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Telemonitoring as a Tool to Improve Glycaemic Control in Patients with Type 2 Diabetes Mellitus

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Abstract

Background: Type 2 diabetes mellitus (T2DM) is a rising global health concern that requires long-term treatment and close monitoring. As a behaviour-directed intervention, telemonitoring has shown promising results in facilitating patient-physician interaction and improving treatment adherence among patients with chronic disease. However, there is lack of evidence about its use in T2DM. This thesis aims to address this gap by analysing the impact of treatment adherence, which is a key self-care behaviour in patients with a chronic illness, on glycaemic control and the overall effectiveness of telemonitoring in T2DM management.

Method: This thesis consists of two parts, a secondary data analysis and a systematic review and meta-analysis. The secondary data analysis utilises a comparative cross-sectional design where data on demographic information, treatment adherence, and glycaemic control were collected from patients with T2DM using a combination of laboratory tests and self-reported questionnaires. The degree of treatment adherence is demonstrated through several aspects including adherence to self-measurement of blood glucose (SMBG), smoking and alcohol cessation, diet control, physical exercise and medication adherence. The dependent variables that reflect glycaemic control and general metabolic health were HbA1c, fasting blood glucose (FBG), total cholesterol (TC), systolic blood pressure (SBP) and diastolic blood pressure (DBP). Multivariate analysis of variance (MANOVA) was used to investigate the association between specific aspects of T2DM treatment adherence and glycaemic control. Data analysis was performed using SPSS with a significance level of 0.05. For the systematic review and meta-analysis, randomised controlled trials regarding the use of telemonitoring intervention in patients with T2DM published between 1990 and 2021 were searched through electronic databases, including MEDLINE, PubMed, PsycINFO, EMBASE, the Cochrane Library, Scopus, and Web of Science. The search results were screened by two reviewers against a list of inclusion criteria that were set to help find articles with appropriate study design and applicable telemonitoring intervention and control arms that are conducted on an adult population with a confirmed diagnosis of T2DM. The methodological quality of the remaining studies was assessed using the PEDro scale before they were included in the study. The primary outcome variables were HbA1c and FBG, with body mass index (BMI) being a secondary outcome variable. Additionally, data on the technical features of telemonitoring intervention, patient characteristics, and incorporation of education programs were extracted for subgroup analysis. The effect size and mean difference (MD) for the primary and secondary outcomes were analysed using random effect models.

Results: A total of 10246 T2DM patients with a mean age of 64.1 years old were included in the secondary data analysis. Most of the respondents self-reported good adherence to SMBG (83.2%), diet control (73.8%) and medication adherence (88.4%). Adhering to regular physical exercise was reported by 31.7% of the respondents. Out of the patients who responded to questions regarding smoking and alcohol cessation, 29.0% and 23.2% reported complete cessation from smoking and alcohol use, respectively. MANOVA showed that all aspects of treatment adherence, except for adherence to diet control, have a statistically significant association with glycaemic control. The subsequent univariate analysis demonstrated that adherence to self-measurement of blood glucose is associated with improved HbA1c, FBG, SBP and DBP; adherence to smoking cessation is associated with improved HbA1c, SBP and

DNP; adherence to alcohol cessation is associated with improved TC, SBP and DBP; adherence to physical exercise is associated with better SBP and DBP; and medication adherence is associated with improved HbA1c, FBG and TC. Thirty studies with a total of 4,678 participants were included in the systematic review and meta-analysis. Pooled results showed that participants who received telemonitoring intervention had significantly lower HbA1c levels (MD 0.294%, 95% CI 0.131–0.458%) and BMI (MD 0.278 kg/m^2, 95% CI 0.003 – 0.553 kg/m^2) when compared to conventional care. No significant overall improvement was seen in terms of FBG. Subgroup analysis demonstrated that the effect of telemonitoring on HbA1c is positively influenced by monitoring more than one parameter simultaneously (MD 0.405%, 95% CI 0.246 – 0.564%), manual input of self-measurement data (MD 0.413%, 95% CI 0.198–0.627), more frequent self-measurement (MD 0.183%, 95% CI 0.057–0.309%), mean age less than 65 years old (MD 0.206%, 95% CI 0.091–0.321%), higher baseline HbA1c level (MD 0.390%, 95% CI 0.010–0.570%) and incorporation of general T2DM education (MD 0.309%, 95% CI 0.139–0.478%).

Conclusions: Findings from the secondary data analysis and the systematic review and meta-analysis provided insight into the factors affecting glycaemic control in patients with T2DM and the potential role that telemonitoring can play in the overall T2DM management. The results demonstrated the impact of self-care behaviours such as treatment adherence on glycaemic control, as well as the need for more targeted approaches that address the low compliance level to smoking and alcohol cessation. As a behaviour-directed intervention, telemonitoring exhibited great potential to improve T2DM management. Several technical features, patient factors and incorporation of education programs were shown to influence the effectiveness of telemonitoring. These

findings have valuable implications for the development of modern telemonitoring interventions and their integration into the healthcare systems.

Statement of Originality

This work has not previously been submitted for a degree or diploma in any university. To the best of my knowledge and belief, the thesis contains no material previously published or written by another person except where due reference is made in the thesis itself.

Signed

[redacted]

Jinxuan Cai

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List of abbreviations

ADA	American diabetes association
ADCES7	Association of Diabetes Care and Education Specialists 7 Self-Care Behaviours
AGE	Advanced glycation end product
ANOVA	Analysis of variance
BMI	Body mass index
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CVD	Cardiovascular disease
DALY	Disability adjusted life year
DASH	Dietary Approaches to Stop Hypertension
DBP	Diastolic blood pressure
DM	Diabetes mellitus
DRC	Diabetes-related complication
DV	Dependent variable
ESRD	End-stage renal disease
FBG	Fasting blood glucose
HbA1c	Glycated haemoglobin
HF	Heart failure
HR	Hazard ratio
IL-1	Interleukin 1
IV	Independent variable
MANOVA	Multivariate analysis of variance
MD	Mean difference
SBP	Systolic blood pressure
SD	Standard deviation
SMBG	Self-measurement of blood glucose
T2DM	Type 2 diabetes mellitus
TC	Total cholesterol
TNF-α	Tumour necrosis factor alpha

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Chapter 1. Introduction

1.1 Background

1.1.1 Global type 2 diabetes mellitus burden

The increasing prevalence of sedentary lifestyles and obesity worldwide, along with population aging, urbanisation and economic development, has led to a rise in type 2 diabetes mellitus (T2DM) (1). As of the year 2015, the International Diabetes Federation estimated that 415 million adults aged 20-79 years were affected by diabetes mellitus (DM) globally (2). Over 90% of DM cases are T2DM, but this is often not distinguished in population-level estimates (3). The number of people with DM has quadrupled since 1980, and it is expected to reach a staggering figure of 642 million by 2040 (2).

T2DM and its related complications put an enormous burden on healthcare systems across the world, contributing to significant disability and mortality. DM was believed to have caused 3.98 million adult deaths globally in 2010 (4). The estimated number of deaths due to DM and its complications increased to over 5 million in 2015, which is equivalent to one death every six seconds, making it the ninth leading cause of reduced life expectancy (2). The incidence of diabetes-related complications (DRC) and associated disabilities has increased dramatically since the last century. Disability-adjusted life years (DALY) is a time-based measure that combines the years of life lost due to premature mortality, living in states of less than full health, and disability (5). Fasting hyperglycaemia was listed as the tenth most common global risk factor for DALY in 1990, and it became the third most common in 2015, accounting for approximately 143 million DALY (6). The onset of T2DM often precedes the actual diagnosis. It is estimated that over 170 million cases of T2DM globally are undiagnosed, making them more vulnerable to complications and disabilities than diagnosed patients who are receiving appropriate treatment (7).

The rising prevalence of DM is most prominently seen in developing countries, with China and India being the top two global epicentres (2). In 2010, a population-based survey in China estimated that over 113 million adults had DM, and over 493 million adults had prediabetes defined as impaired glucose tolerance or impaired fasting glucose (8). Within this cohort, more than two-thirds were undiagnosed, over three-quarters were not receiving treatment, and only 39.7% of the treated cases had achieved glycaemic control with glycated haemoglobin (HbA1c) level less than 7.0% (8). A national study conducted in India in 2011 estimated that 62 million individuals had DM and over 77 million had prediabetes (9). This estimate is expected to rise to 123.5 million by the year 2040 (2).

The US is the third leading country for DM burden, where more than half of the adults over 65 years old are believed to have prediabetes (10). The Middle East is another hotspot of the global DM epidemic, with the prevalence of DM ranging from 9.5% in Oman to 25.4% in Saudi Arabia (11). The prevalence of DM is particularly high in the Pacific nations, reaching over 30% of the nation's population in American Samoa and 25% in Polynesia and Micronesia (12). Limited updated data is available for the trend of DM in Africa. However, it is estimated that DM has a prevalence of 2.1-6.7% in the sub-Saharan part of Africa (2).

T2DM is becoming increasingly prevalent in the paediatric populations as a result of rising childhood obesity, and it has the potential to become another global public health issue (13). In the US, the prevalence of T2DM in children and adolescents has increased by 30.5% from 2001 to 2009, disproportionately affecting the paediatric population of ethnic minorities such as African-American, Indigenous American and

Hispanic youths (14). Similar trends were also seen in Canada and Australia where the indigenous populations suffer a disproportionately higher incidence of T2DM at an earlier age (15, 16). China and India have also seen a large increase in childhood T2DM as suggested by national data (17, 18).

It is estimated that over US$673 billion was spent on the management of DM and DRC in the year 2015 alone, accounting for 12% of global health expenditure (2). Studies from China, India, Thailand and Malaysia showed that the costs of inpatient care for uncomplicated DM accounted for 11-75% of per-capita income in 2007, while DM complicated with DRC incurred up to three times the costs (19). The health expenditure for DM in the North America and Caribbean region is shown to be 85-fold that in southeast Asia, spending more than all other regions combined (2). On average, the management of DM and DRC accounts for 25% of the total health expenditure in Latin American countries, with the heaviest economic burden seen in Brazil and Mexico (20).

1.1.2 Glycaemic control

Glycaemic control refers to the management of the patient's blood glucose level within a relatively healthy range in order to slow down disease progression and prevent the development of DRC, given that persistent hyperglycaemia is one of the main culprits for the associated morbidity and mortality. However, it is estimated that up to 55.6% of patients with T2DM do not have adequate glycaemic control (21). Several barriers may exist that hinder successful control of blood glucose, including treatment non-adherence, insufficient patient education, limited access to healthcare systems, lack of motivation, and high associated costs (22, 23).

Effective glycaemic control usually requires a multidisciplinary approach that involves care from medical professionals, allied health professionals, as well as patients themselves (24, 25). Current treatments for T2DM will be detailed in the following sections, where a combination of pharmacological interventions and lifestyle modifications is often required to achieve optimal result. Once started, T2DM medications are usually continued for a long period of time or lifelong. Daily tablet or injection can be quite burdensome for many patients, thus decreasing compliance. Moreover, treatment dosage needs to be continuously titrated based on individual's response, missed doses or irregular usage can result in unwanted fluctuations in blood glucose level, making it even more challenging to maintain glycaemic control.

Limited health literacy and poor disease understanding can hinder treatment adherence in patients with T2DM. Without fully comprehending the importance of adhering to medication schedules, dietary restrictions and physical exercise recommendations, as well as the long-term consequences of poorly managed T2DM, can undermine patients' motivation and engagement in their self-care, and ultimately result in inadequate glycaemic control.

Access to healthcare system plays a crucial role in the success of glycaemic control. First of all, it allows early detection and diagnosis of T2DM through regular health check-ups and screening tests. Starting treatment early in the disease course can provide significant benefits to the patient and result in a better prognosis. Blood glucose levels can fluctuate for a range of reasons, such as disease progression, inadequate medication, or other concurrent acute illnesses. Therefore, patients with T2DM need regular monitoring and thus timely diagnosis and intervention to maintain good control of blood glucose.

Patients with T2DM often experience repetitive psychological stress and social intimidation, making them a vulnerable population to maladaptation and psychiatric disorders (26).

In addition, due to the lack of patient-physician communication, appropriate action is often not taken when indicated, such as when an abnormally high blood glucose measurement is obtained by the patient at home (27). Therefore, more studies are warranted to address problems in patient behaviours and communication.

The importance of adequate glycaemic control in slowing down T2DM progression and preventing DRC has been well studied (25). Controlling blood glucose is the main goal for both pharmacological and non-pharmacological T2DM treatments (28). Glycaemic control can be assessed by several well-established markers, two of which are used in this study: HbA1c and Fasting blood glucose (FBG).

HbA1c is one of the most commonly used indicators of glycaemic control (29-32). It is an index of the average blood glucose over the lifespan of the erythrocytes containing it and importantly, it is free from the impact of fluctuating blood glucose levels in relation to meals and sicknesses (33). Furthermore, HbA1c measurement has been internationally standardised, making it the tool of choice for not only monitoring long-term glycaemic control, but also diagnosing T2DM, defining treatment targets, and classifying disease subgroups (33). FBG is strongly associated with T2DM (34). Unlike HbA1c, FBG is a measure of temporary glycaemic control by directly measuring the concentration of glucose in serum (34). As shown in previous studies, FBG results are usually evaluated together with other test results such as HbA1c to provide a comprehensive picture of glycaemic control (34-36).

1.1.3 Current management of T2DM

The current management of T2DM involves a multifaceted approach that includes lifestyle modification, pharmacological interventions, regular disease monitoring, patient education, and ongoing support (37). The main aim is to achieve and maintain optimal glycaemic control, therefore reducing the risk of DRC, slowing down disease progression and improving overall quality of life.

Lifestyle factors play a central role in the pathogenesis of T2DM and therefore, modifying them has been a mainstay in T2DM management. Diet control, with an emphasis on more balanced and nutrient-dense foods and less added sugar, sodium, saturated and trans fats, is a major part of the lifestyle modifications recommended to patients with T2DM because it directly interacts with blood glucose (38). Literature has shown that the Mediterranean diet and Dietary Approaches to Stop Hypertension (DASH) diet, which is characterised by a high intake of fruits, vegetables, whole grains, low-fat dairy and lean proteins, have demonstrated favourable outcomes in glycaemic control and reduced cardiovascular disease (CVD) (39, 40). Regular physical activity, including aerobic exercise and resistance training, is another essential aspect of lifestyle medication that is recommended to most patients. Regular exercise has been shown to improve insulin sensitivity, glucose uptake, and overall metabolic health (41). The combination of both aerobic and resistance training appear to have a synergistic effect on glycaemic control and cardiovascular health (42). Both diet control and regular exercise help with weight management. Obesity is an important risk factor for developing T2DM, as the increased amount of fat tissue leads to release of more pro-inflammatory substances and a higher risk of vascular diseases (43). Studies have shown that even modest weight loss can lead to significant improvements in glycaemic control and metabolic profile (44). In addition to food intake and physical activity, other behaviour modification strategies are also essential in promoting sustainable lifestyle changes. These strategies focus on increasing awareness and accountability, as well as developing healthy habits, such as regular self-monitoring, goal setting, problem-solving and stress management (45). Such behavioural modifications can be facilitated by techniques like cognitive-behavioural therapy and motivational interviewing (45).

Pharmacological intervention is an integral part of T2DM management, especially when lifestyle modifications alone are insufficient to achieve glycaemic targets. The armamentarium of pharmacotherapies for T2DM has grown significantly over the past few decades, with new medications constantly under development. Several classes of medications are available, each with unique mechanisms of action and side effect profiles. Oral antihyperglycaemic agents, such as metformin, are generally considered as first-line when pharmacological intervention is indicated because its benefits and risks have been well studied (46). As more evidence becomes available, newer agents like sodium-glucose co-transporter 2 inhibitors have also been increasingly utilised especially in certain populations, including T2DM patients with cardiovascular or renal comorbidities (47). Parenteral medications are another group of pharmacological interventions commonly used in patients with T2DM. Injection of manufactured insulin is often required for patients with more advanced T2DM as they suffer from insulin insufficiency due to pancreatic function decline (48). Many insulin products are available varying in doses and duration of action. Overall, a tailored approach for each individual patient is required. The choice of medication and their doses need to be carefully titrated by healthcare professionals to ensure adequate patient response and to avoid significant harm.

Blood glucose level fluctuates considerably, which is a result of many contributing factors such as meals, exercise, medication effect, and even mood (49).

Therefore, regular monitoring of blood glucose level as well as other parameters, such as blood pressure, lipid profile and renal function, is essential for optimising glycaemic control. Both the healthcare professional and the patient themselves take part in the monitoring for T2DM. Monitoring of the parameters that are easily measurable without laboratory requirements, such as blood glucose level and blood pressure, can usually be done by the patient at their own convenience. This allows for more frequent measuring of the parameters that may change in a short period of time, thus providing a more comprehensive picture of, for example, how the blood glucose level of a patient receiving insulin therapy may vary at different times of the day or in response to the medication. Furthermore, studies have shown that participating in self-measurement may provide additional benefits by enhancing patient engagement and improving medication adherence (50, 51). On the other hand, monitoring of other parameters that are less likely to change acutely, such as HbA1c and renal function, can be done during their visit to the healthcare professionals. Although specific studies focusing solely on the benefits of HbA1c monitoring in T2DM are limited, the long-term level of glycaemic control reflected by HbA1c plays an important role in assessing the effectiveness of therapies and deciding if a change in treatment is needed (32). Regular monitoring not only evaluates a patient’s response to the current treatment and guides future treatment decisions, but it also helps with early detection of disease progression and development of comorbidities, allowing the healthcare professionals to adjust treatment accordingly.

Patient education is another important part of T2DM management as it empowers individuals with the knowledge and skills to actively participate in their own care and make informed decisions about their health (52). By providing T2DM patients with knowledge about their condition, treatment goals, self-monitoring techniques, medication use, dietary recommendations, and the importance of adherence to the management plan, patient education has a positive impact on glycaemic control and prevention of DRC (53-55). The implementation of structured diabetes self-management education and support programs has been recommended by the American Diabetes Association (ADA) as an essential element of care for all patients with T2DM (56). Patient education also links with other components of T2DM management. Literature shows that patients who received education on the importance of medication adherence had higher rates of adherence and better glycaemic control compared to those who did not receive the education (52).

Living with a chronic disease can be both physically and mentally draining. Patients with T2DM often experience repetitive psychological stress and social intimidation, making them a vulnerable population to maladaptation and psychiatric disorders (26). The requirement for long-term treatments and multidisciplinary care can also be costly and difficult to navigate. Therefore, ongoing support from healthcare professionals, diabetes educators, and other support services can greatly impact the success of T2DM management (57, 58). In addition to the regular follow-up visits with healthcare professionals for assessment of treatment progress, monitoring of glycaemic control, and adjustment of medication plan, support from peers and community networks can also significantly enhance T2DM management. Not only can the communities provide valuable advice from the past experiences of others, but they also foster a sense of belonging and understanding, which can be empowering and motivating for the patients, promoting self-management behaviours and general well-being (59). Furthermore, ongoing support extends beyond the clinical setting. The ADA and the European Association for the Study of Diabetes have both emphasised the significance of social support in the management of T2DM, as family members, friends, and caregivers all play a vital role in supporting individuals with T2DM (60). Their understanding, encouragement, and assistance in managing lifestyle changes, medication adherence, and coping with the challenges of diabetes can significantly impact patient outcomes (60).

The mainstays of T2DM management encompass lifestyle modification, pharmacological intervention, regular monitoring, patient education and ongoing support. A comprehensive approach that integrates the aforementioned strategies is essential for achieving and maintaining optimal glycaemic control.

1.1.4 Treatment adherence

T2DM is a chronic disorder that requires long-term management to achieve and maintain optimal glycaemic control and prevent DRC (43). Despite a large number of available treatment options, adherence to treatment remains a significant challenge in T2DM management. Treatment adherence can be roughly broken down into adherence to medication, adherence to lifestyle modification, and adherence to monitoring.

