Gut Reaction: Can Probiotics Improve Wellbeing in Adults with Type 1 Diabetes?

A Randomised, Parallel Arm, Placebo-Controlled Trial in Adults with Type 1 Diabetes

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Abstract

Background: The challenging task of managing type 1 diabetes (T1D) incurs a significant behavioural and psychological burden. T1D is associated with an increased risk of depression and anxiety, which can negatively impact glycaemic control. With T1D incidence increasing each year, developing approaches to optimise glycaemic control and the psychological health of individuals with T1D is imperative. Accumulating evidence suggests that probiotics may be a novel therapy to improve depression and anxiety symptoms and glycaemic control in those with T1D through manipulating the gut microbiota and gut-brain axis. However, no studies have investigated probiotics' effects on mood and glycaemic control in adults with T1D.

Aim: The study aimed to investigate whether consuming probiotics could reduce symptoms of depression and anxiety and improve glycaemic control in adults with T1D. The study also explored the prevalence of depression, anxiety and stress symptoms in adults with T1D and their beliefs of probiotics.

Method: The study was a 1:1 randomised, double-blind, parallel-arm placebo-controlled trial. A total of 74 adults (>18 years old) with T1D were recruited and randomised to consume either a probiotic (*Lactobacillus rhamnosus* HN001 at a dose of 6 x 10^9 cfu/day), or a placebo capsule, daily for 12-weeks. Outcome measures included depression, anxiety and stress symptoms, diabetes quality of life, and glycaemic control, and were assessed at baseline and after the 12-week intervention.

Results: Analyses revealed that *L. rhamnosus* HN001 did not improve symptoms of depression, anxiety or stress, quality of life, or glycaemic control compared to placebo. Rather, all outcome measures displayed a significant improvement across the 12-week

intervention, irrespective of group allocation. Those who reported more severe symptoms of depression, anxiety and stress at baseline did not show greater improvements following probiotic supplementation.

Conclusion: Probiotics did not confer beneficial effects on mental health measures or glycaemic control compared to placebo and therefore cannot be recommended to adults with T1D at present. Further research is required to validate and build upon these findings to establish if different probiotic strains, dosages, and whether pre-existing levels of physiological and psychological health can impact the efficacy of probiotics in this population.

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Table of Contents

List of Figures

List of Tables

Chapter 1 Type 1 Diabetes

Type 1 diabetes (T1D) is a chronic heterogeneous disorder affecting millions of people worldwide (International Diabetes Federation, 2019; Mobasseri et al., 2020). The disorder is characterised by absolute insulin deficiency due to immune-mediated destruction of pancreatic β-cells (Maahs et al., 2010). The discovery of insulin in 1921 transformed T1D from a fatal illness to a chronic degenerative one (Nathan, 1993). Nevertheless, increased survival of patients with T1D gave rise to new challenges, including the burden of managing a relentless chronic health condition and the increased risk for mental health issues. Therapeutic approaches for optimising the management and quality of life for individuals with T1D are steadily improving but remain suboptimal. The need for such strategies is imperative; global T1D incidence grows each year (Derraik et al., 2012; Patterson et al., 2012), and so too does the short and long term impact of T1D on physical and psychological wellbeing. One potential therapeutic approach could be to target the gut microbiota via the administration of probiotics (Cryan et al., 2019; Jamshidi et al., 2019; Knip & Siljander, 2016; Rogers et al., 2016).

The purpose of this chapter is to introduce T1D and highlight its pervasive impact on people living with this condition. Firstly, the epidemiology of T1D is described, followed by a discussion of genetic and environmental influences for the onset and progression of T1D, including the possible role of the gut microbiota. Next, short and long-term complications that individuals with T1D face are summarised before discussing the importance of optimal self-care behaviours and glycaemic control. Finally, the burden of this chronic health condition and its management on people living with T1D is considered.

