may result from stress or illness (50). However, it is not widely available. In addition, it has a lower sensitivity and has problematic correlation with average glucose values in some individuals with diseases (50) such as sickle cell anaemia, chronic liver disease, and iron deficiency anaemia (52). If diagnosis is based on glucose levels, the clinician should be highly confident before confirming a diagnosis of diabetes and it should never be based on one single glucose value (32), unless the patient is having classic symptoms, is in hyperglycaemic crisis and has a random plasma glucose value of more than 200 mg/dl (50).

1.4 Epidemiology of diabetes

In 2017, about 425 million people across the globe were affected by diabetes (53). The number of people with diabetes is projected to rise to about 629 million by 2045 (54). Due to the global rise of overweight and obesity, the prevalence of type 2 diabetes has substantially increased over the past decades (55). Separate estimates of global type 1 and type 2 diabetes prevalence are not available because differentiating the two forms of diabetes requires laboratory sophistications (56). However, evidence indicates that more than 90% of the people with diabetes are affected by type 2 diabetes (54, 55, 57). Moreover, the global prevalence of type 2 diabetes has increased over the last two decades. The Global Burden of Diseases data visualization (GBD compare) shows an increasing trend of type 2 diabetes prevalence in all GBD super regions (Fig 3) while type 1 diabetes (Fig 4) follows a fairly similar pattern across all GBD super regions. Evidence suggests a greater increase in the prevalence of type 2 diabetes in China and the United States, compared to other regions, has been observed. Many factors, including an unhealthy diet and the rise of obesity contributed to this rise of type 2 diabetes in both countries. A recent investigation revealed Coca-Cola's deep involvement in shaping Chinese obesity policy and maneuvering the emerging market in

China. The report revealed that Chinese obesity policy primarily advocates for physical activity while being silent regarding the restriction of sales and consumption of sodas (58). This and other factors must have contributed to the "worst ever" rise of obesity and type 2 diabetes prevalence in China.

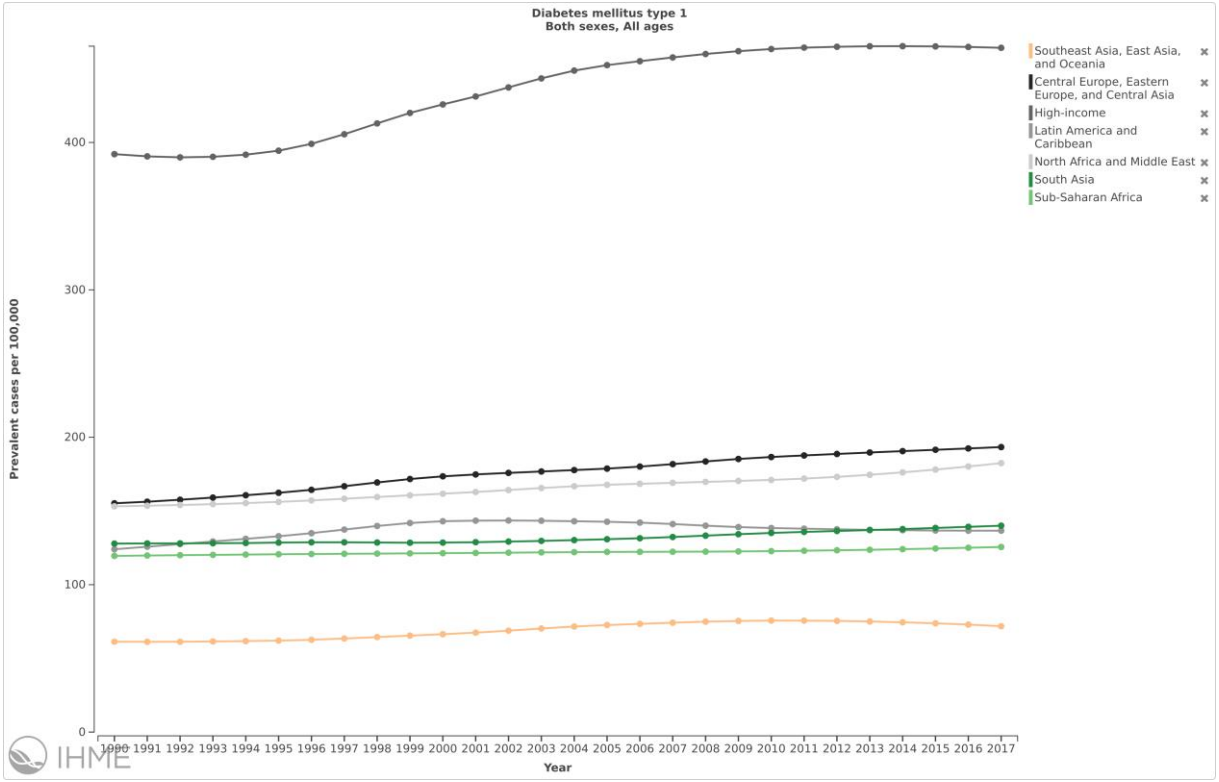


Figure 3: Trend of diabetes type 1 diabetes prevalence in all GBD super regions (Source: https://vizhub.healthdata.org/gbd-compare/) (51)

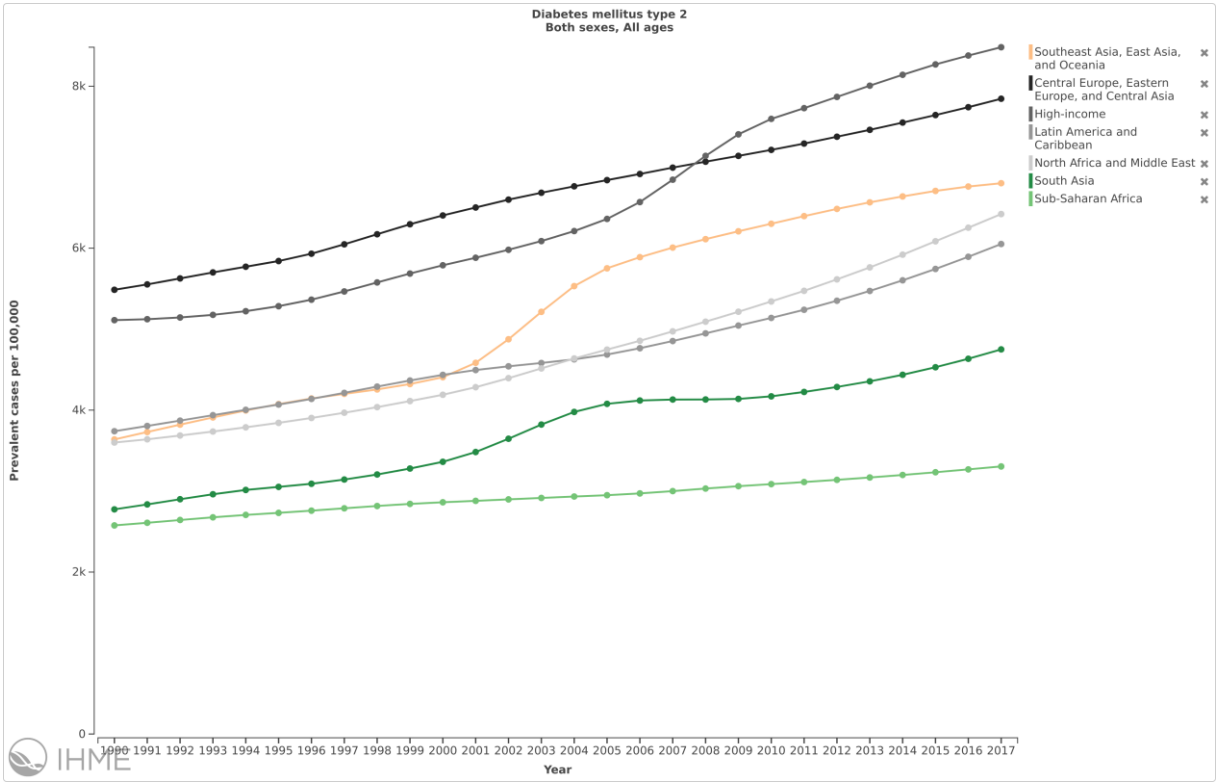


Figure 4: Trend of diabetes type 2 prevalence in high burden countries (Source: https://vizhub.healthdata.org/gbd-compare/) (51)

Diabetes, therefore, remains one of the most challenging health problems of the 21st century (54). In 2015, the three leading causes of years of potential life loss in the world were ischemic heart disease, stroke, and diabetes (59). From 2005 to 2015, diabetes was the seventh leading cause of death and death attributed to diabetes had increased by 32% (59). Type 2 diabetes was the second highest cause for obesity related deaths, accounting for more than half a million deaths and 30.4 million disability adjusted life years in 2015 (60). In 2012, there were about 3.7 million deaths related to diabetes, of which 1.5 million were directly caused by diabetes and the remaining 2.2 million deaths were due to complications related to hyperglycemia (56). More than 43% these deaths occurred before reaching the age of 70 (56). This indicates that diabetes is one of the epidemiologically most relevant diseases reducing life expectancy. Because of this, diabetes has become one of the four main non-communicable disease of global health importance (56).

Regarding the cost of healthcare, diabetes is also one of the most expensive diseases in the world (61). In 2016, the direct annual cost of diabetes was about US$825 billion (62). A year later (2017), US$850 billion USD were spent to cover the direct cost of diabetes (53). This rising healthcare expenditure for diabetes will continue to grow (63). Considering its impact

on national economies across the world, the direct and indirect economic impacts of diabetes were estimated to reach to US$1.7 trillion from 2011 to 2030 (56, 64).

As noted previously, the exact cause of type 1 diabetes is unknown (65-69). Evidence shows type 1 diabetes has substantially increased over the last decades especially among children. This increase cannot be explained mainly by genetic factors. Factors such as life style changes and environmental factors must be playing their role at a population level in changing susceptibility for type 1 diabetes (65). Therefore, it is hypothesized that type 1 diabetes may result from complex interactions of environmental factors with genes (65-69). Rowers and colleagues suggested "environmental triggers" occurring in prenatal and postnatal periods, as well as factors promoting progression may be linked with islets autoimmunity and progression to type 1 diabetes (70). Some groups of enteroviruses causing gastroenteritis among children such as rotavirus infection was associated with diabetes related antibodies (71). In mice studies, rotavirus infection was associated with widespread apoptosis of pancreatic cells reducing pancreas mass, reduced insulin production and transient hyperglycemia (72). Most surprisingly, a recent epidemiological study showed unexpected and off-target benefit of rotavirus vaccination, i.e., reducing incidence of type 1 diabetes (73). A surface protein expressed by rotavirus called VP7 structurally looks similar to pancreatic β-cell autoantigens: a phenomenon called molecular mimicry. This may enhance autoimmune attack and it may explain the association and the probably preventive benefit of rotavirus vaccination in type 1 diabetes (74). Despite growing evidence suggesting that enteroviruses infection in pregnancy (75) or early childhood (76-80) are prime candidates triggering islet autoimmunity, no specific environmental risk factor has been recognized for direct causal link (70, 81). Preventing type 1 diabetes is therefore not possible, at least, with currently available knowledge (44, 56).

In contrast, risk factors of type 2 diabetes are relatively well-established and is mainly determined by interaction of metabolic and genetic factors. These factors include demographic factors, such as ethnicity and age, behavioral factors such as smoking, as well as overweight and obesity resulting from physical inactivity and an unhealthy diet (56, 82-87). Among these factors, evidence shows that excess body fat is the strongest risk factor (56, 88-90). In addition, genetic predisposition also affects susceptibility to type 2 diabetes. Several genome wide association studies have shown TCF7L2 to be the most strongly associated risk gene (86, 91-94). Additional candidate genes were also identified to be potentially related with type 2 diabetes (86, 95, 96). Current available knowledge offers effective approaches to

prevent or potentially reverse type 2 diabetes. These approaches include regular physical activity, healthy eating, avoiding smoking, controlling blood pressure and triglycerides (56, 82-85).

2. DIABETES SELF-MANAGEMENT IN THE DIGITAL AGE

According to the American Diabetes Association guideline, persons with type 2 diabetes are required to have optimal adherence to glucose lowering medications, frequently monitor their blood glucose levels (e.g., fasting, before/after meals) (97, 98), engage in at least 150 min/week of moderate aerobic physical activity spread over two to three days, and avoid the consumption of sugary beverages and low-fat or non-fat products with refined grains and added sugars (99-102). Suboptimal adherence to these recommendations is tied to experiencing multiple episodes of hyper- and hypoglycemia (101, 103, 104) resulting in micro- and macro-vascular complications, poor quality of life and a higher risk of premature death (105, 106). Therefore, patients with diabetes require an evidence-based medical treatment coupled with effective self-management interventions that assist patients in engaging in healthy lifestyle and empower patients for disease management capability (100, 101, 107). Effective diabetes self-management education (DSME) enables patients to regularly monitor their blood glucose levels, track their physical activity and nutrition as well as monitor their emotional health (108, 109). Achieving tight or reasonable glycemic targets, the recommended level of physical activity and nutrition and weight management goals are integral to DSME (110). Therefore, all patients with diabetes are recommended to take part in DSME at diagnosis, when complicating factors arise or during transitions of diabetes care (110). The American Association of Diabetes Educators (AADE) developed seven self-care behaviour components (AADE7) to guide DSME interventions. DSME should, therefore, address the seven self-care behavior components: healthy eating, glucose monitoring, being active, taking medication, problem solving, reducing risks and healthy coping (111).

Effective communication between patients and providers has improved patient satisfactions, treatment adherences and disease outcomes (112-115). For this reason, patient-provider communication and partnership is evidently a key determinant of successful diabetes self-management (115). Collaboratively establishing treatment and behavioral goals, involving patients in medical decision making can improve patients' knowledge about their disease and improve their self-confidence, autonomy and enhance their capacity to manage their disease (115). Therefore, re-organizing chronic care from prescriptive to a more collaborative paradigm has been important during the last two decades (116, 117). One of the models that successfully led to this paradigm shift was the Chronic Care Model (CCM) (118, 119). This

model (Fig 5) provided a fundamental framework for planning productive interactions between patients and care providers. According to this model, productive patient-provider interactions improve chronic illness care by informing and activating patients, as well as by establishing a well-prepared, proactive and pragmatic healthcare provider teams (120). As highlighted in the CCM, productive patient-provider interactions can be facilitated by behaviorally sophisticated self-management systems and information systems that support tracking patients' behaviour, providing reminders and giving feedbacks regarding performance (120). Such systems improve the knowledge, confidence, and skills of patients and empower patients to ultimately be able to manage their diseases (115, 120).

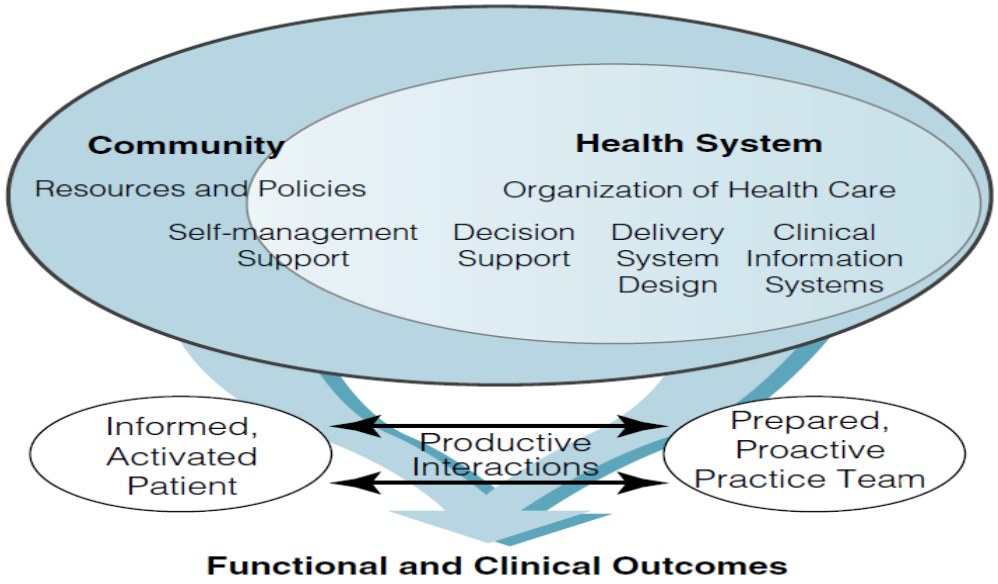


Figure 5: Edward H Wagner's Chronic Care Model (120)

2.1 Digitalising diabetes self-management

Evidence indicates that positive patient outcomes were gained after restructuring medical care with CCM (118, 119). The model has been an important framework for restructuring medical care and presenting it as an interplay among the key components of the health system (118). However, the increasingly important role of digital health in chronic disease self-management was not adequately represented in CCM. A modified chronic care model was therefore necessary (121) which was recently developed by Gee and colleagues, the eHealth Enhanced Chronic Care Model (eCCM) (122). This model (Fig 6) summarizes how eHealth applications such as clinical decision support systems, clinical information systems, self-management

support communication tools and eHealth education facilitate productive interactions between informed patient and proactive providers and eventually improve clinical and behavioral outcomes of patients (122).

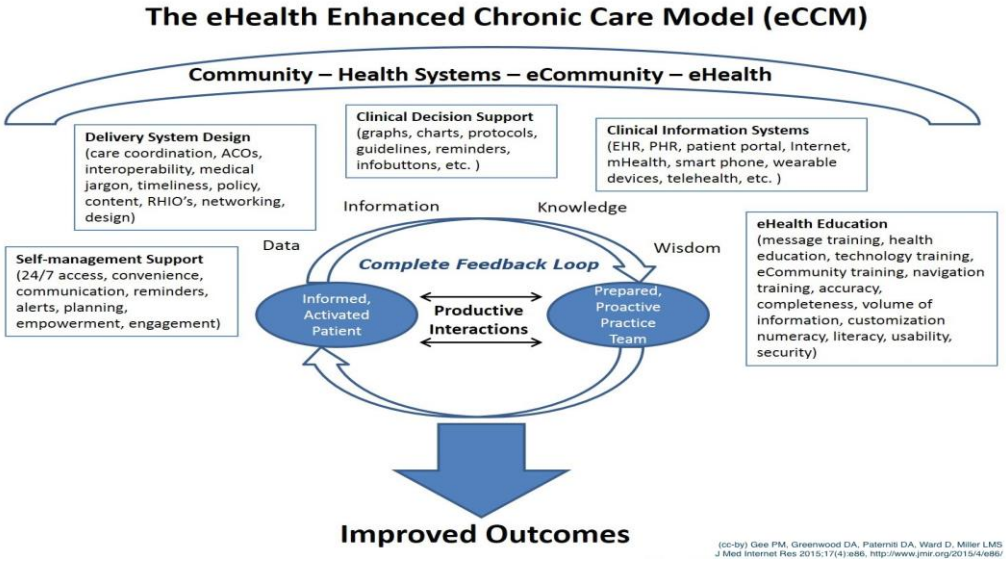


Figure 6: eHealth Enhanced Chronic Care Model (eCCM) (122)

Looking at diabetes through the lens of the eCCM implies clinical and behavioral outcomes of diabetes can be improved through digital health applications such as eHealth enhanced diabetes self-management support, clinical decision support systems (CDSS), clinical information systems and electronic DSME. These applications facilitate patient-provider communications, improve patients' knowledge of diabetes and self-management skills (122). In addition, eHealth applications may deepen the knowledge, skills and preparedness of healthcare providers, and simplify patient-providers bi-directional data sharing for improving knowledge and ultimately creating a "collective wisdom" to improve health outcomes (122, 123). Therefore, adopting digital health in diabetes care has attracted the attention of patients, providers, payers, developers, and other stakeholders of healthcare systems. Demand from patients is central to the transformation of the traditional diabetes care and it is a key driving force for digitalization (124, 125). Digital health technologies facilitate patient-centric care service provisions and behavioral transformations (126, 127).

The American Association of Diabetes Educators (AADE) developed the Technology Enabled Framework (Fig 7) (128) to highlight the need for expansion and leveraging technology and the connected health environment as a strategy to involve diabetes stakeholders and advance diabetes care. In this framework, patients, the health care team and

the community are central to consumer/patient connected health and health system connectivity providing services such as digital health, e-visits, social media and face-to–face visits. Security, privacy and regulation are also important within the loop of the framework (128).

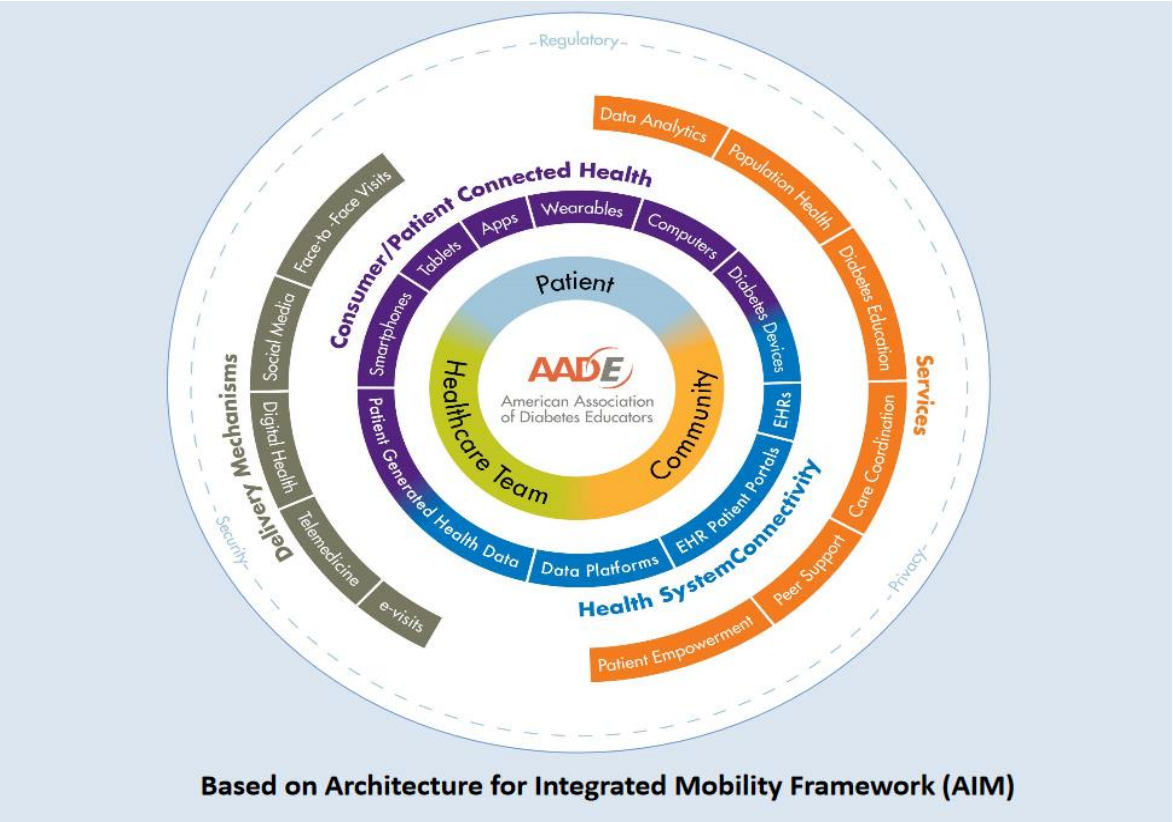


Figure 7: Technology Enabled Framework from the AADE 2016 technology working group (128)

The physiological response to glucose-lowering medications, glycemic dynamics, dietary patterns, lifestyle, and other characteristics vary widely among individual patients with diabetes. Hence, diabetes self-management management goals, DSME, and interventions targeted at improving AADE7 self-care behaviour need to be tailored to the specific problems and characteristics of individual patients (108, 129, 130). Evidence suggest that tailoring is linked with improvements in self-management skills and adoption of healthy behaviour (131-134). Tailoring also facilitates patient provider partnership towards shared decision making and patient centered diabetes care (135).

Digital health has a strong potential for personalizing clinical, behavioral and self-management goals and feedbacks. Achieving these goals may require multi-faceted

interventions which can potentially be tailored by mechanisms such as rule engine algorithms or other machine learning techniques. For example, in a CDSS-based u-health care systems showcased in Fig 8 (136), a patient may be instructed to measure blood glucose, and to track physical activity and dietary intake. These data can then fed into a smartphone application (app) to transmit patient-specific data to a u-healthcare center. Based on patient specific data, rule-based algorithms instantly generate and send real-time messages specific to the individual patient. These messages help patients react quickly and enable clinicians to respond to critical values that need timely intervention (136, 137). Such systems were shown to be effective for improving glycemic control and other clinical and behavioral indicators of diabetes (136-138)

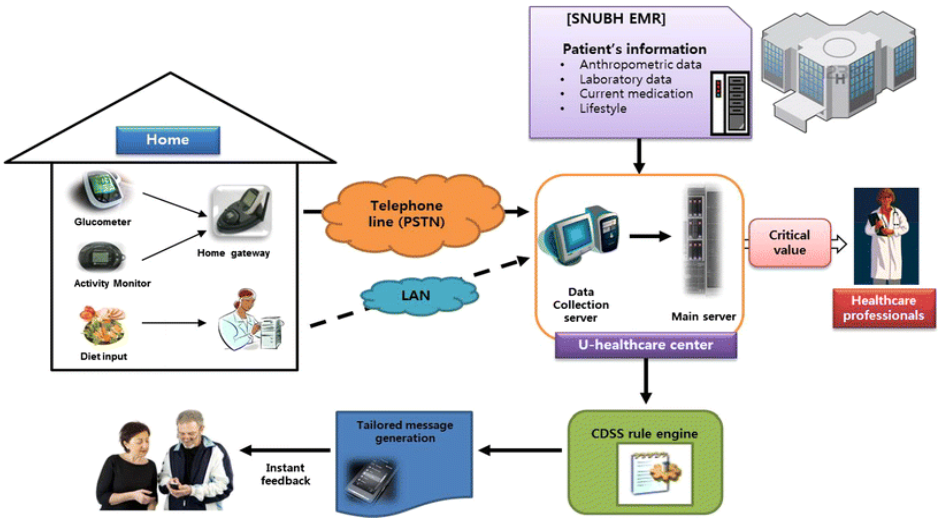


Figure 8: Clinical Decision Support System (CDSS)-based uHealth care system (136)

Digital health can be provided to patients via two main communication archetypes: one-way or two-way. One-way communication may typically be about providing educational materials to a patient with diabetes (139). Evidence indicates that this form of communication has no or minimal impact in improving participant outcomes (140). Whereas, in two-way communication both the sender and the receiver of the message are engaged. Both parties provide feedback reacting to the received messages. In technology enabled diabetes self-management (141) (Fig 9), tailored messages are provided to patients by healthcare providers and the patients provide feedbacks. Both patients and providers engage in the continuous flow of the communication loop by providing feedback to each other (141). Results of two systematic reviews indicated that the majority of studies with two-way communication demonstrated improved patient outcomes, including glycemic control (142, 143).

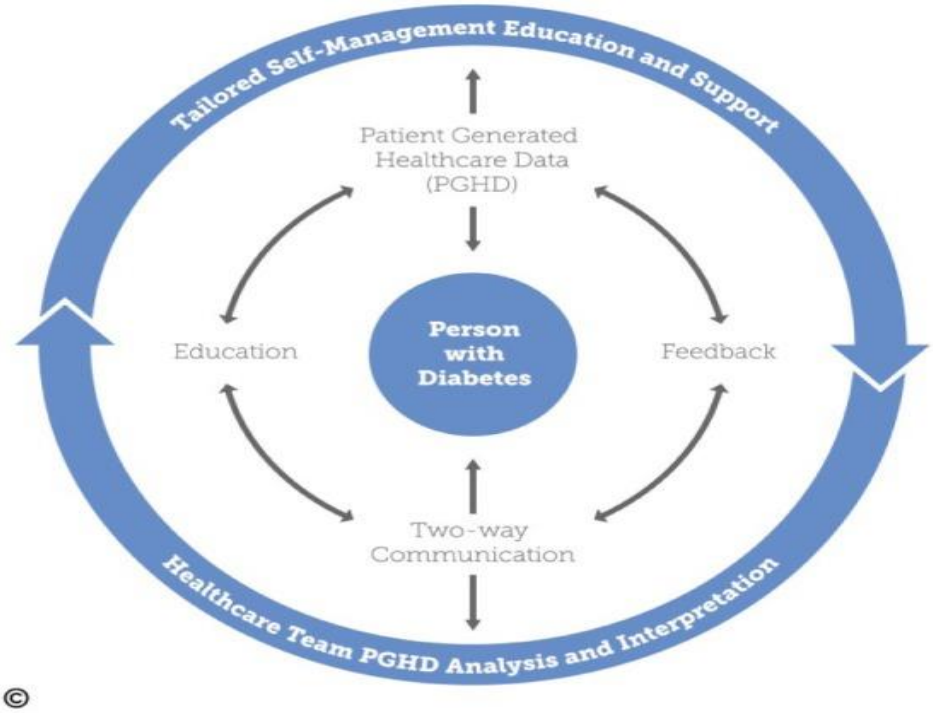


Figure 9: Technology-enabled self-management (TES) feedback loop (141).

Tailoring that is based on technology is often viewed as the most sophisticated form of automated communication (144). It can be simplified through applications of machine learning algorithms, artificial intelligence and internet of things (145-148). In addition, the advanced mobile computing applications in the form of m- and e-Health enable tailoring DSME, and increasing the uptake of AADE7 self-care behavior (149-154). In the advanced form, avatars or bots may be used to simulate real-world patient behaviors and enhance engagement of patients in virtual DSME (155). Collectively, these tools are exciting prospects that are trending the ecosystem of digital and personalized diabetes care as well as revolutionizing it (156).

Digitalization of diabetes care has attracted several stakeholders of diabetes including patients, providers, developers and pharmaceutical companies. A report on mHealth app economics revealed that diabetes is the leading therapy field for digital solutions (157). More than 135 million patients with diabetes have access to smart devices capable of running diabetes apps. This indicates that an estimated one-third of the total global population with diabetes is potentially reachable with diabetes apps (158). Additionally, approximately 34% of the global diabetes expenditure can also be addressed via diabetes app services and products (159). For this reason, diabetes is considered the greatest market opportunity for

digital health innovation (157). In total, the diabetes app market is projected to reach a worth of $742 million by 2022 (160).

Besides the data analytics and tech companies, health insurance and giant pharmaceutical companies are becoming more powerful taking their stake in the digital health market. The future channels of diabetes app distribution are likely to be health insurance companies (157). Pharma companies have also strongly embarked their vested interest in digital health solutions (157, 161) geared towards population-level data acquisition. Data is currently the most expensive item and its values will likely grow further in the future (162). As personalized medicine continues to advance, digital health offers pharmaceutical companies to fetch real-world data from millions of patients than from small study subjects enrolled in the traditionally expensive and under-powered RCTs (161). Together with the current staggering development of digital health innovation, concerns regarding data ownership, privacy, security and confidentiality are increasing.

2.2 The role of digital health in artificial pancreas

Understanding the glucose-insulin dynamics is important for advancing the treatment of diabetes and maintaining tight glycemic control (163). Achieving tight glycemic control without increasing the risk of hypoglycemia is a lifelong problem for patients with diabetes. In fact, treatment of diabetes is conceptualized as "a trade-off between glycemic control and iatrogenic hypoglycemia" (164). Both people with type 1 and type 2 diabetes generally require daily insulin to balance carbohydrate intake and insulin demand and in turn avoid hyperglycemic crisis. In patients with type 1 diabetes, exogenous insulin injection is absolutely necessary. In type 2 diabetes, medications that amplify insulin secretion or lower insulin resistance, basal and prandial insulin injections might be needed. In type 1 diabetes, external insulin can be provided either by multiple daily injections or continuous subcutaneous delivery using insulin pumps. However, this mode of insulin administration is not as effective and efficient as human body producing insulin for itself (endogenous insulin secretion). Acute events such as hypoglycemia expose patients to diabetic ketoacidosis. To solve this, a continuous administration of insulin via insulin pumps coupled with continuous glucose monitoring was proposed (163). This led to the birth of artificial pancreas in the 1970s (165, 166).

The potential of artificial pancreas is predominantly tested in type 1 diabetes although recent advances also indicate the benefits of the system in insulin-treated poorly controlled type 2 diabetes (167, 168). The advanced form of artificial pancreas system encompasses a wearable CGM monitor, an insulin pump and smartphone or computer that run the control algorithm (169). This is commonly referred to as "closed-loop" system (170). The CGM monitor is connected wirelessly to the insulin pump and the digital controller (algorithm run by a smartphone or computer) acts as a brain of the three-part system. The CGM monitor sends glycemic data (measuring every 5 to 10 minutes) to the control algorithm which analyzes the data and makes decisions to make insulin dose adjustments (170). This system is one of the most promising developments of diabetes treatment embracing patients using the digital treatment ecosystems (171). By running the control algorithms and acting as a communication hub connecting all the closed-loop devices, digital health plays a pivotal role in advancing the benefits of artificial pancreas systems: from simple remote monitoring to control, and alerting patients for upcoming hyper- or hypoglycemic events (172). More excitingly, recent developments suggest that equipping artificial pancreas with more advanced learning control algorithms could prevent hypoglycemia via automatically shutting off insulin pumps (173). Future advances in digital health and control algorithms of the artificial pancreas may help track, learn and predict routines of patient behavior, and integrate it for personalized diabetes care. This will mark the foundation of precision diabetes medicine.

2.3 Patient initiatives in the digitalization of diabetes care and self-management

Patients are the key driving force of digitalization (124, 125). With increasing internet connectivity, smartphone ownership and availability of several networking opportunities, patients are taking their own initiative to benefit from digital health. Diabetes smartphone apps, connected devices, coaching devices, online forums and social media groups are some of the most commonly used digital health utilities available to diabetes patients' community. International surveys reported that more than half of German and U.S. American adults who were using mobile phones also downloaded health apps (174, 175). Of all participants of the survey from Germany, more than 84% reported using diabetes apps (175). Particular to diabetes aps, studies from developed countries also indicated a significant proportion of patients with diabetes are already using diabetes apps. More than one-fifth of patients with diabetes in Australia (176) and New Zealand (177) reported using diabetes apps. At the end of 2017, about 325,000 health apps were available with astounding 3.7 billion download rates.

In 2016, about 1800 diabetes apps were available in typical stores for patients and providers (178). Global diabetes applications use had also increased from 2.2% in 2014 to 3.3% in 2016 (178).

Patients' initiative to benefit from digital health is not also limited to using diabetes apps. The use of the internet to search diabetes-related information is increasing (179, 180). In 2011, searching health related information was the third most common use of the internet among U.S. adults (181). With this increased internet use, several virtual patient communities have also emerged. In 2014, there were several diabetes online forums and more than 1000 diabetes Facebook groups (182). These patient forums enhance self-management capabilities (183) by enabling patients to learn from the experience of others or to receive virtual psychological and social support from fellow patients with similar conditions (184-186). These diabetes online communities are also involved in advocacy efforts (182). Online forums such as the well-researched TuDiabetes.org, PatientsLikeMe and many Facebook groups have been used by patients to receive virtual support from fellow patients (187-190). With more than two billion registered users (191), Facebook offers its special feature called "Facebook Group" to connect people with similar interests or health conditions (189). Depending on the groups' interests, there are three options for these groups: public, closed, or secret Facebook groups (192). Evidence indicates that involvement in online forums or Facebook groups was tied to improving glycemic control, diabetes knowledge, self-care behavior, the adoption of healthy behavior, and quality of life (182, 193-196).

All of these digital diabetes solutions empower patients' capability to have a good knowledge of their disease and ultimately to be able to self-manage it. However, there appear to be disparities by age, race/ethnicity, socioeconomic status, health and digital literacy limiting digital health opportunities (197-200). As patients and health systems grow to rely on the internet and technology, the factors resulting in the digital divide may further escalate already existing health inequalities (201-204). This affects patients who are at risk for poor diabetes outcomes to fall further behind due to the poor access or exposure to digital health opportunities (201). Therefore, investments in digital health innovation must take patients with social disparities into consideration (205). In this regard, bridging the gap in digital literacy is of paramount importance (204, 206). This may be done via building partnership between health system actors and local digital health advocates to screen patients for digital

health literacy and provide low-cost internet services, device support and skills training to those who needs it (207).

Evidence also suggest concerns about app functionalities, lack of interoperability, clinical significance, data privacy and safety that need to be addressed (208-212). Almost none of the 600 apps available in the US received the Food and Drug Administration (FDA) clearance (209, 213). Only 11 of the self-management apps abundantly available in typical stores were studied for clinical effectiveness and safety, with only one app verified to lead to clinically significant glycemic control (214). Nearly all of the 46 insulin dose calculators provide erroneous insulin dose calculations (215). Therefore, with the increasing pace of innovation, the evaluation and clinical regulation of diabetes apps are essential (209, 216). In addition, prescription or recommendation by healthcare providers is important before patients use unapproved or perhaps clinically unsafe apps (215, 217, 218).

2.4 The role of digital health for improving diabetes patient outcomes

HbA1c reductions of at least 0.3% are considered clinically significant (219, 220). Several randomized controlled trials (RCTs) examining the effects of digital health interventions in persons with type 2 diabetes demonstrated clinically and statistically significant reductions of glycated hemoglobin levels (221-225). Improvements in other clinical and behavioral patient outcomes such as achieving glycemic control targets without incidents of hypoglycemia (136, 226), knowledge about anti-hyperglycemic medications (227), self-efficacy, and medication adherence (228) were also reported. Particular to diabetes apps in type 2 diabetes, numerous RCTs reported improvements in glycemic control after use of diabetes self-management apps (229-231).

Systematic reviews and meta-analyses on the effects of participation in smartphone-based (232), interactive self-management (233) and all information technology-based (234) interventions in persons with type 2 diabetes suggest reductions in HbA1c-levels. Similarly, authors of three pooled analyses of RCTs investigating the effects of smartphone-based diabetes self-management apps reported clinically significant HbA1c reductions, 0.49% (235), 0.55% (236) and 0.67% (237). Besides glycemic control, meta-analyses show that diabetes apps improve self-efficacy, quality of life and self-care activities (236). These interventions work by enhancing patients' knowledge and skills to adopting healthy

behaviours and improve self-management competencies which collectively result in improved patient outcomes (208, 211, 238-242).

Although there is plenty of pooled evidence indicating the effectiveness of digital interventions for improving glycemic control as measured by the surrogate marker, HbA1c, the current literature has several limitations. These limitations mainly originate from challenges in identifying the components of interventions reported in published RCTs and heterogeneity that arises from the complexity of these interventions. In addition, due to the nature of the outcome (HbA1c) or the design of the some RCTs, statistical challenges that emanate from baseline imbalance and pre-post correlations limit the precession of the effect size estimates reported in the currently available pooled analyses. However, determining the precise effect size estimates is important for informing clinical and public health practice. Hence, robust systematic reviews and meta-analyses that address these limitations and evaluate the meta-analyses methods are timely.

The heterogeneity of these interventions can be tackled via exploring the components of these complex interventions by using the Behavioural Change Techniques Taxonomy (BCTs) tool (243). The effect of each component can then be measured with robust statistical techniques. In addition, advanced methodological guidance is available to deal with the challenges that arise from baseline imbalance and pre-post correlations.

Moreover, despite the availability of several RCTs and pooled evidence indicating the effectiveness of diabetes app use on glycemic control and self-care behaviour, evidence from real-world settings in observational studies is, however; still limited. Additionally, some studies explored the contents of some of the diabetes apps available in typical stores (211, 240, 244, 245). Thus far, evidence regarding the use of the most popular diabetes apps and the association of use with glycemic control and self-care behavior in the digital community of patients with diabetes is lacking.

3. OBJECTIVES

3.1. General objective

To assess the role of digital health for improving glycemic control and self-care behaviour.

3.2 Specific objectives

i. To determine the effectiveness of digital interventions among patients with poorly controlled type 2 diabetes.

ii. To identify and investigate BCTs associated with reducing HbA1c levels among patients with poorly controlled type 2 diabetes.

iii. To estimate and compare the effectiveness of digital interventions in patients with poorly controlled type 2 diabetes using three meta-analytic methods.

iv. To investigate the role of diabetes app use, self-care behaviour and other factors for glycemic control among the online community of patients with type 1 and type 2 diabetes.

v. To identify popular diabetes apps among patients with type 1 and type 2 diabetes.

vi. To investigate the association of diabetes app use and other factors with cumulative self-care behavior in persons with type 1 and 2 diabetes.

4. FRAMEWORK OF THE DISSERTATION

The overall flow of the papers included in this dissertation is conceptualized in Fig 10. The framework presents the core research objectives and the respective designs, data sources as well as the core publications produced. Additional papers are also presented on the right side of the figure. On the left side of the figure, the core research objectives are marked with different colors. Objectives addressed in one study are displayed in a similar color. The colors also correspond with the colors of the methodologies followed, core research papers and related additional papers produced during the doctoral process.

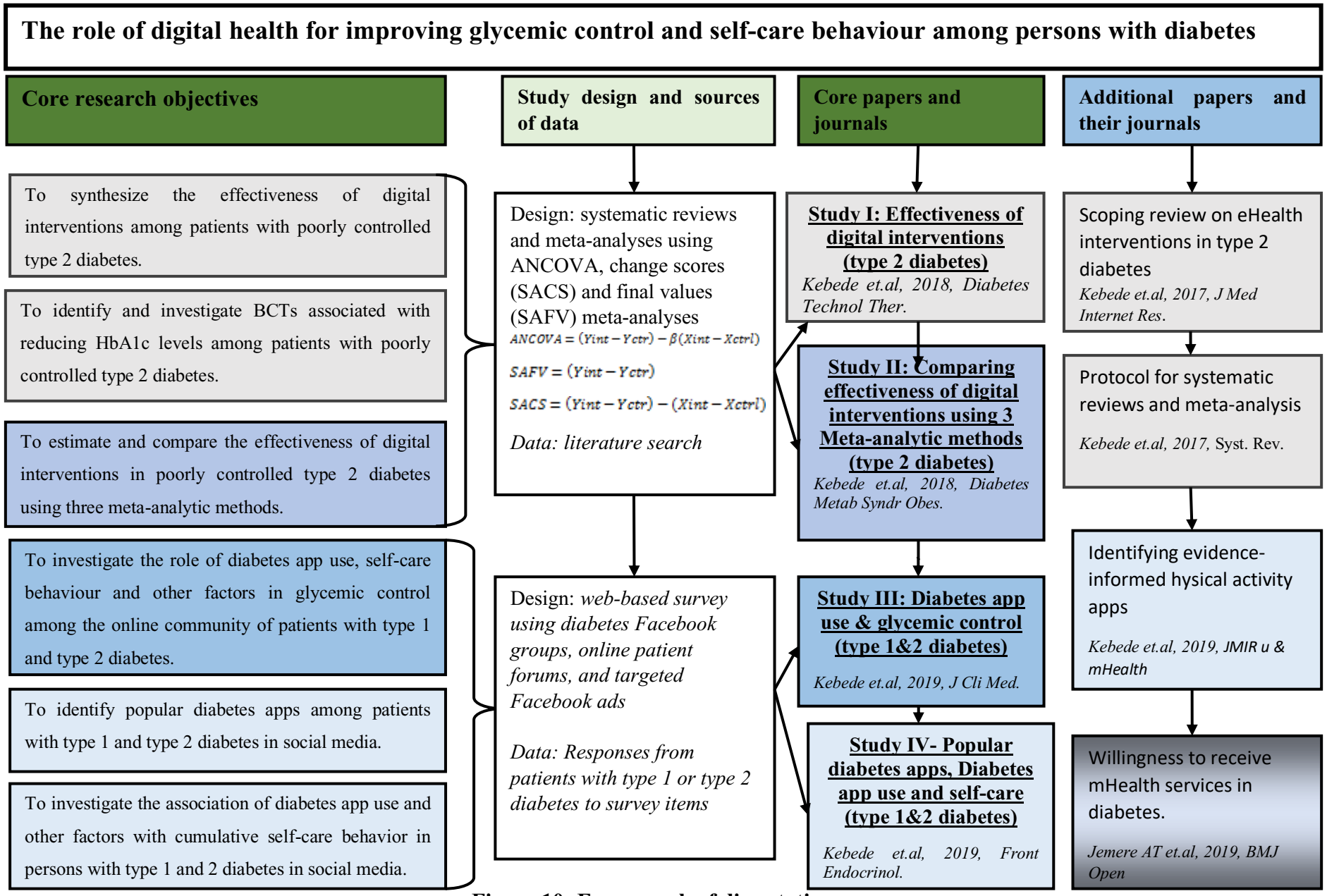


Figure 10: Framework of dissertation

5. METHODS

This chapter summarizes the methods utilized for developing the core research articles that answered the core research objectives. The description of the methods utilized in the respective core studies (study I-IV) are highlighted below. The full description of the methods can be accessed in the respective articles (annex).

5.1. Study I - Effectiveness of Digital Interventions for Improving Glycemic Control in Persons with Poorly Controlled Type 2 Diabetes: A Systematic Review, Meta-analysis, and Meta-regression Analysis

A systematic review, meta-analysis and meta-regression analysis were conducted by following the Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) 2015 guideline (246), and a registered (PROSPERO registration number: 42016049940) and published protocol (247). To identify the relevant papers fulfilling the key inclusion criteria, a comprehensive electronic search was carried out in MEDLINE, Web of Science, and PsycINFO. Studies were included if they were RCTs investigating the effectiveness of any form of digital intervention among patients with poorly controlled type 2 diabetes (HbA1c level > 7.0%), included control groups receiving usual care, were published in English before the end of June 2017 and HbA1c was reported as an outcome. Based on the definition of the American Diabetes Association (ADA), HbA1c-levels above 7.0% were considered poorly controlled diabetes (248).

The titles and abstracts of articles retrieved from the databases were screened for the inclusion criteria. To semi-automate the process of title and abstract screening, full-text screening and quality assessment, Covidence (the Cochrane collaboration web-based tool) was used (60). The quality of articles included in the review was assessed by using the Cochrane Risk of Bias Assessment tool for Randomized Control Trials (249).

Details of each study including author names, titles, journals, and years of publications, objectives, study populations and type of digital interventions were extracted. From the description of the intervention, the type of digital intervention, targeted AADE7 self-care behaviour and included BCTs were documented for each arm of the RCTs. The BCTs included in each intervention were identified using the Behavioural Change Techniques

Taxonomy. This taxonomy includes 93 behavior change techniques organized in 16 hierarchical clusters (243).

Additionally, data on whether interventions were tailored or individualized, or whether the design of interventions were informed by behavioral science models or theories were extracted. Details of baseline and follow-up data about subjects of interventions and outcome data such as sample size, standard errors (SE), standard deviations, 95% confidence intervals, p-values were extracted from each study. Missing data were calculated from the reported summary statistics, or obtained by contacting the authors or imputed by using appropriate statistical methods.

Because the studies were not adequately balanced, adjusting for baseline imbalance and pre-post correlation was important. Hence, the "black-belt" Analysis of Covariance (ANCOVA) approach for synthesizing continuous outcomes was applied. Using ANCOVA, the estimation of the effect sizes was modelled by using this equation, $ANCOVA = (Yint - Yctr) - \beta(Xint - Xctrl)$. In this equation, Yint and Yctr were the follow-up HbA1c values for intervention and control groups respectively, while Xint and Xctr represent the baseline HbA1c values for intervention and control groups. β is a regression coefficient calculated from pooled SD of the treatment (SDy) and control groups (SDx) using this formula $\beta = r\frac{SDy}{SDx}$ (250, 251). Correlation values were estimated using $r = \frac{SDb^2 + SDf^2 - SDd^2}{2SDb^2 SDf^2}$ (251) or $r = 1 - \frac{SDd^2}{SDp^2}$ (252).

In STATA version, overall and subgroup random-effects meta-analyses were performed using studies and relevant arms that were considered combinable. Sensitivity analyses were also performed to investigate the effect of the dimensions of study quality on the pooled effect size estimate. Heterogeneity was assessed by Cochrane Chi-square(x^2) statistics and quantified by using the using I^2 statistics (253). To investigate the effect of BCTs and other intervention features on the overall effect size estimate, a series of univariate and multivariate meta-regression analyses were performed following the recommendation by Borenstein et.al (254).

Finally, publication bias was assessed visually by inspecting the funnel plot(eye-ball test) and statistically using Egger's test (255). The quality of evidence generated with this meta-analysis was graded using the GRADE approach (256, 257) in the GRADEpro online tool (258).

5.2. Study II - Comparison of three meta-analytic methods using data from digital interventions on type 2 diabetes

Study II is based on the extended analysis of data from study I. Therefore, study II shares the methodology for study I as described before. Here, methods only particular to study II are emphasized. In study II, ANCOVA, change scores (SACS), final values (SAFV) meta-analyses approaches were implemented to look deeper into differences across the pooled effect size estimates and investigate the effects of baseline imbalance and pre-post correlations.

Mean difference, standardized mean difference and ratio of means are the most commonly used effect size metrics for continuous outcomes. If the measurements of the underlining continuous outcome are similar across all studies, mean difference is the appropriate metric. In addition, effect sizes of continuous outcomes with inherently similar scale of measurement, such as in HbA1c, can be computed using three effect size estimators: SAFV, SACS and ANCOVA (250-252, 259). All of these methods produce comparable estimates if the outcome data are balanced at the baseline and the pre-post correlations is low. For studies, with high baseline imbalance and high pre-post correlations, ANCOVA is known to produce a relatively more precise and unbiased effect estimate, compared to SACS and SAFV (250-252, 259). Three effect size estimates were computed both at individual studies and at a pooled level to facilitate comparison across effect size estimators. ANCOVA adjusted mean differences were computed using the equation described for study I. Mean differences for SAFV and SACS were computed using $SAFV = (Yint - Yctr)$ and $SACS = (Yint - Yctr) - (Xint - Xctrl)$, respectively. To check whether there is statistically significant difference across the mean difference values computed by the three methods at individual studies level, the multivariate test of means was used. Finally, meta-analyses were performed using the three meta-analytic methods and whether there are differences in the pooled effect sizes and confidence intervals were investigated. The differences in publication bias across the three methods were explored by constructing funnel plots and implementing Egger's test for funnel plot symmetry in Stata.

Sensitivity analyses were performed to investigate the effect of baseline imbalance and pre-post correlations on the pooled effect size estimates. Studies with high baseline difference (baseline mean difference ≥+/-0.2, or ≥+/-0.3) and with high pre-post correlation values (>+/-0.7, and >+/-0.6) were excluded from the meta-analyses. Then, the pooled effect sizes and confidence intervals were compared.

5.3. Study III: The Role of Continuous Glucose Monitoring, Diabetes Smartphone Applications, and Self-Care Behavior in Glycemic Control

The data for studies III and IV were obtained by conducting a web-based survey from November 2017 to March 2018 among the online community of persons with diabetes. The recruitment procedure, the development and content of the online-questionnaire and the analysis strategy are summarized as follows.

5.3.1 Questionnaire design, sources of respondents and recruitment

A web-based cross-sectional survey was conducted among persons with diabetes. The survey questions were prepared in two languages (English and German) and were designed using Lime survey (260). Data on demographic characteristics, self-reported diabetes status, type of diabetes, use of glucose lowering medication, self-reported blood glucose levels, continuous glucose monitoring (CGM) device use, self-reported confidence on diabetes self-management, and perceived metabolic control levels were collected. In addition, the questionnaire includes variables related to diabetes app use for self-management, and self-care behaviour. The items for diabetes app-related questions were adopted from the Mobile App Rating Scale (MARS) (107) which was validated for diabetes app rating in a study from New Zealand (177). Self-care behaviour data were collected using a licenced version of Summary of Diabetes Self-Care Activities (SDSCA) questionnaire which was previously validated in both English (261) and German languages (262). SDSCA is an 11-item questionnaire measuring self-care activities about diet, physical activity, blood glucose monitoring, foot care and smoking.

Respondents of the survey were recruited via three different channels: Facebook groups, diabetes-specific patient forums, and targeted Facebook advertisements (ads). Using key-words in English and German, type 1 and type 2 diabetes Facebook groups were systematically searched on Facebook. After identification of the groups, requests to join the groups were submitted to admins and moderators of the groups. The “join group” requests include informed consent, explanations about the authenticity and purpose of the survey, the survey URL, the minimum time required to complete the questionnaire. Once approval to join a group and to post the survey was received from admins or moderators, the survey URL was posted on the Facebook group page. Periodically, comments were added to bump up the Facebook posts so that they can appear in the newsfeed of group members and to enhance engagement of respondents who might have not seen the original post.

About ten targeted Facebook ads were also placed which reached about 30,000 persons potentially having diabetes. Demographic characteristics (age and country) and interest in diabetes-related terms on Facebook were utilized for tailoring the Facebook ads. The ads contain pictures, emoticons, short descriptions and the URL of the survey.

Additionally, English and German diabetes specific online patient forums were systematically searched on Google. After identifying the relevant diabetes patient forums, two investigators registered to be a member of each identified group. Applications to post the survey in the forum website were submitted to forum admins and moderators. The survey URL was then posted on the forums once approval was secured.

In all of the recruitment channels, information about the survey included an explanation that responding to the survey was voluntarily and anonymous. Information about incentives which were given to randomly selected participants was also included. In addition, respondents were informed that they could stop answering questions at any stage of the survey or could skip any question they were not comfortable with. Each respondent was required to electronically sign to confirm their agreement for participating in the survey before answering any of the questions.

5.3.2. Data analysis

The outcome variable was self-reported glycemic levels. The combined self-reported HbA1c and capillary blood glucose level data were used to categorize glycemic data into normoglycemia, hyperglycaemia and hypoglycaemia following the ADA definitions (263-265). By adjusting for potential confounders, the association of diabetes app use, CGM device use and self-care behaviour with the glycemic control categories was investigated using multinomial logistic regression analyses. The analysis was stratified by type of diabetes.

5.4. Study IV: Popular Diabetes Apps and the Impact of Diabetes App Use on Self-Care Behaviour

Study IV was conducted by using the data collected during the web-based survey described for study III. Here, only the analysis strategy is summarized. After retrieving the data, self-care days for the five self-care behavior components were calculated. The cumulative self-care behavior score was also calculated by adding up the scores for each self-care behavior. To investigate differences in the scores for individual or cumulative self-care behavior between diabetes app users and non-users, two-sample t-tests were conducted. The

associations of diabetes app use and other factors with the cumulative self-care behaviour were investigated by using multiple linear regression analyses stratified by type of diabetes. The regression models for both types of diabetes were evaluated visually by examining linearity of residuals and checking for assumptions of linear regression (266).

To identify the popular diabetes apps, the names of the apps reported by each respondent was retrieved and counted. The frequency of each diabetes app was then calculated for both types of diabetes. All analyses were performed using R version 3.5.1 (267) via R studio IDE.

6. SUMMARY OF RESULTS

In this chapter, the key results of each study are described. The results are summarized in subsections designated for respective studies. The detailed description of results of each study can be read in the respective articles (annex).

6.1. Results of study I - Effectiveness of Digital Interventions for Improving Glycemic Control in Persons with Poorly Controlled Type 2 Diabetes: A Systematic Review, Meta-analysis, and Meta-regression Analysis

From the three databases, 1669 titles and abstracts were retrieved. Only 22 studies (221-223, 228, 268-285) that were published from 2009 to 2017 fulfilled the inclusion criteria and were included in the qualitative and quantitative syntheses. A total of 3787 subjects and twenty-three arms of twenty-one RCTs were included in the meta-analysis.

The mean intervention duration was 7.29 months (SD=3.05). More than half (1991) of the total subjects were assigned to the intervention group. On average, about 84 (SD=62.1) and 83 (SD=62.7) subjects per RCT were assigned to intervention and control groups, respectively. The mean treatment retention rate at the completion of the studies was 89.4%. The majority of the interventions (n=15) were web-based, five were telehealth and three were text message interventions

The pooled estimate suggests a statistically significant reduction of HbA1c, -0.39 (95%CI: -0.51, -0.26) favouring digital interventions. The subgroup analysis indicates that statistically significant reductions of HbA1c after participation in text-message and web-based interventions, with pooled HbA1c mean difference estimates of -0.52% (95%CI: [-1.04, 0.00]) and -0.41% (95%CI: -0.55, -0.27), respectively.

The results of the multivariable meta-regression analysis revealed a higher baseline HbA1c levels, β=-0.44 (95%CI: [-0.81, -0.06]), BCTs such as ‘problem solving’ (β=-1.30 (95%CI: [-2.05, -0.54])), and ‘self-monitoring outcomes of behaviour’ (β=-1.21(95%CI: -1.95, -0.46)) significantly reduced HbA1c levels.

6.2. Results of study II - Comparison of three meta-analytic methods using data from digital interventions on type 2 diabetes

In this study, the baseline HbA1 difference between intervention and control groups ranged from –0.2% (274, 282) to 0.64% (268), with only two interventions reporting perfect baseline balance (222, 270). The pooled HbA1c baseline difference was 0.14% (95%CI: [–0.31, 0.59]). The pre-post correlation values ranged from 0.06 to 0.74.

The mean differences obtained by using the three meta-analytic methods were plotted in a boxplot to visually inspect whether there was overlap. There was high degree of overlap of the three boxplots suggesting the estimates were close to each other. To statistically check this similarity, a multivariate test of means was conducted. The multivariate test of means suggested that there was no evidence of a significant difference (Hotelling T2 = 4.65, Hotelling, F (2, 21) = 2.22, Prob > F = 0.134).

The pooled HbA1c mean differences (95%CI) estimated by ANCOVA, SACS, and SAFV were -0.39% (95%CI: [-0.51, -0.26]), -0.37% (95%CI: [-0.468, -0.268]), and -0.34% (95%CI: [-0.48, -0.19]), respectively. The heterogeneity statistics measured by I^2 were 80.8%, 32.3% and 64.5%, for ANCOVA, SACS and SAFV, respectively. These results show some degree of difference across the three estimates and the confidence intervals. These differences became less prominent, when studies with high baseline difference or high pre-post correlation scores were removed from the meta-analyses. For instance, dropping studies with a high pre-post correlation scores (>+/- 0.7) resulted in -0.40% (95%CI: [-0.53, -0.27]), -0.40% (95%CI: [-0.54, -0.26]) and -0.34% (95%CI: [-0.49, -0.19]) using ANCOVA, SACS and SAFV, respectively.

Assessing publication bias, both with visual inspection of funnel plot and Egger's test for funnel plot symmetry, did not suggest evidence of a publication bias for any of the methods.

6.3. Results of study III: The Role of Continuous Glucose Monitoring, Diabetes Smartphone Applications, and Self-Care Behavior in Glycemic Control

Data were collected via 78 Facebook groups, 8 online forums and 10 targeted Facebook ads. Data of 1052 patients with type 1 diabetes and 630 patients with type 2 diabetes were analysed for this study. More than half of the respondents with type 1 diabetes (n=549, 52.2%) and more than one-third of respondents with type 2 diabetes (n=210, 33.3%) reported

using diabetes apps for self-management. After adjusting for potential confounders, the odds of experiencing hyperglycaemia among respondents with type 2 diabetes were reduced by 37% (AOR = 0.63(95% confidence interval (CI): 0.41 - 0.96)). However, no association of diabetes apps use with experiencing hyperglycaemia and hypoglycaemia in type 1 diabetes was noted.