Medication adherence is crucial in achieving successful glycaemic control since pharmacological treatment is a mainstay of T2DM management. Nonetheless, it has been found that the rate of medication non-adherence ranges from 36% to 93% across multiple studies, with an overall average of approximately 50% (61). Several factors contribute to medication non-adherence, including treatment-related factors such as complex medication regimens, side effects, and unaffordable costs, and patient-related factors such as depression, anxiety, lack of understanding about the importance of medication adherence, and perceived lack of effectiveness (62). Treatment non-adherence has significant implications for patient outcomes in T2DM as it directly affects glycaemic control. Poor adherence has been shown to be associated with higher

HbA1c levels, increased risk of cardiovascular events, hospitalisation, and mortality (63). Various interventions have been explored to enhance medication adherence in T2DM patients. Effective strategies that have been evaluated by studies include more patient education, simplification of medication regimens, reminder systems, and more involvement of healthcare professionals in patient care (43, 64). Furthermore, digital health technologies, such as telemonitoring, have shown promising results in improving medication adherence in chronic diseases (65, 66). In general, a patient-centred approach that emphasises shared decision-making has been recognised as an important way to improve medication adherence in T2DM (67, 68). Engaging patients in treatment decisions, effectively addressing their concerns and preferences, and tailoring medication regimens to individual needs can make the patient more likely to comply with their treatment (69).

Adherence to lifestyle modifications, including dietary changes, increased physical activity, weight control, and abstinence from harmful substances like cigarettes and alcohol, can be quite challenging for many patients as guidelines recommend intensive modifications and these habits have usually been developed over several years (70). Research consistently shows that adherence to dietary change and physical activity recommendations among individuals with T2DM is generally low due to barriers such as lack of motivation, time constraints, lack of support, lack of access, cultural barriers, and physical or mental health limitations (71, 72). As a result, weight management can also be challenging to achieve and maintain. Smoking and alcohol consumption are major risk factors for the development and progression of T2DM and DRC (73). Despite the known risks, a significant portion of T2DM patients continue these habits (74). Various interventions have been utilised to promote adherence to smoking and alcohol cessation, such as individualised motivational counselling, pharmacological therapies, and behavioural interventions. Overall, it is important to adopt an integrated approach that addresses smoking and alcohol cessation alongside other lifestyle modifications, including dietary change and physical activities, to achieve optimal glycaemic control.

Monitoring in T2DM management includes self-monitoring as well as follow-up visits with healthcare professionals. Adherence to self-monitoring of blood glucose and other relevant parameters is crucial for establishing a good understanding of disease progression and treatment effect, whereas follow-up visits are important for ongoing monitoring and adjustment of treatment plan. However, adherence to monitoring can be challenging, particularly for those with limited access to the healthcare system. Several studies have found that living in rural and remote areas can have a negative impact on adherence to self-monitoring and self-care behaviours, leading to worse glycaemic control outcomes (75). In addition to limited access, other barriers such as high costs, forgetfulness, inconvenience, and lack of understanding all play a role in non-adherence to monitoring in patients with T2DM (76).

In general, treatment non-adherence is contributed by patient factors such as lack of knowledge and understanding, environmental factors such as geographical barriers and lack of social support, and treatment factors such as side effects and complexity of treatment (77). Patients who have poor health literacy and disease understanding may not be able to fully comprehend the importance of adhering to medication schedules, dietary changes, physical activity, and smoking and alcohol cessation in the long term. In addition, psychological disorders such as depression and anxiety are common in patients with T2DM, which can lead to hopelessness, lack of motivation, and difficulty in coping with the demands of self-care, further hindering their adherence to treatment (77). The socioeconomic status of a patient also plays a significant role in treatment non-adherence, as it usually determines their access to healthcare resources, including medications, glucose monitoring devices, and regular healthcare visits (78). Furthermore, lower socioeconomic status may be associated with financial constraints, lack of health insurance, and transportation issues, which can further contribute to treatment non-adherence. Similarly, T2DM patients with limited social support system can have an increased risk of developing stress and psychological disorders, and may face difficulties adhering to their treatment plan (79). Treatment factors can also affect a patient's adherence to the management plan. Medication side effects, such as gastrointestinal disturbances or hypoglycaemia, are relatively common among T2DM medications (80). Moreover, the burden of treatment complexity can be overwhelming as T2DM patients are commonly put on treatment plans that involve multiple medications, along with frequent monitoring and lifestyle modifications (43).

1.1.5 Telemonitoring in other chronic diseases before implementing in T2DM

Telemonitoring has been evaluated by many studies as a potential tool for managing chronic diseases (81-88). The goal of telemonitoring is to facilitate better disease monitoring and patient-physician communication by incorporating information technologies such as Bluetooth and 4G/5G networks into daily disease management (89). A variety of different telemonitoring systems exist, with the core concept being remote data transmission (90). Measurement of physiological parameters, such as blood glucose and blood pressure, can be taken by the patient at home using self-measuring devices (91). These data will be sent to their healthcare provider either in real-time (synchronous) or on a regular basis (asynchronous) through an automated electronic system, which is usually a smartphone application or website (91). Based on the up-to-date information, the healthcare provider can make more accurate judgements on the patient's health status, and then provide feedback and make adjustments to therapies if needed (91).

Heart failure (HF) affects more than 2% of the adult population worldwide; it is responsible for about 1 million hospitalisations per year in the US and it carries a high mortality risk, placing an enormous burden on the healthcare system (92). In HF management, regardless of the specific type of HF, a large proportion of costs comprise ambulatory patient visits, emergency department visits and hospitalisations (93). Up to 40% of HF patients experience at least four hospitalisations over the course of their illness, and the risk of mortality rises with more prior hospitalisations (92, 94). Low patient adherence to prescribed medication treatments and lifestyle changes is one of the contributing factors for repeat hospitalisations and has been shown to rapidly decline over time following the prior hospitalisation (95). The development of telemonitoring techniques that would increase patient compliance, anticipate and/or prevent episodes of worsening HF, and enable patients to be more closely monitored without visiting medical facilities has received a lot of attention over the past few decades and increasingly in recent years (93). Numerous techniques for remote patient care, monitoring, and management have been developed during this time. Telemonitoring has been included in the European Society of Cardiology's guidelines for the diagnosis and treatment of acute and chronic HF, but there is still only limited research to support this practice (96). However, according to Ezekowitz (2017) and Yancy (2013), neither the American Heart Association nor the Canadian Cardiovascular Society make any recommendations for telemonitoring in their guidelines for the management of HF (97, 98). The findings of randomised controlled trials that produced mixed results for the telemonitoring of HF patients are what led influential professional associations to make these recommendations. However, consecutive Cochrane reviews demonstrate a significant reduction in major outcomes (all-cause mortality and HF hospitalisations) when using TM, but these were not taken into account in the most recent recommendations (93). In addition to the trials and meta-analyses, there is a growing number of expert opinion and review publications addressing the issue of equivocal evidence for the use of telemonitoring in the management of HF patients (93).

Chronic obstructive pulmonary disease (COPD) is a chronic illness that is primarily caused by cigarette smoking and exacerbated by long-term asthma, affecting 64 million people and contributing to 3 million deaths in the year 2015 alone (99). COPD is expected to become the third leading cause of mortality throughout the world by 2030, with 90% of its victims living in middle-to-low-income countries (99). An overview of the relevant systematic reviews and meta-analyses published in the last decade has shown that, despite no negative effect having been observed, the positive effect of telemonitoring for COPD on mortality, quality of life, exercise capacity and exacerbation-related outcomes remains controversial (100). Another review also emphasised inconsistency in the current literature regarding the positive effect of telemonitoring on improving symptoms and reducing exacerbations, hospitalisations and death (101). It is worth noting that all studies that evaluated the safety and feasibility of telemonitoring use in COPD have shown that the interventions were feasible and free of adverse events (101).

1.1.6 Telemonitoring in T2DM

Regarding T2DM, several studies have reported that the use of telemonitoring is associated with significantly reduced HbA1c and therefore, better glycaemic control (87, 102-104). It has also been demonstrated to result in reduced incidence of DRC, better quality of life, better adherence to medications and lifestyle measures, and reduced overall costs (102, 104). However, like in HF and COPD, controversies also exist in the use of telemonitoring in T2DM and conflicting results have been reported (105, 106). Such inconsistency in the literature may be explained by significant methodological variation among studies, such as different participant recruitment criteria and the number of parameters monitored. It may be difficult to draw conclusion given there is a lack of internationally standardised protocol and the fact that telemonitoring is a rapidly emerging field with many active research still underway.

Nonetheless, telemonitoring has several well-established advantages when compared to conventional T2DM management. One of the most significant benefits is that telemonitoring can be used to overcome geographical barriers, providing patients with easy access to healthcare systems regardless of their location (87). As discussed previously, the disease monitoring of a patient with T2DM demands regular follow-up visits to hospitals or clinics, which can be inconvenient for the patient and burdensome for the healthcare system (91). The use of telemonitoring largely reduces the need for in-person consultations and, consequently, the time and money spent travelling, especially for patients who live far away from their healthcare providers (107). This can then indirectly contribute to reduced productivity loss and overall medico-economical gain (107). Given the trend that more people will be living longer with their condition, telemonitoring also provides a potential solution for the overburdened healthcare systems as it enables multiple patients to be monitored simultaneously whilst utilising a minimum amount of the already scarce healthcare resources.

Blood glucose level fluctuates considerably, which is a result of many contributing factors such as exercise, meals and mood (49). Additionally, it may be caused by an individual’s response to medications as that can vary from one patient to another, making it necessary to individualise T2DM management (108). To achieve optimal glycaemic control, the dose of the majority of T2DM medications must be carefully titrated (108). In the setting of conventional T2DM care, when blood glucose becomes out of control or an adverse event occurs, the healthcare provider will not be aware of it and make appropriate adjustments until the next consultation. This delay in the information delivery may lead to a lack of treatment effectiveness, contributing to the failure of glycaemic control and development of DRC. Through the use of telemonitoring, this process is made safer and more efficient by making sure the healthcare providers are always up to date with the most recent information, allowing them to react to a change in the patient's condition and offer prompt interventions in a timely manner (91).

Telemonitoring also promotes better self-care (109). Self-care refers to a spectrum of pro-health behaviours that play important roles in the management of chronic diseases (110). It requires patients to pay particular attention to their daily activities, such as eating, grooming, and exercising, which can often be challenging as individuals may feel the loss of autonomy, freedom, and pleasure (111-123). The ADA has put much emphasis on the development of a patient-centred approach that empowers patients to take responsibility for their own care (124, 125). Telemonitoring has been demonstrated to be a successful method for patient empowerment; it increases motivation, quality of life, and sense of control, all of which reinforce self-care behaviours and, ultimately, glycaemic control (126-128). Nonetheless, the extent of telemonitoring's effectiveness remains debatable, and whether it is affected by other factors such as sex, age and ethnicity are yet to be understood (91).

1.2 Expected outcome

The expected outcome of the study is to achieve a better understanding of the relationship between treatment adherence and glycaemic control, the effectiveness of telemonitoring on glycaemic control, as well as the significance of various technical features, patient factors and education programs. This is done by analysing the cross-sectional data of 10246 adult T2DM patients and by conducting the systematic review and meta-analysis alongside subgroup analysis. It is expected that better glycaemic control is associated with better treatment adherence and the use of telemonitoring, and that certain technical features, patient factors or education programs can enhance the effectiveness of telemonitoring.

1.3 Significance

Associated with the rising prevalence of sedentary lifestyle and obesity, T2DM is a global health concern that is growing at an unprecedented speed, expected to reach a staggering figure of 642 million by 2040 (129). Being one of the leading causes of reduced life expectancy, T2DM is associated with many debilitating and lifelong complications, such as CVD, psychological disorders, renal disease and blindness (43). T2DM and DRC are causing significant burdens on the healthcare systems across the world, accounting for US$673 billion in the year 2015 alone (2). Despite the growing armamentarium of pharmacological interventions and the improving understanding of the role of lifestyle modifications, glycaemic control remains a difficult problem for patients with T2DM, with up to 55.6% of patients not achieving sufficient control of their blood glucose level (21).

Barriers such as treatment non-adherence, limited access to healthcare system, lack of patient education and high associated costs, continue to hinder successful control of blood glucose (77). Failure to adhere to medications and lifestyle recommendations is potentially one of the most significant factors preventing glycaemic control as it directly diminishes the effort to control blood glucose. Nonetheless, more evidence is needed on how exactly and to what extent treatment non-adherence affects glycaemic control. In an attempt to fill this research gap, part of this study will investigate the relationship between treatment adherence and glycaemic control in a large population of over 10,000 T2DM patients.

Given the high prevalence of T2DM, the healthcare burden it represents, the difficulty in achieving optimal glycaemic control and the dire consequences of unregulated blood glucose, there is an urgent need for effective glycaemic control measures that can address the barriers and prevent DRC. As an attempt to relieve healthcare burden and provide more efficient care to patients, telemonitoring has been rapidly emerging and studied for its effect on the management of chronic illnesses. To date, no conclusive evidence has been reported on its use in T2DM. The findings of this study can directly address this important gap in the current understanding of the management of T2DM by providing a contemporary overview of the current literature. Additionally, this research will yield novel data that can provide insight into the optimal use of telemonitoring and the ideal patient group that will benefit most from it. This knowledge may contribute to the development of new, integrative interventions that offer more stable glycaemic control than the existing therapies.

In terms of the practical aspect, the effectiveness, strengths, and limitations of the telemonitoring interventions discussed in this study can assist in guiding healthcare providers in selecting the most appropriate course of action based on the unique circumstances of each patient. Future studies built on the findings of this study may extend further to investigate the effectiveness of telemonitoring on not only glycaemic control, but also other parameters that play an important role in the overall management of T2DM, such as psychological resilience and self-care behaviours. The results of this study can also be applied to the development of novel interventions for other chronic illnesses like chronic kidney disease and hypertension.

1.4 Study outline

This dissertation consists of six chapters. Chapter 1 provides a background of the study, introduces the rising prevalence of T2DM and DRC, the barriers to treatment adherence and successful glycaemic control, the use of telemonitoring in other chronic diseases as well as T2DM, and explains the research problem along with its significance. Chapter 2 reviews the current literature on the epidemiology and pathophysiology of T2DM, the development of DRC, and telemonitoring in patients with T2DM, while other variables included in the dissertation and their relationships with telemonitoring and glycaemic control are also discussed. Chapter 3 describes the study's conceptual framework, aims and objectives, hypotheses, along with the specific steps taken to conduct the secondary data analysis and the systematic review and meta-analysis. Chapter 4 shows the descriptive statistics and results obtained from the statistical analyses conducted in the secondary data analysis and systematic review and meta-analysis. Key findings from the results are discussed in Chapter 5. Lastly, this study's strengths, limitations, and implications for the overall management of T2DM are discussed in Chapter 6, along with directions for future research.

Chapter 2. Literature review

2.1 Introduction

This chapter defines T2DM and details its pathophysiology, epidemiology, and its associated DRC. The chapter then describes the use of telemonitoring in chronic diseases and specifically, in T2DM. Finally, the chapter discusses the current research gap in the literature and how this study will aim to address it.

2.2 Epidemiology and risk factors of T2DM

T2DM is one of the most prevalent metabolic disorders worldwide. DM is defined by the World Health Organization as a chronic, metabolic disease marked by elevated levels of blood glucose, which, over time, leads to damage to the heart, kidneys, eyes, vasculatures and nerves (43). T2DM accounts for over 90% of cases of DM, it is characterised by insufficient insulin secretion by the pancreatic islet β-cells, tissue insulin resistance and deficient compensatory insulin secretory response (130). As the disease worsens, insulin secretion becomes unable to maintain glucose homeostasis, leading to hyperglycaemia. Patients with T2DM are typically obese or have a higher body fat percentage distributed predominantly in the abdominal region. Through a variety of inflammatory mechanisms, such as adipokine dysregulation, adipose tissue promotes insulin resistance (131). The global T2DM epidemic is the result of rising obesity, sedentary lifestyles, high-caloric diets and population aging (1). The pancreas, liver, skeletal muscle, kidneys, brain, small intestine, and adipose tissue are all involved in the development of T2DM (132). Dysregulation of the immune system and gut microbiota have emerged as important pathophysiological factors during T2DM (133).

Alarming statistics from epidemiological data predict a worrying projected future for T2DM. The International Diabetes Federation (IDF) estimates that 463 million adults aged between 20 and 79 years old were living with DM in 2019, contributing to 4.2 million deaths globally; the prevalence is expected to reach 700 million by the year 2045 (43). At least US$720 billion in healthcare expenditure worldwide was related to DM in 2019 (134). Furthermore, since 1 in 3 people with DM, or approximately 232 million individuals, were undiagnosed, the current figure of disease burden is likely an underrepresentation (135). The age group of 40 to 59 has the highest prevalence of DM (2). The incidence and prevalence of T2DM varies by geographic location, with more than 80% of patients residing in low- to middle-income nations, which adds to the difficulties of providing effective care (2). CVD is the leading cause of morbidity and mortality associated with T2DM, as patients with T2DM have a 15% increased risk of all-cause mortality compared with people without T2DM (136). A meta-analysis has demonstrated the link between T2DM and an increased risk of coronary heart disease (HR=2.00; 95% CI 1.83–2.19), ischaemic stroke (HR=2.27; 95% CI 1.95–2.65), and other vascular disease-related deaths (HR=1.73; 95% CI 1.51–1.98) (137).

Genetics and environmental factors both have an impact on the development of T2DM. Genome-wide association studies have identified common glycaemic genetic variants for T2DM, but these only account for 10% of the variance in all traits, indicating that rare variants are significant (138). Different phenotypes may exist in people of different ethnic backgrounds, increasing their propensity for clusters of CVD risk factors like hypertension, insulin resistance, and dyslipidaemia (131).

Genetic, metabolic, and environmental factors interact with one another, contributing to the prevalence of T2DM. Although there is a strong genetic component to each person's susceptibility to T2DM due to non-modifiable risk factors like ethnicity and family history, epidemiological studies have shown that many cases of T2DM can be prevented by addressing the major modifiable risk factors including obesity, low-level of physical activity, and poor diet (139).

2.2.1 Non-modifiable risk factors

The incidence and prevalence of T2DM are found to vary greatly across the world depending on ethnicity and geographic location, with Japanese, Hispanics, and Native Americans having the highest risks (140-142). Asians have been shown to have a higher incidence of T2DM when compared to the white population in the US (143, 144) or the UK (145), while the highest risk is among the black population (146). Although no clear causes have been identified, there are contributing factors that have been postulated, including modern lifestyle factors, socioeconomic factors, direct genetic predispositions, and gene-environment interactions.

The likelihood of developing T2DM is significantly influenced by genetic predisposition. Numerous genome-wide association studies on T2DM over the past ten years have revealed the complex polygenic nature of the disease, demonstrating that the majority of these loci increase T2DM risk by having primary effects on insulin secretion while the minority act by inhibiting insulin action (147, 148). On the basis of their potential role as intermediate mechanisms in the pathophysiology of T2DM, Dimas et al. categorised these variants into groups: four that fit a clear pattern of insulin resistance, two that lower insulin secretion with fasting hyperglycaemia, nine that lower insulin secretion with normal fasting blood glucose level, and one that modifies insulin processing (149). These findings suggest that the genetic makeup of the T2DM pathophysiology is highly polygenic and that additional association studies are required to identify further T2DM loci (150). Observational studies and clinical trials have shown that the impact of a particular genetic variant can be modulated by the environment and vice versa, suggesting that interactions between susceptibility loci and environmental factors may be the cause of the missing heritability of T2DM (151).

2.2.2 Modifiable risk factors

Obesity is the strongest modifiable risk factor for T2DM (152, 153) and is associated with metabolic abnormalities that lead to insulin resistance (154). A patient's body mass index (BMI) and their age at diagnosis of T2DM show an inverse linear relationship (155). Although the exact mechanisms by which obesity causes insulin resistance and T2DM remain unclear, a number of factors have emerged as being significant in the development of this pathological process, which involves both cell-autonomous mechanisms and inter-organ communication (70).

Sedentary lifestyle is another important risk factor for T2DM, as demonstrated by the Women's Health Study and the Kuipio Ischemic Heart Disease Risk Factor Study that found a reduction in T2DM risk of 34% and 56% in participants who walked 2-3 hours per week or at least 40 minutes per week, respectively (156, 157). Physical activity has three main advantages for delaying the onset of T2DM. First, skeletal muscle contraction increases blood flow into the muscle, which improves glucose uptake from the plasma (158). Second, exercise reduces intra-abdominal fat content, which is known to promote insulin resistance (159). Finally, it has been demonstrated that moderate exercise improves general glucose uptake by up to 40% (160). Overall, in addition to enhancing glucose uptake and insulin sensitivity. Physical activity also improves or even reverses inflammation and oxidative stress, which are predisposing factors for T2DM (158).

