

**The effect of telemedicine and cognitive behavioural therapy on sleep and health outcomes in type 2 diabetes patients: a randomized controlled trial**

**Project description and research protocol**

**Version: V1.0**

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# List of Abbreviations

BMI Body Mass Index

CBT cognitive behavioural therapy

CBT-I cognitive behavioural therapy for insomnia

CI confidence interval

CMS cardiometabolic syndrome

DBP diastolic blood pressure

DM Diabetes Mellitus

HAMA Hamilton Anxiety Rating Scale

HAMD Hamilton Depression Rating Scale

HbA1c Glycated Hemoglobin

HDL-C high density lipoprotein cholesterol

ISI Insomnia Severity Index

LDL-C low density lipoprotein cholesterol

MD mean difference

MFI Multidimensional Fatigue Inventory

PSG Polysomnography

PSQI Pittsburgh Sleep Quality Index

RCT randomized controlled trial

SBP systolic blood pressure

SF-12 12-question short-form survey

SMD standardized mean difference

TC total cholesterol

TG total triglyceride

T2DM Type 2 Diabetes Mellitus

UK United Kingdom

US United States

WHO World Health Organization

WHR waist hip ratio

# Chapter 1: Project Team Roles & Responsibilities

**Principle Investigator**

**Name** Prof. Jing Sun

**Affiliation** School of Medicine and Dentistry, Griffith University, Queensland, Australia

**Position** Professor

**Responsibilities** Overall monitoring of the progress of the project.

Principle supervisor of the PhD candidate and provide direct supervision (disease management, clinical trial conducting and data management).

**Lead Investigator/Researcher**

**Name** Dawei Xu

**Affiliation** School of Medicine and Dentistry, Griffith University, Queensland, Australia

**Position** Doctor of Philosophy (PhD) candidate

**Responsibilities** Participant recruitment, obtaining consent, intervention delivery and data collection.

**Associate Investigators/Researchers**

**Name** Prof. Elizabeth Cardell

**Affiliation** School of Medicine and Dentistry, Griffith University, Queensland, Australia

**Position** Professor

**Responsibilities** Associate supervisor of the PhD candidate and provide direct supervision.

Maintain the overall quality of the project.

**Name** Dr. Li Li

**Affiliation** Department of Endocrinology and Metabolism, Ningbo First Hospital, Ningbo, Zhejiang Province, China

**Position** Chief Physician

**Responsibilities** Participant recruitment

Management of overall physical health of the participants.

 External supervisor providing direct supervision on the PhD candidate (supervision on type 2 diabetes management).

**Name** Dr. Miao Xu

**Affiliation** Department of Endocrinology and Metabolism, Ningbo First Hospital, Ningbo, Zhejiang Province, China

**Position** Associate Chief Physician

**Responsibilities** Participant recruitment

Management of overall physical health of the participants.

 External supervisor providing direct supervision on the PhD candidate (supervision on type 2 diabetes management).

**Name** Dr. Yunxin Ji

**Affiliation** Department of Psychosomatic medicine, Ningbo First Hospital, Ningbo, Zhejiang Province, China

**Position** Chief Physician

**Responsibilities** Participant recruitment

Management of overall mental health and sleep quality of the participants.

 External supervisor providing direct supervision on the PhD candidate (sleep and mental health management).

**Name** Dr. Zhongze Lou

**Affiliation** Department of Psychosomatic medicine, Ningbo First Hospital, Ningbo, Zhejiang Province, China

**Position** Deputy Director of Central Laboratory

Secretary of the Party Branch

**Responsibilities** Maintain the overall quality of the clinical trial.

External supervisor providing direct supervision on the PhD candidate (sleep management and clinical trial management).

# Chapter 2: Resources

**Required resources**

This project requires patients with type 2 diabetes and insomnia. The resource of the potential participants will be provided by the Department of Endocrinology and Metabolism, Ningbo First Hospital, Ningbo, China.

The online delivery of intervention sessions requires the license of online conference software resources. The intervention sessions will be delivered through Microsoft Teams. The license of Microsoft Teams was provided as part of the Microsoft 365 service by Griffith University, and all participants can join the online sessions in Microsoft Teams without charges.

The final data analysis process of de-identified database from this study requires the recruitment of a data analyst. The salary of the data analyst will be covered by the annual financial supported provided by Griffith University to PhD candidates.

**Fundings**

This project did not receive funding from any individuals or organizations.

# Chapter 3: Literature review

## 3.1 Diabetes Mellitus

### 3.1.1 Definition, classification and diagnosis

Diabetes Mellitus is a group of metabolic disease characterized by hyperglycemia caused by the defect of either insulin secretion or insulin action or both1. The pathogenic processes involved in the development of diabetes include the autoimmune destruction of the β-cells of the pancreas, which results in insulin deficiency and the resistance to insulin actions. The deficiency of insulin secretion and insulin actions leads to the abnormalities in the metabolism of carbohydrate, fat, and protein1.

Diabetes can be classified into four main categories: type-1 diabetes, type-2 diabetes and gestational diabetes mellitus and other diabetes. Type-1 diabetes is immune-mediated and caused by a cellular-mediated autoimmune destruction of the β-cells of the pancreas, which has multiple genetic predispositions and usually leads to absolute insulin deficiency. Type-1 diabetes only accounts for 5-10% of diabetes patients. T2DM is the most common form of diabetes, which accounts for up to 90-95% of diabetes patients. Patients with T2DM usually have insulin resistance and relative (rather than absolute) insulin deficiency. In addition, gestational diabetes mellitus usually refers to diabetes with onset or first recognition during pregnancy, and there are also rare cases of diabetes caused by other diseases.1

The diagnosis of T2DM refers to the Standards of Medical Care in Diabetes published by American Diabetes Association in 20192. The diagnosis criteria are summarized in the table below:

**Table 1. Diagnosis criteria of diabetes**

|  |  |
| --- | --- |
| Indicator | Range |
| Fasting plasma glucose (fasting time >8 hours) | ≥7.0 mmol/l |
| OR |  |
| Two-hour postprandial blood glucose | ≥11.1 mmol/l |
| OR |  |
| Random plasma glucose (in patients with classic symptoms of hyperglycemia or hyperglycemic crisis) | ≥11.1 mmol/l |
| OR |  |
| Glycated Hemoglobin (HbA1c) | ≥ 6.5% |

### 3.1.2 Symptoms and long-term complications

Diabetes is a serious, long-term condition with significant impact on the health and well-being of individuals, families, and societies across the world. Studies have suggested that diabetes is among the top 10 causes of death in adults, which was estimated to have caused 4 million deaths globally in 20173. The most common symptoms of diabetes include polyuria, polydipsia and weight loss. Other symptoms include dry mouth, polyphagia, and blurred vision. Chronic hyperglycemia may also cause impairment of growth and susceptibility to certain infections. Uncontrolled diabetes can lead to acute, life-threatening consequences such as diabetic ketoacidosis or the nonketotic hyperosmolar syndrome1.

Long-term complications of diabetes include retinopathy with potential loss of vision and renal failure; peripheral neuropathy with risk of foot ulcers (diabetic foot), amputations, and Charcot joints; autonomic neuropathy causing gastrointestinal, genitourinary, and cardiovascular symptoms and sexual dysfunction. Patients with diabetes have an increased incidence of atherosclerotic cardiovascular, peripheral arterial, and cerebrovascular disease. Hypertension and abnormalities of lipoprotein metabolism are also common in diabetes patients1.

### 3.1.3 Prevalence of diabetes

Diabetes has a high prevalence across the world. According to the results from the Diabetes Atlas published by International Diabetes Federation, the global population with diabetes mellitus was estimated to be 463 million (9.3% of the global population) in 2019, and this number will be rising to 578 million (10.2% of the global population) by 2030 and 700 million (10.9% of the global population) by 20453. The prevalence of diabetes is higher in urban areas (10.8% of the population) than in rural areas (7.2% of the population), and in high-income countries (10.4% of the population) than low-income countries (4.0% of the population)3. In addition, less than 50% of diabetes patients were aware of their diabetic conditions. T2DM accounts for about 90% of the total diabetes cases, and there is a rising trend of the prevalence of T2DM due to ageing, rapid increase in urbanization, and obesogenic environments3. It was also mentioned that the increasing number of younger adults with T2DM in the recent years also contributes to the increase in overall T2DM prevalence, through their longer survival and earlier diagnosis3. Overall, there is a higher prevalence of diabetes in male than in female, and in elder adults than in younger adults. The global diabetes prevalence in different age and gender groups in 2019 are summarized in Figure.



**Figure 1. Diabetes prevalence by age and sex in 20193**

At the country level, China is the country with highest number of people with diabetes across the world. There were approximately 116 million diabetes patients in China in 2019, which accounts for over 12.4% of the total population in this country3, 4. In addition, the estimated prevalence of prediabetes in China in 2018 was 38.1%. Moreover, among Chinese adults with diabetes, only 36.7% reported being aware of their condition, 32.9% reported being treated and only 50.1% of patients receiving diabetes treatment were controlled adequately4. The median age of diabetes patients in China decreased from 55.8 years in 2013 to 51.3 years in 2018, which suggests that there is an increasing trend of diabetes in younger adults4.