Among respondents with type 1 diabetes, those reporting CGM use had a 76% (AOR = 0.24(0.09 - 0.60)) lower odds of experiencing hypoglycaemia. In addition, CGM device use reduced the odds of experiencing hyperglycaemia by 34% (AOR = 0.66(0.44 - 1.00)).

6.4. Results of study IV: Popular Diabetes Apps and the Impact of Diabetes App Use on Self-Care Behaviour

Of the total 1682 respondents, more than 45% (n=759) mentioned using diabetes apps (n=759). The use of one hundred and forty-five different diabetes apps were reported by respondents who mentioned using diabetes apps for self-management. Of which, “mySugr” was the most popular app. In addition, “Dexcom”, “Freestyle Libre” and “Xdrip+” were also popular, particularly among respondents with type 1 diabetes (Fig 11).

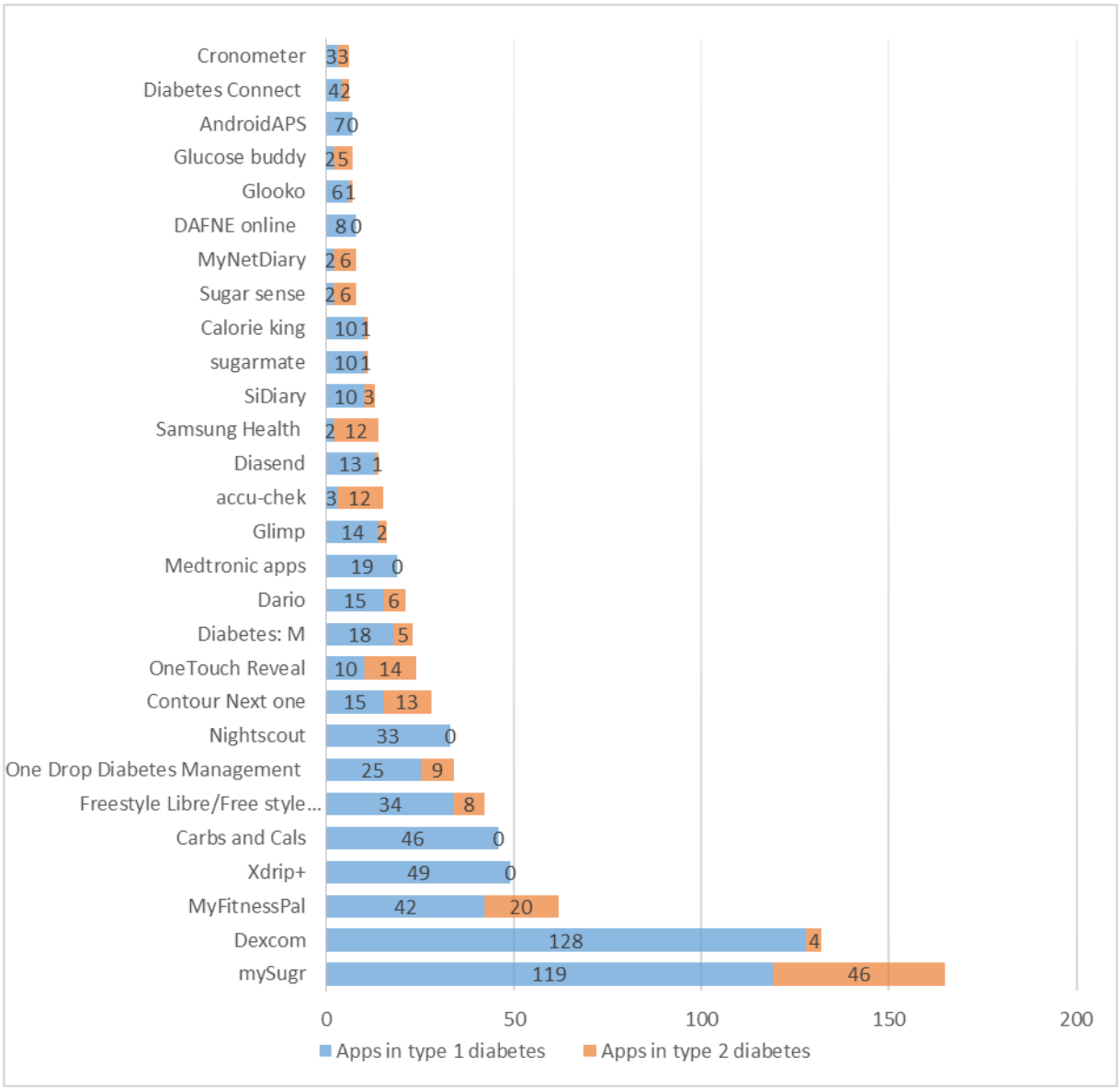
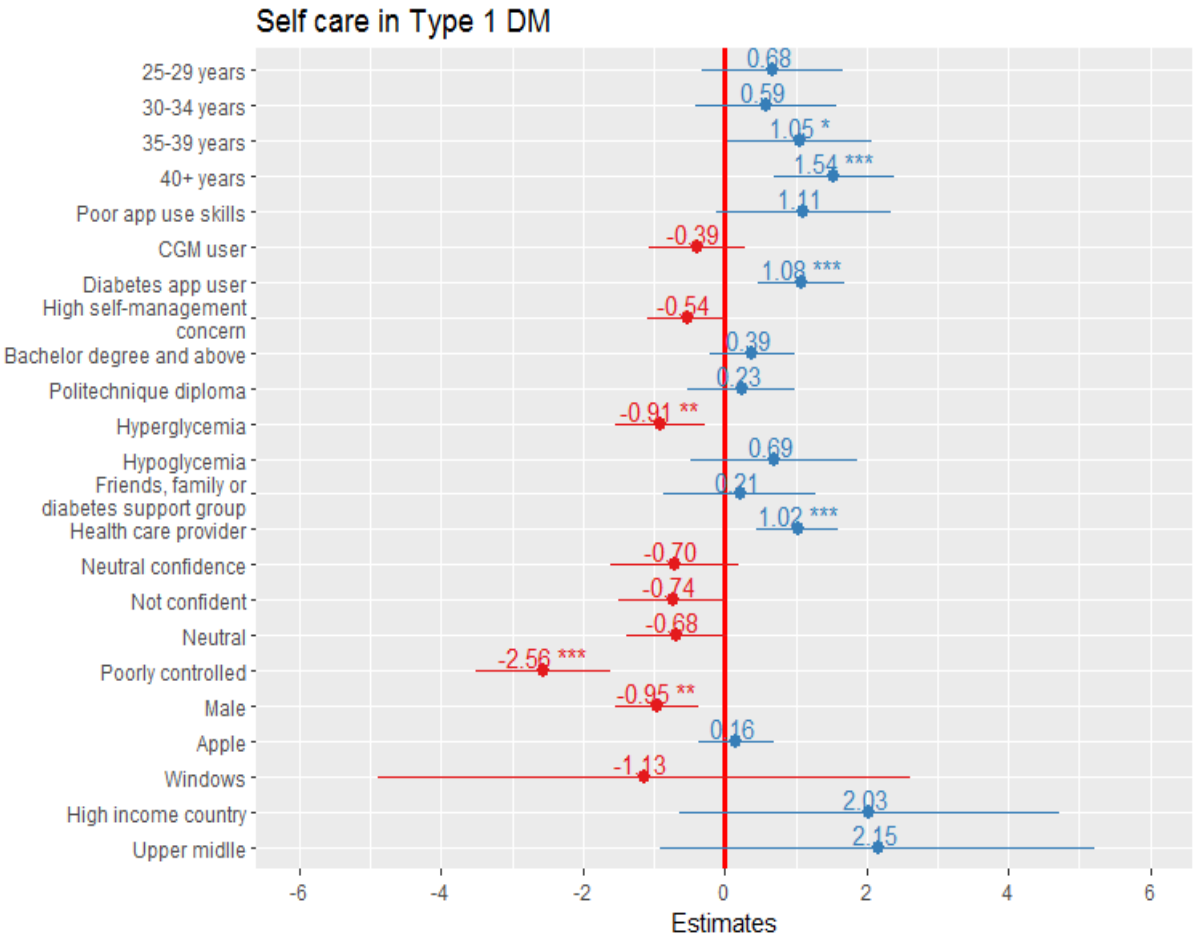


Figure 11: Popular diabetes apps

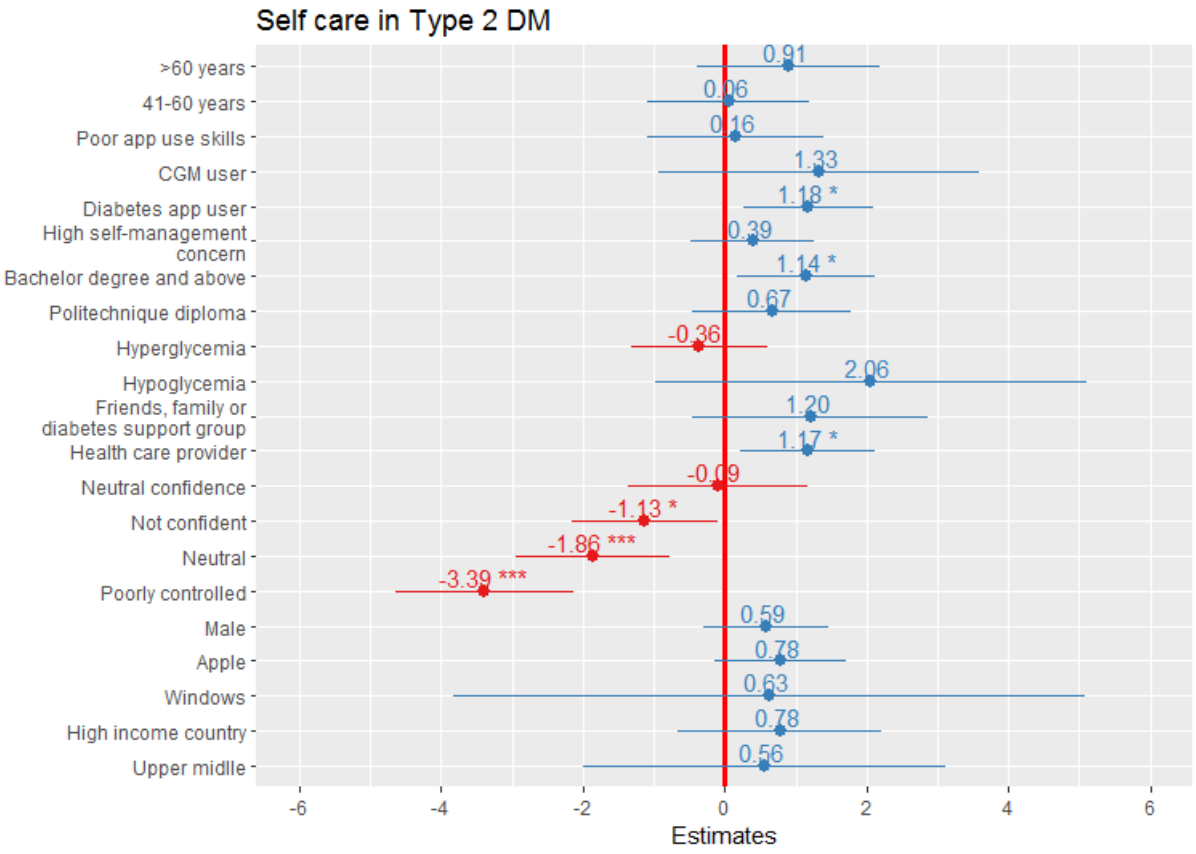
The cumulative self-care score was significantly higher among diabetes app users, both among respondents with type 1 and type 2 diabetes. In addition, compared to non-users, diabetes app users were observed to have significantly higher scores in all individual self-care components except for foot care and specific diet care. This result was consistent in in both with type 1 and type 2 diabetes.

After controlling for key confounders, the use of diabetes for self-management apps was independently associated with increasing the cumulative self-care score by a factor of 1.08(95%CI: 0.46-1.7) units and by a factor of 1.18(95%CI: 0.26 – 2.09) units among persons with type 1 and type 2 diabetes, respectively. The variables adjusted in both models in type are displayed in Fig 12 and 13, respectively.



* Statistically significant at p< 0.05, ** statistically significant at p< 0.005, *** statistically significant at p< 0.001

Figure 12: Forest plot of the coefficients with 95%CI for factors associated with self-care behaviour in persons with type 1 DM.



* Statistically significant at p< 0.05, ** statistically significant at p< 0.005, *** statistically significant at p< 0.001

Figure 13: Forest plot of the coefficients with 95%CI for factors associated with self-care behaviour in persons with type 2 DM.

7. DISCUSSION

This chapter begins with the summary of the principal findings. After that, the findings are explained and compared with the existing literature. The chapter integrates the methods and main findings, outlines strengths and limitations and narrates the broader concept of digital health and its benefits for advancing patient outcomes as well as improving diabetes care. More broadly, it dives deeper into the main aspects of digital health solutions and what they may offer to healthcare and the field of public health, in general.

7.1 Principal findings

This dissertation focused on patient outcomes mainly HbA1c and glycemic abnormalities (clinical outcomes) and self-care behavioural outcomes to illustrate the impact of digital health for improving clinical and behavioural outcomes in patients with diabetes. The results of our systematic reviews and meta-analyses, as well as of the observational studies indicate that digital health improves glycemic and self-care behavioral outcomes of patients with diabetes. The results suggest that glycemic control and self-care behavior were improved via digital health solutions. The pooled analyses showed that web-based digital health interventions provided by mobile phones, Personal Digital Assistants (PDA) or computers provide clinically and statistically significant reductions of HbA1c in persons with type 2 diabetes. The results of the comparative analyses based on three meta-analytic methods also yielded comparable effect sizes that were consistently statistically significant. However, there was some degree of differences across the heterogeneity statistics, pooled effect size estimates and respective confidence intervals. The difference was found to be lower when studies with higher baseline imbalance and/or pre-post correlation were removed from the meta-analyses. The results were all in favour of digital interventions.

In addition, patient's use of diabetes apps for self-management independently reduces the odds of experiencing hyperglycaemia in type 2 diabetes. Furthermore, diabetes app use is associated with improving self-care behaviour in both persons with type 1 and type 2 diabetes. Of all of the apps identified in the study, "mySugr", "MyFitnessPal" and the CGM apps such "Dexcom", and "Xdrip+" were popular.

7.2. Interpretations and comparisons with prior work

The results are in line with results of existing studies that reported clinically and statistically significant HbA1c reductions via internet-based interactive self-management interventions (233, 234) and smartphone-delivered interventions (232). Although numerous studies have reported the effectiveness of digital interventions, the effective combination of specific components of behavioural interventions and their delivery mechanisms were unclear. Our results indicate that the effect of digital interventions was significantly higher among patients having higher baseline glycated haemoglobin levels and if the interventions included approaches of "problem solving" and performed "self-monitoring of outcomes of behaviour". However, these results need to be confirmed by a larger number of studies because meta-regression models are more stable and provide robust results if larger number of studies and fewer covariates are taken into account (286).

Similar to previous studies (287-289), higher levels of glycated haemoglobin level reductions occurred among patients with higher HbA1c levels at the start the interventions. This is in line with previous evidence that patients with poorly controlled diabetes may benefit more from digital health opportunities (290).

The effect size estimates pooled using the three different methods, ANCOVA, SACS and SAFV, suggest that digital interventions significantly reduce glycated haemoglobin levels. However, looking at the differences in pooled effect size estimate, confidence intervals and heterogeneity statistics, particularly in sensitivity analyses, the importance of accounting for baseline imbalance and correlation, at least for studies that are unbalanced and have high pre-post correlations becomes clear. This is in line with previous methodological literature emphasizing the importance of adjusting for baseline imbalance and pre-post correlations (250, 251, 259).

The results revealed a high prevalence of diabetes app use in both patients with type 1 and type 2 diabetes. Patients with type 2 diabetes who reported using diabetes apps for self-management had lower odds of experiencing hyperglycaemia compared to those who did not use diabetes apps. Consistent with these results, patients with type 2 diabetes who were using diabetes app for self-management also reported having a lower risk of hyperglycaemia (291, 292). The benefits of diabetes self-management apps for improving glycaemic control of patients with type 2 DM have been demonstrated in several RCTs (229-231). These apps

improve glycemic control by advancing patients' knowledge about diabetes, self-management competency, and adherence to medication and a healthy lifestyle (208, 211, 238-241). Contrary to persons with type 2 diabetes, for patients with type 1 diabetes, the association of diabetes app use with hyperglycaemia and hypoglycaemia disappeared after "CGM device use" variable was added into the model. Instead, CGM device use turned out to be an important determinant that significantly reduced the odds for experiencing both hyperglycaemia and hypoglycaemia. A growing body of evidence from experimental and observational studies indicates that CGM technologies were successful in improving glycemic control (293-295). CGM coupled with its diabetes apps appears to help patients track their real-time glycemic levels and trends. CGM facilitates the timely counteraction of episodes of hyperglycaemia and hypoglycaemia (294, 295), especially if patients are capable of responding appropriately to these undesirable outcomes by adjusting medication doses in the short term and by changing physical activity and dietary habits in the long term (294, 296).

The benefit of using diabetes apps for self-management was not limited to improving glycemic control. The results also show that using diabetes apps for self-management increases individual and cumulative self-care behaviours for both patients with type 1 and type 2 diabetes. This is consistent with the existing evidence base stemming from various RCTs and observational studies. Numerous studies reported that the use of diabetes apps for self-management increased scores of cumulative (297, 298) and individual self-care domains (299-302). Specifically, scores of blood glucose testing (298-301), physical activity (299, 301), foot care (300, 302), general diet (298, 302) and specific diet (299-301) self-care domains were improved after the use of diabetes apps. Importantly, diabetes apps facilitate tracking behavioural and glycemic patterns that ultimately improve patients' knowledge of diabetes, self-management capability, knowledge of complications and self-care practices (303). These improvements eventually enhance quality of life and reduce premature mortality.

Of all identified apps, "mySugr" was the most popular self-management app in both patients with type 1 and type 2 diabetes. Moreover, CGM apps such as "Dexcom", and "Xdrip+", "FreeStyle Libre" were also popular among patients with type 1 diabetes. Continuous glucose monitoring apps connected with CGM sensors and insulin pump in a closed-loop system are the most promising developments of artificial pancreas in the digital diabetes care (170). Future advances in diabetes apps and learning control algorithms may help tracking, learning, and predicting routines of patients which ultimately help the artificial pancreas systems to be

able to predict upcoming out-of-range glycemic levels (169). These systems are expected to transform the traditional diabetes care into an automated, personalized and patient-centred care.

7.3 Strengths and limitations

Although we have applied state of the art meta-analyses methodologies and innovative survey designs, we cannot completely avoid limitations. Therefore, this dissertation is the result of a trade-off between strengths and limitations.

7.3.1 Strengths

The systematic reviews and meta-analyses parts of this dissertation were the first to report the effectiveness of digital interventions for reducing glycated haemoglobin levels in persons with poorly controlled type 2 diabetes. It was also the first meta-analysis in this area of research that adjusted for baseline imbalances and pre-post correlations using a robust meta-analyses methodology, ANCOVA. Our comparative analyses on meta-analytic methods show the effect size (both at an individual and pooled level) and heterogeneity differences across the three meta-analytic methods that are commonly applied in synthesizing continuous outcomes with similar scales of measurement. In addition, our analyses also implemented a reliable taxonomy (243) and the well-established AADE7 (111) to disentangle complex interventions and help us identify effective components. These tools evidently provide robust mechanisms to handle heterogeneity of multi-component behavioural interventions (141, 242, 304).

7.3.2 Limitations

The limitations mainly arise from two sources: internally from our narrow database search and application of complex methodology and externally from the limitations of the included studies. The search was limited to only three main databases. At the start, we checked whether this may have an impact on our search results. However, there were no noticeable differences. Considering the workload required for applying a more robust methodology, obtaining missing data by first contacting authors and otherwise imputing missing values from the reported data, we decided to focus only on three fundamental databases. We applied robust statistical methods to impute missing data and synthesized them using advanced meta-analytic methodology that helped account for baseline imbalance and correlations. With advanced analyses methods, we produced a more precise effectiveness estimate. However, uncertainties still remain.

Our analyses were also affected by the limitations of the included studies. Identifying components of complex interventions in systematic reviews depends on the quality and detail of descriptions of the interventions. Missing data were calculated by using relevant imputation strategies. In addition, mapping and differentiating the intervention components requires systematic reviewers' subjective judgement (305). We tried to minimize the impact of this limitation by taking online training for applying the BCTTv1 taxonomy and using two-reviewer consensus rating and third reviewer arbitration for resolving any disagreements in the identification of BCTs.

The two core studies that aimed to assess the impact of diabetes app use for improving glycemic control and self-care behaviour also have limitations. Broadly, these limitations emanate from three major themes: study setting, design, and measurement. These limitations are described as follows.

Firstly, responses of the survey were collected using online platforms. Therefore, our sample might not be representative of people with diabetes who did not subscribe to Facebook and/or online forums and those who may have no or limited digital literacy. The role of Facebook and online forums in connecting patients with chronic diseases and promoting self-management is ever increasing. For this reason, patients with diabetes on social media are an important segment of populations that requires attention. This dissertation, therefore, opens an important perspective for surveys in digital and global, but geographically super-diverse contexts.

Due to the nature of the web-based survey, the researchers involved in the study did not have any face-to-face contacts for receiving responses regarding all questions, including those on biochemical parameters. The validity of the results might have been affected by biases that arise from self-report and self-selection. In addition, Facebook and most patient online forums are highly global. Hence, respondents of our study are from multiple countries, most of them from high-income English and German speaking countries. As a result, unobserved variation that arises from respondents' differences in exposition to different healthcare systems and sociocultural and racial differences might have an effect on the generalizability of our results to other specific contexts. However, we did not observe any differences in stratified country-level analyses.

Secondly, due to the cross-sectional design of the studies, causal relationships cannot be determined. Thirdly, only self-reported one-time capillary blood glucose levels combined with HbA1c levels were collected. This might have affected our effort to determine the glycemic abnormalities of our respondents. Future studies need to consider measuring these outcomes more than once in order to more accurately quantify the dynamics of glycemic control. Moreover, we did not investigate psychometric properties of some of the questions, such as those assessing diabetes self-management concern and perceived confidence regarding diabetes self-management. In addition, the dichotomised Yes/No question on whether respondents were taking glucose lowering medication was too broad and did not adequately capture all the additional medications other than insulin prescribed to persons with type 2 diabetes. Interpretation of the results needs to consider these limitations that might collectively have an effect on the validity our results.

7.4 Improving diabetes patient outcomes with digital health: promises and perils

This dissertation focused on three main patient outcomes HbA1c, glycemic abnormalities, and self-care behaviour. These outcomes may broadly be categorized in two categories: clinical and behavioural outcomes. Our results demonstrate the benefits of digital health interventions and the use of diabetes apps for self-management and improving these outcomes. This is consistent with the existing evidence.

In the current literature, although the surrogate marker, HbA1c has been extensively assessed to evaluate the impact or effectiveness of digital health in diabetes, improvements in outcomes other than HbA1c were also reported. A scoping review on eHealth literature in poorly controlled type 2 diabetes reported several outcomes that were improved after participation in digital interventions. This includes biological and clinical markers (e.g. blood pressure, change in incidence of hospitalization; emergency department utilization; self-reported hypoglycaemia), and cognitive and psychosocial outcomes (e.g., diabetes knowledge, self-efficacy, depression, and diabetic distress). Furthermore, improvements in self-management behavioural outcomes (e.g. medication adherence, foot care, physical activity), body composition (e.g., weight loss, body mass index), and long-term outcomes (e.g. quality of life, incidence of diabetic complications) were reported (242). However, current literature on digital health interventions on diabetes mainly focus on short-term successes. Most of the interventions suffer from low power, poor randomization, short intervention durations and short-term outcome measures. Non-glucocentric, or long-term,

sustained and clinical changes in patient outcomes are still open question in digital diabetes research. Further research is required especially interventions that address these limitations.

In general, digital health enables persons with diabetes to monitor their blood glucose level and other data with external devices or wearables. This supports patients in keeping track of their blood glucose, nutrition, physical activity and foot care. Tablet- or smartphone-based self-management apps enable patients to track and visualize their trends and detect out-of-range glycemic values. Tracking glycemic or other behavioural and nutrition outcomes help patients understand their diseases and how their nutrition, physical activity and other behaviour interact to lead into their personal diabetes outcomes. This empowers patients' capacity for appropriate and timely resilience which ultimately provides the key to augmenting diabetes self-management.

Digital health offers persons with diabetes several opportunities and promises scalable and affordable intervention strategies. Despite these early promises, "we are still in the 1.0 days of success of digital health"(306), there are several issues that hamper its rapid and wide-spread adoption in the process of making it an integral part of diabetes care. These perils are summarized as follows.

7.4.1 Data ownership, protection of privacy and confidentiality

Diabetes apps or health apps in general produce a large amount of data. Data are currently the most expensive asset and its value will grow sharply (162). This tremendous value of data provides companies investing in digital health to enjoy unprecedented successes. The success of these companies, to large extent, relies on the value of data collected from users. Yet, who owns the data, how they are used and how the privacy and confidentiality of the users are safeguarded remain unanswered questions. Concerns regarding privacy, security, and confidentiality are increasing as the "digital health tsunami" continues to expand. It is not uncommon that health apps breach these key ethical principles. For example: an LGBTQ dating app, "*Grindr",* recently gave unencrypted HIV status and personal data to third parties (307). Very recently, several other incidents of data breaches and cyberattacks that affected millions of patients reverberated digital health (308). Specific to diabetes, a data security flaw that affected CGM and insulin pumps was detected in 2016. It was reported that a hacker could have possibly used a sophisticated equipment to decrypt the radio signals and remotely program catastrophic insulin doses to be pumped to victims (309). Another security challenge may arise from mobile cloud computing services. Diabetes app developers may provide a

cloud storage system that allows large volumes of consumer data to be stored in the cloud. Both developers and healthcare providers need to ensure the cloud storage system has adequate security systems that protects consumers' data from cyberattacks or loss as well as safeguard consumers from identity theft.

Diabetes apps can also transmit sensitive medical data which breaches privacy and confidentiality. Many app users also do not read the privacy policies (if any) of the apps before installing them. A recent assessment reported that 81% of the 211 diabetes apps included in the analysis did not have any privacy policies. More than 80% of the apps collected user data and about 50% shared personal data with third parties. Of the 19% (41) of the apps that had privacy policies, more than 75% shared the data with third party users (310).

Opting-in or -out consents for specific issues, informed and meaningful choices, users control over their data or autonomy for data ownership are non-existent (309). Patients might mistakenly believe personal medical data that is entered into an app is private (310). These situations suggest that digital health should embrace the fundamental ethical principles if trust from users is to be earned and long-term success is to be warranted.

The American Health Insurance Portability and Accountability Act (HIPPA) requires de-identification of 18 data elements that could be used to identify a user. Some digital health developers disclose that they abide by this policy with little or no description how this can be done. Without adequate transparency, it is not reasonable to suggest that the de-identification methods are effectively implemented (309).

In May 2018, the European Union (EU) ratified the new General Data Protection Regulation (GDPR). Under this regulation, the code of conduct on mobile health apps to protect the safety of users and to control migration of users' data outside the EU is set. Practical guidance for app developers regarding principles of the data protection including users consent, purpose limitation and data minimization, data retention, privacy, disclosure, data transfers and personal data breaches are outlined (311). This law seems to be the most comprehensive and it may be necessary to customize it to countries outside of the EU. Further research is required to evaluate mHealth apps, if not diabetes apps, to assess how the new EU data protection regulation is changing the privacy policies of the apps. It also needs continuous evaluation and follow up to ensure these apps continue to abide by this regulation.

7.4.2 Lack of evidence of clinical effectiveness and safety

The International Diabetes Federation-Europe (IDF-Europe) recently suggested a "well-suited" diabetes apps may transform ubiquitous mobile phones into a medical device that supports patients self-management practices (312, 313). An overwhelming level of evidence indicates that diabetes apps have a great promise for improving diabetes outcomes. However, there are safety concerns. Currently, there is a paucity of data that shows congruence between evidence-based clinical guidelines and diabetes apps functionalities (208-212, 314). Among 600 diabetes apps that were available in the United States, only one received the US Food and Drug Administration (FDA) clearance (209, 213). In 2015, the performance of 65 diabetes self-management apps that were freely available in three stores were evaluated for tracking four major indicators: blood glucose levels, insulin therapy, diet and physical activity. The assessment found that 56 of these apps did not meet these basic criteria or did not function properly (315). Most worryingly, the majority of the diabetes apps that calculate insulin doses were revealed to be faulty, with only one of the 46 insulin dose calculator apps proved to be clinically safe. These errors put users at risk for "catastrophic insulin overdoses" (215). Recent evidence that evaluated the literature in self-management apps also strengthened the safety concerns. Of all diabetes self-management apps that are abundantly available in typical stores, only 11 were studied for clinical effectiveness. Of these 11 apps evaluated for effectiveness, only one provided clinically significant HbA1c reductions (214). In sum, it is still a long way to go for diabetes apps in terms of clinical effectiveness and safety. The use of health apps without evidence of effectiveness has been labelled as using "pure snake oil" (316). Because of this, healthcare providers need to be cautious before prescribing or recommending the apps to their patients (215).

Patients also need to be curious and ask recommendations from their physicians before taking the initiative to use these apps. Patients who download apps might be misled by download rates rather than safety and effectiveness recommendations. However, download rates do not suggest safety or clearance by any regulatory body. Most of the apps are free of charge and there is a fierce market competition which made the developers and digital health start-ups to struggle economically (314). There is a possibility that download rates could be manipulated. It was reported that app developers may recruit users for as little as 5$ to skew user ratings in favour of their app or negatively rate apps developed by competitors (317, 318). Hence, independent international and national regulatory bodies are necessary to ensure formal

evaluation and clearance (209, 216). The American FDA considers mobile applications as a medical device if the mobile app

1. connects one or more medical devices for the purpose of controlling the device(s), patient monitoring or analysing the data from the medical device(s),
2. transforms a mobile platform into a regulated medical device by using attachments, display screens, sensors, or other such methods by including functionalities similar to those of currently regulated medical devices,
3. becomes a regulated medical device (software) by performing patient-specific analysis and providing patient-specific diagnosis, or treatment recommendations.

FDA considers these apps to be subject to regulatory approval and encourages developers of these apps to submit to the FDA regulatory process and perform safety and effectiveness testing. Based on these "non-binding recommendations" of the FDA, mobile apps that meets section *510(k) of the Food, Drug and Cosmetic Act* can be marketed in the United States (319). However, it is difficult for app developers to meet the suggested recommendations because of the rapidly changing technology. One of the main challenges for these apps is the "kitchen-sink syndrome" or scope creeps. The apps continue to change/upgrade their features on a regular basis or be removed from stores (310, 314). The developers of the apps state that at this pace, conducting a traditional randomized controlled trial is almost impossible. For this reason, evaluation or re-evaluation to keep up with safety regulations is complicated (314).

7.4.3. Digital health literacy, digital divide and health inequality

The intersection of health and digital literacy led to the emergence of digital health literacy. Digital health literacy is a key success factor for the expansion and democratization of digital health in healthcare. A very comprehensive concept of digital health literacy was introduced by Norman and Skinner in 2006. They defined digital health literacy as "the ability to seek, find, understand, and appraise health information from electronic sources and apply the knowledge gained to addressing or solving a health problem". It consists of several literacy dimensions: health literacy, computer literacy, media literacy, science literacy, information literacy and traditional literacy and numeracy (320). Evidence suggests that digital health literacy is a crucial precondition for digital health adoption (321) and it affects health literacy by a sizable extent (322)

A growing number of patients and health systems are relying on the internet and related technology. However, factors such as age, race, and socioeconomic conditions that hinder patients and healthcare systems from adopting internet and its related technology create a digital divide (197-200). Digital divide that moderates digital health literacy deepens the existing health inequality (197-200, 323).

On the other hand, the burden of diabetes and its complications is disproportionately higher in people with lower socioeconomic standards. However, their participation in innovative digital diabetes care, including CGM and artificial pancreas is unfairly low (324). Patients who do not have access to digital health opportunities or have low levels of digital health literacy are falling further behind (201). Digital health innovators must therefore understand the level of marginalized, low literacy level users (205) and perhaps offer services in plain-language and that are easier and motivating alternatives. In this context, Baldwin and colleagues recommended increasing digital health adoption using simplified data displays, easy log-in accesses and providing alerts or notifications in layman's terms (325). Shelon and colleagues suggested screening patients for digital health literacy and then offering low-cost internet services, subsidizing devices and providing skills training for patients with low digital health literacy levels. In addition, building partnerships between healthcare systems, digital health innovators and local health advocates is important for larger digital health literacy screening (207). Improving access to smartphones is also important because the world has gone mobile and "mobile is where we can finally reduce digital divide" (326).

7.4.4 Finding an app that perfectly suits the interest of patients is almost impossible

In our study, 145 different diabetes apps were named by respondents who used Android, iPhone or Windows smartphones. There are diabetes apps that may be available only in one app store. The functionalities or design features across the apps also differ. These factors affect consumers' choices and confidence with the technology. There is a growing lack of confidence with the app functionalities and their ease of navigation despite an increasing interest for acquiring apps for diabetes self-management (327). Although it is not possible to develop an app that offers "one-size fit all", developers may consider adding basic services so that at least some of these basic functionalities are cross-cutting across the apps. This may also partly alleviate the existing challenges of interoperability.

Systematically searching an app in the major stores is complex because the app search functionalities are not standardized. It is not possible to conduct searches with key words and

Boolean operators in all stores. It is not also clear whether search outputs are based on advertisements, relevance, download rates, user reviews or rating. It is speculated that android and apple are continually tweaking their app search algorithms which has an effect on consumers' access and choices (328).

7.5 The future of digital health

7.5.1 Wearables and the transformation of healthcare and public health

In the past few years, wearables have become popular in academia, industry and public health. They are advanced applications of digital health and the Internet of Things. Wearables are defined as "devices that can be worn or mate with human skin to continuously and closely monitor individual's activities, without interrupting or limiting the user's motions" (329). It includes a wide range of devices or systems that are worn on various parts of the body. Sensors integrated as textiles, smart watches, motion trackers, belt-worn personal computers, or smart glasses are only few examples(330).

Wearables can broadly be classified into three categories: mechanical, physiological and biochemical. Wearable devices are being implemented in several settings including hospital care, metabolic, cardiovascular, gastrointestinal, sleep, neurology, mental health, maternal and neonatal care as well as in monitoring pulmonary health and tracking environmental health exposures (331). As described in earlier chapters, the CGM devices or artificial pancreas systems (closed loop) are important developments of wearable technology transforming and penetrating diabetes care at a very fast pace. Smart watches and motion trackers are the most popular wearable mechanical devices that have particular importance to precision public health.

While the current development of wearable technologies is exciting, the future of wearables is uncertain because of several factors. First, the success of companies manufacturing wearables mainly relies on consumerism that affects long term device use. Second, the acceptability of the devices and the associated stigma against people using wearables may limit their use and expansion (332). Third, challenges related with calibration, accuracy of measurements, size of the device, and power capacity of the devices are causing future uncertainties (330, 331). Hence, further research and development is required to address these uncertainties and establish the benefits of these devices in healthcare and public health. There is also limited evidence regarding the acceptability of these devices in the patient community (333).

7.5.2 Social media and public health

In this age of digitalization, social media has become a dynamic force in revolutionizing the wave of marketing and politics. In politics, it has been an incredibly powerful tool to engage a large population, target and change the attitude of individual voters, and possibly skew the results of elections and referendums. The recent revelation of the Facebook scandal that was led by the "Cambridge Analytica" is an important example to realize the power of social media in social manipulations and changing the attitudes of large-scale populations in a very short period of time. Although social media has been both a blessing and a curse for politics, its importance for changing political attitudes and free speech is uncontroversial. In marketing, influencing customer's purchasing behaviour at a very individualized level by using digital profiling has been an impressive application of social media. It is clear that politics and marketing are benefiting from the applications of digital profiling and targeted interventions. The question is why not public health?

After 2013, new methods of predicting personality and demographics by using Facebook 'likes' emerged (334, 335). Youyou and colleagues compared the accuracy of personality judgements by using 100-item self-rated personality questionnaire versus Facebook "likes" known as "generic digital footprint" left by users. They demonstrated computers outsmarted humans in judging personality by just using Facebook "likes" (336). These novel methods demonstrated how the personality profiles of users can be traced using the data they leave behind their online activities. This is known as digital phenotyping or digital user profiling (337). Digital phenotyping coupled with targeted digital communication interventions has been successful in influencing purchasing and voting behaviours (338, 339).

Digital profiling may also be used to target health behaviours. However, public health interventions are lagging behind marketing and politics and still continue with the traditional intervention methods. It is not too late for public health researchers to adopt these concepts in designing personalized digital interventions which will mark the foundations of precision public health. There is little evidence on applying these methods to design personalized large-scale public health interventions. This lag is partly due to the limitation that social media platforms may produce a biased representation of location or demographics of different target groups and the traditionally conservative nature of public health interventions require validated models and ethical interventions. However, there is no reason to ponder digital profiling methods cannot be successful in public health. In fact, there are some early

evidences that demonstrated the success of personalized digital interventions which targeted health behaviours (339, 340). Early developments of this type of intervention are mainly remain in the area of mental health (339). This is an exciting prospect, but there is little certainty with respect to designing ethical interventions and formulating sound evaluation methods.

In addition, digital profiling can be used as cost effective method for recruiting respondents or conducting public health surveys. In Australia, this method of recruitment was used to reach respondents who are in remote areas (341-343). In our research, we also demonstrated the potential of using targeted Facebook advertisements to conduct web-based surveys. As mentioned earlier, persons potentially having diabetes were targeted by using applications of digital profiling methods. Demographic, location, interest in diabetes related terms on Facebook (likes) and other variables were used to build the digital profiling method and subsequently place the targeted advertisements. Although we were able to recruit our respondents, we did not evaluate the cost effectiveness of recruiting survey participants using targeted advertisements. We call for further research to evaluate the cost effectiveness of using targeted Facebook ads for recruitment and the validity of the data collected using this method.

Facebook has also several tools which are already playing a role in public health. Worth mentioning is Facebook's "community help" tool that was initiated in 2017 to support people in times of disasters. With this tool, users in crises affected areas can let their family and friends know about their safety using the "safety check" tool or creating fundraisers that facilitate donations, asking or providing community help and distribution of crisis messages through sharing articles, photos and videos so that people can learn more about crises and its magnitude (344). This has been a powerful communication tool for enhancing the velocity of crises response, improving public awareness regarding the crisis situation and facilitating evacuations (345).

While social media can be a powerful tool for raising awareness, promoting health behaviours and improving public health, it can also be used for misinformation and exposing vulnerable groups to unhealthy products. There is an overwhelming evidence that misinformation in social media is one of the key determinants of vaccine hesitancy and increasing polarized anti-vax stances (346-349). Countries have already indicated vaccination fake news is harming vaccination uptakes (346). Misinformation, especially on vaccines, has resulted in a

significance rise of vaccine hesitancy and drop of vaccination rates in the western world. For this reason, misinformation poses significant threats to public health. In addition, social media may be used to target vulnerable populations (350). Many countries ratified new laws banning advertisements of smoking, alcohol and other unhealthy products in the traditional media. Companies producing these products are increasingly turning their attention to social media because these media are not regulated and offer them a unique opportunity to associate customer's personality with their brands (351, 352). These tools are increasingly being used to target vulnerable groups such as adolescents (352, 353). Evidence suggests that digital marketing of unhealthy products influences youth's use and attitude of the products (354). Therefore, public health should be prepared to counteract misinformation in health, limit harmful contents from certain age groups and tackle unhealthy Facebook advertisements to protect the safety and health of vulnerable communities.

8. CONCLUSIONS AND FUTURE DIRECTIONS

8.1. Conclusions

This dissertation has demonstrated that digital health facilitates diabetes self-management and adoption of a healthier lifestyle that ultimately improves clinical and behavioural outcomes of patients with diabetes.

- Digital interventions provide clinically significant reductions in HbA1c levels among patients with poorly controlled type 2 diabetes.
- The effects of these interventions were larger among patients with higher baseline HbA1c levels and with mid-level (6 to 8 months) of intervention period.
- Interventions including the BCTs 'problem solving' and 'self-monitoring outcomes of behaviour' were associated with a reduction of HbA1c-levels.
- In addition, the use of diabetes apps for self-management was associated with reducing the odds of experiencing hyperglycaemia among patients with type 2 diabetes while the use of CGM technology was associated with reducing the odds of experiencing both hyper- and hypoglycaemia among patients with type 1 diabetes.
- Using diabetes apps for self-management positively influenced self-care behaviour in both patient groups with type 1 and type 2 diabetes.
- Diabetes self-management apps such as "mySugar" and CGM apps mainly "Dexcom", "Freestyle Libre" and "Xdrip+" were some of the most popular diabetes apps in the study population.
- Future research on diabetes self-management needs to include information on patients' use of diabetes apps as it may be an important care-moderating factor.

8.2. Future directions

Rigorous meta-analysis offers a fundamental method to estimate the effect of interventions to inform clinical and public health practice (355-357). However, synthesizing continuous outcomes reported from randomized controlled trials having a high baseline imbalance and pre-post correlations has been challenging. Baseline imbalance may result from chance especially in small trials, or bias that arises from selection, inadequate allocation concealment or poor randomization (358). Synthesizing continuous outcomes with similar scales of measurement that are reported from RCTs having a high baseline imbalance and pre-post

correlations requires adjustments of effect sizes. Adjustments for baseline imbalance and pre-post correlations can be done by applying a more advanced meta-analytic approach, Analyses of Covariance (ANCOVA) (250-252, 259). Although there is an overwhelming literature with methodological guidance emphasizing the need to apply ANCOVA, none of the previous meta-analyses which we identified through scoping used this method in diabetes research. This is mainly due to the complexity of ANCOVA, unavailability of individual participant data or summary data necessary to calculate ANCOVA effect size estimates. We recommend that the authors of future meta-analyses consider applying this method for adjusting effect sizes at individual study levels, at least for studies having a high baseline imbalance and/or pre-post correlation. It is also important to conduct meta-analyses of the underlying outcome using the baseline difference data. If the pooled baseline difference is not close to zero, authors should consider applying ANCOVA. Researchers conducting future RCTs should also consider reporting adequate summary data or providing access to individual participant data. This will ease synthesis and estimation of the true effect of interventions.

This dissertation applied an innovative data collection method. We used targeted Facebook advertisements, Facebook groups, and diabetes specific online forums to recruit respondents. Behavioural and public health research may consider applying these methods more frequently in the future. However, evidence regarding the cost effectiveness of this method for data collection, how to ensure the validity of the collected data, efficient mechanisms for running the targeted advertisements and engaging the majority of Facebook group members in a survey is almost non-existent. During the survey, we learned some of the most important strategies to increase response rates. These strategies were engaging group members as much as possible by collaborating with group champions (admins, moderators, and/or any influential members of the group) of Facebook groups, adding incentives, and posting comments to make the survey appear in the newsfeed of members. Running the ads on weekend days and bumping the Facebook post up during the evening hours were also quite successful in attracting a greater number of respondents.

Using these method of data collection also posed challenges. For example, searching the groups on Facebook was challenging because many groups have informal names which made it difficult for us to find all relevant groups. This process could be simplified if Facebook implements indexing mechanisms. In addition, using social media for surveys mainly relies

on self-selection and self-reporting. Validation of the data, especially in a geographically super diverse population, is challenging. The members of the Facebook groups are also possibly from multiple countries which requires consideration of different time zones when running surveys on Facebook groups or targeted ads. Ethical guidelines are also required to develop ethically sound strategies for recruiting survey participants via Facebook groups and targeted advertisements.

To conclude, we demonstrated the effectiveness of digital interventions for improving glycemic control, identified popular diabetes apps, and investigated the effect of diabetes app use for increasing self-care behaviour and lowering the odds of experiencing hyperglycaemia and hypoglycaemia in type 1 and type 2 diabetes. Several diabetes apps are readily available in typical stores which makes them easily accessible to patients owning smartphones or tablets. Looking at the results of this dissertation, it is reasonable to endorse the use of diabetes apps for self-management as they may help patients achieve their behavioural and clinical goals. However, to date, many of these apps are still faulty and only a small minority of them meets clinical recommendations for diabetes care. National and international regulatory bodies need to further regulate diabetes apps and ensure clinical safety and effectiveness. Clinicians should therefore consider only prescribing the use of evidence-based and/or regulatory body-approved diabetes apps.

In general, digital diabetes care improves diabetes self-management and supports patients in achieving individualized behavioral and glycaemic targets. Diabetes apps and CGM are laying the foundations of digital diabetes care. As digital diabetes care continues to evolve, personalized and precision diabetes medicine is moving to the forefront.

9. REFERENCES

1. Laios K, Karamanou M, Saridaki Z, Androutsos G. Aretaeus of Cappadocia and the first description of diabetes. Hormones (Athens). 2012;11(1):109-13.
2. Karamanou M, Protogerou A, Tsoucalas G, Androutsos G, Poulakou-Rebelakou E. Milestones in the history of diabetes mellitus: The main contributors. World J Diabetes. 2016;7(1):1-7.
3. Tekiner H. Aretaeus of Cappadocia and his treatises on diseases. Turk Neurosurg. 2015;25(3):508-12.
4. Eknoyan G, Nagy J. A history of diabetes mellitus or how a disease of the kidneys evolved into a kidney disease. Adv Chronic Kidney Dis. 2005;12(2):223-9.
5. Guthrie DW, Humphreys SS. Diabetes urine testing: an historical perspective. Diabetes Educ. 1988;14(6):521-6.
6. Papaspyros NS. The history of diabetes mellitus: G. Thieme; 1964.
7. Macfarlane I. Mathew Dobson (1735-1784) and diabetes. Medical Historian. 1993(7):15-22.
8. Zaccardi F, Webb DR, Yates T, Davies MJ. Pathophysiology of type 1 and type 2 diabetes mellitus: a 90-year perspective. Postgraduate medical journal. 2016;92(1084):63-9.
9. Ahmed AM. History of diabetes mellitus. Saudi Med J. 2002;23(4):373-8.
10. H Kenneth Walker, MD WDH, J Willis Hurst. In: rd, Walker HK, Hall WD, Hurst JW, editors. Clinical Methods: The History, Physical, and Laboratory Examinations. Boston: Butterworth Publishers, a division of Reed Publishing.; 1990.
11. Huisman TH, Martis EA, Dozy A. Chromatography of hemoglobin types on carboxymethylcellulose. J Lab Clin Med. 1958;52(2):312-27.
12. Bookchin RM, Gallop PM. Structure of hemoglobin AIc: nature of the N-terminal beta chain blocking group. Biochem Biophys Res Commun. 1968;32(1):86-93.
13. Rahbar S, Blumenfeld O, Ranney HM. Studies of an unusual hemoglobin in patients with diabetes mellitus. Biochem Biophys Res Commun. 1969;36(5):838-43.
14. Gebel E. The start of something good: the discovery of HbA(1c) and the American Diabetes Association Samuel Rahbar Outstanding Discovery Award. Diabetes care. 2012;35(12):2429-31.
15. Koenig RJ, Peterson CM, Jones RL, Saudek C, Lehrman M, Cerami A. Correlation of glucose regulation and hemoglobin AIc in diabetes mellitus. N Engl J Med. 1976;295(8):417-20.
16. Banting F, Best C, Collip J, Campbell W, Fletcher A. PANCREATIC EXTRACTS IN THE TREATMENT OF DIABETES-MELLITUS-PRELIMINARY-REPORT. Canadian Medical Association Journal. 1991;145(10):1281-6.
17. Mering Jv, Minkowski O. Diabetes mellitus nach Pankreasexstirpation. Archiv für experimentelle Pathologie und Pharmakologie. 1890;26(5-6):371-87.
18. Rosenfeld L. Insulin: Discovery and Controversy. Clinical Chemistry. 2002;48(12):2270.
19. Aronoff SL, Berkowitz K, Shreiner B, Want L. Glucose Metabolism and Regulation: Beyond Insulin and Glucagon. Diabetes Spectrum. 2004;17(3):183-90.
20. Allan FN. Diabetes before and after insulin. Medical history. 1972;16(3):266-73.
21. Himsworth HP. Diabetes mellitus. Its differentiation into insolin-sensitive and insulin-insensitive types. Lancet. 1936;230:127-30.
22. Yalow RS, Berson SA. Immunoassay of endogenous plasma insulin in man. The Journal of clinical investigation. 1960;39(7):1157-75.
23. Amercan Diabetes Association. History of Diabetes 2014 [Available from: http://www.diabetes.org/research-and-practice/student-resources/history-of-diabetes.html, Archive: https://archive.is/7FdBi.

24. Lean ME, Leslie WS, Barnes AC, Brosnahan N, Thom G, McCombie L, et al. Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. Lancet. 2018;391(10120):541-51.
25. Lean MEJ, Leslie WS, Barnes AC, Brosnahan N, Thom G, McCombie L, et al. Durability of a primary care-led weight-management intervention for remission of type 2 diabetes: 2-year results of the DiRECT open-label, cluster-randomised trial. Lancet Diabetes Endocrinol. 2019.
26. Bruen D, Delaney C, Florea L, Diamond D. Glucose Sensing for Diabetes Monitoring: Recent Developments. Sensors (Basel). 2017;17(8).
27. Klonoff DC. Technological advances in the treatment of diabetes mellitus: better bioengineering begets benefits in glucose measurement, the artificial pancreas, and insulin delivery. Pediatr Endocrinol Rev. 2003;1(2):94-100.
28. Kennedy ED, Oliver N. Emerging technologies for diabetes. Practical Diabetes. 2017;34(7):240-4.
29. American Diabetes A. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2010;33 Suppl 1:S62-9.
30. Harry Keen, Weir GC. Joslin's Diabetes Mellitus. 14th ed. Philadelphia: Lippincott; 2005; 2005.
31. Chamberlain JJ, Rhinehart AS, Shaefer CF, Jr., Neuman A. Diagnosis and Management of Diabetes: Synopsis of the 2016 American Diabetes Association Standards of Medical Care in Diabetes. Ann Intern Med. 2016;164(8):542-52.
32. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med. 1998;15(7):539-53.
33. Röder PV, Wu B, Liu Y, Han W. Pancreatic regulation of glucose homeostasis. Experimental & molecular medicine. 2016;48(3):e219-e.
34. Moore CX, Cooper GJ. Co-secretion of amylin and insulin from cultured islet beta-cells: modulation by nutrient secretagogues, islet hormones and hypoglycemic agents. Biochem Biophys Res Commun. 1991;179(1):1-9.
35. Eisenbarth GS. Update in type 1 diabetes. The Journal of Clinical Endocrinology & Metabolism. 2007;92(7):2403-7.
36. Atkinson MA, von Herrath M, Powers AC, Clare-Salzler M. Current Concepts on the Pathogenesis of Type 1 Diabetes—Considerations for Attempts to Prevent and Reverse the Disease. Diabetes Care. 2015;38(6):979-88.
37. Peakman M. Immunological pathways to β-cell damage in Type 1 diabetes. Diabetic Medicine. 2013;30(2):147-54.
38. Moole H, Moole V, Mamidipalli A, Dharmapuri S, Boddireddy R, Taneja D, et al. Spontaneous complete remission of type 1 diabetes mellitus in an adult - review and case report. J Community Hosp Intern Med Perspect. 2015;5(5):28709.
39. Martin S, Pawlowski B, Greulich B, Ziegler AG, Mandrup-Poulsen T, Mahon J. Natural course of remission in IDDM during 1st yr after diagnosis. Diabetes Care. 1992;15(1):66-74.
40. Koivisto VA, Aro A, Cantell K, Haataja M, Huttunen J, Karonen SL, et al. Remissions in newly diagnosed type 1 (insulin-dependent) diabetes: influence of interferon as an adjunct to insulin therapy. Diabetologia. 1984;27(2):193-7.
41. Scholin A, Berne C, Schvarcz E, Karlsson FA, Bjork E. Factors predicting clinical remission in adult patients with type 1 diabetes. J Intern Med. 1999;245(2):155-62.
42. Herold KC, Bundy BN, Long SA, Bluestone JA, DiMeglio LA, Dufort MJ, et al. An Anti-CD3 Antibody, Teplizumab, in Relatives at Risk for Type 1 Diabetes. New England Journal of Medicine.0(0):null.

43. Campbell-Thompson M, Wasserfall C, Montgomery EL, Atkinson MA, Kaddis JS. Pancreas organ weight in individuals with disease-associated autoantibodies at risk for type 1 diabetes. Jama. 2012;308(22):2337-9.
44. Atkinson MA, Eisenbarth GS, Michels AW. Type 1 diabetes. The Lancet. 2014;383(9911):69-82.
45. Eisenbarth GS. Update in type 1 diabetes. J Clin Endocrinol Metab. 2007;92(7):2403-7.
46. Holst JJ, Vilsboll T, Deacon CF. The incretin system and its role in type 2 diabetes mellitus. Mol Cell Endocrinol. 2009;297(1-2):127-36.
47. Holst JJ, Knop FK, Vilsbøll T, Krarup T, Madsbad S. Loss of Incretin Effect Is a Specific, Important, and Early Characteristic of Type 2 Diabetes. Diabetes Care. 2011;34(Supplement 2):S251-S7.
48. Pilkis SJ, Granner DK. Molecular physiology of the regulation of hepatic gluconeogenesis and glycolysis. Annu Rev Physiol. 1992;54:885-909.
49. Tabak AG, Jokela M, Akbaraly TN, Brunner EJ, Kivimaki M, Witte DR. Trajectories of glycaemia, insulin sensitivity, and insulin secretion before diagnosis of type 2 diabetes: an analysis from the Whitehall II study. Lancet. 2009;373(9682):2215-21.
50. 2. Classification and Diagnosis of Diabetes. Diabetes Care. 2015;38(Supplement 1):S8-S16.
51. GBD. GBD Compare | Viz Hub 2019 [Available from: https://vizhub.healthdata.org/gbd-compare/.
52. Gallagher EJ, Le Roith D, Bloomgarden Z. Review of hemoglobin A(1c) in the management of diabetes. J Diabetes. 2009;1(1):9-17.
53. Cho NH, Shaw JE, Karuranga S, Huang Y, da Rocha Fernandes JD, Ohlrogge AW, et al. IDF Diabetes Atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045. Diabetes Res Clin Pract. 2018;138:271-81.
54. IDF. IDF Diabetes Atlas Eight edition. International Diabetes Federation; 2017.
55. Darnton-Hill I, Nishida C, James WP. A life course approach to diet, nutrition and the prevention of chronic diseases. Public Health Nutr. 2004;7(1A):101-21.
56. Organization WH. Global report on diabetes: World Health Organization; 2016.
57. IDF. International Diabetes Federation Diabetes Atlas. 2015.
58. Greenhalgh S. Making China safe for Coke: how Coca-Cola shaped obesity science and policy in China. BMJ. 2019;364:k5050.
59. GBD 2015 Mortality and Causes of Death Collaborators. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet. 2016;388(10053):1459-544.
60. Bovet P, Chiolero A, Gedeon J. Health Effects of Overweight and Obesity in 195 Countries. N Engl J Med. 2017;377(15):1495-6.
61. Dieleman JL, Baral R, Birger M, et al. Us spending on personal health care and public health, 1996-2013. JAMA. 2016;316(24):2627-46.
62. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4.4 million participants. Lancet. 2016;387(10027):1513-30.
63. Bommer C, Sagalova V, Heesemann E, Manne-Goehler J, Atun R, Bärnighausen T, et al. Global Economic Burden of Diabetes in Adults: Projections From 2015 to 2030. Diabetes Care. 2018.
64. Bloom DE, Cafiero E, Jané-Llopis E, Abrahams-Gessel S, Bloom LR, Fathima S, et al. The global economic burden of noncommunicable diseases. Program on the Global Demography of Aging; 2012.
65. Knip M, Simell O. Environmental triggers of type 1 diabetes. Cold Spring Harbor perspectives in medicine. 2012;2(7):a007690-a.
66. Biros E, Jordan MA, Baxter AG. Genes mediating environment interactions in type 1 diabetes. The review of diabetic studies : RDS. 2005;2(4):192-207.

67. Akerblom HK, Vaarala O, Hyoty H, Ilonen J, Knip M. Environmental factors in the etiology of type 1 diabetes. Am J Med Genet. 2002;115(1):18-29.
68. Knip M, Veijola R, Virtanen SM, Hyoty H, Vaarala O, Akerblom HK. Environmental triggers and determinants of type 1 diabetes. Diabetes. 2005;54 Suppl 2:S125-36.
69. Peng H, Hagopian W. Environmental factors in the development of Type 1 diabetes. Rev Endocr Metab Disord. 2006;7(3):149-62.
70. Rewers M, Ludvigsson J. Environmental risk factors for type 1 diabetes. Lancet (London, England). 2016;387(10035):2340-8.
71. Honeyman MC, Coulson BS, Stone NL, Gellert SA, Goldwater PN, Steele CE, et al. Association between rotavirus infection and pancreatic islet autoimmunity in children at risk of developing type 1 diabetes. Diabetes. 2000;49(8):1319-24.
72. Honeyman MC, Laine D, Zhan Y, Londrigan S, Kirkwood C, Harrison LC. Rotavirus infection induces transient pancreatic involution and hyperglycemia in weanling mice. PLoS One. 2014;9(9):e106560.
73. Perrett KP, Jachno K, Nolan TM, Harrison LC. Association of Rotavirus Vaccination With the Incidence of Type 1 Diabetes in Children. JAMA Pediatr. 2019.
74. Abbasi J. Quick Uptakes: After Rotavirus Vaccine, Australia's Type 1 Diabetes Incidence Declines. JAMA. 2019.
75. Allen DW, Kim KW, Rawlinson WD, Craig ME. Maternal virus infections in pregnancy and type 1 diabetes in their offspring: Systematic review and meta-analysis of observational studies. Rev Med Virol. 2018;28(3):e1974.
76. Yeung WC, Rawlinson WD, Craig ME. Enterovirus infection and type 1 diabetes mellitus: systematic review and meta-analysis of observational molecular studies. BMJ. 2011;342:d35.
77. Kim KW, Horton JL, Pang CNI, Jain K, Leung P, Isaacs SR, et al. Higher abundance of enterovirus A species in the gut of children with islet autoimmunity. Scientific reports. 2019;9(1):1749-.
78. Lin HC, Wang CH, Tsai FJ, Hwang KP, Chen W, Lin CC, et al. Enterovirus infection is associated with an increased risk of childhood type 1 diabetes in Taiwan: a nationwide population-based cohort study. Diabetologia. 2015;58(1):79-86.
79. Yeung W-CG, Al-Shabeeb A, Pang CNI, Wilkins MR, Catteau J, Howard NJ, et al. Children With Islet Autoimmunity and Enterovirus Infection Demonstrate a Distinct Cytokine Profile. Diabetes. 2012;61(6):1500-8.
80. Oikarinen M, Tauriainen S, Oikarinen S, Honkanen T, Collin P, Rantala I, et al. Type 1 Diabetes Is Associated With Enterovirus Infection in Gut Mucosa. Diabetes. 2012;61(3):687-91.
81. Schneider DA, von Herrath MG. Potential viral pathogenic mechanism in human type 1 diabetes. Diabetologia. 2014;57(10):2009-18.
82. Helmrich SP, Ragland DR, Leung RW, Paffenbarger RS, Jr. Physical activity and reduced occurrence of non-insulin-dependent diabetes mellitus. N Engl J Med. 1991;325(3):147-52.
83. Lynch J, Helmrich SP, Lakka TA, Kaplan GA, Cohen RD, Salonen R, et al. Moderately intense physical activities and high levels of cardiorespiratory fitness reduce the risk of non-insulin-dependent diabetes mellitus in middle-aged men. Arch Intern Med. 1996;156(12):1307-14.
84. Hu FB, Manson JE, Stampfer MJ, Colditz G, Liu S, Solomon CG, et al. Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. N Engl J Med. 2001;345(11):790-7.
85. Willi C, Bodenmann P, Ghali WA, Faris PD, Cornuz J. Active smoking and the risk of type 2 diabetes: a systematic review and meta-analysis. JAMA. 2007;298(22):2654-64.
86. Ali O. Genetics of type 2 diabetes. World journal of diabetes. 2013;4(4):114-23.
87. Wu Y, Ding Y, Tanaka Y, Zhang W. Risk factors contributing to type 2 diabetes and recent advances in the treatment and prevention. International journal of medical sciences. 2014;11(11):1185-200.