2.3 T2DM pathophysiology

T2DM is primarily brought on by a combination of two main factors: impaired insulin secretion by pancreatic β-cells and inadequate response to insulin by the insulin-sensitive tissues (161). The molecular processes involved in the synthesis and release of insulin, as well as the insulin response in tissues, must be tightly regulated in order for it to precisely meet the metabolic demand. Therefore, metabolic imbalances and, consequently, the pathogenesis of T2DM can be a result of any defects in the regulatory mechanisms involved (43).

In terms of the disease's pathophysiology, the abnormally high levels of blood glucose are caused by a breakdown of the feedback loops between insulin action and insulin secretion (130). In the case of β-cell dysfunction, the body’s ability to maintain physiological blood glucose levels is constrained due to the reduction in insulin secretion (43). On the other hand, insulin resistance contributes to reduced glucose uptake in adipose tissue, liver and muscle as well as increased hepatic glucose production via gluconeogenesis (162). Pancreatic β-cell dysfunction and reduced secretion is typically more severe than insulin resistance, even though both processes may occur early and contribute to the pathogenesis of the disease. However, hyperglycaemia is amplified when both processes are present, leading to the progression of T2DM (2, 163).

2.3.1 Pathophysiology regarding insulin secretion in T2DM

Insulin is produced by pancreatic β-cells. It is first synthesised as pre-proinsulin, which then goes through a number of conformational changes with the assistance of several proteins in the endoplasmic reticulum and Golgi apparatus to become mature insulin, which is then stored inside the cells (164, 165). High blood glucose concentration and, to a lesser extent, other factors including fatty acids, amino acids and hormones are the primary trigger for insulin release (166).

Historically, β-cell dysfunction has been linked to β-cell death (167). Recent research, however, points to a more complex network of interactions between the environment and various molecular pathways involved in cell biology as the potential cause of the dysfunction of β-cells in T2DM (168). Hyperglycaemia and hyperlipidaemia are frequently present in an excessive nutritional state with energy surplus, similar to that found in obesity, which favours insulin resistance and chronic inflammation. Under these conditions, due to differences in their genetic susceptibility, pancreatic β-cells are subject to toxic pressures such as inflammatory stress, oxidative stress and amyloid stress, which have the potential to ultimately result in the loss of pancreatic islet integrity (167).

The high fats and carbohydrates content in the high-calorie Western diet elevate blood glucose levels and the levels of circulating very-low-density lipoproteins, chylomicrons, and chylomicron remnants, which are triglyceride-rich particles. As a result of this, the level of reactive oxygen species increases, leading to a spike in the generation of inflammatory molecules. Given that inflammation is a recognised inducer of oxidative stress, the two processes interact synergistically after a large meal, amplifying any negative postprandial effects (43). The pathogenesis of insulin resistance and T2DM is significantly influenced by the sustained and marked increase in steady-state levels of reactive oxygen species. Increased intracellular reactive oxygen species impair angiogenesis in response to ischemia, activate several proinflammatory pathways, and results in long-lasting epigenetic changes that continue to promote proinflammatory gene expression even after glycaemia returns to normal (169).

Associated with increased markers of low-grade systemic inflammation, both reduced physical activity and increased sedentary behaviours mediate the relationship between obesity and T2DM (170). Interleukin 1 (IL-1) and tumour necrosis factor-alpha (TNF-α) are examples of proinflammatory molecules that are released and are involved in the autoimmune response to pancreatic -cells, inhibition of -cell function, and activation of apoptosis (158). Intentional weight loss continues to be one of the mainstay therapies to improve insulin sensitivity and, in some individuals with obesity and prediabetes, reduce the risk of developing T2DM (43). Regular physical activity increases the production of anti-inflammatory cytokines like soluble TNF receptor and IL-1 receptor antagonist, which have antagonistic effects against IL-1 and TNF-α, respectively (43). Exercise can also reduce the oxidative stress that contributes to the pathogenesis of T2DM by promoting the synthesis of antioxidants like glutathione, a significant non-enzymatic antioxidant, and other antioxidant enzymes that result in long-term reduction in free radical levels (158, 171).

The development of T2DM has also been linked to other pathological conditions, such as gut dysbiosis and mitochondrial dysfunction (43). Gut microbiota is composed of numerous microorganism species that affect human physiology and take part in various biological processes (172). They participate in the synthesis of metabolites, modulate the immune system and inflammatory response, and control the integrity of the gut barrier and human metabolism (172). Numerous metabolites that are created by the microorganisms residing in the human gastrointestinal tract play important roles in the physiology of a healthy individual (173). However, changes brought on by inherited and acquired factors like age, nutrition, lifestyle, genetic predisposition, or underlying diseases can affect the proportion of metabolites produced by the gut microbiota, which can result in metabolic disturbances that can culminate in disease (131, 174). The importance of the gut microbiota in the pathogenesis of DM has been evidenced as recent research suggests that gut dysbiosis may promote insulin resistance and thus T2DM (173). In mouse models, a high-fat diet can increase lipopolysaccharide production from Gram-negative gut bacteria by up to threefold, which can lead to low-grade inflammation and insulin resistance (175, 176). Additionally, intestinal dysbiosis can inhibit the production of short-chain fatty acids, which support the integrity of the gastrointestinal tract barrier, the proliferation of pancreatic β-cells, and the synthesis of insulin (177, 178). The production of other metabolites including trimethylamine and branched-chain amino acids may also be disrupted by gut dysbiosis, compromising glucose homeostasis and contributing to the development of T2DM (179). Further study is needed to better elucidate the relationship between gut microbiota and T2DM as the clinical implications of the gut microbiome are still a relatively new field.

A growing body of evidence links mitochondrial dysfunction to age-related insulin resistance, T2DM pathogenesis, and the development of DRC (180). Reduced mitochondrial biogenesis and decreased expression of mitochondrial oxidative proteins occur in mitochondrial dysfunction, which in turn disrupts the insulin signalling pathway (181). Specific details around the molecular biology on how mitochondrial functions are associated with insulin signalling is beyond the scope of this thesis. In summary, a highly nuanced and reciprocal relationship exists between mitochondrial dysfunction and T2DM. Nutrient overload, reactive oxygen species accumulation, and subsequent insulin resistance all contribute to mitochondrial dysfunction. On the other hand, mitochondrial dysfunction may render individuals more prone to developing T2DM. To fully understand the connection between mitochondrial health and T2DM, more study is required.

As was already mentioned, insulin secretion needs to be carefully controlled to precisely meet the metabolic demands. Therefore, the integrity of pancreatic β-cells must be preserved in order to respond to metabolic needs. The mechanism mentioned above can, in pathogenic circumstances, result in disruption of pancreatic islet integrity, affecting cell-to-cell communication within pancreatic islets, causing dysregulated release of insulin and glucagon, and ultimately exacerbating hyperglycaemia (43). The secretory dysfunction of insulin, which is the main cause of pancreatic β-cell failure, may also result from defects in the synthesis of any insulin precursors or insulin itself, as well as from disruption of the secretion mechanism (43).

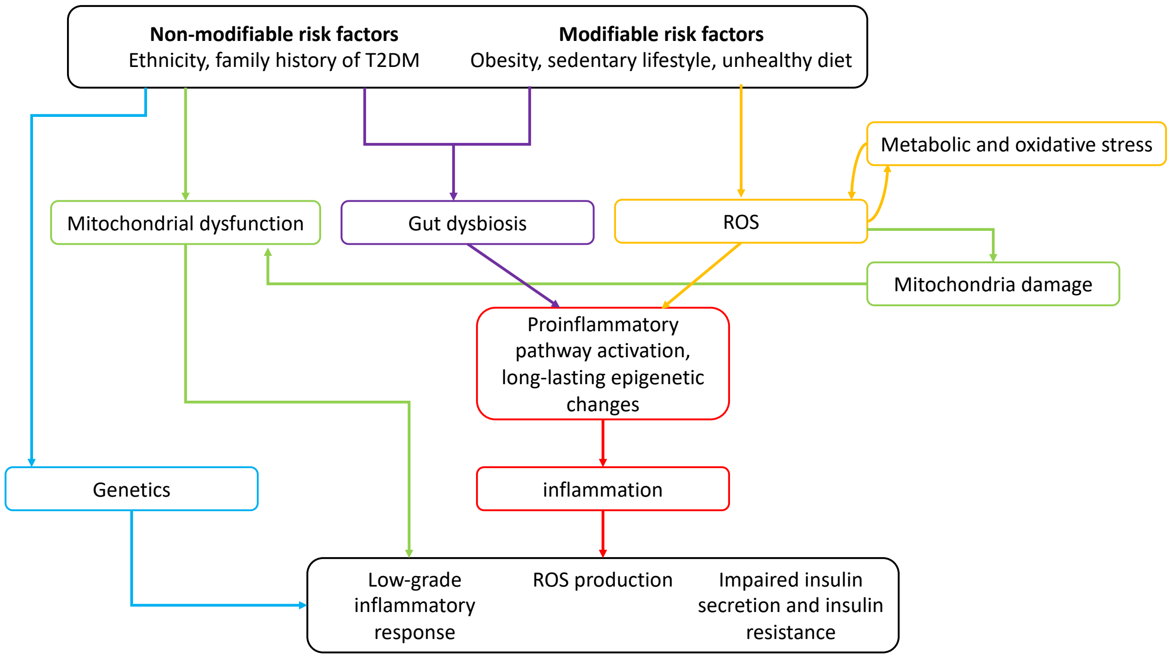

Figure 1. Pathological changes that lead to the perpetuation of insulin dysfunction (43).

2.3.2 Pathophysiology regarding insulin resistance in T2DM

Insulin resistance is the term used to describe a reduction in the metabolic response of insulin-responsive cells to insulin or, more generally, a systemic impairment of the response of blood glucose levels to circulating insulin (182). The interplay of additional molecules, such as growth hormone in the fed state and glucagon, glucocorticoids, and catecholamines in the fasting state, affects the action of insulin (43). The liver, skeletal muscle, and adipose tissue are the three main extra-pancreatic insulin-sensitive organs that are prone to insulin resistance (183). Defective insulin action in these tissues often occurs before the onset of systemic insulin resistance, which gradually progresses to T2DM (183).

In the liver, insulin not only regulates the production and utilisation of glucose but also plays a role in lipid metabolism (184). Under physiological conditions, the coordinated actions of insulin and glucagon allow for the precise control of hepatic glucose output. While glucagon stimulates the hepatic production of glucose, insulin acts as a powerful inhibitor of glucose synthesis when its concentration in blood is elevated (185). In states of insulin resistance, the appropriate response to insulin in the hepatic cells can no longer be elicited by the physiological level of circulating insulin (186). Glycogen synthesis is impaired and, as the liver fails to suppress glucose production, both lipogenesis and production of proinflammatory proteins are enhanced (186). On the other hand, abnormal production of proinflammatory proteins such as adipokines and cytokines, along with other morbid conditions like oxidative stress, can result in an inflammatory state that may worsen insulin resistance by the liver, entering a vicious cycle (187).

Insulin resistance in skeletal muscle is thought to be the most important extra-pancreatic factor contributing to the development of T2DM (188). In physiological states, insulin promotes glucose uptake from plasma, which in turn stimulates the synthesis of glycogen inside the skeletal muscle cells. By increasing the expression of glucose transporters on the plasma membrane of skeletal muscle cells, insulin facilitates more glucose to be taken up by the cells and therefore reduces the circulating blood glucose level (189). Impaired glucose uptake and, consequently, a hyperglycaemic state would result from mutations that decrease the expression of the insulin receptor or glucose transporters on the surface of skeletal muscle cells, as well as from any defect in the upstream or downstream signalling pathway (182). In addition to mutations or defective epigenetic regulations, environmental factors can also have a significant impact on the uptake of glucose by skeletal muscle cells. Physical activity improves glucose utilisation by increasing blood flow to skeletal muscle cells (158). On the other hand, growing evidence indicates that, as a consequence of obesity, increased immune cell infiltration and proinflammatory molecule secretion in the perimuscular adipose tissue lead to chronic myocyte inflammation and impaired myocyte metabolism, ultimately contributing to insulin resistance through paracrine effects (190).

Adipose tissue is metabolically dynamic and capable of producing a variety of biologically active substances that control metabolic homeostasis on a systemic level (191). Insulin acts on adipose tissue in a few different ways, such as promoting the cellular uptake of glucose from the blood, stimulating the synthesis of triglyceride and inhibiting its hydrolysis, and increasing the uptake of free fatty acids and glycerol from the circulation (192). In states of insulin resistance, glucose uptake and triglyceride synthesis are impaired, while more free fatty acids are released into the circulation even in the presence of high insulin levels (193). As a result, free fatty acids build up in other tissues, like the liver, where it encourages hepatic gluconeogenesis and disrupts the insulin response to glucose, leading to the development of T2DM (43). It has been demonstrated that pathologic vascularisation, hypoxia, fibrosis, and macrophage-mediated inflammation are all associated with abnormally increased adipose tissue mass and adipocyte size, which are worsened by a high-fat diet and obesity (194). Hypertrophied adipocytes as well as immune cells that are found in adipose tissue cause increasing levels of circulating proinflammatory cytokines, which facilitates the emergence of a persistent low-grade systemic inflammatory state, also known as metabolic inflammation (161). This chronic inflammatory state is thought to play a key role in the development of insulin resistance and the pathogenesis of T2DM (195).

T2DM is a heterogeneous and progressive disorder that encompasses a number of metabolic conditions linked to hyperglycaemia and brought on by deficiencies in the secretion or action of insulin as a result of a complex pathological cascade. There are numerous pathways that interact and mutually reinforce one another, driven by various genetic and environmental factors, increasing the risk of other complications like cardiac, peripheral arterial and cerebrovascular disease, obesity, and non-alcoholic fatty liver disease.

2.4 T2DM-related morbidity and mortality

Owing to dysregulated blood glucose, patients with T2DM are at high risk of developing a range of debilitating, long-term complications, making it one of the main causes of cardiovascular and renal diseases (196-198), blindness (199), and non-traumatic amputations (30, 200-203). These DRC are difficult to manage, and they incur heavy financial burdens on the healthcare systems (204-208). Although the origin of DRC is certainly multifactorial, the main contributing factor seems to be the persistently elevated blood glucose and the resulting organ injury via glucotoxicity (28). Glucotoxicity causes disruption of normal cellular mechanisms and accumulation of toxic metabolic wastes, which leads to damage to both insulin-producing cells and target tissues of insulin (28).

DRC have traditionally been divided into macrovascular complications, such as CVD, and microvascular complications, such as diabetic retinopathy and neuropathy. A large international observational study across Asia, Africa, South America and Europe showed that approximately 1 in 2 patients with T2DM will present with microvascular complications and 1 in 4 will present with macrovascular complications (209). The risk of developing micro- and macrovascular diseases among patients with T2DM is estimated to be at least 10-20 times higher and 2-4 times higher, respectively, than in people without T2DM (210). The risks of developing renal complications and stroke seem to be higher particularly in developing countries in comparison to developed countries (211).

On average, the life expectancy of patients with T2DM is 8 years shorter than the non-diabetic population, with CVD being the leading cause of mortality (212, 213). The presence of T2DM significantly raises the patient's risk of developing coronary artery disease, stroke, myocardial infarction, peripheral artery disease, and HF via a complex mechanism that involves a combination of metabolic, vascular and inflammatory abnormalities (137). CVD is twice as likely to develop in patients with T2DM, and typically develops 14.6 years earlier with greater severity in comparison to individuals without the disease (137, 214, 215). Furthermore, the risk of death from vascular diseases is more than doubled in patients with T2DM (216). Risks of CVD may vary depending on the geographical region as it has been shown that patients with T2DM from Asian countries have a lower risk of developing major coronary events in comparison to Eastern Europe (217). The strong relationship between CVD and glycaemic control has been repeatedly shown by studies (28). In the Study of Norfolk, the overall relative risk of CVD was significantly lower in participants with HbA1c <5% and it increased continuously with each percentage point of HbA1c over 5% corresponding to a 20% higher CVD risk (218). Persistent hyperglycaemia promotes the formation and accumulation of toxic products, such as advanced glycation end products

(AGE) and reactive oxygen species, inside the blood vessel or other tissues, causing endothelial dysfunction, vascular inflammation, smooth muscle cell proliferation and impaired relaxation, which ultimately lead to the development and progression of atherosclerotic plaques (219, 220). Hyperglycaemia also increases the coagulability of blood, which favours the occurrence of thromboembolic events (28, 221). In addition, resistance to insulin also plays an important role in the pathogenesis of CVD in T2DM patients. Insulin resistance is associated with dyslipidaemia, including elevated triglyceride and low-density lipoprotein and reduced high-density lipoprotein (222). The abnormalities in lipid profile further contribute to the development of atherosclerotic plaques inside the arterial wall and subsequent CVD (222). Insulin resistance also increases the serum level of inflammatory cytokines including TNF-α and interleukin 6, which also contribute to endothelial dysfunction and the development of CVD (223). Moreover, T2DM shares many traditional risk factors with CVD, such as sedentary lifestyles, unhealthy diet, hypertension, obesity, cigarette smoking and many more. Therefore, T2DM patients with these risk factors at baseline are already at a higher risk of developing CVD.

Diabetic nephropathy is one of the leading causes of end-stage renal disease (ESRD) worldwide (224). It shares many pathogenetic mechanisms with the development of CVD in T2DM patients. As a hallmark of T2DM, dyslipidaemia and its associated activation of pro-inflammatory cascades play a central role in the development and progression of diabetic nephropathy by causing vascular wall damage and atherosclerotic plaque formation (225). As a consequence of persistent hyperglycaemia and renal vasculature injury, activation of the renin-angiotensin-aldosterone system further promotes vasoconstriction and expansion of intravascular volume, exacerbating renal damage (226). These inflammatory processes and the resulting fibrotic changes progressively diminish the functional reserve of the kidneys and lead to irreversible damage (224). Diabetic nephropathy affects about 25% of patients with T2DM in the US, while renal failure accounts for approximately 10% of T2DM-related mortality (2) (227). In China, diabetic nephropathy has also replaced glomerulonephritis and become the leading cause of ESRD (228). It appears that the risk of developing diabetic nephropathy is much higher in Asian countries than in Western countries, as shown in the Action in Diabetes and Vascular Disease trial (217). Genetic background, lifestyle and patient awareness of complications might account for the ethnic differences in diabetic nephropathy among patients with T2DM (229).

Diabetic retinopathy, a major cause of visual impairment and blindness in adults globally, describes primarily damage to the blood vessels in the light-sensitive retina of the eye in patients with T2DM (230). The mechanism of diabetic retinopathy resembles the macro- and microvascular impact of hyperglycaemia and insulin resistance discussed above. As the damage progresses, the blood-retinal barrier will be weakened with increased vascular permeability and leakage of fluid and blood into the retina, causing intraretinal haemorrhages, microaneurysms, formation of new, fragile blood vessels and retinal detachment (231). Other complications such as diabetic macular oedema, which is the accumulation of fluid in the central retina due to chronic inflammation and increased vascular permeability, have also been described in the literature (232). The prevalence of diabetic retinopathy in the US is approximately 28.5% while it ranges from 16% to 35% in Asian countries (2).

Furthermore, T2DM is also a leading cause of non-traumatic amputation. T2DM may also, directly or indirectly, increase the risks of conditions affecting the musculoskeletal, hepatic, and digestive systems, as well as the brain and mental health. It may also increase the risk of certain cancers, such as those of the liver, pancreas, and endometrium (233). T2DM is associated with several key comorbidities bi-directionally, such as non-alcoholic fatty liver disease (234), obstructive sleep apnoea (235) and depression (236). Such interrelationships are at least partially caused by obesity.