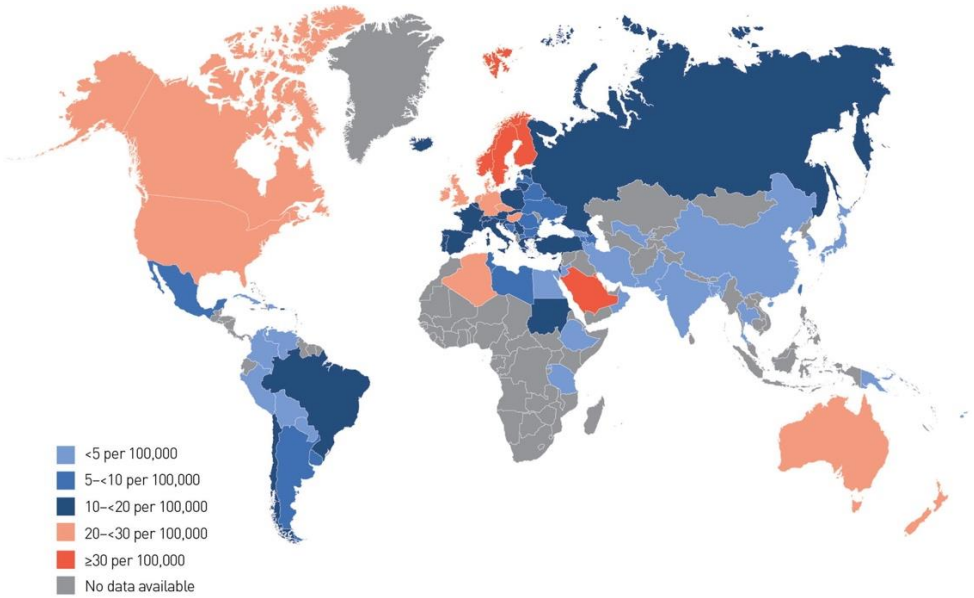
1.1 Epidemiology

Typically diagnosed in childhood, T1D is one of the most prevalent chronic conditions in this age group (Atkinson & Eisenbarth, 2001). Latest global estimates indicate 1.1 million children and adolescents are living with T1D, while across all age groups, for every 100,000 people, there are 15 individuals with T1D (International Diabetes Federation, 2019; Mobasseri et al., 2020). However, the true prevalence of T1D may be underestimated from misdiagnosis of T1D as type 2 diabetes (T2D) (de Lusignan et al., 2012; Thomas et al., 2018). Alarmingly, it appears that more people are being diagnosed with T1D each year, with epidemiological studies consistently revealing an annual increase in the incidence of T1D by 2-5% (Derraik et al., 2012; DIAMOND Project Group, 2006; Lipman et al., 2013; Mobasseri et al., 2020; Patterson et al., 2012).

There are striking geographical disparities in T1D incidence (See Figure 1) (Karvonen et al., 2000; Kondrashova et al., 2005; Patterson et al., 2012). China, India and Venezuela report the lowest incidence of T1D (~0.1 cases per 100,000 people per year), in marked contrast to Sardinia and Finland who report the highest rates of T1D (~40 cases per 100,000 people per year and >60 cases per 100,000 people per year, respectively) (Patterson et al., 2009). Substantial differences in incidence exist even between neighbouring countries. For instance, despite sharing a border, the incidence of T1D is almost six-fold lower in Russian Karelia than in Finland (Kondrashova et al., 2005). Within-country variation is also observed, with incidence rates three to five times greater in Sardinia than continental Italy (Karvonen et al., 2000). Furthermore, migrating populations adopt the incidence rates of their new countries within a short period. For example, the incidence of T1D of South Asian children in the UK is similar to their peers, rather than the notably lower incidence rates reported from Asia (Raymond et al., 2001).

Figure 1

Map of Age-Sex Standardised Global Incidence Rates of T1D in Children Aged Under 15 Years



Note. From "Worldwide estimates of incidence, prevalence and mortality of type 1 diabetes in children and adolescents: Results from the International Diabetes Federation Diabetes Atlas, 9th edition" by C. Patterson, S. Karuranga, P. Salpea, P. Saeedi, G. Dahlquist, G. Soltesz, G. Ogle, 2019, *Diabetes Research and Clinical Practice*, *157*, p.4 (https://doi.org/10.1016/j.diabres.2019.107842).