88. Sung K-C, Jeong W-S, Wild SH, Byrne CD. Combined Influence of Insulin Resistance, Overweight/Obesity, and Fatty Liver as Risk Factors for Type 2 Diabetes. Diabetes Care. 2012;35(4):717-22.
89. Kahn SE, Hull RL, Utzschneider KM. Mechanisms linking obesity to insulin resistance and type 2 diabetes. Nature. 2006;444(7121):840-6.
90. Meisinger C, Doring A, Thorand B, Heier M, Lowel H. Body fat distribution and risk of type 2 diabetes in the general population: are there differences between men and women? The MONICA/KORA Augsburg cohort study. Am J Clin Nutr. 2006;84(3):483-9.
91. Tong Y, Lin Y, Zhang Y, Yang J, Zhang Y, Liu H, et al. Association between TCF7L2 gene polymorphisms and susceptibility to type 2 diabetes mellitus: a large Human Genome Epidemiology (HuGE) review and meta-analysis. BMC Med Genet. 2009;10:15.
92. Grant SF, Thorleifsson G, Reynisdottir I, Benediktsson R, Manolescu A, Sainz J, et al. Variant of transcription factor 7-like 2 (TCF7L2) gene confers risk of type 2 diabetes. Nat Genet. 2006;38(3):320-3.
93. Jin T. Current understanding and dispute on the function of the Wnt signaling pathway effector TCF7L2 in hepatic gluconeogenesis. Genes & diseases. 2015;3(1):48-55.
94. Adams JD, Vella A. What Can Diabetes-Associated Genetic Variation in TCF7L2 Teach Us About the Pathogenesis of Type 2 Diabetes? Metab Syndr Relat Disord. 2018;16(8):383-9.
95. Song Y, Niu T, Manson JE, Kwiatkowski DJ, Liu S. Are variants in the CAPN10 gene related to risk of type 2 diabetes? A quantitative assessment of population and family-based association studies. Am J Hum Genet. 2004;74(2):208-22.
96. Zhou X, Wang Y, Zhang Y, Gao P, Zhu D. Association of CAPN10 gene with insulin sensitivity, glucose tolerance and renal function in essential hypertensive patients. Clin Chim Acta. 2010;411(15-16):1126-31.
97. Elgart JF, Gonzalez L, Prestes M, Rucci E, Gagliardino JJ. Frequency of self-monitoring blood glucose and attainment of HbA1c target values. Acta Diabetol. 2016;53(1):57-62.
98. American Diabetes A. 6. Glycemic Targets. Diabetes Care. 2017;40(Suppl 1):S48-S56.
99. American Diabetes A. Foundations of Care and Comprehensive Medical Evaluation. Diabetes Care. 2016;39 Suppl 1:S23-35.
100. IDF. Diabetes Atlas sixth edition. International Diabetes Federation; 2013. Contract No.: September 27/2014.
101. WHO. Global report on Diabetes Geneva, Switzerland World Health organization 2016.
102. Diabetes Prevention Program Research G. The Diabetes Prevention Program (DPP): description of lifestyle intervention. Diabetes Care. 2002;25(12):2165-71.
103. Brown MT, JK B. Medication adherence: WHO cares? Mayo Clin Proc. 2011 86(3):304-14.
104. Tuomi T, Santoro N, Caprio S, Cai M, Weng J, Groop L. The many faces of diabetes: a disease with increasing heterogeneity. Lancet. 2014;383(9922):1084-94.
105. Girach A, Manner D, Porta M. Diabetic microvascular complications: can patients at risk be identified? A review. Int J Clin Pract. 2006;60(11):1471-83.
106. Avramopoulos I, Moulis A, Nikas N. Glycaemic control, treatment satisfaction and quality of life in type 2 diabetes patients in Greece: The PANORAMA study Greek results. World J Diabetes. 2015;6(1):208-16.
107. American Diabetes Association. Standards of medical care in diabetes—2013. Diabetes care. 2013;36(Supplement 1):S11-S66.
108. Beck J, Greenwood DA, Blanton L, Bollinger ST, Butcher MK, Condon JE, et al. 2017 National Standards for Diabetes Self-Management Education and Support. Diabetes Care. 2017;40(10):1409-19.

109. Kebede MM, Zeeb H, Peters M, Heise TL, Pischke CR. Effectiveness of Digital Interventions for Improving Glycemic Control in Persons with Poorly Controlled Type 2 Diabetes: A Systematic Review, Meta-analysis, and Meta-regression Analysis. Diabetes Technol Ther. 2018.
110. American Diabetes Association. Standards of Medical Care in Diabetes—2018 Abridged for Primary Care Providers. Clinical Diabetes. 2018;36(1):14-37.
111. Tomky D, Cypress M, Dang D, Maryniuk M, Peyrot M, Mensing C. AADE7 Self-Care Behaviors. Diabetes Educ. 2008;34(3):445-9.
112. DiMatteo MR. The physician-patient relationship: effects on the quality of health care. Clin Obstet Gynecol. 1994;37(1):149-61.
113. Lorig KR, Sobel DS, Stewart AL, Brown BW, Jr., Bandura A, Ritter P, et al. Evidence suggesting that a chronic disease self-management program can improve health status while reducing hospitalization: a randomized trial. Med Care. 1999;37(1):5-14.
114. Sherbourne CD, Hays RD, Ordway L, DiMatteo MR, Kravitz RL. Antecedents of adherence to medical recommendations: results from the Medical Outcomes Study. J Behav Med. 1992;15(5):447-68.
115. Heisler M, Bouknight RR, Hayward RA, Smith DM, Kerr EA. The relative importance of physician communication, participatory decision making, and patient understanding in diabetes self-management. Journal of general internal medicine. 2002;17(4):243-52.
116. Holman H, Lorig K. Patients as partners in managing chronic disease. Partnership is a prerequisite for effective and efficient health care. BMJ. 2000;320(7234):526-7.
117. Von Korff M, Gruman J, Schaefer J, Curry SJ, Wagner EH. Collaborative management of chronic illness. Ann Intern Med. 1997;127(12):1097-102.
118. Stellefson M, Dipnarine K, Stopka C. The chronic care model and diabetes management in US primary care settings: a systematic review. Preventing chronic disease. 2013;10:E26-E.
119. FORTMANN AL, PRECIADO JL, WALKER C, MORRISEY R, BARGER K, MILLS D, et al. Effects of a Primary Care–Based Chronic Care Model on Diabetes Self-Management, Diabetes Distress, and Health Care Experience. Diabetes. 2018;67(Supplement 1):659-P.
120. Wagner EH. Chronic disease management: what will it take to improve care for chronic illness? Effective clinical practice: ECP. 1998;1(1):2.
121. Georgeff M. Digital technologies and chronic disease management. Aust Fam Physician. 2014;43(12):842-6.
122. Gee PM, Greenwood DA, Paterniti DA, Ward D, Miller LM. The eHealth Enhanced Chronic Care Model: a theory derivation approach. J Med Internet Res. 2015;17(4):e86.
123. Gee PM, Greenwood DA, Kim KK, Perez SL, Staggers N, DeVon HA. Exploration of the e-patient phenomenon in nursing informatics. Nurs Outlook. 2012;60(4):e9-16.
124. Lewis D, Leibrand S. Real-World Use of Open Source Artificial Pancreas Systems. J Diabetes Sci Technol. 2016;10(6):1411.
125. Meskó B, Drobni Z, Bényei É, Gergely B, Győrffy Z. Digital health is a cultural transformation of traditional healthcare. mHealth. 2017;3:38-.
126. Patel MS, Asch DA, Volpp KG. Wearable Devices as Facilitators, Not Drivers, of Health Behavior ChangeWearable Devices and Health Behavior ChangeWearable Devices and Health Behavior Change. JAMA. 2015;313(5):459-60.
127. Osborn CY, Mayberry LS, Mulvaney SA, Hess R. Patient web portals to improve diabetes outcomes: a systematic review. Current diabetes reports. 2010;10(6):422-35.
128. Malinda Peeples, Deborah Greenwood, Perry M Gee. Technology-Enabled Diabetes Self-Management Education & Support. Diabetes Technology Meeting; Bethesda, USANov 2-4, 2017.
129. Burke SD, Sherr D, Lipman RD. Partnering with diabetes educators to improve patient outcomes. Diabetes, metabolic syndrome and obesity : targets and therapy. 2014;7:45-53.

130. Captieux M, Pearce G, Parke HL, Epiphaniou E, Wild S, Taylor SJC, et al. Supported self-management for people with type 2 diabetes: a meta-review of quantitative systematic reviews. BMJ Open. 2018;8(12):e024262.
131. Enwald HP, Huotari ML. Preventing the obesity epidemic by second generation tailored health communication: an interdisciplinary review. J Med Internet Res. 2010;12(2):e24.
132. Noar SM, Benac CN, Harris MS. Does tailoring matter? Meta-analytic review of tailored print health behavior change interventions. Psychol Bull. 2007;133(4):673-93.
133. Lustria ML, Cortese J, Noar SM, Glueckauf RL. Computer-tailored health interventions delivered over the Web: review and analysis of key components. Patient Educ Couns. 2009;74(2):156-73.
134. Nuti L, Turkcan A, Lawley MA, Zhang L, Sands L, McComb S. The impact of interventions on appointment and clinical outcomes for individuals with diabetes: a systematic review. BMC health services research. 2015;15:355.
135. Ekman I, Swedberg K, Taft C, Lindseth A, Norberg A, Brink E, et al. Person-centered care--ready for prime time. Eur J Cardiovasc Nurs. 2011;10(4):248-51.
136. Lim S, Kang SM, Kim KM, Moon JH, Choi SH, Hwang H, et al. Multifactorial intervention in diabetes care using real-time monitoring and tailored feedback in type 2 diabetes. Acta Diabetol. 2016;53(2):189-98.
137. Kang SM, Kim MJ, Ahn HY, Yoon JW, Moon MK, Jung HS, et al. Ubiquitous healthcare service has the persistent benefit on glycemic control and body weight in older adults with diabetes. Diabetes care. 2012;35(3):e19-e.
138. Lim S, Kang SM, Shin H, Lee HJ, Won Yoon J, Yu SH, et al. Improved glycemic control without hypoglycemia in elderly diabetic patients using the ubiquitous healthcare service, a new medical information system. Diabetes care. 2011;34(2):308-13.
139. Greenwood DA, Gee PM, Fatkin KJ, Peeples M. A Systematic Review of Reviews Evaluating Technology-Enabled Diabetes Self-Management Education and Support. J Diabetes Sci Technol. 2017;11(5):1015-27.
140. Jimison H, Gorman P, Woods S, Nygren P, Walker M, Norris S, et al. Barriers and drivers of health information technology use for the elderly, chronically ill, and underserved. Evid Rep Technol Assess (Full Rep). 2008(175):1-1422.
141. Greenwood DA, Gee PM, Fatkin KJ, Peeples M. A Systematic Review of Reviews Evaluating Technology-Enabled Diabetes Self-Management Education and Support. Journal of diabetes science and technology. 2017;11(5):1015-27.
142. Peterson A. Improving type 1 diabetes management with mobile tools: a systematic review. J Diabetes Sci Technol. 2014;8(4):859-64.
143. Greenwood DA, Young HM, Quinn CC. Telehealth Remote Monitoring Systematic Review: Structured Self-monitoring of Blood Glucose and Impact on A1C. J Diabetes Sci Technol. 2014;8(2):378-89.
144. Kreuter MW, Strecher VJ, Glassman B. One size does not fit all: the case for tailoring print materials. Annals of behavioral medicine. 1999;21(4):276.
145. Mauseth R, Hirsch IB, Bollyky J, Kircher R, Matheson D, Sanda S, et al. Use of a "fuzzy logic" controller in a closed-loop artificial pancreas. Diabetes Technol Ther. 2013;15(8):628-33.
146. Contreras I, Vehi J. Artificial Intelligence for Diabetes Management and Decision Support: Literature Review. Journal of medical Internet research. 2018;20(5):e10775-e.
147. Alfian G, Syafrudin M, Ijaz MF, Syaekhoni MA, Fitriyani NL, Rhee J. A Personalized Healthcare Monitoring System for Diabetic Patients by Utilizing BLE-Based Sensors and Real-Time Data Processing. Sensors (Basel). 2018;18(7).
148. Gia TN, Ali M, Dhaou IB, Rahmani AM, Westerlund T, Liljeberg P, et al. IoT-based continuous glucose monitoring system: A feasibility study. Procedia Computer Science. 2017;109:327-34.

149. Chen L, Chuang LM, Chang CH, Wang CS, Wang IC, Chung Y, et al. Evaluating self-management behaviors of diabetic patients in a telehealthcare program: longitudinal study over 18 months. J Med Internet Res. 2013;15(12):e266.
150. Heitkemper EM, Mamykina L, Travers J, Smaldone A. Do health information technology self-management interventions improve glycemic control in medically underserved adults with diabetes? A systematic review and meta-analysis. J Am Med Inform Assoc. 2017;24(5):1024-35.
151. Farmer A, Gibson OJ, Tarassenko L, Neil A. A systematic review of telemedicine interventions to support blood glucose self-monitoring in diabetes. Diabet Med. 2005;22(10):1372-8.
152. Baron J, McBain H, Newman S. The impact of mobile monitoring technologies on glycosylated hemoglobin in diabetes: a systematic review. J Diabetes Sci Technol. 2012;6(5):1185-96.
153. Heintzman ND. A Digital Ecosystem of Diabetes Data and Technology: Services, Systems, and Tools Enabled by Wearables, Sensors, and Apps. J Diabetes Sci Technol. 2015;10(1):35-41.
154. Kaufman N, Khurana I. Using Digital Health Technology to Prevent and Treat Diabetes. Diabetes Technology & Therapeutics. 2016;18(Suppl 1):S-56-S-68.
155. Johnson C, Feenan K, Setliff G, Pereira K, Hassell N, Beresford HF, et al. Building a Virtual Environment for Diabetes Self-Management Education and Support. International journal of virtual communities and social networking. 2013;5(3):111359.
156. Neborachko M, Pkhakadze A, Vlasenko I. Current trends of digital solutions for diabetes management. Diabetes Metab Syndr. 2018.
157. R2G. mHealth Economics 2017 – Current Status and Future Trends in Mobile Health berlin, Germany2017 [Available from: https://research2guidance.com/product/mhealth-economics-2017-current-status-and-future-trends-in-mobile-health/.
158. Ralf-Gordon Jahns. The addressable market for diabetes apps in 2016 has increased to 135.5M potential app users (diagnosed diabetics), out of which 4.1M are active users Berlin, Germany: Research 2 Guidance(R2G); 2016 [Available from: https://research2guidance.com/the-addressable-market-for-diabetes-apps-in-2016-has-increased-to-135-5m-potential-app-users-diagnosed-diabetics-out-of-which-4-1m-are-active-users/.
159. R2G. Diabetes App Market Report 2016-2021 Berlin, Germany: Research 2 Guidance(R2G); 2016 [Available from: https://research2guidance.com/the-addressable-market-for-diabetes-apps-in-2016-has-increased-to-135-5m-potential-app-users-diagnosed-diabetics-out-of-which-4-1m-are-active-users/, Archive: https://archive.is/BrqAk.
160. R2G. Digital Diabetes Care Market 2018-2022: Ready To Take Off. Berlin, Germany; 2018.
161. Ben Hirschler. Big pharma, big data: why drugmakers want your health records. Reuters. 2018.
162. The Economist. The world's most valuable resource is no longer oil, but data. The Economist: New York, NY, USA. 2017.
163. Kovatchev B. Automated closed-loop control of diabetes: the artificial pancreas. Bioelectronic Medicine. 2018;4(1):14.
164. Cryer PE. Glycemic goals in diabetes: trade-off between glycemic control and iatrogenic hypoglycemia. Diabetes. 2014;63(7):2188-95.
165. Albisser AM, Leibel BS, Ewart TG, Davidovac Z, Botz CK, Zingg W. An artificial endocrine pancreas. Diabetes. 1974;23(5):389-96.
166. Kraegen EW, Campbell LV, Chia YO, Meler H, Lazarus L. Control of blood glucose in diabetics using an artificial pancreas. Aust N Z J Med. 1977;7(3):280-6.
167. Reiterer F, Reiter M, Del Re L, Bechmann Christensen M, Norgaard K. Analyzing the Potential of Advanced Insulin Dosing Strategies in Patients With Type 2 Diabetes: Results From a Hybrid In Silico Study. J Diabetes Sci Technol. 2018;12(5):1029-40.

168. Schliess F, Heise T, Benesch C, Mianowska B, Stegbauer C, Broge B, et al. Artificial Pancreas Systems for People With Type 2 Diabetes: Conception and Design of the European CLOSE Project. J Diabetes Sci Technol. 2019;13(2):261-7.
169. Farrington C. The artificial pancreas: challenges and opportunities. Lancet Diabetes Endocrinol. 2015;3(12):937.
170. Trevitt S, Simpson S, Wood A. Artificial Pancreas Device Systems for the Closed-Loop Control of Type 1 Diabetes: What Systems Are in Development? Journal of diabetes science and technology. 2015;10(3):714-23.
171. Kovatchev B, Tamborlane WV, Cefalu WT, Cobelli C. The Artificial Pancreas in 2016: A Digital Treatment Ecosystem for Diabetes. Diabetes Care. 2016;39(7):1123-6.
172. Cobelli C, Renard E, Kovatchev B. Artificial pancreas: past, present, future. Diabetes. 2011;60(11):2672-82.
173. Buckingham B, Cobry E, Clinton P, Gage V, Caswell K, Kunselman E, et al. Preventing hypoglycemia using predictive alarm algorithms and insulin pump suspension. Diabetes Technol Ther. 2009;11(2):93-7.
174. Krebs P, Duncan DT. Health App Use Among US Mobile Phone Owners: A National Survey. JMIR mHealth and uHealth. 2015;3(4):e101-e.
175. Kramer U, Zehner F. Diabetes-Management mit APPs: Derzeitige & zukünftige Nutzung, Einstellungen, Erfahrungen und Erwartungen von Betroffenen. Online-Befragung von Diabetikern. Aktuelle Ernährungsmedizin. 2016;41(03):V07.
176. Steven T, L. BJ, L. HV, Christel H, Elizabeth H-T, Frans P, et al. The Use of Mobile Applications Among Adolescents with Type 1 Diabetes: Results from Diabetes MILES Youth—Australia. Diabetes Technology & Therapeutics. 2016;18(12):813-9.
177. Boyle L, Grainger R, Hall RM, Krebs JD. Use of and Beliefs About Mobile Phone Apps for Diabetes Self-Management: Surveys of People in a Hospital Diabetes Clinic and Diabetes Health Professionals in New Zealand. JMIR Mhealth Uhealth. 2017;5(6):e85.
178. Research2Guidance. Diabetes App Market Report 2016-2021 Berlin, Germany: © Research2guidance Novemeber, 2016 [Available from: https://research2guidance.com/product/diabetes-app-market-report-2016-2021/, Last accessed date Oct 30/2017.
179. Nordfeldt S, Johansson C, Carlsson E, Hammersjo JA. Use of the Internet to search for information in type 1 diabetes children and adolescents: a cross-sectional study. Technol Health Care. 2005;13(1):67-74.
180. Lui CW, Col JR, Donald M, Dower J, Boyle FM. Health and social correlates of Internet use for diabetes information: findings from Australia's Living with Diabetes Study. Aust J Prim Health. 2015;21(3):327-33.
181. Shaw RJ, Johnson CM. Health Information Seeking and Social Media Use on the Internet among People with Diabetes. Online journal of public health informatics. 2011;3(1):10.5210/ojphi.v3i1.3561 ojphi.v3i1.
182. Hilliard ME, Sparling KM, Hitchcock J, Oser TK, Hood KK. The emerging diabetes online community. Current diabetes reviews. 2015;11(4):261-72.
183. Strom JL, Egede LE. The impact of social support on outcomes in adult patients with type 2 diabetes: a systematic review. Curr Diab Rep. 2012;12(6):769-81.
184. Labate C. The influence of social media on diabetes treatment and self-care. Diabetes Voice. 2013;58(1):14-5.
185. White K, Gebremariam A, Lewis D, Nordgren W, Wedding J, Pasek J, et al. Motivations for Participation in an Online Social Media Community for Diabetes. J Diabetes Sci Technol. 2018:1932296817749611.

186. Brady E, Segar J, Sanders C. Accessing support and empowerment online: The experiences of individuals with diabetes. Health Expect. 2017;20(5):1088-95.
187. Bove R, Secor E, Healy BC, Musallam A, Vaughan T, Glanz BI, et al. Evaluation of an online platform for multiple sclerosis research: patient description, validation of severity scale, and exploration of BMI effects on disease course. PLoS One. 2013;8(3):e59707.
188. Weitzman ER, Kelemen S, Quinn M, Eggleston EM, Mandl KD. Participatory surveillance of hypoglycemia and harms in an online social network. JAMA Intern Med. 2013;173(5):345-51.
189. Partridge SR, Gallagher P, Freeman B, Gallagher R. Facebook Groups for the Management of Chronic Diseases. J Med Internet Res. 2018;20(1):e21.
190. Abedin T, Al Mamun M, Lasker MAA, Ahmed SW, Shommu N, Rumana N, et al. Social Media as a Platform for Information About Diabetes Foot Care: A Study of Facebook Groups. Can J Diabetes. 2017;41(1):97-101.
191. Mike Nowak, Guillermo Spiller. Two Billion People Coming Together on Facebook: Facebook Newsroom; 2017 [updated October 21/2017. Available from: https://newsroom.fb.com/news/2017/06/two-billion-people-coming-together-on-facebook/.
192. NHS. Guidance on the use of social media to actively involve people in research July 2017 [Available from: http://www.invo.org.uk/wp-content/uploads/2017/07/Social-Media-Guide-web-2017.pdf.
193. Petrovski G, Zivkovic M, Stratrova SS. Social media and diabetes: can Facebook and Skype improve glucose control in patients with type 1 diabetes on pump therapy? One-year experience. Diabetes Care. 2015;38(4):e51-2.
194. Song M, Choe MA, Kim KS, Yi MS, Lee I, Kim J, et al. An evaluation of Web-based education as an alternative to group lectures for diabetes self-management. Nurs Health Sci. 2009;11(3):277-84.
195. Litchman ML, Edelman LS, Donaldson GW. Effect of Diabetes Online Community Engagement on Health Indicators: Cross-Sectional Study. JMIR Diabetes. 2018;3(2):e8.
196. Alanzi T. Role of Social Media in Diabetes Management in the Middle East Region: Systematic Review. J Med Internet Res. 2018;20(2):e58.
197. Cresci MK, Yarandi HN, Morrell RW. The Digital Divide and urban older adults. Comput Inform Nurs. 2010;28(2):88-94.
198. Wen KY, Kreps G, Zhu F, Miller S. Consumers' perceptions about and use of the internet for personal health records and health information exchange: analysis of the 2007 Health Information National Trends Survey. J Med Internet Res. 2010;12(4):e73.
199. Miller EA, West DM. Characteristics associated with use of public and private web sites as sources of health care information: results from a national survey. Med Care. 2007;45(3):245-51.
200. Sarkar U, Karter AJ, Liu JY, Adler NE, Nguyen R, Lopez A, et al. The literacy divide: health literacy and the use of an internet-based patient portal in an integrated health system-results from the diabetes study of northern California (DISTANCE). J Health Commun. 2010;15 Suppl 2:183-96.
201. Sarkar U, Karter AJ, Liu JY, Adler NE, Nguyen R, López A, et al. Social disparities in internet patient portal use in diabetes: evidence that the digital divide extends beyond access. Journal of the American Medical Informatics Association : JAMIA. 2011;18(3):318-21.
202. Perzynski AT, Roach MJ, Shick S, Callahan B, Gunzler D, Cebul R, et al. Patient portals and broadband internet inequality. Journal of the American Medical Informatics Association : JAMIA. 2017;24(5):927-32.
203. McAuley A. Digital health interventions: widening access or widening inequalities? Public Health. 2014;128(12):1118-20.
204. Poduval S, Ahmed S, Marston L, Hamilton F, Murray E. Crossing the Digital Divide in Online Self-Management Support: Analysis of Usage Data From HeLP-Diabetes. JMIR Diabetes. 2018;3(4):e10925.

205. López L, Green AR, Tan-McGrory A, King RS, Betancourt JR. Bridging the digital divide in health care: the role of health information technology in addressing racial and ethnic disparities. The Joint Commission Journal on Quality and Patient Safety. 2011;37(10):437-45.
206. Mayberry LS, Kripalani S, Rothman RL, Osborn CY. Bridging the digital divide in diabetes: family support and implications for health literacy. Diabetes technology & therapeutics. 2011;13(10):1005-12.
207. Sheon AR, Bolen SD, Callahan B, Shick S, Perzynski AT. Addressing Disparities in Diabetes Management Through Novel Approaches to Encourage Technology Adoption and Use. JMIR Diabetes. 2017;2(2):e16.
208. El-Gayar O, Timsina P, Nawar N, Eid W. Mobile applications for diabetes self-management: status and potential. J Diabetes Sci Technol. 2013;7(1):247-62.
209. Eng DS, Lee JM. The promise and peril of mobile health applications for diabetes and endocrinology. Pediatr Diabetes. 2013;14(4):231-8.
210. Chomutare T, Fernandez-Luque L, Arsand E, Hartvigsen G. Features of mobile diabetes applications: review of the literature and analysis of current applications compared against evidence-based guidelines. J Med Internet Res. 2011;13(3):e65.
211. Demidowich AP, Lu K, Tamler R, Bloomgarden Z. An evaluation of diabetes self-management applications for Android smartphones. J Telemed Telecare. 2012;18(4):235-8.
212. Health CfDaR. Mobile Medical Applications – Guidance for Industry and Food and Drug Administration Staff 2015 [Available from: http://www.fda.gov/downloads/MedicalDevices/.../UCM263366.pdf Last accessed November 02/ 2017.
213. Dolan B. FDA clears WellDoc for diabetes management: Mobilehealthnews 2010 [Last accessed date November 02/2017]. Available from: http://mobihealthnews.com/8539/fda-clears-welldoc-for-diabetes-management.
214. Veazie S WK, Gilbert J, Paynter R, Ivlev I, Eden K, Nussbaum K, Weiskopf N, Guise J-M, Helfand M.,. Mobile Applications for Self-Management of Diabetes. Rockville, MD: Agency for Healthcare Research and Quality; 2018. Contract No.: AHRQ Publication No. 18-EHC010-EF.
215. Huckvale K, Adomaviciute S, Prieto JT, Leow MK, Car J. Smartphone apps for calculating insulin dose: a systematic assessment. BMC Med. 2015;13:106.
216. Shuren J, Patel B, Gottlieb S. FDA Regulation of Mobile Medical Apps. JAMA. 2018.
217. Ristau RA, Yang J, White JR. Evaluation and Evolution of Diabetes Mobile Applications: Key Factors for Health Care Professionals Seeking to Guide Patients. Diabetes Spectrum. 2013;26(4):211-5.
218. Boudreaux ED, Waring ME, Hayes RB, Sadasivam RS, Mullen S, Pagoto S. Evaluating and selecting mobile health apps: strategies for healthcare providers and healthcare organizations. Translational behavioral medicine. 2014;4(4):363-71.
219. Avery L, Flynn D, van Wersch A, Sniehotta FF, Trenell MI. Changing physical activity behavior in type 2 diabetes: a systematic review and meta-analysis of behavioral interventions. Diabetes Care. 2012;35(12):2681-9.
220. Tricco AC, Ivers NM, Grimshaw JM, Moher D, Turner L, Galipeau J, et al. Effectiveness of quality improvement strategies on the management of diabetes: a systematic review and meta-analysis. Lancet. 2012;379(9833):2252-61.
221. Fortmann AL, Gallo LC, Garcia MI, Taleb M, Euyoque JA, Clark T, et al. Dulce Digital: An mHealth SMS-Based Intervention Improves Glycemic Control in Hispanics With Type 2 Diabetes. Diabetes Care. 2017;40(10):1349-55.
222. Egede LE, Williams JS, Voronca DC, Knapp RG, Fernandes JK. Randomized Controlled Trial of Technology-Assisted Case Management in Low Income Adults with Type 2 Diabetes. Diabetes Technol Ther. 2017;19(8):476-82.

223. Ralston JD, Hirsch IB, Hoath J, Mullen M, Cheadle A, Goldberg HI. Web-Based Collaborative Care for Type 2 Diabetes A pilot randomized trial. Diabetes Care. 2009;32(2):234-9.
224. Quinn CC, Shardell MD, Terrin ML, Barr EA, Ballew SH, Gruber-Baldini AL. Cluster-Randomized Trial of a Mobile Phone Personalized Behavioral Intervention for Blood Glucose Control. Diabetes Care. 2011;34(9):1934-42.
225. Quinn CC, Shardell MD, Terrin ML, Barr EA, Park D, Shaikh F, et al. Mobile Diabetes Intervention for Glycemic Control in 45-to 64-Year-Old Persons With Type 2 Diabetes. Journal of Applied Gerontology. 2016;35(2):227-43.
226. Hu Y, Wen X, Wang F, Yang D, Liu S, Li P, et al. Effect of telemedicine intervention on hypoglycaemia in diabetes patients: A systematic review and meta-analysis of randomised controlled trials. J Telemed Telecare. 2018:1357633X18776823.
227. Heisler M, Choi H, Palmisano G, Mase R, Richardson C, Fagerlin A, et al. Comparison of Community Health Worker-Led Diabetes Medication Decision-Making Support for Low-Income Latino and African American Adults With Diabetes Using E-Health Tools Versus Print Materials A Randomized, Controlled Trial. Annals of Internal Medicine. 2014;161(10):S13-S22.
228. Arora S, Peters AL, Burner E, Lam CN, Menchine M. Trial to examine text message-based mHealth in emergency department patients with diabetes (TExT-MED): a randomized controlled trial. Ann Emerg Med. 2014;63(6):745-54 e6.
229. Waki K, Fujita H, Uchimura Y, Omae K, Aramaki E, Kato S, et al. DialBetics: A Novel Smartphone-based Self-management Support System for Type 2 Diabetes Patients. J Diabetes Sci Technol. 2014;8(2):209-15.
230. Kirwan M, Vandelanotte C, Fenning A, Duncan MJ. Diabetes Self-Management Smartphone Application for Adults With Type 1 Diabetes: Randomized Controlled Trial. Journal of Medical Internet Research. 2013;15(11):e235.
231. Kumar S, Moseson H, Uppal J, Juusola JL. A Diabetes Mobile App With In-App Coaching From a Certified Diabetes Educator Reduces A1C for Individuals With Type 2 Diabetes. Diabetes Educ. 2018;44(3):226-36.
232. Liang X, Wang Q, Yang X, Cao J, Chen J, Mo X, et al. Effect of mobile phone intervention for diabetes on glycaemic control: a meta-analysis. Diabetic Medicine. 2011;28(4):455-63.
233. Cheng L, Sit JW, Choi KC, Chair SY, Li X, He XL. Effectiveness of Interactive Self-Management Interventions in Individuals With Poorly Controlled Type 2 Diabetes: A Meta-Analysis of Randomized Controlled Trials. Worldviews Evid Based Nurs. 2017;14(1):65-73.
234. Alharbi NS, Alsubki N, Jones S, Khunti K, Munro N, de Lusignan S. Impact of Information Technology-Based Interventions for Type 2 Diabetes Mellitus on Glycemic Control: A Systematic Review and Meta-Analysis. J Med Internet Res. 2016;18(11):e310.
235. Hou C, Carter B, Hewitt J, Francisa T, Mayor S. Do Mobile Phone Applications Improve Glycemic Control (HbA1c) in the Self-management of Diabetes? A Systematic Review, Meta-analysis, and GRADE of 14 Randomized Trials. Diabetes Care. 2016;39(11):2089-95.
236. Aminuddin HB, Jiao N, Jiang Y, Hong J, Wang W. Effectiveness of smartphone-based self-management interventions on self-efficacy, self-care activities, health-related quality of life and clinical outcomes in patients with type 2 diabetes: A systematic review and meta-analysis. International Journal of Nursing Studies. 2019.
237. Wu Y, Yao X, Vespasiani G, Nicolucci A, Dong Y, Kwong J, et al. Mobile App-Based Interventions to Support Diabetes Self-Management: A Systematic Review of Randomized Controlled Trials to Identify Functions Associated with Glycemic Efficacy. JMIR Mhealth Uhealth. 2017;5(3):e35.
238. Froisland DH, Arsand E, Skarderud F. Improving diabetes care for young people with type 1 diabetes through visual learning on mobile phones: mixed-methods study. J Med Internet Res. 2012;14(4):e111.

239. Kirwan M, Vandelanotte C, Fenning A, Duncan MJ. Diabetes self-management smartphone application for adults with type 1 diabetes: randomized controlled trial. J Med Internet Res. 2013;15(11):e235.
240. Williams JP, Schroeder D. Popular Glucose Tracking Apps and Use of mHealth by Latinos With Diabetes: Review. JMIR Mhealth Uhealth. 2015;3(3):e84.
241. Ryan EA, Holland J, Stroulia E, Bazelli B, Babwik SA, Li H, et al. Improved A1C Levels in Type 1 Diabetes with Smartphone App Use. Can J Diabetes. 2017;41(1):33-40.
242. Kebede MM, Liedtke TP, Möllers T, CR P. Characterizing Active Ingredients of eHealth Interventions Targeting Persons with Poorly Controlled Type 2 Diabetes Mellitus Using the Behavioral Change Technique Taxonomy. J Med Internet Res. 2017.
243. Michie S, Richardson M, Johnston M, Abraham C, Francis J, Hardeman W, et al. The behavior change technique taxonomy (v1) of 93 hierarchically clustered techniques: building an international consensus for the reporting of behavior change interventions. Ann Behav Med. 2013;46(1):81-95.
244. Ye Q, Khan U, Boren SA, Simoes EJ, Kim MS. An Analysis of Diabetes Mobile Applications Features Compared to AADE7: Addressing Self-Management Behaviors in People With Diabetes. J Diabetes Sci Technol. 2018;12(4):808-16.
245. Veazie S, Winchell K, Gilbert J, Paynter R, Ivlev I, Eden K, et al. Mobile Applications for Self-Management of Diabetes. Rockville MD2018 May.
246. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7):e1000097.
247. Kebede M, Christianson L, Khan Z, Heise TL, Pischke CR. Effectiveness of behavioral change techniques employed in eHealth interventions designed to improve glycemic control in persons with poorly controlled type 2 diabetes: a systematic review and meta-analysis protocol. Syst Rev. 2017;6(1):211.
248. American Diabetes A. Standards of medical care in diabetes--2014. Diabetes Care. 2014;37 Suppl 1:S14-80.
249. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343(d5928).
250. McKenzie JE, Herbison GP, Deeks JJ. Impact of analysing continuous outcomes using final values, change scores and analysis of covariance on the performance of meta-analytic methods: a simulation study. Res Synth Methods. 2016;7(4):371-86.
251. Fu R, Vandermeer BW, Shamliyan TA, O'Neil ME, Yazdi F, Fox SH, et al. Handling Continuous Outcomes in Quantitative Synthesis. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. AHRQ Methods for Effective Health Care. Rockville (MD)2008.
252. Morris SB, DeShon RP. Combining effect size estimates in meta-analysis with repeated measures and independent-groups designs. Psychol Methods. 2002;7(1):105-25.
253. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557-60.
254. Borenstein M, Hedges LV, Higgins JPT, Rothstein HR. Notes on Subgroup Analyses and Meta-Regression. Introduction to Meta-Analysis: John Wiley & Sons, Ltd; 2009. p. 205-12.
255. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315(7109):629-34.
256. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336(7650):924-6.
257. Schünemann H, Brożek J, Guyatt G, Oxman A. GRADE handbook for grading quality of evidence and strength of recommendations. Updated October 2013. [Available from: Available from http://gdt.guidelinedevelopment.org/app/handbook/handbook.html, Last accessed date 20/10/2017.

258. GDT G. GRADEpro Guideline Development Tool [Software]. McMaster University, 2015 (developed by Evidence Prime, Inc.). Available from gradepro.org. 2015 [
259. Riley RD, Kauser I, Bland M, Thijs L, Staessen JA, Wang J, et al. Meta-analysis of randomised trials with a continuous outcome according to baseline imbalance and availability of individual participant data. Stat Med. 2013;32(16):2747-66.
260. LimeSurvey: An Open Source survey tool [Internet]. LimeSurvey Project. 2012. Available from: http://www.limesurvey.org.
261. Toobert DJ, Hampson SE, Glasgow RE. The summary of diabetes self-care activities measure: results from 7 studies and a revised scale. Diabetes Care. 2000;23(7):943-50.
262. Kamradt M, Bozorgmehr K, Krisam J, Freund T, Kiel M, Qreini M, et al. Assessing self-management in patients with diabetes mellitus type 2 in Germany: validation of a German version of the Summary of Diabetes Self-Care Activities measure (SDSCA-G). Health Qual Life Outcomes. 2014;12:185.
263. American Diabetes Association. Standards of medical care in diabetes--2014. Diabetes Care. 2014;37 Suppl 1:S14-80.
264. American Diabetes Association. Glycemic Targets. Diabetes Care. 2017;40(Supplement 1):S48-S56.
265. Beck RW, Connor CG, Mullen DM, Wesley DM, Bergenstal RM. The Fallacy of Average: How Using HbA1c Alone to Assess Glycemic Control Can Be Misleading. Diabetes Care. 2017;40(8):994-9.
266. Pena EA, Slate EH. gvlma: Global validation of linear models assumptions. R package version. 2014;1(0.2).
267. Team R. RStudio: Integrated Development for R. Boston, MA: RStudio, Inc.; 2018.
268. Agboola S, Jethwani K, Lopez L, Searl M, O'Keefe S, Kvedar J. Text to Move: A Randomized Controlled Trial of a Text-Messaging Program to Improve Physical Activity Behaviors in Patients With Type 2 Diabetes Mellitus. Journal of Medical Internet Research. 2016;18(11).
269. Capozza K, Woolsey S, Georgsson M, Black J, Bello N, Lence C, et al. Going mobile with diabetes support: a randomized study of a text message-based personalized behavioral intervention for type 2 diabetes self-care. Diabetes Spectr. 2015;28(2):83-91.
270. Cho JH, Kim HS, Yoo SH, Jung CH, Lee WJ, Park CY, et al. An Internet-based health gateway device for interactive communication and automatic data uploading: Clinical efficacy for type 2 diabetes in a multi-centre trial. J Telemed Telecare. 2017;23(6):595-604.
271. Cho J-H, Kwon H-S, Kim H-S, Oh J-A, Yoon K-H. Effects on diabetes management of a health-care provider mediated, remote coaching system via a PDA-type glucometer and the Internet. Journal of Telemedicine and Telecare. 2011;17(7):365-70.
272. Dario C, Toffanin R, Calcaterra F, Saccavini C, Stafylas P, Mancin S, et al. Telemonitoring of Type 2 Diabetes Mellitus in Italy. Telemed J E Health. 2017;23(2):143-52.
273. Hansen CR, Perrild H, Koefoed BG, Zander M. Video consultations as add-on to standard care among patients with type 2 diabetes not responding to standard regimens: a randomized controlled trial. Eur J Endocrinol. 2017;176(6):727-36.
274. Holmen H, Torbjornsen A, Wahl AK, Jenum AK, Smastuen MC, Arsand E, et al. A Mobile Health Intervention for Self-Management and Lifestyle Change for Persons With Type 2 Diabetes, Part 2: One-Year Results From the Norwegian Randomized Controlled Trial RENEWING HEALTH. JMIR mHealth and uHealth. 2014;2(4):e57-e.
275. Khanna R, Stoddard PJ, Gonzales EN, Villagran-Flores M, Thomson J, Bayard P, et al. An automated telephone nutrition support system for Spanish-speaking patients with diabetes. J Diabetes Sci Technol. 2014;8(6):1115-20.
276. Kim HS, Sun C, Yang SJ, Sun L, Li F, Choi IY, et al. Randomized, Open-Label, Parallel Group Study to Evaluate the Effect of Internet-Based Glucose Management System on Subjects with Diabetes in China. Telemed J E Health. 2016;22(8):666-74.

277. Kleinman NJ, Shah A, Shah S, Phatak S, Viswanathan V. Improved Medication Adherence and Frequency of Blood Glucose Self-Testing using an m-Health Platform Versus Usual Care in a Multisite Randomized Clinical Trial Among People with Type 2 Diabetes in India. Telemed J E Health. 2017;23(9):733-40.
278. Liou JK, Soon MS, Chen CH, Huang TF, Chen YP, Yeh YP, et al. Shared Care Combined with Telecare Improves Glycemic Control of Diabetic Patients in a Rural Underserved Community. Telemedicine and E-Health. 2014;20(2):175-8.
279. Tang PC, Overhage JM, Chan AS, Brown NL, Aghighi B, Entwistle MP, et al. Online disease management of diabetes: engaging and motivating patients online with enhanced resources-diabetes (EMPOWER-D), a randomized controlled trial. J Am Med Inform Assoc. 2013;20(3):526-34.
280. Tildesley HD, Mazanderani AB, Chan JHM, Ross SA. Efficacy of A1C Reduction Using Internet Intervention in Patients with Type 2 Diabetes Treated with Insulin. Canadian Journal of Diabetes. 2011;35(3):250-3.
281. Torbjørnsen A, Jenum AK, Småstuen MC, Årsand E, Holmen H, Wahl AK, et al. A Low-Intensity Mobile Health Intervention With and Without Health Counseling for Persons With Type 2 Diabetes, Part 1: Baseline and Short-Term Results From a Randomized Controlled Trial in the Norwegian Part of RENEWING HEALTH. JMIR mHealth uHealth. 2014;2(4):e52.
282. Wakefield BJ, Koopman RJ, Keplinger LE, Bomar M, Bernt B, Johanning JL, et al. Effect of Home Telemonitoring on Glycemic and Blood Pressure Control in Primary Care Clinic Patients with Diabetes. Telemedicine and E-Health. 2014;20(3):199-205.
283. Wang G, Zhang Z, Feng Y, Sun L, Xiao X, Wang G, et al. Telemedicine in the Management of Type 2 Diabetes Mellitus. Am J Med Sci. 2017;353(1):1-5.
284. Welch G, Zagarins SE, Santiago-Kelly P, Rodriguez Z, Bursell SE, Rosal MC, et al. An internet-based diabetes management platform improves team care and outcomes in an urban Latino population. Diabetes Care. 2015;38(4):561-7.
285. Wild SH, Hanley J, Lewis SC, McKnight JA, McCloughan LB, Padfield PL, et al. Supported Telemonitoring and Glycemic Control in People with Type 2 Diabetes: The Telescot Diabetes Pragmatic Multicenter Randomized Controlled Trial. Plos Medicine. 2016;13(7).
286. Thompson SG, Higgins JP. How should meta-regression analyses be undertaken and interpreted? Stat Med. 2002;21(11):1559-73.
287. Liang X, Wang Q, Yang X, Cao J, Chen J, Mo X, et al. Effect of mobile phone intervention for diabetes on glycaemic control: a meta-analysis. Diabet Med. 2011;28(4):455-63.
288. Welch G, Garb J, Zagarins S, Lendel I, Gabbay RA. Nurse diabetes case management interventions and blood glucose control: results of a meta-analysis. Diabetes Res Clin Pract. 2010;88(1):1-6.
289. Health Quality O. Behavioural interventions for type 2 diabetes: an evidence-based analysis. Ont Health Technol Assess Ser. 2009;9(21):1-45.
290. Shah VN, Garg SK. Managing diabetes in the digital age. Clinical diabetes and endocrinology. 2015;1:16-.
291. Offringa R, Sheng T, Parks L, Clements M, Kerr D, Greenfield MS. Digital Diabetes Management Application Improves Glycemic Outcomes in People With Type 1 and Type 2 Diabetes. J Diabetes Sci Technol. 2018;12(3):701-8.
292. Orsama AL, Lahteenmaki J, Harno K, Kulju M, Wintergerst E, Schachner H, et al. Active assistance technology reduces glycosylated hemoglobin and weight in individuals with type 2 diabetes: results of a theory-based randomized trial. Diabetes Technol Ther. 2013;15(8):662-9.
293. Sheikh K, Bartz SK, Lyons SK, DeSalvo DJ. Diabetes Device Use and Glycemic Control among Youth with Type 1 Diabetes: A Single-Center, Cross-Sectional Study. Journal of Diabetes Research. 2018;2018:6.

294. Diabetes Canada Clinical Practice Guidelines Expert C, Berard LD, Siemens R, Woo V. Monitoring Glycemic Control. Can J Diabetes. 2018;42 Suppl 1:S47-S53.
295. Wallia A, Umpierrez GE, Nasraway SA, Klonoff DC. Round Table Discussion on Inpatient Use of Continuous Glucose Monitoring at the International Hospital Diabetes Meeting. Journal of Diabetes Science and Technology. 2016;10(5):1174-81.
296. Klonoff DC, Ahn D, Drincic A. Continuous glucose monitoring: A review of the technology and clinical use. Diabetes Res Clin Pract. 2017;133:178-92.
297. Zhou W, Chen M, Yuan J, Sun Y. Welltang - A smart phone-based diabetes management application - Improves blood glucose control in Chinese people with diabetes. Diabetes Res Clin Pract. 2016;116:105-10.
298. Kexin Yu, Shinyi Wu, Iris Chi, Hsinyi Hsiao, Peyjiuan Lee. The Impact of Diabetes Self-Management Mobile Technology Application Usage on Self-Care Behaviors Among Older Adults. Society for Social Work and Research 22nd Annual Conference - Achieving Equal Opportunity, Equity, and Justice; Washington DCJanuary 12, 2018.
299. Kim YJ, Rhee SY, Byun JK, Park SY, Hong SM, Chin SO, et al. A Smartphone Application Significantly Improved Diabetes Self-Care Activities with High User Satisfaction. Diabetes & Metabolism Journal. 2015;39(3):207-17.
300. Greenwood DA, Blozis SA, Young HM, Nesbitt TS, Quinn CC. Overcoming Clinical Inertia: A Randomized Clinical Trial of a Telehealth Remote Monitoring Intervention Using Paired Glucose Testing in Adults With Type 2 Diabetes. J Med Internet Res. 2015;17(7):e178.
301. Lee DY, Park J, Choi D, Ahn H-Y, Park S-W, Park C-Y. The effectiveness, reproducibility, and durability of tailored mobile coaching on diabetes management in policyholders: A randomized, controlled, open-label study. Scientific Reports. 2018;8:3642.
302. Forjuoh SN, Reis MD, Couchman GR, Ory MG. Improving diabetes self-care with a PDA in ambulatory care. Telemed J E Health. 2008;14(3):273-9.
303. Hernandez-Tejada MA, Campbell JA, Walker RJ, Smalls BL, Davis KS, Egede LE. Diabetes empowerment, medication adherence and self-care behaviors in adults with type 2 diabetes. Diabetes Technol Ther. 2012;14(7):630-4.
304. Michie S, Fixsen D, Grimshaw JM, Eccles MP. Specifying and reporting complex behaviour change interventions: the need for a scientific method. Implement Sci. 2009;4:40.
305. Johnston M, Johnston D, Wood CE, Hardeman W, Francis J, Michie S. Communication of behaviour change interventions: Can they be recognised from written descriptions? Psychology & Health. 2017:1-11.
306. Iyengar V, Wolf A, Brown A, Close K. Challenges in Diabetes Care: Can Digital Health Help Address Them? Clinical diabetes : a publication of the American Diabetes Association. 2016;34(3):133-41.
307. TheGurdian. Grindr shared information about users' HIV status with third parties TheGurdian; 2018 [Available from: Archived version: https://archive.is/CLWPE.
308. Steve Turner. 2019 Data Breaches - The Wors So Far: IdentityForce; 2019 [Available from: Source: https://www.identityforce.com/blog/2019-data-breaches Archive : https://archive.is/4BjAV.
309. Britton KE, Britton-Colonnese JD. Privacy and Security Issues Surrounding the Protection of Data Generated by Continuous Glucose Monitors. J Diabetes Sci Technol. 2017;11(2):216-9.
310. Blenner SR, Kollmer M, Rouse AJ, Daneshvar N, Williams C, Andrews LB. Privacy Policies of Android Diabetes Apps and Sharing of Health Information. JAMA. 2016;315(10):1051-2.
311. Privacy Code of Conduct on mobile health apps, (May 2018).
312. Jacques Rose K, Petrut C, L'Heveder R, de Sabata S. IDF Europe position on mobile applications in diabetes. Diabetes Res Clin Pract. 2017.
313. IDF. IDF Europe Position on Mobile Applications in Diabetes. Internation Diabetes Federation Europe; February 2017.

314. Klonoff DC, Kerr D. Overcoming Barriers to Adoption of Digital Health Tools for Diabetes. J Diabetes Sci Technol. 2018;12(1):3-6.
315. Brzan PP, Rotman E, Pajnkihar M, Klanjsek P. Mobile Applications for Control and Self Management of Diabetes: A Systematic Review. J Med Syst. 2016;40(9):210.
316. Kerr D, Axelrod C, Hoppe C. Patient Inputs for Mobile Health Systems for Type 1 Diabetes Care. Diabetes Technol Ther. 2017;19(4):201-2.
317. Siegel E. Fake Reviews in Google Play and Apple App Store 2014 [Available from: https://www.apptentive.com/blog/2014/05/27/fake-reviews-google-play-apple-app-store/, Last accessed date 04/10/2017.
318. BinDhim NF, Hawkey A, Trevena L. A systematic review of quality assessment methods for smartphone health apps. Telemed J E Health. 2015;21(2):97-104.
319. U.S. Department of Hea lth and Human Services Food and Drug Administration. Mobile Medical Applications Guidance for Industry and Food and Drug Administration Staff. In: Center for Devices and Radiological Health CfBEaR, editor. USA: FDA.
320. Norman CD, Skinner HA. eHealth Literacy: Essential Skills for Consumer Health in a Networked World. J Med Internet Res. 2006;8(2):e9.
321. Samerski S, Müller H, Hofreuter-Gätgens K. Refining and promoting digital health literacy for patients and organizations: The "TK-DiSK" study. European Journal of Public Health. 2018;28(suppl_4).
322. Del Giudice P, Bravo G, Poletto M, De Odorico A, Conte A, Brunelli L, et al. Correlation Between eHealth Literacy and Health Literacy Using the eHealth Literacy Scale and Real-Life Experiences in the Health Sector as a Proxy Measure of Functional Health Literacy: Cross-Sectional Web-Based Survey. J Med Internet Res. 2018;20(10):e281.
323. Neter E, Brainin E. eHealth literacy: extending the digital divide to the realm of health information. J Med Internet Res. 2012;14(1):e19.
324. Huyett L, Dassau E, Pinsker JE, Doyle FJ, 3rd, Kerr D. Minority groups and the artificial pancreas: who is (not) in line? Lancet Diabetes Endocrinol. 2016;4(11):880-1.
325. Baldwin JL, Singh H, Sittig DF, Giardina TD. Patient portals and health apps: Pitfalls, promises, and what one might learn from the other. Healthc (Amst). 2017;5(3):81-5.
326. National Academies of Sciences E, and Medicine 2016,. The Promises and Perils of Digital Strategies in Achieving Health Equity: Workshop Summary. Washington DC: The National Academies Press.
327. Sarkar U, Gourley GI, Lyles CR, Tieu L, Clarity C, Newmark L, et al. Usability of Commercially Available Mobile Applications for Diverse Patients. J Gen Intern Med. 2016;31(12):1417-26.
328. Eng DS, Lee JM. The promise and peril of mobile health applications for diabetes and endocrinology. Pediatric diabetes. 2013;14(4):231-8.
329. Gao W, Emaminejad S, Nyein HYY, Challa S, Chen K, Peck A, et al. Fully integrated wearable sensor arrays for multiplexed in situ perspiration analysis. Nature. 2016;529(7587):509-14.
330. Haghi M, Thurow K, Stoll R. Wearable Devices in Medical Internet of Things: Scientific Research and Commercially Available Devices. Healthcare informatics research. 2017;23(1):4-15.
331. Dunn J, Runge R, Snyder M. Wearables and the medical revolution. Per Med. 2018;15(5):429-48.
332. Farrington C. Wearable technologies and stigma in diabetes: the role of medical aesthetics. Lancet Diabetes Endocrinol. 2016;4(7):566.
333. Sprogis SK, Currey J, Considine J. Patient acceptability of wearable vital sign monitoring technologies in the acute care setting: a systematic review. J Clin Nurs. 2019.
334. Schwartz HA, Eichstaedt JC, Kern ML, Dziurzynski L, Ramones SM, Agrawal M, et al. Personality, gender, and age in the language of social media: the open-vocabulary approach. PLoS One. 2013;8(9):e73791.

335. Kosinski M, Stillwell D, Graepel T. Private traits and attributes are predictable from digital records of human behavior. Proc Natl Acad Sci U S A. 2013;110(15):5802-5.
336. Youyou W, Kosinski M, Stillwell D. Computer-based personality judgments are more accurate than those made by humans. Proc Natl Acad Sci U S A. 2015;112(4):1036-40.
337. Onnela J-P, Rauch SL. Harnessing Smartphone-Based Digital Phenotyping to Enhance Behavioral and Mental Health. Neuropsychopharmacology. 2016;41(7):1691-6.
338. Matthew Rosenberg, Nicholas Confessore, Carole Cadwalladr. How Trump Consultants Exploited the Facebook Data of Millions. The Newyork Times2018.
339. Dunn AG, Mandl KD, Coiera E. Social media interventions for precision public health: promises and risks. npj Digital Medicine. 2018;1(1):47.
340. Matz SC, Kosinski M, Nave G, Stillwell DJ. Psychological targeting as an effective approach to digital mass persuasion. Proceedings of the National Academy of Sciences. 2017;114(48):12714-9.
341. Choi I, Milne DN, Glozier N, Peters D, Harvey SB, Calvo RA. Using different Facebook advertisements to recruit men for an online mental health study: Engagement and selection bias. Internet Interventions. 2017;8:27-34.
342. Batterham PJ. Recruitment of mental health survey participants using Internet advertising: content, characteristics and cost effectiveness. Int J Methods Psychiatr Res. 2014;23(2):184-91.
343. Nash EL, Gilroy D, Srikusalanukul W, Abhayaratna WP, Stanton T, Mitchell G, et al. Facebook advertising for participant recruitment into a blood pressure clinical trial. J Hypertens. 2017;35(12):2527-31.
344. Facebook, cartographer A New Center for Crisis Response on FacebookSept 14, 2017.
345. Wendling C, Radisch J, Jacobzone S. The Use of Social Media in Risk and Crisis Communication. 2013.
346. Iacobucci G. Vaccination: “fake news” on social media may be harming UK uptake, report warns. BMJ. 2019;364:l365.
347. Donzelli G, Palomba G, Federigi I, Aquino F, Cioni L, Verani M, et al. Misinformation on vaccination: A quantitative analysis of YouTube videos. Human Vaccines & Immunotherapeutics. 2018;14(7):1654-9.
348. Schmidt AL, Zollo F, Scala A, Betsch C, Quattrociocchi W. Polarization of the vaccination debate on Facebook. Vaccine. 2018;36(25):3606-12.
349. Carrieri V., Madio L., Principe F. Vaccine Hesitancy and Fake News: Quasi-experimental Evidence from Italy. Health, Econometrics and Data Group (HEDG) Working Papers. 2019;19(03).
350. Dunlop S, Freeman B, Jones SC. Marketing to youth in the digital age: The promotion of unhealthy products and health promoting behaviours on social media. Media and Communication. 2016;4(3):35-49.
351. Freeman B, Chapman S. British American Tobacco on Facebook: undermining article 13 of the global World Health Organization Framework Convention on Tobacco Control. Tobacco Control. 2010;19(3):e1-e9.
352. Montgomery KC, Chester J. Interactive food and beverage marketing: targeting adolescents in the digital age. J Adolesc Health. 2009;45(3 Suppl):S18-29.
353. Moore ES, Rideout VJ. The Online Marketing of Food to Children: Is It Just Fun and Games? Journal of Public Policy & Marketing. 2007;26(2):202-20.
354. Buchanan L, Kelly B, Yeatman H, Kariippanon K. The Effects of Digital Marketing of Unhealthy Commodities on Young People: A Systematic Review. Nutrients. 2018;10(2):148.
355. Haidich AB. Meta-analysis in medical research. Hippokratia. 2010;14(Suppl 1):29-37.
356. Biondi-Zoccai G, Landoni G, Modena MG. A journey into clinical evidence: from case reports to mixed treatment comparisons. HSR Proc Intensive Care Cardiovasc Anesth. 2011;3(2):93-6.
357. Greco T, Zangrillo A, Biondi-Zoccai G, Landoni G. Meta-analysis: pitfalls and hints. Heart Lung Vessel. 2013;5(4):219-25.

358. William F. Rosenberger, John M. Lachin. Randomization in Clinical Trials: Theory and Practice. New York: Wiley; 2005.