Metabolic memory refers to the persistence of DRC even after adequate glycaemic control is restored and maintained (43). This concept was developed from the findings of multiple large-scale clinical studies, which demonstrated that after the onset of T2DM, complications continue to worsen despite the restoration of glycaemic control through pharmacological interventions (237-239). In particular, the Steno-2 trial and UKPDS post-trial study demonstrated that early intervention in glycaemic control can prevent DRC, with a significant reduction in CVD endpoints in both the standard treatment and intensive treatment patient groups (239). In-vitro cell cultures and animal models of diabetes later proved that the initial hyperglycaemic period causes permanent abnormalities, such as aberrant gene expression, in the target tissues (240-243). The hyperglycaemia-induced excessive production of reactive oxygen species by mitochondria results in DRC that may persist even when blood glucose level is under control (244). When good glycaemic control is initiated very early, the damage caused by hyperglycaemia-induced oxidative stress can be avoided; however, if poor glycaemic control is maintained for an extended period of time, it may not be easily reversed (245, 246). There is a connection between hyperglycaemia, elevated oxidative stress, and excessive AGE formation in the early stages of T2DM (247). As the disease progresses, the combination of mitochondrial DNA damage and persistent protein glycation affecting components of the respiratory chain can lead to a synergistic effect that is independent of blood glucose level (240). This metabolic imbalance triggers inflammatory processes that can result in changes in the composition and structure of the extracellular matrix, leading to endothelial dysfunction and eventually, atherosclerosis (248). Multiple studies have shown that dysregulation of microRNA, which controls the silencing or degradation of the target gene, may remain even after returning to normoglycaemia (248-250). It has been demonstrated that hyperglycaemia may change the activity of DNA methyltransferases and post-translational histone modifications, which cause irreversible alterations that explain the long-term negative effects of metabolic memory (251-254).

The large increase in the number of cases of T2DM and undiagnosed T2DM globally, together with advances in the treatment of T2DM, resulted in more patients being able to live longer with the condition than they used to, which has led to an increase in the incidence of DRC. On the other hand, in the past few decades, the rate of mortality from CVD and many other DRC has been steadily decreasing due to earlier and more effective medical interventions (28, 255). As a result, more people will be living with T2DM and DRC, requiring care from the already burdened healthcare systems. A study has shown that 53% of the lifetime direct medical costs associated with T2DM in the US have been attributed to treating major DRC, such as coronary artery disease, renal disease, retinopathy, neuropathy and stroke (256). Intensive glycaemic control and other T2DM management have led to improvement in care in some developed countries, but little data is available for the rest of the world (210).

2.5 Factors that may influence the effectiveness of telemonitoring

As a remote monitoring technology that holds the potential to enhance patient care, improve disease management, and reduce resource utilisation through real-time data collection and timely interventions, telemonitoring has garnered increasing academic attention in recent years.

2.5.1 Feasibility and safety

Numerous studies have investigated the feasibility and safety of implementing telemonitoring in chronic disease management. In studies dealing with asthma and COPD, many considered their intervention feasible with good patient satisfaction (257-262). Patients found the system easy to use and over 80% of participants in one study would continue to use the intervention (259, 261). The feasibility is also indirectly reflected by the high completion rate where 98% of participants finished the 12-month trial (259). No major side effect associated with the use of telemonitoring was reported across the studies (257, 260, 262). Similarly, multiple review articles have suggested that current evidence supports the feasibility of telemonitoring as part of HF management (257, 258). Moreover, promising results have been shown by studies looking at the use of telemonitoring in T2DM management, showing a good level of satisfaction and adherence (263, 264).

From a technical standpoint, telemonitoring systems have evolved significantly, becoming more user-friendly and accessible. This is, in part, due to the advancement in measuring devices such as glucometers and electronic sphygmomanometers, which are now smaller and simpler to use, making them more feasible for the elderly and less technology-savvy patients. In addition, new technologies in wireless communication and mobile phone applications enable real-time data transmission to healthcare providers, ensuring timely assessment and intervention. Many telemonitoring systems utilise automatic data transmission where the patient does not need to perform any more tasks other than the measurement itself. Abnormality alert has also been implemented in many systems, where an abnormal reading automatically triggers a warning to the healthcare providers and, sometimes, to the patient's emergency contact. This usually led to additional consultations, education, or reassurance depending on the particular situation. All these features contribute to the feasibility of telemonitoring systems in the management of chronic diseases.

The clinical outcomes linked with the use of telemonitoring in chronic diseases also support its feasibility. As discussed previously, telemonitoring is associated with reduced mortality and morbidity in HF and COPD (93, 100). This positive impact on clinical outcomes underscores the feasibility of using telemonitoring as a tool to manage chronic diseases.

However, challenges related to the implementation of telemonitoring in chronic disease management should not be overlooked. It has been reported that the level of integration of telemonitoring in the healthcare system needs to be optimised (257). In addition, it has been discussed that incorrect use of devices by the patients or omission of the collected data by the healthcare provider may lead to the lack of positive effects by telemonitoring as shown in some studies (101). This indicates that telemonitoring alone may not have any direct effect on health status, instead, its effectiveness is likely moderated by behavioural and implementation factors (101). Therefore, greater attention is needed regarding patient behaviours and the system's user-friendliness. Similarly, the use of telemonitoring data in clinical decisions by healthcare providers also needs to be evaluated to ensure effectiveness. Ensuring patient privacy and data security, integrating telemonitoring data into electronic health records, and addressing issues related to reimbursement and healthcare policies are important considerations that need to be addressed for successful implementation.

2.5.2 Acceptability and compliance

Patient acceptance of telemonitoring in chronic disease management has been increasingly positive. High patient satisfaction and compliance were found in multiple studies, and the appreciation for the intervention was also high especially when the intervention was user-friendly (259, 261). Patients reported feeling more empowered and connected to their healthcare team, which enhanced their confidence in practising self-care and managing their own conditions (263, 264). Additionally, the convenience of not needing frequent in-person visits and the proactive nature of telemonitoring in detecting early signs of HF exacerbation contributed to its high acceptability (265).

2.5.3 Technical features in telemonitoring

There is limited evidence regarding how the effectiveness of telemonitoring on glycaemic control in T2DM can be influenced by various technical features and settings of the telemonitoring system. Nonetheless, it is reasonable to believe that the technical features have a significant impact as they directly affect the system's practicality, data accuracy, communication, as well as the user-friendliness for both the patient and the healthcare provider, which is known to influence the effectiveness of telemonitoring (101).

2.5.3.1 Parameters monitored

The single most important physiological parameter to monitor in patients with DM is their blood glucose level, which is incorporated in all telemonitoring systems designed for T2DM. However, many systems integrate the monitoring of other parameters such as blood pressure and body weight (266-268). As previously discussed, T2DM is a chronic, systemic disease that impacts multiple organ systems (269). Therefore, monitoring multiple parameters simultaneously can provide healthcare professionals with a more comprehensive picture of disease progression and inform relevant decision-making, though it may mean more tasks for the patient.

2.5.3.2 Telemonitoring duration

The optimal duration of telemonitoring is still up for debate. T2DM is a chronic illness that usually requires continuous and lifelong treatments (214). Most of the existing studies had an intervention duration of six months to a year, making it difficult to investigate the long-term sustainability and effectiveness of telemonitoring interventions in T2DM management. The benefits of telemonitoring may become more evident over time as patients become accustomed to the use of this technology. However, it is also possible that an extended program can suppress patient's participation as they feel exhausted or their autonomy compromised. Thus, evidence from more long-term studies is needed to evaluate its effect.

2.5.3.3 Communication method and mode of data input

Remote patient-physician communication is a core component of telemonitoring, which can be done via text-based communications (e.g. emails and text messages), phone calls, or a mixture of both. The way communication is conducted may affect the effectiveness of telemonitoring due to the potential differences in the level of patient engagement and motivation. Patients reached by phone in other studies related to health interventions showed higher rates of participation in their health management than those who received text-based communications (270). In contrast to passively receiving text-based communications, active real-time interaction with healthcare providers through phone calls can be more engaging and may have an impact on the overall outcomes. A similar rationale may be applied to different modes of data input. Some self-measuring devices input data into the recording system automatically after each measurement, whereas others require the user to manually enter the measurement data into the system. While the automatic system may be less prone to mistakes and easier to use especially for elderly and the less technology-savvy patients, manual data input might be more engaging and motivating.

2.5.3.4 Mode of data transmission

The way a self-measuring device sends data to its destination, usually a cloud server, is referred to as the method of data transmission and can be broadly divided into using Wi-Fi, 4G or 5G network, or Bluetooth, where the device itself is not connected to the internet but requires an intermediate device, such as a laptop, to upload data to the cloud. Devices utilising 4G or 5G networks may grant patients more freedom on self-measurement since they can transmit data readily in most places and are not restricted by the need for a Wi-Fi modem or Bluetooth-paired terminal nearby, allowing patients to conduct self-measurement at various occasions such as during exercise or social event. This can not only promote frequent self-measurement but also provide a more comprehensive picture of the patient's glycaemic control. On the other hand, devices using Wi-Fi or Bluetooth may provide a more stable connection and a more reliable data backup and recovery mechanism.

2.5.3.5 Frequency of patient-physician communication and involvement of in-person session

Despite the convenience that comes with remote monitoring, patient-physician communication remains an essential part of T2DM management. Telemonitoring provides means for collecting physiological data but not subjective feedback. The feelings and concerns of a patient, which are crucial for medication titration, treatment adjustment, and patient compliance, can only be obtained by direct patient-physician communication (271). Good patient-physician communication predicts better T2DM self-care and overall clinical outcomes (271). Therefore, the frequency a patient interacts with their healthcare provider during the course of telemonitoring intervention may pose an impact to the effectiveness of the intervention. The advancements in technology allow such communications to be made either in-person or remotely via an online platform, both ways are seen in different telemonitoring interventions. The traditional face-to-face consultation could be a disadvantage since one of the main advantages of telemonitoring is that it overcomes geographical barriers and facilitates remote access to healthcare for those who would otherwise struggle, such as people who lives remotely or have mobility issues (90). Nonetheless, in-person consultation still holds multiple benefits like being able to perform physical examination and take formal blood tests. It is difficult to determine, with the available literature, whether one way is better than the other.

2.5.3.6 Incorporation of abnormality alert and third-party

An abnormality alarm is a feature used by some systems where an alert is generated and sent to family members or healthcare teams when an abnormal result has been recorded, such as a low blood glucose level. This feature facilitates timely intervention and treatment adjustment in response to inadequately controlled blood glucose, which reduces the risk of further deterioration (272). A third party that is neither a patient nor a healthcare provider may be involved in the telemonitoring system, mainly as an information relay centre. Although a third party can assist in organising the collected data and screen for false alarms where an abnormality alert is incorporated, it may cause delays in communication and the delivery of information.

2.5.3.7 Other technical features

As the technologies continue to develop, telemonitoring platforms that are integrated with wearable devices, such as continuous glucose monitors or fitness trackers, can provide a continuous stream of blood glucose data, which offers a more comprehensive view of the patient's glycaemic control pattern. Integration of telemonitoring systems into electronic health records can also greatly improve healthcare provider's access to the patient's monitoring data, leading to more informed decision-making. In addition, as several ethnic minorities are at higher risk of developing T2DM and DRC, systems that are adaptable to different languages and cultural contexts can enhance effective communication and engagement among diverse patient populations (264).

2.5.4 Baseline patient characteristics in telemonitoring

As a system that is heavily dependent on the patient's participation, different patient attributes and disease factors may interact with telemonitoring intervention, shaping its impact on glycaemic control in patients with T2DM.

2.5.4.1 Age and disease severity

Older patients may face challenges and find it difficult to adopt new technology like telemonitoring, which could impact the accuracy of the data collected as well as their adherence to the intervention. Whereas the younger cohort may have better technology literacy and find new technologies more intuitive and more engaged, potentially leading to better results. Moreover, older patients are more likely to have long-standing T2DM, its associated DRC, and other health conditions, which require more intricate treatment regimens (273). Telemonitoring could be particularly beneficial in such patients by providing more personalised care and the ability to collect and integrate data from multiple physiological parameters. It is anticipated that the effect of telemonitoring may appear more significant in patients with high baseline T2DM severity as there is greater room for improvement, leading to more noticeable positive outcomes. Furthermore, older patients may have a more profound understanding of their condition and are more experienced in self-care and self-management than their younger counterparts (273).

2.5.4.2 Motivation, self-management and frequency of self-measurement

Patients who are motivated and have strong self-management skills are more likely to utilise telemonitoring effectively. They may show better adherence to recommendations and make necessary adjustments based on the data collected. The frequency of self-measurement reflects the patient's level of engagement and motivation, which significantly affect their adaptation to lifestyle modifications and adherence to treatments (274). In addition, more frequent measurements promote self-awareness by providing patients with a better idea of their disease progression and the effect of current treatment. This circles back to the idea that the benefits of telemonitoring are dependent on the user's motivation and self-care behaviours since the patient themselves are responsible for the majority of the monitoring tasks.

2.5.4.3 Other patient characteristics

A patient's socioeconomic status, cultural background, and social support may all play a role in determining the effectiveness of telemonitoring. Not only does an individual's socioeconomic status affect their access to technology and healthcare resources, but also their ability to afford diet changes and take the time to exercise (275). While cultural sensitivity was discussed as a technical feature with potential impact on telemonitoring's effectiveness, an individual's cultural beliefs and practices can also impact how patients engage with healthcare interventions such as telemonitoring. Lastly, the amount of support available for a patient is likely to have an impact on the effectiveness of telemonitoring as sufficient support can mitigate many of the issues mentioned above, including difficulties with technologies and behavioural changes (58).

2.5.5 Education program in telemonitoring

A structured interactive educational component has been shown to enhance the effectiveness of telemonitoring in the management of other chronic diseases such as HF and COPD (101, 276). Although the approach varied from study to study, most telemonitoring systems included some form of patient education before or during the intervention. This can range from general disease knowledge, disease management advice, diet and exercise instructions, action plans, warning signs and symptoms, telemonitoring system education, and training to use the measuring devices (101). On the other hand, several studies that showed no positive effect from the use of telemonitoring provided no patient education, where participants were required to simply monitor symptoms and the chosen parameters (257, 277-279). It has also been reported that the beneficial effect of telemonitoring intervention was only seen in patients who participated in at least 25% of the structured education sessions (260).

The clinical outcomes appear to be improved by active patient involvement through education or skill delivery to support coping with the disease (280). This mediating effect might be due to the fact that telemonitoring is dependent on behavioural change in the patient and healthcare provider. The use of telemonitoring to deliver patient education has been reported to empower patients by providing them with greater insight and the tools to manage their illness (281). Therefore, it is important for patients to adhere to the telemonitoring instructions and for healthcare professionals to utilise the telemonitoring data appropriately in their management. Studies on home-based exercise therapy have shown that patient education delivered in the form of automated feedback can also improve long-term adherence (282). In addition, better self-management can improve lifestyle modification and treatment adherence, which could also explain the greater effectiveness of telemonitoring seen with associated patient education component (101).

2.6 Gaps and limitations of existing research

Despite a growing body of evidence suggesting that telemonitoring has the potential to enhance patient care, reduce healthcare costs and improve overall disease management through real-time remote data collection and timely intervention, there remain notable gaps in the current literature that warrant further investigation. Numerous studies have highlighted the positive impact of telemonitoring in various chronic diseases, but several key aspects have not yet been thoroughly explored.

Regarding the use of telemonitoring in T2DM management, the most prominent gap is the lack of high-quality, conclusive evidence on its effectiveness in terms of glycaemic control. Although many recent trials have been published, existing reviews on this topic are largely outdated and have included a very limited number of primary studies. Given that telemonitoring is a rapidly emerging field with new trials being conducted on a regular basis, there is a need for new evidence to be synthesised based on updated, contemporary data.

Another significant research gap revolves around the methodological variations among telemonitoring studies. Many existing articles have slightly different approaches when implementing the telemonitoring intervention, such as different durations, methods of data transmission, parameters monitored and the incorporation of abnormality alarm. As an intervention that greatly depends on patient engagement, minor variations in these technical features may have an impact on the practicality and user-friendliness, causing much more significant changes in the overall effectiveness. Therefore, it is important to assess the performance of telemonitoring based on various technical features across the study, in order to develop an optimal protocol for future research and clinical implementation.

Another area where research is lacking is the impact of telemonitoring on specific subpopulations within the T2DM patient cohort. As previously elucidated, T2DM management is complex and can vary based on factors such as age, sex, disease severity, socioeconomic status, comorbidities, and cultural background. Research studies often do not adequately represent the diversity within the T2DM population. There is a need for studies that assess how telemonitoring interventions may differ in their effectiveness across these different subgroups. For example, older adults may have unique challenges in using telemonitoring technologies, and individuals at different stages of their disease may respond differently to remote interventions.

Lastly, as a key aspect of T2DM management, patient education encompasses understanding the disease, its complications, self-care practices, and the importance of lifestyle modifications. However, the literature often provides limited insight into how educational content is integrated into telemonitoring platforms and how it influences patient outcomes. While telemonitoring facilitates the timely exchange of data between patients and healthcare providers, the effectiveness of these interventions could be significantly enhanced by incorporating tailored educational content. The diverse range of telemonitoring technologies and platforms available makes it challenging to compare results across studies, as educational strategies may differ substantially in their delivery methods and content. However, comprehensive evidence exploring the general impact of the educational component within telemonitoring could provide valuable insight into whether tailored educational content can enhance the impact of telemonitoring, improving patient engagement, self-care behaviours, and ultimately, the long-term outcomes of individuals with T2DM.

Overall, while there is growing evidence supporting the potential benefits of telemonitoring in the management of T2DM, several research gaps persist. This study can help filling the current gap and clearing up part of the ambiguity by evaluating a greater number of recent studies, providing high-level evidence using systematic review and meta-analysis method, while addressing the role of various technical features, patient factors and education component of telemonitoring in the management of T2DM. This study will provide a more comprehensive understanding of the role of telemonitoring in T2DM management and inform the development of effective, patient-centered interventions that can enhance the quality of care and outcomes for individuals with T2DM.

Chapter 3. Methodology

The aims and objectives, research questions, hypotheses and conceptual framework will be described in this chapter. Secondary data analysis was performed based on the cross-sectional data collected from 19 suburbs in Changshu, China as part of the investigation on the association between treatment adherence and glycaemic control. A keyword search was conducted across seven databases to identify articles that were included in the systematic review and meta-analysis that concludes the overall efficacy of telemonitoring on glycaemic control. The research design of the secondary data analysis and the systematic review and meta-analysis will also be detailed in this chapter.

3.1 Aims and objectives

This study aims to conduct secondary data analysis and a systematic review and meta-analysis to provide high-level evidence on the effectiveness of telemonitoring on glycaemic control in people with T2DM with a particular focus on the impact of various methodological approaches.

The study objectives are to:

1) Describe the demographics and treatment adherence pattern in a large T2DM population consisting of both metropolitan and rural populations.
2) Describe the relationship between treatment adherence and glycaemic control
3) Conduct a database search to identify evidence on the effectiveness of telemonitoring on glycaemic control in patients with T2DM
4) Conduct meta-analysis to determine the effectiveness of telemonitoring on glycaemic control in patients with T2DM

5) Conduct subgroup analysis to determine the impact of various technical features of telemonitoring, patient factors and incorporation of education programs on the effectiveness of telemonitoring.

3.2 Research questions

1) Is there an association between better treatment adherence and better glycaemic control in patients with T2DM?
2) Is there an association between the use of telemonitoring and better glycaemic control in patients with T2DM?
3) Is there an association between various technical features of telemonitoring, patient factors and incorporation of education programs in the delivery of telemonitoring and the ultimate effect on glycaemic control?

3.3 Hypotheses

Alternative hypothesis 1: Treatment adherence is associated with better glycaemic control as shown by better HbA1c and FBG in patients with T2DM.

Null hypothesis 1: Treatment adherence is not associated with better glycaemic control as shown by better HbA1c and FBG in patients with T2DM.

Alternative hypothesis 2: Telemonitoring is associated with better glycaemic control as shown by better HbA1c and FBG in patients with T2DM.

Null hypothesis 2: Telemonitoring is not associated with better glycaemic control as shown by better HbA1c and FBG in patients with T2DM.

Alternative hypothesis 3: The effect of telemonitoring on glycaemic control in patients with T2DM is impacted by the technical features, patient characteristics and the use of education programs.