### 3.1.4 Risk factors for T2DM

The development of T2DM is affected by the intercorrelation and contribution of genetic, environmental, and metabolic risk factors5. Common risk factors for T2DM include genetic factors, aging, obesity, hypertension, dyslipidaemia, smoking, alcohol consumption, high fat, high sugar and low fibre diet, insufficient physical activity, low sleep quality and poor mental health status6.

Although the pathophysiology of T2DM is not completely elucidated so far, it can be sure that genetic factors played an important role in the disease development. Studies have found that over 40% of first-degree relatives of T2DM patients may develop diabetes, while the overall incident rate in the general population is only 6%7. Since 2007, a large number of genome-wide association studies has been carried out to discover the susceptibility loci of T2DM6, 8-12, and these studies have successfully identified approximately 75 susceptibility loci related to T2DM. However, there are still many unsorted loci for the pathogenesis of T2DM.

Increased aging greatly contributes to the risk of developing T2DM, and this is confirmed by the higher prevalence of T2DM in older adults. Older adults are at high risk for the development of T2DM because aging can lead to increasing insulin resistance and impaired pancreatic islet function13. The cause might be due to the long term effects of adiposity, sarcopenia, and physical inactivity13. Studies also mentioned that aging is associated with changes in body composition, including both fat gains, change in fat distribution and muscle loss, and this is associated with increased risk of type 2 diabetes14.

Obesity is the most important risk factor for T2DM. A constant overweight condition has great influence on the development of insulin resistance and disease progression15. Study has shown that the risk of developing diabetes increased 20.1-fold at a body mass index (BMI) of 30.0 to 34.9 kg/m2 and 38-fold at a BMI of 35 kg/m2 or greater16. According to the report provided by World Health Organization, approximately 90% of prediabetic patients develop T2DM mostly relating to excess body weight5.

T2DM is also greatly affected by a wide variety of lifestyle factors, including lack of physical activity17, 18, unhealthy diet18, smoking19 and alcohol consumption20, 21. Many studies have shown that the intake of low-fibre diet with a high glycaemic index and specific dietary fatty acids may affect insulin resistance and increase the risk of diabetes in various degrees22. Excessive fat intake is also associated with an increased risk of T2DM. Soft drinks with high sugar contents also have close association with increased risk of T2DM and metabolic syndrome, because they are directly associated with the development of obesity23, 24. In addition, lack of physical activity can also lead to the increase of body weight and development of obesity, and smoking and alcohol consumption increases the risks of developing various cardiovascular diseases, which also increases the risk of the development of T2DM17-21. The lifestyle factors are always considered as modifiable risk factors, which means the development and progression of T2DM can be prevented by having a balanced diet, increasing physical activities and limiting tobacco and alcohol consumption.

Recent studies have also found that mental health problems, including depression, anxiety and sleep disorders, are highly prevalent in T2DM patients25-27. These mental health problems might have been existing before the development of T2DM, or they can be developed due to the disease diagnosis, lifestyle treatment or other reasons25-27. Mental health problems are especially common among the younger populations, as they are receiving more pressure from workings and daily life26. Overall, a poor mental health condition has a negative effect in maintaining the regulated blood sugar regulation and lifestyle treatment for T2DM.

### 3.1.5 Treatment of T2DM

The primary aim of the treatment of T2DM is to lower the blood glucose closing to a normal level under control. The treatment of T2DM usually includes the combination of drug treatment and lifestyle treatment. Generally, T2DM cannot be completely cured but only be properly controlled under the treatment. When considering the drug treatment of T2DM, non-insulin antidiabetic drugs are always the first choice. Biguanides are one of the major classes of antidiabetic drugs, among which metformin is the most common drug recommended as the first line therapy for T2DM, and the use of metformin monotherapy is recommended as initial treatment28. When T2DM cannot be properly controlled by lifestyle and single oral antidiabetic drugs, it will be necessary for the therapists to consider combination therapy with two or more antidiabetic drugs29. Other commonly used oral antidiabetic drugs include Sulphonylureas30, Thiazolidinediones31, α-Glucosidase inhibitors32, Incretin-based therapies33 and GLP-1 receptor agonists34, which all have different mechanisms on blood glucose regulation. The advantages of combination therapy over monotherapy include greater efficacy at a lower dose (of single drug), reduced risk of negative effect, lower costs and improved medication concordance29. When lifestyle treatment and oral antidiabetic drugs fail to achieve adequate blood glucose control in T2DM patients, it is generally required for the patients to initiate insulin therapies using insulin or insulin analogues35.

In addition to the drug treatment, lifestyle changes are also very important to T2DM patients, especially for those at an early stage of the disease. It has been widely recognized that lifestyle factors, including lack of physical activity17, 18, unhealthy diet18, smoking19 and alcohol consumption20, 21 play an important role in the development of T2DM. These factors are modifiable and can be changed by the patients during their daily life36. Patients are recommended to have a diet with high fibre, low carbohydrate and low-fat intake while meeting the daily energy requirements23. The increase of physical exercise and reduce of tobacco and alcohol intake is also recommended36. The change in lifestyle promotes the control of body weight, stop the development of obesity, and therefore reduce the risk of T2DM development and progressing. More importantly, lifestyle changes should be life-long persisted, otherwise the reverse of obesity and T2DM would be very difficult.

As many T2DM patients have faced stress and mental health problems related to the disease, psychological treatment is also very important. Negative emotions brought by the mental health problems provide negative effects on the incidence of T2DM and are harmful to the prognosis of the disease37. In addition, a poor mental health condition has a negative effect in maintaining the regulated blood sugar and lifestyle treatment. Treatments targeting mental health such as CBT can improve the self-management of T2DM and improve the glycaemic control38.

## 3.2 Insomnia

### 3.2.1 Disease overview

Insomnia is a typical mental disorder that influence the quality, timing and amount of sleep, resulting in the impairment in daytime functioning and mental distress39. The common causes of insomnia include chronic diseases, such as metabolic disease, chronic pain and cancer, and pre-existing psychiatric diseases including depression and anxiety39. Insomnia has a high prevalence across the world. It was reported that the global prevalence of insomnia was up to 10% of the population, and another 20% experiences occasional insomnia symptoms40. Insomnia may occur individually or as a complication with other psychiatric diseases such as depression and anxiety41. Insomnia exerts a great impact on the daytime functionally physical, mental, and cognitive abilities, leading to a significant drop of quality of life42. Mentally, insomnia can impair daytime concentration and generate anxious or depressed feels that may lead to other psychiatric diseases such as depression and anxiety43. Physically, a chronic condition of insomnia can increase the risks of a great amount of chronic diseases such as diabetes, cardiovascular diseases and cancer44.

### 3.2.2 Treatment of insomnia

Currently, the treatment designs for insomnia include pharmacological and non-pharmacological treatments. Pharmacological treatment involves taking sleep medicines, also known as hypnotics, such as benzodiazepines, Z drugs and melatonin receptor agonists45. To reduce the symptoms of insomnia complicated with other diseases, drugs may also be used to treat the underlying health issues, including antidepressants, anti-allergic drugs and drugs for chronic pain39. The problem for the pharmacological treatment is the adverse effects induced by the intake of the drugs, and human body may resist to the effect of certain type of the drug under a long period of intake. Therefore, non-pharmacological treatments with fewer adverse effects were developed to support and replace a part of pharmacological treatments46. Some commonly used non-pharmacological treatments for sleep include physical training, light therapy, mindfulness-based interventions and acupuncture47-50.

### 3.2.3 Insomnia and T2DM

A recent meta-analysis study have found that the prevalence of insomnia and insomnia symptom in T2DM patients was 39%51, which was nearly four times higher than the prevalence in the general population (11%)40. However, the exact percentage of insomnia that is directly caused by T2DM still remains unclear. Studies also mentioned that insomnia was highly associated with poor HbA1c and blood glucose control52. Therefore, managing and treating insomnia plays an important role in the management of T2DM.

When treating insomnia in T2DM patients, studies have confirmed that pharmacological treatment such as Z drugs and benzodiazepines have significant acute effect on improving the ability to fall and stay asleep53. However, studies also found that existing therapeutic options of treating insomnia have possible side effects, including addiction and impairment on glucose metabolism and glycaemic control, which was not favourable in the management of T2DM53. In this case, non-pharmacological treatment with fewer adverse effects and long-lasting beneficial effects on sleep is very important in the management of insomnia in T2DM patients.

## 3.3 Cognitive Behavioural Therapy

### 3.3.1 Definition

Cognitive behavioural therapy (CBT) is developed based on the concept of CBT triangle presented in Figure 2. The CBT triangle contains three parts: thoughts, behaviours and emotions. The CBT concepts believe that health problems, especially psychological problems are based, in part, on faulty ways of thinking and unhelpful behaviour towards the disease54. The CBT concepts also believe that such health problems can be relieved if the patients learn better ways of coping with the unhelpful thinking and behaviour54. CBT intervention involves multiple strategies to change the thinking and behavioural patterns, including instructions to identify and re-evaluate unhelpful thoughts, using problem-solving skills to cope with difficult situations, using role playing to prepare for potentially problematic interactions with others, etc.55. CBT has been confirmed to be effective for a range of problems including depression56, 57, anxiety58, 59, substance abuse60, eating disorders61, and other severe mental illness62, 63. Previous research studies indicated that CBT leads to significant improvement in normal functioning and overall quality of life56-62. In many studies, CBT has been found to be as effective as, or more effective than, other forms of non-pharmacological therapies or medications64, 65.