10. APPENDIX

10.1. Appendix A: Research articles

I. **Kebede MM**, Zeeb H, Peters M, Heise TL, Pischke CR. Effectiveness of digital interventions for improving glycemic control in persons with poorly controlled type 2 diabetes: a systematic review, meta-analysis, and meta-regression analysis. Diabetes Technology & Therapeutics, 20(2), 10.1089/dia.2018.0216

II. **Kebede MM,** Peters M, Heise TL, Pischke CR. Comparison of three meta-analytic methods using data from digital interventions on type 2 diabetes. Diabetes Metab Syndr Obes 2019;12:59-73, 10.2147/DMSO.S180106

III. **Kebede MM,** Schuett C, Pischke CR. The role of continuous glucose monitoring, diabetes smartphone applications, and self-care behavior in glycemic control: results of a multi-national online survey. J Clin Med 2019;8(1), 10.3390/jcm8010109

IV. **Kebede MM**, Pischke CR. Popular diabetes apps and the impact of diabetes app use on self-care behaviour: a survey among the digital community of persons with diabetes on social media. Front Endocrinol (Lausanne) 2019;10:135, 10.3389/fendo.2019.00135

STUDY I

DIABETES TECHNOLOGY & THERAPEUTICS
Volume 20, Number 11, 2018

DOI: 10.1089/dia.2018.0216

META-ANALYSIS

Effectiveness of Digital Interventions for Improving Glycemic Control in Persons with Poorly Controlled Type 2 Diabetes: A Systematic Review, Meta-analysis, and Meta-regression Analysis

Mihiretu M. Kebede, BSc, MPH,[1–3] Hajo Zeeb, MD, MSc, Professor,[1,2] Manuela Peters, BS, MSc,[1,2] Thomas L. Heise, BSc, MSc,[1,2] and Claudia R Pischke, BSc, MSc, PhD[1,4]

Abstract

Background: Digital interventions may assist patients with type 2 diabetes in improving glycemic control. We aimed to synthesize effect sizes of digital interventions on glycated hemoglobin (HbA1c) levels and to identify effective features of digital interventions targeting patients with poorly controlled type 2 diabetes.
Materials and Methods: MEDLINE, ISI Web of Science, and PsycINFO were searched for randomized controlled trials (RCTs) comparing the effects of digital interventions with usual care. Two reviewers independently assessed studies for eligibility and determined study quality, using the Cochrane Risk of Bias Assessment Tool. The Behavioral Change Technique Taxonomy V1 (BCTTv1) was used to identify BCTs used in interventions. Mean HbA1c differences were pooled using analysis of covariance to adjust for baseline differences and pre–post correlations. To examine effective intervention features and to evaluate differences in effect sizes across groups, meta-regression and subgroup analyses were performed.
Results: Twenty-three arms of 21 RCTs were included in the meta-analysis ($n = 3787$ patients, 52.6% in intervention arms). The mean HbA1c baseline differences ranged from –0.2% to 0.64%. The pooled mean HbA1c change was statistically significant (–0.39 {95% CI: [–0.51 to –0.26]} with substantial heterogeneity [I^2 statistic, 80.8%]) and a significant HbA1c reduction was noted for web-based interventions. A baseline HbA1c level above 7.5%, $\beta = -0.44$ (95% CI: [–0.81 to –0.06]), the BCTs ''problem solving,'' $\beta = -1.30$ (95% CI: [–2.05 to –0.54]), and ''self-monitoring outcomes of behavior,'' $\beta = -1.21$ (95% CI: [–1.95 to –0.46]) were significantly associated with reduced HbA1c levels.
Conclusions: Digital interventions appear effective for reducing HbA1c levels in patients with poorly controlled type 2 diabetes.

Keywords: e-Health intervention, Poorly controlled type 2 diabetes, HbA1c.

[1]Applied Health Intervention Research, Department of Prevention and Evaluation, Leibniz Institute for Prevention Research and Epidemiology–BIPS, Bremen, Germany.
[2]University of Bremen, Health Sciences, Department Public Health, Bremen, Germany.
[3]Institute of Public Health, University of Gondar College of Medicine and Health Sciences, Gondar, Ethiopia.
[4]Institute of Medical Sociology, Centre for Health and Society, Medical Faculty, Heinrich Heine University Düsseldorf, Düsseldorf, Germany.
This article was presented at the 78th ADA conference in Orlando as a poster presentation. The abstract of this article is published in diabetes journal http://diabetes.diabetesjournals.org/content/67/Supplement_1/840-P

Background

In 2017, more than 425 million adults were living with diabetes. This number is estimated to reach 629 million cases by 2045. More than 90% of this burden is due to type 2 diabetes.[1–3] Type 2 diabetes is the second highest cause for obesity-related deaths, accounting for more than half a million deaths and 30.4 million disability-adjusted life years in 2015.[4]

Type 2 diabetes is a multifactorial metabolic disease linked with obesity, dietary behavior, and a sedentary lifestyle.[5,6] A recent trial conducted in the United Kingdom demonstrated remission to a nondiabetic state after changes in dietary behavior and significant weight loss in persons with type 2 diabetes.[7] Hence, type 2 diabetes has recently been recognized as a potentially reversible metabolic state.[8] However, the likelihood of a remission of the reversed state of the disease is still unclear. In addition, remission is less likely among persons with longer duration of type 2 diabetes.[7,9] Therefore, regular monitoring of blood glucose levels, as well as an optimal adherence to glucose-lowering medications, a healthy diet, and moderate-to-high-intensity physical activity (PA) remain important factors contributing to the prevention of macrovascular and microvascular complications of the disease.[10–13]

Failure to strictly adhere to medication, nutrition, and PA recommendations leads to hyper- and hypoglycemic levels[12,14,15] that worsen quality of life and increase the risk of mortality.[16,17] Ideally, tight glycemic control or maintaining glycated hemoglobin (HbA1c) levels between 5.7% and 6.5% is generally recommended to prevent complications and comorbidities. To help patients achieve tight glycemic control targets of HbA1c levels of 5.7%–6.5%,[18] the American Association of Diabetic Educators (AADE) identified seven self-care behaviors (AADE7). Healthy eating, being physically active, monitoring, taking medication, problem solving, reducing risks, and healthy coping are the listed AADE7 self-care behaviors to guide diabetes education and care.[19] The uptake of these self-care behaviors among patients can be strongly supported with digital interventions, such as text messaging and web-based and telemedicine interventions.[20–23] By integrating digital technologies, e-health interventions help patients change their behavior toward regular monitoring of blood glucose levels, regular PA, a balanced diet, and other healthy lifestyle behaviors.[23–29] Hence, diabetes-related behavioral and clinical outcomes can be improved through active engagement in e- and m-health interventions. In general, diabetes care is increasingly incorporating interactive digital e- and m-health interventions because the use of modern information and communication technologies comes with many advantages regarding the self-monitoring of the disease and self-regulation of lifestyle behaviors.[30–34]

HbA1c remains a surrogate marker of diabetes interventions after Stratton et al. demonstrated an independent log linear relationship between HbA1c- and diabetes-related complications.[26] Furthermore, recent reports suggest that interventions leading to a reduction in HbA1c of at least 0.3% among persons with type 2 diabetes are considered clinically significant.[24,29] Clinically significant reductions of HbA1c were achieved from various randomized controlled trials (RCTs) of digital interventions.[33–37] Findings of several systematic reviews and meta-analyses on the effectiveness of digital interventions have also reported clinically significant HbA1c reductions, with varying level of effectiveness. For example, HbA1c reductions of −0.63%, −0.5%, −0.43% have been documented for videoconferencing,[25] mobile-based interventions,[31] and interactive self-management interventions,[28] respectively.

Meta-analysis results also suggest that the changes in HbA1c levels were different across duration and mode of interventions.[21,32] A review on the effects of health information technology self-management interventions reported an aggregated HbA1c reduction of 0.36% at 6 and 0.27% at 12 months.[21] In another review, all information technology-based interventions led to a reduction of 0.33%.[38] Participation in telemedicine, telecare, teleconsultation, and videoconferencing interventions was associated with HbA1c reductions of 0.31%,[39] 0.37%,[40] 0.54%,[41] and 0.63%,[25] respectively. Furthermore, meta-analysis results suggest a reduction of HbA1c when participating in interactive self-management interventions by 0.43%,[28] whereas participation in computer-based interventions was only associated with a reduction of 0.2%[32] and mobile-based interventions with a reduction of 0.5%.[31] Two different reviews on the effects of mobile short message services reported an HbA1c level reduction of 0.22%[30] and 0.60%.[42] It can be argued that these HbA1c changes are small[32] but, in the long run, these small changes can help patients attain the target HbA1c level of less than 6.5% and thus prevent the risk of microvascular complications and diabetic-related deaths.[43,44]

One limitation of the existing evidence of systematic reviews on the topic is the disregard of the influence of baseline HbA1c, the mean baseline HbA1c difference between control and intervention groups, and the pre–post correlation in the overall estimates of effect sizes for interventions. Results of subgroup and meta-regression analysis indicate that baseline HbA1c is associated with overall pooled effect sizes estimated using meta-analysis.[31,45] Available methodological literature on meta-analysis of a continuous outcome emphasizes the importance of accounting for baseline imbalance and pre–post correlations to determine precise and unbiased effect size estimates of a continuous outcome, such as HbA1c. However, the methodology to account for baseline imbalance and pre–post correlations is complex in the absence of individual participant data (IPD) and necessary summary data from published RCTs. Nevertheless, if relevant summary data are reported in RCTs, it is recommended to use analysis of covariance (ANCOVA) rather than change scores and final value effect size estimators.[46–49]

Importantly, e-health interventions targeting persons with type 2 diabetes are generally multicomponent behavioral interventions and complex in nature.[50] One way to simplify the complexity of reporting and analyzing the effect size of such interventions is by describing the active ingredients of the interventions by using the Behavioral Change Technique Taxonomy V1 (BCTTv1)[51,52] and/or the AADE7 self-care behaviors.[19] The AADE7 self-care behaviors provide an evidence-based framework to identify contents of diabetes self-management interventions.[19] The effectiveness of the active ingredients for reducing HbA1c levels in patients with poorly controlled type 2 diabetes has, to our knowledge, not yet been investigated. The results of our previous scoping review suggested the need for a detailed investigation of the individual and combined effects of BCTs on HbA1c and their

role as mediators in Hba1c change.[53] Therefore, this systematic review and meta-analysis aimed to synthesize the effectiveness of digital interventions and identify BCTs associated with reductions of HbA1c levels.

Materials and Methods

The design, conduct, and reporting of this systematic review was guided by the Preferred Reporting Items for Systematic review and Meta-analysis (PRISMA) 2015 guideline.[54] The protocol of this systematic review was registered a priori (PROSPERO Registration No. 42016049940). The full description of the protocol for this systematic review can be accessed elsewhere.[55]

Study inclusion criteria

Type of studies. Studies were included if (1) the design of the studies examining intervention effects was an RCT, including multiple arms RCT; (2) patients in the intervention have documented poorly controlled type 2 diabetes defined by an HbA1c level of >7.0%; (3) interventions were technology based, such as m-health (mobile health) interventions, web-based interventions, interventions delivered through the use of a personal digital assistant, a tablet, a computer, the Internet, telemedicine, videoconferencing, telehealth, or other forms of e-health; (4) HbA1c was reported as an outcome; (5) the control group received usual care, standard care, or existing care, and (6) if the study results were published in English. We used the American Diabetes Association (ADA) definition to define poorly controlled type 2 diabetes. Hence, having an HbA1c value of greater than 7.0% was considered poorly controlled type 2 diabetes.[56] Studies examining interventions that targeted either persons with type 1 diabetes or both type 1 and 2, and those including control groups receiving interventions other than usual care, were excluded from the review.

Search strategy for identification of studies. Studies published up to June 30, 2017, were searched in MEDLINE via PubMed, ISI Web of Science via Thomson Reuters, and PsycINFO via OvidSP using a comprehensive search strategy. The search terms suiting the different databases were created in collaboration with a research librarian. MeSH terms, keywords, and Boolean operators were used to develop the search strategy. The search was first completed in June 7, 2016, and updated on June 30, 2017.

Article screening. Two authors (M.M.K. and M.P.) screened titles and abstracts, as well as full-texts independently. If the two authors could not reach consensus, a third author (C.R.P.) was consulted to resolve disagreement. Covidence, a web-based screening tool, was used to document the screening process.[57] Information regarding the search and screening process is displayed in Figure 1.

Data extraction process. Two authors extracted the following information: citation information (authors, titles, journals, year of publication), study location, study population (ethnicity, sex, age), study objectives, intervention type and delivery mode, AADE7 self-care behavior targeted, inclusion criteria, information on whether the intervention was guided by the use of behavioral science models or theories, individualization or tailoring of the interventions, and BCTs included in interventions. Moreover, sample size, intervention period, HbA1c values, and respective standard deviations (SDs), *P*-values, and 95% confidence intervals (CIs) were extracted for each study. The mean HbA1c change scores (SD), mean HbA1c difference (SD), type of statistical test (e.g., *t*-test, *z*-test), and data on intention-to-treat analysis (ITT) were collected for each study. If not reported in the articles, mean HbA1c change scores for both, control and intervention groups, were calculated for a particular time point (3, 4, 6, 8, 9, and 12 months). Based on the full description of the interventions in the articles reporting the study results or in study protocols, BCTs were identified and coded using the BCTTv1.[58]

Two authors (M.M.K. and T.L.H.) read the description of the interventions to collect data about the seven AADE7 self-care behaviors addressed in each intervention. Two reviewers (M.M.K. and C.R.P.) experienced in using the BCTTv1[58] coded the description of intervention contents independently and meetings were held to reach consensus on which BCTs were coded for each individual intervention.

Quality assessment. The Cochrane Risk of Bias Assessment Tool for randomized control trials[59] was used to assess the quality of the included studies. Two authors (M.M.K. and M.P.) independently assessed the risk of bias, resolving differences with consensus. Covidence was used to semi-automate the process.[57] Using this tool, seven domains of risk of bias can be identified: allocation concealment, sequence generation, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective outcome reporting, and other sources of bias. The terms low, high, or unclear risk of bias were used to label the quality of studies for each domain. The seventh domain, ''other sources of bias,'' was assessed following the recommendation by Fu et al. Hence, baseline balance of HbA1c levels between control and intervention groups, information on loss to follow-up, retention and attrition rates, and reported competing interests were considered.[46] Finally, the consensus quality ratings were exported to RevMan[60] to receive the final graphical representation of all risk of bias ratings.

Missing data. Missing data were obtained by contacting corresponding authors or computed based on the reported data. Using Excel functions, SD values, which were initially not reported for some of the studies, were calculated based on the reported 95% CIs, standard error (SE), or *P*-values.[46,61] Contacting corresponding author and computing missing SD values with reported data did not work for a study by Wakefield et al.[62] Therefore, this missing SD value was imputed using arithmetic means by following an existing methodological guideline.[46] For one study,[63] the mean and SD values were calculated based on the reported median and range using Hozo's formula.[64] The pre–post correlation values, both for control and intervention groups, were calculated based on formulas described in previous methodological studies and formulas by Fu et al.[46] and Morris and DeShon.[48]

Data syntheses and analysis. Simple analysis of final values, simple analysis of change scores, and ANCOVA effect size estimator are the main methods used to calculate

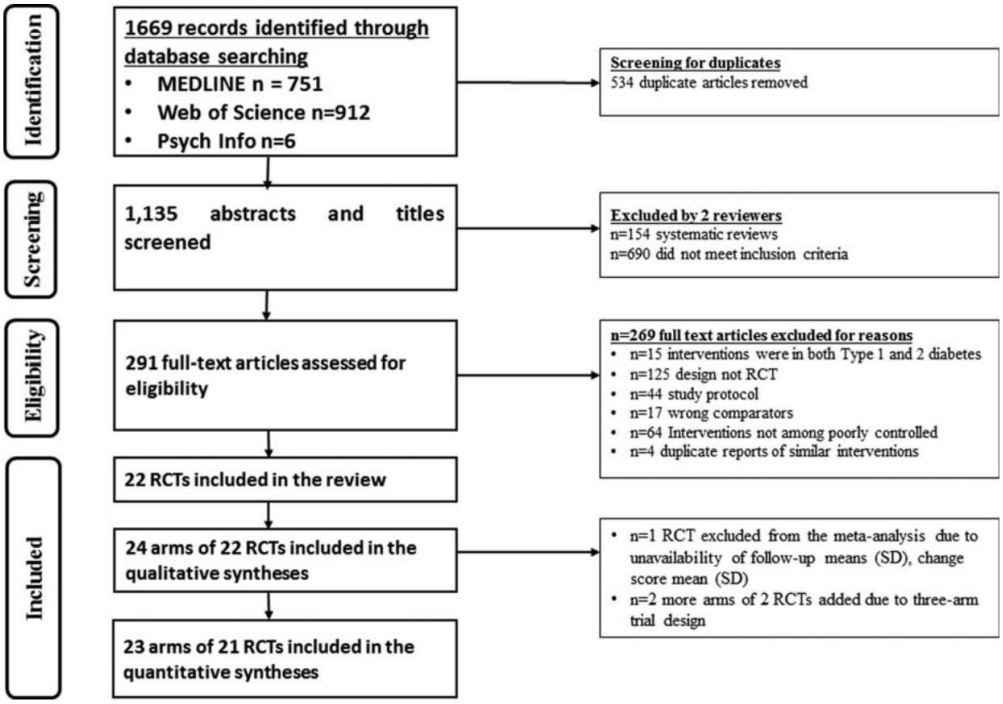


FIG. 1. Preferred reporting items for systematic reviews and meta-analyses flowchart for database search and study selection.

effect sizes of a continuous outcome with a similar scale of measurement.[46–49] Methodological guidelines show that adjusting for baseline imbalance and pre–post correlation is important in meta-analyzing continuous outcomes. The baseline HbA1c differences in the studies included in our review ranged from 0% to 0.64%, with only two RCTs having a mean HbA1 difference of 0%.[36,65] Assuming publication bias is negligible, meta-analysis of the baseline differences should be close to zero if the two treatment groups are balanced.[46] In our case, meta-analysis of baseline HbA1c mean difference was 0.14% (95% CI: −0.31 to 0.59). In addition, pre–post correlation ranged from 0.06[37] to 0.74.[66] For this reason, accounting for baseline imbalance and pre–post correlation was essential. In this review, the ANCOVA effect size estimator was preferred because it helps to adjust for baseline imbalance and pre–post correlations.[46–49] Therefore, the effect size estimates were computed using the "black-belt" ANCOVA approach using the following equation: $\text{ANCOVA} = (\text{Yint} - \text{Yctr}) - \beta(\text{Xint} - \text{Xctrl})$, where β is a regression coefficient computed from pooled SD of the treatment (SDy) and control groups (SDx). Hence, $\beta = r\frac{SDy}{SDx}$.[46,47] Equations by McKenzie et al.[47] and Riley et al.[49] were used to calculate the variances of the final values, change scores, and ANCOVA effect size estimates. If there was no possibility to compute ANCOVA effect size estimates from the reported data, the estimate with smaller effect size obtained from change score and final value estimates was pooled with the ANCOVA effect size estimates following existing methodology.[46,47,49]

Meta-analyses. Stata version 13 statistical software was used to perform the meta-analyses. The outcome data reported at study closure were used to perform the overall meta-analysis. HbA1c reductions of at least 0.3% were labeled as clinically significant.[24,29,67] For studies reporting the results of RCTs with three or more arms, relevant arms were considered in the pooled analysis if they were deemed combinable.

Following Cochrane recommendations, observed statistical heterogeneity was assessed with the Cochrane's χ^2-test (a P-value of less than 0.1 indicates statistically significant heterogeneity) and quantified by using I^2. With I^2 value of ≥50%, a random-effects model was used, else a fixed-effects model.[68]

Sensitivity analyses were performed by excluding studies judged as having a "high risk" of bias for more than three dimensions of the risk of bias assessment tool. Several subgroup analyses were performed to estimate the effects of various intervention features (e.g., tailoring, mode of intervention, and BCTs included). The differences across subgroups were assessed using the random-effects model.

A series of univariate meta-regression analyses were performed by regressing intervention effect sizes across studies on intervention features (i.e., duration of intervention, mode of delivery, theory based, tailoring, baseline HbA1c inclusion criterion [HbA1c >7.0% vs. >7.5%], type of BCT [present or absent], and total number of BCTs included in the interventions). Then, multivariate meta-regression analyses were performed to identify effective BCTs and intervention features associated with HbA1c level. Following the recommendation by Borenstein et al.,[69] BCTs were added in the

subgroup and meta-regression analyses if they were included in at least two studies.

Visual inspection of contour funnel plot was used to detect publication bias. In addition, Egger's test using a *P*-value of less than 0.1 was conducted to assess publication bias.[70] If publication bias was suspected, the ''trim and fill'' imputation method was used to estimate the number of missing studies in the funnel plot.[71] Finally, the quality of evidence generated through meta-analysis was classified as high, moderate, and low using the GRADE approach.[72,73] The GRADEpro online tool was used to systematically evaluate the synthesized evidence.[74]

Results

Study selection and characteristics

In the database search, 1669 titles and abstracts were retrieved, with only 22 studies fulfilling the inclusion criteria.[35–37,62,63,65,66,75–89] Two studies[66,80] were three-arm RCTs, and 20 of them were two-arm RCTs. Because of this, 24 arms of 22 RCTs were considered in the meta-analysis. However, one RCT[76] had most of the required data missing, and hence excluded from the quantitative syntheses. Finally, 23 arms of the 21 RCTs were used in the meta-analyses (Fig. 1).

Studies were published between the years 2009 and 2017, with the majority conducted in the United States ($n=9$). A total of 3787 subjects were included in the 23 arms of the 21 RCTs and followed for a mean duration of 7.29 months (SD = 3.05). One thousand nine hundred ninety-one (52.6%) participants were assigned to the intervention arms. The mean number of participants randomized into control and intervention groups was 82.6 (SD = 62.7) and 83.9 (SD = 62.12), respectively. On average, treatment retention rate at study closure was 89.4% (SD = 9.97, range = 25%, min. = 75% to max. = 100%).

Nearly two-thirds of interventions ($n=15$; 65.22%) were web based delivered via smartphones, tablets, PDA, and computers. Five interventions implemented telehealth (21.74%) and three (13.04%) text messaging. Eleven of the 21 RCTs (52.4%) targeted patients with baseline HbA1c values greater than 7.5%, while the rest were targeted patients having an HbA1c level of greater than 7.0%.

Quality of studies

Less than half of the included studies described ITT with 12 studies not stating ITT procedures. Only one study was judged as having a low risk of bias on all of the risk of bias assessment dimensions.[89] Four studies (18.2%) were judged as having a high risk of bias on three of seven dimensions.[76,78,82,84] Eighteen (81.2%) studies adequately described the randomization procedure and were judged as having a low risk of bias with regard to this dimension.[35–37,62,63,65,66,75–81,83,85,86,89] Seven studies (31.2%) did not adequately describe how the allocation was performed and were unclear for judgment (Fig. 2).[63,65,77,82,86–88]

Regarding intervention-related adverse events, only eight studies[36,37,62,66,77,80,85,89] reported that adverse events were assessed. All of these studies reported that there were no intervention-related adverse events. One study reported two deaths but not due to intervention participation[66] and one reported trouble among intervention participants with regard to using the digital devices or connecting with Bluetooth.[80]

Only seven interventions were designed following behavioral health theories. The theories used were the ''health belief model,''[75,83] the ''trans-theoretical model of behavioral change,''[75] the ''health action process approach,'' the ''theory of planned behavior,'' and the ''Bandura's theory of self-efficacy.''[83] In addition, ''Green and Kreuter's PRECEDE-PROCEED model,''[81] ''cognitive behavioral therapy,'' the ''Reach Out'' problem-solving model, and ''motivational interviewing''[66,80] were used to guide intervention design. Seventeen interventions[36,37,62,65,66,77–83,85–89] were tailored according to individual patient characteristics (Table 1).

AADE7 self-care behaviors targeted in the interventions

Inter-rater agreement determined by using Cohen's kappa and prevalence adjusted bias kappa (PABAK) was 0.6 and 0.8, respectively, suggesting a high reliability. A mean of 4 (SD = 1.74, range 1–7) AADE7 self-care behaviors were addressed in interventions. Of the seven AADE7 self-care behaviors, ''monitoring'' was the most frequently included (in 21 of 24 intervention arms) followed by ''healthy eating'' and ''taking medication,'' which were addressed 16 and 15 times, respectively. However, ''healthy coping'' was included in only nine intervention arms.

Of the 22 interventions included in this review, only one intervention addressed seven of the AADE7 self-care behaviors.[88] Four interventions targeted six self-care behaviors each (Table 1).[65,76,77,85]

BCTs used in e-health interventions targeting persons with poorly controlled type 2 diabetes

Inter-rater agreement determined by using percent agreement was 96.5% and PABAK was 0.93, suggesting a very good agreement. A total of 27 BCTs with a minimum of 4[36,84,89] and a maximum of 11 BCTs[75] were addressed in interventions. Of the 27 BCTs, ''instruction how to perform behavior'' was used most frequently, included in 21 intervention arms.[35–37,62,63,65,66,75–77,79–82,84–86,88,89] Eight BCTs were included only once. None of the intervention arms had a similar combination of BCTs (Supplementary Table S1, available online at https://www.liebertpub.com/suppl/doi/10.1089/dia.2018.0216).

Impact of interventions in terms of reducing HbA1c

The pooled mean HbA1c difference suggests a statistically significant HbA1c reduction, –0.39 (95% CI: –0.51 to –0.26), favoring digital intervention groups. However, heterogeneity was high (I^2 statistic: 80.8%).

Publication bias. Visual inspection of the contour funnel plot shows that the majority of the effect sizes of the interventions are in the significant region as well as in the upper left part of the plot, suggesting the predominance of published significant findings. Only one study falls on the non-significant region ($P>0.5$) of the contour-enhanced funnel plot (Supplementary Fig. S1). This asymmetry of the plot might possibly be due to either the presence of publication bias or due to factors other than publication bias. To confirm

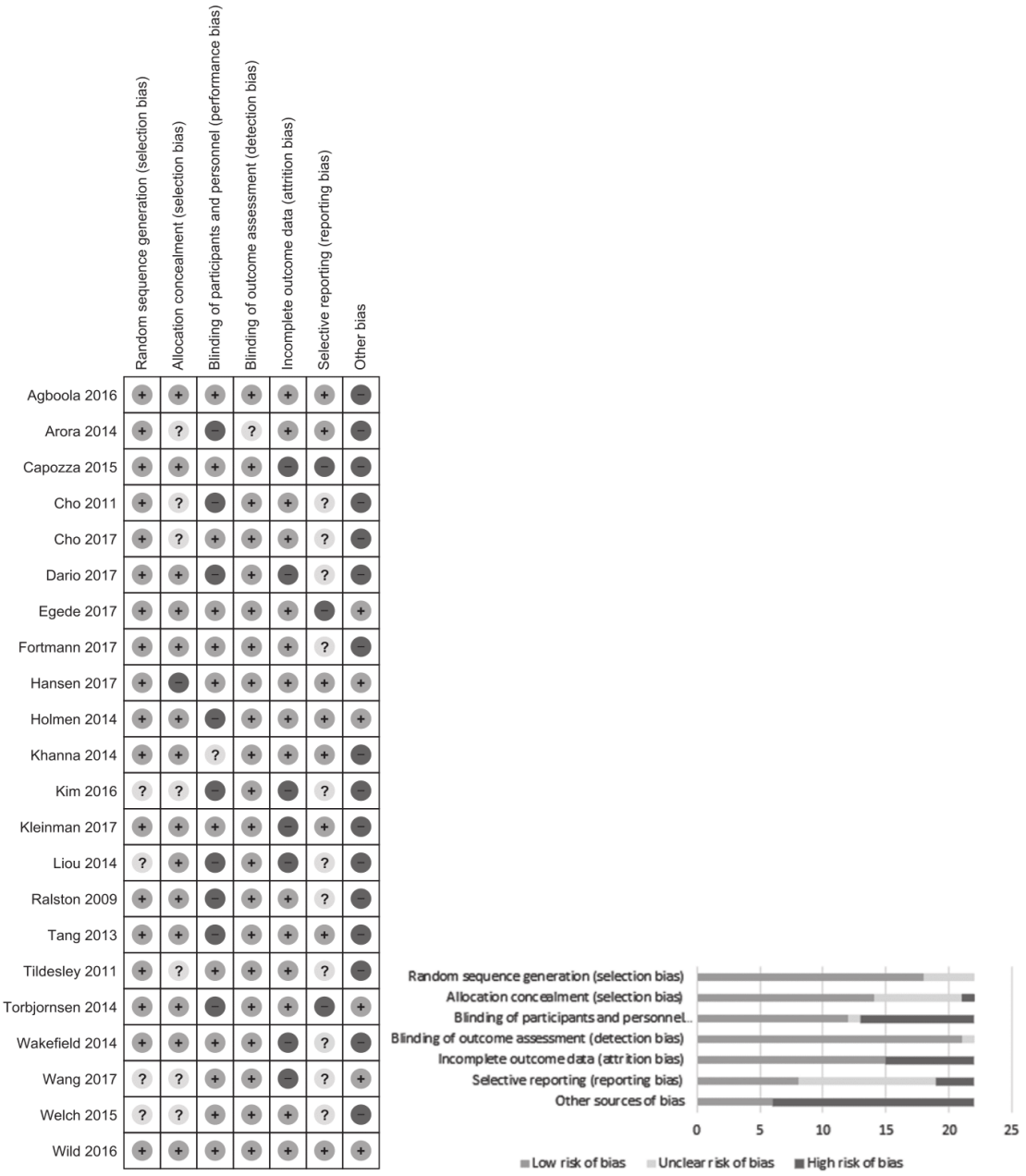


FIG. 2. Risk of bias assessment of individual studies and aggregated summary.

this, Egger's test and then ''trim and fill'' test were performed. Egger's test indicated that there is not enough evidence of small-study effects (coefficient = −1.13, $P = 0.182$). Performing the ''trim and fill'' test also did not result in changes in the pooled effect size estimate. Therefore, both Egger's and the ''trim and fill'' tests indicated that the influence of publication bias is negligible.

Sensitivity analyses

Sensitivity analyses were conducted excluding four studies judged as having a ''high risk'' of bias in more than three dimensions of the risk of bias assessment. The pooled HbA1c MD and heterogeneity I^2 statistics were not substantially changed, resulting in a pooled HbA1c MD of –0.38% (95%

Table 1. Characteristics of Included Studies

Study	Location	Intervention	Intervention time endpoints, months	Tailoring	Theory	Study population	Baseline HbA1c inclusion criteria, %	AADE7 self-care behavior targeted	Adverse event
Mobile phone-delivered text message interventions									
Agboola et al.[75]	United States	Text to move (text message)	6	No	Yes, trans-theoretical model of behavior change	Spanish- or English-speaking low-income and ethnic minorities, type 2 diabetes patients	>7.0	Being active, healthy coping, taking medication, healthy coping	Not reported
Arora et al.[63]	United States	Two daily text messages for 6 months. Education/ motivation—1 text per day, medication reminders—3 per week, healthier living challenge—2 per week, trivia. Unidirectional text message	6	No	Yes, health belief model	English- or Spanish-speaking Latino and black type 2 diabetes patients	>7.5	Being active, healthy eating, monitoring, taking medication, reducing risks	Not reported
Capozza et al.[76]	United States	Text message (Care4Life program) for education and motivation, medication adherence, glucose control, weight, and exercise	3 and 6	No, allowed patients to send text messages to providers	No	No specific population, adult patients with type 2 diabetes patients	>7.5	Being active, monitoring, taking medication, healthy coping, reducing risks, problem solving	Not reported
Fortmann et al.[35]	Canada	Dulce Digital: An m-health SMS-based intervention	3 and 6	Culturally and ethnically tailored, but not tailored to individual characteristics	No	Underserved Hispanics with poor glycemic control, type 2 diabetes patients	≥7.5	Healthy eating, monitoring, taking medication, problem solving	Not reported
PDA-, tablet-, computer-, and/or smartphone-delivered web-based interventions									
Cho et al.[65]	South Korea	Internet diabetes management	3	Yes	No	No specific population, type 2 diabetes patients, Koreans	>7.0	Healthy eating, being active, monitoring, taking medication, problem solving, reducing risks	Not reported
Cho et al.[77]	Korea	Healthcare provider mediated, remote coaching system via a PDA-type glucometer and the Internet	3 and 6	Tailored	No	Koreans, no specific population, patients with type 2 diabetes	7–10.0	Healthy eating, being active, monitoring, taking medication, problem solving, reducing risks	No adverse event detected
Egede et al.[36]	United States	Telehealth and clinical decision support system	3 and 6	Tailored	No	18 Years or older, type 2 diabetes patients	≥8.0	Monitoring, taking medication, problem solving	No adverse event detected

(*continued*)

Table 1. (Continued)

Study	Location	Intervention	Intervention time endpoints, months	Tailoring	Theory	Study population	Baseline HbA1c inclusion criteria, %	AADE7 self-care behavior targeted	Adverse event
Holmen et al.[80] (usual care vs. FTA-HC)	Norway	FTA (diabetes diary app) with HC	12	Tailored	Yes, cognitive behavioral therapy, the "Reach Out" problem-solving model, and MI	No specific population, adult patients with type 2 diabetes	>7.0	Healthy eating, being active, monitoring, problem solving, healthy coping	No adverse event, but only trouble with use of the digital devices
Holmen et al.[80] (usual care vs. FTA)	Norway	FTA (diabetes diary app) without HC	12	Tailored	Yes, cognitive behavioral therapy, the "Reach Out" problem-solving model, MI	No specific population, adult patients with type 2 diabetes	>7.0	Healthy eating, being active, monitoring	No adverse event, but only trouble with use of the digital devices
Kim et al.[82]	China	Internet-based glucose monitoring system	3 and 6	Tailored	No	Male and female outpatients with type 2 diabetes patients	7.0–10.0	Monitoring	Not reported
Kleinman et al.[83]	India	Smart phone app for patients and smart phone app and a web-based portal for providers	3	Tailored	Health belief model, health action process approach, theory of planned behavior, Bandura's theory of self-efficacy	No specific population, type 2 diabetes patients for >6 months	7.5–12.5	Monitoring, problem solving, reducing risks, taking, medication	Not reported
Ralston et al.[37]	United States	Web-based care management	12	Tailored	Yes, Wagner's chronic care model	No specific population, adult patients with type 2 diabetes	>7.0	Healthy eating, monitoring, taking, medication, problem solving	No adverse event
Tang et al.[85]	United States	Online disease management system	6 and 12	Tailored	Yes, Universal models of behavior change, MI, and chronic care model	No specific population, adult patients with type 2 diabetes	>7.5	Healthy eating, being active, monitoring, taking medication, reducing risks, problem solving	No adverse event
Tildesley et al.[86]	Canada	IBGMS	3, 6 and 12	Tailored	No	No specific population, type 2 diabetes patients	>7.0	Monitoring, taking medication	Not reported
Torbjørnsen et al.[66] (usual care vs. FTA-HC)	Norway	FTA (diabetes diary app) with HC	4	Tailored	Yes, cognitive behavioral therapy, the "Reach Out" problem-solving model, MI	No specific population, adult patients with type 2 diabetes	>7.0	Healthy eating, being active, monitoring, problem solving, healthy coping	Two deaths, but unrelated with the interventions
Torbjørnsen et al.[66] (usual care vs. FTA)	Norway	FTA (diabetes diary app) without HC	4	Tailored	Yes, cognitive behavioral therapy, the "Reach Out" problem-solving model, MI	No specific population, adult patients with type 2 diabetes	>7.0	Healthy eating, being active, monitoring	Two deaths, but unrelated with the interventions

(*continued*)

TABLE 1. (CONTINUED)

Study	*Location*	*Intervention*	*Intervention time endpoints, months*	*Tailoring*	*Theory*	*Study population*	*Baseline HbA1c inclusion criteria, %*	*AADE7 self-care behavior targeted*	*Adverse event*
Wang et al.[87]	China	Monitoring via computer/web/mobile phone connected to glucometer via cable	3 and 6	Tailored	No	No specific population, type 2 diabetes patients confirmed for over 1 year	7–10.0	Healthy eating, being active, monitoring	Not reported
Welch et al.[88]	United States	Internet-based integrated diabetes management system	6	Tailored	No	Latino, type 2 diabetes patients	>7.5	Healthy eating, being active, monitoring, taking medication, problem solving, reducing risks, healthy coping	Not reported
Wild et al.[89]	Scotland	Monitoring through computer/web based/ mobile phone connected to glucometer via modem	9	Tailored	No	No specific population, type 2 diabetes patients aged more than 17 years	>7.5	Monitoring, taking medication, reducing risks	Adverse events were equally distributed between in intervention and control groups
Telehealth (communication with provider via telephone or video)									
Dario et al.[78]	Italy	Videoconferencing	12	Tailored	No	Italy, no specific population, type 2 diabetes patients	>7.0	Monitoring, reducing risks	Not reported
Hansen et al.[79]	Denmark	Videoconferencing	8	Tailored	No	Danish-speaking type 2 diabetes patients	>7.5	Monitoring, problem solving, reducing risks	Not reported
Khanna et al.[81]	United States	Automated telephone support with dialogic telephone card	3	Tailored	Yes, Green and Kreuter's PRECEDE-PROCEED model	Spanish-speaking patients with type 2 diabetes	>7.5	Healthy eating	Not reported
Liou et al.[84]	Taiwan	Web-based and videoconferencing	6	No	No	No specific population, adult type 2 diabetes patients	>7.0	Healthy eating, taking medication, reducing risks, healthy coping, problem solving	Not reported
Wakefield et al.[62]	United States	Telemonitoring	3 and 6	Tailored	No	No specific population, subjects with established type 2 diabetes	>8.0	Monitoring, taking medication	No adverse events

FTA-HC, Few Touch Application health counseling; HbA1c, glycated hemoglobin; IBGMS, Internet-based glucose monitoring system; m-health, mobile health; MI, motivational interviewing.

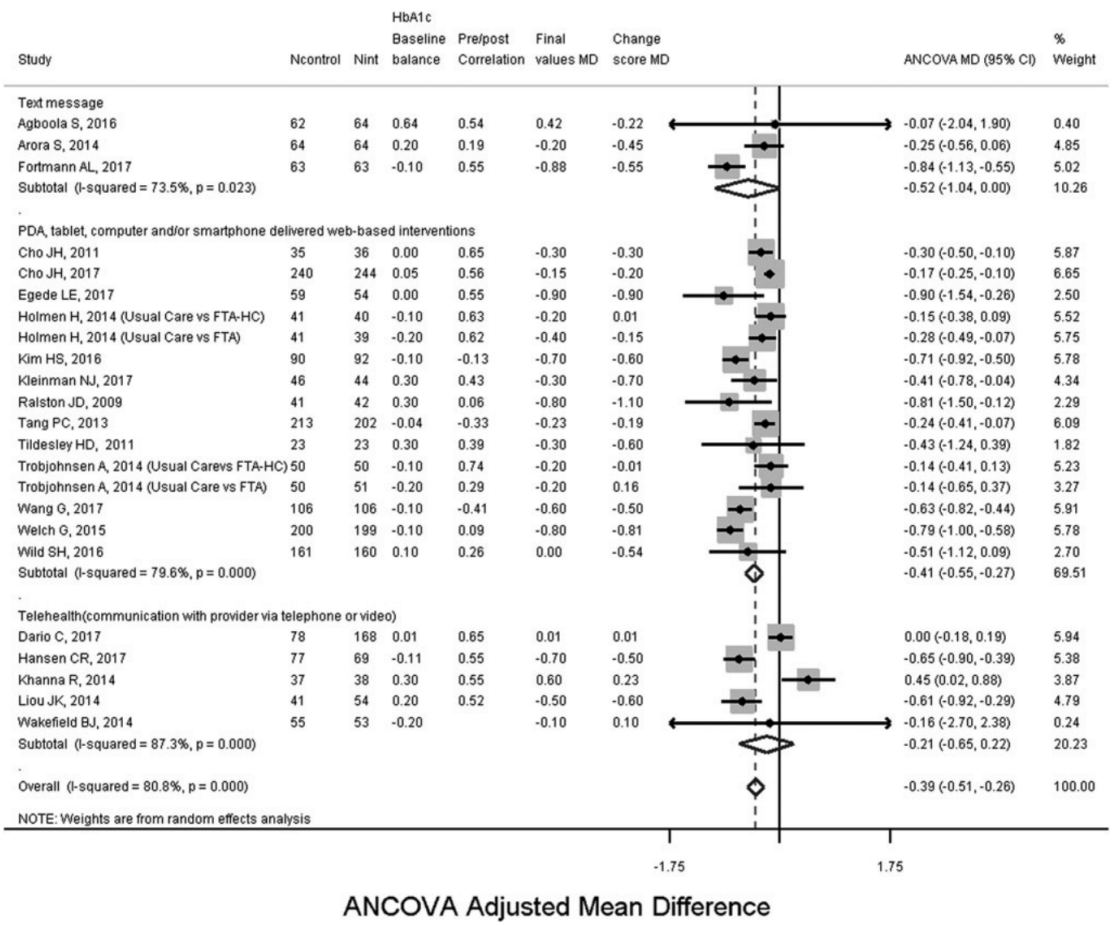


FIG. 3. Subgroup analysis of the effectiveness of digital interventions for reducing HbA1c-levels by mode of delivery. HbA1c, glycated hemoglobin.

CI: [−0.51 to −0.24]) and I^2 of 77.9%. However, removing eight studies having a ''high'' and an ''unclear'' risk of bias for allocation concealment resulted in a lower effect size estimate, −0.30% (95% CI: [−0.45 to −0.15]). I^2 statistic was also lowered to 68.4%. Further sensitivity analysis conducted by removing the four studies with inadequate description of randomization yielded a lower effect size estimate, −0.29% (95% CI: −0.41 to −0.17).

Subgroup analyses by intervention features and BCTs

The pooled mean HbA1c difference was −0.52% (95% CI: [−1.04 to 0.00]), −0.41% (95% CI: −0.55 to −0.27), −0.21% (95% CI: [−0.65 to 0.22]) for text message-delivered, web-based, and telehealth interventions, respectively. Statistically significant pooled HbA1c reductions favoring the intervention group were only noted for web-based interventions. However, there was substantial statistical heterogeneity across the three intervention subgroups (Fig. 3).

A subgroup analysis on the duration of interventions yielded an ANCOVA-adjusted mean HbA1c difference of −0.30 (95% CI: −0.495 to −0.11), −0.59 (95% CI: −0.78 to −0.39), and −0.21 (95% CI: −0.35 to −0.075) for interventions having outcome endpoints after 3–4, 6–8, and 9–12 months, respectively. However, there was substantial heterogeneity in the 3–4 months ($I^2 = 89\%$) and 6–8 months ($I^2 = 85\%$) subgroups (Supplementary Fig. S2).

Additional subgroup analysis was performed to investigate the differences in mean HbA1c reduction for interventions that ''included'' versus ''did not include'' a specific BCT. Hence, we noted HbA1c mean differences favoring the intervention group for the presence of the following BCTs: ''information about health consequences'' (−0.77%), ''instruction on how to perform behavior'' (−0.35%), ''self-monitoring of behavior'' (−0.27%), ''self-monitoring outcomes of behavior'' (−0.15%), ''adding objects to the environment'' (−0.13%), and ''feedback on outcomes of behavior'' (−0.12%). However, as can be seen above, only two BCTs led to clinically

Table 2. Multivariable Meta-regression Model of Intervention Features and BCTs

Intervention features & BCTs	*Coefficient*	*Std. Err.*	t	P	*[95% confidence interval]*
Type of intervention					
Web-based interventions	−0.39	0.18	−2.23	0.076	[−0.85 to 0.06]
Text message based	0.38	0.35	1.08	0.331	[−0.52 to 1.28]
Duration of intervention, months					
3–4	−0.003	0.13	−0.02	0.987	[−0.35 to 0.34]
6–8	−0.17	0.16	−1.11	0.318	[−0.58 to 0.23]
Tailoring	1.15	0.39	2.91	0.033	[0.14 to 2.17][a]
Baseline HbA1c >7.5	−0.44	0.15	−2.97	0.031	[−0.81 to −0.06][a]
Theory use	0.05	0.15	0.33	0.752	[−0.33 to 0.42]
Problem solving	−1.30	0.29	−4.41	0.007	[−2.05 to −0.54][a]
Review outcome goals	−0.44	0.20	−2.22	0.077	[−0.96 to 0.07]
Self-monitoring of behavior	−0.22	0.24	−0.92	0.399	[−0.84 to 0.40]
Self-monitoring outcomes of behavior	−1.21	0.29	−4.15	0.009	[−1.95 to −0.46][a]
Feedback on outcomes of behavior	0.68	0.23	2.91	0.033	[0.08 to 1.28][a]
Instruction how to perform behavior	0.05	0.20	0.24	0.823	[−0.46 to 0.55]
Salience of consequences	−0.14	0.12	−1.12	0.312	[−0.45 to 0.18]
Prompts/cues	0.44	0.16	2.77	0.040	[0.03 to 0.85][a]
Adding objects to the environment	0.04	0.28	0.16	0.882	[−0.68 to 0.76]
Total number of BCTs	−0.02	0.05	−0.42	0.695	[−0.14 to 0.10]
Intercept	−0.40	0.36	−1.11	0.317	[−1.33 to 0.53]

Number of studies included in the model = 23, estimate of between-study variance tau2 = 0.022, adjusted R^2 = 79.83, I^2 = 97.76%, Joint test for all covariates $F(17.5) = 5.34$, $P = 0.037$.
[a]Statistically significant at a P-value of 0.05.
ANCOVA, analysis of covariance; BCT, behavior change technique.

significant HbA1c changes (delta > −0.3%) (Supplementary Table S2 available at https://www.liebertpub.com/suppl/doi/10.1089/dia.2018.0216).

Furthermore, subgroup analysis on the effect size differences shows that interventions implemented among patients with HbA1c levels of greater than 7.5% led to higher reductions (delta = −0.12%) of HbA1c levels relative to interventions among patients with HbA1c of greater than 7.0% (Supplementary Table S3).

Subgroup analysis on the baseline HbA1c inclusion criteria resulted in relatively bigger effect size for interventions targeting patients with HbA1c levels greater than 7.5% (i.e., −0.45% {95% CI: [−0.70 to −0.21]} vs. −0.33% {95% CI: [−0.478 to −0.18]}) (Supplementary Fig. S3 available at https://www.liebertpub.com/suppl/doi/10.1089?dia.2018.0216).

Identifying intervention features and BCTs associated with HbA1c reductions

The univariate meta-regression analysis, obtained by regressing the effect sizes of interventions on intervention features indicated that none of the features, except for duration of interventions, was significant. Interventions with 3- to 4-month duration ($\beta = 0.42$, $P = 0.016$, tau2 = 0.085, $R^2 = 21.7\%$) and a 6- to 8-month duration ($\beta = -0.29$, $P = 0.03$, tau2 = 0.089, $R^2 = 17.7\%$) displayed significant associations with the effect size indicating that 6–8 months of intervention duration resulted in a pronounced reduction of HbA1c levels. Only two BCTs, "feedback on behavior" ($\beta = 0.29$, $P = 0.037$, tau2 = 0.092, $R^2 = 15.4\%$) and "social support practical" ($\beta = 0.42$, $P = 0.016$, tau2 = 0.0085, $R^2 = 21.6\%$), were significantly associated with the effect size. Because the β coefficients were positive, the use of these BCTs did not demonstrate HbA1c reductions.

Multivariable meta-regression revealed that the presence/absence of nine BCTs and other intervention features in the model explained 79.8% of the variance in the effect size. Tailoring the interventions, $\beta = 1.15$ (95% CI: [0.14 to 2.17]), baseline HbA1c higher than 7.5, $\beta = -0.44$ (95% CI: [−0.81 to −0.06]), and the presence or absence of four BCTs were significantly associated with HbA1c levels. Hence, the BCTs "problem solving" ($\beta = -1.30$; 95% CI: [−2.05 to −0.54]), "feedback on outcomes of behavior" ($\beta = 0.68$; 95% CI: [0.08 to 1.28]), "self-monitoring outcomes of behavior" ($\beta = -1.21$; 95% CI: −1.95 to −0.46), and "prompts/cues" ($\beta = 0.44$; 95% CI: [0.03 to 0.85]) were significantly associated with the HbA1c levels. Of these, baseline HbA1c higher than 7.5%, "problem solving," and "self-monitoring outcomes of behavior" were associated with reduced HbA1c-levels (Table 2).

Grading the quality of evidence generated from the meta-analyses

Applying the GRADE principles,[74] the quality of evidence generated through this meta-analysis can be considered "moderate quality" (Supplementary Tables S4 and S5 available at https://www.liebertpub.com/suppl/doi/10.1089/dia.201.2018.0216).

Discussion

This systematic review is the first to demonstrate the effectiveness of digital interventions for reducing HbA1c levels in patients with poorly controlled type 2 diabetes. It is also the first review to account for baseline imbalance and pre–post correlations using an available robust statistical method, ANCOVA. The review also used a reliable taxonomy[52] to identify effective BCTs used in digital interventions targeting

persons with type 2 diabetes, as well as the well-established AADE7[19] to unravel the effects of intervention components on HbA1c levels. These tools offer a great opportunity to handle heterogeneity across multicomponent and complex interventions.[51,53,90]

In this review, we report clinically and statistically significant effects of PDA-, mobile phone-, or computer-delivered web-based interventions on HbA1c. A clinically significant HbA1c reduction is associated with lower rates of deaths, myocardial infractions, and reduced microvascular complications.[24]

Similar to our results, clinically and statistically significant pooled HbA1c reductions were reported for Internet-based interactive self-management interventions[28] and mobile phone-based Internet interventions.[31] Our findings thus support the previously reported evidence on beneficial effects of web-based interventions.[38] However, we could not show a statistical significant reduction of HbA1c levels after participation in text message and telehealth interventions. Contrary to our findings, previous results of meta-analyses reported significant HbA1c reductions after participation in telehealth[39,41] and text message interventions.[42] This may possibly be due to the number of telehealth and text message interventions included in our meta-analyses, which was relatively low.

Sensitivity analyses performed by removing studies with a high risk of bias for more than three dimensions suggest that there was no change in the direction of the overall effect estimate. However, the two additional meta-analyses performed after dropping studies with an inadequate description of randomization and a high or unclear risk of bias regarding allocation concealment resulted in a lower effect size estimate. This supports the finding that studies with inadequate or unclear allocation concealment may report inflated treatment effect estimates.[91,92]

Results of the subgroup analyses by duration of intervention suggest higher effect size estimates for longer intervention periods. This is likely due to the fact that it takes time for behavioral interventions to change patterns of thoughts and feelings toward behavior change and behavior itself, in turn leading to a change in HbA1c. Yet, the effect size estimate decreased 9–12 months into the intervention. This is in line with other recent meta-analysis results that reported similar effects of digital interventions on HbA1c reduction by duration.[21,28,67] However, a review by Cradock et al. reported a higher HbA1c reduction at month 3 compared with month 6 during the intervention period.[67] It should be noted though that only a small number of studies (four) were included and that baseline HbA1c levels were not taken into account in the subgroup analyses performed by Cradock et al.[67] Previous literature also suggests that more pronounced reductions of HbA1c occur among patients with higher HbA1c levels at the beginning of the intervention.[31,45,93] This was confirmed in both our subgroup and meta-regression analyses. Patients with an HbA1c level greater than 7.5% displayed higher effect estimates. Clinically, this supports the usefulness of digital interventions, particularly among patients with poor initial glycemic control.

Only interventions addressing the following two BCTs, ''information about health consequences'' and ''instruction on how to perform behavior,'' led to clinically significant HbA1c changes in patients with poorly controlled type 2 diabetes. Cradock et al. also reported a clinically significant effect of using the BCT ''instruction on how to perform behavior,''[67] as did another meta-analysis reported by Avery et al.[94] Future meta-analyses, including more studies and larger study populations as well as concise intervention descriptions, are needed to validate these findings.

The results of the multivariable meta-regression analysis indicate that nine BCTs, as well as additional intervention features in the model, explained more than three-fourths of the variance in the effect size. Baseline HbA1c above 7.5% and the presence of the two BCTs ''problem solving'' and ''self-monitoring outcomes of behavior'' were associated with significant reductions in HbA1c levels. Contrary to the results of a meta-analysis by Kassavou and Sutton, our results suggest that interventions using the BCT ''problem solving'' had a higher beneficial pooled effect.[95] It is known that meta-regression models provide robust results when a greater number of studies and fewer covariates are taken into account.[96] Future meta-regression analyses therefore ought to pool a larger number of trials to develop relatively stable and precise meta-regression results.

Although tailoring the interventions and ''feedback on outcomes of behavior'' were significantly associated, these associations were inverse, which indicates that the presence of tailoring and this BCT do not lead to reductions in HbA1c levels. A systematic review of reviews by Greenwood et al. reported interventions with two-way communication, patient-generated data tracking and analysis, tailored education and individualized feedbacks were most effective.[90] There was also no evidence of an association between HbA1c levels and the use of theories for designing interventions. Although the use of theories ideally offers scientific explanations of the process of change and is helpful for linking observed changes in outcomes with active intervention ingredients, the existing evidence regarding the benefits of theory use for intervention development is mixed.[97]

Our results did not suggest an association between the number of BCTs addressed in interventions and changes in HbA1c. In contrast, two previous systematic reviews demonstrated an association between a greater number of BCTs included in behavioral and self-management interventions and reductions in HbA1c levels.[67,94] The substantial variation in the breadth and depth of BCT descriptions included in the articles could partially explain this finding. Greater quality of intervention descriptions enhances reliability and validity of characterization of the multicomponent interventions and improves reliability and the power of results.[53,98]

Limitations

The study has several limitations. Our search was limited to three main databases. However, during the preliminary search, we did not observe major differences in search results when using EMBASE, CINAHL and Cochrane library. Therefore, we concluded that our search in PubMed, ISI Web of Science, and PsycINFO covered the relevant articles. We also did not search in unindexed databases and gray literature.

Previous research suggests that each additional intervention increases the unspecific ''attention factor'' for patients. Testing a digital intervention against a standard care might therefore overestimate the specific effect of digital

interventions, since the ''attention factor'' is not well controlled. In addition, higher dropout rates were reported from previous digital interventions. This might be due to self-selection indicating that people who like digital media stay in the interventions and people who have difficulties with digital interventions may drop out from the study, leading to overestimation of the results. However, in this review, a high retention rate was observed from individual studies.

Mapping and differentiating the intervention content to determine which BCTs were addressed in interventions rely on the quality and depth of descriptions available for various interventions.[99] In addition, it is based on a subjective judgment. We tried to minimize this limitation by taking online training in using the BCTTv1, applying consensus ratings, and using a third experienced reviewer to resolve any disagreement.

Two studies[33,34] that passed our inclusion criteria were not included in the meta-analysis. This is mainly because of two limitations related to methodology and missing values. Because the design of these studies was cluster RCT, the effect sizes and SEs were needed to be adjusted for design effect by considering intracluster correlation (ICC). This analysis is more complicated when cluster RCTs have high baseline imbalance and did not report ICC. Hence, application of ANCOVA was not feasible for these two studies. We considered change scores or final values as alternatives. However, SD for change scores in each intervention endpoint (3, 6, 9, and 12 months) for both control and intervention groups were not available from the two trials. For this reason, we did not include these studies in our meta-analysis. We suggest future interventions to report details of summary data. Future research is needed on methodological guideline for handling continuous outcomes from cluster RCTs with a high baseline imbalance.

Conclusions

In conclusion, the results of this systematic review and meta-analysis indicate that participation in digital interventions, particularly web-based interventions, favorably influences HbA1c levels among patients with poorly controlled type 2 diabetes. Intervention effects were more pronounced among patients with higher baseline HbA1c levels and greater effects were observed 6–8 months into an intervention. Moreover, the results of the meta-regression analyses suggest that baseline HbA1c >7.5% and the two BCTs ''problem solving'' and ''self-monitoring outcomes of behavior'' were associated with a reduction of HbA1c levels. Hence, considering these two BCTs in future interventions may lead to clinically meaningful reductions in HbA1c.

The effort to adjust for baseline imbalance and pre–post correlation relies on the level of detail of reporting available for individual studies. We suggest to authors of future intervention studies, particularly with baseline imbalance, to report detailed information that allows authors of systematic reviews to calculate ANCOVA effect size estimates or, ideally, to provide access to IPD.

Acknowledgments

We are grateful to Professor Richard D. Riley, Dr. Jochen Wilhelm, Dr. James E. Pustejovsky, Professor Vanessa Didelez, and Dr. Fleur Fritz for the methodological support provided particularly to the first author. We also acknowledge our research librarian, Lara Christianson, for her support in developing the search strategy. In addition, we are very grateful to all authors of the studies included in this meta-analysis particularly to Caroline R. Hansen, Sarah Wild, Richard Parker, Nora Kleinman, Professor Leonard Egede, Dr. Addie Fortmann, Heidi Holmen, Dr. James Ralston, Dr. Raman Khanna, and Elisa Visentin for providing us with the data we requested and simplifying our effort in handling the missing data.

Availability of Data

The data collected for this study are available from the corresponding author and can be received on request.

Authors' Contributions

M.M.K. conceptualized and designed the study, conducted the systematic literature search with the help of research librarian, performed the title and abstract screening, quality assessment, data extraction, data analysis and interpretation of the data, and wrote the article.

H.Z. participated in the conception and the design of the study and the development of the methodology, and critically revised the article for important intellectual content.

M.P. conducted the title and abstract screening, quality assessment, and participated in the draft of the article.

T.L.H. contributed to the extraction of the data and critically revised the article.

C.R.P. participated in the conception, data extraction, and critically revised the article for important intellectual content.

All authors read and approved the final version of the article.

Author Disclosure Statement

No competing financial interests exist.

References

1. IDF: International Diabetes Federation Diabetes Atlas, 7th ed. IDF, Brussels, Belgium, 2015.
2. Darnton-Hill I, Nishida C, James WP: A life course approach to diet, nutrition and the prevention of chronic diseases. Public Health Nutr 2004;7:101–121.
3. IDF: IDF Diabetes Atlas, 8th ed. International Diabetes Federation, IDF, Brussels, Belgium, 2017.
4. Bovet P, Chiolero A, Gedeon J: Health effects of overweight and obesity in 195 countries. N Engl J Med 2017; 377:1495–1496.
5. Despres JP, Poirier P: Diabetes: looking back at look AHEAD—giving lifestyle a chance. Nat Rev Cardiol 2013; 10:184–186.
6. Taylor R: Pathogenesis of type 2 diabetes: tracing the reverse route from cure to cause. Diabetologia 2008;51: 1781–1789.
7. Lean MEJ, Leslie WS, Barnes AC, et al.: Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. Lancet 2018;391:541–551.
8. Taylor R: Type 2 diabetes: etiology and reversibility. Diabetes Care 2013;36:1047–1055.
9. Steven S, Hollingsworth KG, Small PK, et al.: Weight loss decreases excess pancreatic triacylglycerol specifically in type 2 diabetes. Diabetes Care 2016;39:158–165.