Null hypothesis 3: The effect of telemonitoring on glycaemic control in patients with T2DM is not impacted by the technical features, patient characteristics and the use of education programs.

3.4 Conceptual framework

Figure 2 shows the conceptual framework of this study. It demonstrates the interactions and relationships among the variables concerned. As mentioned above, telemonitoring is associated with a range of effects including better treatment adherence, easier and more efficient access to healthcare, better patient engagement and motivation, and at a reduced cost. These mediating factors allow telemonitoring to indirectly affect the patient's glycaemic control and other metabolic health measures such as HbA1c, FBG, BMI, cholesterol and blood pressure, which ultimately contribute to the overall T2DM disease progression and the development of DRC. As a relatively new technique with limited evidence, there is no internationally standardised approach in using telemonitoring. With the large methodological variation that exists in the current literature, especially on the technical specification of telemonitoring and the baseline characteristics of sample population, they may confound the effect of telemonitoring and its overall usefulness. In addition, as part of the secondary data analysis, age, sex, education level, income level, and rural residency were also taken into consideration when determining how one of the most important mediating factors, treatment adherence, is associated with glycaemic control. T2DM can develop at any stage of adulthood and its progression may differ with age and sex (2). An individual's income and education level serve as a rough reflection of their socioeconomic status, which determines how the individual perceives the disease, its treatments, and its complications and whether they have sufficient resources to support their management

(283). Finally, residency in urban or rural settings plays a role in deciding an individual's lifestyle, income and education level, and access to healthcare (284).

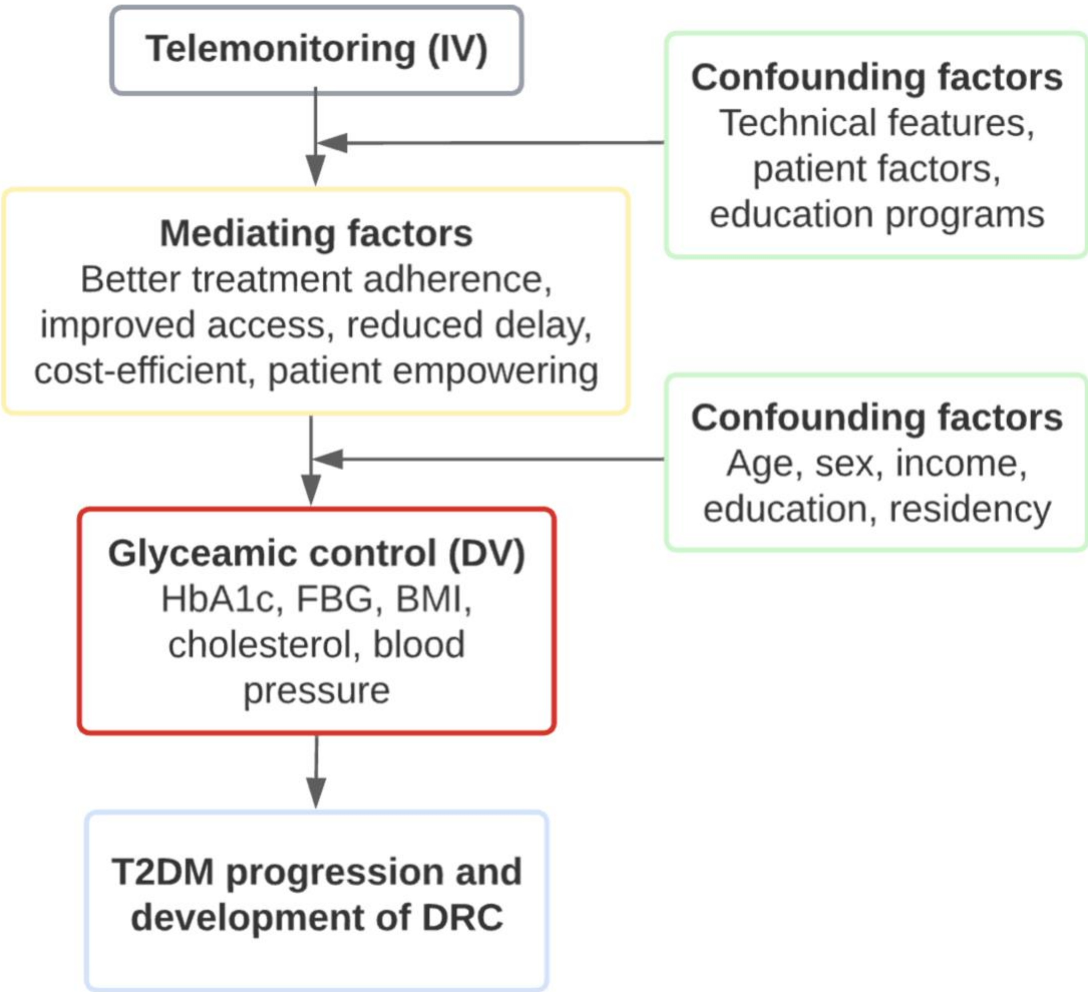

Figure 2. Conceptual framework the relationship between telemonitoring and glycaemic control through mediating factors, as well as the impact of confounding factors.

3.5 Research design

1) Firstly, the study analysed cross-sectional data collected from 10,246 patients with T2DM from Changshu, China. This design allows for the investigation of the direct association between treatment adherence and glycaemic control.
2) Secondly, a systematic review and meta-analysis was conducted across the major databases. This design supports the exploration of the effectiveness of

telemonitoring on glycaemic control in patients with T2DM, while allowing for the subgroup analysis to determine the impact of various technical features of telemonitoring, patient characteristics and education programs on the effectiveness of telemonitoring.

3.6 Secondary data analysis

3.6.1 Participant selection and data collection

The participants involved in the secondary data analysis were adult T2DM patients from Changshu, China. Cross-sectional data was collected using a mixture of self-reported questionnaires, clinical assessments, and laboratory tests.

The sampling method was one-stage random sampling. A random selection of 50% of the districts in Changshu City was conducted first. Invitations were then sent out to all adults aged 18 years and older within the selected districts who were diagnosed with T2DM and monitored by community physicians to participate in completing the laboratory tests and survey questionnaire.

3.6.2 Outcome variables

A comparative cross-sectional design was used in this study, where data on the demographics, treatment adherence, and biochemical markers of participants were collected. In order to assess the patient's glycaemic control and general metabolic health, the dependent variables were selected to be HbA1c, FBG, total cholesterol (TC), systolic blood pressure (SBP) and diastolic blood pressure (DBP). HbA1c and FBG levels provide objective measures of both long-term and short-term glycaemic control. On the other hand, TC, SBP and DBP are important markers in metabolic syndrome, as well as predictors of the development of major diabetes-related micro- and macrovascular complications.

The degree of treatment adherence, which is considered as the independent variable, is demonstrated through adherence to self-measurement of blood glucose (SMBG), smoking and alcohol cessation, diet, physical activities, and prescribed medications. Regular SMBG gathers information about the patient's disease status, risk of complications, and response to treatments, which plays a vital role in planning the overall disease management for the patient (285). In terms of lifestyle factors, cigarette smoking and alcohol are both detrimental to general health and therefore, complete cessation is usually recommended to all patients. The promotion of healthy behaviours is also important in T2DM management, such as a healthy diet and regular physical exercise, which are crucial components of managing patients with chronic illnesses, particularly those with metabolic disorders like T2DM (286). Pharmacological treatment is a mainstay of T2DM management and therefore, adherence to medications is a major factor that needs to be considered when evaluating the overall treatment adherence.

The age, gender, income, education, and place of residence of participants were all taken into consideration as confounding variables. These factors and the socioeconomic status reflected by them can significantly influence the participant's lifestyle and baseline biochemical parameters, as well as their access to resources, understanding of the disease, and ability to afford treatments.

3.6.3 Statistical analysis

The demographics of the participants, treatment adherence and biochemical outcomes are described using descriptive statistics with frequencies, means and standard deviations (SD). Multivariate analysis of variance (MANOVA) was used to explore the impact of treatment adherence on the biochemical measurements of participants. The significance level (alpha level) for the MANOVA test was set to be 0.05. univariate analysis was conducted in cases where statistical significance was found ($p<0.05$) to determine which biochemical measurement was contributing to the group difference, testing the hypotheses of whether better treatment adherence is associated with improved glycaemic control and metabolic health.

3.7 Systematic review and meta-analysis

3.7.1 Search strategy

The protocol of this review was registered at Prospero (registration ID: CRD42021265979). The database search was conducted in PubMed, MEDLINE, EMBASE, Web of Science, the Cochrane Library (Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Cochrane Methodology Register), Scopus, and PsycINFO. The keywords used were: (type-2-Diabet* OR T2DM) AND (telemonitor* OR remote-monitor* OR home-monitor*) AND (glycaemic OR glycemic OR HbA1c OR glucose OR blood-sugar OR insulin-resistance OR HOMA-IR) AND ("clinical trials" OR "clinical trials as a topic" OR "randomized controlled trial" OR "Randomized Controlled Trials as Topic" OR "controlled clinical trial" OR "Controlled Clinical Trials as Topic" OR "random allocation" OR "randomly allocated" OR "allocated randomly" OR "Double-Blind Method" OR "Single-Blind Method" OR "Cross-Over Studies" OR "Placebos" OR "cross-over trial" OR "single blind" OR "double blind" OR "factorial design" OR "factorial trial"). A manual search was conducted on the bibliographies of relevant review articles for additional references.

3.7.2 Inclusion criteria

1) Participants must be at least 18 years old and diagnosed with T2DM, with no concurrent serious illness other than T2DM and its complications.
2) The study must be a randomised controlled trial published within the last 20 years.
3) The intervention group must be treated by a healthcare professional using the telemonitoring approach where physiological data of the patient are remotely transmitted to the treating team on a regular basis using information technology.
4) The control group must be any form of standard T2DM care with in-person consultations being the mainstay of care delivery.
5) The outcomes of interest must include at least one of HbA1c, FBG, or BMI.
6) The article must be written in English.

3.7.3 Study selection

Study selection was done through a three-step process once the search was completed. Firstly, the search results were merged using EndNote to identify and remove duplicates. Secondly, the title and abstract of all articles were independently screened by two reviewers where the obviously irrelevant articles were excluded. Finally, the full text of the remaining articles was retrieved and assessed by two independent reviewers against the pre-defined eligibility criteria. In cases of discrepancy between the two reviewers, a third reviewer was invited to resolve the disagreement.

Articles that passed the three-step selection process were assessed for their methodological quality by two independent reviewers using the PEDro scale, which is consisted of 10 items and a score of one was granted for each item satisfied. Studies were categorised into high-quality (>7 points), moderate-quality (4 – 7 points), or low-quality (<4 points) studies based on the score. Any studies that fell into the low-quality group were excluded.

3.7.4 Data extraction

Data extraction was performed by two independent reviewers. For each study, data was collected on the primary and secondary outcomes of interest, as well as the study's title, year of publication, country, sample size, participant demographics (sex ratio, mean age, disease severity, duration of disease, rural or urban residency), and details of the intervention and control measures. Additionally, data relating to the technical features of the telemonitoring system (mode of data input and data transmission, follow-up duration, parameters monitored, communication method, abnormality alert, frequency of physician communication, and involvement of in-person sessions), patient characteristics (mean age, baseline HbA1c level, insulin requirement, and frequency of self-measurement) and incorporation of patient education programs (general disease education, guidance on physical activity, diet, and self-measuring techniques and skills) were extracted for subgroup analysis.

3.7.5 Outcome measures

HbA1c and FBG are two well-established markers for glycaemic control (29, 287). The tool of choice for tracking long-term glycaemic control is HbA1c, while FBG reflects temporary blood glucose level (33). Significantly higher risks of developing DRC are associated with even a moderately increased BMI (288). Therefore, data on BMI was collected as a secondary outcome measure, which also indirectly reflects the effect that telemonitoring may have on the patient's lifestyle modifications and self-care.

3.7.6 Subgroup criteria

The method of data transmission refers to the means a telemonitoring device utilises to send data to its recipient, and it is divided into Wi-Fi, 4G/5G, or Bluetooth (where the device itself is not connected to the internet and requires an intermediate device, such as a smart phone, to upload data). A core component of telemonitoring revolves around remote patient-physician communication, which is carried out via text-based methods (such as text messages and email), phone calls, or a combination of both. The mode of data input can be either manual, where the measurement data need to be manually entered into the recording system, or automatic, where this step is automatically done by the machine after each measurement. An abnormality alarm is a feature used by some systems where an alert message is automatically generated and sent to the healthcare providers and emergency contacts when an abnormal result has been recorded, such as a dangerously low blood glucose level.

Patient education programs are often incorporated into the telemonitoring systems. This includes any form of education or guidance delivered to patients during or just prior to the telemonitoring intervention. The patient education programs can be categorised, based on the topics covered, into general disease education, physical exercise, diet, and self-measuring skills and techniques, each leading to its own subgroup analysis.

3.7.7 Statistical analysis

The effect size and mean difference (MD) for primary and secondary outcomes were analysed using random effects models. I^2 was used to assess for heterogeneity of the studies with a statistical significance set to $p<0.05$. A high level of heterogeneity is indicated by an I^2 value of more than 50%, warranting further subgroup analysis to identify the source of heterogeneity. Egger regression analysis was used to assess for publication bias, again with statistical significance set to $p<0.05$. In cases of significant publication bias, further sensitivity analysis would be conducted to identify whether the publication bias was due to any particular study.

Chapter 4. Results

This chapter outlines the results from the secondary data analysis and the systematic review and meta-analysis. It will be divided into two sections accordingly. Patient demographics, descriptive statistics of treatment adherence and glycaemic control, MANOVA and associated univariate tests will be presented in the section for the secondary analysis of the T2DM patients from Changshu, China. The second section, which is for the systematic review and meta-analysis, will present the characteristics of the included studies, the forest plots showing telemonitoring's efficacy on glycaemic control, as well as the subgroup analysis investigating the impact of technical features and patient factors on telemonitoring's efficacy.

4.1 Secondary data analysis

4.1.1 Participant characteristics

A total of 10246 patients were included in this study. As illustrated in Table 1, the mean age was 64.1±9.5 years old, with more females (59.4%) than males (40.6%). Over half (55.6%) of the sample population had not attended or completed primary school level of study, while those with high school level of education and above only represented 8.1% of the sample population. Most participants had an annual household income between ¥40,000 and ¥109,999 (54.6%), which is approximately equivalent to US$6,500-17,880 at the time of data collection. Furthermore, there were more participants living in urban settings (56.0%) as opposed to a rural setting (44.0%).

Table 1. General characteristics of the study sample

	N	(%)
Age (mean±SD)	64.1±9.5	
Gender		
Male	4157	(40.6%)
Female	6089	(59.4%)
Education level		
No formal education	3403	(33.2%)
Did not finish primary school	2292	(22.4%)
Primary school	1824	(17.8%)
Middle school	1907	(18.6%)
High school	644	(6.3%)
Certificate/Diploma	133	(1.3%)
Bachelor degree	36	(0.4%)
Master degree and above	1	(0.1%)
Annual household income		
<¥10,000	719	(7.0%)
¥10,000-39,999	1612	(15.7%)
¥40,000-109,999	5594	(54.6%)
¥110,000-159,999	1618	(15.8%)
¥160,000-200,000	405	(4.0%)
>¥200,000	259	(2.5%)
Residency		
Urban	5733	(56.0%)
Rural	4513	(44.0%)

4.1.2 Treatment adherence

Pattern of treatment adherence is demonstrated in Table 2. A total of 9945 participants reported on their adherence to SMBG, of which 83.2% reported consistent self-measurement routine. There were 2282 and 1831 responses about adherence to smoking and alcohol cessation, where 29.0% and 23.2% of respondents reported achieving complete cessation, respectively. Most participants reported on their adherence to healthy diet (n=9987) and physical exercise (n=10069), where 73.8% and 31.7% of respondents reported good adherence, respectively. Out of the 9388 participants who self-reported on medication adherence, 88.4% of them were compliant with their medication dosage and frequency as prescribed by their healthcare professional.

[Table 2: see Appendices]

4.1.3 MANOVA results

Table 3 and 4 confirms that the assumptions for using MANOVA were met. The dependent variables are shown to have normal distribution as demonstrated by their skewness and kurtosis values between -3 and 3, and not highly correlated to each other as shown by Pearson correlation less than 0.85, as seen in Table 3. Each independent variable has at least two independent categorical groups. Lastly, multiple confounding factors were identified as demonstrated in Table 4 where the Analysis of Variance (ANOVA) results show a significant relationship between the confounding factors and the dependent variables.

Table 3. Pearson correlation and normality check among dependent variables

	HbA1c	FBG	TC	SBP	DBP	Skewness	Kurtosis
HbA1c	1					1.28	2.26
FBG	0.708	1				1.47	2.47
TC	0.128	0.106	1			1.98	2.41
SBP	0.018	0.022	0.107	1		0.52	0.65
DBP	0.059	0.077	0.081	0.480	1	0.31	1.05

Table 4. ANOVA analysis of confounding factors and dependent variables

	HbA1c F statistic	FBG F statistic	TC F statistic	SBP F statistic	DBP F statistic
Age	5.839***	36.842***	2.155	174.711***	165.012***
Gender	60.395***	33.211***	202.193***	12.343***	345.801***
Education	3.658***	2.569*	6.862***	24.932***	16.285***
Income	1.692	1.517	0.951	9.653***	4.469***
Residency	40.733***	46.991***	0.098	24.105***	17.855***

*p<0.05, **p<0.01, ***p<0.001

MANOVA results from Table 5 showed that a significant relationship is seen between the biochemical measurements and adherence to SMBG (F=8.880, p<0.001, eta-squared=0.026), adherence to smoking cessation (F=4.018, p<0.001, eta-squared=0.009), adherence to alcohol cessation (F=5.350, p<0.001, eta-squared=0.029), adherence to physical exercise (F=2.869, p<0.001, eta-squared=0.003), and medication adherence (F=7.451, p<0.001, eta-squared=0.029). Adherence to diet control did not show any statistical significance (F=1.669, p=0.082).

Table 5. MANOVA general F-test on factors affecting the biochemical readings

Factor	F statistic	P-value	Eta-squared
Adherence to SMBG	8.880	<0.001	0.031
Adherence to smoking cessation	4.018	<0.001	0.009
Adherence to alcohol cessation	5.350	<0.001	0.029
Adherence to diet control	1.669	0.082	0.001
Adherence to physical exercise	2.869	0.002	0.003
Adherence to medication	7.451	<0.001	0.029

4.1.4 Univariate analysis

As demonstrated in Table 6, significant MANOVA results incur univariate analysis to determine which biochemical measurement was showing group difference to which independent variable. Better adherence to SMBG was associated with improvement seen in most measured biochemical parameters including HbA1c (F=35.693, p<0.001), FBG (F=31.813, p<0.001), SBP (F=4.264, p=0.039), and DBP (F=5.101, p=0.024). Better adherence to smoking cessation was associated with better HbA1c (F=10.899, p<0.001), SBP (F=4.940, p=0.007) and DBP (F=4.084, p=0.017). Similarly, a statistically significant relationship was found between better adherence to alcohol cessation and improved TC (F=17.181, p<0.001), SBP (F=7.997, p<0.001) and DBP (F=8.935, p<0.001). Better adherence to physical exercise was associated with improved SBP (F=7.438, p<0.001) and DBP (F=7.823, p<0.001). Lastly, better medication adherence has been linked with better HbA1c (F=25.788, p<0.001), FBG (F=22.976, p<0.001) and TC (F=2.006, p=0.042). The R^2 values at the end of Table 6 represent the proportion of variance of each biochemical measurement explained by adherence to treatment. Overall, the model explains 6.1% of the variance in HbA1c, 7.7% of the variance in FBG, 5.3% of the variance in TC, 7.3% of the variance in SBP, and 12.1% of the variance in DBP.