1.2 Aetiology

T1D is caused by an autoimmune destruction of the insulin-producing β-cells of the pancreas leading to insulin deficiency (Anderson & Bluestone, 2005). The trigger (or triggers) of the autoimmune response remains unclear. The predominant model of T1D development postulates that everyone is born with a degree of inherent susceptibility to develop T1D (Eisenbarth, 1986). Some may have a greater risk, and others lower, and this vulnerability to develop the condition is largely inherited. Depending on one's individual

propensity to develop T1D, the model proposes that one or more environmental factors then triggers the autoimmune destruction of the pancreatic β-cells (Bluestone et al., 2010).

1.2.1 Genetic Factors

Genomic studies have uncovered a myriad of genes that increase risk for and protect against the development of T1D (Erlich et al., 2008). At least one of the high-risk genotypes are present in up to 90% of individuals with T1D, and both are present in 30% of this population, contrasting to 2% of the general population (Redondo et al., 2018). Additionally, prospective studies of relatives of patients with T1D found that those with the high-risk genotypes are significantly more likely to develop the condition than those without (Aly et al., 2006; Redondo et al., 2006). However, the genetic influence in the development of T1D is not straightforward, with other genes found to offer protective functions against the condition (Erlich et al., 2008).

1.2.2 Environmental Factors

While there is undoubtedly genetic influence in the aetiology of T1D, we cannot attribute the rate of T1D incidence increase to genetic shift or more children born from mothers with T1D (Maahs et al., 2010; Soltesz et al., 2007). Indeed, several studies report a temporal trend where fewer adolescents diagnosed with T1D have the aforementioned high-risk genotypes (Gillespie et al., 2004; Hermann et al., 2003; Steck et al., 2011; Vehik et al., 2008). The authors propose that an increase in environmental factors may reduce the need for genetic susceptibility in T1D development. Furthermore, as previously mentioned, migrating individuals adopt the same risk of T1D as those in their new country, and populations merely separated by a socioeconomic border exhibit substantially different T1D incidence despite

being genetically similar. This literature points towards a critical role of environmental factors in the aetiology of T1D.

Researchers suggest the increase in the incidence of T1D may result from the marked changes in diet and lifestyle that has accompanied the rapid social change of the past century (Karvonen et al., 2000). Research spanning decades have identified numerous putative environmental triggers and factors that may promote the initiation and progression of T1D. For instance, T1D development is associated with infectious agents, particularly enteroviral infections (Stene & Rewers, 2012; Yeung et al., 2011), dietary factors such as early introduction of cow's milk (Lamb et al., 2015; Vaarala et al., 1999), and early stressful life events such as a death in the family (Hägglöf et al., 1991; Sepa et al., 2005; Thernlund et al., 1995; Vlajinac et al., 2006). Research has also revealed potential protective environmental factors, including breastfeeding and Vitamin D (Frederiksen et al., 2013; Mayer et al., 1988).

Recently a prospective cohort study across North America and Northern Europe termed The Environmental Determinants of Diabetes in the Young (TEDDY) study (Rewers et al., 2018) was initiated to identify environmental factors that trigger or protect against T1D by intensively following 8678 children from birth with high-risk T1D genotypes. Results thus far suggest that islet autoimmunity, which the authors consider to predispose T1D onset, is associated with respiratory infections in early childhood, enteroviral infections, use of hydrolysed infant formula, and accelerated weight gain (Hummel et al., 2017; Knip et al., 2008; Lönnrot et al., 2017). Sufficient Vitamin D, fish-derived fatty acids and exposure to probiotics in early infancy, on the other hand, was associated with a decreased risk of islet autoimmunity (Norris et al., 2018; Rewers et al., 2018; Uusitalo et al., 2016).