**Figure 2. CBT triangle66**

### 3.3.2 Cognitive behavioural therapy for insomnia

Cognitive behavioural therapy for insomnia (CBT-I) is a widely studied non-pharmacological treatment option for insomnia with significant long-term and short-term effects67. CBT-I is recommended as the first-line treatment in managing numerous psychiatric diseases, including depression, anxiety and insomnia46. The CBT theories have pointed out that psychiatric symptoms are greatly affected by distorted cognition and related behaviours, and these symptoms can be reduced if the distorted cognition and behaviours are properly identified and corrected by patients68. Based on the CBT principles, multiple CBT strategies have been developed to change thinking and behavioural patterns via CBT intervention sessions69.

Previous studies have found that it is common for patients with insomnia to have dysfunctional understandings about sleep and worries about falling asleep70. These understandings may lead to behavioural changes, such as spending more time in bed trying to fall asleep and developing irregular sleep times. These behaviours can make falling asleep more difficult and further reinforce the dysfunctional understandings, creating a loop that exacerbates the existing insomnia symptoms70.

### 3.3.3 CBT-I Intervention components

CBT is considered a multi-component treatment approach. First, the cognitive therapy (sometimes also called cognitive restructure) component of CBT helps patients identify and alter thoughts that may contribute to insomnia. Second, the stimulus control component teaches patients to use beds only for sleep and to eliminate habits that cause difficulty in falling asleep, such as eating, watching television and using smartphones in bed71. Third, the sleep restriction component limits the time spent in bed and asks patients to stay in bed only if they are sleepy. In addition, the sleep hygiene usually acts as education component, which teaches patients to establish an appropriate bedroom environment and daily schedule for sleep72. Fourth, patients can learn essential relaxation techniques in the relaxation training component73. The relaxation training session usually include mental relaxation techniques, such as giving up negative thoughts, and physical relaxation techniques such as muscle relaxation and breath control73. Other components such as treatment rationales, relapse prevention and basic sleep education can also be included in a CBT intervention to enhance understandings of sleep and the overall effect of the intervention74.

### 3.3.4 Cognitive behavioural therapy for T2DM

Self-management of lifestyle and blood glucose monitoring is a very important factor in managing T2DM. To enhance the self-efficacy of self-management behaviours, CBT can also be applied in the management of T2DM. CBT for T2DM also involves cognitive restructure components targeting to change the unhelpful beliefs and understandings on diabetes and blood glucose control75. Furthermore, behaviour therapy is also included in RCT studies targeting T2DM related blood glucose management, exercise, substance intake and diet changes75. A recent meta-analysis study consisting of 7 RCT studies76 have found that CBT for T2DM has a significant effect in improving blood glucose level, HbA1c and quality of life.

### 3.3.5 Application status

CBT has been commonly delivered in a face-to face format, in which patients have face-to-face consultations with therapists. These consultations can either occur between one patient and the therapist individually or between therapist(s) and multiple patients. This leads to the two major categories of face-to-face delivered CBT: individual-delivered CBT and group-delivered CBT. Although there has been rapid development of remote-delivered CBT over the past 10 years, the traditional face-to-face delivery of CBT is still commonly used. Previous studies have shown that CBT provides similar effect in treating insomnia compared with pharmacological treatments77. Further, it has been found that CBT treatment has fewer side effects than sleep medication67. A standard design of CBT intervention usually contains 4 to 8 intervention sessions, and the duration for each session ranges from 30 minutes to up to 90 minutes. In order to maintain the effect of the intervention, the intervention sessions are usually delivered weekly or bi-weekly78.

In T2DM patients, CBT have already been applied for the management of glucose control and sleep problems. However, existing RCT studies focused either on glucose control or insomnia only. Meta-analysis studies have found that CBT interventions targeting glucose control did not report any effects on sleep improvement79. Similarly, CBT interventions targeting sleep improvement reported limited effects in blood glucose and HbA1c control80. Therefore, a combination of CBT intervention targeting both blood glucose and insomnia control will be more efficient in improving the overall health status in T2DM patients with insomnia.

### 3.3.6 Effect of CBT intervention on sleep outcomes

A meta-analysis of 15 RCT studies and 2174 participants assessing the effect of CBT intervention on sleep and health outcomes in patients with cardiometabolic syndrome was carried out as a background study of this project. The results from our background meta-analysis showed that overall sleep quality measured by Pittsburgh Sleep Quality Index, overall insomnia severity measured by Insomnia Severity Index, total sleep time and sleep efficiency was more significantly improved in CBT intervention group compared with the control group, which was consistent with the results from previous studies81. Similar results were also found in other studies analysing the effect of CBT on sleep problems in different disease groups82-84, which suggested that CBT intervention provide similar positive effect in improving sleep quality and prolonging sleep duration in CMS patients by changing their cognitive and behavioural patterns. However, the effect of CBT on sleep onset latency and wake after sleep onset was not significant, and this was quite different from the results in existing studies81. A possible explanation for this could be the limited number of studies that reported these two outcomes, as sleep onset latency was only presented in five studies and wake after sleep onset was only reported in four studies. For now, we could not conclude that CBT intervention was not effective in improving the continuity of sleep in CMS patients.

Subgroup analysis was conducted on Pittsburgh Sleep Quality Index to identify the specific intervention components that has greatest effect on overall sleep quality. We found that the inclusion of sleep hygiene component was especially important in improving the efficiency of CBT intervention, and this finding was consistent with existing studies85. Existing studies have mentioned that sleep hygiene education can be used alone as non-pharmacological treatment for insomnia, and the independent use of sleep hygiene education already showed significant effect on sleep improvement85. In CBT designs, the main contents of behavioural therapy were sleep restriction and stimulus control. The target of these two components was limited on the behaviours in the bed86, 87, while the overall sleep quality was also greatly affected by factors out of the bed, such as the environment of bedrooms and substance intake. As an important complement of behavioural treatment, sleep hygiene education provided comprehensive education on behaviours promoting sleep, including keeping a quiet sleep environment, maintaining regular sleep schedules and limiting alcohol and tobacco intake88.

Another effective component identified through subgroup analysis was the absence of self-help manuals. Studies providing self-help manuals showed worse effect on sleep quality compared with studies without self-help manuals. Although some of the existing studies have concluded that fully self-help CBT intervention had promising effect in improving sleep quality89, intervention under the guidance of an experienced therapist would be a better choice, because patients might have questions or misunderstandings on the intervention contents in fully self-help interventions, and the support from the therapists would be necessary to ensure the intervention contents are properly delivered.

In addition, the length of intervention did not show significant effects on CBT intervention effects. The length of intervention in RCT included in this study ranged from 4 weeks to 8 weeks, which means there were no studies providing extremely long or extremely short intervention. Further research is required to find out if the CBT intervention effects are affected by extremely long or brief intervention designs. Subgroup analysis also found similar effects in studies with different disease groups, delivery methods and use of medications, which was in line with the findings from previous studies90, 91. This suggested that the effect of CBT intervention was not significantly affected by comorbid diseases, delivery methods and medications.

### 3.3.7 Effect of CBT intervention on depression and anxiety

Our background meta-analysis found that CBT intervention had significant effect on depression, which was similar to the findings in existing research92, 93. Studies have mentioned that there was a close relationship between low sleep quality and depression, and the improvement of sleep quality and amount could also lead to the improvement of depression symptoms94.

Subgroup analysis was also conducted on depression, and the results showed that the effect of CBT intervention was more significant when the length of intervention was shorter than six weeks. A possible explanation would be patients might lose concentration and enthusiasm to participate in the intervention sessions across a longer intervention period. The subgroup analysis also found that relapse prevention, homework and problem-solving components did not provide significant effect on depression, which was out of our expectation. The possible reason would be the limited number of studies, so more studies are required to evaluate the effect of CBT on depression.

The meta-analysis also found that CBT intervention did not have significant effect on anxiety, which was different from the findings in existing studies95, 96. This is possibly because the main target of CBT interventions in these studies was sleep problems instead of anxiety, so the information related to insomnia management was relatively limited. But we also need to mention that anxiety was reported in only seven studies, and the results might be different when more studies are included.

### 3.3.8 Effect of CBT intervention on fatigue

Our background meta-analysis also found that CBT intervention had a significant effect on daytime fatigue. Fatigue is an important measurement of daytime functioning in patients with sleep problems, and studies have mentioned that the insufficiency of sleep was the greatest cause of daytime fatigue97. The CBT intervention successfully created a regulated sleep pattern, which enabled the patients to be fully rested in bed, and this directly reduces the daytime fatigue level.

### 3.3.9 Effect of CBT intervention on HbA1c and blood pressure

Consistent with the findings in previous studies98, CBT intervention was effective in the improvement of metabolic profiles, especially HbA1c in CMS patients. It was reported that the loss of sleep could lead to heavy metabolic burdens, and some CBT components, such as sleep restriction, have been confirmed to compromise the metabolic control in healthy individuals99, 100. However, further research is required to provide a more detailed overview of the effect of CBT intervention and sleep improvement on the metabolic profiles.