Table 6. MANOVA univariate analysis

Biochemical measurement	Factor	F statistic	P-value	Eta-squared
HbA1c [a]	Adherence to SMBG	35.693	<0.001	0.026
FBG [b]		31.813	<0.001	0.016
SBP [d]		4.264	0.039	0.005
DBP [e]		5.101	0.024	0.003
HbA1c [a]	Adherence to smoking cessation	10.899	<0.001	0.010
SBP [d]		4.940	0.007	0.004
DBP [e]		4.084	0.017	0.004
TC [c]	Adherence to alcohol cessation	17.181	<0.001	0.019
SBP [d]		7.997	<0.001	0.009
DBP [e]		8.935	<0.001	0.010
SBP [d]	Adherence to physical exercise	7.438	<0.001	0.001
DBP [e]		7.823	<0.001	0.002
HbA1c [a]	Adherence to medication	25.788	<0.001	0.028
FBG [b]		22.976	<0.001	0.024
TC [c]		2.006	0.042	0.002

a R^2 = 0.061, b R^2 = 0.077, c R^2 = 0.053
d R^2 = 0.073, e R^2 = 0.121

4.2 Systematic review and meta-analysis

4.2.1 Inclusion of studies

The initial database search yielded 1,264 potential records, which were merged using Endnote 20 and 259 duplicates were removed. A further 969 studies were excluded after the screening of their title and abstract. The full text of the remaining 36 studies were retrieved and a further 6 studies were excluded after being checked against the eligibility criteria. The reasons for exclusion are as indicated in Figure 2. The 30 articles that passed the selection process were included in this review.

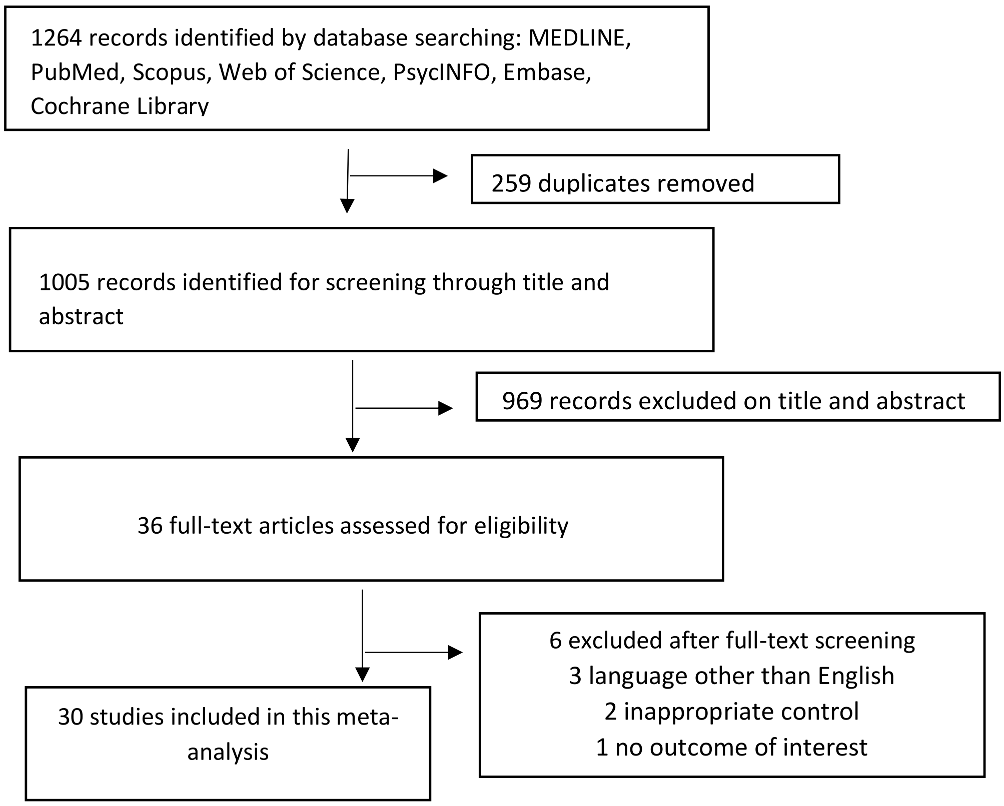

Figure 3. PRISMA flow diagram for study selection in the systematic review and meta-analysis.

4.2.2 Participants and study characteristics

Table 7 shows the characteristics of the included studies. All studies included a total of 4,678 participants, 59.3% of them being male. The mean age was 57.7 years old. The sample size of individual studies ranged from 37 (289) to 430 (290). Among the included studies, 21 of them utilised telemonitoring to monitor more than one parameter (25, 87, 104, 266-268, 289-303). The country where the studies were conducted included the US (25, 87, 266, 267, 300, 304-306), China (298, 303, 307, 308), Malaysia (289, 309, 310), UK (104, 291, 295), South Korea (297, 299, 302), Australia (311), Finland (290), Germany (301), Italy (312), Norway (293), Poland (292), Slovenia (294), Sweden (268) and Thailand (296).

[Table 7: see Appendices]

4.2.3 Outcome Measurement

Data on HbA1c was analysed using the National Glycohemoglobin Standardization Program unit (%). In studies that FBG was reported in mg/dL, conversion to mmol/L was undertaken prior to data analysis.

Table 8. Analysis result of outcome variables

Variables	Studies (n)	Participants (n)	MD (95% CI)	Effect size (95% CI)
HbA1c	26	4333	-0.294 (-0.459, -0.131)***	-0.327 (-0.525, -0.129)***
FBG	10	1415	-0.616 (-1.269, -0.036)	-0.484 (-0.846, -0.122)**
BMI	12	1512	-0.278 (-0.553, -0.003)*	-0.212 (-0.423, 0)*

*p<0.05, **p<0.01, ***p<0.001

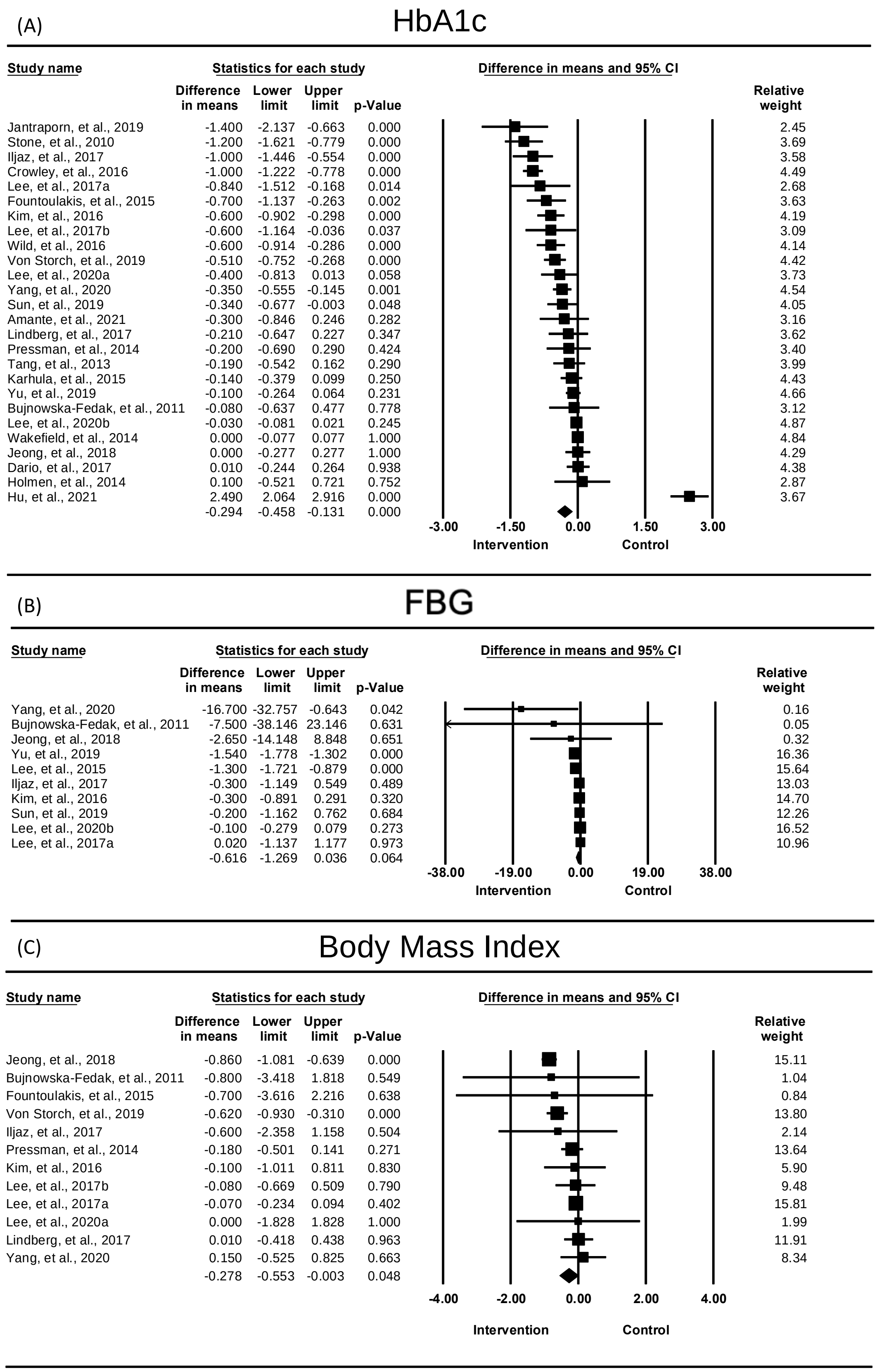

Figure 4. Forrest plots of the random effects model meta-analysis for the comparison between telemonitoring and control group in terms of HbA1c (A), FBG (B) and BMI (C).

4.2.4 HbA1c

A total of 26 studies with 4333 participants measured HbA1c as one of the outcomes (25, 87, 104, 266-268, 290, 292-294, 296-305, 307-312). As demonstrated in Figure 4, participants received telemonitoring intervention achieved significantly lower HbA1c levels in comparison to participants that were managed conventionally in the control groups (MD=-0.294%; 95%CI: -0.458 to -0.131%; $p<0.001$) with a moderate effect size of -0.327 (95%CI: -0.525 to -0.129; $p<0.001$). The heterogeneity was statistically significant (Q=331.76, I^2=92.46%, $p<0.001$).

Table 9 demonstrates the subgroup analysis for HbA1c, which found that telemonitoring resulted in a greater reduction in HbA1c level when more than 1 parameter was monitored (MD=-0.405%; 95%CI: -0.564 to -0.246%; $p<0.001$) and when manual input of self-measurement data was used by the system (MD=-0.413%; 95%CI: -0.627 to -0.198%; $p<0.001$) when compared to their counterparts.

Regarding patient factors, mean age less than 65 years old (MD=-0.206%; 95%CI: -0.321 to -0.091%; $p<0.001$), more frequent SMBG (MD=-0.183%; 95%CI: -0.309 to -0.057%; $p=0.01$), and higher baseline HbA1c level (MD=-0.390%; 95%CI: -0.570 to -0.01%; $p<0.05$) were all associated with greater reduction in HbA1c level. Moreover, the incorporation of general T2DM education was also shown to cause greater reductions in HbA1c (MD=-0.309%; 95%CI: -0.478 to -0.139%; $p<0.001$). The rest of the subgroup analysis did not reveal any significant between-group differences.

[Table 9: see Appendices]

4.2.5 FBG

A total of 10 studies with 1415 participants measured FBG as one of the outcomes (289, 292, 294, 297, 298, 302, 303, 308-310). Collectively, no statistically significant difference was found in the reduction of FBG between telemonitoring intervention and control groups (MD=-0.616 mmol/L; 95%CI: -1.269 to -0.036 mmol/L; p=0.064). The heterogeneity was statistically significant (Q=107.31, I^2=91.61%, p<0.001).

4.2.6 BMI

A total of 12 studies with 1525 participants investigated on BMI (25, 268, 292, 294, 297-302, 310, 311). Participants using telemonitoring had statistically significant difference in the reduction of BMI when compared against control groups (MD=-0.278 kg/m^2; 95%CI: -0.553 to -0.003 kg/m^2; p=0.048) with an effect size of -0.212 (95%CI: -0.423 to 0; p=0.05). The heterogeneity was statistically significant (Q=41.63, I^2=73.58%, p<0.001).

4.2.7 Publication bias

Egger regression test demonstrated minimal publication bias for HbA1c (p=0.072), FBG (p=0.711), and BMI (p=0.718). Therefore, sensitivity analysis was not indicated.

Chapter 5. Discussion

This chapter discusses the findings detailed in the previous chapter. Results from the secondary data analysis and the systematic review and meta-analysis will be interpreted separately and then together. The concordance of the results with the current literature will also be discussed.

5.1 Secondary data analysis

The results of the secondary analysis support the premise that patients with better adherence to their T2DM treatments achieve better glycaemic control and metabolic health than those who are less adherent to treatments. The MANOVA and the subsequent univariate analysis demonstrated that better adherence to SMBG, smoking cessation, alcohol cessation, physical exercise and medications were all associated with improvements in at least three of the five metabolic parameters measured. In particular, better adherence to SMBG was associated with significant improvements in nearly all biochemical parameters measured. Whereas better adherence to a healthy diet was not shown to be associated with significant change in any of the biochemical parameters.

5.1.1 Participant characteristics

A total of 10246 patients are included in the secondary data analysis and their demographics are illustrated in Table 1. All participants are residents of Changshu, which is a county-level city with a population of 1.52 million. The large sample size ensures a good representation of the entire population, which in turn provides a snapshot of the nation's incidence of T2DM. The mean age is 64.1±9.5 years old, with more females (59.4%) than males (40.6%). The age at onset for T2DM is usually over 40 years old but there is a decreasing trend as more young adults and children are affected by unhealthy diets and lack of physical activity (313). Age can have a significant impact on glycaemic control in patients with T2DM through various mechanisms. Firstly, T2DM is a chronic illness that usually progresses over time as both insulin production and tissue's response to insulin decline with age (314). In addition, most DRC are more likely to develop as the individual ages, complicating disease management and making it more difficult to control blood glucose (315). On the other hand, elderly patients often have multiple health conditions that, along with their corresponding medications, may interact with T2DM management and affect glycaemic control. Other age-related changes, such as reduced levels of physical activity and cognitive decline, all play a part in making glycaemic control in the elderly population more challenging. Furthermore, age may also affect treatment adherence. In addition to the challenges described above, elderly patients may have different treatment goals, personal beliefs and other individual variations that can alter their motivation to adhere to T2DM treatments.

Sex may be a confounding factor as well due to the differences in hormonal factors, body fat distribution, and psychosocial differences between males and females (316). Globally, 17.7 million more men than women are diagnosed with DM, as men are usually diagnosed at a younger age and lower BMI than women (134). However, it is important to note that the prevalence of T2DM among sexes can vary by region, ethnicity, culture, lifestyle factors and other variables, as it has been shown that in some populations males and females have similar or near-equal T2DM prevalence (316). For example, certain factors might influence the apparent prevalence, such as that males might be more reluctant to seek medical support and tend to ignore or self-manage the early symptoms of T2DM. At the time of diagnosis, females tend to have a higher risk factor burden, such as excess weight gain and hypertension, and carry higher relative risk of CVD complications and mortality than males with T2DM (317). It has also been reported that women are less likely than men to receive guideline-recommended treatments and risk-reduction therapies (318). Moreover, psychosocial risk factors have a greater impact on women than men (316). Psychiatric disorders such as depression and anxiety can increase the likelihood of an unhealthy lifestyle and reduce patient compliance, since it has been shown that medication adherence is generally lower in women than men with T2DM (316, 319).

More than half (55.6%) of the sample population of this study have either not started or not completed primary school study, while those with high school education and above only represent 8.1% of the cohort. Epidemiological data consistently suggests that those with lower education levels are disproportionately affected by T2DM (320). This association is largely mediated by modifiable risk factors such as unhealthy diet, lack of physical activity, obesity, and other unhealthy lifestyles, which in turn correlate to a higher likelihood of poor glycaemic control and development of DRC (321). Low education level has also been directly associated with higher HbA1c levels (322). Furthermore, low education level often correlates with limited health literacy, leading to difficulty comprehending complex treatment instructions, misunderstanding of treatment effects, and other barriers that may hinder the patient's compliance with treatment recommendations.

The majority of participants had an annual household income between ¥40,000 and ¥109,999 (54.6%), which is approximately equivalent to US$6,500-17,880 at the time of data collection. Consistent evidence has shown that low socioeconomic status is associated with a higher risk of developing T2DM in low-, middle- and high-income countries (320). It can have a significant impact on the management and outcome of patients with T2DM since it directly affects their access to healthcare resources, nutritious food, opportunities for physical exercise, and social support (320). As a result, patients from a lower socioeconomic background are more likely than their counterparts to suffer from poorly controlled T2DM and subsequent DRC (275). On the other hand, lower socioeconomic status also limits the patient's ability to receive treatment and adhere to them as they may not be able to afford medications, medical appointments and other T2DM-related supplies such as glucose monitoring devices and test strips. Such individuals might also have more work and time constraints, making it challenging to attend appointments or take sick leave.

Lastly, there were more participants living in urban areas (56.0%) as opposed to a rural setting (44.0%). Living in a rural area can have both positive and negative impacts as several factors unique to rural environments can influence how individuals manage their T2DM. Although urban populations usually have access to more diverse food options compared to rural residents, they often have more exposure to refined carbohydrates and processed foods, which can contribute to obesity and metabolic disorders (323). Some studies report a minor reduction in overall T2DM-related mortality rate in rural populations compared to urban populations (324-326). On the other hand, data from multiple countries suggest that patients with T2DM who live in rural regions demonstrate poorer health outcomes, lower income and education, and more chronic disease risk factors when compared to their metropolitan counterparts (284, 327). Nonetheless, rural patients have restricted access to medical and allied health services they need for effective T2DM management (328). Therefore, all the factors mentioned above were considered as confounding factors that have an impact on both treatment adherence and glycaemic control in patients with T2DM, and were accounted for during statistical analysis and result synthesis.

5.1.2 Adherence to self-measurement of blood glucose

A total of 9945 participants (97.1%) self-reported on their adherence to SMBG, showing that this is an essential part of T2DM management regardless of the patient's demographics and disease status. The vast majority (83.2%) reported good adherence to SMBG, which is drastically higher than the rate of guideline-directed SMBG adherence reported by other studies investigating similar patient cohorts (329, 330). This difference may be attributed to the fact that good adherence to SMBG in this study is purely based on the patient's subjective assessment, whereas other studies often record the details of the patient's SMBG routine and compare that against guidelines to determine if it meets the standards. A MD of 0.24% in HbA1c level and 0.38 mmol/L in FBG was observed between patients who were adherent to SMBG and those who were not. Regular blood sugar monitoring gathers quality data on the patient's disease progression, risk of complications, and response to treatments, which are critical information for individualising treatments and initiating prompt interventions if the glycaemic control is not satisfactory (331). Regular measurements also enables close blood glucose monitoring throughout sick days so that the patient can recognise when to seek medical attention (331). Moreover, patients with better adherence to SMBG typically have a higher level of motivation and are more involved in their self-care, which in turn providing them with the sense of empowerment and awareness that are likely to contribute to better adherence to other treatments, resulting in better overall outcomes (332).

5.1.3 Adherence to smoking and alcohol use cessation

There were 2282 and 1831 participants who self-reported on their adherence to smoking and alcohol cessation, respectively. Adherence to smoking cessation has been shown to be associated with improved HbA1c in this patient cohort. A relatively large MD of

0.41% in HbA1c was noticed between patients who completely stopped smoking as recommended and patients who made no change to their smoking habits. However, it is worth noting that only 64.4% of the participants self-reported attempting to quit smoking and 29.0% have achieved complete cessation. Smoking not only increases the risk of developing T2DM independently, but it also makes it harder to control T2DM because nicotine raises blood sugar and causes insulin resistance (333). Smoking is also linked to chronic inflammation, which has been repeatedly mentioned in the previous sections regarding its critical role in the pathogenesis of T2DM and DRC. In addition to the general benefits such as better mood, cost savings and improved physical well-being, the long-term benefits of quitting smoking include improved insulin sensitivity and reduced risk of vascular complications in T2DM patients, which is in agreement with the significant decrease in HbA1c observed in this study (333). Given the small proportion of patients who were able to successfully cease smoking and the significant improvement in glycaemic control seen in them, it is reasonable to consider smoking cessation as a focus for health promotion in the T2DM population.