Another notable finding from the TEDDY study is the association between T1D and the gut microbiota. The study revealed that compared to the microbiota of children who

developed islet immunity or T1D, the microbiota of children who did not develop these conditions contained more genes responsible for fermentation and the production of their beneficial by-product, short-chain fatty acids (Vatanen et al., 2018). Several studies have also demonstrated an association between altered gut microbiota composition and development of T1D, with a recent systematic review of 26 studies revealing a significant correlation between altered gut microbiota structure and T1D (Alkanani et al., 2015; Davis-Richardson et al., 2014; de Goffau et al., 2013; Harbison et al., 2018; Jamshidi et al., 2019; Kostic et al., 2015; Mejía-León et al., 2014; Mullaney et al., 2018; Murri et al., 2013). Interestingly, the aforementioned risk factors for T1D, such as lack of breastfeeding, stress, and exposure to probiotics, have also reliably shown to influence the composition of the gut microbiota (Bailey et al., 2011; Lee et al., 2015; Ma et al., 2020; Murakami et al., 2017; Uusitalo et al., 2016). The above findings suggest gut dysbiosis may potentially have a causative role for T1D. Importantly, this information also supports exploring the use of probiotics to restore gut microbiota balance as a possible therapeutic approach for individuals with T1D.

1.3 Complications of T1D

While researchers continue to elucidate possible triggers of the pathogenesis of T1D, the complications associated with T1D are well known. T1D-associated complications include both short and long-term complications. Many of these complications result from either low or high blood glucose levels (hypoglycaemia and hyperglycaemia, respectively). Although theoretically, these complications are preventable, maintaining glycaemic concentrations within a narrow physiologic range is extremely challenging. For example, intensive insulin therapy is endorsed as the gold standard of care for T1D as it markedly reduces the risk of T1D-associated complications (Diabetes Control and Complications Trial Research Group, 1993). Unfortunately, intensive insulin therapy also increases the risk of

another complication, hypoglycaemia (Diabetes Control and Complications Trial Research Group, 1997).

1.3.1 Short-term Complications

Hypoglycaemia is a common yet potentially debilitating short-term complication of T1D. Estimates reveal that patients with T1D can experience up to ten symptomatic hypoglycaemic episodes a week and more severe hypoglycaemic episodes at least once per year (Briscoe & Davis, 2006; Diabetes Control and Complications Trial Research Group, 1997). Causes include administering too much insulin, insufficient consumption of carbohydrates, and physical activity or illness, with previous hypoglycaemic episodes increasing the risk of subsequent ones (Briscoe & Davis, 2006; Fidler et al., 2011). Glucose is the brains primary source of energy (McAulay et al., 2001). Given the brains inability to store or synthesise glucose itself, it is vulnerable to severe drops in blood glucose concentrations brought on by excessive insulin. When glycaemic levels fall below ~3.8mmol/L, the body initiates a protective counterregulatory response against insulin (Schwartz et al., 1987). As a result, individuals with T1D experience symptoms including shakiness, anxiety, sweating, and palpitations, and if glucose levels become extremely low (<2 mmol/L) can lead to confusion, coma and seizure (Briscoe & Davis, 2006; McAulay et al., 2001).

Along with physical symptoms, hypoglycaemia can induce negative affect. A study demonstrated that hypoglycaemia increased feelings of lethargy, tension and led to significantly more negative appraisals of life obstacles (McCrimmon et al., 1999). Hypoglycaemia is also associated with reduced quality of life (Fidler et al., 2011; Rossi et al., 2019). It is, therefore, unsurprising that fear of the various unpleasant symptoms associated with hypoglycaemia is common and can significantly impede an individual's ability to achieve their glycaemic targets (Briscoe & Davis, 2006; Wild et al., 2007). In fact, patients

with T1D sometimes mitigate their fear of hypoglycaemia by reducing or omitting insulin doses and increasing carbohydrate intake to increase blood glucose levels (Fidler et al., 2011; Lawton et al., 2013). Consequently, fear of hypoglycaemia can be a significant obstacle to achieving optimal glycaemic control.