In addition, Our background meta-analysis found that the effect of CBT was not significant on blood pressure, even though previous studies have reported that poor sleep quality was related to a higher blood pressure101. This can be explained by the time required to reflect the CBT intervention effects on blood pressure. The patients experience sleep improvement immediately during or after CBT intervention, but it might take more time for the effect to be showed on blood pressure reduction. Also, the number of studies reporting blood pressure was limited, and the results might be different when more studies with bigger sample size are included.

# Chapter 4: Research Background

## 4.1 Research rationale

Diabetes mellitus is a group of metabolism disturbances characterized by chronic hyperglycemia. The cause of diabetes mellitus could either be the impairment of insulin secretion or the impairment of insulin action or both102. National Diabetes Statistics Report published by US Centres for Disease Control and Prevention has shown that the incidence of diabetes is up to 11.8% of the total population in America103. Among all types of diabetes, T2DM is the most common, and the proportion of T2DM patients is over 90% of diabetes patients104, 105. In China, the number of T2DM patients was over 140.9 million in 2021, which was approximately 10% of the total population, and the prevalence rate was estimated to rise to over 12.5% by 2025, which is about 174.4 millions of people will have T2DM106, 107. The estimated globally health expenditures related to were 966 billion US dollars in 2021 and were projected to reach 1,054 billion US dollars by 2045107. Currently, T2DM cannot be completely cured, only be reversed108. Diabetes is a lifelong disease with many complications, especially cardiovascular diseases109. A chronic presence of diabetes also effects the mental health status of the patients, leading to mental disorders such as insomnia, depression and anxiety110. Studies have also shown that the average diagnosis age of T2DM has become much younger than 20 years ago109, 111, which suggested that more attention should be raised on the prevention and treatment of T2DM at an earlier age.

Insomnia is a typical mental disorder that influence the quality, timing and amount of sleep, resulting in the impairment in daytime functioning and mental distress in patients with diabetes39. Insomnia has a high prevalence across the world. It was reported that the global prevalence of insomnia was up to 30% of the population112. Studies have mentioned that approximately 37-50% of T2DM patients have sleep problems, and the prevalence of insomnia in T2DM patients is over 30%, even higher than in normal population113, 114. Insomnia exerts a great impact on the daytime functionally physical, mental, and cognitive abilities, leading to a significant drop of quality of life42. Insomnia can impair daytime concentration and generate anxious or depressed feels that may lead to other psychiatric diseases such as depression and anxiety43. Studies have shown that insomnia can be associated with higher risk of incident of T2DM115. On the other hand, existing diabetes can also lead to the incidence and worsen of insomnia115. The recommended treatment of insomnia in patients with diabetes include pharmacological treatment and non-pharmacological treatment69.

Cognitive behavioural therapy (or cognitive behavior therapy, CBT) is recommended as the first-line non-pharmacological treatment in managing numerous mental health problems, including insomnia, depression and anxiety.46 Studies have pointed out that mental health problems are greatly affected by negative understandings, cognition and related behaviours, and these symptoms can be reduced if the negative cognition and behaviours are properly corrected.68 Based on the CBT principles, multiple CBT strategies have been developed to change thinking and behavioural patterns via CBT treatments in patients with diabetes78. When treating diabetic patients with insomnia, CBT is specially adapted to a new form called “cognitive behavioural therapy for insomnia (CBT-I)”. A complete delivery of CBT-I usually combines multiple modules, including sleep education, sleep hygiene, sleep restriction, stimulus control, cognitive restructure, relaxation training and relapse prevention116.

Instead of keeping sleep diaries or making interviews with the patients, recent findings show that sleep characteristics can be monitored using telemedicine technology, such as smartphone applications and wearable polysomnography (PSG) or actigraphy devices117. In China, due to the large population base, there is a big pressure on medical resources to meet the continuous increase in patient needs. In public hospitals in China, the number of qualified general practitioners and specialists was significantly low compared to the number of patients, which means patients must spend large amount of time staying in the queue waiting for the interview with the doctors, and doctors always have a heavy workload to meet all patients. Under this condition, popularizing telemedicine technology which patients can easily operate by themselves at home is highly essential to save the human resources. Moreover, using telemedicine technology at home also saves time and transportation costs for the patients to get access to the first-line medical resources, especially for patients living in rural areas. Telemedicine is especially suitable for sleep monitoring due to the large amount of patients and the less reliance on physical examinations118. Positive evidence has been found that sleep related data can be captured and collected through telemedicine technology, with minimized influence of the overall sleep quality and mental health117. Originally, sleep patterns can be remotely monitored through polysomnography (PSG) and actigraphy, but these two measurements are not considered convenient for patients as special devices are usually needed117. In recent years, the development of technology has enabled the monitor of sleep through smartphones and wearable devices, which was much smaller in size and more convenient to use117. Studies have shown that smartphones and wearable devices can be used to measure various outcomes related to sleep, including sleep duration, sleep midpoint, sleep onset latency, wake time after sleep onset and sleep disruptions117, 119-121. In addition to sleep monitoring, intervention contents such as CBT interventions can also be delivered through telemedicine technology117.

This study focuses on improving blood glucose control and insomnia in T2DM patients and investigate the effect of internet-delivered cognitive behavioural therapy on sleep improvement and overall health improvement. Cognitive behavioural therapy was chosen as the intervention method of insomnia. This intervention was approved as efficient and highly popular in treating insomnia while minimizing the possible adverse effects on overall health46. In addition, this study uses telemedicine technology to monitor the sleep outcomes of the patients using a wearable device and deliver intervention materials to small groups of patients in social media applications. In existing studies, sleep outcomes are usually recorded through the self-recorded sleep diaries by the patients, which has several limitations such as patients forgot their sleep characteristics and could not record them correctly. Telemedicine devices used in this study will provide a more accurate measurement in sleep outcomes, and the use of telemedicine technology will be the future direction in this field of research122.

## 4.2 Knowledge gaps

Existing studies have found that CBT interventions targeting insomnia delivered by telemedicine technology had similar effects compared with traditional face-to-face delivery123-125, but these studies did not mention the intervention effects on diabetes-related indicators in T2DM patients. Similarly, several studies utilizing CBT intervention for glycaemic control was found78, but these studies provided very limited information on mental health outcomes and biomedical indicators other than blood glucose and HbA1c. Although there is a close relationship between T2DM and insomnia, no randomized controlled trials was found evaluating the impact of CBT intervention on T2DM management and insomnia at the same time. In addition, no study developed CBT intervention plans that specially targets T2DM patients with insomnia. Furthermore, chronic kidney disease is very common in T2DM patients126, but no existing studies mentioned the effect of CBT intervention on kidney function related biomedical indicators, such as serum creatinine, blood urea nitrogen and uric acid.

Existing studies have found that it is possible to utilize telemedicine technology on sleep monitoring, but these studies all focus on patients with obstructive sleep apnea127, 128. No randomized controlled trial studies were found using telemedicine to monitor sleep patterns in insomnia patients, especially in insomnia patients with T2DM.

## 4.3 Aims, objectives and hypothesis

The aim of this project is to evaluate the effect of internet-delivered CBT intervention on sleep quality, blood glucose level, blood lipid level, kidney function, blood pressure, obesity, psychiatric diseases, fatigue and quality of life in adults with T2DM and insomnia.

The detailed research objectives include:

(1) To improve the overall sleep quality and sleep efficiency using internet-delivered CBT based intervention in adults with T2DM.

(2) To improve the overall blood glucose level, blood lipid level, kidney function, blood pressure and obesity through internet-delivered CBT based intervention in adults with T2DM

(3) To reduce depression, anxiety, fatigue and improve quality-of-life through internet-delivered CBT based intervention in adults with T2DM.

The research hypothesis are as follows:

1. It is hypothesized thatinternet-delivered CBT-based intervention can provide positive effect in improving sleep outcomes, including insomnia severity measured by Insomnia Severity Index, sleep quality measured by Pittsburgh Sleep Quality Index, total sleep time, sleep efficiency, sleep onset latency, wake time after sleep onset and number of awakenings.
2. It is hypothesized thatinternet-delivered CBT-based intervention can improve biochemical indicators relating to T2DM, blood lipid and kidney function, including fasting blood glucose, Glycated Hemoglobin (HbA1c), total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL), triglyceride (TG), serum creatinine, blood urea nitrogen, uric acid, blood pressure, body weight, body mass index (BMI) and waist-hip ratio (WHR).
3. It is also hypothesized thatthe internet-delivered CBT-based intervention can improve other health outcomes, including depression, anxiety, fatigue and quality of life.

## 4.4 Research significance

The results from this study will contribute to the theoretical understanding of the overall effect of internet-delivered CBT based intervention on sleep outcomes, blood glucose level, blood lipid level, kidney function, mental health and quality of life in T2DM patients with insomnia. This study will also contribute to the understanding of the effect of a combined CBT intervention targeting two diseases (T2DM and insomnia) at the same time. This study provides evidence on the application of telemedicine technology for sleep monitoring and intervention delivery in patients with T2DM and insomnia for future studies in this field.