Alcohol consumption, on the other hand, is a direct source of carbohydrates and results in more metabolic disturbances. A total of 1831 participants reported on their adherence to alcohol cessation recommendations. Heavy drinking leads to hypertriglyceridaemia, which explains why participants in this study who continued their drinking habits had elevated TC with a significant MD of 0.46 mmol/L (334). In T2DM patients, it is also linked to hypoglycaemia, ketoacidosis, and ultimately higher mortality from non-cardiovascular causes (334). Nonetheless, less than a quarter (23.2%) of the respondents self-reported that they had completely stopped drinking alcohol. Overall, despite clear evidence on both short- and long-term benefits, only a small portion of patients were able to achieve smoking or alcohol cessation, indicating a need for more targeted, behavioural-directed health intervention that promotes awareness and provides support in this population.

5.1.4 Adherence to a healthy diet and physical exercise

Besides abstaining from harmful behaviours like smoking and alcohol consumption, it is also critical to adopt healthy behaviours as part of a holistic strategy for T2DM management. The Association of Diabetes Care and Education Specialists has identified regular exercise and a balanced, healthy diet as two extremely important self-care practices (335). However, no statistically significant association was found between glycaemic control and adherence to these healthy behaviours in the current study. Dietary control and physical exercise recommendations have been given to almost all participants, as indicated by the high response rates of 97.5% and 98.3%, respectively. Out of the 9987 participants who responded about their adherence to diet control, only 5.1% of them reported making no changes to their diets while the majority of respondents (73.8%) claimed to follow a healthy diet completely, which may help to explain why diet control was not found to be responsible for any improvement in glycaemic control and metabolic health in the current study. A patient's health literacy and their perception of healthy behaviours play an important role in the success of lifestyle modification. With more than half of the respondents having an education level below primary school, it is especially important for healthcare professionals to provide targeted, individualised education on what constitutes a healthy diet and where to look for reliable, evidence-based information. Although the data are based purely on self-reporting, the results at least confirmed that most participants were aware of the need to improve their diet and were making an effort to achieve that.

By utilising the intracellular energy reserves and encouraging glucose transportation, physical exercise contributes to maintaining glucose homeostasis and insulin sensitivity (336). It has also been demonstrated to lower the risk of many DRC such as CVD (336). Despite this, close to half (42.0%) of the respondents reported limited or no physical exercise, which fits into the global picture of rising sedentary lifestyles. The large difference in the adherence to diet control and physical exercise may be explained by the fact that one's diet can be improved quickly as long as one has access to healthy food and are provided with appropriate guidance, whereas committing to physical exercise can be a relatively bigger change as a patient would need to have access to a place for exercise and allocate time in their day that is dedicated to physical activities, which may interrupt their other daily routines. The intensity and frequency of physical exercise are both important (336). Among the rest of the participants who reported engaging in regular or occasional exercise, the intensity of this physical activity was not specified, which may contribute to the lack of a significant improvement in glycaemic control seen in this study.

5.1.5 Medication adherence

Pharmacological treatments and lifestyle modifications are the mainstay of T2DM management. Most medications used to treat T2DM directly interfere with blood glucose levels, which must be kept within a relatively narrow range to prevent potentially dangerous side effects like hypoglycaemia (337). Therefore, adherence to individualised medication regimens is essential. Patients may respond differently to medications, and the dose of many T2DM medications needs to be titrated carefully to achieve optimal effects (67). Thus, manipulating or missing doses can reduce the efficacy of the medications and increase the risk of experiencing side effects. Out of the

9388 participants who responded to this question, most (88.4%) of them took their medication as prescribed, whereas the rest admitted to not adhering to the medication regimens in some form. A study from the US that is also based on patient's self-reporting showed an average medication non-adherence rate of 24.3% across three years (338). A meta-analysis of 10 studies done in Malaysia showed a pooled prevalence of low medication adherence of 34.2% (95% CI 27.4–41.2) (339). It is evident from the literature that adherence to medication varies greatly, likely under the influence of multiple factors such as country, culture, and access to healthcare resources. The importance of medication adherence in the overall management of T2DM has been discussed previously, and the improvement in glycaemic control associated with better medication adherence has been shown repeatedly in the literature as well as by this study (67). Therefore, individualised non-adherence reason-based interventions remain to be an important focus in terms of T2DM management.

5.1.6 Relationship between treatment adherence and blood pressure

Better adherence to SMBG, smoking and alcohol cessation, as well as physical exercise have all demonstrated significant association with improvement in SBP and DBP in this study. The MD of these associations were, however, all under 3 mmHg. Such minor differences are unlikely to result in any changes in the prognosis or clinical outcomes and therefore, their clinical significance is low. Due to vascular remodelling and an increase in body fluid volume brought on by hyperglycaemia and hyperinsulinemia, patients with T2DM frequently experience increased peripheral artery resistance (340). As a result, the changes in blood pressure represent a chronic pathological process and are unlikely to improve as readily as HbA1c and FBG, which could explain the small changes in SBP and DBP observed in this secondary data analysis.

5.1.7 Treatment adherence and telemonitoring

Telemonitoring has emerged as a transformative approach in healthcare, showcasing its potential to significantly improve treatment adherence among patients with chronic diseases. This innovative strategy leverages technology to remotely monitor patient's physiological parameters, facilitating real-time data collection and communication between patients and healthcare providers. A growing body of research has underscored the positive impact of telemonitoring on treatment adherence (265, 341, 342).

Patients with chronic diseases often face multifaceted challenges that can hinder their adherence to treatment plans. Factors such as complex medication regimens, lifestyle adjustments, and the need for ongoing monitoring can lead to non-adherence, compromising the effectiveness of interventions. However, telemonitoring addresses many of these barriers by providing continuous support and engagement. One of the primary mechanisms through which telemonitoring enhances treatment adherence is its ability to provide patients with actionable insights into their condition. By consistently tracking the physiological parameters, such as blood glucose and blood pressure, and sharing this data with patients, telemonitoring empowers individuals with a deeper understanding of how their dietary choices, physical activity, and medication regimens directly impact their health outcomes. This increased awareness helps patients make informed decisions that align with their treatment goals, fostering a sense of responsibility and accountability for their own well-being.

Moreover, telemonitoring bridges geographical barriers, ensuring that patients can access high-quality care regardless of their location. This is particularly significant for those residing in remote or underserved areas, where traditional healthcare facilities might be limited. The convenience of telemonitoring reduces the need for frequent in-person visits, making it more feasible for patients to engage in continuous monitoring without major disruptions to their daily lives. Consequently, treatment adherence becomes less burdensome, translating into better health outcomes.

Behavioural psychology also plays a crucial role in the success of telemonitoring in enhancing adherence. Regular data tracking empowers patients with tangible evidence of their progress, reinforcing positive behaviours and decisions. This data-driven feedback loop encourages patients to make healthier choices, such as adhering to medication schedules, maintaining dietary modifications, and engaging in physical activity. The immediate correlation between their efforts and the recorded outcomes strengthens patients' motivation to stay consistent with their treatment plans. It has been shown that, through reinforcing self-management strategies, patients often benefit from ongoing support in their chronic disease care and achieve better outcomes (343). The surveillance effect from merely being monitored may also play a role in enhancing the patient's treatment adherence pattern (344).

Furthermore, the educational component of telemonitoring equips patients with a deeper understanding of their condition and the rationale behind the recommended treatments. Interactive platforms often provide patients with information, resources, and self-care tips that empower them to actively manage their health. Empowered patients are more likely to adhere to treatment plans because they comprehend the significance of each component and how it contributes to their overall well-being.

5.2 Systematic review and meta-analysis

5.2.1 Characteristics of included studies

A total of 4,678 participants were included, with 59.3% being male and a mean age of 57.7 years old. The sample size of individual studies ranged from 37 (289) to 430 (290).

Of the 30 studies, 21 utilised telemonitoring to monitor more than one parameter (25, 87, 104, 266-268, 289-303). As expected, blood glucose is the most commonly measured parameter across the included studies. Other parameters measured include BP, body weight, BMI, waist circumference, lipid profile, and hypoglycaemic events. Studies were conducted in the US (25, 87, 266, 267, 300, 304-306), China (298, 303, 307, 308), Malaysia (289, 309, 310), UK (104, 291, 295), South Korea (297, 299, 302), Australia (311), Finland (290), Germany (301), Italy (312), Norway (293), Poland (292), Slovenia (294), Sweden (268) and Thailand (296). Most of the included studies have allocated a similar number of patients to the control and intervention groups, with a comparable male-to-female ratio. The studies included are from both developing and developed countries across Asia, Europe and North America.

5.2.2 Effectiveness of telemonitoring on HbA1c, FBG and BMI

The results confirmed that telemonitoring intervention leads to better glycaemic control, reflected in greater reductions of HbA1c. This finding is consistent with those of previously published studies (24, 309, 345, 346). It was also evident that telemonitoring intervention is associated with a greater reduction in BMI when compared with control groups. The subgroup analysis demonstrated that the effect of telemonitoring on HbA1c was influenced by several technical features of telemonitoring, patient factors, and incorporation of patient education programs.

A reduction in HbA1c by as little as 0.2% can significantly lower the risk of developing micro- and macrovascular complications, reducing the all-cause mortality by up to 10% (347). The MD in HbA1c reduction of 0.3% from this study with the use of a telemonitoring intervention is therefore considered clinically significant.

5.2.3 The impact of technical features of telemonitoring

The complex disease course of T2DM affects a number of organ systems, exerting effect on vision, blood pressure, body weight and so on (269). Therefore, monitoring multiple parameters simultaneously can provide a more comprehensive picture of disease progression and better inform relevant decision-making, resulting in more effective glycaemic control in contrast to monitoring blood glucose alone. Results also showed that patients who had to manually input their measurement data achieved better glycaemic control than those who had their measurements uploaded automatically. Patients may be more engaged in their own care as a result of more active interaction with the telemonitoring devices and systems, leading to better adherence to interventions and ultimately better outcomes. Although not demonstrated in our results, patients who interacted with healthcare providers through phone calls in another study showed a higher level of engagement and participation in their health management and self-care than those who received text-based communications (270). In terms of the mode of data transmission, it was expected that devices utilising the 4G/5G networks would grant patients more freedom in self-measurement given they are not restricted by the need for a Wi-Fi modem or Bluetooth-paired terminal nearby, allowing them to conduct self-measurement on various occasions such as during exercise or at social events. However, results from the current study did not show any significant difference among the different modes of data transmission. It is possible that the impact of different modes of data transmission is attenuated by the high prevalence of Wi-Fi coverage in public spaces nowadays and portable Bluetooth devices. Most included studies had a telemonitoring intervention duration of around 6 months, making it difficult to investigate the long-term effect on glycaemic control. The benefits of telemonitoring were expected to be more pronounced over time as patients become accustomed to the use of this technology and able to provide more accurate measurements. On the other hand, a prolonged intervention program may also suppress participation as patients feel exhausted or their autonomy compromised. Therefore, more long-term studies are needed to provide conclusive evidence on this.

5.2.4 The impact of patient factors

The HbA1c level was found to be better in patients with more frequent self-measurement in comparison to those with less frequent self-measurement. This may again relate to a patient's level of engagement and motivation, which is reflected through their self-management behaviours such as self-measurement (274). More frequent self-measurements can also promote self-awareness by providing patients with a better idea of their disease progression and the effect of current treatment. This finding implies that the benefits of telemonitoring are dependent on its user since patient themselves are responsible for the majority of the monitoring tasks. The younger patient cohort achieved significantly better results with telemonitoring. This was somewhat expected as the older adults are more likely to have long-standing T2DM and associated comorbidities, and they may find it harder to adopt new technologies when compared to their younger counterparts (273). Baseline disease severity was reflected by the HbA1c level. It was shown that patients with higher baseline disease severity had greater HbA1c reduction after telemonitoring intervention, which is in agreement with findings of previous studies (348, 349). This may be explained by the more extensive and frequent management required by patients with more advanced disease, which will benefit more from the improved healthcare access facilitated by telemonitoring. The impact of the complexity of a patient's T2DM management may be something to be explored in future studies on telemonitoring.

5.2.5 The impact of incorporated education programs

Active patient involvement through education or skills delivery to support coping with the disease seems to improve the outcomes. A reason for this mediating effect might be that telemonitoring is dependent on behavioural change in the patient and healthcare provider. It is important for patients to follow the monitoring instructions and for healthcare providers to use the results of the monitoring in their management, and using telehealth to deliver education can empower patients by giving them greater insight and the tools to manage their disease (281). Bonnevie et al. showed that interventions with automated feedback, representing a form of patient education, improved long-term adherence to home-based exercise therapy (282). Enhanced self-management can improve physical activity, avoidance and medication adherence. This could explain the greater effectiveness of telemonitoring programs with an educational component.

The Association of Diabetes Care and Education Specialists 7 Self-Care Behaviors (ADCES7) identifies essential behaviours for managing diabetes that include monitoring, being active, healthy eating, risk reduction, healthy coping, problem solving and taking medications (335). Most included studies have incorporated patient education components on at least one element described by the ADCE7 into their telemonitoring intervention. The subgroup analysis demonstrated a greater reduction in HbA1c from telemonitoring with the incorporation of general T2DM education programs. This is in line with the literature as patients who have a more thorough understanding of their condition are more likely to engage in healthy behaviours and avoid things that may be detrimental to their condition (350). However, we have not found any particular element or education topic to be superior to others in terms of glycaemic control. Previous studies focusing on self-measurement in patients with

T2DM have also found that no greater reduction of HbA1c was seen when more education topics were delivered simultaneously as patients may be overwhelmed by the additional management tasks (351, 352). Future studies may consider investigating on the individualisation of education topics incorporated in the education program and how it may be optimised based on the patient's level of self-care.

Chapter 6 Strengths, limitations, implications and recommendations

The strengths and limitations of the study will be discussed in this section, along with directions for future research to be conducted based on the results of the current study. The implications and recommendations regarding the use of telemonitoring in patients with T2DM derived from the results will also be discussed.

6.1 Strengths

Collectively, the secondary data analysis and the systematic review and meta-analysis add novel knowledge to the field and fill important gaps in the current literature. They have several advantages. A large study sample consisting of 10246 participants was used in the secondary data analysis, while 30 high-quality studies with a total sample size of 4,678 participants were included in the systematic review and meta-analysis as a result of a more extensive and rigorous literature search. Few studies have investigated the impact of each specific aspect of treatment adherence like in this secondary data analysis. Our subgroup analysis from the systematic review and meta-analysis also yielded novel findings including the influence of technical features, patient factors and patient education on the effectiveness of telemonitoring in glycaemic control, which has not been studied by any previous systematic review and meta-analysis.

6.2 Limitations

6.2.1 Secondary data analysis

The secondary data analysis has a few limitations that need to be acknowledged. Firstly, the accuracy of the self-reported treatment adherence may vary depending on the participant’s knowledge and awareness, given it is entirely based on subjective selfassessment. Secondly, the severity of T2DM and its comorbidities that may affect glycaemic control and metabolic health were not accounted for in the data analysis. Lastly, the data was gathered between 2013 and 2015, so it may not be an accurate reflection of the current situation.

6.2.2 Systematic review and meta-analysis

Several limitations of the systematic review and meta-analysis should also be noted. Firstly, high heterogeneity was seen across most outcome variables. This is believed to be due to the large methodological variations that exist in the telemonitoring interventions used in different studies. The conventional care received by the control groups among studies may also differ based on each country's own guidelines. Furthermore, variations were also evident in participant demographics and recruitment criteria. Secondly, a between-study, rather than within-study, approach was used for the subgroup analysis. Thirdly, other informative outcome variables such as insulin resistance, quality of life, and self-efficacy were not analysed in this study due to insufficient data. Lastly, despite a thorough database search being conducted, relevant studies written in other languages may have been overlooked as the search was limited to English only.

6.3 Implications and recommendations

The findings from this study have important implications in terms of T2DM management. Firstly, the findings of this study demonstrate the value of behaviour-directed interventions aimed at improving treatment adherence among T2DM patients, which should be an integral part of T2DM care. Healthcare professionals need to take a patient-centred approach that addresses the individual needs and preferences of patients and provides tailored interventions to enhance treatment adherence. Such interventions could be in the form of motivational support, more frequent consultation, or assistance with medication and self-monitoring, which can be done through telemonitoring. The pooled results of the systematic review and meta-analysis showed that telemonitoring has a positive effect on glycaemic control in patients with T2DM, as demonstrated by reduced HbA1c levels in comparison to conventional care. This finding provides evidence to support telemonitoring's integration into clinical practice where it can facilitate better healthcare accessibility, informed decision-making, timely interventions, and a wide range of other benefits that were discussed in the previous sections. This finding also opens up more opportunities for research and innovations to promote continuous advancement and refinement of telemonitoring technologies and strategies. More evidence is needed on the nuances of this relatively new management approach to support establishing a standardised telemonitoring intervention that may be used on a larger scale. The role of multiple technical features and patient factors has already been discussed in this study. The remaining research gaps are also discussed at the end of this section.

In addition to providing evidence that telemonitoring is effective in improving glycaemic control in patients with T2DM, the results also provide important knowledge on the specifics of telemonitoring and patient selection to optimise its efficacy. T2DM management is influenced by a combination of factors, including diet, physical activity, medication adherence, stress, and sleep quality. Monitoring multiple parameters provides a holistic view of a patient's overall health, it also helps identify patterns and trends that might not be evident by monitoring a single parameter. This allows healthcare providers to identify potential contributors to glycaemic fluctuations and tailor treatment interventions accordingly. When healthcare providers have a comprehensive dataset, they can make well-informed decisions about adjustments to medication regimens, lifestyle changes, and other interventions. This data-driven approach enhances the precision of T2DM management strategies. Healthcare providers should shift from a singular focus on blood glucose levels to a more comprehensive approach that addresses the interconnected nature of various health factors. This approach will enhance the effectiveness of telemonitoring, leading to more personalised and targeted interventions with improved glycaemic control, reduced risk of complications, and enhanced overall well-being for individuals with T2DM. Additionally, patients will be empowered with a deeper understanding of their health, enabling them to actively participate in managing their condition and making informed decisions about their lifestyle choices.

Manually inputting self-measured data by patients themselves can offer several advantages in comparison to automated data input. This process can lead to more accurate, comprehensive, and contextual data, which can have transformative effects on T2DM management on a larger scale. Firstly, manual data input allows patients to provide additional contextual information that automated devices might miss, such as details about their diet, stress levels, medication changes, and other factors that influence blood glucose fluctuations. This added context aids healthcare providers in making more informed decisions and adjustments to treatment plans. Secondly, patient engagement is enhanced through manual input. Actively participating in data recording fosters a sense of ownership and accountability, encouraging patients to become more invested in their disease management. This engagement is particularly crucial in chronic conditions like T2DM, where self-management plays a significant role. Thirdly, manual input promotes patient education and understanding of how various factors affect their blood glucose levels. By requiring them to manually input data, patients learn about the relationships between their actions, diet, physical activity, and blood sugar levels. This educational component empowers patients to make informed choices and empowers them to manage their T2DM more effectively. Lastly, the personal touch of manual data input reinforces the patient-physician relationship. When healthcare providers see patients taking an active role in managing their condition, it enhances trust and collaboration. It helps creating an environment where patients and physicians work together to achieve optimal glycaemic control. This approach aligns with patient-centred care, encouraging patients to take charge of their health rather than relying solely on automated devices. It promotes a holistic understanding of T2DM management and encourages patients to consider their overall well-being. This finding supports the incorporation of manual data input as a standard practice within telemonitoring programs. In addition, this could foster the development of more interactive and user-friendly telemonitoring platforms that accommodate manual data input and provide personalised feedback.

The results suggest more frequent SMBG is associated with a greater reduction in HbA1c. Telemonitoring in conjunction with more frequent self-measurements provides a more comprehensive and nuanced view of physiological fluctuations, allowing for more timely interventions and adjustments to treatment plans. This finding again emphasises the importance of patient motivation and engagement in chronic disease management, where the focus should shift from periodic, reactive care to continuous, proactive management. Chronic conditions like T2DM require consistent, long-term self-care. When patients are motivated and engaged, they are more likely to adhere to treatment plans, adopt healthy behaviours, and effectively manage their condition. Future interventions should focus on empowering patients with knowledge, self-awareness, and the tools to monitor their own health, which facilitates the healthcare system's transition from being purely provider-driven to a collaborative partnership between patients and healthcare teams.