10. American Diabetes Association: Foundations of care and comprehensive medical evaluation. Diabetes Care 2016; 39(Suppl 1):S23–S35.
11. IDF: Diabetes Atlas, 6th ed. International Diabetes Federation, IDF, Brussels, Belgium, 2013.
12. WHO: Global Report on Diabetes. Geneva, Switzerland: World Health Organization, 2016.
13. Diabetes Prevention Program Research Group: The Diabetes Prevention Program (DPP): description of lifestyle intervention. Diabetes Care 2002;25:2165–2171.
14. Brown MT, Bussell JK: Medication adherence: WHO cares? Mayo Clin Proc 2011;86:304–314.
15. Tuomi T, Santoro N, Caprio S, et al.: The many faces of diabetes: a disease with increasing heterogeneity. Lancet 2014;383:1084–1094.
16. Girach A, Manner D, Porta M: Diabetic microvascular complications: can patients at risk be identified? A review. Int J Clin Pract 2006;60:1471–1483.
17. Avramopoulos I, Moulis A, Nikas N: Glycaemic control, treatment satisfaction and quality of life in type 2 diabetes patients in Greece: The PANORAMA study Greek results. World J Diabetes 2015;6:208–216.
18. The National Collaborating Centre for Chronic Conditions: Type 2 diabetes: the management of type 2 diabetes. NICE clinical guideline. In: NICE Guideline [NG28]. London: Royal College of Physicians, 2015.
19. Tomky D, Cypress M, Dang D, et al.: AADE7 self-care behaviors. Diabetes Educ 2008;34:445–449.
20. Chen L, Chuang LM, Chang CH, et al.: Evaluating self-management behaviors of diabetic patients in a telehealthcare program: longitudinal study over 18 months. J Med Internet Res 2013;15:e266.
21. Heitkemper EM, Mamykina L, Travers J, Smaldone A: Do health information technology self-management interventions improve glycemic control in medically underserved adults with diabetes? A systematic review and meta-analysis. J Am Med Inform Assoc 2017;24:1024–1035.
22. Farmer A, Gibson OJ, Tarassenko L, Neil A: A systematic review of telemedicine interventions to support blood glucose self-monitoring in diabetes. Diabet Med 2005;22: 1372–1378.
23. Baron J, McBain H, Newman S: The impact of mobile monitoring technologies on glycosylated hemoglobin in diabetes: a systematic review. J Diabetes Sci Technol 2012; 6:1185–1196.
24. Tricco AC, Ivers NM, Grimshaw JM, et al.: Effectiveness of quality improvement strategies on the management of diabetes: a systematic review and meta-analysis. Lancet 2012;379:2252–2261.
25. Su D, Zhou J, Kelley MS, et al.: Does telemedicine improve treatment outcomes for diabetes? A meta-analysis of results from 55 randomized controlled trials. Diabetes Res Clin Pract 2016;116:136–148.
26. Stratton IM, Adler AI, Neil HA, et al.: Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000;321:405–412.
27. Farmer AJ, McSharry J, Rowbotham S, et al.: Effects of interventions promoting monitoring of medication use and brief messaging on medication adherence for people with type 2 diabetes: a systematic review of randomized trials. Diabet Med 2016;33:565–579.
28. Cheng L, Sit JW, Choi KC, et al.: Effectiveness of interactive self-management interventions in individuals with poorly controlled type 2 diabetes: a meta-analysis of randomized controlled trials. Worldviews Evid Based Nurs 2017;14:65–73.
29. Avery L, Flynn D, van Wersch A, et al.: Changing physical activity behavior in type 2 diabetes: a systematic review and meta-analysis of behavioral interventions. Diabetes Care 2012;35:2681–2689.
30. Farmer AJ, McSharry J, Rowbotham S, et al.: Effects of interventions promoting monitoring of medication use and brief messaging on medication adherence for people with type 2 diabetes: a systematic review of randomized trials. Diabet Med 2016;33:565–579.
31. Liang X, Wang Q, Yang X, et al.: Effect of mobile phone intervention for diabetes on glycaemic control: a meta-analysis. Diabet Med 2011;28:455–463.
32. Pal K, Eastwood SV, Michie S, et al.: Computer-based interventions to improve self-management in adults with type 2 diabetes: a systematic review and meta-analysis. Diabetes Care 2014;37:1759–1766.
33. Quinn CC, Shardell MD, Terrin ML, et al.: Cluster-randomized trial of a mobile phone personalized behavioral intervention for blood glucose control. Diabetes Care 2011; 34:1934–1942.
34. Quinn CC, Shardell MD, Terrin ML, et al.: Mobile diabetes intervention for glycemic control in 45-to 64-year-old persons with type 2 diabetes. J Appl Gerontol 2016;35:227–243.
35. Fortmann AL, Gallo LC, Garcia MI, et al.: Dulce digital: an mHealth SMS-based intervention improves glycemic control in Hispanics with type 2 diabetes. Diabetes Care 2017; 40:1349–1355.
36. Egede LE, Williams JS, Voronca DC, et al.: Randomized controlled trial of technology-assisted case management in low income adults with type 2 diabetes. Diabetes Technol Ther 2017;19:476–482.
37. Ralston JD, Hirsch IB, Hoath J, et al.: Web-based collaborative care for type 2 diabetes a pilot randomized trial. Diabetes Care 2009;32:234–239.
38. Alharbi NS, Alsubki N, Jones S, et al.: Impact of information technology-based interventions for type 2 diabetes mellitus on glycemic control: a systematic review and meta-analysis. J Med Internet Res 2016;18:e310.
39. Verhoeven F, van Gemert-Pijnen L, Dijkstra K, et al.: The contribution of teleconsultation and videoconferencing to diabetes care: a systematic literature review. J Med Internet Res 2007;9:e37.
40. Zhai YK, Zhu WJ, Cai YL, et al.: Clinical- and cost-effectiveness of telemedicine in type 2 diabetes mellitus: a systematic review and meta-analysis. Medicine (Baltimore) 2014;93:e312.
41. Huang ZR, Tao H, Meng QD, Jing L: Management of endocrine disease effects of telecare intervention on glycemic control in type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials. Eur J Endocrinol 2015;172:R93–R101.
42. Saffari M, Ghanizadeh G, Koenig HG: Health education via mobile text messaging for glycemic control in adults with type 2 diabetes: a systematic review and meta-analysis. Prim Care Diabetes 2014;8:275–285.
43. UK Prospective Diabetes Study (UKPDS) Group: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of compli-

cations in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837–853.
44. Svensson E, Baggesen LM, Johnsen SP, et al.: Early glycemic control and magnitude of HbA1c reduction predict cardiovascular events and mortality: population-based cohort study of 24,752 metformin initiators. Diabetes Care 2017;40:800–807.
45. Welch G, Garb J, Zagarins S, et al.: Nurse diabetes case management interventions and blood glucose control: results of a meta-analysis. Diabetes Res Clin Pract 2010;88:1–6.
46. Fu R, Vandermeer BW, Shamliyan TA, et al.: Handling continuous outcomes in quantitative synthesis. In: Methods Guide for Effectiveness and Comparative Effectiveness Reviews. Rockville, MD, 2008.
47. McKenzie JE, Herbison GP, Deeks JJ: Impact of analysing continuous outcomes using final values, change scores and analysis of covariance on the performance of meta-analytic methods: a simulation study. Res Synth Methods 2016;7:371–386.
48. Morris SB, DeShon RP: Combining effect size estimates in meta-analysis with repeated measures and independent-groups designs. Psychol Methods 2002;7:105–125.
49. Riley RD, Kauser I, Bland M, et al.: Meta-analysis of randomised trials with a continuous outcome according to baseline imbalance and availability of individual participant data. Stat Med 2013;32:2747–2766.
50. van Vugt M, de Wit M, Cleijne WH, Snoek FJ: Use of behavioral change techniques in web-based self-management programs for type 2 diabetes patients: systematic review. J Med Internet Res 2013;15:e279.
51. Michie S, Fixsen D, Grimshaw JM, Eccles MP: Specifying and reporting complex behaviour change interventions: the need for a scientific method. Implement Sci 2009;4:40.
52. Michie S, Richardson M, Johnston M, et al.: The behavior change technique taxonomy (v1) of 93 hierarchically clustered techniques: building an international consensus for the reporting of behavior change interventions. Ann Behav Med 2013;46:81–95.
53. Kebede MM, Liedtke TP, Möllers T, Pischke P: Characterizing active ingredients of eHealth interventions targeting persons with poorly controlled type 2 diabetes mellitus using the behavioral change technique taxonomy. J Med Internet Res 2017;19:e348.
54. Moher D, Liberati A, Tetzlaff J, et al.: Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6:e1000097.
55. Kebede M, Christianson L, Khan Z, et al.: Effectiveness of behavioral change techniques employed in eHealth interventions designed to improve glycemic control in persons with poorly controlled type 2 diabetes: a systematic review and meta-analysis protocol. Syst Rev 2017;6:211.
56. American Diabetes Association: Standards of medical care in diabetes—2014. Diabetes Care 2014;37(Suppl 1):S14–S80.
57. Covidence: Systematic Review Software. Melbourne, Australia: Veritas Health Innovation.
58. Michie S, van Stralen MM, West R: The behaviour change wheel: a new method for characterising and designing behaviour change interventions. Implement Sci 2011;6:42.
59. Higgins JPT, Altman DG, Gøtzsche PC, et al.: The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.
60. Review Manager (RevMan) [Computer Program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.
61. Cochrane Handbook [article online]. 2011. http://handbook-5-1.cochrane.org (accessed May 20, 2018).
62. Wakefield BJ, Koopman RJ, Keplinger LE, et al.: Effect of home telemonitoring on glycemic and blood pressure control in primary care clinic patients with diabetes. Telemed J E Health 2014;20:199–205.
63. Arora S, Peters AL, Burner E, et al.: Trial to examine text message-based mHealth in emergency department patients with diabetes (TExT-MED): a randomized controlled trial. Ann Emerg Med 2014;63:745–754.e6.
64. Hozo SP, Djulbegovic B, Hozo I: Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol 2005;5:13.
65. Cho J-H, Kwon H-S, Kim H-S, et al.: Effects on diabetes management of a health-care provider mediated, remote coaching system via a PDA-type glucometer and the Internet. J Telemed Telecare 2011;17:365–370.
66. Torbjørnsen A, Jenum AK, Småstuen MC, et al.: A low-intensity mobile health intervention with and without health counseling for persons with type 2 diabetes, part 1: baseline and short-term results from a randomized controlled trial in the Norwegian part of RENEWING HEALTH. JMIR Mhealth Uhealth 2014;2:e52.
67. Cradock KA, ÓLaighin G, Finucane FM, et al.: Behaviour change techniques targeting both diet and physical activity in type 2 diabetes: a systematic review and meta-analysis. Int J Behav Nutr Phys Act 2017;14:18.
68. Higgins JP, Thompson SG, Deeks JJ, Altman DG: Measuring inconsistency in meta-analyses. BMJ 2003;327:557–560.
69. Borenstein M, Hedges LV, Higgins JPT, Rothstein HR: Notes on subgroup analyses and meta-regression. In: Introduction to Meta-Analysis, Hoboken, New Jersey, USA. John Wiley & Sons, Ltd., 2009, pp. 205–212.
70. Egger M, Davey Smith G, Schneider M, Minder C: Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–634.
71. Duval S, Tweedie R: A nonparametric ''Trim and Fill'' method of accounting for publication bias in meta-analysis. J Am Stat Assoc 2000;95:89–98.
72. Guyatt GH, Oxman AD, Vist GE, et al.: GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924–926.
73. GRADE Handbook for Grading Quality of Evidence and Strength of Recommendations [article online]. Updated October 2013. http://gdt.guidelinedevelopment.org/app/handbook/handbook.html (accessed October 20, 2017).
74. GRADEpro Guideline Development Tool [Software]. McMaster University, 2015 (developed by Evidence Prime, Inc.). 2015. gradepro.org (accessed July 9, 2018).
75. Agboola S, Jethwani K, Lopez L, et al.: Text to move: a randomized controlled trial of a text-messaging program to improve physical activity behaviors in patients with type 2 diabetes mellitus. J Med Internet Res 2016;18:e307.
76. Capozza K, Woolsey S, Georgsson M, et al.: Going mobile with diabetes support: a randomized study of a text message-based personalized behavioral intervention for type 2 diabetes self-care. Diabetes Spectr 2015;28:83–91.
77. Cho JH, Kim HS, Yoo SH, et al.: An Internet-based health gateway device for interactive communication and automatic data uploading: clinical efficacy for type 2 diabetes in a multi-centre trial. J Telemed Telecare 2017;23:595–604.
78. Dario C, Toffanin R, Calcaterra F, et al.: Telemonitoring of type 2 diabetes mellitus in Italy. Telemed J E Health 2017;23:143–152.

79. Hansen CR, Perrild H, Koefoed BG, Zander M: Video consultations as add-on to standard care among patients with type 2 diabetes not responding to standard regimens: a randomized controlled trial. Eur J Endocrinol 2017;176: 727–736.
80. Holmen H, Torbjornsen A, Wahl AK, et al.: A mobile health intervention for self-management and lifestyle change for persons with type 2 diabetes, part 2: one-year results from the Norwegian randomized controlled trial RENEWING HEALTH. JMIR Mhealth Uhealth 2014;2:e57.
81. Khanna R, Stoddard PJ, Gonzales EN, et al.: An automated telephone nutrition support system for Spanish-speaking patients with diabetes. J Diabetes Sci Technol 2014;8: 1115–1120.
82. Kim HS, Sun C, Yang SJ, et al.: Randomized, open-label, parallel group study to evaluate the effect of internet-based glucose management system on subjects with diabetes in China. Telemed J E Health 2016;22:666–674.
83. Kleinman NJ, Shah A, Shah S, et al.: Improved medication adherence and frequency of blood glucose self-testing using an m-Health platform versus usual care in a multisite randomized clinical trial among people with type 2 diabetes in India. Telemed J E Health 2017;23:733–740.
84. Liou JK, Soon MS, Chen CH, et al.: Shared care combined with telecare improves glycemic control of diabetic patients in a rural underserved community. Telemed J E Health 2014;20:175–178.
85. Tang PC, Overhage JM, Chan AS, et al.: Online disease management of diabetes: engaging and motivating patients online with enhanced resources-diabetes (EMPOWER-D), a randomized controlled trial. J Am Med Inform Assoc 2013;20:526–534.
86. Tildesley HD, Mazanderani AB, Chan JHM, Ross SA: Efficacy of A1C reduction using Internet intervention in patients with type 2 diabetes treated with insulin. Can J Diabetes 2011;35:250–253.
87. Wang G, Zhang Z, Feng Y, et al.: Telemedicine in the management of type 2 diabetes mellitus. Am J Med Sci 2017; 353:1–5.
88. Welch G, Zagarins SE, Santiago-Kelly P, et al.: An internet-based diabetes management platform improves team care and outcomes in an urban Latino population. Diabetes Care 2015;38:561–567.
89. Wild SH, Hanley J, Lewis SC, et al.: Supported telemonitoring and glycemic control in people with type 2 diabetes: the Telescot diabetes pragmatic multicenter randomized controlled trial. PLoS Med 2016;13:1–16.
90. Greenwood DA, Gee PM, Fatkin KJ, Peeples M: A systematic review of reviews evaluating technology-enabled diabetes self-management education and support. J Diabetes Sci Technol 2017;11:1015–1027.
91. Schulz KF, Chalmers I, Hayes RJ, Altman DG: Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. JAMA 1995;273:408–412.
92. Wood L, Egger M, Gluud LL, et al.: Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study. BMJ 2008;336:601–605.
93. Health Quality Ontario: Behavioural interventions for type 2 diabetes: an evidence-based analysis. Ont Health Technol Assess Ser 2009;9:1–45.
94. Avery L, Flynn D, Dombrowski SU, et al.: Successful behavioural strategies to increase physical activity and improve glucose control in adults with type 2 diabetes. Diabet Med 2015;32:1058–1062.
95. Kassavou A, Sutton S: Automated telecommunication interventions to promote adherence to cardio-metabolic medications: meta-analysis of effectiveness and meta-regression of behaviour change techniques. Health Psychol Rev 2018;12:25–42.
96. Thompson SG, Higgins JP: How should meta-regression analyses be undertaken and interpreted? Stat Med 2002;21: 1559–1573.
97. Michie S, Wood CE, Johnston M, et al.: Behaviour change techniques: the development and evaluation of a taxonomic method for reporting and describing behaviour change interventions (a suite of five studies involving consensus methods, randomised controlled trials and analysis of qualitative data). Health Technol Assess 2015; 19:1–188.
98. Borrelli B: The assessment, monitoring, and enhancement of treatment fidelity in public health clinical trials. J Public Health Dent 2011;71:S52–S63.
99. Johnston M, Johnston D, Wood CE, et al.: Communication of behaviour change interventions: can they be recognised from written descriptions? Psychol Health 2018; 33:713–723.

Address correspondence to:
Mihiretu M. Kebede, BSc, MPH
Unit Applied Health Intervention Research
Department of Prevention and Evaluation
Leibniz Institute for Prevention Research
and Epidemiology–BIPS
Achterstrasse 30
Bremen D-28359
Germany

E-mail: kebede@leibniz-bips.de

STUDY II

Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy Dovepress
open access to scientific and medical research

Open Access Full Text Article

METHODOLOGY

Comparison of three meta-analytic methods using data from digital interventions on type 2 diabetes

This article was published in the following Dove Press journal:
Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy

Mihiretu M Kebede[1–3]
Manuela Peters[1,2]
Thomas L Heise[1,2]
Claudia R Pischke[2]

[1]Department of Public Health, University of Bremen, Health Sciences, Bremen, Germany; [2]Department of Prevention and Evaluation, Leibniz Institute for Prevention Research and Epidemiology – BIPS, Bremen, Germany; [3]Department of Health Informatics, University of Gondar, College of Medicine and Health Science, Institute of Public Health, Gondar, Ethiopia

Aims: Pooling the effect sizes of randomized controlled trials (RCTs) from continuous outcomes, such as glycated hemoglobin level (HbA1c), is an important method in evidence syntheses. However, due to challenges related to baseline imbalances and pre/post correlations, simple analysis of change scores (SACS) and simple analysis of final values (SAFV) meta-analyses result in under- or overestimation of effect estimates. This study was aimed to compare pooled effect sizes estimated by Analysis of Covariance (ANCOVA), SACS, and SAFV meta-analyses, using the example of RCTs of digital interventions with HbA1c as the main outcome.

Materials and methods: Three databases were systematically searched for RCTs published from 1993 through June 2017. Two reviewers independently assessed titles and abstracts using predefined eligibility criteria, assessed study quality, and extracted data, with disagreements resolved by arbitration from a third reviewer.

Results: ANCOVA, SACS, and SAFV resulted in pooled HbA1c mean differences of –0.39% (95% CI: [–0.51, –0.26]), –0.39% (95% CI: [–0.51, –0.26]), and –0.34% (95% CI: [–0.48–0.19]), respectively. Removing studies with both high baseline imbalance (≥±0.2%) and pre/post correlation of ≥±0.6 resulted in a mean difference of –0.39% (95% CI: [–0.53, –0.26]), –0.40% (95% CI: [–0.54, –0.26]), and –0.33% (95% CI: [–0.48, –0.18]) with ANCOVA, SACS, and SAFV meta-analyses, respectively. Substantial heterogeneity was noted. Egger's test for funnel plot symmetry did not indicate evidence of publication bias for all methods.

Conclusion: By all meta-analytic methods, digital interventions appear effective in reducing HbA1c in type 2 diabetes. The effort to adjust for baseline imbalance and pre/post correlation using ANCOVA relies on the level of detail reported from individual studies. Reporting detailed summary data and, ideally, access to individual patient data of intervention trials are essential.

Keywords: baseline imbalance, ANCOVA, change scores, final values, systematic reviews, HbA1c, diabetes, eHealth

Background

The number of published research doubles every 9 years,[1] and its growth particularly in medicine and health care is exponential.[2] In 2010, 11 systematic reviews and 75 trials were reported to be published every day. In this fast growing era of medical research publishing, being up-to-date in the latest medical and health care evidence is important but not easy.[2]

Medical or health care studies often deal with similar or related research questions at different locations, with different populations, at different time points. These studies are many in number, and their results are often diverse or sometimes contradictory.[3]

Correspondence: Mihiretu M Kebede
Department of Prevention and Evaluation, Leibniz Institute for Prevention Research and Epidemiology – BIPS, Achterstrasse 30, D-28359 Bremen, Germany
Tel +49 421 2185 6916
Fax +49 421 2185 6941
Email kebede@leibniz-bips.de

submit your manuscript | www.dovepress.com
Dovepress
http://dx.doi.org/10.2147/DMSO.S180106

Importantly, medical and health care decisions require up-to-date and consolidated evidence. Meta-analysis offers a strategy to collect evidence available from individual studies and quantify the effect of interventions, prevalence of diseases, or risk factors associated with diseases.[4]

Rigorous meta-analyses are fundamental for estimating the true effects of interventions which guide clinical and public health practice.[3,5,6] Most medical journals encourage or call for aggregation of evidence using meta-analyses and the number of meta-analyses in the medical research has exponentially grown from what it was in the 1990s.[3,6] Meta-analysis has also become a very important aspect of diabetes research. A simple PubMed search on diabetes and meta-analysis resulted in about 10,000 meta-analyses articles published so far (https://www.ncbi.nlm.nih.gov/pubmed/?term=diabetes+and+(meta-analys*+or+metaanalys*)).[7]

A well-conducted meta-analysis is a powerful tool for informing medicine and health care decisions.[3,6,8] However, there are many challenges that meta-analyses authors face, for instance, clinical, methodological and statistical heterogeneity, publication bias, language barriers, outcome definitions, and statistical challenges.[6,8,9] Meta-analyses of continuous outcomes are recognized to be more challenging than those with binary outcomes.[10,11]

In meta-analyses of continuous outcomes, mean difference (MD), standardized mean difference, and ratio of means are used as effect size measures. The choice of the two most commonly used effect size measures, ie, MD and standardized mean difference, of continuous outcomes is mainly determined by the scale of measurement. If the scale of measurement is similar as in glycated hemoglobin level (HbA1c), the MD can be used to aggregate effect sizes across studies. To pool the effect sizes of continuous outcomes, it is important to consider whether the baseline MD of the outcome data between the intervention and control groups is adequately balanced.[12,13] In general, baseline imbalance can result from chance especially in small trials, or selection bias due to inadequate allocation concealment or poor randomization.[14] Therefore, in meta-analysis, it is important to consider accounting for baseline imbalance and pre/post correlation.[13,15–17] However, the meta-analyses available so far have by and large not taken into account a specific methodological challenge posed by baseline imbalances between groups.

None of the previous meta-analyses on digital interventions on type 2 diabetes that we have identified through scoping were adjusted for baseline imbalances and pre/post correlations. Meta-analyses of randomized control trials reporting continuous outcomes, such as HbA1c, with high baseline imbalances require adjustments using an Analyses of Covariance (ANCOVA effect size estimator, both at a pooled and individual study levels.[13,15–17] ANCOVA produces a relatively more precise effect size estimate than simple analysis of change scores (SACS) and simple analysis of final values (SAFV).[13,15,16]

While there is methodological guidance available to employ ANCOVA effect size, the unavailability of summary data from randomized controlled trials (RCTs) or absence of individual participant data (IPD), as well as the complexity of the ANCOVA methodology, has limited its application to synthesize continuous outcomes in the medical literature.[13,15–17] Although it is important to recognize that determining precise effect sizes is essential to understand the true effect of interventions to guide clinical and public health practice, to our knowledge, no study has applied ANCOVA to determine changes in HbA1c level effect sizes of digital interventions on type 2 diabetes. Therefore, this study was aimed to compute and compare changes in HbA1c effect sizes of digital interventions on type 2 diabetes using ANCOVA, SACS, and SAFV meta-analyses.

Materials and methods

This meta-analysis uses data from our recently completed systematic review and meta-analyses on digital interventions among poorly controlled type 2 diabetes mellitus (T2DM) patients.[18] The detailed description of the protocol and the systematic review methods followed can be accessed elsewhere.[18,19] Briefly, we searched three databases (MEDLINE via PubMed, ISI Web of Science via Thomson Reuters, and PsycINFO via OvidSP) for English language RCTs employing digital interventions among persons with poorly controlled type 2 diabetes, and published until the end of June 2017. Details of search strategy are available elsewhere.[18,19] In this study, technology-based interventions delivered via mHealth, web-based applications, Personal Digital Assistant, tablet, computer, or other forms of eHealth applications were considered as digital interventions.[18,20]

Two authors (MK and MP) independently conducted title, abstract, and full-text screening using Covidence. Methodological quality assessment was conducted using the Cochrane Risk of Bias Assessment tool for RCTs.[21] Two reviewers (MK and MP) independently conducted the risk of bias assessment by using Covidence[22] and discussed quality ratings until consensus was reached. The risk of bias tool consists of seven domains which were rated as low, high,

or unclear risk of bias. To rate "other sources of bias," the recommendation by Fu et al[13] was used, which focuses on the question whether the baseline distribution of participant characteristics and outcome data of both control and intervention groups are sufficiently described and balanced. Beside this, quality rating should include whether there was baseline imbalance and high rate of attrition. Therefore, quality ratings for this domain were downgraded if important baseline prognostic factors and outcome variables were not balanced in the included studies.[13]

Missing crude or pooled SD values were computed from the reported standard errors, confidence intervals, or from exact reported *P*-values using functions in Microsoft Excel. If an exact *P*-value was reported, depending on the statistical test used, we calculated *z*- or *t*-scores using the function normsinv(1 – *P*-value/2) or tinv(*P*-value, degree of freedom).[13,23] Whenever SD could not be calculated from the reported data, we contacted the corresponding and the last authors. If no response was obtained, SD values were imputed using arithmetic means.[13] Using this method, we computed the SD values for the follow-up mean HbA1c values from a study by Wakefield et al.[24] One study[25] reported median HbA1c with its range, but mean and SD values were not available from the authors. After contacting the corresponding author was not successful, we estimated the mean and SD values from the reported median and range using Hozo's formula.[26]

Pre/post correlations were not reported in the majority of the studies. However, it is necessary to account for them in meta-analyzing the effect sizes of continuous outcomes.[13,15] Our approach accounting for this issue was based on recommendations of previous methodological studies. If a study reported baseline and follow-up standard deviations (SDb and SDf), and standard deviation values for change scores (SDd), we computed pre/post correlation using $r = \frac{SDb^2 SDf^2 - SDd^2}{2SDb^2 SDf^2}$.[13] Whenever, baseline and follow-up SD were not known, correlation was estimated from the pooled SD (SDp) and change score SD (SDd) values using $r = 1 - \frac{SDd^2}{SDp^2}$.[16]

Data syntheses and analysis

As highlighted in the previous sections, effect sizes of continuous outcomes with an inherently similar scale of measurement can be computed using three methods: SAFV, SACS, or using the ANCOVA effect size estimator.[13,15–17] In comparison to MD computed through using either SAFV or SACS, the ANCOVA effect size estimator provides a more precise and unbiased effect size estimates.[13,15–17] The ANCOVA effect size estimator reduces the bias that arises from baseline imbalance across the included studies and accounts for pre-/post-test correlation.[13,15,17,27] In this systematic review, the absolute value of the mean baseline HbA1c differences between intervention and control groups in the included studies ranged from 0% to 0.64%, with only two RCTs having perfectly balanced MDs.[28,29] Given no publication bias, if the two treatment groups are balanced, meta-analysis of baseline score differences between control and intervention groups produces a combined effect size estimate of close to zero.[13] Therefore, we conducted a meta-analysis of the baseline MDs across the included studies. Further, random-effects meta-analysis of the baseline MDs resulted in a pooled HbA1c difference of 0.14% (95%CI: [–0.31, 0.59]). In addition, the computed pre/post correlation values ranged from –0.06 in a study by Ralston et al[30] to 0.74 in a study by Torbjønsen et al.[31] Hence, to adjust for the observed baseline imbalance and pre-/post-test correlation, ANCOVA effect size estimator was preferred to pool the mean HbA1c difference. If reported, ANCOVA effect size estimates were extracted directly from studies. Whether studies reported effect sizes using SACS, SAFV, or ANCOVA was also documented.

Assuming *Xint* and *Xctrl* are the baseline mean values of intervention and control groups while *Yint* and *Yctrl* are the follow-up mean values, the MD from SAFVs was computed as follows: $SAFS = Yint - Yctrl$, while MD from SACS was computed using $SACS = (Yint - Yctrl) - (Xint - Xctrl)$. Moreover, an ANCOVA effect size estimate was modeled using $ANCOVA = (Yint - Yctrl) - \beta\,(Xint - Xctrl)$, where β is a regression coefficient calculated by using $\beta = r\frac{SDy}{SDx}$. *SDy* and *SDx* are the pooled SD values of the treatment and control groups.[13,15] The variances of the final values, change scores, and ANCOVA effect size estimates were computed using equations by Jo McKenzie et al[15] and Riley et al.[17] Whenever there was no possibility to compute the ANCOVA effect size estimator, the reported change scores or final values were pooled with the ANCOVA effect size estimates, following the strategy documented in the existing methodology literature.[13,15,17] If a study reported both SACS and final values, the estimate with a smaller effect size was combined with the ANCOVA effect size estimates. Practically, studies having zero or negligible baseline MD, equivalent or close to equivalent MD values were obtained using any of the three methods. Therefore, for studies having no or a negligible baseline difference, adding any of the three estimates in the meta-analysis yielded comparable pooled estimates.[13,15]

Meta-analyses

All meta-analyses were performed using Stata version 13. Studies that were judged as homogenous in terms of participants, type of interventions, and type and scale of measurement of the outcome were subsequently combined to determine the overall pooled effectiveness of digital interventions for reducing HbA1c levels.

For each study, we calculated three effect size measures using the "black-belt" ANCOVA, SACS, and SAFV approaches to compare individual and pooled effect size differences.

For all meta-analyses, observed statistical heterogeneity across studies was assessed with Cochrane's chi-squared test. The degree of heterogeneity was quantified using the I^2 statistic. In addition to statistical heterogeneity, the diversity of studies with respect to clinical and methodological aspects was assessed to choose from random- or fixed-effects meta-analysis. Hence, random-effects meta-analysis was used for all meta-analyses.[32] Sensitivity analyses were performed by 1) dropping studies with baseline imbalance (baseline mean difference ≥±0.2, or ≥±0.3) and 2) removing studies having high pre/post correlations (>±0.7 and >±0.6).

For all the three meta-analytic methods, differences in the publication bias were compared using visual inspection of the funnel plots and statistically using Egger's test with a *P*-value <0.1 indicating publication bias.[33] The number of missing studies in the funnel plots was estimated using the "trim and fill" imputation method to determine the changes in effect size estimate across the three methods.[34]

Results

Study selection and characteristics

In total, 1,669 abstracts and titles were retrieved from the database search. Twenty-two studies fulfilled the inclusion criteria.[24,25,28–31,35–50] Twenty-three arms of 21 RCTs were included in the quantitative syntheses. Two studies reported results of three-armed RCTs.[31,41] All of the 21 control groups of the 21 RCTs received standard or usual care. The details of the study selection procedure and the PRISMA flowchart can be accessed in our previously reported meta-analysis.[18]

Studies included in our review were published between 2009 and 2017. A majority (n=9) of the studies were conducted in the United States. In the 23 intervention arms of the 21 RCTs, 3,787 patients were included and followed for an average of 7.3 months (SD=3.05). Average retention rate at a study end point was 89.4% (SD=10.0, range =75% to100%), whereas attrition rate was 10.6% (SD=10.0; Table 1). One study was judged to have low risk of bias on all dimensions of the Cochrane risk of bias assessment tool.[50] Four studies were considered to have a high risk of bias on three domains.[36,38,43,45]

The mean HbA1c baseline difference of the studies included in the quantitative syntheses ranged from –0.2%[24,41] to 0.64%.[35] Only two RCTs[29,37] had a perfect baseline balance with a mean HbA1c difference of 0.0%. The pooled baseline difference was 0.14% (95%CI: [–0.31, 0.59]).

Differences in individual and pooled effect sizes

Multivariate test of means showed that the MDs estimated using the three methods across the studies were not statistically different (Hotelling $T2$=4.65, Hotelling, $F(2, 21)$=2.22, Prob>F=0.134). Visual inspection of a box plot constructed using the individual studies' MD values obtained using the three methods also did not indicate substantial differences (Figure 1).

The pooled mean HbA1c difference calculated using the ANCOVA approach yielded a statistically significant pooled HbA1c reduction of –0.39% (95%CI: [–0.51, –0.26]) favoring the intervention group, with considerable heterogeneity statistic (I^2=80.8%; Figure 2).

MD aggregated using meta-analysis of change scores and final values also yielded statistically significant effect estimates ie, –0.39% (95%CI: [–0.51, –0.26]; Figure 3) and –0.34% (95%CI: [–0.48, –0.19]; Figure 4), respectively. The heterogeneity I^2 statistics for change scores and final values meta-analyses were 32.3% and 64.5%, respectively. All of the above results are from the random effects meta-analysis. Considering the I^2 statistics for change scores, we conducted a fixed-effects meta-analysis. The pooled MD was –0.37% (95%CI: [–0.468, –0.268]; Figure 5).

Publication bias

Visual inspection of the funnel plots that were obtained using effect sizes of ANCOVA and SACS shows symmetry at the top of the plot, and there were studies missing at the bottom of the funnel plot indicating publication bias. However, a relatively symmetric funnel plot was obtained from effect sizes computed using SAFV (Figure 6).

Egger's test for funnel plot symmetry obtained from the three methods suggested that there is not enough evidence for small-study effects (Table 2).

Performing the "trim and fill" test using effect sizes of ANCOVA and SAFV did not result in changes suggesting that the influence of publication bias was negligible. However, performing the "trim and fill" test using effect sizes

Table 1 Characteristics of the included studies

Study	Location	Intervention	Intervention end points (in months)	Study population	Baseline HbA1c (%)	Included (N)	Intention to treat analysis						
							N control group	N intervention group	Analyzed control	Analyzed intervention	Loss to follow-up	Loss to follow-up %	Retention %
	Mobile phone-delivered text message interventions												
Agboola et al, 2016[35]	USA	Text to move (text message)	6	Spanish- or English-speaking low-income and ethnic minorities, T2DM patients	>7.0	126	62	64	62	64	0	0.00	100.0
Arora et al, 2014[25]	USA	Two daily text messages for 6 months. Education/ motivation–one text per day, medication reminders–three per week, healthier living challenge–two per week. Trivia: Unidirectional text message	6	English- or Spanish-speaking Latino and black T2DM patients	>7.5	128	64	64	45	47	36	28.1	71.9
Capozza et al, 2015[36]	USA	Text message (Care4Life program) for education and motivation, medication adherence, glucose control, weight, and exercise	3 and 6	No specific population, adult patients with T2DM	>7.5	156	Not reported	Not reported	35	58	11	7.0	93
Fortmann et al, 2017[39]	Canada	Dulce Digital: An mHealth SMS-Based Intervention	3 and 6	Underserved Hispanics with poor glycemic control, T2DM patients	≥7.5	126	63	63	60	53	13	10.3	89.7
	PDA, tablet, computer, and/or smartphone delivered web-based interventions												
Cho et al, 2011[28]	South Korea	Internet diabetes management	3	No specific population, T2DM patients, South Koreans	>7.0	71	35	36	32	32	7	9.9	90.1

(*Continued*)

Table 1 (*Continued*)

Study	Location	Intervention	Intervention end points (in months)	Study population	Baseline HbA1c (%)	Included (N)	Intention to treat analysis						
							N control group	N intervention group	Analyzed control	Analyzed intervention	Loss to follow-up	Loss to follow-up %	Retention %
Egede et al, 2017[29]	USA	Telehealth and clinical decision support system	3 and 6	Type 2 diabetes, ≥18 years, T2DM patients	≥8.0	113	59	54	44	41	28	24.8	75.2
Holmen et al, 2014[41] (Usual Care vs FTA-HC)	Norway	Few Touch Application (diabetes diary app with health counseling (FTA-HC)	12	No specific population, adult patients with T2DM	>7.0	100	50	50	41	40	18	18.0	82
Holmen et al, 2014[41] (Usual Care vs FTA)	Norway	Few Touch Application (diabetes diary app without health counseling (FTA-HC)	12	No specific population, adult patients with T2DM	>7.0	101	50	51	41	39	19	19.0	81
Kim et al, 2016[43]	China	Internet-based glucose monitoring system	3 and 6	Male and female outpatients with T2DM patients	7.0 to 10.0	182	90	92	90	92	0	0.0	100.0
Kleinman et al, 2017[44]	India	Smart phone app for patients and smart phone app and a web-based portal for providers	3	No specific population, T2DM patients for >6 months	7.5 to 12.5	90	46	44	33	35	22	24.4	75.6
Ralston et al, 2009[30]	USA	Web-based care management	12	No specific population, adult patients with T2DM	>7.0	83	41	42	35	39	9	10.8	89.2
Tang et al, 2013[46]	USA	Online disease management system	6 and 12	No specific population, adult patients with T2DM	>7.5	415	213	202	193	186	36	8.67	91.33
Tildesley et al, 2011[47]	Canada	Internet-based glucose monitoring system (IBGMS)	3, 6, and 12	No specific population, T2DM patients	>7.0	46	23	23	23	23	0.0	0.0	100.0
Trobjohnsen 2014[69] (Usual Care vs FTA-HC)	Norway	Few Touch Application (diabetes diary app with health counseling (FTA-HC)	4	No specific population, adult patients with T2DM	>7.0	100	50	50	43	44	13	13.0	87

Trobjohnsen 2014 (Usual Care[69] vs FTA)	Norway	Few Touch Applications (diabetes diary app without health counseling (FTA-HC)	4	No specific population, adult patients with T2DM	>7.0	101	50	51	42	44	12	12.0	88
Wang et al, 2017[48]	China	Monitoring via computer/web/ mobile phone connected to glucometer via cable	3 and 6	No specific population, T2DM patients confirmed for over 1 year	7 to 10.0	212	106	106	106	106	0	0.0	100.0
Welch et al, 2015[49]	USA	Internet-based integrated diabetes management system	6	Latino, T2DM patients	>7.5	399	200	199	181	172	46	11.5	88.5
Wild et al, 2016[50]	Scotland	Monitoring through computer-/web-based/mobile phone connected to glucometer via modem	9	No specific population, T2DM aged >17 years	>7.5	321	161	160	139	146	36	11.2	88.8
Telehealth (communication with provider via telephone or video)													
Dario et al, 2017[38]	Italy	Videoconferencing	12	No specific population, T2DM patients	>7.0	246	78	168	77	166	3	1.2	98.8
Hansen et al, 2017[40]	Denmark	Videoconferencing	8	Danish speaking T2DM patients	>7.5	165	82	83	71	68	26	15.8	84.2
Khanna et al, 2014[42]	USA	Automated telephone support with dialogic telephone card	3	Spanish-speaking patients with T2DM	>7.5	75	37	38	37	38	0.0	0.0	100.0
Liou et al, 2014[45]	Taiwan	Web-based and videoconferencing	6	No specific population, adult T2DM patients	>7.0	95	41	54	41	54	0	0.0	100.0
Wakefield et al, 2014[24]	USA	Tele-monitoring	3 and 6	No specific population, subjects with established T2DM	>8.0	108	55	53	43	40	25	23.1	76.9
			Mean			180.3	85.5	94.8	75.8	84.6	16.45	9.2	89.8
			Standard deviation			123.8	63.0	63.2	60.7	61.4	15.6	9.8	11.6

Abbreviations: FTA-HC, Few Touch Application (diabetes diary app with health counseling); HbA1c, glycated hemoglobin level; IBGMS, Internet-based glucose monitoring system; T2DM, type 2 diabetes mellitus.

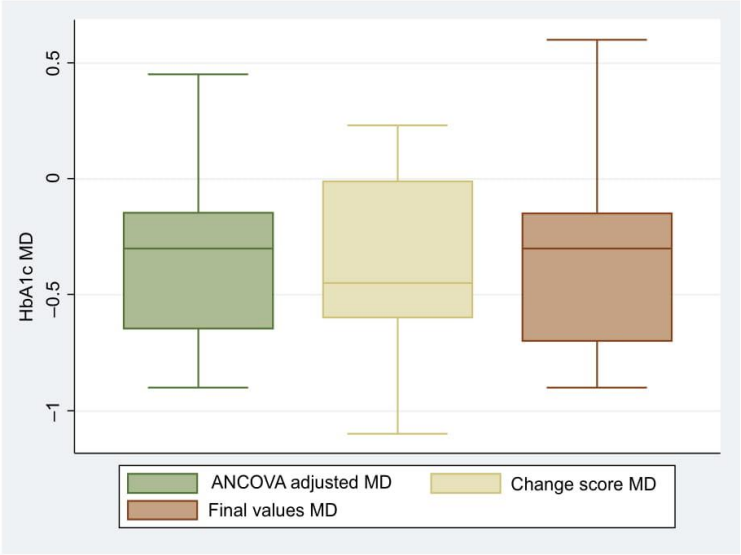


Figure 1 Box plots of ANCOVA, change scores, and final values MDs.
Abbreviations: ANCOVA, analysis of covariance; MD, mean difference.

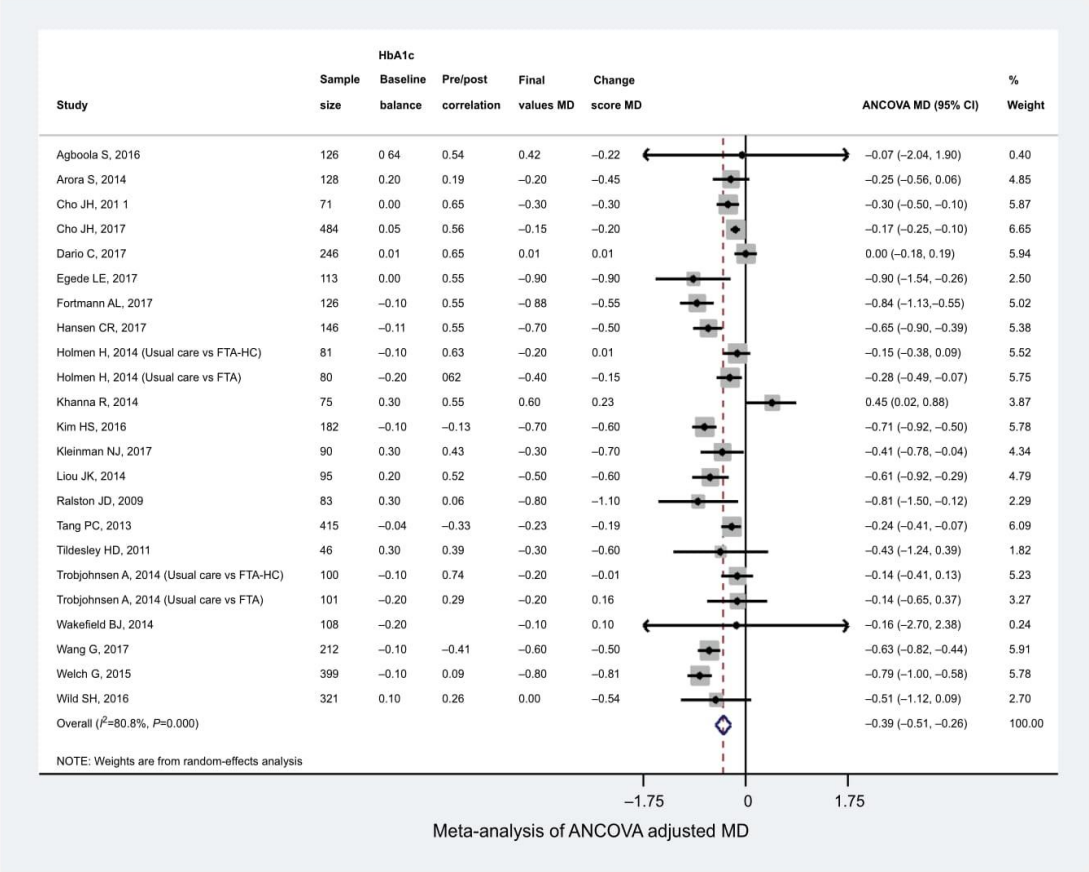


Figure 2 Random-effects meta-analysis of ANCOVA adjusted MDs.
Abbreviation: ANCOVA, analysis of covariance; FTA-HC, Few Touch Application (diabetes diary app with health counseling); MD, mean difference.

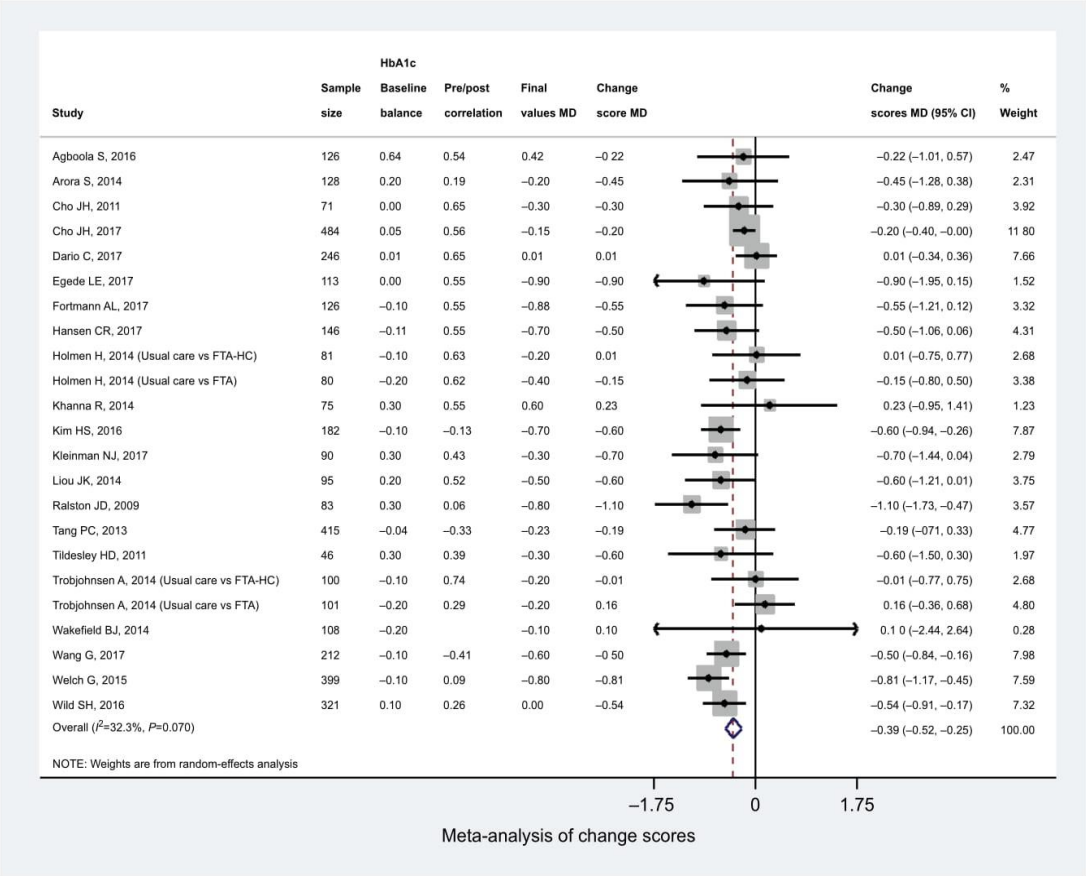


Figure 3 Random-effects meta-analysis of change scores.
Abbreviations: FTA-HC, Few Touch Application (diabetes diary app with health counseling); HbA1c, glycated hemoglobin level; MD, mean difference.

obtained from SACS resulted in imputation of one study and the pooled HbA1c difference was changed into –0.40% (95%CI: −0.53,–0.26) using a random-effects meta-analysis.

Sensitivity analyses

We performed a sensitivity analysis by removing five studies with high baseline imbalance (≥±0.3) from the meta-analysis. The ANCOVA approach resulted in an MD of –0.41% (95%CI: [–0.54, –0.28]), while SAFV and SACS showed an MD of –0.37% (95%CI: [–0.52, –0.22]) and –0.35% (95%CI: [–0.45, –0.242]), respectively (see Supplementary material 1). Expectedly, the differences in the aggregated MDs across the three methods became less prominent when all studies having a baseline MD of ≥0.2 were removed from the meta-analyses. The ANCOVA approach resulted in an MD of –0.43% (95%CI: [–0.597, –0.27]), while SAFV and SACS show an MD of –0.40% (95%CI: [–0.59, –0.216]) and –0.39% (95%CI: [–0.55, –0.23]), respectively (see Supplementary material 1).

Additional sensitivity analyses were performed to check the effect of pre/post correlation on the effect size estimates obtained by the three methods. ANCOVA and SACS resulted in similar estimates but higher than SAFV effect size estimates after dropping studies with high pre/post correlation from the meta-analyses. Hence, ANCOVA and SACS resulted in a pooled effect size estimate of –0.40% (95%CI: [–0.53, –0.27]) and –0.40% (95%CI: [–0.54, –0.26]), respectively, while SAFV resulted in –0.34% (95%CI: [–0.49, –0.19]) after dropping one study with pre/post correlation value >0.7 (see Supplementary material 2). Similarly, dropping five studies with pre/post correlation value >±0.6 shows ANCOVA and SACS yielded a pooled effect size estimate of –0.47% (95%CI: [–0.64, –0.30]), –0.47% (95% CI: [–0.62, –0.32]) respectively, while SAFV provided –0.37% (95%CI: [–0.54,

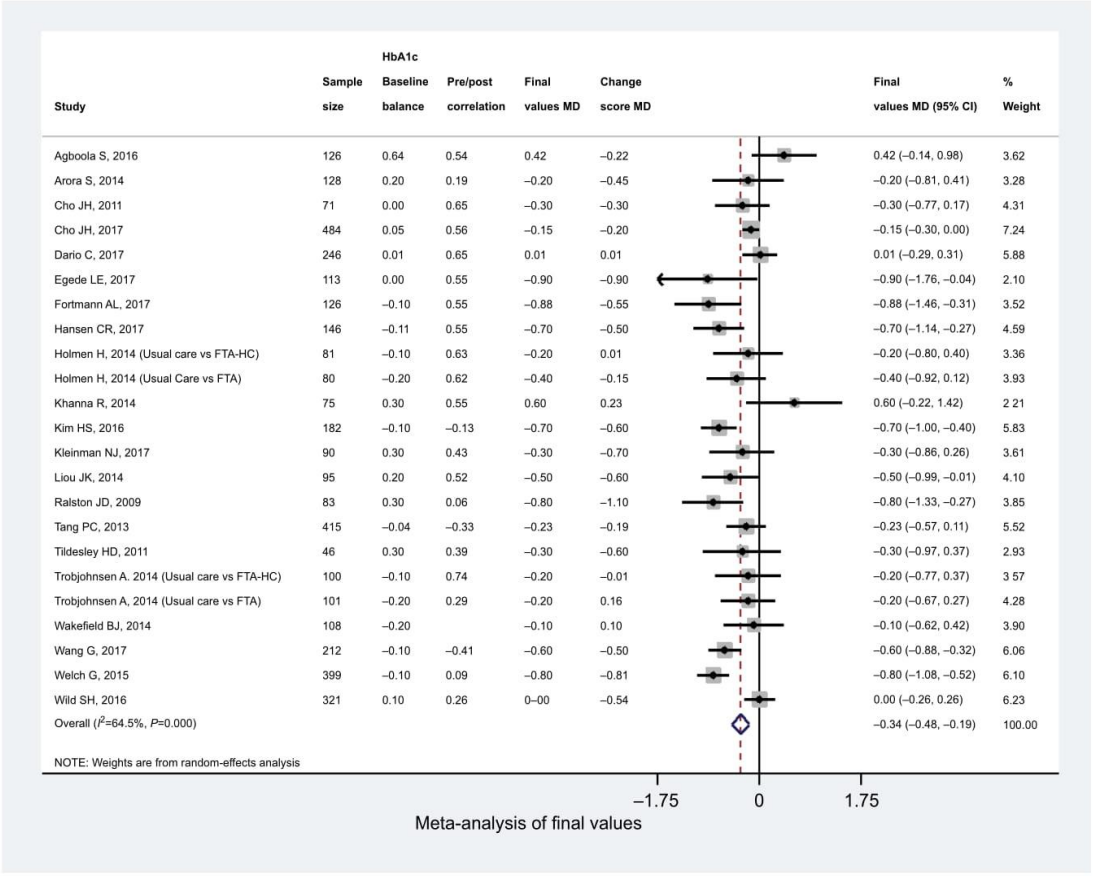


Figure 4 Random-effects meta-analysis of final values.
Abbreviations: FTA-HC, Few Touch Application (diabetes diary app with health counseling); HbA1c, glycated hemoglobin level; MD, mean difference.

–0.20]; see Supplementary material 2). Meta-analyses performed by removing studies with both high baseline imbalance (≥±0.2%) and pre/post correlation of >±0.6 resulted in a pooled MD of –0.39% (95%CI: [–0.53, –0.26]), –0.40% (95%CI: [–0.54, –0.26]), and –0.33% (95%CI: [–0.48, –0.18]) using ANCOVA, SACS, and SAFV meta-analyses, respectively (see Supplementary material 2).

Discussion

This systematic review is the first to compare the effectiveness of digital interventions on changes in HbA1c levels by computing effect size estimates using SACS, SAFV, and ANCOVA adjusted MDs. This is also the first review to account for baseline imbalance and pre/post correlations using available robust statistical methods.

The pooled estimates obtained using the SACS, SAFV, and ANCOVA suggest clinically significant effects of digital interventions meaning reduced HbA1c levels of persons with poorly controlled T2DM. These findings reinforce the previously reported evidence regarding the beneficial effects of digital interventions.[51–53] Digital interventions facilitate diabetes self-management by supporting patients with diabetes to keep track of their blood glucose, physical activity, nutrition, and other clinical and behavioral outcomes related with diabetes.[54–65]

Random-effects meta-analysis using ANCOVA and change scores provided identical effect size estimates. However, fixed-effects meta-analysis using change scores and comparing the results with ANCOVA and final values meta-analyses shows a slight difference in the pooled effect estimates acquired using the three methods. For all meta-analyses, the direction of the effect estimate remained unchanged. Sensitivity analyses performed by removing studies with higher baseline imbalance resulted in relatively

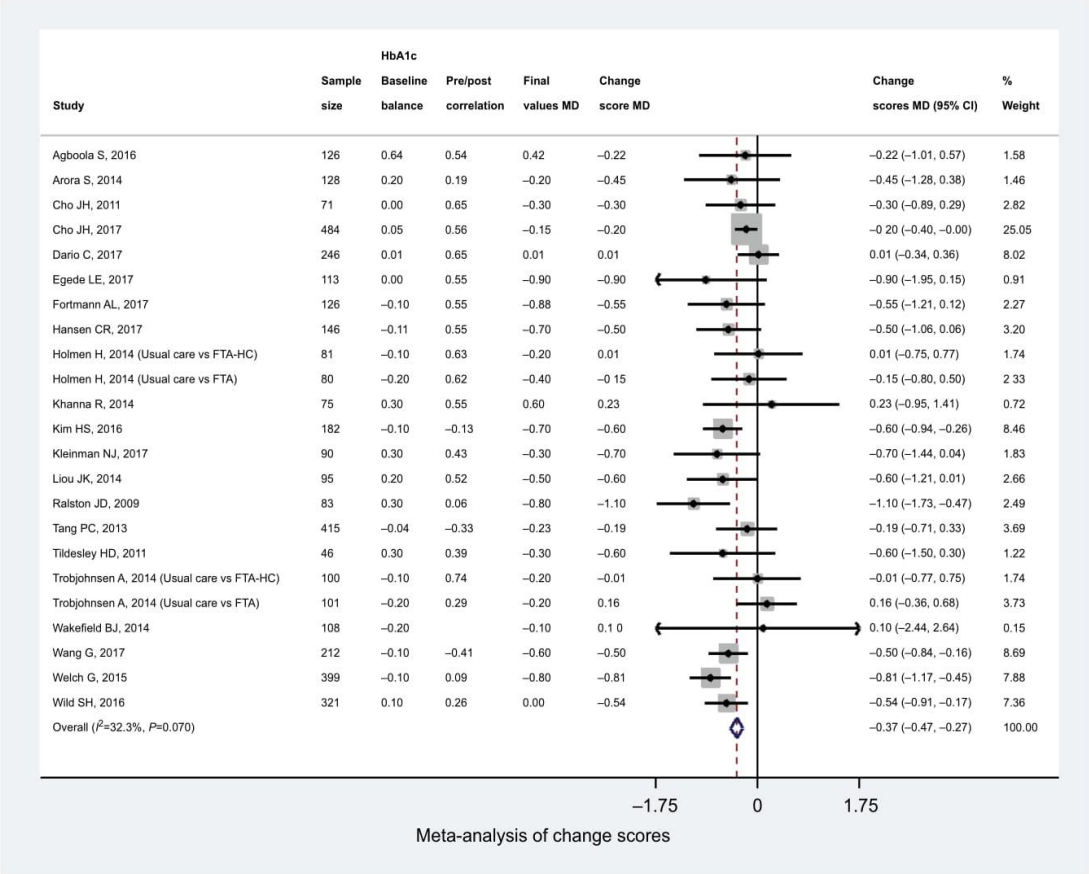


Figure 5 Fixed-effects meta-analysis of change scores.
Abbreviations: HbA1c, glycated hemoglobin level; MD, mean difference.

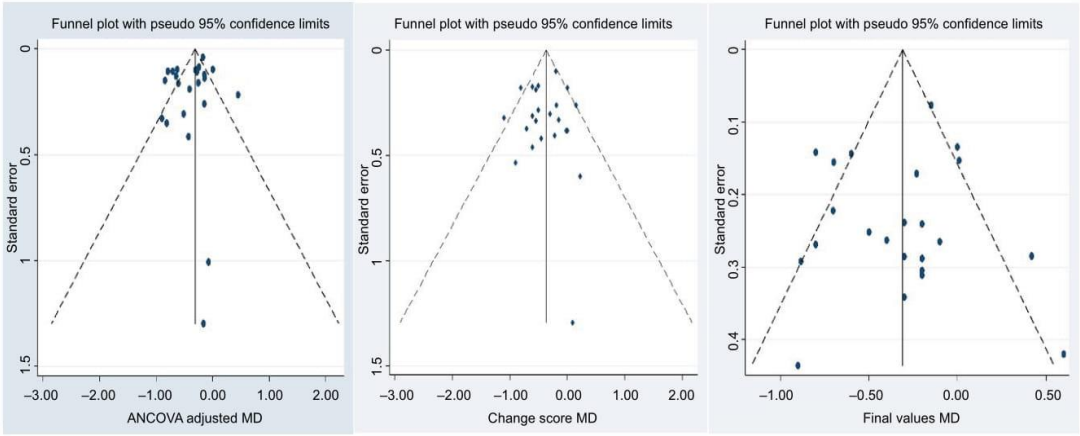


Figure 6 Funnel plots for assessing publication bias.
Abbreviation: MD, mean difference.