Another common short-term complication of T1D is diabetic ketoacidosis, which, in contrast to hypoglycaemia, is caused by a lack of insulin. Children often present with symptoms of diabetic ketoacidosis at the point of diagnosis, however, the complication remains a significant concern throughout adulthood (Stephenson et al., 1994; Usher-Smith et al., 2012). Insulin deficiency in those already diagnosed with T1D can be due to individuals inadvertently or intentionally missing doses, a technological failure with ones' insulin pump, or augmented levels of counterregulatory hormones, such as from stress or infection (Wolfsdorf et al., 2007). Symptoms of diabetic ketoacidosis include excessive hunger and thirst, abdominal pain, fatigue, acetone smelling breath, and vomiting. Unless the individual receives fluid and electrolyte therapy and exogenous insulin, these symptoms can provoke a vicious cycle increasing the severity of the diabetic ketoacidosis, leading to coma or death (Misra & Oliver, 2015).

1.3.2 Long-term Complications

Although hypoglycaemia and diabetic ketoacidosis can certainly be life-threatening, the majority of morbidity and mortality in T1D is associated with long-term microvascular (small blood vessels) and macrovascular (large blood vessels) complications (Daneman, 2005). Risk factors of microvascular complications include hyperglycaemia, high blood pressure, high cholesterol levels and smoking, as well as unmodifiable factors such as genes, age of T1D diagnosis and disease duration (Daneman, 2005). Microvascular complications include retinopathy (eye disease), nephropathy (kidney disease) and neuropathy (nerve

damage). Macrovascular complications include stroke and cardiovascular disease, which is also the leading cause of death in patients with T1D (Calles-Escandon & Cipolla, 2001).

1.4 Treatment & Management of T1D

Patients with T1D may never be completely free from the risk of short and long-term complications; however, they can drastically reduce their risk of diabetes-related complications by optimising their self-care behaviours and glycaemic control.

1.4.1 Glycaemic Control

Glycaemic control is seen as the cornerstone of diabetes management. It is indicated by Haemoglobin A1c (HbA1c) concentrations in the blood, which acts as a measure of average blood glucose levels in the previous 90-120 days (Sacks, 2005). The importance of glycaemic control for patients with T1D became apparent during the influential Diabetes Control and Complications Trial (DCCT), a large multicentre randomised controlled study involving 1441 patients with T1D, and the Epidemiology of Diabetes Interventions and Complications (EDIC) observational follow-up study (Diabetes Control and Complications Trial Research Group, 1993). The DCCT confirmed a causal relationship between hyperglycaemia and the onset or progression of microvascular and macrovascular complications (Nathan et al., 2013). They observed no threshold effect; any decrease in HbA1c concentrations was associated with a decreased risk of complications. These findings highlight the pivotal role of glycaemic control in the risk of developing complications in T1D.

1.4.2 Self-management

Self-care behaviours are crucial in helping individuals with T1D achieve their recommended glycaemic targets, developed in collaboration with the patient, family, and health care team (American Diabetes Association, 2013). One vital component of T1D self-management is lifelong exogenous insulin replacement, with intensive insulin therapy being the predominant treatment choice. It involves multiple daily injections where a long-acting insulin analogue establishes basal insulin levels, and those with T1D administer fast-acting insulin before meals based on the amount of carbohydrate ingested (Atkinson et al., 2014). An alternative, increasingly utilised mode is via continuous subcutaneous insulin infusions, or insulin pumps, which automatically administers fast-acting insulin at preselected rates (Alsaleh et al., 2010).

Another fundamental aspect of T1D management is blood glucose monitoring. By facilitating appropriate insulin delivery, dietary choices and amount of physical activity, regular self-monitoring of blood sugar levels can improve glycaemic control and reduce the risk of hypoglycaemia and diabetic ketoacidosis (American Diabetes Association, 2013; Evans et al., 1999; Karter et al., 2001). One self-monitoring method is pricking one's fingertip and drawing a small amount of blood to test in a blood glucose monitoring device, ideally performed three to four times per day (American Diabetes Association, 2013). Alternatively, a continuous blood glucose monitoring device can record real-time blood glucose levels using a sensor placed under the skin's surface. Continuous blood glucose monitoring provides greater insight into one's glucose levels over the day, and as such, studies have found that continuous blood glucose monitoring is associated with improved glycaemic control compared to traditional self-monitoring (Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group, 2008; Klonoff, 2005; Ludvigsson

& Hanas, 2003). Closed-loop insulin pump systems, where continuous blood glucose monitors control insulin delivery using sophisticated algorithms, are also increasingly being tested (Bergenstal et al., 2016). These rapidly evolving devices are promising but remain out of reach for most people living with T1D due to their cost.