The subgroup analysis has also found that telemonitoring is more effective in reducing HbA1c in patient cohorts with a mean age of less than 65 in comparison to their older counterparts. Younger individuals are typically more comfortable with technology, making them more likely to embrace telemonitoring tools and interventions. Their familiarity with smartphones, apps, and wearable devices streamlines the integration of telemonitoring into their daily routines. Similarly, patients with various cultural, language, and religious background may find it easier or harder to adapt to telemonitoring, resulting in altered effectiveness. T2DM is a chronic disease that affects populations across all regions and age groups. Therefore, it is pivotal to incorporate user-friendly designs that are adaptable to patients with different background and various level of tech-savviness into future telemonitoring interventions, ensuring the management is truly personalised and patient-centred.

Another factor that was associated with better glycaemic control in telemonitoring was the incorporation of general T2DM education. T2DM is a complex disease and disease education helps patients understand the underlying causes of T2DM, the impact of lifestyle choices, and the importance of medication adherence. When patients are well-informed, they become active participants in their care, confidently using their knowledge to make meaningful adjustments to their diet, exercise, and medication routines. Moreover, education on the use of telemonitoring systems can ensure correct data collection and better data accuracy, which helps the healthcare team make informed decisions and maintain glycaemic control. Data collected by telemonitoring can be used for data-driven, personalised education that is tailored based on the patient's monitoring pattern, addressing each patient's unique needs and the specific challenges they face. Integrating education and telemonitoring bridges gaps in understanding, enhances patient engagement, and facilitates informed decision-making. As the benefits of the aforementioned factors on telemonitoring become evident, healthcare systems and policymakers might prioritise funding and supporting these integrated initiatives, ultimately reshaping the way telemonitoring can be delivered, and helping shift towards more holistic, empowered, and individualised T2DM management.

Furthermore, results from the secondary data analysis have also shown that adherence to certain aspects of T2DM treatment is low. Only 64.4% of the respondents have attempted to quit smoking and 29% have reported complete cessation. In terms of alcohol cessation, about 70% of respondents reported they have attempted to reduce their intake, and only 23.2% have achieved abstinence. These results indicate that, for both smoking and alcohol cessation, about one-third of the population were not aware of the importance of stopping these harmful behaviours in T2DM management or were not sufficiently motivated to make a change. It can also be seen from the results that, despite understanding the harmful effects of these unhealthy behaviours and making an effort to cut them down, a significant portion of the patients were unable to achieve complete cessation. A similar pattern can be seen for adherence to physical exercise, where 42% of participants reported minimal or no physical exercise and only less than one-third thought they were exercising regularly.

The harm of cigarette smoking and alcohol intake in terms of worsening insulin resistance and causing vascular complications have been discussed extensively (73, 74). Smoking exacerbates insulin resistance and thus worsens T2DM through multiple mechanisms. Nicotine and other harmful compounds in tobacco smoke make target cells less responsive to insulin's glucose-regulating effects (353). Smoking also promotes inflammation and oxidative stress, further impairing insulin sensitivity and increasing the severity of T2DM (353). Moreover, smoking compounds the CVD risks associated with diabetes, raising the likelihood of complications like ischaemic heart disease, stroke, and peripheral vascular disease (354). Excessive alcohol can also disrupt glucose metabolism, leading to fluctuations in blood sugar levels and impairing insulin sensitivity (355). Alcohol contributes to weight gain as a result of its high caloric content and reduced physical activity from its sedating effect, which further worsens insulin resistance (355). Additionally, alcohol can interact with medications commonly used to manage T2DM, potentially affecting their efficacy. A sedentary lifestyle also promotes weight gain, reducing insulin sensitivity, and increasing inflammation (356). Prolonged sitting and lack of physical activity contribute to metabolic dysfunction, making it challenging to maintain glucose homeostasis. Physical exercise, on the other hand, improves insulin sensitivity, aids in weight management, and enhances glucose uptake by muscles (357). Regular exercise helps mitigate insulin resistance, lowers blood sugar levels, and reduces the risk of DRC (357).

Many factors may contribute towards unhealthy lifestyles. In this population, the overall low education levels and thus low health literacy may be a significant contributing factor to this problem. Reducing cigarette smoking and alcohol intake, as well as encouraging regular physical exercise, with a view to promoting public health is therefore an integral task, which should be considered a health promotion priority and be acted upon by both government and non-government organisations. Public health campaigns that promote awareness of the harmful effects of unhealthy behaviours and the supportive services available to quit should be a main focus, especially among populations with lower health literacy. Public education, in the form of brochures, social media, newspapers and community notice boards, is both an effective and important way of improving the public's knowledge about T2DM and highlighting the detrimental effect of unhealthy behaviours on disease progression, therefore enabling healthier lifestyle choices (358). Through educational efforts that offer clear and evidence-based information, public campaigns promote behavioural changes and empower individuals with T2DM by arming them with knowledge. Understanding the risks associated with alcohol and smoking motivates patients to consider quitting, as they realise the potential for improved health outcomes and a better quality of life. In addition, they can also outline the support available, such as helplines, counselling services, and pharmacological options, for people to adopt a healthier lifestyle. Importantly, public campaigns can advocate for policies that create smoke-free environments and increase alcohol and tobacco taxes, making them less accessible and less appealing. Policies that mandate health risk labelling on the packages may also play a role in reminding people of the detrimental effects of these substances. Furthermore, better access to healthy food options, safe places for exercise, and support services such as dietitians, psychologists and telephone helplines, should be facilitated by the policies. Public health initiatives can advocate for the creation and maintenance of safe and accessible exercise facilities, such as parks, trails, and community gyms. Making exercise options readily available can encourage individuals with T2DM to engage in physical activity.

One significant research gap revolves around the long-term sustainability and effectiveness of telemonitoring interventions in T2DM management. Many existing studies have focused on relatively short-term outcomes whereas T2DM is a chronic condition that requires continuous and lifelong management. There is a need for studies that assess the durability of the benefits observed with telemonitoring over extended periods. Another area where research is lacking is the effectiveness of telemonitoring on specific subpopulations, as T2DM management can vary based on factors such as socioeconomic status, comorbidities, and cultural background and research studies often do not adequately represent the diversity within the T2DM population. Furthermore, the integration of telemonitoring into routine clinical care and its impact on healthcare systems requires further exploration. While studies have demonstrated the potential for telemonitoring to reduce hospitalisations and improve patient outcomes, there is limited research on how healthcare providers and systems can effectively implement and sustain telemonitoring programs. Understanding the barriers and facilitators of integrating telemonitoring into existing healthcare workflows, as well as assessing its impact on healthcare utilisation and cost-effectiveness, is crucial for informing policy decisions and broader implementation strategies. Lastly, research gaps exist in exploring the patient's perspective. Patient attitudes, preferences, and perceptions about the technology can greatly impact telemonitoring’s adoption and long-term use. Investigating factors such as patient satisfaction, perceived autonomy, privacy concerns, and the perceived value of telemonitoring in managing their T2DM is essential for tailoring interventions to better meet patients' needs.

6.4 Conclusion

In conclusion, the study confirms that better treatment adherence, particularly adherence to medications, SMBG and smoking cessation, is associated with better glycaemic control in patients with T2DM. The study also provides robust evidence that telemonitoring is effective in improving glycaemic control in patients with T2DM, as demonstrated by a greater reduction in HbA1c, in comparison to conventional care. Subgroup analyses have found that more severe disease at baseline, incorporation of general disease education, as well as certain technical features that improve system practicality and patient engagement have all positively influenced the effectiveness of telemonitoring. These findings provide valuable insight into the factors affecting glycaemic control in patients with T2DM and the potential role that telemonitoring can play in the overall T2DM management. They also have important implications for the development of modern telemonitoring interventions and their integration into the healthcare systems to facilitate better glycaemic control and reduce global burden of T2DM.

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Appendices

Table 2. Treatment adherence and biochemical readings of study sample

Factor	N	(%)	HbA1c (%)	FBG (mmol/L)	TC (mmol/L)	SBP (mmHg)	DBP (mmHg)
Adherence to SMBG (n=9945)							
Yes	8274	(83.2%)	7.56±1.54	8.77±2.66	5.24±1.10	149.81±19.77	80.73±10.23
No	1671	(16.8%)	7.80±1.75	9.15±2.91	5.28±1.17	151.47±21.15	81.09±10.88
Adherence to smoking cessation (n=2282)							
Complete cessation	661	(29.0%)	7.52±1.49	8.78±2.61	5.01±1.07	151.46±20.73	82.71±11.11
Reduced smoking	807	(35.4%)	7.86±1.61	9.08±2.84	5.06±1.05	146.87±18.81	82.68±10.50
No change	814	(35.6%)	7.93±1.67	9.31±2.83	5.14±1.07	148.38±19.48	83.58±10.26
Adherence to alcohol cessation (n=1831)							
Complete cessation	425	(23.2%)	7.63±1.62	8.72±2.81	4.86±1.01	148.44±19.86	81.33±9.79
Reduced intake	855	(46.7%)	7.71±1.55	9.20±2.77	5.17±1.04	149.93±19.35	84.62±10.35
No change	551	(30.1%)	7.72±1.69	9.32±2.96	5.32±1.13	151.94±20.79	85.67±10.35
Adherence to diet control (n=9987)							
Complete adherence	7372	(73.8%)	7.62±1.55	8.86±2.68	5.25±1.12	149.95±19.97	80.64±10.25
Partial adherence	2109	(21.1%)	7.57±1.64	8.79±2.71	5.23±1.10	150.16±20.24	81.08±10.61
No change	506	(5.1%)	7.47±1.73	8.54±2.91	5.26±1.13	150.52±20.41	81.32±10.62
Adherence to physical exercise (n=10069)							
Regular physical exercise	3189	(31.7%)	7.64±1.53	8.81±2.66	5.23±1.06	148.86±19.44	80.36±10.12
Occasional exercise	2646	(26.3%)	7.57±1.56	8.80±2.70	5.27±1.17	149.47±19.65	80.77±10.43
Minimal/no exercise	4234	(42.0%)	7.60±1.63	8.88±2.74	5.24±1.11	151.27±20.72	81.09±10.42
Medication adherence (n=9388)							
As prescribed	8299	(88.4%)	7.74±1.58	9.06±2.74	5.23±1.11	150.26±20.08	80.60±10.27
Take bigger/smaller dose	64	(0.6%)	7.91±1.67	8.53±2.33	5.58±1.52	153.83±22.16	79.85±12.83
Take more/less frequent	251	(2.7%)	7.21±1.38	8.24±1.94	5.32±0.97	150.38±19.81	82.11±10.23
Take intermittently	58	(0.6%)	7.19±1.11	8.16±2.05	5.30±0.92	144.11±20.83	81.63±11.14
Stopped taking	426	(4.5%)	7.02±1.43	7.90±2.39	5.33±1.19	149.25±19.52	81.18±10.72
Other reason	290	(3.1%)	7.12±1.38	8.07±2.40	5.32±1.02	148.97±20.29	80.30±10.06

Table 7. Study characteristics

Author (year)	Country	Mean age	n	Intervention n (M:F)	Control n (M:F)	Parameters monitored	Outcome of interest	PEDro score
Amante et al. (2021)	US	56.7	119	59 (25:34)	60 (31:29)	SMBG	HbA1c	6
Baron et al. (2017)	UK	57.2	81	45	36	SMBG, BP, weight, insulin dose, exercise	HbA1c	7
Bujnowska-Fedak et al. (2011)	Poland	55.3	95	47 (26:21)	48 (25:23)	SMBG, insulin dose	HbA1c, FBG, BMI	6
Crowley et al. (2016)	US	60	50	25 (25:0)	25 (23:2)	SMBG	HbA1c	7
Dario et al. (2017)	Italy	73	299	208 (119:89)	91 (49:42)	SMBG	HbA1c	6
Fountoulakis et al. (2015)	Australia	62	80	54 (37:17)	26 (18:8)	SMBG	HbA1c, BMI	7
Greenwood et al. (2015)	US	58	90	45 (26:19)	45 (22:23)	SMBG	HbA1c	7
Holmen et al. (2014)	Norway	57	100	50 (25:25)	50 (30:20)	SMBG, exercise, diet	HbA1c	6
Hu et al. (2021)	China	51.1	142	72 (51:21)	70 (43:27)	SMBG	HbA1c	6
Iljaz et al. (2017)	Slovenia	55.4	120	58 (36:22)	62 (37:25)	BMI, functional health status, BP	HbA1c, FBG, BMI	7
Istepanian et al. (2009)	UK	58.5	137	72	65	BP, SMBG	HbA1c	6
Jantraporn et al. (2019)	Thailand	53.1	53	26 (09:17)	27 (09:18)	SMBG, diet	HbA1C	5
Jeong et al. (2018)	South Korea	53.4	226	113 (75:38)	113 (76:37)	SMBG, lipid profile, weight, BMI	HbA1c, FBG, BMI	7
Karhula et al. (2015)	Finland	66.2	430	180 (99:81)	250 (220:30)	BP, weight, waist circumference, lipid profile	HbA1c	6
Kim et al. (2016)	China	54.03	182	92 (49:43)	90 (39:51)	BP, SMBG, weight, lipid profile	HbA1C, BMI, FBG	6
Lee et al. (2020)a	South Korea	51.3	66	39 (32:7)	27 (16:11)	SMBG, BP, diet, exercise, medications, weight	HbA1c, BMI	7

Lee et al. (2020)b	Malaysia	56.2	240	120 (53:67)	120 (55:65)	SMBG	HbA1c, FBG	7
Lee et al. (2015)	Malaysia	50.7	37	18 (9:9)	19(7:12)	SMBG, hypoglycaemic events, medication, diet	FBG	7
Lee et al. (2017)a	Malaysia	53.49	85	45 (24:21)	40 (16:24)	SMBG	HbA1c, FBG, BMI	7
Lee et al. (2017)b	US	56.18	144	53 (35:18)	91 (55:36)	SMBG, BP, weight	HbA1c, BMI	5
Lindberg et al. (2017)	Sweden	67.52	165	86 (62:24)	79 (55:29)	SMBG, BP, exercise	HbA1c, BMI	6
Pressman et al. (2014)	US	55.54	198	107 (67:40)	91 (55:36)	SMBG, BP, weight	HbA1c, BMI	8
Stone et al. (2010)	US		150	73	77	SMBG, BP, weight	HbA1c	7
Sun et al. (2019)	China	68	91	44 (19:25)	47 (18:29)	SMBG	HbA1c, FBG	7
Tang et al. (2013)	US	53.7	415	202 (119:83)	213 (130:83)	SMBG, diet, exercise, insulin dose	HbA1c	8
Von Storch et al. (2019)	Germany	58.9	115	60 (47:13)	55 (47:8)	SMBG, exercise, diet	HbA1c, BMI	5
Wakefield et al. (2014)	US	60	108	53 (25:28)	55(23:32)	SMBG, BP	HbA1c	6
Wild et al. (2016)	UK	61	321	160 (106:54)	161 (108:53)	BP, SMBG, weight	HbA1c	8
Yang et al. (2020)	South Korea	56.7	247	150 (80:70)	97 (45:52)	SMBG, BP	FBG, HbA1c, BMI	7
Yu et al. (2019)	China	53.3	92	45 (31:14)	47 (29:18)	SMBG, BP, HbA1c, diet, exercise	HbA1c, FBG	7

SMBG – self-measured blood glucose; BP – blood pressure; FBG – fasting blood glucose; BMI – body mass index

Table 9. Subgroup analysis for HbA1c

Subgroups	Studies (n)	Participants (n)	MD (95% CI)	Effect size (95% CI)	P
Parameters monitored					
1 parameter	9	1159	-0.019 (-0.601, 0.563)	-0.370 (-0.958, 0.217)	**0.009**
>1 parameter	17	3056	-0.405 (-0.564, -0.246)	-0.329 (-0.469, -0.19)	
Frequency of patient-physician communication					
At least once weekly	16	2840	-0.310 (-0.439, -0.181)	-0.340 (-0.486, -0.194)	0.409
Less than once weekly	7	1031	-0.063 (-0.871, 0.745)	-0.298 (-1.102, 0.506)	
Communication method					
Text-based	6	1369	-0.348 (-0.593, -0.103)	-0.343 (-0.52, -0.166)	0.408
Phone call	8	1292	-0.512 (-0.873, -0.151)	-0.619 (-1.05, -0.188)	
Mix	10	1460	-0.047 (-0.469, 0.376)	-0.047 (-0.443, 0.349)	
Mode of data input					
Automated	11	2210	-0.072 (-0.418, 0.273)	-0.110 (-0.461, 0.242)	**0.005**
Manual	14	2070	-0.413 (-0.627, -0.198)	-0.444 (-0.672, -0.216)	
Mode of data transmission					
Wi-Fi	13	1791	-0.230 (-0.594, 0.134)	-0.241 (-0.606, 0.125)	0.437
Bluetooth	8	1584	-0.388 (-0.677, -0.099)	-0.447 (-0.752, -0.142)	
4G/5G	3	412	-0.495 (-1.184, 0.194)	-0.389 (-0.817, 0.039)	
Abnormality alert					
No	13	2364	-0.174 (-0.493, 0.146)	-0.300 (-0.662, 0.063)	0.214
Yes	13	1969	-0.413 (-0.615, -0.211)	-0.363 (-0.533, -0.193)	
Telemonitoring duration					
<6 months	5	719	-0.346 (-0.659, -0.034)	-0.355 (-0.673, -0.037)	0.123
6 months or more	21	3614	-0.271 (-0.493, -0.05)	-0.319 (-0.555, -0.083)	
Follow-up duration					
<6 months	10	1708	-0.203 (-0.584, 0.179)	-0.238 (-0.687, 0.211)	0.312
6 months or more	16	2454	-0.367 (-0.561, -0.172)	-0.361 (-0.544, -0.178)	
Involvement of in-person sessions					
No					
Yes	20	3412	-0.434 (-0.604, -0.263)	-0.437 (-0.599, -0.275)	0.099
	6	921	0.157 (-0.525, 0.839)	0.096 (-0.545, 0.737)	
Frequency of self-measurement					
At least once daily	21	3273	-0.183 (-0.309, -0.057)	-0.345 (-0.599, -0.092)	**0.008**
Less than once daily	4	969	-0.075 (-0.172, 0.011)	-0.289 (-0.54, -0.038)	
Mean age					
<65 years old	22	3518	-0.206 (-0.321, -0.091)	-0.358 (-0.592, -0.125)	**0.031**
65 years old or above	4	815	-0.136 (-0.281, -0.009)	-0.144 (-0.305, 0.017)	
Baseline HbA1c					
8% or less	9	1176	-0.315 (-0.547, -0.083)	-0.338 (-0.575, -0.101)	**0.008**
>8%	16	2910	-0.390 (-0.57, -0.01)	-0.323 (-0.615, -0.031)	
Baseline insulin requirement					
No	15	2256	-0.498 (-0.647, -0.249)	-0.425 (-0.582, -0.267)	0.060
Yes	4	796	-0.457 (-0.7, -0.215)	-0.374 (-0.671, -0.078)	
Mix	3	494	0.007 (-0.209, 0.224)	0.006 (-0.193, 0.205)	
Disease education					
No	1	299	0.010 (-0.244, 0.254)	0.011 (-0.258, 0.29)	**0.041**
Yes	25	4034	-0.309 (-0.478, -0.139)	-0.343 (-0.549, -0.136)	
Guidance on diet					
No	7	1783	-0.210 (-0.406, -0.015)	-0.219 (-0.411, -0.026)	0.289

Yes	19	2550	-0.335 (-0.588, -0.082)	-0.377 (-0.656, -0.099)	
Guidance on exercise					
No	8	1782	-0.143 (-0.262, -0.025)	-0.218 (-0.4, -0.036)	0.202
Yes	18	2549	-0.354 (-0.671, -0.037)	-0.375 (-0.662, -0.089)	
Guidance on self-measure skills and techniques					
No	5	893	-0.206 (-0.45, 0.039)	-0.253 (-0.511, 0.004)	0.325
Yes	20	3348	-0.332 (-0.594, -0.07)	-0.353 (-0..606, -0.1)	