Table 2 Egger's test for assessing publication bias

	Std_Eff	Coeff.	SE	t	P>|t|	CI
ANCOVA	Slope	−0.207	0.093	−2.23	0.037	(−0.400, −0.014)
	Bias	−1.13	0.815	−1.38	0.182	(−2.82, 0.569)
SACS	Slope	−0.322	0.137	−2.35	0.028	(−0.606, −0.038)
	Bias	−0.215	0.559	0.38	0.704	(−1.38, 0.948)
SAFV	Slope	−0.237	0.153	−1.54	0.138	(−0.556, 0.083)
	Bias	−0.430	0.812	−0.53	0.602	(−2.12, 1.26)

Abbreviations: ANCOVA, analysis of covariance; Coeff, coefficient; SACS, simple analysis of change score; SAFV, simple analysis of final values; Std_Eff, standard effect; SE, standard error.

similar pooled effect estimates across the three methods. This supports the recommendations in previous methodological literature pointing to the importance of adjusting for baseline MD using the ANCOVA approach in meta-analyses of trials with baseline imbalance.[13,15,17] However, practical application of ANCOVA to synthesize effect sizes of continuous outcomes is complex due to the unavailability of summary data from RCTs or absence of IPD. Nevertheless, with available methodological guidance, it is possible to calculate ANCOVA adjusted MDs given that study authors report summary data for all intervention and control groups, such as baseline and follow-up mean values, as well as corresponding SDs, mean and SD values for changes over time, and finally sample sizes.[13] Because the results of systematic reviews rely on the summary findings of individual studies, future RCTs, particularly those with baseline imbalance, need to be reported with extensive detail if they are to be included in more advanced meta-analyses. Beside this, publishing IPD with the results of the interventions will enhance transparency of the results at the primary study level and simplify evidence syntheses subsequently.

In this review, the heterogeneity I^2 statistics computed using the three methods shows differences across the choice of meta-analytic methods. A lower heterogeneity estimate was obtained using SACS. Eyeball test on the forest plots of the three methods shows the confidence intervals of one study (a study by Khanna et al)[42] deviates from the general pattern of the other studies on the plots. The deviation by this study gets smaller in the forest plot for SACS meta-analysis. This explains the reason why SACS has the lowest heterogeneity compared with ANCOVA and SAFV. Previously, Fu and Holmer described that there is no clear pattern of heterogeneity estimates among the three methods.[12] Whether to use random-effects or fixed-effects meta-analyses can be statistically guided by the results of the I^2 statistics.[32] Which meta-analytic method produces decreased or increased heterogeneity statistics or whether there is a particular pattern across the three methods requires further research.

The results of publication bias assessment via an inspection of funnel plots were not consistent across the three methods. A relatively more symmetric funnel plot was constructed using the estimates obtained from the SAFV. However, funnel plots displayed for ANCOVA and SACS indicated the presence of symmetry at the top and studies missing at the lower half of the plot indicating a publication bias with regard to our sample of included studies. However, Egger's test for all the three methods suggested that there was no evidence suggesting publication bias. Further publication bias analyses using "trim and fill" method did not impute any missing study for ANCOVA and SAFV. However, one missing study was imputed for the SACS. Literature regarding comparison of publication bias across the three meta-analytic methods is currently lacking.

Performing sensitivity analyses is important to check the robustness of estimates obtained from trials with baseline imbalance.[13,66] Following this previously stated recommendation, we performed sensitivity analyses by removing studies with high baseline imbalance values. These analyses show that relatively comparable pooled estimates were obtained using ANCOVA, SACS, and SAFV meta-analyses. These results, in line with existing studies, suggest the importance of accounting for baseline imbalance by aggregating continuous outcome measures.[12,13,27,67]

ANCOVA and SACS yielded similar pooled estimates after removing studies with high pre/post correlation values from the meta-analyses. Similar to our result, existing evidence shows that when the value of pre/post correlation gets closer to 1.0, ANCOVA and SACS tend to produce similar effect size estimates.[12,13,27] Inspecting individual study effect sizes obtained using the three methods also shows that, ANCOVA and SAFV tend to produce similar effect size estimates as correlation values approach zero.[68]

Limitations

The study has limitations. First, our search was limited to three databases only: MEDLINE, ISI Web of Science, and PsycINFO. We tried to check whether this had an impact on our search output. There was no noticeable difference compared with our preliminary search in additional search databases, such as EMBASE and CINAHL. Hence, we

decided to focus on the three included databases, especially considering the workload to request and impute missing data which was crucial to answer our research questions of interest. Second, we did not consider unindexed databases and gray literature. Third, most of the studies did not report ANCOVA effect sizes. Our ANCOVA effect size calculation mainly relies on imputation from the reported data using robust statistical methods, but uncertainties remain.

Conclusion

All three meta-analytic methods show a significant effect of digital interventions on changing HbA1c levels. Analysis on the effect sizes computed for each study using the three methods did not differ significantly. However, some differences were noted among the pooled effect sizes applying different statistical methods by accounting for baseline imbalances of the outcome. Authors of future systematic reviews and meta-analyses should consider using ANCOVA to estimate effect sizes, at least for interventions with baseline imbalance. However, we recognize the statistical challenge of computing ANCOVA effect sizes, if the necessary data are not reported for individual studies. Hence, future RCTs, particularly those with baseline imbalance, should report ANCOVA effect sizes. In addition, publishing IPD along with the changes in the outcomes as a result of intervention participation is helpful to simplify robust evidence syntheses.

Data sharing statement

The data collected for this study can be received from the corresponding author.

Acknowledgments

We would like to thank our research librarian, Lara Christianson, for her support in developing the search strategy and optimizing it to each search database. We are grateful to Professor HajoZeeb, Professor Richard D Riley, Dr Jochen Wilhelm, Dr James E Pustejovsky, Professor Vanessa Didelez, and Dr Fleur Fritz for the methodological support. In addition, we are also very grateful to all corresponding authors of the individual studies for providing us with the data we requested. We disclose that the results of this study were presented as oral presentation at the *10th Biennial Joanna Briggs Institute Colloquium 2018* in Antwerp, Belgium.

Author contributions

MMK performed conceptualization, design, systematic literature search, title and abstract screening, quality assessment, data extraction, data analysis and interpretation of the data, and write-up. MP performed title and abstract screening, and quality assessment write-up. TLH and CRP performed conceptualization, extraction of the data, and critical review. All authors contributed toward data analysis, drafting and critically revising the paper, gave final approval of the version to be published and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Lutz B, Rüdiger M. Growth rates of modern science: a bibliometric analysis based on the number of publications and cited references. *J Assoc Inf Sci Technol*. 2015;66(11):2215–2222.
2. Bastian H, Glasziou P, Chalmers I. Seventy-five trials and eleven systematic reviews a day: how will we ever keep up? *PLoS Med*. 2010;7(9):e1000326.
3. Haidich AB. Meta-analysis in medical research. *Hippokratia*. 2010;14(Suppl 1):29–37.
4. Glass GV. Primary, secondary, and meta-analysis of research. *Educ Res*. 1976;5(10):3–8.
5. Biondi-Zoccai G, Landoni G, Modena MG. A journey into clinical evidence: from case reports to mixed treatment comparisons. *HSR Proc Intensive Care Cardiovasc Anesth*. 2011;3(2):93–96.
6. Greco T, Zangrillo A, Biondi-Zoccai G, Landoni G. Meta-analysis: pitfalls and hints. *Heart Lung Vessel*. 2013;5(4):219–225.
7. PubMed. diabetes and (meta-analys* or metaanalys*) Secondary diabetes and (meta-analys* or metaanalys*); 2018. Available from: https://www.ncbi.nlm.nih.gov/pubmed/?term=diabetes+and+(meta-analys*+or+metaanalys*). Accessed December 4, 2018.
8. Shinogle JA. *Methodological Challenges Associated with Meta-Analyses in Health Care and Behavioral Health Research*. Baltimore, MD: University of Maryland; 2012.
9. Lorenc T, Felix L, Petticrew M, et al. Meta-analysis, complexity, and heterogeneity: a qualitative interview study of researchers' methodological values and practices. *Syst Rev*. 2016;5(1):192.
10. Alahdab F, Zaiem F, Wang Z, Murad MH. Interpreting meta-analysis of continuous outcomes with pre and postvalues. *Evid Based Med*. 2016;21(4):139–140.
11. Chogtu B, Magazine R, Bairy KL. Statin use and risk of diabetes mellitus. *World J Diabetes*. 2015;6(2):352–357.
12. Fu R, Holmer HK. Change score or follow-up score? Choice of mean difference estimates could impact meta-analysis conclusions. *J Clin Epidemiol*. 2016;76:108–117.
13. Fu R, Vandermeer BW, Shamliyan TA, et al. Handling continuous outcomes in quantitative synthesis. *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*. Rockville, MD: Agency for Healthcare Research and Quality; 2008.
14. William F, Rosenberger JML. *Randomization in Clinical Trials: Theory and Practice*. New York: Wiley; 2005.
15. Mckenzie JE, Herbison GP, Deeks JJ. Impact of analysing continuous outcomes using final values, change scores and analysis of covariance on the performance of meta-analytic methods: a simulation study. *Res Synth Methods*. 2016;7(4):371–386.
16. Morris SB, Deshon RP. Combining effect size estimates in meta-analysis with repeated measures and independent-groups designs. *Psychol Methods*. 2002;7(1):105–125.
17. Riley RD, Kauser I, Bland M, et al. Meta-analysis of randomised trials with a continuous outcome according to baseline imbalance and availability of individual participant data. *Stat Med*. 2013;32(16):2747–2766.

18. Kebede MM, Zeeb H, Peters M, Heise TL, Pischke CR. Effectiveness of digital interventions for improving glycemic control in persons with poorly controlled Type 2 diabetes: a systematic review, meta-analysis, and meta-regression analysis. *Diabetes Technol Ther*. 2018;20(11):767–782.
19. Kebede M, Christianson L, Khan Z, Heise TL, Pischke CR. Effectiveness of behavioral change techniques employed in eHealth interventions designed to improve glycemic control in persons with poorly controlled type 2 diabetes: a systematic review and meta-analysis protocol. *Syst Rev*. 2017;6(1):211.
20. Eysenbach G. What is e-health? *J Med Internet Res*. 2001;3(2):e20.
21. Higgins JP, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928.
22. Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia.
23. Higgins JPT, Green S. *Cochrane Handbook for Systematic Reviews of Interventions*; 2011. Available from: http://handbook-5-1.cochrane.org/. Accessed October 25, 2018.
24. Wakefield BJ, Koopman RJ, Keplinger LE, et al. Effect of home telemonitoring on glycemic and blood pressure control in primary care clinic patients with diabetes. *Telemed J E Health*. 2014;20(3):199–205.
25. Arora S, Peters AL, Burner E, Lam CN, Menchine M. Trial to examine text message-based mHealth in emergency department patients with diabetes (TExT-MED): a randomized controlled trial. *Ann Emerg Med*. 2014;63(6):745–754.
26. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Methodol*. 2005;5:13.
27. Vickers AJ, Altman DG. Statistics notes: analysing controlled trials with baseline and follow up measurements. *BMJ*. 2001;323(7321):1123–1124.
28. Cho JH, Kwon HS, Kim HS, Oh JA, Yoon KH. Effects on diabetes management of a health-care provider mediated, remote coaching system via a PDA-type glucometer and the Internet. *J Telemed Telecare*. 2011;17(7):365–370.
29. Egede LE, Williams JS, Voronca DC, Knapp RG, Fernandes JK. Randomized controlled trial of technology-assisted case management in low income adults with type 2 diabetes. *Diabetes Technol Ther*. 2017;19(8):476–482.
30. Ralston JD, Hirsch IB, Hoath J, Mullen M, Cheadle A, Goldberg HI. Web-based collaborative care for type 2 diabetes: a pilot randomized trial. *Diabetes Care*. 2009;32(2):234–239.
31. Torbjørnsen A, Jenum AK, Småstuen MC, et al. A low-intensity mobile health intervention with and without health counseling for persons with Type 2 diabetes, part 1: baseline and short-term results from a randomized controlled trial in the Norwegian Part of RENEWING HEALTH. *JMIR Mhealth Uhealth*. 2014;2(4):e52.
32. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):557–560.
33. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315(7109):629–634.
34. Duval S. Tweedie R. A nonparametric "Trim and Fill" method of accounting for publication bias in meta-analysis. *J Am Stat Assoc*. 2000;95(449):89–98.
35. Agboola S, Jethwani K, Lopez L, Searl M, O'Keefe S, Kvedar J. Text to move: a randomized controlled trial of a text-messaging program to improve physical activity behaviors in patients with Type 2 diabetes mellitus. *J Med Internet Res*. 2016;18(11):e307.
36. Capozza K, Woolsey S, Georgsson M, et al. Going mobile with diabetes support: a randomized study of a text message-based personalized behavioral intervention for type 2 diabetes self-care. *Diabetes Spectr*. 2015;28(2):83–91.
37. Cho JH, Kim HS, Yoo SH, et al. An Internet-based health gateway device for interactive communication and automatic data uploading: clinical efficacy for type 2 diabetes in a multi-centre trial. *J Telemed Telecare*. 2017;23(6):595–604.
38. Dario C, Toffanin R, Calcaterra F, et al. Telemonitoring of Type 2 diabetes mellitus in Italy. *Telemed J E Health*. 2017;23(2):143–152.
39. Fortmann AL, Gallo LC, Garcia MI, et al. Dulce digital: an mHealth SMS-based intervention improves glycemic control in Hispanics with Type 2 diabetes. *Diabetes Care*. 2017;40(10):1349–1355.
40. Hansen CR, Perrild H, Koefoed BG, Zander M. Video consultations as add-on to standard care among patients with type 2 diabetes not responding to standard regimens: a randomized controlled trial. *Eur J Endocrinol*. 2017;176(6):727–736.
41. Holmen H, Torbjørnsen A, Wahl AK, et al. A Mobile health intervention for self-management and lifestyle change for persons with Type 2 diabetes, part 2: One-year results from the Norwegian randomized controlled trial RENEWING HEALTH. *JMIR Mhealth Uhealth*. 2014;2(4):e57.
42. Khanna R, Stoddard PJ, Gonzales EN, et al. An automated telephone nutrition support system for Spanish-speaking patients with diabetes. *J Diabetes Sci Technol*. 2014;8(6):1115–1120.
43. Kim HS, Sun C, Yang SJ, et al. Randomized, open-label, parallel group study to evaluate the effect of internet-based glucose management system on subjects with diabetes in China. *Telemed J E Health*. 2016;22(8):666–674.
44. Kleinman NJ, Shah A, Shah S, Phatak S, Viswanathan V. Improved medication adherence and frequency of blood glucose self-testing using an m-Health platform versus usual care in a multisite randomized clinical trial among people with Type 2 diabetes in India. *Telemed J E Health*. 2017;23(9):733–740.
45. Liou JK, Soon MS, Chen CH, et al. Shared care combined with telecare improves glycemic control of diabetic patients in a rural underserved community. *Telemed J E Health*. 2014;20(2):175–178.
46. Tang PC, Overhage JM, Chan AS, et al. Online disease management of diabetes: engaging and motivating patients online with enhanced resources-diabetes (EMPOWER-D), a randomized controlled trial. *J Am Med Inform Assoc*. 2013;20(3):526–534.
47. Tildesley HD, Mazanderani AB, Chan JHM, Ross SA. Efficacy of A1C reduction using internet intervention in patients with Type 2 diabetes treated with insulin. *Can J Diabetes*. 2011;35(3):250–253.
48. Wang G, Zhang Z, Feng Y, et al. Telemedicine in the management of Type 2 diabetes mellitus. *Am J Med Sci*. 2017;353(1):1–5.
49. Welch G, Zagarins SE, Santiago-Kelly P, et al. An internet-based diabetes management platform improves team care and outcomes in an urban Latino population. *Diabetes Care*. 2015;38(4):561–567.
50. Wild SH, Hanley J, Lewis SC, et al. Supported telemonitoring and glycemic control in people with Type 2 diabetes: the telescot diabetes pragmatic multicenter randomized controlled trial. *PLOS Med*. 2016;13(7):e1002163.
51. Alharbi NS, Alsubki N, Jones S, et al. Impact of information technology-based interventions for Type 2 diabetes mellitus on glycemic control: a systematic review and meta-analysis. *J Med Internet Res*. 2016;18(11):e310.
52. Zhai YK, Zhu WJ, Cai YL, Sun DX, Zhao J. Clinical- and cost-effectiveness of telemedicine in type 2 diabetes mellitus: a systematic review and meta-analysis. *Medicine*. 2014;93(28):e312.
53. Verhoeven F, van Gemert-Pijnen L, Dijkstra K, Nijland N, Seydel E, Steehouder M. The contribution of teleconsultation and videoconferencing to diabetes care: a systematic literature review. *J Med Internet Res*. 2007;9(5):e37.
54. Tricco AC, Ivers NM, Grimshaw JM, et al. Effectiveness of quality improvement strategies on the management of diabetes: a systematic review and meta-analysis. *Lancet*. 2012;379(9833):2252–2261.
55. Su D, Zhou J, Kelley MS, et al. Does telemedicine improve treatment outcomes for diabetes? A meta-analysis of results from 55 randomized controlled trials. *Diabetes Res Clin Pract*. 2016;116:136–148.
56. Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ*. 2000;321(7258):405–412.
57. Farmer AJ, Mcsharry J, Rowbotham S, Mcgowan L, Ricci-Cabello I, French DP. Effects of interventions promoting monitoring of medication use and brief messaging on medication adherence for people with Type 2 diabetes: a systematic review of randomized trials. *Diabet Med*. 2016;33(5):565–579.

58. Cheng L, Sit JW, Choi KC, et al. Effectiveness of interactive self-management interventions in individuals with poorly controlled Type 2 diabetes: a meta-analysis of randomized controlled trials. *Worldviews Evid Based Nurs*. 2017;14(1):65–73.
59. Avery L, Flynn D, van Wersch A, Sniehotta FF, Trenell MI. Changing physical activity behavior in type 2 diabetes: a systematic review and meta-analysis of behavioral interventions. *Diabetes Care*. 2012;35(12):2681–2689.
60. Baron J, Mcbain H, Newman S. The impact of mobile monitoring technologies on glycosylated hemoglobin in diabetes: a systematic review. *J Diabetes Sci Technol*. 2012;6(5):1185–1196.
61. Kirwan M, Vandelanotte C, Fenning A, Duncan MJ. Diabetes self-management smartphone application for adults with type 1 diabetes: randomized controlled trial. *J Med Internet Res*. 2013;15(11):e235.
62. El-Gayar O, Timsina P, Nawar N, Eid W. Mobile applications for diabetes self-management: status and potential. *J Diabetes Sci Technol*. 2013;7(1):247–262.
63. Williams JP, Schroeder D. Popular glucose tracking apps and use of mHealth by Latinos with diabetes: review. *JMIR Mhealth Uhealth*. 2015;3(3):e84.
64. Ryan EA, Holland J, Stroulia E, et al. Improved A1C levels in Type 1 diabetes with Smartphone app use. *Can J Diabetes*. 2017;41(1):33–40.
65. Kebede MM, Liedtke TP, Möllers T, Pischke CR. Characterizing active ingredients of eHealth interventions targeting persons with poorly controlled Type 2 diabetes mellitus using the behavior change techniques taxonomy: scoping review. *J Med Internet Res*. 2017;19(10):e348.
66. Aiello F, Attanasio M, Tinè F. Assessing covariate imbalance in meta-analysis studies. *Stat Med*. 2011;30(22):2671–2682.
67. Trowman R, Dumville JC, Torgerson DJ, Cranny G. The impact of trial baseline imbalances should be considered in systematic reviews: a methodological case study. *J Clin Epidemiol*. 2007;60(12):1229–1233.
68. Mckenzie J. Meta-analysis of continuous data: final values, change scores, and ANCOVA. In: Cochrane Statistical Methods Training Course: Addressing advanced issues in meta-analytical techniques; March 4–5, 2010; Cardiff, UK.
69. Torbjornsen A, Jenum AK, Smastuen MC, et al. A Low-Intensity Mobile Health Intervention With and Without Health Counseling for Persons With Type 2 Diabetes, Part 1: Baseline and Short-Term Results From a Randomized Controlled Trial in the Norwegian Part of RENEWING HEALTH. *JMIR mhealth uhealth*. 2014;2(4):e52. doi:10.2196/mhealth.3535

STUDY III

Journal of Clinical Medicine

MDPI

Article

The Role of Continuous Glucose Monitoring, Diabetes Smartphone Applications, and Self-Care Behavior in Glycemic Control: Results of a Multi-National Online Survey

Mihiretu M. Kebede [1,2,3,*], Cora Schuett [2] and Claudia R. Pischke [2,4]

1 Health Sciences, University of Bremen, Grazerstrasse 2, D-28359 Bremen, Germany
2 Leibniz Institute for Prevention Research and Epidemiology—BIPS, Achterstrasse 30, D-28359 Bremen, Germany; coraschuett@gmail.com (C.S.); ClaudiaRuthPischke@med.uni-duesseldorf.de or claudia.pischke@leibniz-bips.de (C.R.P.)
3 Institute of Public Health, College of Medicine and Health Science, University of Gondar, Po.box-196 Gondar, Ethiopia
4 Institute of Medical Sociology, Centre for Health and Society, Medical Faculty, University of Duesseldorf, Universitätsstrasse 1, D-40225 Duesseldorf, Germany
* Correspondence: kebede@leibniz-bips.de; Tel.: +49-421-218-56-916; Fax: +49-421-218-56-941

Received: 19 November 2018; Accepted: 14 January 2019; Published: 17 January 2019

Abstract: Background: This study investigated the determinants (with a special emphasis on the role of diabetes app use, use of continuous glucose monitoring (CGM) device, and self-care behavior) of glycemic control of type 1 and type 2 diabetes mellitus (DM). **Methods:** A web-based survey was conducted using diabetes Facebook groups, online patient-forums, and targeted Facebook advertisements (ads). Demographic, CGM, diabetes app use, and self-care behavior data were collected. Glycemic level data were categorized into hyperglycemia, hypoglycemia, and good control. Multinomial logistic regression stratified by diabetes type was performed. **Results:** The survey URL was posted in 78 Facebook groups and eight online forums, and ten targeted Facebook ads were conducted yielding 1854 responses. Of those owning smartphones (n = 1753, 95%), 1052 (62.6%) had type 1 and 630 (37.4%) had type 2 DM. More than half of the type 1 respondents (n = 549, 52.2%) and one third the respondents with type 2 DM (n = 210, 33.3%) reported using diabetes apps. Increased odds of experiencing hyperglycemia were noted in persons with type 1 DM with lower educational status (Adjusted Odds Ratio (AOR) = 1.7; 95% Confidence Interval (CI): 1.21–2.39); smokers (1.63, 95% CI: 1.15–2.32), and high diabetes self-management concern (AOR = 2.09, 95% CI: 1.15–2.32). CGM use (AOR = 0.66, 95% CI: 0.44–1.00); "general diet" (AOR = 0.86, 95% CI: 0.79–0.94); and "blood glucose monitoring" (AOR = 0.88, 95%CI: 0.80–0.97) self-care behavior reduced the odds of experiencing hyperglycemia. Hypoglycemia in type 1 DM was reduced by using CGM (AOR = 0.24, 95% CI: 0.09–0.60), while it was increased by experiencing a high diabetes self-management concern (AOR = 1.94, 95% CI: 1.04–3.61). Hyperglycemia in type 2 DM was increased by age (OR = 1.02, 95% CI: 1.00–1.04); high self-management concern (AOR = 2.59, 95% CI: 1.74–3.84); and poor confidence in self-management capacity (AOR = 3.22, 2.07–5.00). Conversely, diabetes app use (AOR = 0.63, 95% CI: 0.41–0.96) and "general diet" self-care (AOR = 0.84, 95% CI: 0.75–0.94), were significantly associated with the reduced odds of hyperglycemia. **Conclusion:** Diabetes apps, CGM, and educational interventions aimed at reducing self-management concerns and enhancing dietary self-care behavior and self-management confidence may help patients with diabetes to improve glycemic control.

Keywords: diabetes; CGM; self-care; glycemic control; hyperglycemia; hypoglycemia

1. Introduction

In 2017, more than 425 million adults were reported to be living with diabetes mellitus (DM). This estimate is expected to rise to 629 million cases by 2045 [1].

Effective DM self-management is often a challenging responsibility [2–4] which requires regular monitoring of blood glucose levels, adherence to glucose lowering medications, regular physical activity, and adhering to healthy nutrition recommendations [3,5–7]. Evidence suggests that receiving psychological and social support from other people affected by DM may help persons with DM tackle these challenges and enhance self-management capabilities [8]. People with similar conditions tend to connect with each other to learn from each other's experiences. Social media, such as Facebook and disease-specific forums, may help to facilitate connections among persons with DM. In disease-specific Facebook groups and online forums, persons with DM can receive virtual support from fellow patients with similar conditions [9,10]. Therefore, the use of Facebook groups and other social media may be associated with improved knowledge regarding disease management, increased skills, and an increased likelihood for adopting the recommended lifestyle changes [11].

Facebook, having more than 2 billion users [12], has a special feature known as the "Facebook Group" to engage people with similar interests or similar health conditions [13]. These groups help patients exchange information through forming public, closed, or secret Facebook groups [14]. Facebook users have used this opportunity and many chronic disease specific Facebook groups have emerged over the past few years. Disease-specific Facebook groups and online forums are becoming popular among patients with chronic conditions. These new communication platforms may facilitate the exchange of experiences and support between people with similar problems [15].To date, diabetes is one of the most common chronic diseases by which Facebook groups are popular [11,13,16,17]. In recent studies, improvements in glycemic values, disease management capacity, and peer support as a result of participation in diabetes Facebook groups were reported [11,18].

Engaging in Facebook groups may help people with diabetes improve their knowledge of the disease and to help them learn more about the latest technological developments in diabetes, such as diabetes smartphone applications (apps). Diabetes smartphone apps aiming to support diabetes self-management are widely available [19,20]. Self-management responsibilities, such as blood glucose monitoring, adherence to insulin and dose calculations, tracking physical activity and nutrition can effectively be supported using diabetes apps [19,21–23]. Results of three studies suggest that the tracking of self-monitoring of blood glucose levels is the most common used functionality of diabetes apps [19,22,24]. A plethora of evidence also suggests that active use of diabetes and self-management apps plays an important role in improving clinical and behavioral outcomes of DM [25–28]. Findings of systematic reviews and meta-analyses of randomized-controlled trials suggested that diabetes apps and digital interventions led to reductions in glycated hemoglobin levels [27,29,30].

Supporting diabetes self-management efforts with mobile apps has become a cost-effective strategy due to the ubiquitous, multi-tasking, and easily portable nature of smart phones. Hence, there is a growing interest in using diabetes apps for diabetes care. In 2016, approximately 1800 diabetes apps were available for patients and providers. The global diabetes app use statistics have also increased from 2.2% in 2014 to 3.3 % in 2016 [31]. Of the more than four hundred million people living with DM, 135.5 million are potentially reachable via diabetes apps [31]. In addition, a survey with 500 app developers found that the biggest app market was targeted towards diabetes [32]. For this reason, diabetes has been perceived as a particular niche for smartphone health app innovation and marketing [33–36].

Recently, the International Diabetes Federation-Europe stated that well-suited diabetes apps might be worth a try, since it could transform mobile phones into medical devices promoting self-management practices, preventing complications, and improving the quality of life [37,38]. Although diabetes apps have a great potential for improving diabetes outcomes, concerns are also being raised regarding gaps between evidence-based recommendations and the app functionalities, the lack of integration between the apps and the healthcare delivery system, data privacy, clinical appropriateness, and

safety [19,24,35,39,40]. In 2013, only one of 600 apps available in the United States received the Food and Drug Administration (FDA) approval [35,41]. The majority of these apps, particularly insulin dose calculator apps, were also reported to be erroneous. In fact, only one out of the total of 46 insulin dose calculator apps were found to be clinically suitable [42]. A recent report (May 2018) indicated that only 11 self-management apps were studied for clinical effectiveness, and only five were found to be clinically significant in terms of affecting HbA1c-levels [43]. For this reason, health care providers are required to exercise substantial caution and to systematically evaluate diabetes apps before prescribing them to their patients [42]. In addition, the need for formal evaluation and review remain essential [35,44].

Studies mainly stemming from developed countries indicate that a high proportion of people with DM own a smartphone and diabetes mobile apps. In Australia, 21% of patients with type 1 DM were reported to be using diabetes apps [45]. In New Zealand, approximately 20% of people with DM were using diabetes apps [46]. Survey results from Germany indicated that more than half of the respondents (60%) were using health apps, of which 84% were diabetes apps. Nearly 80% of the respondents in the German survey reported believing that diabetes apps were helpful to better cope with diabetes [47].

The American Food and Drug Administration Authority (FDA) developed classification regulations to evaluate and approve diabetes apps [48]. While there are ongoing efforts to clinically evaluate and approve diabetes apps, it is still unclear whether certified or other diabetes apps are being used and by whom, and which proportion of patients are using these apps. Furthermore, the relationship between use and glycemic control, diabetes self-management, and self-care behavior remain unclear. Additionally, we are unaware of evidence on the use of diabetes apps among persons with DM who subscribed to Facebook groups and other online forums. Therefore, in this study, we aimed at investigating the determinants (with special emphasis on the role of continuous glucose monitoring (CGM) device use, diabetes app use, and self-care behavior) of glycemic control among the online community of patients with type 1 and type 2 diabetes.

2. Materials and Methods

2.1. Ethics Approval and Consent to Participate

The content and implementation of the survey adheres with the overall ethical guidelines of the Leibniz Institute for Prevention Research and Epidemiology. In addition, the University of Bremen Central Research Development Fund committee approved the study and funded the cost of the Amazon vouchers. Before entering the survey, all participants were informed that the survey was voluntary, anonymous, and that they could skip any question that they were not comfortable to answer or could stop at any stage of the survey. Each participant was required to read and declare that he/she agreed or disagreed to answer questions of the survey. Participants were also required to electronically sign before their participation in the study. No personal data was collected. For the purpose of delivering incentives for the randomly selected participants, email addresses were collected in a separate database. However, no email addresses were linked to the responses of the participants. Email addresses were deleted after randomly selecting the participants for winning the draw.

2.2. Study Design, Questionnaire and Source of Respondents

From November 2017 to March 2018, we conducted a web-based cross-sectional survey among persons with diabetes using Facebook groups and diabetes-specific patient forums, and via targeted Facebook advertisements (ads). The survey questions were prepared in two languages (German and English) and were designed using Lime survey [49]. Self-reported diabetes status, demographic characteristics, type of diabetes, use of medication, self-care behavior, self-reported blood glucose level, use of continuous glucose monitoring (CGM), self-reported confidence in diabetes self-management, and perceived metabolic control were assessed in the survey. In addition, we asked about the use

and names of diabetes smartphone apps by employing an adapted version of the mobile app rating scale [6], which has been used and validated in another diabetes app use survey conducted in New Zealand [46]. Self-care behavior was measured using a licensed version of the summary of diabetes self-care activities (SDSCA) scale. From previous studies, the SDSCA scale was evaluated for adequate reliability and was validated in the English [50] and German languages [51]. It included 11 questions measuring self-care activities related to diet, physical activity, blood glucose monitoring, foot care, and smoking [50].

2.3. Recruitment of Survey Participants

Survey participants were recruited via Facebook groups, targeted Facebook ads, and diabetes specific online forums.

2.3.1. Recruitment via Facebook Groups

Facebook groups for type 1 or type 2 DM in English and German were systematically searched for on Facebook. Two Facebook accounts were used for the search. One of them was created for the purpose of the study. Before the search was conducted, the search histories of the two Facebook accounts were erased to avoid the impact of any previous searches. Key words, such as 'diabetes', 'diabetic', 'type 1 diabetes', 'type 2 diabetes', 'support', 'group', 'diabetic', and 'diabetic friendly' were used to search for relevant groups. Additional diabetes groups suggested by Facebook were also included. Groups for gestational DM, parents of children with DM, or owners of diabetic support pets were excluded. Two investigators M.M.K. and C.S. collected the group names, nature of the group (closed, public, and secret), URL, and the number of group members. After identification of the groups, two investigators (M.M.K. for the English groups and C.S. for the German groups) submitted applications to join the groups with explanations regarding the aims of the survey. Three Facebook accounts were used for requesting to join the groups and contacting the administrators (admins) of the groups. Admins were subsequently contacted to explain the authenticity and purpose of the survey, informed consent, and the amount of time necessary to complete the survey. Upon reception of approval, the survey link and an explanation of the purpose of the study, informed consent, and the time required to complete the survey was posted on each group page. Either an English or German version of the questionnaire was posted in the groups considering the language of communication of the groups. To make the post appear in the newsfeed of members and possibly enhance its visibility, it was periodically (at least every 24 h) bumped up by posting comments on the existing post. To encourage participation, the post included €50 Amazon voucher incentives to be given to randomly selected respondents.

2.3.2. Recruitment via Targeted Facebook Ads

Facebook ads containing the survey URL were used to target potentially eligible people with DM by tailoring the advertisement to specific locations and interests. The ads were in English and German to target people with special interests and living in English and German speaking countries. The ads targeted persons who were 18 years and older living in Australia, Canada, the United Kingdom, the United States, Germany, Switzerland, and Austria and who had a special interest in diabetes-related Facebook pages using specific terms, such as "diabetes health", "healthy low-carb living", "cure for diabetes", "glucose buddy", "glycemic index", "eating healthy food", and "diabetic kitchen". Additional terms suggested by Facebook and judged as relevant were also considered. The full list of terms used for the targeted ads can be accessed in the screenshot of one of our ads, presented in the supplementary Figure (Figure S1). We assumed that Facebook pages with these terms predominantly attracted users with DM or those at an increased risk for DM.

2.3.3. Recruitment Using Diabetes Online Patient Forums

English and German diabetes patient forums were searched in Google using key words, such as 'diabetes', 'forums', 'patient forums', and 'discussion forums.' After collecting the names and URLs of the forums, two authors (M.M.K. and C.S.) registered or submitted registration requests to the forums. The two authors sent emails or personal messages to the forum admins and moderators to explain the purpose of the survey. After permission was received from the forum admins and moderators, the survey was posted on the diabetes forum website. The post also included information regarding the authenticity and purpose of the survey, informed consent, and the amount of time required to complete the survey.

2.4. Quality of Data

Periodically, the primary investigator checked the quality and authenticity of responses one by one. Multiple responses were removed using IP addresses. Incomplete responses were excluded from the final analysis.

2.5. Data Analysis

The data retrieved from lime survey were exported to MS Excel. STATA version 14 and R were used for analyses. Statistical packages such as "dplyr" and "ggplot2" packages in R were used to understand and prepare the data for analyses. The main outcome variable was the self-reported glycemic levels. Self-reported HbA1c and capillary blood glucose level data were collected. Respondents were asked to provide HbA1c values and to mention where the test was obtained. In addition, data on capillary blood glucose values and the timing of the test (pre-prandial, post-prandial, etc.) were also obtained. Moreover, data regarding how frequent respondents had hyperglycemia or hypoglycemia were collected. The combined self-reported HbA1c and capillary blood glucose data corresponding to the timing of the measure (pre-prandial, post-prandial) was assessed. The self-reported glycemic level data was then classified into three categories: hypoglycemia, hyperglycemia, and good glycemic control, following the American Diabetes Association guideline. Hence, self-reported HbA1c-levels of <7.0% or <53 mmol/mol, or a pre-prandial capillary plasma glucose levels between 80–130 mg/dL or 4.4–4.7 mmol/L, or post-prandial capillary glucose levels <180 mg/dL or <10.0 mmol/L were considered as good glycemic control levels. Self-reported HbA1c-levels of >7.0% or >53 mmol/mol, or a pre-prandial capillary plasma glucose level >130 mg/dL or >4.7 mmol/L, or post-prandial capillary glucose levels >180 mg/dL or >10.0 mmol/L were classified as hyperglycemia. HbA1c-levels reported as ≤70mg/dL or ≤3.9mmol/L were categorized as hypoglycemia [52–54].

Descriptive statistics and multinomial logistic regression analyses were performed. Associations of the independent variables with glycemic control were assessed using multinomial logistic regression analyses stratified by the type of diabetes. Variables were entered step-by-step in the model. The variables entered in the model included age, sex, and educational status, use of glucose lowering medication, use of a CGM device, self-care behavior, smoking status, diabetes self-management concern, and diabetes app use. Self-care behavior data were analyzed according to the recommendation provided in the summary of diabetes self-care activities (SDSCA) questionnaire [50,52]. Accordingly, the mean number of self-care days was calculated for all the self-care activities (i.e., "general diet", "specific diet", "exercise", "blood glucose testing", and "foot care"). Diabetes self-management concern was measured by aggregating the total responses of eight "yes" or "no" questions, which were coded as 1 and 0, respectively. These questions included concerns about hypoglycemia, hyperglycemia, forgetting to measure blood glucose levels, forgetting to take medications, not knowing whom to contact in case of a need for assistance, being left out of medication or supplies, and feeling unsure about how to calculate insulin doses. The total number of diabetes self-management concerns was calculated for each respondent. Checking for normal distribution using the Shapiro–Wilk test, we

found that diabetes self-management concern was not normally distributed. Hence, respondents having more than or equal to the median number of diabetes self-management concerns (median = 3) were coded as having a "high concern" otherwise it was coded as a "low concern".

Country level sub-group analyses were conducted to investigate whether the factors associated with glycemic level differed across countries. We conducted the sub-group analyses for respondents from the US, the UK, and Germany. Odds ratios with 95% confidence intervals and *p*-values of less than 0.05 were used to declare statistically significant association. The goodness of fit of the model was investigated using the McKelvey & Zavoina Pseudo-R2 method [55]. Stata 14 (StataCorp LP., Texas, TX, USA) version 14 and R studio (RStudio, Inc., Boston, MA, USA) were used for the analyses.

3. Results

3.1. Data Source and Characteristics of the Survey Participants

A total of 117 Facebook groups were identified through key-words searching. Contacting admins and moderators, as well as group joining requests, were submitted to all Facebook groups identified through the key-words search. The majority of the Facebook group joining requests (n = 98 (84%), were approved. Of the 98 Facebook groups which approved the group requests, more than three-fourths (n = 78, 80%) of the Facebook groups approved the survey URL to be posted on the group page (Figure 1).

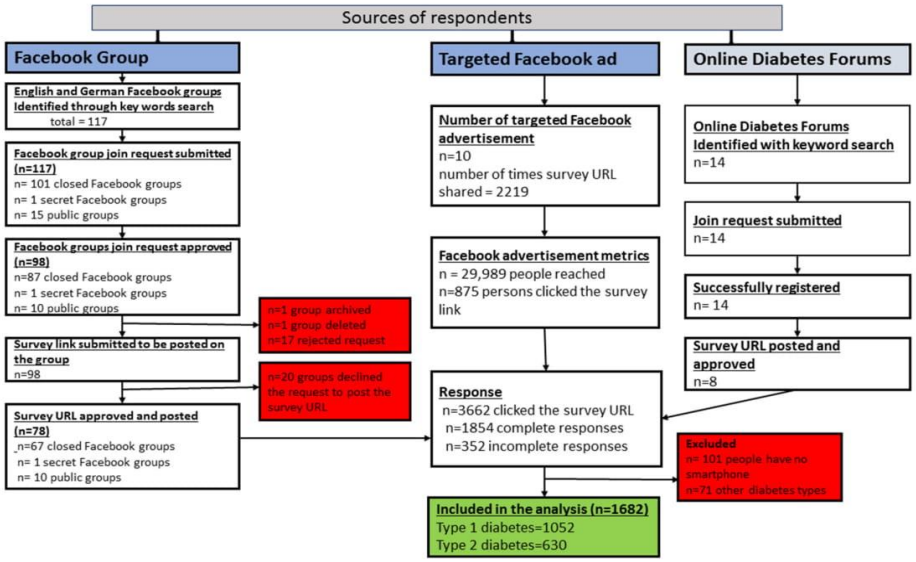


Figure 1. Flow diagram for the sources of respondents of the survey.

A total of ten targeted Facebook ads were published on Facebook reaching about 30,000 people potentially having diabetes. In addition, 14 diabetes patient online forums were identified, and the survey URL was posted on more than half of the forums (Figure 1).

In total, 1854 complete and 352 incomplete responses were obtained. Of the 1854 persons with complete questionnaires, 1753 persons with diabetes reported owning a smartphone. Of those who owned a smartphone, 1682 respondents were persons with type 1 DM (n = 1052, 62.6%) or type 2 DM (n = 630, 37.4%) (Figure 1).

The mean age of the respondents with type 1 DM was 39 (SD = ±12.9) years, while it was 52.9 (SD = ±11.4) years for respondents with type 2 DM. More than two-thirds of the respondents in both type 1 and type 2 were females (763, 72.5% vs. 420, 66.7%, respectively).

The respondents were from 62 countries. However, according to the World Bank 2017–2018 country classifications [56] nearly all of the respondents were from high income countries (n = 1557, 92.3%) (Table 1). More than two-thirds of the respondents were from three countries: The United States (n = 543, 32.8%), Germany (n = 385, 22.9%), and the United Kingdom (n = 224, 13.3%).

Table 1. Characteristics of the respondents.

Variable	Respondents with Type 1 DM Glycemic Control Levels *N* (%)				Respondents with Type 2 DM Glycemic Control Levels *N* (%)			
	Good	Hyper	Hypo	Total	Good	Hyper	Hypo	Total
Age, Mean (SD)	40 (12.9)	36.7 (12.5)	36 (13.2)	39 (12.9)	52.8 (11.4)	52.8 (11.1)	61.5 (14.1)	52.9 (11.4)
≤40	379 (52.8)	178 (64)	34 (60.7)	591 (56.2)	70 (17.8)	29 (12.8)	0 (0)	99 (15.7)
40–60	294 (40.9)	86 (31)	20 (35.7)	400 (38)	203 (51.7)	137 (60.6)	6 (54.6)	346 (54.9)
60+	45 (6.3)	14 (5)	2 (3.6)	61 (5.8)	120 (30.5)	60 (26.6)	5 (45.4)	185 (29.4)
Sex								
Female	509 (70.9)	215 (77.3)	39 (69.6)	763 (72.5)	255 (64.9)	156 (69)	9 (81.8)	420 (66.7)
Male	209 (29.1)	63 (22.3)	17 (30.4)	289 (27.5)	138 (35.1)	70 (31)	2 (18.2)	210 (33.3)
Educational Status								
Primary to secondary	252 (35.1)	141 (50.7)	17 (30.4)	410 (39)	156 (39.7)	116 (51.3)	6 (54.5)	278 (44.1)
Polytechnic diploma	121 (16.9)	51 (18.4)	12 (21.4)	184 (17.5)	76 (19.3)	37 (16.4)	4 (36.4)	117 (18.6)
Bachelor degree and above	345 (48)	86 (30.9)	27 (48.2)	458 (43.5)	161 (40.1)	73 (32.3)	1 (9.1)	235 (37.3)
Continent								
USA/Canada/Central America	237 (33)	96 (34.5)	20 (35.7)	353 (33.6)	181 (46.1)	93 (41.2)	2 (43.8)	276 (43.8)
Europe	418 (58.2)	161 (58)	28 (50)	607 (55.7)	143 (36.4)	90 (39.8)	6 (55)	239 (38)
Oceania	49 (5.4)	8 (2.9)	5 (8.9)	52 (4.9)	18 (4.6)	4 (1.8)	2 (18.1)	24 (3.8)
Asia	10 (1.4)	4 (1.4)	1 (1.8)	15 (1.4)	41 (10.4)	25 (11)	1 (9.1)	67 (10.6)
Africa and Latin America	14 (2)	9 (3.2)	2 (3.6)	25 (2.4)	10 (2.5)	14 (6.2)	0 (0)	24 (3.8)
Country income levels *								
Low to lower-middle income	8 (1.1)	2 (0.7)	0 (0)	19 (1)	41 (10.4)	26 (11.5)	1 (9.1)	68 (10.7)
Upper-middle income	16 (2.2)	12 (4.3)	2 (3.6)	30 (3)	9 (2.3)	13 (5.8)	0 (0)	22 (3.6)
High income	694 (96.7)	264 (95)	54 (96.4)	1012 (96)	343 (87.3)	187 (82.7)	10 (90.9)	540 (85.7)
Total	718 (68.2)	278 (26.4)	56 (5.3)	1052 (100)	393 (62.4)	226 (35.8)	11 (1.8)	630 (100)

* Based on the World Bank 2017–2018 country classifications [56].

3.2. Diabetes Clinical and Self-Management Characteristics of Respondents

The majority of the respondents, both with type 1 DM and type 2 DM reported taking glucose lowering medications (1004 (95.4%) vs. 541(85.9%)). About 4.6% of the respondents with type 1 diabetes did not report taking glucose-lowering medications or data about their treatment history were not available. A quarter of the respondents with type 1 DM and more than one third of the respondents with type 2 DM had hyperglycemia. More than a quarter of the respondents with type 1 DM reported using CGM technology (n = 296, 28.1%). More than half of the respondents with type 1 DM (n = 655, 62.4%) or type 2 (n = 323, 51%) rated their metabolic control as "well-controlled." In addition, more than two-thirds of the respondents with type 1 DM (n = 706, 67.2%) rated their confidence in diabetes self-management as "very confident", compared to less than half of the respondents with type 2 DM (n = 282, 44.8%) who felt "very confident". More than half of the respondents with type 1 diabetes (n = 549, 52.2%) and more than one third of the respondents with type 2 diabetes (n = 210, 33.3%) reported using diabetes apps. More than a quarter of the respondents with type 1 or type 2 DM reported they first consulted Facebook groups, the internet, or diabetes apps, whenever they had concerns regarding their diabetes self-management (Table 2).

Table 2. Clinical and self-management characteristics of the respondents.

	Respondents with Type 1 DM Glycemic Control Levels *N* (%)				Respondents with Type 2 DM Glycemic Control Levels *N* (%)			
	Good	**Hyper**	**Hypo**	**Total**	**Good**	**Hyper**	**Hypo**	**Total**
On glucose lowering medication								
Yes	684 (95.3)	266 (95.7)	54 (96.4)	1004 (95.4)	332 (84.5)	202 (89.4)	7 (63.6)	541 (85.9)
No	34 (4.7)	12 (4.3)	2 (3.6)	48 (4.6)	61 (15.5)	24 (10.6)	4 (36.4)	89 (14.1)
If you have concerns regarding your diabetes management where do you go first for assistance?								
Diabetes specialist team/healthcare provider	445 (62)	180 (64.8)	35 (62.5)	660 (62.7)	265 (67.4)	156 (69)	10 (90.9)	431 (68.4)
Facebook group/Internet/Smartphone App	214 (29.8)	85 (30.6)	17 (30.4)	316 (30)	98 (24.9)	54 (23.9)	1 (9.1)	153 (24.3)
Support group/Friends/Family	50 (7)	12 (4.3)	4 (7.1)	66 (6.3)	24 (6.1)	14 (6.2)	0 (0)	38 (6)
Other	9 (1.25)	1 (0.36)	0 (0)	10 (1)	6 (1.5)	2 (0.9)	0 (0)	8 (1.3)
Problems with Diabetes Self-Management								
Feeling Symptomatic Low Blood Sugar								
Yes	443 (61.7)	182 (65.5)	38 (67.9)	663 (63)	87 (22.1)	33 (14.6)	1 (9.1)	121 (19.2)
No	275 (38.3)	96 (34.5)	18 (32.1)	389 (37)	306 (77.9)	193 (85.4)	10 (90.9)	509 (80.8)
Feeling Symptomatic High Blood Sugar								
Yes	321 (44.7)	180 (64.8)	31 (55.4)	532 (50.6)	87 (22.1)	109 (48.2)	4 (36.4)	200 (31.8)
No	397 (35.3)	98 (35.3)	25 (44.6)	520 (49.4)	306 (77.9)	117 (51.8)	7 (65.6)	430 (68.2)
Forgetting to Measure Blood Sugar Levels								
Yes	121 (16.9)	113 (40.7)	13 (23.2)	247 (23.4)	82 (20.9)	92 (40.7)	1 (9.1)	175 (22.8)
No	597 (83.2)	165 (59.4)	43 (76.8)	805 (76.5)	311 (79)	134 (59.3)	10 (90.1)	455(72.2)
Forgetting to Take Medication or Insulin								
Yes	106 (14.8)	70 (25.2)	10 (17.9)	186 (17.7)	49 (12.5)	58 (25.7)	2 (18.2)	109 (17.3
No	612 (85.2)	208 (74.8)	46 (82.1)	866 (82.3)	344 (87.5)	168 (74.3)	9 (81.8)	521 (82.7)
Not knowing how to identify high or low blood sugars								
Yes	37 (5.2)	15 (5.4)	5 (8.9)	57 (5.4)	34 (8.7)	31 (13.7)	0 (0)	65 (10.3)
No	681 (94.9)	263 (94.6)	51 (91.1)	995 (94.6)	359 ((91.4)	195 (86.3)	11 (100)	565 (89.7)
Not Knowing whom to Contact when in Need of Assistance								
Yes	29 (4)	11 (4)	1 (1.8)	41 (3.9)	26 (6.6)	24 (10.6)	0 (0)	50 (7.9)
No	689 (96)	267 (96)	55 (98.2)	1011 (96.1)	367 (93.4)	302 (89.4)	11 (100)	580 (92.1)
Being Left without Medication/Supplies								
Yes	64 (8.9)	36 (13)	5 (9)	105 (10)	25 (6.4)	19 (8.4)	0 (0)	44 (7)
No	624 (91.1)	242 (87)	51 (91)	947 (90)	368 (93.6)	207 (91.6)	11 (100)	586 (93)
Felt Unsure about How to Calculate Your Insulin/Glucose lowering Medication Dose								
Yes	105 (14.6)	64 (23)	18 (32.1)	187 (17.8)	14 (3.6)	16 (8.4)	1 (9.1)	34 (5.4)
No	613 (85.4)	214 (77)	38 (79.9)	865 (82.2)	379 (96.4)	207 (91.6)	10 (90.9)	596 (94.6)
Diabetes App Use								
Yes	401 (55.9)	122 (43.9)	26 (46.4)	549 (52.2)	156 (39.7)	53 (23.5)	1 (9.1)	210 (33.3)
No	317 (44.2)	156 (56.1)	30 (53.4)	503 (47.8)	237 (60.3)	173 (76.6)	10 (90.9)	420 (66.7)

Table 2. *Cont.*

	Respondents with Type 1 DM Glycemic Control Levels *N* (%)				Respondents with Type 2 DM Glycemic Control Levels *N* (%)			
	Good	**Hyper**	**Hypo**	**Total**	**Good**	**Hyper**	**Hypo**	**Total**
Use CGM								
Yes	234 (32.6)	56 (20.1)	6 (10.7)	296 (28.1)	17 (4.3)	4 (1.8)	0 (0)	218 (3.3)
NO	484 (67.4)	222 (79.9)	50 (89.3)	756 (71.9)	376 (95.7)	222 (98.2)	11 (100)	609 (96.7)
Self-Reported Rating of Blood Glucose Control								
Well controlled	521 (72.8)	107 (38.5)	27 (48)	655 (62.4)	264 (67.5)	52 (23)	7 (63.6)	323 (51)
Neutral	149 (20.8)	96 (34.5)	11 (20)	256 (24.4)	88 (22.5)	63 (27.9)	3 (27.3)	154 (25)
Poorly controlled	46 (6.4)	75 (27)	18 (32)	139 (13.2)	39 (10)	111 (49.1)	1 (9.1)	151 (24)
Self-Reported Confidence on Diabetes Self-Management								
Very confident	533 (74.3)	140 (50.5)	33 (58.9)	706 (67.2)	221 (56)	55 (24.3)	6 (54.6)	282(44.8)
Neutral	66 (9.2)	48 (17.3)	8(14.3)	122 (11.6)	54(14)	41 (18.1)	2 (18.2)	97(15.4)
Not confident at all	118 (26.5)	89 (32.1)	15 (26.8)	222 (21.1)	118 (36)	130 (57.5)	3 (27.3)	251(39.8)
Smoking								
Yes	120 (16.7)	90 (32.4)	15 (32.4)	225 (21.4)	60 (15.3)	48 (21.2)	1 (9.1)	109 (17.3)
No	598 (83.3)	188 (67.6)	41 (73.2)	827 (78.6)	333 (84.7)	178 (78.8)	10 (90.9)	521 (82.7)
Total	718 (100)	278 (100)	56 (100)	1052 (100)	393 (100)	226 (100)	11 (100)	630 (100)

3.3. Self-Care Behavior of the Respondents

The mean (SD) for self-care activity days spent per week on general diet was 4.5 (±2.01) amongst the respondents with type 1 DM and 4.7 (±1.92) amongst those with type 2 DM. The mean number of days per week for blood glucose testing self-care activity was 6.3 (1.47) among persons with type 1 diabetes, while it was 4.6 (2.58) among respondents with type 2 diabetes. Compared to the respondents with type 2 DM, respondents with type 1 DM reported a significantly higher mean number of days for blood glucose testing (difference = 1.7, two sample *t*-test *p*-value < 0.001). Furthermore, more self-care days were spent on foot care among respondents with type 1 DM compared to those with type 2 DM (difference = 0.8, two sample *t*-test value < 0.001) (Table 3).

Table 3. Self-care behavior characteristics.

Self-Care Behavior	Type 1 Diabetes Mean (SD)	Type 2 Diabetes Mean (SD)	Difference (*p* value)
Diet			
How many of the last SEVEN DAYS have you followed a healthful eating plan?	4.5 (2.13)	4.6 (2.11)	0.412
On average, over the past month, how many DAYS PER WEEK have you followed your eating plan?	4.6 (2.07)	4.8 (1.97)	0.067
On how many of the last SEVEN DAYS did you eat five or more servings of fruits and vegetables	3.7 (2.51)	3.6 (2.54)	0.345
On how many of the last SEVEN DAYS did you eat high fat foods such as red meat or full-fat dairy products?	3.7 (2.3)	3.4 (2.41)	0.070
General diet (aggregate)	4.5 (2.01)	4.7 (1.92)	0.153
Specific diet(aggregate)	3.5 (1.78)	3.6 (1.81)	0.608
Physical activity			
On how many of the last SEVEN DAYS did you participate in at least 30 min of physical activity? (Total minutes of continuous activity, including walking).	4.0 (2.35)	3.7 (2.48)	0.022 *
On how many of the last SEVEN DAYS did you participate in a specific exercise session (such as swimming, walking, biking) other than what you do around the house or as part of your work?	2.4 (2.34)	2.5 (2.56)	0.524
Physical activity (aggregate)	3.2 (2.09)	3.1 (2.26)	0.356
Blood Glucose Monitoring			
On how many of the last SEVEN DAYS did you test your blood sugar?	6.7 (1.15)	5.0 (2.63)	<0.001 *
On how many of the last SEVEN DAYS did you test your blood sugar the number of times recommended by your health care provider?	6.0 (2.09)	4.2 (2.95)	<0.001 *
Blood glucose monitoring (aggregate)	6.3 (1.47)	4.6 (2.58)	<0.001 *
Foot Care			
On how many of the last SEVEN DAYS did you check your feet?	2.6 (2.76)	3.6 (2.89)	<0.001 *
On how many of the last SEVEN DAYS did you inspect the inside of your shoes?	0.9 (1.96)	1.6 (2.56)	<0.001 *
Foot care (aggregate)	1.8 (2.04)	2.6 (2.38)	<0.001 *

* statistically significant.

Amongst the respondents with type 1 DM, for the self-care activity 'blood glucose monitoring', the highest mean number of days was reported. Respondents with type 1 DM with good glycemic control, hyperglycemia, or hypoglycemia reported 6.5 (±1.3), 5.9 (±1.8), and 6.2 (±1.8) days of blood glucose testing per week, respectively. However, persons with type 2 DM reported the highest number of self-care days for 'general diet' followed by 'blood glucose monitoring' (Table 4).

Table 4. Glycemic control status by self-care behavior in type 1 and type 2 diabetes.

Self-Care Behavior	Respondents with Type 1 DM Glycemic Control Levels *N* (%)				Respondents with Type 2 DM Glycemic Control Levels *N* (%)			
	Good	Hyper	Hypo	Total	Good	Hyper	Hypo	Total
General Diet (Mean(SD))	4.8 (1.9)	3.8 (2.1)	4.5 (2.1)	4.6 (2.0)	5.1 (1.8)	3.9 (2.0)	4.8 (1.2)	4.7 (1.9)
Specific Diet (Mean(SD))	3.6 (1.8)	3.3 (1.7)	3.6 (1.9)	3.5 (1.8)	3.7 (1.8)	3.4 (1.8)	4 (1.9)	3.6 (1.8)
Physical Activity (Mean(SD))	3.4 (2.1)	2.7 (2.0)	3.5 (2.3)	3.2 (2.1)	3.4 (2.2)	2.5 (2.2)	3.5 (2.2)	3.1 (2.3)
Blood Glucose Monitoring (Mean(SD))	6.5 (1.3)	5.9 (1.8)	6.2 (1.8)	6.3 (1.5)	4.9 (2.5)	4.1 (2.6)	5.5 (2.1)	4.6 (2.6)
Foot Care (Mean(SD))	1.8 (2.1)	1.6 (1.9)	1.9 (2.2)	1.8 (2.0)	2.7 (2.4)	2.4 (2.4)	3.5 (2.5)	2.6 (2.4)

Both the persons with type 1 and type 2 DM who reported good glycemic control, also reported a nearly similar mean number of days spent on each self-care activity, except for foot care. Respondents with hyperglycemia or hypoglycemia reported generally fewer days spent on self-care compared to respondents with well-controlled type 1 or type 2 DM (Figure 2).