T1D management involves a high level of self-awareness and self-discipline, particularly in monitoring one's diet. Variations in carbohydrate intake, engaging in physical activity or experiencing illness or life stress are commonplace occurrences that can alter blood glucose levels (American Diabetes Association, 2013). Following dietary guidelines and counting carbohydrates is one of the central self-care behaviours to help achieve optimal glycaemic control (Franz et al., 2002). Current recommendations suggest dietary planning should consider the individual's dietary preferences, age, stage of development, weight, culture and lifestyle (American Diabetes Association, 2004).

Those living with diabetes are also encouraged attend regular screening appointments for diabetes-related complications and common co-morbid disorders, including thyroid and coeliac disease (Holmes, 2001; Kordonouri et al., 2005). Moreover, people with T1D should be made aware of and encouraged to utilise psychological resources if they need them. Psychological conditions such as eating disorders, depression and anxiety are common in individuals with T1D and have shown to negatively impact self-care behaviours and subsequently hinder optimal diabetes management (Jones et al., 2000; Roy & Lloyd, 2012; Schmitt, McSharry, et al., 2021; K. Smith et al., 2013).

1.5 Mental Health in T1D

T1D-management is unequivocally demanding, both behaviourally and psychologically. Individuals with T1D must make numerous decisions, be acutely aware of

their physiological and psychological state, and exercise a high standard of self-care and self-discipline all day, every day. Additionally, people with T1D are well aware of their risk of numerous microvascular and macrovascular conditions associated with the condition, further increasing the stress of living with T1D. Effective initial and ongoing education and care from a multidisciplinary team involving physicians, nurses, dieticians, psychologists and behavioural specialists experienced in the management of T1D improves the clinical outcomes of patients (Griffin & Kinmonth, 2000; Keers et al., 2005; Renders et al., 2001). Nonetheless, in reality, the majority of the burden of T1D management falls upon the patient. Due to the chronic nature of T1D and the burden of self-management, it is not surprising that T1D is associated with an increased risk of psychological disorders such as depression and anxiety (Roy & Lloyd, 2012; K. Smith et al., 2013). The significant implications of mental health comorbidities in T1D are discussed in more detail in the following chapter (Chapter 2).

1.6 Summary

Type 1 diabetes (T1D) is a chronic, heterogeneous condition affecting millions of individuals worldwide. It is characterised by autoimmune-mediated destruction of insulin-producing pancreatic β-cells, leading to absolute insulin deficiency and the need for immediate and lifelong exogenous insulin. Although the scientific community is still trying to elucidate the exact mechanisms underlying disease onset and progression, the prevailing model theorises that T1D results from a combination of genetic susceptibility and environmental triggers. Individuals with T1D are faced with numerous challenges related to their self-care regimen: the onerous day-to-day management of T1D, coping with short-term complications of suboptimal glycaemic control, and screening for and treating long-term T1D-associated complications. There is a profound psychological impact of living with T1D, contributing to reduced quality of life and prevalence of mental health conditions such as

depression and anxiety. With the knowledge that the incidence of T1D consistently increases each year, further research into aetiology and influencing factors of the condition is imperative; so that cures, preventative measures and therapeutic advances are possible.

Chapter 2 Mental Health in Type 1 Diabetes

Living with T1D incurs an extensive behavioural and psychological burden. People with T1D are required to live according to a strict management plan involving hundreds of daily decisions to achieve their blood glucose targets. On top of that, individuals with T1D are at greater risk of developing mental health comorbidities (Roy & Lloyd, 2012; K. Smith et al., 2013). Ordinarily, mental health conditions incur serious repercussions on the inflicted individual, family, and wider healthcare system, especially if left untreated (Kessler et al., 2009; Schonfeld et al., 1997; Trautmann et al., 2016). When combined with T1D, the consequences can be even more detrimental.