Practically, this study will develop a CBT plan combining CBT targeting T2DM and CBT targeting insomnia. The intervention contents will include cognitive restructure sessions that help the patients identify and change the negative understandings towards sleep management, blood glucose control and lifestyle factors such as diet and exercise. The intervention will also include behavioural therapy sessions that help the patients develop diet, exercise, sleep and other lifestyle habits that are beneficial to sleep quality and blood glucose control. The successful result from this study will encourage the use of internet-delivered CBT intervention when considering the management of both insomnia problems and blood glucose level in T2DM patients. In addition, this study also encourages the use of telemedicine devices to provide a more accurate sleep monitoring in insomnia patients in future research. In this case, this study promotes the implementation of CBT intervention to public hospitals in China and across the world as a normal treatment method of T2DM. The implementation of this intervention in T2DM treatment can save the time and money for the patients, as well as the workload of psychologists in the mental health department. The intervention will also contribute to the establishment of a closer relationship and trust between T2DM patients and their responsible doctors, leading to a better long-term management of the disease and a higher quality-of-life.

## 4.5 Expected outcomes

After the successful completion of the intervention program, patients in the intervention group are expected to have an average decrease in ISI scores for 4-5 points, an average 2-3 points decrease in PSQI scores. The average total sleep time is expected to be increased for at least 20 minutes, and the average sleep efficiency is expected to be increased for at least 5% in the intervention group. Both average sleep onset latency and average wake time after sleep onset are expected to be decreased for at least 10 minutes in the intervention group. For the secondary outcomes, fasting blood glucose, HbA1c, blood lipid indicators, kidney function indicators, blood pressure, body weight, BMI and WHR are expected to be decreased more significantly in intervention group than in the control group. The average scores for HAMD, HAMA, MFI and SF-12 in the intervention group are also expected to be decreased more significantly than in the control group. If the intervention is successful, this study can provide evidence that internet delivered CBT intervention can lead to a positive cognitive and behavioural changes in this patient group and provide further improvement on their sleep quality. In addition, a successful intervention will improve the diabetes related biomedical indicators, which indicates that the intervention provided by this program can increase the probability of reversing the diabetes symptoms through the improvement of sleep quality and reduce the possibility of the progression of T2DM.

# Chapter 5: Project Design

## 5.1 Research project setting

This is a randomized controlled trial study. This study involves 10 online intervention sessions covering insomnia and T2DM management delivered at a weekly basis in T2DM patients with insomnia. All participants will be recruited at the Department of Endocrinology and Metabolism, Ningbo First Hospital, Ningbo, Zhejiang, China. The online intervention sessions will be delivered through Microsoft Teams. Participants will complete an online data collection survey through Microsoft Forms and a physical examination at Ningbo First Hospital every three months.

## 5.2 Methodological approach

The problem that this project addresses is that there is a huge number of T2DM patients in China. Among these T2DM patients, there is a large proportion of them that has experienced or currently suffering from insomnia problems. Failing to manage T2DM and co-morbid insomnia can lead to further mental health problems and significant decrease in quality of life. When Chinese patients want to resolve the T2DM and insomnia problems, they are usually required to go to two different departments in public hospitals, which was highly time consuming and not cost-effective. To say the least, even if patients have the time and money for seeking for doctor advice at the same time, they usually tend to trust more on medications, which can provide more significant acute effect on blood glucose and sleep management. However, a persistent intake of drugs can lead to decreased drug actions, which forces the patients to increase the dose or start using multiple drugs, and this can result in an increasing risk of adverse effects. Existing non-pharmacological treatment all target T2DM or insomnia independently. Although non-pharmacological intervention such as CBT have positive effect on T2DM and sleep management, a separate intervention plan for T2DM and insomnia still could not solve the problem of time and money consuming for patients in the hospital.

To solve the problem stated above, a non-pharmacological treatment option targeting T2DM and insomnia at the same time, which provide long-term effect on disease management and fewer adverse effects, need to be developed to benefit all T2DM patients with insomnia in China and across the world. In this study, a CBT intervention plan targeting both T2DM and insomnia will be developed to provide a possible solution for blood glucose and sleep management in T2DM patients with insomnia, which is more cost effective with fewer adverse effects.

The control arm of this study is a normal care control. Participants in the normal care control group will only receive basic sleep hygiene and T2DM education materials every week during the project as a normal care of T2DM and insomnia. We want to ensure that all participants included in this project can receive the intervention we have developed, but the therapist responsible for online delivery will not be in China any more after the end of the project and will not be available for the intervention delivery. Therefore, participants in the normal care control group will receive full intervention materials after the end of the project for self-help reading only.

## 5.3 Participants

### 5.3.1 Description and number

The participants included in this project are adults with T2DM and insomnia. All participants will be recruited at the Department of Endocrinology and Metabolism, Ningbo First Hospital, Ningbo, Zhejiang, China. As we expected a large amount of T2DM patients with insomnia in China, we will try to include as many patients as possible in this project. We have also considered a possible dropout rate and non-response rate, and we have decided at least 300 participants are required to provide an accurate result.

### 5.3.2 Inclusion criteria

Diagnostic criteria for T2DM:

The diagnosis of T2DM is completed by qualified doctors from the Department of Endocrinology.

The diagnosis of T2DM refers to the Standards of Medical Care in Diabetes published by American Diabetes Association in 20192.

(1) Fasting plasma glucose ≥7.0 mmol/l (fasting time >8 hours)

(2) Two-hour postprandial blood glucose ≥11.1 mmol/l

(3) Random plasma glucose ≥11.1 mmol/L in patients with classic symptoms of hyperglycemia or hyperglycemic crisis

(4) Glycated Hemoglobin (HbA1c) ≥ 6.5%

In addition, all biomedical factors will be measured once if the patients already reported T2DM symptoms, including polydipsia, increased hunger, polyuria and abnormal weight loss. All biomedical factors will be measured twice to confirm the diagnosis if no typical symptoms are reported.

Inclusion criteria for insomnia:

The preliminary screening of insomnia will be completed using the Insomnia Severity Index (ISI) questionnaire129. The cut point for insomnia is 10 points129. Patients scoring above 10 in ISI will be considered as potentially insomnia.

Other inclusion criteria

(1) Patients meet the diagnostic criteria for both T2DM and insomnia, and T2DM is the primary cause of insomnia

(2) Patients aged over 18

(3) Patients not currently participating in similar intervention programs

(4) Patients fully understand the program contents, willing to participate and signed the informed consent form

(5) Patients able to use smart phones or computers to receive and view intervention materials

### 5.3.3 Exclusion criteria

(1) Patients with severe primary diseases, including severe heart, liver or renal system diseases and cancer

(2) Patients with severe psychiatric diseases that affect regular cognition and communication, including severe depression (HAMD score>18), anxiety (HAMA score>14) and schizophrenia

(3) Patients diagnosed with sleep disorders other than insomnia, including obstructive sleep apnoea, restless leg syndrome, parasomnia and hypersomnia through self-report or PSG devices.

(4) Patients who are pregnant

(5) Patients who are illiterate and cannot understand the intervention contents.

### 5.3.4 sample size calculation

Sample size is calculated through the equation130 below:

$$n=\frac{2(Zα+Z1-β)^{2}σ^{2}}{Δ^{2}}$$

Zα is a constant decided by the accepted α error and whether the study is one-sided or two-sided effect. Z1-β is a constant set by the power of the study. σ is estimated standard deviation and Δ is the estimated effect size.

In this study, we accept a *p* value<0.05 as statistically significant and a study power of 80%. A two-tailed test is used, as the results could be bidirectional. Therefore, the Zα value is 1.96, and Z1-β value is 0.8416130. Choosing sleep efficiency as main outcome and based on the published studies, the estimated standard deviation is 0.96, and the estimated effect size is 39%51. The calculated sample size for this study is at least 102 patients per arm. Considering a 30% attrition rate and 30% non-response rate in the study, the final sample size in this study is at least 326 (163 patients per arm).

## 5.4 Participant recruitment strategies and timeframes

The expected time frame of participant recruitment is 8 months. The recruitment process of the participants follows the following steps:

(1) Specialists give diagnosis of T2DM at the Department of Endocrinology.

(2) Specialists ask T2DM patients whether they have sleep difficulties.

(3) Screening of insomnia by specialist from Department of Psychosomatic Medicine in a short interview and complete screening questionnaire.

(4) Screening of sleep disorders other than insomnia using polysomnography (PSG) devices at hospital or portable PSG devices (optional).

(5) Interviewer gives diagnosis of insomnia and decide if the patients are eligible to be included in this study based on the developed inclusion and exclusion criteria.

(6) For the eligible patients, the interviewer introduces the program briefly and ask them if they are willing to participate in this project.

(7) If the patients agree to participate in the project, they will be enrolled in the study and will be randomly grouped later.

(8) Distribute informed consent to all participants prior to enrolment, and make sure they understand all contents and signed properly.

## 5.5 Approaches to provision of information to participants and consent

A paper-based information sheet containing detailed information about research team members, research design, benefits, possible risks and privacy issues of personal information will be provided to the participants during an individual face-to-face interview between one participant and one of our researchers. The participants will be allowed to read through the information consent and ask questions about the contents at any time. The researcher will answer the questions and make sure that the participants fully understand the information provided in the information sheet. The participants will then have 24 hours to decide if they want to participate in this project. If the participants agreed to participate in this project, the researcher will then present them with two copies of paper-based consent form. The researcher will explain every statement on the consent form to make sure that the participants have full understanding of the project design, benefits, risks, voluntary nature and contact details. Participants will then be asked to tick the statement: “I agree to participate in the project.”, “I consent to the inclusion of my personal information in publications or presentations resulting from this research.”, “I consent to being contacted about future research”, and sign their names, signature and date on both copies of the consent form. The participants will receive one copy of the signed consent form and the other copy will be sealed in an opaque envelope and stored in a locked locker.