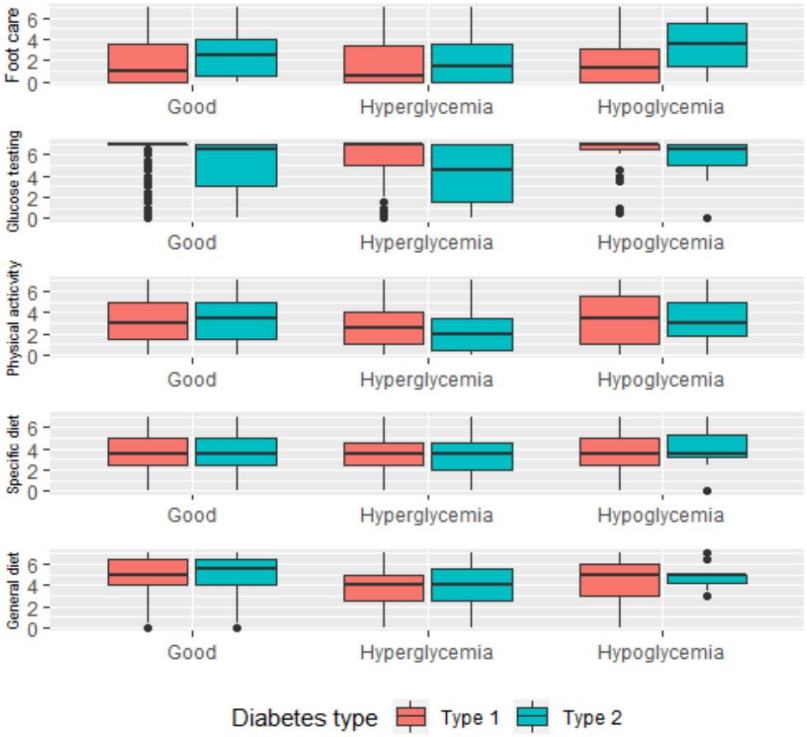


Figure 2. Self-care behavior distribution by glycemic levels.

3.4. Factors Associated with Hyperglycemia and Hypoglycemia amongst Respondents with Type 1 Diabetes

Amongst the respondents with type 1 DM, educational status, smoking, CGM use, diabetes self-management concern, and only two of the self-care activities (general diet and blood glucose monitoring), were significantly associated with the odds of having hyperglycemia. Compared to the respondents with type 1 DM having a bachelor's degree and above, respondents with a primary to secondary school educational level were 1.7 times (95% CI: 1.21–2.39) more likely to have hyperglycemia. Similarly, respondents who were smokers and had reported having a high diabetes self-management concern were 1.63 (95% CI: 1.15–2.32) and 2.09 (95% CI: 1.15–2.32) times more likely to have hyperglycemia, respectively. Respondents who were using CGM technology were 34% less likely to have hyperglycemia. In addition, a one-point increase on the scale for "general diet" self-care behavior and "blood glucose monitoring" reduced the odds of hyperglycemia by 14% and 12%, respectively (Table 5).

Table 5. Multinomial logistic regression model of glycemic control in type 1 and type 2 DM.

Variables	Type 1 Diabetes (n = 1052)		Type 2 Diabetes (n = 630)	
	Hyperglycemia vs. Good Glycemic Control	Hypoglycemia vs. Good Glycemic Control	Hyperglycemia vs. Good Glycemic Control	Hypoglycemia vs. Good Glycemic Control
	AOR (95% CI)	AOR (95% CI)	AOR (95% CI)	AOR (95% CI)
Age group				
≤40	1 (reference)	1 (reference)		
40–60	0.78 (0.56–1.10)	0.80 (0.43–1.48)		
60+	1.09 (0.54–2.18)	0.62 (0.14–2.81)		
Age (continuous)			1.02 (1.00–1.04) *	1.07 (1.01–1.14) *
Sex				
Female	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Male	0.80 (0.56–1.15)	1.17 (0.63–2.19)	1.12 (0.74–1.67)	0.24 (0.04–1.34)
Education				
Primary to secondary school	1.70 (1.21–2.39) **	0.69 (0.36–1.34)	1.30 (0.85–1.98)	8.56 (0.88–83.31)
Poly technique diploma	1.47 (0.95–2.27)	1.07 (0.51–2.23)	0.84 (0.49–1.44)	11 (1.06–113.9) *
Bachelor degree and above	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Diabetes app use				
Yes	0.98 (0.69–1.39)	1.19 (0.65–2.20)	0.63 (0.41– 0.96) *	0.13 (0.01–1.14)
No	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Self-care behavior				
General diet	0.86 (0.79–0.94) **	0.93 (0.79–1.09)	0.84 (0.75–0.94) **	0.80 (0.51–1.23)
Specific diet	1.00 (0.91–1.10)	1.01 (0.85–1.20)	1.02 (0.91–1.14)	1.13 (0.75–1.70)
Physical activity	0.93 (0.86–1.01)	1.09 (0.95–1.26)	0.96 (0.87–1.05)	1.12 (0.80–1.58)
Blood glucose monitoring	0.88 (0.80–0.97) *	0.91 (0.76–1.10)	0.96 (0.88–1.03)	1.26 (0.92–1.72)
Foot care	1.00 (0.92–1.08)	1.03 (0.90–1.19)	0.97 (0.89–1.05)	1.11 (0.84–1.47)
Smoking				
Yes	1.63 (1.15–2.32) **	1.67 (0.86–3.25)	1.16 (0.70–1.90)	0.57 (0.06–5.09)
No	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Glucose lowering medication				
Yes	1.25 (0.61–2.54)	1.45 (0.33–6.36)	0.93 (0.52–1.68)	0.27 (0.06–1.22)
No	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Diabetes self-management concern				
High concern	2.09 (1.50–2.92) **	1.94 (1.04–3.61) *	2.59 (1.74–3.84) **	0.83 (0.16–4.39)
Low concern	1 (reference)	1(reference)	1 (reference)	1 (reference)
Use CGM				
Yes	0.66 (0.44–1.00) *	0.24 (0.09–0.60) **		
No	1	1		
Self-reported confidence on diabetes self-management				
Very confident	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Neutral			2.13 (1.23–3.72) **	1.53 (0.24–10.00)
Not confident at all			3.22 (2.07–5.00) **	1.12 (0.21–6.01)

** $p < 0.01$, * $p < 0.05$.

However, only CGM use and diabetes self-management concern were significantly associated with hypoglycemia among respondents with type 1 diabetes. The odds of having hypoglycemia were 76% lower amongst respondents who were using CGM technology. Compared to respondents having low concern in their diabetes self-management, respondents with a high concern were 1.94 times (95% CI: 1.04–3.61) more likely to experience hypoglycemia (Table 5).

3.5. Factors Associated with Hyperglycemia and Hypoglycemia Among Respondents with Type 2 DM

Age, diabetes app use, general diet, diabetes self-management concern, and self-reported confidence regarding diabetes self-management were significantly associated with experiencing hyperglycemia amongst respondents with type 2 DM.

Respondents who were using diabetes apps were 37% less likely to experience hyperglycemia than those who did not. A one-point increase on the "general diet" self-care scale was associated with a 16% reduction of the odds of experiencing hyperglycemia.

Respondents with type 2 DM that reported a high concern regarding their diabetes self-management were 2.59 (95% CI: 1.74–3.84) times more likely to experience hyperglycemia than

those who had a low concern. Moreover, respondents who were not confident in their diabetes self-management capacity were 3.22 (95% CI: 2.07–5.00) times more likely to experience hyperglycemia than those who were confident. For each year increase in age, the odds of having hyperglycemia increased by a factor of 1.02 (95% CI: 1.00–1.04) (Table 5).

Regarding hypoglycemia among respondents with type 2 DM, the likelihood of hypoglycemia increased by a factor of 1.07 (95% CI: 1.01–1.14) for each additional increase in age. In addition, respondents that had a polytechnic diploma were 11(1.06–113.9) times more likely to report hyperglycemia compared to respondents who had a bachelor's degree and above (Table 5).

Stratified analyses to investigate the country-level differences between the US, Germany, and the UK, regarding the factors associated with hyperglycemia and hypoglycemia among persons with type 1 and type 2 diabetes were conducted. The results were generally consistent with the pooled analyses. The results revealed that high diabetes self-management concern was consistently associated with increasing the odds of experiencing hyperglycemia amongst respondents with Type 1 diabetes who were from the US and Germany. Conversely, an increment in the blood glucose monitoring self-care days was consistently associated with reducing the odds of experiencing hyperglycemia amongst US and German respondents living with type 1 diabetes (Supplementary Tables S1 and S3). However, for US respondents with type 1 diabetes, an increment in the physical activity self-care days was significantly associated with reducing the odds of experiencing hyperglycemia (Supplementary Table S1). For respondents with type 1 diabetes who were from the UK, the odds of experiencing hyperglycemia were significantly reduced, particularly by using CGM and increments in the specific diet self-care days (Supplementary Table S5).

Among respondents with type 2 diabetes who were from Germany or the US, an increment in the general diet self-care behavior days was significantly associated with reducing the odds of experiencing hyperglycemia in type 2 diabetes. However, having a high diabetes self-management concern and being in older age groups consistently increased the odds of experiencing hyperglycemia for both the respondents from the US and Germany (Supplementary Tables S2 and S4)

4. Discussion

This was the first multi-national study aimed at investigating the role of CGM, diabetes app use, and self-care behavior in reducing glycemic control amongst persons with type 1 and type 2 DM. The study revealed that more than half of the respondents with type 1 diabetes and more than one third of the respondents with type 2 diabetes reported using diabetes smartphone apps to assist them in their disease self-management. Diabetes app use in this study was higher than reported from other studies. For example, a study conducted in New Zealand reported a use of 20% among people with type 1 diabetes [46], another study conducted in Australia reported user rates of 24% for persons with type 1 DM and 8% for persons with type 2 DM [57]. It was also much higher than user rates reported in studies from the US (4%) [22] and Scotland (7%) [58]. This difference was possibly due to the difference in the digital literacy among respondents [59–61]. People who use social media have a higher level of digital literacy. The relatively higher proportion of diabetes app use among people with type 1 diabetes was due to their younger age because of an earlier onset of the disease. Younger adults have a higher level of digital literacy. This is in line with other studies which found higher levels of app use in younger populations [57,62,63]. Possibly, it might also be due to the improved awareness of the consequences of failing to monitor blood glucose levels.

On average, respondents of this study reported spending more than two days per week on almost all self-care activities. Blood glucose monitoring and general diet were the two most commonly practiced self-care behaviors in both groups of respondents. Similarly, results by Tricia et.al indicated that patients with type 2 DM in the US spent more days on healthy eating and self-monitoring of blood glucose than on any other self-care activities [64]. However, whether there is a difference in the self-care behavior among diabetes app users and non-users who have type 1 or type 2 DM needs further investigation.

Having a lower educational status, smoking, and having a higher diabetes self-management concern increased the odds of experiencing hyperglycemia among respondents with type 1 DM. Previous studies reported a similar relationship between lower educational status and hyperglycemia [65,66]. This can partly be explained by the lower educational status which may inhibit the success of an interactive oral and written communication, which are key aspects of a successful patient–provider relationship and diabetes self-management [67–69]. In addition, education is an established mechanism that affects health literacy, where persons with higher levels of education may also have a greater diabetes self-management capacity and may feel more confident in achieving metabolic control [70].

Similar to the findings of our study, a plethora of evidence suggests that smoking increases the risk of hyperglycemia in persons with type 1 DM [66,71–74]. Smoking induced hyperglycemia, as explained in previous studies, might be due to the acute biochemical reactions caused by smoking, particularly the mobilization of catecholamines and increased cortisol productions [71]. In addition, smoking increases the risk of hyperglycemia by inhibiting insulin sensitivity and resistance [75,76].

Encouragingly, two self-care behaviors, namely "general diet" and "blood glucose monitoring", were significantly associated with the reduced odds of experiencing hyperglycemia. Similarly, Schmitt and colleagues reported a higher number of self-care days for "general diet" and "blood glucose monitoring", which were in turn correlated with glycemic control [77]. A generalized diet plan, regardless of specific calorie levels, with consistent carbohydrate intake is considered apractical methods of serving food while potentially improving glycemic control [78].

Interestingly, the use of CGM technology for glucose monitoring was inversely associated with both hyperglycemia and hypoglycemia among respondents with type 1 DM. In comparison, in numerous other experimental and observational studies, the use of CGM was associated with improved glycemic control [79–81]. CGM plays an important role in successful glycemic control by helping patients to timely and effectively detect and counteract hyperglycemia and hypoglycemia. It is considered as an optimal way to respond to glycemic abnormalities and glycemic variabilities in a timely manner [80,81]. However, CGM is more effective when combined with behavioral and educational strategies to respond to abnormal glycemic readings through the appropriate corrective actions, such as adjusting medication doses and changes to physical activity and nutrition [80,82].

Having a higher diabetes self-management concern increased the odds of experiencing hyperglycemia or hypoglycemia in persons with type 1 DM. This might be due to the poor self-management capacity, lack of problem-solving skills, and poor capacity of how to timely detect and appropriately respond to any episode of glycemic abnormalities [83–85]. Due to the frequent requirements of self-monitoring of blood glucose and other highly demanding self-management responsibilities, as well as lack of sleep, and worries about glycemic abnormalities, patients with type 1 diabetes have an increased risk of depression, anxiety, and emotional stress [86]. This may also increase the risk of experiencing hyperglycemia and hypoglycemia [87].

Looking at the factors associated with hyperglycemia among respondents with type 2 diabetes, it shows that diabetes app use and "general diet" appear to be two of the key factors to lowering the odds of having hyperglycemia. On the other hand, higher diabetes self-management concern and lower self-reported confidence with regard to diabetes self-management increased the odds of experiencing hyperglycemia.

Similar to the results reported in the current study, previous studies have reported lower risks of hyperglycemia among diabetes smartphone app users with type 2 diabetes [88,89]. Numerous randomized controlled trials also demonstrated the benefits of using diabetes smartphone apps for improving glycemic control in patients with type 2 DM [21,90,91]. Diabetes apps help improve glycemic control by enhancing diabetes knowledge, self-management capabilities, adherence to medication, and healthy life style recommendations [19,21–24,92]. Diabetes apps have the potential to facilitate personalized medicine by helping patients with type 2 diabetes to achieve their personalized self-management goals and improve clinical and behavioral outcomes. However, the quality and

content of the apps requires further research to help patients and providers to identify effective and user-friendly diabetes apps. In addition, considering the large number of diabetes apps currently available online, choosing the right app might be difficult for patients. Hence, the evaluation and recommendation of physicians are important before using them. Further research is also required to identify the most popular diabetes apps.

In the current study, the odds of experiencing hyperglycemia were reduced with increments in the "general diet" self-care behavior. Related to this finding, previous studies also reported that poor compliance to a healthy diet was a significant predictor of hyperglycemia [93–96]. Consistent meal planning, particularly to maintain the consistency of carbohydrate intake, has been an accepted standard for improving glycemic control [78]. However, whether low or high carbohydrate meals are preferable for improving glycemic control is controversial and there is still conflicting evidence on the issue [97–100].

Although the association was not strong, each additional year increase in age significantly increased the odds of having both hyperglycemia and hypoglycemia among respondents with type 2 diabetes. Diabetes is considered a progressive disease and glycemic levels worsen with increasing age [6,101]. This is partly due to the decline in beta-cell function, impaired insulin secretion, as well as lack of metformin effectiveness among the elderly patients [101–104].

Similar to patients with type 1 diabetes, patients with type 2 DM reporting a high diabetes self-management concern were more likely to have hyperglycemia. This might be due to their lack of diabetes knowledge, and psychosocial and emotional challenges [105] affecting self-management skills and resilience to glycemic abnormalities [83–85].

Patients with low self-rated confidence in their diabetes self-management management capacity were more likely to experience hyperglycemia compared to patients who rated their confidence as high. In line with this finding, a study by Whittemore and colleagues reported diabetes self-management confidence as one of the most consistent predictors of metabolic control [106]. Educational interventions aiming to enhance confidence in the self-management capacity of patients may help patients to attain their personalized glycemic control goals.

Limitations

This study had several limitations. All the respondents of the survey were recruited using online platforms. Hence, patients who do not subscribe to Facebook and diabetes online forums were not represented in this study, which limits the generalizability of the study. In addition, participants of the study came from multiple countries. The impact of a broad range of factors, such as differences in the healthcare systems, and social, cultural, and racial differences were not investigated in the study. A further stratified analyses of the data based on the nationality or income category of respondents may provide a better insight and help minimize the bias due to unobserved variation arising from the health care systems, as well as socio-economic and cultural differences among respondents. These factors potentially limit the applicability of the results to a specific context. However, patients with diabetes who are subscribers to social media are also an important population presenting an interesting paradigm of self-management and social support. Therefore, considering the ever-increasing presence and interest of patients with diabetes on social media, who are seeking diabetes-related information and support, this particular community of diabetes requires attention. In this regard, our research attempted to investigate glycemic control in this particular population. Moreover, the responses to all questions, including biochemical parameters, were based on self-reported responses and were not objectively measured. Social desirability may have played a role while completing the survey. This may also have an impact on our results.

In addition, due to the cross-sectional nature of the study, the results should be carefully interpreted because HbA1c and one-time capillary glucose levels may not be adequate to understand the hyperglycaemic and hypoglycaemic episodes of patients with diabetes. Measuring several glucose levels per day is more helpful to understand the dynamics of glycemic control. Recent studies

demonstrated that determining the coefficient of glycemic variation (CV) is an important metric to assess glycemic variability rather than using HbA1c. Ideally, this is only possible with access to CGM.

We noted that conducting a survey using Facebook groups was very challenging. Importantly, the members of these groups came from many parts of the world, which was very demanding because the researchers needed to work with multiple time zones. Keeping the survey active on the newsfeed of members required an extended effort. We did this by trying to engage and motivate members of the group to enter comments to the survey posted on the Facebook groups, and by periodically bumping the post so that members of a group who did not see the survey post may see it and participate in the survey. This was not as effective as we thought, especially in groups with tens of thousands of members. In larger Facebook groups that had a very active flow of information, the information posted on the group page vanished from the newsfeed in just a matter of a few minutes, unless the members entered comments or influential group admins were engaged to keep it active on the page. Hence, we advise future researchers to consider actively involving group champions (admins and moderators) in their research. Group champions, being the most influential members of Facebook groups, enhance the participation and response rates by motivating members, triggering discussions, and most importantly pinning the survey on a group page for a particular period of time.

5. Conclusions

Diabetes app use reduces the odds of experiencing hyperglycemia in type 2 DM. The use of CGM technology for monitoring blood glucose significantly reduces the odds of experiencing hyperglycemia and hypoglycemia in type 1 DM. Diabetes apps and the use of CGM may facilitate personalized medicine to helping patients achieve individualized glycemic goals. Educational interventions targeted at reducing self-management concern, improving dietary self-care behavior, and self-management confidence may help patients with type1 and type 2 DM reduce glycemic abnormalities.

Supplementary Materials: The following are available online at http://www.mdpi.com/2077-0383/8/1/109/s1, Figure S1: Screenshot of one of the targeted Facebook advertisements and the list of terms used for the advertisement, Table S1: Multinomial logistic regression model of glycemic control in type 1 DM using data from US only respondents, Table S2: Multinomial logistic regression model of glycemic control in type 2 DM using data from US respondents, Table S3: Multinomial logistic regression model of glycemic control in type 1 DM using data from respondents only from Germany, Table S4: Multinomial logistic regression model of glycemic control in type 2 DM using data from respondents only from Germany, Table S5: Multinomial logistic regression model of glycemic control in type 1 DM using data from UK respondents.

Author Contributions: M.M.K.: conceptualized the study, designed the study, performed the Facebook group search and targeted advertisements, conducted the survey, collected the data, performed the data analysis, and wrote the manuscript. C.S.: participated in the search process and ran the survey posted on the German Facebook groups and online forums, and revised the manuscript. C.R.P.: conceived the study, contributed to the survey design, and critically revised the manuscript. All authors contributed toward data analysis, drafting and critically revising the paper, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

Acknowledgments: We are grateful to Jana Sill for her support during our search of the Facebook groups.

Availability of Data and Materials: The datasets collected, used, and analyzed for the study can be obtained from the corresponding author on a reasonable request. The University of Bremen Central Research Development Fund committee funded the cost of the Amazon vouchers given to survey participants in a lottery.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. International Diabetes Federation (IDF). *IDF Diabetes Atlas*, 8th ed.; International Diabetes Federation: Brussels, Belgium, 2017.
2. Brown, M.T.; Bussell, J.K. Medication adherence: WHO cares? *Mayo Clin. Proc.* **2011**, *86*, 304–314. [CrossRef] [PubMed]
3. World Health Organization (WHO). *Global Report on Diabetes*; World Health Organization: Geneva, Switzerland, 2016.

4. Tuomi, T.; Santoro, N.; Caprio, S.; Cai, M.; Weng, J.; Groop, L. The many faces of diabetes: A disease with increasing heterogeneity. *Lancet* **2014**, *383*, 1084–1094. [CrossRef]
5. International Diabetes Federation (IDF). *Diabetes Atlas*, 6th ed.; International Diabetes Federation: Brussels, Belgium, 2013.
6. American Diabetes Association. Standards of medical care in diabetes—2013. *Diabetes Care* **2013**, *36*, S11–S66.
7. Evert, A.B.; Boucher, J.L.; Cypress, M.; Dunbar, S.A.; Franz, M.J.; Mayer-Davis, E.J.; Neumiller, J.J.; Nwankwo, R.; Verdi, C.L.; Urbanski, P.; et al. Nutrition Therapy Recommendations for the Management of Adults with Diabetes. *Diabetes Care* **2014**, *37*, S120–S143. [CrossRef] [PubMed]
8. Strom, J.L.; Egede, L.E. The impact of social support on outcomes in adult patients with type 2 diabetes: A systematic review. *Curr. Diabetes Rep.* **2012**, *12*, 769–781. [CrossRef]
9. Labate, C. The influence of social media on diabetes treatment and self-care. *Diabetes Voice* **2013**, *58*, 14–15.
10. White, K.; Gebremariam, A.; Lewis, D.; Nordgren, W.; Wedding, J.; Pasek, J.; Garrity, A.; Hirschfeld, E.; Lee, J.M. Motivations for Participation in an Online Social Media Community for Diabetes. *J. Diabetes Sci. Technol.* **2018**, *12*, 712–718. [CrossRef]
11. Petrovski, G.; Zivkovic, M.; Stratrova, S.S. Social media and diabetes: Can Facebook and Skype improve glucose control in patients with type 1 diabetes on pump therapy? One-year experience. *Diabetes Care* **2015**, *38*, e51–e52. [PubMed]
12. Nowak, M.; Spiller, G. Two Billion People Coming Together on Facebook. Available online: https://newsroom.fb.com/news/2017/06/two-billion-people-coming-together-on-facebook/ (accessed on 13 February 2017).
13. Partridge, S.R.; Gallagher, P.; Freeman, B.; Gallagher, R. Facebook Groups for the Management of Chronic Diseases. *J. Med. Internet Res.* **2018**, *20*, e21. [CrossRef] [PubMed]
14. NHS. Guidance on the Use of Social Media to Actively Involve People in Research. Available online: http://www.invo.org.uk/wp-content/uploads/2017/07/Social-Media-Guide-web-2017.pdf (accessed on 13 February 2017).
15. Al Mamun, M.; Ibrahim, H.M.; Turin, T.C. Social media in communicating health information: An analysis of Facebook groups related to hypertension. *Prev. Chronic Dis.* **2015**, *12*, E11. [CrossRef] [PubMed]
16. Abedin, T.; Al Mamun, M.; Lasker, M.A.A.; Ahmed, S.W.; Shommu, N.; Rumana, N.; Turin, T.C. Social Media as a Platform for Information About Diabetes Foot Care: A Study of Facebook Groups. *Can. J. Diabetes* **2017**, *41*, 97–101. [CrossRef] [PubMed]
17. Greene, J.A.; Choudhry, N.K.; Kilabuk, E.; Shrank, W.H. Online social networking by patients with diabetes: A qualitative evaluation of communication with Facebook. *J. Gen. Intern. Med.* **2011**, *26*, 287–292. [CrossRef] [PubMed]
18. Alanzi, T. Role of Social Media in Diabetes Management in the Middle East Region: Systematic Review. *J. Med. Internet Res.* **2018**, *20*, e58. [CrossRef] [PubMed]
19. El-Gayar, O.; Timsina, P.; Nawar, N.; Eid, W. Mobile applications for diabetes self-management: Status and potential. *J. Diabetes Sci. Technol.* **2013**, *7*, 247–262. [CrossRef]
20. American Diabetes Association. Standards of medical care in diabetes—2012. *Diabetes Care* **2012**, *35* (Suppl. 1), S11–S63. [CrossRef] [PubMed]
21. Kirwan, M.; Vandelanotte, C.; Fenning, A.; Duncan, M.J. Diabetes self-management smartphone application for adults with type 1 diabetes: Randomized controlled trial. *J. Med. Internet Res.* **2013**, *15*, e235. [CrossRef] [PubMed]
22. Williams, J.P.; Schroeder, D. Popular Glucose Tracking Apps and Use of mHealth by Latinos with Diabetes: Review. *JMIR mHealth uHealth* **2015**, *3*, e84. [CrossRef] [PubMed]
23. Ryan, E.A.; Holland, J.; Stroulia, E.; Bazelli, B.; Babwik, S.A.; Li, H.; Senior, P.; Greiner, R. Improved A1C Levels in Type 1 Diabetes with Smartphone App Use. *Can. J. Diabetes* **2017**, *41*, 33–40. [CrossRef]
24. Demidowich, A.P.; Lu, K.; Tamler, R.; Bloomgarden, Z. An evaluation of diabetes self-management applications for Android smartphones. *J. Telemed. Telecare* **2012**, *18*, 235–238. [CrossRef]
25. Muralidharan, S.; Ranjani, H.; Anjana, R.M.; Allender, S.; Mohan, V. Mobile Health Technology in the Prevention and Management of Type 2 Diabetes. *Indian J. Endocrinol. Metab.* **2017**, *21*, 334–340.
26. Hamine, S.; Gerth-Guyette, E.; Faulx, D.; Green, B.B.; Ginsburg, A.S. Impact of mHealth chronic disease management on treatment adherence and patient outcomes: A systematic review. *J. Med. Internet Res.* **2015**, *17*, e52. [CrossRef]

27. Hou, C.; Carter, B.; Hewitt, J.; Francisa, T.; Mayor, S. Do Mobile Phone Applications Improve Glycemic Control (HbA1c) in the Self-management of Diabetes? A Systematic Review, Meta-analysis, and GRADE of 14 Randomized Trials. *Diabetes Care* **2016**, *39*, 2089–2095. [CrossRef] [PubMed]
28. Kebede, M.M.; Liedtke, T.P.; Möllers, T.; Pischke, C.R. Characterizing Active Ingredients of eHealth Interventions Targeting Persons with Poorly Controlled Type 2 Diabetes Mellitus Using the Behavioral Change Technique Taxonomy. *J. Med. Internet Res.* **2017**, *19*, e348. [CrossRef] [PubMed]
29. Kebede, M.M.; Zeeb, H.; Peters, M.; Heise, T.L.; Pischke, C.R. Effectiveness of Digital Interventions for Improving Glycemic Control in Persons with Poorly Controlled Type 2 Diabetes: A Systematic Review, Meta-analysis, and Meta-regression Analysis. *Diabetes Technol.* **2018**, *20*, 767–782. [CrossRef] [PubMed]
30. Kebede, M.M.; Peters, M.; Heise, T.L.; Pischke, C.R. Comparison of three meta-analytic methods using data from digital interventions on type 2 diabetes. *Diabetes Metab. Syndr. Obes.* **2019**, *12*, 59–73. [CrossRef] [PubMed]
31. Research2Guidance. Diabetes App Market Report 2016–2021. Available online: https://research2guidance.com/product/diabetes-app-market-report-2016-2021/ (accessed on 30 October 2017).
32. Research2Guidance. mHealth App Developer Economics 2016. Available online: https://research2guidance.com/product/mhealth-app-developer-economics-2016/ (accessed on 30 October 2017).
33. Lanzola, G.; Capozzi, D.; D'Annunzio, G.; Ferrari, P.; Bellazzi, R.; Larizza, C. Going mobile with a multiaccess service for the management of diabetic patients. *J. Diabetes Sci. Technol.* **2007**, *1*, 730–737. [CrossRef] [PubMed]
34. Rao, A.; Hou, P.; Golnik, T.; Flaherty, J.; Vu, S. Evolution of data management tools for managing self-monitoring of blood glucose results: A survey of iPhone applications. *J. Diabetes Sci. Technol.* **2010**, *4*, 949–957. [CrossRef]
35. Eng, D.S.; Lee, J.M. The promise and peril of mobile health applications for diabetes and endocrinology. *Pediatr. Diabetes* **2013**, *14*, 231–238. [CrossRef]
36. R2G. *mHealth Economics 2017—Current Status and Future Trends in Mobile Health*; Research 2 Guideance: Berlin, Germany, 2017.
37. Jacques Rose, K.; Petrut, C.; L'Heveder, R.; de Sabata, S. IDF Europe position on mobile applications in diabetes. *Diabetes Res. Clin. Pract.* **2017**. [CrossRef]
38. Internation Diabetes Federation (IDF). *IDF Europe Position on Mobile Applications in Diabetes*; Internation Diabetes Federation: Brussels, Belgium, 2017.
39. Chomutare, T.; Fernandez-Luque, L.; Arsand, E.; Hartvigsen, G. Features of mobile diabetes applications: Review of the literature and analysis of current applications compared against evidence-based guidelines. *J. Med. Internet Res.* **2011**, *13*, e65. [CrossRef]
40. Center for Devices and Radiological Health. Mobile Medical Applications—Guidance for Industry and Food and Drug Administration Staff. Available online: http://www.fda.gov/downloads/MedicalDevices/.../UCM263366.pdf (accessed on 2 November 2017).
41. Dolan, B. FDA Clears WellDoc for Diabetes Management. Available online: http://mobihealthnews.com/8539/fda-clears-welldoc-for-diabetes-management (accessed on 19 November 2018).
42. Huckvale, K.; Adomaviciute, S.; Prieto, J.T.; Leow, M.K.; Car, J. Smartphone apps for calculating insulin dose: A systematic assessment. *BMC Med.* **2015**, *13*, 106. [CrossRef]
43. Veazie, S.; Winchell, K.; Gilbert, J.; Paynter, R.; Ivlev, I.; Eden, K.; Nussbaum, K.; Weiskopf, N.; Guise, J.M.; Helfand, M. *Mobile Applications for Self-Management of Diabetes*; Agency for Healthcare Research and Quality: Rockville, MD, USA, 2018.
44. Shuren, J.; Patel, B.; Gottlieb, S. FDA Regulation of Mobile Medical Apps. *JAMA* **2018**, *320*, 337–338. [CrossRef] [PubMed]
45. Trawley, S.; Browne, J.L.; Hagger, V.L.; Hendrieckx, C.; Holmes-Truscott, E.; Pouwer, F.; Skinner, T.C.; Speight, J. The Use of Mobile Applications Among Adolescents with Type 1 Diabetes: Results from Diabetes MILES Youth—Australia. *Diabetes Technol. Ther.* **2016**, *18*, 813–819. [CrossRef] [PubMed]
46. Boyle, L.; Grainger, R.; Hall, R.M.; Krebs, J.D. Use of and Beliefs About Mobile Phone Apps for Diabetes Self-Management: Surveys of People in a Hospital Diabetes Clinic and Diabetes Health Professionals in New Zealand. *JMIR mHealth uHealth* **2017**, *5*, e85. [CrossRef] [PubMed]
47. Kramer, U.; Zehner, F. Diabetes-Management mit APPs: Derzeitige & zukünftige Nutzung, Einstellungen, Erfahrungen und Erwartungen von Betroffenen. Online-Befragung von Diabetikern. *Aktuelle Ernährungsmedizin* **2016**, *41*, V07.

48. Brooke, M.J.; Thompson, B.M. Food and Drug Administration regulation of diabetes-related mHealth technologies. *J. Diabetes Sci. Technol.* **2013**, *7*, 296–301. [CrossRef] [PubMed]
49. Schmitz, C.; LimeSurvey Project Team. *LimeSurvey: An Open Source Survey Tool*; LimeSurvey Project: Hamburg, Germany, 2012.
50. Toobert, D.J.; Hampson, S.E.; Glasgow, R.E. The summary of diabetes self-care activities measure: Results from 7 studies and a revised scale. *Diabetes Care* **2000**, *23*, 943–950. [CrossRef] [PubMed]
51. Kamradt, M.; Bozorgmehr, K.; Krisam, J.; Freund, T.; Kiel, M.; Qreini, M.; Flum, E.; Berger, S.; Besier, W.; Szecsenyi, J.; et al. Assessing self-management in patients with diabetes mellitus type 2 in Germany: Validation of a German version of the Summary of Diabetes Self-Care Activities measure (SDSCA-G). *Health Qual. Life Outcomes* **2014**, *12*, 185. [CrossRef] [PubMed]
52. American Diabetes Association. Standards of Medical Care in Diabetes—2014. *Diabetes Care* **2014**, *37* (Suppl. 1), S14–S80. [CrossRef]
53. American Diabetes Association. Glycemic Targets. *Diabetes Care* **2017**, *40*, S48–S56. [CrossRef]
54. Beck, R.W.; Connor, C.G.; Mullen, D.M.; Wesley, D.M.; Bergenstal, R.M. The Fallacy of Average: How Using HbA1c Alone to Assess Glycemic Control Can Be Misleading. *Diabetes Care* **2017**, *40*, 994–999. [CrossRef]
55. Langer, W. The Assessment of Fit in the Class of Logistic Regression Models: A Pathway out of the Jungle of Pseudo-R^2s Using Stata. In Proceedings of the Meeting of the German Stata User Group at GESIS, Cologne, Germany, 10 June 2016.
56. World Bank. World Bank Country and Lending Groups: Country Classification. Available online: https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups (accessed on 19 September 2018).
57. Trawley, S.; Baptista, S.; Browne, J.L.; Pouwer, F.; Speight, J. The Use of Mobile Applications Among Adults with Type 1 and Type 2 Diabetes: Results from the Second MILES-Australia (MILES-2) Study. *Diabetes Technol.* **2017**, *19*, 730–738. [CrossRef] [PubMed]
58. Conway, N.; Campbell, I.; Forbes, P.; Cunningham, S.; Wake, D. mHealth applications for diabetes: User preference and implications for app development. *Health Inform. J.* **2016**, *22*, 1111–1120. [CrossRef] [PubMed]
59. Mathiesen, A.S.; Thomsen, T.; Jensen, T.; Schiotz, C.; Langberg, H.; Egerod, I. The influence of diabetes distress on digital interventions for diabetes management in vulnerable people with type 2 diabetes: A qualitative study of patient perspectives. *J. Clin. Transl. Endocrinol.* **2017**, *9*, 41–47. [CrossRef] [PubMed]
60. Rodriguez, J.A.; Singh, K. The Spanish Availability and Readability of Diabetes Apps. *J. Diabetes Sci. Technol.* **2018**, *12*, 719–724. [CrossRef] [PubMed]
61. Schramm, W. Digital Diabetes Self-Management: A Trilateral Serial. *J. Diabetes Sci. Technol.* **2018**, *12*, 709–711. [CrossRef] [PubMed]
62. Ernsting, C.; Dombrowski, S.U.; Oedekoven, M.; O'Sullivan, J.L.; Kanzler, M.; Kuhlmey, A.; Gellert, P. Using Smartphones and Health Apps to Change and Manage Health Behaviors: A Population-Based Survey. *J. Med. Internet Res.* **2017**, *19*, e101. [CrossRef] [PubMed]
63. Krebs, P.; Duncan, D.T. Health App Use Among US Mobile Phone Owners: A National Survey. *JMIR mHealth uHealth* **2015**, *3*, e101. [CrossRef]
64. Tang, T.S.; Brown, M.B.; Funnell, M.M.; Anderson, R.M. Social Support, Quality of Life, and Self-Care Behaviors Among African Americans With Type 2 Diabetes. *Diabetes Educ.* **2008**, *34*, 266–276. [CrossRef]
65. Andrade, C.S.; Ribeiro, G.S.; Santos, C.; Neves, R.C.S.; Moreira, E.D., Jr. Factors associated with high levels of glycated haemoglobin in patients with type 1 diabetes: A multicentre study in Brazil. *BMJ Open* **2017**, *7*, e018094. [CrossRef]
66. Sastre, J.; Pines, P.J.; Moreno, J.; Aguirre, M.; Blanco, B.; Calderon, D.; Herranz, S.; Roa, C.; Lopez, J.; Grupo de estudio, D. Metabolic control and treatment patterns in patients with type 1 diabetes in Castilla-La Mancha: The DIAbetes tipo 1 in Castilla La Mancha study. *Endocrinol. Nutr.* **2012**, *59*, 539–546. [CrossRef]
67. Grohmann, B.; Espin, S.; Gucciardi, E. Patients' experiences of diabetes education teams integrated into primary care. *Can. Fam. Physician* **2017**, *63*, e128–e136. [PubMed]
68. Castro, C.M.; Wilson, C.; Wang, F.; Schillinger, D. Babel babble: Physicians' use of unclarified medical jargon with patients. *Am. J. Health Behav.* **2007**, *31* (Suppl. 1), S85–S95. [CrossRef]
69. Williams, M.V.; Davis, T.; Parker, R.M.; Weiss, B.D. The role of health literacy in patient-physician communication. *Fam. Med.* **2002**, *34*, 383–389. [PubMed]

70. Schillinger, D.; Barton, L.R.; Karter, A.J.; Wang, F.; Adler, N. Does literacy mediate the relationship between education and health outcomes? A study of a low-income population with diabetes. *Public Health Rep.* **2006**, *121*, 245–254. [CrossRef] [PubMed]
71. Bornemisza, P.; Suciu, I. Effect of cigarette smoking on the blood glucose level in normals and diabetics. *Med. Interne* **1980**, *18*, 353–356. [PubMed]
72. Gerber, P.A.; Locher, R.; Schmid, B.; Spinas, G.A.; Lehmann, R. Smoking is associated with impaired long-term glucose metabolism in patients with type 1 diabetes mellitus. *Nutr. Metab. Cardiovasc. Dis.* **2013**, *23*, 102–108. [CrossRef] [PubMed]
73. Scott, L.J.; Warram, J.H.; Hanna, L.S.; Laffel, L.M.; Ryan, L.; Krolewski, A.S. A nonlinear effect of hyperglycemia and current cigarette smoking are major determinants of the onset of microalbuminuria in type 1 diabetes. *Diabetes* **2001**, *50*, 2842–2849. [CrossRef]
74. Gunton, J.E.; Davies, L.; Wilmshurst, E.; Fulcher, G.; McElduff, A. Cigarette smoking affects glycemic control in diabetes. *Diabetes Care* **2002**, *25*, 796–797. [CrossRef]
75. Vu, C.U.; Siddiqui, J.A.; Wadensweiler, P.; Gayen, J.R.; Avolio, E.; Bandyopadhyay, G.K.; Biswas, N.; Chi, N.W.; O'Connor, D.T.; Mahata, S.K. Nicotinic acetylcholine receptors in glucose homeostasis: The acute hyperglycemic and chronic insulin-sensitive effects of nicotine suggest dual opposing roles of the receptors in male mice. *Endocrinology* **2014**, *155*, 3793–3805. [CrossRef]
76. Attvall, S.; Fowelin, J.; Lager, I.; Von Schenck, H.; Smith, U. Smoking induces insulin resistance—A potential link with the insulin resistance syndrome. *J. Intern. Med.* **1993**, *233*, 327–332. [CrossRef]
77. Schmitt, A.; Gahr, A.; Hermanns, N.; Kulzer, B.; Huber, J.; Haak, T. The Diabetes Self-Management Questionnaire (DSMQ): Development and evaluation of an instrument to assess diabetes self-care activities associated with glycaemic control. *Health Qual. Life Outcomes* **2013**, *11*, 138. [CrossRef] [PubMed]
78. Ryan, D.B.; Swift, C.S. The Mealtime Challenge: Nutrition and Glycemic Control in the Hospital. *Diabetes Spectr.* **2014**, *27*, 163–168. [CrossRef] [PubMed]
79. Sheikh, K.; Bartz, S.K.; Lyons, S.K.; DeSalvo, D.J. Diabetes Device Use and Glycemic Control among Youth with Type 1 Diabetes: A Single-Center, Cross-Sectional Study. *J. Diabetes Res.* **2018**, *2018*, 1–6. [CrossRef] [PubMed]
80. Canadian Diabetes Association Clinical Practice Guidelines Expert Committee; Berard, L.D.; Siemens, R.; Woo, V. Monitoring Glycemic Control. *Can. J. Diabetes* **2018**, *42* (Suppl. 1), S47–S53. [CrossRef] [PubMed]
81. Wallia, A.; Umpierrez, G.E.; Nasraway, S.A.; Klonoff, D.C. Round Table Discussion on Inpatient Use of Continuous Glucose Monitoring at the International Hospital Diabetes Meeting. *J. Diabetes Sci. Technol.* **2016**, *10*, 1174–1181. [CrossRef] [PubMed]
82. Klonoff, D.C.; Ahn, D.; Drincic, A. Continuous glucose monitoring: A review of the technology and clinical use. *Diabetes Res. Clin. Pract.* **2017**, *133*, 178–192. [CrossRef] [PubMed]
83. Wang, J.; Zgibor, J.; Matthews, J.T.; Charron-Prochownik, D.; Sereika, S.M.; Siminerio, L. Self-monitoring of blood glucose is associated with problem-solving skills in hyperglycemia and hypoglycemia. *Diabetes Educ.* **2012**, *38*, 207–218. [CrossRef] [PubMed]
84. Ward, J.E.; Stetson, B.A.; Mokshagundam, S.P. Patient perspectives on self-monitoring of blood glucose: Perceived recommendations, behaviors and barriers in a clinic sample of adults with type 2 diabetes. *J. Diabetes Metab. Disord.* **2015**, *14*, 43. [CrossRef]
85. Simmons, J.H.; Chen, V.; Miller, K.M.; McGill, J.B.; Bergenstal, R.M.; Goland, R.S.; Harlan, D.M.; Largay, J.F.; Massaro, E.M.; Beck, R.W. Differences in the Management of Type 1 Diabetes Among Adults Under Excellent Control Compared with Those Under Poor Control in the T1D Exchange Clinic Registry. *Diabetes Care* **2013**, *36*, 3573–3577. [CrossRef]
86. Snow, R.; Humphrey, C.; Sandall, J. What happens when patients know more than their doctors? Experiences of health interactions after diabetes patient education: A qualitative patient-led study. *BMJ Open* **2013**, *3*. [CrossRef]
87. Reddy, M.; Rilstone, S.; Cooper, P.; Oliver, N.S. Type 1 diabetes in adults: Supporting self management. *BMJ* **2016**, *352*, i998. [CrossRef] [PubMed]
88. Offringa, R.; Sheng, T.; Parks, L.; Clements, M.; Kerr, D.; Greenfield, M.S. Digital Diabetes Management Application Improves Glycemic Outcomes in People with Type 1 and Type 2 Diabetes. *J. Diabetes Sci. Technol.* **2018**, *12*, 701–708. [CrossRef] [PubMed]

89. Orsama, A.L.; Lahteenmaki, J.; Harno, K.; Kulju, M.; Wintergerst, E.; Schachner, H.; Stenger, P.; Leppanen, J.; Kaijanranta, H.; Salaspuro, V.; et al. Active assistance technology reduces glycosylated hemoglobin and weight in individuals with type 2 diabetes: Results of a theory-based randomized trial. *Diabetes Technol.* **2013**, *15*, 662–669. [CrossRef] [PubMed]
90. Waki, K.; Fujita, H.; Uchimura, Y.; Omae, K.; Aramaki, E.; Kato, S.; Lee, H.; Kobayashi, H.; Kadowaki, T.; Ohe, K. DialBetics: A Novel Smartphone-based Self-management Support System for Type 2 Diabetes Patients. *J. Diabetes Sci. Technol.* **2014**, *8*, 209–215. [CrossRef] [PubMed]
91. Kumar, S.; Moseson, H.; Uppal, J.; Juusola, J.L. A Diabetes Mobile App with In-App Coaching From a Certified Diabetes Educator Reduces A1C for Individuals With Type 2 Diabetes. *Diabetes Educ.* **2018**, *44*, 226–236. [CrossRef] [PubMed]
92. Froisland, D.H.; Arsand, E.; Skarderud, F. Improving diabetes care for young people with type 1 diabetes through visual learning on mobile phones: Mixed-methods study. *J. Med. Internet Res.* **2012**, *14*, e111. [CrossRef] [PubMed]
93. Sayed, M.H.; Hegazi, M.A.; Abdulwahed, K.; Moussa, K.; El-Deek, B.S.; Gabel, H.; Ragheb, R. Risk factors and predictors of uncontrolled hyperglycemia and diabetic ketoacidosis in children and adolescents with type 1 diabetes mellitus in Jeddah, western Saudi Arabia. *J. Diabetes* **2017**, *9*, 190–199. [CrossRef]
94. Tan, S.L.; Juliana, S.; Sakinah, H. Dietary compliance and its association with glycemic control among poorly controlled type 2 diabetic outpatients in Hospital Universiti Sains Malaysia. *Malays. J. Nutr.* **2011**, *17*, 287–299.
95. Zhang, Y.; Ting, R.Z.W.; Yang, W.; Jia, W.; Li, W.; Ji, L.; Guo, X.; Kong, A.P.S.; Wing, Y.K.; Luk, A.O.Y.; et al. Depression in Chinese patients with type 2 diabetes: Associations with hyperglycemia, hypoglycemia, and poor treatment adherence. *J. Diabetes* **2015**, *7*, 800–808. [CrossRef]
96. Barnard, N.D.; Cohen, J.; Jenkins, D.J.; Turner-McGrievy, G.; Gloede, L.; Jaster, B.; Seidl, K.; Green, A.A.; Talpers, S. A low-fat vegan diet improves glycemic control and cardiovascular risk factors in a randomized clinical trial in individuals with type 2 diabetes. *Diabetes Care* **2006**, *29*, 1777–1783. [CrossRef]
97. Davis, N.J.; Tomuta, N.; Schechter, C.; Isasi, C.R.; Segal-Isaacson, C.J.; Stein, D.; Zonszein, J.; Wylie-Rosett, J. Comparative Study of the Effects of a 1-Year Dietary Intervention of a Low-Carbohydrate Diet Versus a Low-Fat Diet on Weight and Glycemic Control in Type 2 Diabetes. *Diabetes Care* **2009**, *32*, 1147–1152. [CrossRef] [PubMed]
98. Jonsson, T.; Granfeldt, Y.; Ahren, B.; Branell, U.C.; Palsson, G.; Hansson, A.; Soderstrom, M.; Lindeberg, S. Beneficial effects of a Paleolithic diet on cardiovascular risk factors in type 2 diabetes: A randomized cross-over pilot study. *Cardiovasc. Diabetol.* **2009**, *8*, 35. [CrossRef] [PubMed]
99. Khoo, J.; Piantadosi, C.; Duncan, R.; Worthley, S.G.; Jenkins, A.; Noakes, M.; Worthley, M.I.; Lange, K.; Wittert, G.A. Comparing effects of a low-energy diet and a high-protein low-fat diet on sexual and endothelial function, urinary tract symptoms, and inflammation in obese diabetic men. *J. Sex. Med.* **2011**, *8*, 2868–2875. [CrossRef] [PubMed]
100. Wolever, T.M.; Gibbs, A.L.; Mehling, C.; Chiasson, J.L.; Connelly, P.W.; Josse, R.G.; Leiter, L.A.; Maheux, P.; Rabasa-Lhoret, R.; Rodger, N.W.; et al. The Canadian Trial of Carbohydrates in Diabetes (CCD), a 1-y controlled trial of low-glycemic-index dietary carbohydrate in type 2 diabetes: No effect on glycated hemoglobin but reduction in C-reactive protein. *Am. J. Clin. Nutr.* **2008**, *87*, 114–125. [CrossRef] [PubMed]
101. Selvin, E.; Parrinello, C.M. Age-related differences in glycaemic control in diabetes. *Diabetologia* **2013**, *56*, 2549–2551. [CrossRef] [PubMed]
102. Crandall, J.; Barzilai, N. Treatment of diabetes mellitus in older people: Oral therapy options. *J. Am. Geriatr. Soc.* **2003**, *51*, 272–274. [CrossRef] [PubMed]
103. Knowler, W.C.; Barrett-Connor, E.; Fowler, S.E.; Hamman, R.F.; Lachin, J.M.; Walker, E.A.; Nathan, D.M. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N. Engl. J. Med.* **2002**, *346*, 393–403. [PubMed]
104. Pani, L.N.; Korenda, L.; Meigs, J.B.; Driver, C.; Chamany, S.; Fox, C.S.; Sullivan, L.; D'Agostino, R.B.; Nathan, D.M. Effect of aging on A1C levels in individuals without diabetes: Evidence from the Framingham Offspring Study and the National Health and Nutrition Examination Survey 2001–2004. *Diabetes Care* **2008**, *31*, 1991–1996. [CrossRef]

105. Tong, W.T.; Vethakkan, S.R.; Ng, C.J. Why do some people with type 2 diabetes who are using insulin have poor glycaemic control? A qualitative study. *BMJ Open* **2015**, *5*, e006407. [CrossRef]
106. Whittemore, R.; D'Eramo Melkus, G.; Grey, M. Metabolic control, self-management and psychosocial adjustment in women with type 2 diabetes. *J. Clin. Nurs.* **2005**, *14*, 195–203. [CrossRef]

STUDY IV

frontiers in Endocrinology

ORIGINAL RESEARCH
published: 01 March 2019
doi: 10.3389/fendo.2019.00135

Popular Diabetes Apps and the Impact of Diabetes App Use on Self-Care Behaviour: A Survey Among the Digital Community of Persons With Diabetes on Social Media

Mihiretu M. Kebede[1,2,3*] *and Claudia R. Pischke*[1,4]

[1] Leibniz Institute for Prevention Research and Epidemiology-BIPS, Bremen, Germany, [2] Health Sciences, University of Bremen, Bremen, Germany, [3] College of Medicine and Health Science, Institute of Public Health, University of Gondar, Gondar, Ethiopia, [4] Medical Faculty, Centre for Health and Society, Institute of Medical Sociology, University of Düsseldorf, Düsseldorf, Germany

OPEN ACCESS

Edited by:
Charumathi Sabanayagam, Singapore Eye Research Institute, Singapore

Reviewed by:
Eva Harper, Duke-NUS Medical School, Singapore
Margaret Udahogora, University of Maryland, College Park, United States

***Correspondence:**
Mihiretu M. Kebede
kebede@leibniz-bips.de

Specialty section:
This article was submitted to Diabetes, a section of the journal Frontiers in Endocrinology

Received: *23 November 2018*
Accepted: *13 February 2019*
Published: *01 March 2019*

Citation:
Kebede MM and Pischke CR (2019) Popular Diabetes Apps and the Impact of Diabetes App Use on Self-Care Behaviour: A Survey Among the Digital Community of Persons With Diabetes on Social Media. Front. Endocrinol. 10:135. doi: 10.3389/fendo.2019.00135

Introduction: This study aimed to identify popular diabetes applications (apps) and to investigate the association of diabetes app use and other factors with cumulative self-care behaviour.

Methods: From November 2017 to March 2018, we conducted a web-based survey with persons 18 years of age and above. We recruited respondents via diabetes Facebook groups, online patient-forums and targeted Facebook advertisements (ads). Data on participants' demographic, clinical, and self-management characteristics, as well as on self-care behaviour and characteristics of the diabetes apps use were collected. Self-care behaviour was measured using a licensed version of the Summary of Diabetes Self-care Activities (SDSCA) questionnaire. The cumulative self-care score was calculated by summing up scores for "general diet," "specific diet," "exercise," "blood glucose testing," "foot care" and "smoking." To identify popular diabetes apps, users were requested to list all apps they use for diabetes self-management. Two sample *t*-test and multiple linear regression stratified by type of diabetes were performed to examine associations between app use and self-care behaviour, by controlling for key confounders.

Results: One thousand fifty two respondents with type 1 and 630 respondents with type 2 diabetes mellitus (DM) entered the survey. More than half, 549 (52.2%), and one third, 210 (33.3%), of respondents with type 1 and 2 DM, respectively, reported using diabetes apps for self-management. "mySugr" and continuous glucose monitoring apps, such as "Dexcom," "Freestyle Libre," and "Xdrip+" were some of the most popular diabetes apps. In both respondent groups, the cumulative self-care behaviour score was significantly higher among diabetes app users (compared to non-users) and scores for three individual self-care components, namely "blood glucose monitoring," "general diet," and "physical activity" were significantly higher among diabetes app users than among non-users. After

adjusting for confounding factors, diabetes app use increased the cumulative self-care score by 1.08 (95%CI: 0.46–1.7) units among persons with type 1 DM and by 1.18 (95%CI: 0.26–2.09) units among persons with type 2 DM, respectively.

Conclusion: For both, persons with type 1 and type 2 diabetes, using diabetes apps for self-management was positively associated with self-care behaviour. Our findings suggest that apps can support changes in lifestyle and glucose monitoring in these populations.

Keywords: self-care, diabetes applications, diabetes apps, diabetes, type 1 diabetes, type 2 diabetes

INTRODUCTION

In 2045, the global population affected by diabetes mellitus (DM) is projected to rise from 425 million reported in 2017 (1) to 693 million (2). Diabetes is considered as one of the most challenging health problems of the Twenty first century (2) and remains one of the most expensive diseases (3). About 850 billion USD were spent on the treatment of the disease only in the year 2017 (1). This global diabetes healthcare expenditure is expected to continue growing (4).

Good diabetes management following a standardized medical and behavioural treatment protocol improves quality of life, and may prevent complications and premature mortality (5). In addition to medical treatment, effective interventions promoting healthy behaviour are important aspects of diabetes care (6–8). Regular physical activity, blood glucose monitoring, and optimal adherence to medication and recommendations for a balanced diet are integral to effective diabetes self-management (9, 10). Diabetes self-management is a key determinant of successful and cost-effective diabetes care that markedly reduces hospital admissions as well as complications (11–13). However, diabetes self-management is a highly demanding responsibility which requires continuous diabetes education and support to empower patients in improving health literacy and maintaining the necessary self-care behaviours (14, 15). Evidence suggests that diabetes applications (apps) support patients in advancing their knowledge of the disease, including awareness of complications and their personal self-management capabilities (16–20). Previous studies showed improvements in glycemic controls from digital health interventions including the use of diabetes apps (10, 18, 21–23). Smartphone diabetes apps enable patients to keep track of their physical activity, nutrition, and blood glucose monitoring (24–27). In addition, tailored diabetes self-management interventions and personalized recommendations can be facilitated by diabetes apps (28, 29). Through diabetes apps, patients can monitor their progress towards achieving personal glycemic and behavioural goals (30). The Agency for Health Care Research and Quality reported five diabetes applications (apps) which were effective in reducing glycated hemoglobin levels (HbA1c) (31). Additional apps were shown to support patients in reducing high or low glycemic abnormalities, improving treatment satisfaction, and self-care behaviour (31). Further, the International Diabetes Federation (IDF) recently indicated that "well-suited" diabetes apps might be important for promoting diabetes self-management practices and to prevent complications (32, 33). The rapid progress of internet of things, big data analytics, machine learning, artificial intelligence and other advances in mobile computing (34) are revolutionizing the future of personalized diabetes medicine.

The opportunities availed by diabetes apps have attracted many healthcare stakeholders including providers, payers, consumers and developers. The digital diabetes market is rapidly growing and it is expected to reach a worth of 742 million USD in 2022 (35). In 2017, the R2G(Research to guidance) released a report on mHealth app economics that stated diabetes is the best market for digital health innovation (36). Many diabetes apps are already available on typical app stores.

Multiple intervention studies have investigated the role of diabetes apps in improving self-care behaviour, such as glucose monitoring, diet, foot care, and physical activity in clinical settings (24, 37–40). Evidence on whether diabetes apps improve diabetes self-care behaviour in real world settings is still limited. Moreover, only few studies evaluated the content of diabetes apps available in the popular stores (26, 41–43), and remains unclear to date which are the most frequently used and appraised DM apps. Therefore, this study aimed to identify popular diabetes apps and to investigate the association of diabetes app use and other factors with cumulative self-care behaviour in persons with type 1 and 2 diabetes, applying a social media survey approach.

METHODS

Study Design, Source of Respondents, and Questionnaire Design

From November, 2017 to March, 2018, we conducted a web-based survey in the online community of persons with diabetes. The design of the web-based survey was adjusted to have computer and smartphone friendly layout options.

We used Facebook groups, targeted Facebook advertisements (ads) and online diabetes patient-forums to recruit respondents. The full detail of the recruitment process is described elsewhere (21). In short, using lime survey (44), a web-based questionnaire was designed in German and English which included questions about diabetes status, demographic characteristics, type of diabetes, medication use, self-care behaviour, blood-glucose level, perceived confidence regarding self-management capacity and perceived metabolic control. In addition, questions about smartphone ownership, type of smartphone owned and diabetes smartphone app use were asked.

Self-care behaviour was measured with a licensed version of the Summary of Diabetes Self-care Activities Questionnaire(SDSCA) (45). Questions regarding diabetes smartphone apps were adapted based on questions of the Mobile App Rating Scale (MARS) (8). To identify popular diabetes apps, app users were requested to list all apps they use for diabetes self-management.

To recruit respondents, we used a systematic keyword search on Facebook to identify closed, secret and public diabetes Facebook groups held in English or German. After identification of the Facebook groups, we submitted requests to join each group. The group requests were submitted with messages containing the survey URL and information about the aim of our study. Personal messages were sent to admins and moderators of the Facebook groups to explain the purpose of the survey, ethical aspect of the study, authenticity, and the time required to complete the survey. After receiving approval for the submitted requests, the survey URL accompanied by explanations about informed consent and the time required to complete the survey was posted on each diabetes group's Facebook page to invite group members to anonymously participate in the survey. In addition, we run 10 targeted ads reaching about 30,000 people potentially living with diabetes in German and English speaking countries. The targeted Facebook ads were conducted to address persons who were 18 years and older, living in English (Australia, Canada, United Kingdom and United States) or German speaking countries (Germany, Switzerland and Austria). People living in these countries with an interest in pages containing diabetes-related terms, such as "cure diabetes," "diabetes health," and "glycemic index" were targeted. Moreover, we searched diabetes-specific online forums available on Google. To incentivize participation, 10 Amazon vouchers each costing 50 euros were given to participants in a lottery.

Ethical Standards

The survey adheres with the ethical standards of the Leibniz Institute for Prevention Research and Epidemiology. The University of Bremen Central Research Development Fund committee also approved the study and funded the cost of the Amazon vouchers. Before taking part in the survey, written explanation was provided to inform all respondents about the anonymity of the survey. They were also informed about taking part to the survey is fully voluntarily, their responses will be kept confidential and can skip from answering any question they are not comfortable or stop participating in the survey at any stage. Respondents were also required to electronically give their consent before their taking part in the survey. Participants were asked to provide their email addresses if and only if they want to participate in the 50€ Amazon vouchers. The email addresses were redirected to be stored in a separate database and answers were not linked to any of the email addresses. After, the random selection of the email addresses for providing the incentives for winners, email addresses data were permanently erased.

Data Management and Statistical Analysis

To warrant the quality of data, the primary investigator checked the responses one by one on a daily basis until the survey period was completed. Multiple responses received from a similar Internet Protocol (IP) address were discarded.

After completion of the survey, data from lime survey were exported to Microsoft Excel. R studio version 3.5.1 statistical software (46) was used to analyze the data. Descriptive statistics and linear regression analyses were conducted. Characteristics of diabetes app use were analyzed using descriptive statistics. To identify popular diabetes apps in both persons with type 1 and 2 diabetes, all the names of the apps listed by each respondent were investigated one by one and counted for each respondent. Frequency of the named diabetes apps were calculated for both types of diabetes.