## 5.6 Research activity

Intervention group:

Participants in the intervention group will be divided into smaller groups (approximately 10-12 people per group) in the social media, in which they can communicate with each other and share experience. The intervention contains ten weekly sessions, and the length of each session is approximately 60 minutes. Each of the sessions contains CBT-I intervention contents and CBT for T2DM self-management education contents. The CBT-I intervention is designed based on the CBT-I session-by-session guide131 by Perlis and colleagues. The T2DM self-management education contents were designed and published by Jing and colleagues. Materials for each intervention session contain brief revision from the previous session, PowerPoint slides, short video clips and a short quiz (3-5 multiple choice questions through Microsoft Forms). Participants will be required to complete the weekly quiz online and send the feedback to the therapists. One therapist will be available for the patients to provide help and answer questions through telephone, message and online meetings at any time. Participants completing all ten sessions (completing the end-of-session quiz) will receive a $10 transportation reimbursement at the end of the program. Patients will be required to complete an exam every four sessions to test their knowledge from the previous sessions. The exams contain short answer questions relating to sleep and diabetes, and space for patient comments and feedbacks about the program. Therapist will give comments to the answers and provide feedback to the patients individually and maintain communication with patients through weekly telephone interviews. The expected length of the treatment is 10-12 weeks. The brief contents of each session are presented in **Table 2**.

**Table 2. Contents of intervention sessions**

|  |  |  |
| --- | --- | --- |
| **Session number** | **Session contents (CBT-I)** | **Session contents (CBT for T2DM self-management)** |
| Session 1 | Introduction of team members and therapists.Introduction of the whole program and weekly plans of intervention sessions (including Q&A).  |
| Learn to keep sleep diary and use sleep-monitoring devices.Basic information about sleep.   | Basic knowledge of diabetes.Master self-management knowledge and skills.Learn to brainstorm, solve problems, and make action plans. |
| Session 2 | Review and comments on the sleep diary last week.Basic information about insomnia.Introduce concepts of sleep restriction and stimulus control.Set up plans and learn skills related to sleep restriction and stimulus control. | Learn the steps of problem solving.Learn self-monitoring methods.Learn to make a self-monitoring plan.Learn analyse the results of blood glucose monitoring. |
| Session 3 | Review and comments on the sleep diary last week.Evaluate the effect of intervention and adjust the sleep plans (if required).Sleep hygiene education. | Understand and manage hypoglycemia.Understand and manage high blood sugar.Understand and respond to acute complications.Understand and prevent chronic complications. |
| Session 4 | Review and comments on the sleep diary last week.Evaluate the effect of intervention and adjust the sleep plans (if required).Sleep hygiene education132, 133. | Understand the relationship between diet and health.Master the principles of diet for diabetic patients.Learn how to calculate the amount of diabetic diet and make their own diet plan. |
| Session 5 | Review and comments on the sleep diary last week.Evaluate the effect of intervention and adjust the sleep plans (if required).Cognitive restructure: Introduce negative understandings towards sleep. | Understand the benefits of exercise.Choose the type, amount and intensity of exercise that suits you.Make exercise plans. |
| Session 6 | Review and comments on the sleep diary last week.Evaluate the effect of intervention and adjust the sleep plans (if required).Cognitive restructure: Share the findings and experience with group members.  | Understand the commonly used oral antidiabetic drugs.Understand the insulin treatment of diabetes. |
| Session 7 | Review and comments on the sleep diary last week.Evaluate the effect of intervention and adjust the sleep plans (if required).Relaxation training: muscle relaxation, breath control | Understand common negative emotions and how to deal with them.Learn communication and communication skills. |
| Session 8 | Review and comments on the sleep diary last week.Evaluate the effect of intervention and adjust the sleep plans (if required).Relaxation training: Self training and imagination training | Understand behavioural change theory.Self-evaluate on daily behaviors and share with group members. |
| Session 9 | Review and comments on the sleep diary last week.Evaluate the effect of intervention and adjust the sleep plans (if required). | Recognize the dangers of substance consumption and stay away from it.Group discussion and share own experience. |
| Session 10 | Review and comments on the sleep diary last week.Evaluate and conclude the overall effect of intervention.Relapse prevention: make future plans and share the harvest from intervention | Conclusion of the whole project.Sharing the harvest and looking forward to the future. |

Normal care control group

Participants in the normal care control group are provided with basic education materials containing sleep hygiene information and T2DM education contents. Patients in this group are also required to complete the information collecting questionnaire at baseline, at 3 months and at 6-month follow up time points. Participants in control group will receive self-help materials of the intervention contents through email after the end of the project. Participants completing the questionnaires will also receive a $10 transportation reimbursement at the end of the program.

## 5.7 Outcome measurements

Primary outcomes:

(1) Insomnia Severity Index

The Insomnia Severity Index is a self-report questionnaire developed by Morin129, which is used to assess the severity of insomnia. The questionnaire contains seven questions evaluating severity of sleep onset, sleep maintenance, early morning awakening problems, sleep dissatisfaction, interference of sleep difficulties with daytime functioning, noticeability of sleep problems by others, and distress caused by sleep difficulties.134 The questions use a five-point Likert scale, where 0 = no problem and 4 = very severe problem. The range of the final score for the questionnaire is 0 to 28, and a higher score indicates a more severe insomnia condition. The scores for the questionnaire can be divided into four groups based on the final score: absence of insomnia (score 0 to 7), sub-threshold insomnia (score 8 to 14), moderate insomnia (score 15 to 21) and severe insomnia (score 22 to 28)129. ISI has an overall Cronbach α coefficient of 0.91 in clinical samples, and correlations between individual items and total ISI scores range from 0.50 to 0.85, which suggests that all items have a significant contribution to the total score134. The suggested time to complete this questionnaire is around 5 minutes.

(2) Pittsburgh Sleep Quality Index

The Pittsburgh Sleep Quality Index is a 19-question self-reported questionnaire assessing sleep quality135. Questions 1 to 4 are open questions, while the remaining questions use a five-point Likert scale. The 19 questions contribute to seven rating components: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication and daytime dysfunction135. Each of the components are given scores from 0 to 3, and the total score of the seven components is the final Pittsburgh Sleep Quality Index score. A final Pittsburgh Sleep Quality Index score greater than 5 suggests that the patient has poor sleep quality135.

The overall Cronbach α coefficient for PSQI is 0.83, suggesting that there is a high level of internal consistency135. Correlations between individual items and total PSQI score range from 0.35 to 0.76135. It takes about 5 minutes to complete this survey.

(3) Other sleep outcomes: total sleep time, sleep efficiency, sleep onset latency, wake after sleep onset, time in bed, number of awakenings, self-rated sleep quality

A sleep diary is considered the most important and reliable measurement to assess sleep characteristics subjectively in research and clinical conditions136. Patients are required to fill in the sleep diary every day. In sleep diaries, patients are required to record the following information about their sleep: time of nap during the day; time get into bed; time get out of bed; time try to go to sleep; time takes to fall asleep; number of awakenings; length of awakenings; final awakening time; if the patient wakes earlier than desired (yes/no) and how much time earlier; self-rated sleep quality (1 very poor to 5 very good) and comments136. Total sleep time is the total time an individual spends while asleep and total time in bed is the time an individual spends on the bed both awake and asleep137. Sleep onset latency refers to the time it takes for an individual from fully awake to fully asleep138. The normal sleep onset latency time for a healthy individual should be around ten to twenty minutes139. And wake after sleep onset refers to the total time of wakefulness after the onset of sleep, which was a good indicator of fragmentation of sleep137. The sleep diary related outcomes can be collected through self-reported sleep diaries filled by the patients, or through PSG devices during their sleep.

Secondary outcomes:

(1) Biochemical indicators (diabetes related): fasting blood glucose, Glycated Hemoglobin (HbA1c)

Fasting blood glucose refers to an overnight fasting for at least 8 hours. Blood samples will be collected in the hospital and analysed with instruments. The reference range for fasting blood glucose is 3.89-6.11 mmol/L. The reference range for HbA1c is 4-6%. These reference ranges are developed based on the 2022 version of clinical guidelines for prevention and treatment of type 2 diabetes mellitus in the elderly in China140.

(2) Biochemical indicators (blood lipid): total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), triglyceride (TG)

Venous blood samples will be collected and analysed at the hospital. The reference ranges141 for the blood lipid outcomes are:

TC: 3.00-5.70 mmol/L; HDL-C: 1.03-1.55 mmol/L; LDL-C: 1.89-3.37 mmol/L; TG: 0.00-1.70 mmol/L

(3) Biochemical indicators (kidney function): serum creatinine, blood urea nitrogen, uric acid

Venous blood samples will be collected and analyzed at the hospital. The reference ranges for kidney function outcomes142 are:

Serum creatinine: 41-73 μmol/L; Blood urea nitrogen: 2.60-7.50 mmol/L; Uric acid: 154.7-357.0 μmol/L

(4) Blood pressure: systolic blood pressure (SBP), diastolic blood pressure (DBP)

Blood pressure is measured under a quiet environment. Patients should not smoke, drink alcohol, coffee and tea drinks, engage in strenuous exercise, and empty their bladders within 30 minutes before the measurement. The patient rests quietly for at least 5 minutes before the measurement. After the first measurement, patients are asked to wait for 5 minutes, and blood pressure is measured for the second time. The final result of the blood pressure will be the average of the two measurements.

(5) Metabolic related indicators: height, weight, Body Mass Index (BMI), waist circumference, hip circumference, waist-hip ratio (WHR)

Height, weight, waist circumference and hip circumference will be measured at the hospital. Patients will be asked to take off their shoes, hat and coat, stand barefoot, keep heels tight, look straight ahead and breathe calmly during the measurement. BMI and WHR will be calculated by the computer based on the measured height, weight, waist circumference and hip circumference values.

BMI is calculated by taking a person's weight (in kilograms) divided by their height (in meters squared)143. BMI less than 16.5kg/m2 indicates severely underweight, under 18.5kg/m2 indicates underweight, 18.5 to 23.9 indicates normal weight. For Asian population, BMI between 23 and 24.9kg/m2 is overweight and BMI greater than 25kg/m2 is obesity143.

WHR is calculated by dividing the waist circumference by hip circumference. A healthy WHR should be less than 0.9 in males, and less than 0.85 in females144. A WHR higher than 1.0 in males and higher than 0.86 in females indicates a high risk of health problems144.

(6) Depression: Hamilton Depression Rating Scale145 (HDRS, HAM-D)

The HDRS (also known as the HAM-D) is the most widely used clinician-administered depression assessment scale. The original version of HDRS contains 17 items (HDRS17) pertaining to symptoms of depression experienced over the past week, including depressed mood, feelings of guilt, suicide attempts, insomnia, difficulty in works and activities, retardation, agitation, anxiety, somatic symptoms, genital symptoms, hypochondriasis, loss of weight and self-insight of illness145. The total score ranges from 0 to 52 points. A total score <10 points indicates no depression, 10-13 indicates mild depression, 14-17 indicates mild to moderate depression, and >17 indicates moderate to severe depression145. The overall Cronbach α coefficient for HDRS is 0.789146, which suggests that HRSD provides a reliable assessment of depression. The time required to complete this questionnaire is about 5 minutes.

(7) Anxiety: Hamilton Anxiety Rating Scale147 (HARS, HAM-A)

The HARS is one of the first rating scales developed to measure the severity of anxiety symptoms, and it is still widely used today in both clinical and research settings. The HARS consists of 14 items, each defined by a series of symptoms, and measures both psychic anxiety (mental agitation and psychological distress) and somatic anxiety (physical complaints related to anxiety). The items include levels of anxious mood, tension, fears, insomnia, intellectual, depressed mood, somatic symptoms, cardiovascular symptoms, respiratory symptoms, gastrointestinal symptoms, genitourinary symptoms, autonomic symptoms and behavior at interview147. The HARS score ranges are: mild anxiety = 8-14; moderate anxiety = 15-23; severe anxiety ≥ 24 (scores ≤ 7 were considered to represent no/minimal anxiety)148. The HARS showed good internal consistency (Cronbach α=0.893), and is suggested to screen for general anxiety disease148. It takes about 5 minutes to complete this questionnaire.

(8) Fatigue: Multidimensional Fatigue Inventory (MFI)149

The Multidimensional Fatigue Inventory (MFI) is a 20-item self-report questionnaire designed to measure fatigue. All items are rated on a 5-point Likert score (point 1: Yes, that is true to point 5: No, that is not true), with 10 positively items reverse scored (items 2, 5, 9, 10, 13, 14, 16, 17, 18, 19). A total of five dimensions are covered in this questionnaire: general fatigue (items 1, 5, 12, 16), physical fatigue (items 2, 8, 14, 20), mental fatigue (items 7, 11, 13, 19), reduced motivation (items 4, 9, 15, 18) and reduced activity (items 3, 6, 10, 17). The overall Cronbach α coefficient for MFI is 0.84149. It takes approximately 3 to 5 minutes to complete this questionnaire.

(9) Quality of life: 12-question short-form survey (SF-12)150

SF-12 contains 12 items assessing the overall quality-of-life of the patients in eight domains:

1) Limitations in physical activities because of health problems.

2) Limitations in social activities because of physical or emotional problems

3) Limitations in usual role activities because of physical health problems

4) Bodily pain

5) General mental health (psychological distress and well-being)

6) Limitations in usual role activities because of emotional problems

7) Vitality (energy and fatigue)

8) General health perceptions

The overall Cronbach α coefficient for SF-12 is 0.89151, and it takes about five minutes to complete the whole questionnaire.

Other factors:

(1) Demographic characteristics:

* Age (in years)
* Gender (Male/Female/Other)
* Marital status (Married/Never married/Divorced, widowed, separated/Other)
* Personal income (Approximate range of average monthly income)
* Education level (Primary/Secondary/Tertiary/Graduated and above)
* Occupation (Specify the job)
* Family size (Number of family members that live together)
* Homeownership (No/One/More than one)
* Ethnicity (Han/Other)
* Religion (Buddhism/Christianity/Islam/Hinduism/Atheism/Other)

(2) Lifestyle related factors: exercise rate, diet and nutrition information, alcohol consumption (amount and frequency), tobacco consumption (amount and frequency), addictive substance use (amount and frequency)

Diet, and exercise information is collected using the questionnaire developed by Jing and colleagues. This questionnaire contains three parts. The first part includes 34 items assessing the intake frequency and intake amount of four dietary patterns in the Chinese population152.

The dietary patterns include:

1) Traditional food pattern, including vegetable, fruit, rice, pork and fish

2) Fast and processed food pattern, including processed snacks, fast food and soft drinks

3) Soybean products, grain and flour food pattern

4) Dairy, animal liver and other animal food pattern

The second part assesses the confidence of the patients to change their eating habits for at least 6 months using a 5-point Likert scale, in which 1 indicates least confident and 5 indicates very confident152.

The third part is developed based on the exercise behavior scales by Sallis and collegues153. This part contains 4 questions assessing the confidence of patients to motivate themselves to do certain exercises consistently for at least 6 months. This part also uses a 5-point Likert scale, in which 1 indicates least confident and 5 indicates very confident152.

(3) Disease related factors:

* Length of diagnosis of T2DM (in months)
* Family history of T2DM (Yes or No family history, exact number of T2DM patients in family)
* History of insomnia (Length of developing sleep problems, frequency in days per week)
* History of any other diseases (specify disease names and history)

(4) Medication information:

* Type and dose of drugs used to treat diabetes (drug category, frequency and dose)
* Type and dose of drugs used to treat sleep problems (drug category, frequency and dose)
* Type and dose of drugs used to treat any other diseases (drug category, frequency and dose)

(5) Understandings of intervention contents:

* Knowledge relating to T2DM (blood glucose monitoring and management)
* Insomnia (insomnia related understandings and behaviours)
* Behavioural changes (Ability to judge right and wrong habits in diet, exercise, sleep patterns)

## 5.8 Data collection

All data relating to research outcomes and confounding factors will be collected at baseline, at the end of intervention (3 months) and 3 months after the end of intervention (6 months). There is a regular physical examination for T2DM patients every 3 months, and data relating to biochemical indicators will be collected during the regular physical examination and will be available from the patient medical records from the hospital. Participants will receive a small PSG device (wrist band shape, FDA approved) once enrolled in this program. Participants will be advised to put on the device during sleep at least once a week, and the device will record sleep diary related outcomes and report back to the researcher. Other information will be collected using an online survey either during a face-to-face meeting session upon the regular visit of the patients to the hospital (every 3 months), or through an online interview session if participants are unable to come to the hospital. Sleep diary related outcomes will also be included in the survey in case of the lack of data from the telemedicine device. When collecting data from sleep diaries, patients are required to complete the sleep diary for at least five days a week, and the final data for sleep diary outcomes will be calculated and collected as the average value of multiple days. Based on the recommended completing time for each section, it takes approximately 40 minutes to complete the whole survey.

## 5.9 Data management

All personal information collected during this research will be coded so that it is possible to know that data relate to the same person, but it does not identify them. All identifiers will be removed from the data prior to any publication of the data, re-use of the data or sharing of the data. All data collected in this research will be presented in research publications in a way that will not allow the participants to be identified by third parties. This research will not collect any data involving photography, audio recording or audio-visual recording that make participants identifiable in the photographs/recordings.

All of the personal information will only be available to researchers that leads this research project. The researchers will only receive de-identified data with Griffith University maintaining control over the mechanisms to reidentify.

All personal information collected paper-based will be sealed in a separate opaque file bag for each participant, and the file bags will be locked in a file locker. Only researchers in the research team listed at the beginning of this document will have access to the personal information.

Part of the personal information will be collected by online survey or passed between research partners or email between Griffith employees or stored in Griffith staff Office 365 services. Griffith University’s email system and document management system involves the storage of emails/documents within the cloud (i.e. sometimes outside of Australia) and as a result personal information may be stored overseas. The University has entered into arrangements which protect the privacy of this data, any data stored outside of Australia may be subject to compulsory access through process of law, under the relevant jurisdiction in which it is stored.