By following the American Diabetes Association guideline, self-reported glycemic control and HbA1c-level were categorized into hypoglycemia, hyperglycemia and good glycemic control (47, 48). In addition, eight "yes" or "no" questions were asked to measure respondents' concerns regarding their diabetes self-management. The questions were about respondent's concern feeling hypoglycaemia and hyperglycaemia, forgetting to measure blood glucose levels and to take medications, not knowing whom to contact in case of a need for assistance, being left out of medication or supplies and feeling unsure about how to calculate insulin doses. The "yes" and "no" responses for these questions were coded as 1 and 0, respectively. The total score for diabetes self-management concern was calculated for each respondent by adding up all the individual scores of the scale. The total score was then categorized into "low" and "high" concern using a median split (median = 3) after checking for normal distribution using the Shapiro-Wilk test.

Perceived confidence on diabetes self-management was measured by a likert scale question by which the response ranges from "not confident at all" to "very confident." Similarly, perceived metabolic control was also measured by a likert scale question with responses ranging from "very well-controlled" to "very poorly-controlled."

The SDSCA includes subscales that measure "general diet," "specific diet," "exercise," "blood glucose testing," "foot care" and "smoking" over the past week. Scores were created as recommended for the tool (45). Accordingly, the total number of days for each self-care activity was calculated for each respondent. Responses for smoking were recoded as "1" for "non-smokers" and "0" for smokers. Then a cumulative score of self-care was calculated for each respondent by summing up all scores of the individual self-care behaviours. To check whether there was a statistically significant difference between diabetes app users and non-users regarding the scores of the cumulative and individual self-care components, two-sample *t*-tests were performed.

In addition, after checking normality of the self-care data distribution, the association of diabetes app use with the self-care score was analysed using multiple linear regression stratified by type of diabetes. Two linear models were fit for type 1 and type 2 diabetes, respectively. Variables, such as age, sex, educational status, glucose lowering medication use, self-reported rating of metabolic control, perceived confidence in diabetes self-management, diabetes self-management concern, and mobile app use skill and diabetes app use were included a priori in the models.

Regression coefficients with $p < 5\%$ were considered statistically significant. Models were evaluated by visually examining the linearity of residuals and assumptions underlying multiple linear regression were checked by using appropriate R commands (49). Hence, multiple linear regression such as homoscedasticity of variance were checked by using Breuch Pagan test ("bptest") from the "lmtest" package (50) and using the "gvlma" packages in R (49). Multicollinearity among the variables was evaluated by checking the correlation matrix of the variables included in the model and by investigating the variance inflation factor of each variable. The effect of multicollinearity was ignored if the correlation value was <0.4 and the variance inflation factor <2.0. There was no evidence of violations of linear model assumptions. In addition, the results of the multicollinearity assessment for both models shows that no variable has a variance inflation factor value of more than 2.0 suggesting multicollinearity among the variables is negligible. Visualization of the data and exportation of the outputs of regression were performed using the Hadley Wickham's "ggplot2" as well as "sjPlot packages in R, respectively (51, 52).

RESULTS

Characterstics of Respondents

A total of 1682 complete responses were received from respondents with type 1 or type 2 diabetes who owned a smartphone. Of these, 1,052 (62.6%) were respondents with type 1 DM. The majority of respondents with type 1 diabetes were female 763 (72.5%) and 420 (66.7%) were female and had type 2 DM. The mean age (SD) of the respondents were 39 ($SD = \pm 12.9$) for DM type 1 and 52.9 ($SD = \pm 11.4$) years for DM type 2, respectively. Most respondents came from high income countries (see **Table 1**).

TABLE 1 | Characteristics of the respondents.

	Persons with type 1 DM	Persons with type 2 DM
Age, mean(SD)	39 (12.9)	52.9 (11.4)
≤40	591 (56.2)	99 (15.7)
40-60	400 (38)	346 (54.9)
60+	61 (5.8)	185 (29.4)
SEX		
Female	763 (72.5)	420 (66.7)
Male	289 (27.5)	210 (33.3)
EDUCATIONAL STATUS		
Primary to secondary	410 (39)	278 (44.1)
Polytechnic diploma	184 (17.5)	117 (18.6)
Bachelor degree and above	458 (43.5)	235 (37.3)
CONTINENT		
USA/Canada/Central America	353 (33.6)	276 (43.8)
Europe	607 (55.7)	239 (37.9)
Oceania	52 (4.9)	24 (3.8)
Asia	15 (1.4)	67 (10.6)
Africa and Latin America	25 (2.4)	24 (3.8)
RESPONDENTS' COUNTRY INCOME LEVELS *		
High income	1,012 (96.2)	540 (85.7)
Upper-middle income	30 (2.9)	22 (3.5)
Low to lower-middle income	19 (0.95)	68 (10.8)
Total	1,052 (100)	630 (100)

* *Based on the World Bank 2017–2018 country classifications (53).*

Clinical Characteristics and Diabetes Self-Management Experiences of Respondents

More than 95% (1,004) and 86% (541) of respondents with type 1 and type 2 DM reported taking glucose lowering medications, respectively. Nearly one-third of respondents with type 1 and one-fourth with type 2 DM reported that they first consult Facebook groups, diabetes smartphone apps or the internet whenever they have concerns regarding their diabetes self-management. Only approximately two-thirds reported first consulting a diabetes specialist team or other health care providers. Regarding the problems experienced in diabetes self-management, the feelings of symptomatic hyperglycaemia and hypoglycaemia were reported among both, respondents with type 1 and type 2 DM (**Table 2**).

Characteristics of Diabetes App Use

More than half, 572 (54.5%) respondents with type 1 and more than two third, 432 (68.8%), with type 2 DM reported owning an Android smartphone. The majority of the respondents with type 1 DM, 572 (54.5%) reported being highly skilled or experts in installing and using a mobile app. Of those who were currently using diabetes apps for their self-management, 120 (21.9%) of respondents with type 1 diabetes reported using their app for calculating insulin doses, of which 29 (25%) mentioned that they had erroneous results in calculating insulin doses with these apps. The most commonly used app functionality were using them as diaries for blood glucose and for tracking meal and carbohydrate intakes. The majority of the respondents with type 1 (58.4%) and type 2 (65.4%) reported that their diabetes app was perfectly easy to navigate (**Table 3**).

Overall, 145 different diabetes apps were reported by respondents. A detailed list of all reported diabetes apps is available in the **Supplementary Material**. The app "mySugr" was the most popular app reported by 165 of the 759 of respondents who reported using apps for diabetes self-management. Continuous glucose monitoring apps such as "Dexcom," "Freestyle Libre" and "Xdrip+" were the most popular diabetes apps among respondents with type 1 DM (**Figure 1**).

Association of Diabetes App Use With Self-Care Behaviour Among Persons With Type 1 and Type 2 DM

Figure 2 displays the distribution of the self-care scores for different components comparing app users and non-users, stratified by DM type. For both, persons with type 1 and type 2 DM, the total scores of almost all self-care components and the cumulative self-care score were higher among diabetes app users. The difference is larger for both groups of respondents in

TABLE 2 | Clinical and self-management characteristics of respondents with type 1 and type 2 DM.

	Persons with type 1 DM N (%)	Persons with type 2 DM N (%)
ON GLUCOSE LOWERING MEDICATION		
Yes	1,004 (95.4)	541(85.9)
No	48 (4.6)	89 (14.1)
IF YOU HAVE CONCERNS REGARDING YOUR DIABETES MANAGEMENT		
WHERE DO YOU GO FIRST FOR ASSISTANCE?		
Diabetes specialist team/healthcare provider	660 (62.7)	431 (68.4)
Facebook group/Internet/smartphone app	316 (30)	153 (24.3)
Support group/friends/family	66 (6.3)	38 (6)
Other	10 (1)	8 (1.3)
PROBLEMS WITH DIABETES SELF-MANAGEMENT		
Feeling symptomatic low blood sugar		
Yes	663 (63)	121 (19.2)
No	389 (37)	509 (80.8)
Feeling symptomatic high blood sugar		
Yes	532 (50.6)	200 (31.8)
No	520 (49.4)	430 (68.2)
Forgetting to measure blood sugar levels		
Yes	247 (23.4)	175 (22.8)
No	805 (76.5)	455 (72.2)
Forgetting to take medication or insulin		
Yes	186 (17.7)	109 (17.3)
No	866 (82.3)	521 (82.7)
Not knowing how to identify high or low blood sugars		
Yes	57 (5.4)	65 (10.3)
No	995 (94.6)	565 (89.7)
Not knowing whom to contact when in need of assistance		
Yes	41 (3.9)	50 (7.9)
No	1,011 (96.1)	580 (92.1)
Being left without medication/supplies		
Yes	105 (10)	44 (7)
No	947 (90)	586 (93)
Felt unsure about how to calculate your insulin/glucose lowering medication dose		
Yes	187 (17.8)	34 (5.4)
No	865 (82.2)	596 (94.6)
Diabetes self-management concern		
High concern	637 (39.3)	411 (65.2)
Low concern	415 (60.7)	219 (34.8)
Diabetes app use		
Yes	549 (52.2)	210 (33.3)
No	503 (47.8)	420 (66.7)
Use CGM		
Yes	296 (28.1)	218 (3.3)
No	756 (71.9)	609 (96.7)
Perceived metabolic control		
Well controlled	655 (62.4)	323 (51)
Neutral	256 (24.4)	154 (25)
Poorly controlled	139 (13.2)	151 (24)
Self-reported confidence on diabetes self-management		
Very confident	706 (67.2)	282 (44.8)
Neutral	122 (11.6)	97 (15.4)
Not confident at all	222 (21.1)	251 (39.8)
Total	1,052 (100)	630 (100)

two self-care behaviours: "general diet" and "physical activity" (**Figure 2**).

The cumulative self-care score, as well as the individual self-care components, except for foot care and specific diet were significantly higher among diabetes app users, both with type 1 and type 2 DM (**Table 4**).

Factors Associated With Self-Care Behaviour Among Persons With Type 1 DM

In persons with type 1 DM, using diabetes apps for self-management, being older, consulting diabetes specialist teams or other health care providers were positively associated with higher self-care behaviour scores. However, male sex, having hyperglycaemia, and having a self-rated "poorly-controlled" metabolic control were significantly associated with lower self-care behaviour (**Figure 3**). Using diabetes apps for self-management increased self-care by 1.08 (95%CI: 0.46–1.7) units. Self-care behaviour among respondents with type 1 diabetes increased by 1.05 (95%CI: 0.04–2.07) and 1.54 (95%CI: 0.70–2.39) units among those respondents who were 35–39 years and older than 40 years of age, respectively than respondents who were between 18 and 24 years old. Respondents who consulted diabetes specialist team or health care provider had 1.02 units of higher self-care behaviour compared to respondents who first consult Facebook groups/smartphone apps/internet for assistance (**Table 5**).

However, being male, having hyperglycaemia and having a self-rated "poorly-controlled" metabolic control significantly reduced self-care behaviour by −0.95 (95%CI: −1.54 to −0.36), −0.91 (95%CI: −1.54 to −0.27) and −2.56(95%CI: −3.51 to −1.61) units, respectively (**Table 5**).

Factors Associated With Self-Care Behaviour Among Persons With Type 2 DM

Using diabetes apps for self-management, educational status, consulting diabetes specialist teams or other health care providers for assistance and were positively associated with self-care behaviour among respondents with type 2 DM. Conversely, having neutral or poorly-controlled self-rated metabolic control and not feeling confident with regard to diabetes self-management were negatively associated with self-care behaviour (**Figure 3**). Using diabetes apps, having bachelor's degree and above, consulting diabetes specialist teams or other health-care provider for assistance in dealing with self-management concerns, and increased self-care behaviour by 1.18 (95%CI: 0.26–2.09), 1.14 (95%CI: 0.16–2.12), and 1.17 (95%CI: 0.22–2.12) units, respectively. However, respondents who rated their perceived metabolic control as neutral or poorly-controlled also reported reductions in self-care behaviour by −1.86 (95%CI: −2.95 to −0.77) and −3.36 (95%CI: −4.65 to −2.14) units, respectively. In addition, self-care behaviour among respondents who were not confident in their diabetes self-management was reduced by −1.13(95%CI: −2.17 to −0.09) units compared to respondents who felt highly confident (**Table 5**).

TABLE 3 | Distribution of characteristics of diabetes app use by diabetes type.

Choice	Persons with type 1 DM, N (%)	Persons with type 2 DM, N (%)
Type of smartphone	572 (54.5)	432 (68.8)
Android	458 (43.7)	174 (27.7)
Apple (iPhone)	13 (1.7)	172.7
Windows	6 (0.6)	5 (0.8)
APP INSTALLING/USING SKILL		
Highly skilled or expert user	560 (53.4)	232 (37)
Good skill	436 (41.6)	309 (49.4)
Poor skill	53 (5)	85 (13.6)
INSTALLED DIABETES APP		
No	503 (47.8)	420 (63.7)
Yes	549 (52.2)	210 (33.3)
	1,052	630
Problems encountered with the diabetes apps	$N = 549$	$N = 210$
Crashing of software	66 (12)	13 (6.2)
Difficulty of understanding advice given by the app	32 (5.8)	9 (4.3)
Results that do not align with other medical advise you have been given	33 (4.3)	12 (5.7)
No problems	395 (72)	161 (76.7)
USE YOUR APP TO CALCULATE YOUR INSULIN DOSE		
Yes	120 (21.9)	17 (8)
No	429 (78.1)	193 (92)
Had problems with insulin does calculator	$N = 120$	$N = 17$
Wrong insulin dose calculations	22 (18.3)	0
Insulin dose provided without entering the necessary values	7 (5.8)	0
USEFUL FEATURES OF THE APPS: MULTIPLE RESPONSES		
Diary of blood glucose levels	423 (77)	184 (91.4)
Reminders to check blood glucose levels	131 (23.9)	47 (22.4)
Diary of meals and carbohydrate intake	279 (52.5)	106 (50.5)
Calculation device to determine insulin dose	134 (24.2)	24 (11.4)
Guidelines of ideal blood glucose measurements	116 (21.1)	57 (27.1)
Calendar of diabetes related appointments	62 (11.3)	22 (10.5)
Contact details for your diabetes team or General practitioner	64 (11.8)	27 (12.8)
Dietary advice	85 (15.5)	40 (19)
Your contact details and condition information	55 (10)	30 (14.3)
FREQUENCY OF APP USE		
Never	26 (4.7)	7 (3.3)
Only when needing guidance	52 (9.5)	7 (3.3)
Monthly	17 (3.1)	3 (1.4)
Weekly	21 (3.8)	12 (5.7)
Few days per week	44 (8)	26 (12.4)
Daily	168 (30.7)	60 (28.6)
Every time a person eats or takes	220 (40.2)	95 (45)
USEFULNESS OF THE DIABETES APP		
Not at all useful	10 (1.8)	5 (2.4)
Not very useful	17 (3.1)	11 (5.3)
Somewhat useful	143 (26)	62 (29.7)
Very useful	184 (33.6)	76 (36.4)
Extremely useful	194 (35)	55 (26.3)
HOW WELL DOES THE DIABETES APP FUNCTION		
Does not function	5 (0.9)	4 (1.9)
Some functions work, but slow or has technical problems	14 (2.6)	7 (3.4)

(Continued)

TABLE 3 | Continued

Choice	Persons with type 1 DM, N (%)	Persons with type 2 DM, N (%)
App works overall, but slow or has technical problems at times	46 (8.4)	19 (9.2)
Mostly functional with minor problems	275 (50.5)	55 (26.6)
Perfect with no technical problems	205 (37.6)	122 (58.9)
HOW EASY IS IT TO LEARN HOW TO USE THE DIABETES APP		
There are no/limited user instructions, or it is confusing	7 (1.3)	7 (3.3)
Useable after a lot of time/effort	21 (3.8)	4 (1.9)
Useable after some time/effort	75 (13.7)	23 (10.9)
Easy to learn to use with given instructions	186 (34)	69 (32.9)
Able to use immediately, simple	258 (47.2)	107 (51)
HOW EASY IS IT TO NAVIGATE THROUGH YOUR APP?		
Different sections within the App are disconnected	9 (1.7)	7 (3.3)
Easy after a lot of time/effort	16 (2.9)	6 (2.9)
Easy after some time/effort	98 (18)	32 (15.4)
Easy but missing minor links	104 (19)	27 (13)
Perfectly easy	319 (58.4)	136 (65.4)
HOW DO YOU FIND THE LAYOUT/DESIGN OF YOUR APP?		
Very poor, some options are impossible to locate	6 (1.1)	4 (1.9)
Poor, some options are difficult to locate	24 (4.4)	10 (4.8)
Satisfactory, few problems with selecting options	119 (21.8)	37 (17.9)
Good, able to locate all options	240 (44)	96 (46.4)
Excellent, logical and clear layout	156 (28.6)	60 (29)
REASONS FOR NOT USING AN APP		
Didn't know they existed	83 (16.8)	175 (42.9)
They do not work on my mobile phone	32 (6.5)	11 (2.7)
Cost	24 (4.9)	29 (7.1)
Feel confident without one	111 (22.5)	77 (18.9)
Have tried one before and didn't like it	156 (31.6)	63 (15.44)
WOULD YOU BE INTERESTED IN USING A SMARTPHONE APP TO ASSIST WITH YOUR DIABETES MANAGEMENT?		
Yes	310 (61.6)	218 (51.9)
No	193 (38.4)	202 (48.1)

DISCUSSION

This study revealed that "mySugr" was the most popular diabetes app in both groups of respondents with type 1 and type 2 diabetes. Continuous glucose monitoring apps were particularly popular apps among respondents with type 1 DM. Compared to those who did not use diabetes apps, those who did had significantly higher cumulative self-care scores, independent of key confounding variables such a age, sex and educational status. Results were similar in respondents with type 1 and type 2 diabetes. Both type 1 and type 2 diabetes respondent groups reported that keeping track of blood glucose levels and keeping a diary of dietary intakes were the most useful features of these apps. A study on popular glucose tracking apps on android and apple store identified 20 most popular apps and reported glucose tracking and physical activity as the most common features of the apps (26). Similarly, Boyle and colleagues reported that recording blood glucose levels was the most favoured functionality in diabetes apps (54). This is due to the fact that glucose tracking is the top priority of diabetes self-management (55). However, whether the apps include additional contents designed according to the Association of American Diabetes Educators' evidence-based self-care recommendations, such as "problem solving," "reducing risks," or "healthy coping" requires further exploration of the features of the apps.

In this study, the cumulative and individual scores for self-care behaviour, except for "foot care" and "specific diet" were significantly higher among diabetes app users (compared to non-users), both in respondents with type 1 and type 2 diabetes. These results were confirmed by the findings obtained in the linear models which indicated the significant association of diabetes app use with improved self-care behaviour. The majority of previous studies indicate that app use was significantly related to improving blood glucose monitoring. This might be due to the fact that most apps are mainly designed to support blood glucose monitoring. Randomized control trials and observational studies have shown that using diabetes apps for self-management significantly improves scores of cumulative (40, 56) or individual

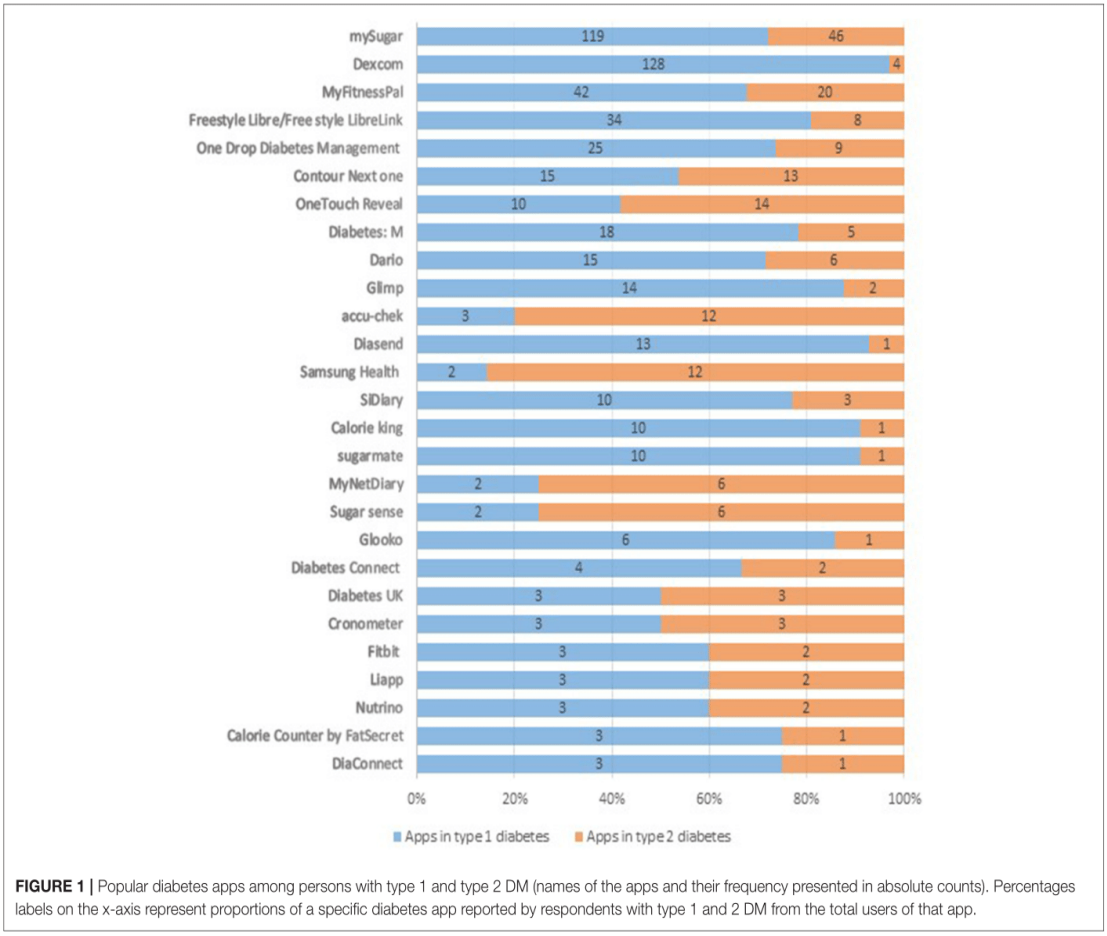


FIGURE 1 | Popular diabetes apps among persons with type 1 and type 2 DM (names of the apps and their frequency presented in absolute counts). Percentages labels on the x-axis represent proportions of a specific diabetes app reported by respondents with type 1 and 2 DM from the total users of that app.

self-care components (39, 57–59). Blood glucose monitoring (56–59), physical activity (57, 59), general diet (39, 56), specific diet (57–59), and foot care (39, 58) behaviours have been reported to be significantly improved by using diabetes apps. This is mainly due to the reason that diabetes app use may indeed be a useful approach to improve diabetes knowledge, self-management skills, and knowledge about complications which may ultimately enhance self-care practices (60).

For both groups of patients examined in our study, primarily consulting diabetes specialist teams or other health-care providers for assistance to deal with self-management concerns was positively associated with improved self-care behaviour, compared to consulting Facebook groups or internet. Previous studies found that diabetes specialist teams are central to addressing patients' self-care challenges, timely responding to complications and enhancing patient's self-management confidence which ultimately improves the ability to complete self-care tasks (61, 62). Consistent with other studies (63, 64), findings of our study also indicate that having a self-rated poor metabolic control appears to be associated with reduced self-care behaviour in both persons with type 1 and 2 DM.

Not feeling confident regarding diabetes self-management capacity was significantly associated with lower self-care behaviour among respondents with type 2 DM, whereas, higher levels of education was positively associated with increased self-care behaviour. Similar to our findings, another study reported that patients who felt confident regarding self-management experienced less difficulties in completing self-care tasks (65).

Moreover, in our study older age was positively associated with improved self-care behaviour in persons with type 1 DM. In comparison, the evidence demonstrating the association of increasing age with self-care is mixed. Similar to our study, previous studies reported older age-groups to be positively associated with improved self-care behaviour (66, 67), while ability to perform self-care tasks was also found to deteriorate in frail older adults (68, 69). The association of older age and improved self-care behaviour in persons with type 1 DM is partly due to the duration of the disease. Because the onset of the disease occurs at a relatively young age, older age groups with type 1 DM have cultivated self-management knowledge and experience which may enrich the completion of self-care tasks (67). Using apps

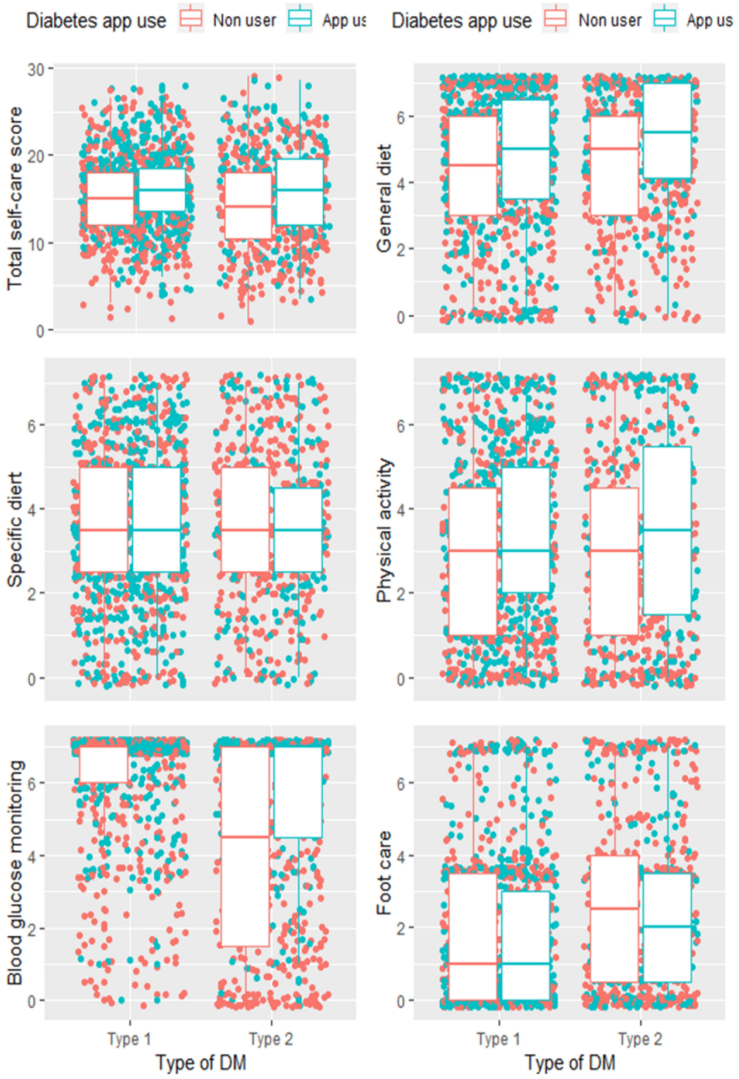


FIGURE 2 | Distribution of individual and total self-care scores for diabetes app users and non-users with type 1 and type 2 DM.

in this group may therefore just be an expression of high patient competence.

Being male and experiencing hyperglycaemia were negatively associated with self-care in persons with type 1 DM. In line with this finding, a study from Australia reported that men had significantly lower composite self-care scores (67). Findings of studies conducted in the United States and Canada examining gender disparities in self-care behaviour indicated that women reported higher levels of fruit and vegetable consumption, blood glucose testing and foot care than men (70, 71). Causes of gender differences in self-care behaviour needs further research.

In this study, although we looked at the differences between app users and non-users regarding the individual self-care components, we did not examine the factors for each individual self-care component. More research to understand the impact of predictors in addition to diabetes app use is necessary.

LIMITATIONS

The limitations of our study include the fact that all results are based on the data obtained by a web-based survey. The respondents of the survey were recruited via diabetes-specific Facebook groups, targeted advertisements and online forums. As a result, only respondents presumably with high health and digital literacy might have participated in the study which

TABLE 4 | Self-care behaviour differences among diabetes app users and non-users.

Self-care behaviour	Type 1 diabetes			Type 2 diabetes		
	Diabetes app non-users mean(SD)	Diabetes app users mean(SD)	Difference (*p*-value)	Diabetes app non-users mean(SD)	Diabetes app users mean(SD)	Difference (*p*-value)
General diet (aggregate)	4.34 (2.08)	4.75 (1.93)	0.000*	4.44 (1.93)	5.2 (1.79)	0.000*
Specific diet (aggregate)	3.54 (1.83)	3.56 (1.74)	0.86	3.63 (1.8)	3.54 (1.85)	0.564
Physical activity (aggregate)	2.93 (207)	3.43 (2.09)	0.0001*	2.91 (2.18)	3.46 (2.38)	0.006*
Blood Glucose Monitoring	6.03 (1.8)	6.63 (1.0)	0.0000*	4.06 (2.7)	5.71 (1.92)	0.000*
Foot care(aggregate)	1.86 (2.07)	1.67 (2.02)	0.132	2.66 (2.41)	2.48 (2.32)	0.358
Cumulative self-care score	15.1 (4.82)	16.1 (4.15)	0.000*	14.1 (5.37)	16.0 (5.33)	0.000*

** statistically significant.*

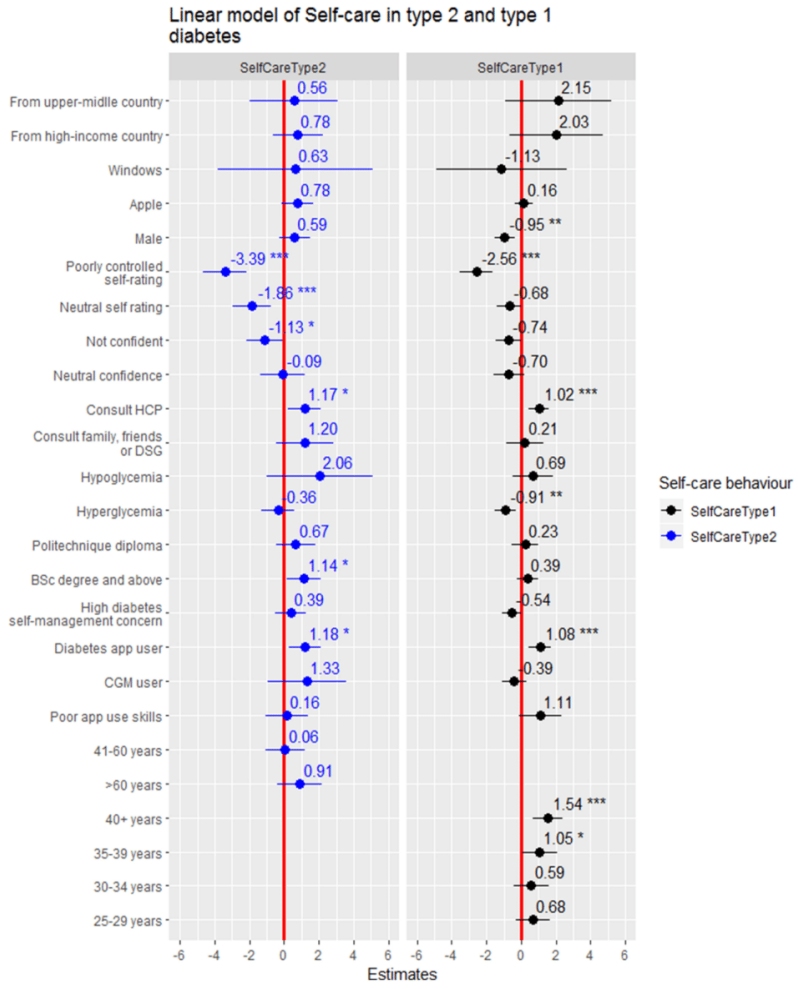


FIGURE 3 | Forest plot of the coefficients with 95%CI for factors of self-care behaviour in persons with type 1 vs. type 2 DM.*statistical significant at $p < 0.05$, **statistical significant at $p < 0.005$, *** statistical significant at $p < 0.001$.

TABLE 5 | Factors associated with self-care behaviour in persons with type 1 and type 2 diabetes.

	Linear model for type 1 DM model			Linear model for type 2 DM model		
Predictors	**Estimates**	**Conf. Int (95%)**	***p***	**Estimates**	**Conf. Int (95%)**	***p***
Intercept	12.69	9.84 to 15.54	<0.001*	13.13	11.10 to 15.17	<0.001*
AGE GROUP						
18–24	Ref	Ref	Ref			
25–29 years	0.68	−0.32 to 1.68	0.181			
30–34 years	0.59	−0.41 to 1.58	0.249			
35–39 years	1.05	0.04 to 2.07	0.042*			
40 + years	1.54	0.70 to 2.39	<0.001*			
≤40 years				Ref	Ref	Ref
41–60 years				0.06	−1.09 to 1.20	0.923
>60 years				0.91	−0.38 to 2.20	0.168
EDUCATIONAL STATUS						
Politechnique diploma	0.23	−0.53 to 0.99	0.550	0.67	−0.45 to 1.79	0.242
Bachelor degree and above	0.39	−0.22 to 1.00	0.211	1.14	0.16 to 2.12	0.022*
SEX						
Female	Ref	Ref	Ref	Ref	Ref	Ref
Male	−0.95	−1.54 to −0.36	0.002*	0.59	−0.30 to 1.47	0.193
FIRST CONTACT FOR ASSISTANCE						
Facebook group/Internet/Smartphone app	ref	Ref	Ref	Ref	Ref	Ref
Health care provider	1.02	0.44 to 1.60	0.001*	1.17	0.22 to 2.12	0.015*
Friends, family or DSG	0.21	−0.87 to 1.29	0.702	1.20	−0.46 to 2.87	0.155
RESPONDENTS'ORIGIN						
From low-income country	Ref	Ref	Ref		Ref	Ref
Upper-midlle country	2.15	−0.90 to 5.21	0.167	0.56	−2.00 to 3.11	0.668
High-income country	2.03	−0.65 to 4.71	0.138	0.78	−0.66 to 2.22	0.287
TYPE OF SMARTPHONE						
Android	Ref	Ref		Ref	Ref	Ref
Apple	0.16	−0.38 to 0.69	0.563	0.78	−0.14 to 1.71	0.097
Windows	−1.13	−4.90 to 2.63	0.555	0.63	−3.84 to 5.09	0.782
APP USE SKILLS						
Highly skilled	Ref	Ref	Ref	Ref	Ref	Ref
Poorrly skilled	1.11	−0.12 to 2.34	0.077	0.16	−1.09 to 1.41	0.800
DIABETES APP USE						
Non-user	Ref	Ref	Ref	Ref	Ref	Ref
User	1.08	0.46 to 1.70	0.001*	1.18	0.26 to 2.09	0.012*
DIABETES SELF-MANAGEMENT CONCERN						
Low	ref	ref	ref	ref	Ref	ref
High	−0.54	−1.10 to 0.03	0.062	0.39	−0.49 to 1.27	0.383
CGM USER						
No	Ref	Ref	Ref	Ref	Ref	Ref
Yes	−0.39	−1.08 to 0.29	0.260	1.33	−0.93 to 3.59	0.248
GLYCEMIC CONTROL						
Good	Ref	Ref	Ref	Ref	Ref	Ref
Hyperglycemia	−0.91	−1.54 to −0.27	0.005*	−0.36	−1.32 to 0.61	0.467
Hypoglycemia	0.69	−0.49 to 1.86	0.253	2.06	−0.99 to 5.10	0.185
PERCEIVED METABOLIC CONTROL						
Well-controlled	Ref	Ref	Ref	Ref	Ref	Ref
Neutral	−0.68	−1.39 to 0.03	0.062	−1.86	−2.95 to −0.77	0.001*
Poorly-controlled	−2.56	−3.51 to −1.61	<0.001*	−3.39	−4.65 to −2.14	<0.001*
PERCEIVED CONFIDENCE IN DIABETES SELF-MANAGEMENT						
Highly confident	Ref	Ref	Ref	Ref	Ref	Ref
Neutral	−0.70	−1.61 to 0.21	0.131	−0.09	−1.36 to 1.18	0.889
Not confident	−0.74	−1.49 to 0.01	0.054	−1.13	−2.17 to −0.09	0.034*

statistically significant.

may not reflect self-care behaviour in the general population of persons with diabetes. Interpretation of the results should also take into account self-selection. Psychometric properties of the diabetes self-management concern questions were not also investigated. The question on glucose lowering medication is also too broad to capture difference for those on insulin or other medications unique to type 2 diabetes. Due to the cross-sectional nature of the study, causal relationships cannot be determined. It might be possible those with higher self-care behaviour are more motivated to use diabetes apps. Respondents in our study came from multiple countries, although the majority of them were from high-income German and English speaking countries. For this reason, there is unobserved variation introduced by the diversity of the respondents. This variation may be due to the difference in unobserved individual and population-level characteristics such as sociocultural and healthcare system differences across countries. This variation was not captured in our study. However, considering the significant growth of Facebook use by older adults (72) and looking at the emerging role of social media connectivity in chronic disease self-management education and health promotion (73, 74), persons with diabetes on social media constitute an important and growing population. In this line, a recent study reported that nearly 90% of older adults reported using Facebook and Twitter to find health information (75). In light of this, our research identified popular diabetes apps and investigated the association of diabetes app use with self-care behaviour. However, more research with larger samples is needed to confirm these findings. Using social media for surveying patient groups relies on self-report, and validation especially in a geographically highly diverse sample is a challenge.

CONCLUSION

From all reported diabetes apps, "mySugr" and continuous glucose monitoring apps such as "Dexcom," "Freestyle Libre," and "Xdrip+" were few of the most popular diabetes apps. After adjusting for the effects of confounders, using diabetes apps for self-management was positively associated with higher self-care behaviour in both types of diabetes. The findings indicate diabetes apps have the potential to augment diabetes self-management and to develop healthier life style. Considering to prescribe a well-suited diabetes app may be important. Future research on diabetes care should include information on app use as it may become an even more important care-moderating factor.

DATA AVAILABILITY

The datasets collected, used analysed for study can be obtained from the corresponding author on a reasonable request. The codes written for fitting the regression models, graphs and evaluation of the models are publicly available (https://gitlab.com/Mihiretu/diaapprcodes/blob/master/Self_care%20linear%20model.R).

AUTHOR CONTRIBUTIONS

MK conceptualized and designed the study, searched the Facebook groups and online forums search, conducted the targeted advertisements, collected the data, performed the data analysis and wrote the manuscript. CP participated in the conception of the study, contributed to the survey design, and critically revised the manuscript.

FUNDING

We received a partial funding (1,100 euros) from the University of Bremen 01 Impulse Grants for Research Projects (Grant reference number: 12).

ACKNOWLEDGMENTS

We are grateful to Professor Hajo Zeeb for their outstanding guidance and constructive comments from the conception of the study until the development of this manuscript. We would like to thank Janna Sill, Cora Schuett for their support during searching of the diabetes Facebook groups in German language. In addition, we are indebted to Dr. Fleur Fritz and Nicholas Adjei for their kind support during the design of the methods and analyses plans. We would also like to extend our gratitude to the University of Bremen Young Researchers Committee for granting us 1,100 euros to cover the cost of a licensed version of SDSCA checklist and incentives that we provided to randomly selected respondents of the study.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2019.00135/full#supplementary-material

REFERENCES

1. Cho NH, Shaw JE, Karuranga S, Huang Y, da Rocha Fernandes JD, Ohlrogge AW, et al. IDF diabetes atlas: global estimates of diabetes prevalence for 2017 and projections for 2045. *Diabetes Res Clin Pract.* (2018) 138:271–81. doi: 10.1016/j.diabres.2018.02.023
2. IDF. *IDF Diabetes Atlas, Eight 8th Edn.* Brussels: International Diabetes Federation (2017).
3. Dieleman JL, Baral R, Birger M, Bui AL, Bulchis A, Chapin A, et al. Us spending on personal health care and public health, 1996-2013. *JAMA* (2016) 316:2627–46. doi: 10.1001/jama.2016.16885
4. Bommer C, Sagalova V, Heesemann E, Manne-Goehler J, Atun R, Bärnighausen T, et al. Global economic burden of diabetes in adults: projections from 2015 to 2030. *Diabetes Care* (2018). 41:963–70. doi: 10.2337/dc17-1962
5. World Health Organization. *Global Report on Diabetes.* World Health Organization. (2016).

6. IDF. *Diabetes Atlas, 6th Edn*. Brussels: International Diabetes Federation (2013)
7. World Health Organization. *Global Report on Diabetes*. Geneva: World Health Organization (2016).
8. American Diabetes Association. Standards of medical care in diabetes−2013. *Diabetes Care* (2013) 36(Suppl. 1):S11–S66. doi: 10.2337/dc13-S011
9. Beck J, Greenwood DA, Blanton L, Bollinger ST, Butcher MK, Condon JE, et al. 2017 National standards for diabetes self-management education and support. *Diabetes Care* (2017) 40:1409–19. doi: 10.2337/dci17-0025
10. Kebede MM, Zeeb H, Peters M, Heise TL, Pischke CR. Effectiveness of digital interventions for improving glycemic control in persons with poorly controlled type 2 diabetes: a systematic review, meta-analysis, and meta-regression analysis. *Diabetes Technol Ther*. (2018) 20:767–82. doi: 10.1089/dia.2018.0216
11. Brown HS , Wilson KJ, Pagan JA, Arcari CM, Martinez M, Smith K, et al. Cost-effectiveness analysis of a community health worker intervention for low-income Hispanic adults with diabetes. *Prev Chronic Dis*. (2012) 9:E140. doi: 10.5888/pcd9.120074
12. Robbins JM, Thatcher GE, Webb DA, Valdmanis VG. Nutritionist visits, diabetes classes, and hospitalization rates and charges. *Urban Diabetes Study* (2008) 31:655–60. doi: 10.2337/dc07-1871
13. Healy SJ, Black D, Harris C, Lorenz A, Dungan KM. Inpatient diabetes education is associated with less frequent hospital readmission among patients with poor glycemic control. *Diabetes Care* (2013) 36:2960–7. doi: 10.2337/dc13-0108
14. Shin KS, Lee EH. Relationships of health literacy to self-care behaviors in people with diabetes aged 60 and above: empowerment as a mediator. *J Adv Nurs*. (2018) 74:2363–72. doi: 10.1111/jan.13738
15. Powers MA, Bardsley J, Cypress M, Duker P, Funnell MM, Hess Fischl A, et al. Diabetes Self-management education and support in Type 2 diabetes: a joint position statement of the american diabetes association, the american association of diabetes educators, and the academy of nutrition and dietetics. *Diabetes Care* (2015) 38:1372–82. doi: 10.2337/dc15-0730
16. Muralidharan S, Ranjani H, Anjana RM, Allender S, Mohan V. Mobile health technology in the prevention and management of Type 2 diabetes. *Ind J Endocrinol Metab*. (2017) 21:334–40. doi: 10.4103/ijem.IJEM_407_16
17. Hamine S, Gerth-Guyette E, Faulx D, Green BB, Ginsburg AS. Impact of mHealth chronic disease management on treatment adherence and patient outcomes: a systematic review. *J Med Internet Res*. (2015) 17:e52. doi: 10.2196/jmir.3951
18. Hou C, Carter B, Hewitt J, Francisa T, Mayor S. Do mobile phone applications improve glycemic control (HbA1c) in the self-management of diabetes? a systematic review, meta-analysis, and GRADE of 14 randomized trials. *Diabetes Care* (2016) 39:2089–95. doi: 10.2337/dc16-0346
19. Kebede MM, Liedtke TP, Möllers T, CR P. Characterizing active ingredients of ehealth interventions targeting persons with poorly controlled type 2 diabetes mellitus using the behavioral change technique taxonomy. *J Med Internet Res*. (2017). 19:e348. doi: 10.2196/jmir.7135
20. Husted GR, Weis J, Teilmann G, Castensøe-Seidenfaden P. Exploring the influence of a smartphone app (young with diabetes) on young people's self-management: qualitative study. *JMIR Mhealth Uhealth* (2018) 6:e43. doi: 10.2196/mhealth.8876
21. Kebede MM, Schuett C, Pischke CR. The role of continuous glucose monitoring, diabetes smartphone applications, and self-care behavior in glycemic control: results of a multi-national online survey. *J Clin Med*. (2019) 8:e109. doi: 10.3390/jcm8010109
22. Kebede MM, Peters M, Heise TL, Pischke CR. Comparison of three meta-analytic methods using data from digital interventions on type 2 diabetes. *Diabetes Metab Syndr Obes*. (2019) 12:59–73. doi: 10.2147/DMSO.S180106
23. Bonoto BC, de Araújo VE, Godói IP, de Lemos LLP, Godman B, Bennie M, et al. Efficacy of mobile apps to support the care of patients with diabetes mellitus: a systematic review and meta-analysis of randomized controlled trials. *JMIR Mhealth Uhealth* (2017) 5:e4. doi: 10.2196/mhealth.6309.
24. Kirwan M, Vandelanotte C, Fenning A, Duncan MJ. Diabetes self-management smartphone application for adults with type 1 diabetes: randomized controlled trial. *J Med Internet Res*. (2013) 15:e235. doi: 10.2196/jmir.2588
25. El-Gayar O, Timsina P, Nawar N, Eid W. Mobile applications for diabetes self-management: status and potential. *J Diabetes Sci Technol*. (2013) 7:247–62. doi: 10.1177/193229681300700130
26. Williams JP, Schroeder D. Popular glucose tracking apps and use of mhealth by latinos with diabetes: review. *JMIR Mhealth Uhealth* (2015) 3:e84. doi: 10.2196/mhealth.3986
27. Ryan EA, Holland J, Stroulia E, Bazelli B, Babwik SA, Li H, et al. Improved A1C levels in type 1 diabetes with smartphone app use. *Can J Diabetes* (2017) 41:33–40. doi: 10.1016/j.jcjd.2016.06.001
28. Heintzman ND. A digital ecosystem of diabetes data and technology: services, systems, and tools enabled by wearables, sensors, and apps. *J Diabetes Sci Technol*. (2015) 10:35–41. doi: 10.1177/1932296815622453
29. Kaufman N, Khurana I. Using digital health technology to prevent and treat diabetes. *Diabetes Technol Ther*. (2016) 18(Suppl. 1):S56–68. doi: 10.1089/dia.2016.2506
30. Årsand E, Frøisland DH, Skrøvseth SO, Chomutare T, Tatara N, Hartvigsen G, et al. Mobile health applications to assist patients with diabetes: lessons learned and design implications. *J Diabetes Sci Technol*. (2012) 6:1197–206. PubMed PMID: PMC3570855.
31. Veazie S, Winchell K, Gilbert J, Paynter R, Ivlev I, Eden KB, et al. Rapid evidence review of mobile applications for self-management of diabetes. *J General Inter Med*. (2018) 33:1167–76. doi: 10.1007/s11606-018-4410-1
32. Jacques Rose K, Petrut C, L'Heveder R, de Sabata S. IDF Europe position on mobile applications in diabetes. *Diabetes Res Clin Pract*. (2017) 149:39–46. doi: 10.1016/j.diabres.2017.08.020
33. IDF. *IDF Europe Position on Mobile Applications in Diabetes*. Brussels: Internation Diabetes Federation Europe (February 2017).
34. Neborachko M, Pkhakadze A, Vlasenko I. Current trends of digital solutions for diabetes management. *Diabetes Metab Syndr*. (in press). doi: 10.1016/j.dsx.2018.07.014
35. R2G. *Digital Diabetes Care Market 2018-2022: Ready To Take Off*. Berlin: Research2Guidance. (2018).
36. R2G. *mHealth Economics 2017 – Current Status and Future Trends in Mobile Health* Berlin (2017). Available online at: https://research2guidance.com/product/mhealth-economics-2017-current-status-and-future-trends-in-mobile-health/ (Accessed Oct 11, 2018).
37. Nundy S, Mishra A, Hogan P, Lee SM, Solomon MC, Peek ME. How do mobile phone diabetes programs drive behavior change? evidence from a mixed methods observational cohort study. *Diabetes Educ*. (2014) 40:806–19. doi: 10.1177/0145721714551992
38. Ruggiero L, Moadsiri A, Quinn LT, Riley BB, Danielson KK, Monahan C, et al. Diabetes island: preliminary impact of a virtual world self-care educational intervention for african americans with type 2 diabetes. *JMIR Serious Games* (2014) 2:e10.doi: 10.2196/games.3260
39. Forjuoh SN, Reis MD, Couchman GR, Ory MG. Improving diabetes self-care with a PDA in ambulatory care. *Telemed J E Health* (2008) 14:273–9. doi: 10.1089/tmj.2007.0053
40. Zhou W, Chen M, Yuan J, Sun Y. Welltang - A smart phone-based diabetes management application - Improves blood glucose control in Chinese people with diabetes. *Diabetes Res Clin Pract*. (2016) 116:105–10. doi: 10.1016/j.diabres.2016.03.018
41. Ye Q, Khan U, Boren SA, Simoes EJ, Kim MS. An analysis of diabetes mobile applications features compared to AADE7: addressing self-management behaviors in people with diabetes. *J Diabetes Sci Technol*. (2018) 12:808–16. doi: 10.1177/1932296818754907
42. Demidowich AP, Lu K, Tamler R, Bloomgarden Z. An evaluation of diabetes self-management applications for Android smartphones. *J Telemed Telecare*. (2012) 18:235–8. doi: 10.1258/jtt.2012.111002
43. Veazie S, Winchell K, Gilbert J, Paynter R, Ivlev I, Eden K, et al. *Mobile Applications for Self-Management of Diabetes*. Rockville MD: Agency for Healthcare Research and Quality (2018).
44. LimeSurvey: *An Open Source Survey Tool [Internet]*. LimeSurvey Project (2012). Available online at: http://www.limesurvey.org
45. Toobert DJ, Hampson SE, Glasgow RE. The summary of diabetes self-care activities measure: results from 7 studies and a revised scale. *Diabetes Care* (2000) 23:943–50. doi: 10.2337/diacare.23.7.943
46. Team R. *RStudio: Integrated Development for R*. Boston, MA: RStudio, Inc. (2018).

47. American Diabetes Association. Standards of medical care in diabetes—2014. *Diabetes Care* (2014) 37(Suppl. 1):S14–80.
48. American Diabetes Association. Glycemic Targets. *Diabetes Care* (2017) 40(Suppl. 1):S48–56. doi: 10.2337/dc17-S009
49. Pena EA, Slate EH. gvlma: *Global Validation of Linear Models Assumptions*. R package version (2014) 1(0.2).
50. T H. *Package 'lmtest' - CRAN-R - R Project*. (2018).
51. Wickham H. *ggplot2: Elegant Graphics for Data Analysis*. New York, NY: Springer (2016).
52. Ludecke D, Schwemmer C. *sjPlot: Data Visualization for Statistics in Social Science* (version 2.3. 1) (software). (2017).
53. World Bank. *World Bank Country and Lending Groups: Country Classification*, Available online at: https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups (2018).
54. Boyle L, Grainger R, Hall RM, Krebs JD. Use of and beliefs about mobile phone apps for diabetes self-management: surveys of people in a hospital diabetes clinic and diabetes health professionals in New Zealand. *JMIR Mhealth Uhealth* (2017) 5:e85. doi: 10.2196/mhealth.7263
55. Subramaniam S, Dhillon JS, Ahmad MS, WS LJ, Teoh C, Huang CS. Eliciting user requirements to design a prediabetes self-care application: a focus group study with prediabetics and diabetics. *Ind J Sci Technol.* (2016) 9:1–8. doi: 10.17485/ijst/2016/v9iS(1)/106819
56. Yu K, Wu S, Chi I, Hsiao H, Lee P. "The Impact of Diabetes Self-Management Mobile Technology Application Usage on Self-Care Behaviors Among Older Adults," in *Society for Social Work and Research 22nd Annual Conference - Achieving Equal Opportunity, Equity, and Justice*. Washington, DC (January 12, 2018).
57. Kim YJ, Rhee SY, Byun JK, Park SY, Hong SM, Chin SO, et al. A smartphone application significantly improved diabetes self-care activities with high user satisfaction. *Diabetes Metab J.* (2015) 39:207–17. doi: 10.4093/dmj.2015.39.3.207
58. Greenwood DA, Blozis SA, Young HM, Nesbitt TS, Quinn CC. Overcoming clinical inertia: a randomized clinical trial of a telehealth remote monitoring intervention using paired glucose testing in adults with type 2 diabetes. *J Med Internet Res.* (2015) 17:e178. doi: 10.2196/jmir.4112
59. Lee DY, Park J, Choi D, Ahn H-Y, Park S-W, Park C-Y. The effectiveness, reproducibility, and durability of tailored mobile coaching on diabetes management in policyholders: a randomized, controlled, open-label study. *Sci Rep.* (2018) 8:3642. doi: 10.1038/s41598-018-22034-0
60. Hernandez-Tejada MA, Campbell JA, Walker RJ, Smalls BL, Davis KS, Egede LE. Diabetes empowerment, medication adherence and self-care behaviors in adults with type 2 diabetes. *Diabetes Technol Ther.* (2012) 14:630–4. doi: 10.1089/dia.2011.0287
61. Beverly EA, Worley M, Prokopakis K, Ivanov N. Patient-physician communication and diabetes self- care. *Journal of Clinical Outcomes Management.* (November 2016) 23:11. Available online at: https://www.mdedge.com/jcomjournal/article/146123/diabetes/patient-physician-communication-and-diabetes-self-care (Accessed February 2, 2019).
62. Bonds DE, Camacho F, Bell RA, Duren-Winfield VT, Anderson RT, Goff DC. The association of patient trust and self-care among patients with diabetes mellitus. *BMC Fam Pract.* (2004) 5:26. doi: 10.1186/1471-2296-5-26
63. Skinner TC, Hampson SE. Personal models of diabetes in relation to self-care, well-being, and glycemic control. *A Prospec Study Adoles.* (2001) 24:828–33. doi: 10.2337/diacare.24.5.828
64. Goh CSY, Mohamed A, Lee YS, Loke KY, Wee HL, Khoo EYH, et al. The associations of self-care, illness perceptions and psychological distress with metabolic control in Singaporean adolescents with Type 1 Diabetes Mellitus. *Health Psychol Behav Med.* (2016) 4:1–14. doi: 10.1080/21642850.2015.1115728
65. Lee S, Lee D, Choun S. Determinants of high self-confidence in diabetes management among older diabetes patients. *Innovation in Aging* (2017) 1(suppl. 1):324–5. doi: 10.1093/geroni/igx004.1196
66. Bonger Z, Shiferaw S, Tariku EZ. Adherence to diabetic self-care practices and its associated factors among patients with type 2 diabetes in Addis Ababa, Ethiopia. *Patient Prefer Adher.* (2018) 12:963–70. doi: 10.2147/PPA.S156043
67. Zimbudzi E, Lo C, Ranasinha S, Kerr PG, Polkinghorne KR, Teede H, et al. The association between patient activation and self-care practices: a cross-sectional study of an Australian population with comorbid diabetes and chronic kidney disease. *Health Expect* (2017) 20:1375–84. doi: 10.1111/hex.12577
68. Dhaliwal R, Weinstock RS. Management of Type 1 Diabetes in Older Adults. *Diabetes Spectrum* (2014) 27:9–20. doi: 10.2337/diaspect.27.1.9
69. Zhou Y, Liao L, Sun M, He G. Self-care practices of Chinese individuals with diabetes. *Exp Ther Med.* (2013) 5:1137–42. doi: 10.3892/etm.2013.945
70. Yu MK, Lyles CR, Bent-Shaw LA, Young BA. Sex disparities in diabetes process of care measures and self-care in high-risk patients. *J Diabetes Res.* (2013) 2013:575814. doi: 10.1155/2013/575814
71. Gucciardi E, Wang SC, DeMelo M, Amaral L, Stewart DE. Characteristics of men and women with diabetes: observations during patients' initial visit to a diabetes education centre. *Can Fam Phys.* (2008) 54:219–27. http://www.cfp.ca/content/54/2/219 (Accessed February 2, 2019).
72. Duggan M, Ellison NB, Lampe C, Lenhart A, Madden M. Social media update 2014. *Pew Res Center* (2015) 1–17. Available online at: http://www.pewinternet.org/2015/01/09/social-media-update-2014/ (Accessed February 2, 2019).
73. Partridge SR, Gallagher P, Freeman B, Gallagher R. Facebook groups for the management of chronic diseases. *J Med Int Res.* (2018) 20:e21. doi: 10.2196/jmir.7558
74. Alanzi T. Role of social media in diabetes management in the middle east region: systematic review. *J Med Inter Res.* (2018) 20:e58. doi: 10.2196/jmir.9190
75. Tennant B, Stellefson M, Dodd V, Chaney B, Chaney D, Paige S, et al. eHealth literacy and Web 2.0 health information seeking behaviors among baby boomers and older adults. *J Med Internet Res.* (2015) 17:e70. doi: 10.2196/jmir.3992

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Appendix B: Author's contributions

Study I: MM Kebede conceptualized and designed the study, conducted the systematic literature search with the help of research librarian, performed the title and abstract screening, quality assessment, data extraction, analyses, interpretation and wrote the manuscript. Zeeb H. participated in the conception and the design of the study and the development of the methodology, and critically revising the manuscript for important intellectual content. Peters M. conducted the title and abstract screening, quality assessment and participated in the draft of the manuscript. Hese TL contributed to the extraction of the data and critically revised the manuscript. Pischke CR participated in the conception, data extraction, and critically revised the manuscript for important intellectual content.

Study II: Kebede MM performed conceptualization, design, systematic literature search, title and abstract screening, quality assessment, data extraction, analyses, interpretation, and write-up. Peters M. performed title and abstract screening, and quality assessment and contributed to the write-up. Heise TL and Pischke CR performed conceptualization, extraction of the data, and critical review.

Study III: Kebede MM conceptualized and designed the study, performed the Facebook group search and targeted advertisements, conducted the survey, collected the data, performed the data analysis, and wrote the manuscript. Schütt C. participated in the search process and ran the survey posted on the German Facebook groups and online forums, and revised the manuscript. Pischke CR conceived the study, contributed to the survey design, and critically revised the manuscript.

Study IV: Kebede MM conceptualized and designed the study, searched the Facebook groups and online forums search, conducted the targeted advertisements, collected the data, performed the data analysis and wrote the manuscript. Pischke CR participated in the conception of the study, contributed to the survey design, and critically revised the manuscript.

10.2. Appendix C: Declaration

Versicherung der eigenständigen Verfassung

Hiermit versichere ich, dass ich die vorlie gende Dissertation selbständig verfasst und keine weiteren als die angegebenen Quellen und Hilfsmittel verwendet habe. Alle Stellen, die ich wörtlich oder sinngemäß aus an deren Werken entnommen habe, sind unter Angabe der Quellen als solche kenntlich gemacht.

Diese Arbeit hat in gleicher oder ähnlicher Form noch keiner anderen Prüfungsbehörde vorgelegen.

_____ _____

Ort und Datum Unterschrift