## 5.10 Data analysis

The SPSS software is used for the analysis of the data. The level of significance is set at 0.05. A *p* value smaller than 0.05 is considered as statistically significant. The data analysis process in this study involves description of baseline characteristics, identifying confounding factors and final data analysis using the intention-to-treat method.

**Description of baseline characteristics**

The baseline characteristics for all primary, secondary outcomes and other factors in all participants, intervention group and control group will be summarized and presented in one table. The levels of Skewness and Kurtosis for all variables will be measured to determine if the data is normally distributed154. The data is determined as normally distributed when the Skewness coefficient is within -3 to 3, and the Kurtosis coefficient is also within -3 to 3154. For continuous variables that are normally distributed, baseline characteristics will be presented as means and standard deviations. For continuous variables that are not normally distributed, baseline characteristics will be presented as medians and ranges. For categorical variables, baseline characteristics will be presented as the number of cases for each category and the percentage in the groups.

**Identifying confounding factors**

Independent samples t-test155 (when normally distributed) or Mann-Whitney U-test156 (when not normally distributed) will be performed to assess if there is any difference between intervention group and control group for continuous variables. A Chi square test157 will be performed to identify the difference between groups for categorical variables. If statistically significant difference between groups is identified in any variable, it will be included in the final data analysis as a possible confounding factor.

**Imputation of missing data**

The final analysis of intervention data utilizes an intention-to-treat method158. The data of all participants in this study will be included in the statistical analysis and analysed according to the original group assigned, regardless of the intervention received, drop-out and no response cases158.

For all dependent variables and confounding factors at 3 months and 6 months’ time points included in the statistical analysis, the patterns of missing data will be assessed to show the percentage of missing data. Variables with more than 5% of missing data will undergo multiple data imputation process, which aims to fill all missing data with uniform pseudorandom numbers. Mersenne Twister algorithm159, a most widely used general-purpose pseudorandom number generator which generates values with long period and high equal distribution, will be used to generate pseudorandom numbers to replace the missing data. New dataset with all missing data imputed will be generated, and the data imputation process will be repeated five times to generate a total of five iteration datasets. Next, one-way analysis of variance (ANOVA) tests with post-hoc method will be presented to analyse the difference between the five iteration datasets and the original dataset. One of the iteration datasets that does not show significant difference with the original dataset will be used for the final data analysis.

**Final data analysis**

The summary of descriptive statistics for all dependent variables at 3 months and 6 months’ time points, both pooled and in two groups, will be presented in the final result tables as means, standard deviations and number of cases.

Intention-to-treat method will be used to analyse the CBT intervention effect on dependent variables. For each of the hypothesis, Multivariate F-statistics160 will be used on dependent variables to examine whether there is significant variance between independent variable groups, in this case, if there is significant difference between the intervention and control group at different time points. Significant values of F-statistics indicate significant variance between groups. The results will be displayed as F values with degrees of freedom, Wilks’ Lambda values and *p* values. Partial eta square (η2) shows how much variance is explained by the independent variable, and it will be used as the effect size for the model.

If there is a significant difference between groups, tests of between-group effects will be performed using the univariate ANOVA tests to determine how the dependent variables differ in different groups. The Bonferroni correction161 will also be included to reduce the instance of a false positive result. The results will also be presented as F values with degrees of freedom, p values and partial η2.

For dependent variables that show significant between-group difference, further post hoc tests162 will be performed to determine where the significant differences lie, in other words, which specific independent variable level significantly differs from another. The results from post hoc tests will be presented as mean difference, standard errors, *p* values and 95% confidence intervals. Marginal means plots will also be generated to visualize the overall intervention effect across the time.

The detailed analysis method, dependent variables, independent variables and confounding factors included in the analysis of three research hypothesis are listed in the tables below.

**Table 3. Data analysis method and variable design for hypothesis 1**

|  |
| --- |
| **Hypothesis 1: Effect of internet-delivered CBT intervention on sleep outcomes** |
| **Analysis method** | **Dependent variables** | **Independent variables** | **Confounding factors** |
| * **Intention-to-treat method**
* **MANOVA test**
 | * **Overall sleep quality: Pittsburgh Sleep Quality Index**
	+ Total score
	+ Subjective sleep quality
	+ Sleep latency
	+ Sleep duration
	+ Habitual sleep efficiency
	+ Sleep disturbances
	+ Use of sleeping medication
	+ Daytime dysfunction
* **Insomnia severity: Insomnia Severity Index**
	+ Total score
	+ Score of each question
* **Sleep diary (self-reported and PSG)**
	+ Total sleep time
	+ Sleep efficiency
	+ Sleep onset latency
	+ Wake after sleep onset
	+ Number of awakenings
	+ Time in bed
	+ Self-rated sleep quality
 | * **CBT intervention**

InterventionControl* **Time**

Baseline 3 months 6 months | * **Demographic characteristics:**

Age, gender, marital status, monthly income, education level, occupation, family size, homeownership, ethnicity and religion* **Lifestyle related factors**

Exercise rate, alcohol consumption, tobacco consumption, substance use, nutrition information* **Disease related factors**

Length of diagnosis of T2DM, family history of T2DM, history of insomnia, history of any other diseases* **Medication information**

Type and dose of drugs used to treat diabetes, type and dose of drugs used to treat sleep problems, type and dose of drugs used to treat any other diseases* **Understandings of intervention contents**

Knowledge relating to T2DM and insomnia, knowledge of helpful behaviours (diet, exercise, sleep patterns) |

**Table 4. Data analysis method and variable design for hypothesis 2**

|  |
| --- |
| **Hypothesis 2: Effect of internet-delivered CBT intervention on biochemical indicators relating to T2DM, blood lipid, kidney function, blood pressure and biomedical indicators** |
| **Analysis method** | **Dependent variables** | **Independent variables** | **Confounding factors** |
| * **Intention-to-treat method**
* **MANOVA test**
 | * **T2DM related indicators:**

Fasting blood glucose, HbA1c* **Blood lipid:**

Total cholesterol, HDL, LDL, triglyceride* **Kidney function:**

Serum creatinine, blood urea nitrogen, uric acid* **Blood pressure:**

SBP, DBP* **Metabolic factors:**

Weight, BMI, waist circumference, hip circumference, WHR | * **CBT intervention**

InterventionControl* **Time**

Baseline 3 months 6 months | * **Demographic characteristics:**

Age, gender, marital status, monthly income, education level, occupation, family size, homeownership, ethnicity, race and religion* **Lifestyle related factors**

Exercise rate, alcohol consumption, tobacco consumption, substance use, nutrition information* **Disease related factors**

Length of diagnosis of T2DM, family history of T2DM, history of insomnia, history of any other diseases* **Medication information**

Type and dose of drugs used to treat diabetes, type and dose of drugs used to treat sleep problems, type and dose of drugs used to treat any other diseases* **Understandings of intervention contents**

Knowledge relating to T2DM and insomnia, knowledge of helpful behaviours (diet, exercise, sleep patterns) |

**Table 5. Data analysis method and variable design for hypothesis 3**

|  |
| --- |
| **Hypothesis 3: Effect of internet-delivered CBT intervention on depression, anxiety, fatigue and quality-of-life** |
| **Analysis method** | **Dependent variables** | **Independent variables** | **Confounding factors** |
| * **Intention-to-treat method**
* **MANOVA test**
 | * **Depression: Hamilton Depression Inventory**
	+ Total score
	+ Score of each item
* **Anxiety: Hamilton Anxiety Inventory**
	+ Total score
	+ Score of each item
* **Fatigue: MFI**
	+ Total score
	+ General fatigue
	+ Physical fatigue
	+ Mental fatigue
	+ Reduced motivation
	+ Reduced activity
* **Quality-of-life: SF-12**
	+ Total score
	+ Physical health
	+ Mental health
 | * **CBT intervention**

InterventionControl* **Time**

Baseline 3 months 6 months | * **Demographic characteristics:**

Age, gender, marital status, monthly income, education level, occupation, family size, homeownership, ethnicity, race and religion* **Lifestyle related factors**

Exercise rate, alcohol consumption, tobacco consumption, substance use, nutrition information* **Disease related factors**

Length of diagnosis of T2DM, family history of T2DM, history of insomnia, history of any other diseases* **Medication information**

Type and dose of drugs used to treat diabetes, type and dose of drugs used to treat sleep problems, type and dose of drugs used to treat any other diseases* **Understandings of intervention contents**

Knowledge relating to T2DM and insomnia, knowledge of helpful behaviours (diet, exercise, sleep patterns) |

# Chapter 6: Results, Outcomes and Future Plans

## 6.1 Plans for return of results or findings of research to participants

Participants will receive the paper-based results of medical examinations within 5 business days after the completion of the examination. Participants will receive the scores and therapist feedbacks of online survey via email within 5 business days after the completion of the survey.

## 6.2 Plans for dissemination and publication of project outcomes

The results from this project will be reported and published in three separate peer-reviewed journal articles.

## 6.3 Project closure process

After the end of the project, the Lead Investigator will make sure that all paper-based documents are properly documented and archived. All participants will be requested to provide their feedbacks on this project, and the feed backs will be evaluated by the research team members. A project outcomes meeting will be held in the research group to report the outcomes of the project, summarize the problems found and discuss for any further research. All research group members, participants and organizations will receive a letter of appreciation to thank their support and participation in this project.

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