This chapter introduces two of the most prevalent mental health disorders among individuals with T1D; depression and anxiety. Although eating disorders and disordered eating behaviours are also significant concerns in this population, with estimates that the conditions are twice as prevalent in individuals with T1D compared to those without T1D (Jones et al., 2000; Mannucci et al., 2005; Young et al., 2013), they are beyond the scope of this thesis. This chapter focusses on the prevalence and impact of depression and anxiety on individuals with T1D, followed by a discussion of possible underlying mechanisms for the associations between these comorbidities. Thereafter, the treatment options for depression and anxiety and their efficacy for individuals with T1D are described. Due to depression and anxiety frequently co-occurring, their treatment options will be discussed as a whole (Kessler et al., 1994). Finally, a novel therapeutic avenue for improving anxiety and depression in T1D, the use of probiotics, will be introduced.

2.1 Depression

2.1.1 Definition and Conceptualisation

Major Depressive Disorder, or depression, is defined as experiencing one or more depressive episodes comprising at least two weeks of depressed mood or diminished interest or pleasure, accompanied by a minimum of four other depressive symptoms (American Psychiatric Association, 2013; Beck & Alford, 2009). Such symptoms include loss of energy, loss of or heightened appetite, sudden loss or gain in weight, concentration difficulties, difficulties with sleep, slowing of physical movement, feelings of worthlessness or excessive guilt, and recurrent thoughts of death and suicide (American Psychiatric Association, 2013). Depression is associated with impairments in psychosocial, occupational and physiological functioning and imposes an extensive financial burden on society (Ayuso-Mateos et al., 2010; Evans et al., 2013; Hirschfeld et al., 2000; Moldin et al., 1993; Wang et al., 2003).

One must reach a predetermined threshold of symptoms to be considered clinically depressed (American Psychiatric Association, 2013). However, the literature suggests that depressive disorders may be better conceptualised along a continuum of severity (Ayuso-Mateos et al., 2010; Judd & Akiskal, 2000). Ayuso-Mateos et al. (2010) found that depressive disorders form a spectrum of symptom severity, and across the entire range of this spectrum, those with depression experienced a significant reduction in health status compared to those without. These findings imply that the presence of any symptoms of depression, irrespective of a clinical diagnosis, carries significant implications for one's health and wellbeing.

2.1.2 Prevalence

Depression is a common experience endured by individuals with T1D, with estimates that depression is present in up to one-third of individuals with T1D (Castellano-Guerrero et

al., 2018; Pouwer et al., 2010). Worryingly, mounting evidence indicates those with T1D have an increased risk of developing depression compared to those without (Anderson et al., 2001; Barnard et al., 2006; Gendelman et al., 2009; Poulsen & Pachana, 2012; Roy & Lloyd, 2012). In fact, meta-analyses have demonstrated the risk of depression for those with diabetes is approximately triple that of the general population (Anderson et al., 2001; Roy & Lloyd, 2012).

2.1.3 Impact

As outlined above, depression is associated with substantial detriments in almost all aspects of functioning. Unfortunately, patients with T1D are already at greater risk of morbidity and mortality due to the challenging task of maintaining blood glucose levels within a narrow physiologic range. Depression and depressive symptoms, therefore, have the potential to augment the risk of adverse health outcomes for this already vulnerable population.

Depressive symptoms at all levels of symptom severity are associated with suboptimal self-management and glycaemic control (Schmitt, McSharry, et al., 2021). Specifically, studies have found that depression in people with T1D is associated with missed medical appointments, reduced adherence to dietary recommendations and lower frequency of blood glucose monitoring (Ciechanowski et al., 2000; Gonzalez et al., 2008; Van Tilburg et al., 2001). Suboptimal glycaemic control, primarily observed as high blood glucose levels, is also associated with depression and depressive symptoms (Lustman, Anderson, et al., 2000; Lustman & Clouse, 2005; Pouwer et al., 2010; Roy & Lloyd, 2012; Van Tilburg et al., 2001). Given the understanding that adherence to one's T1D self-management regime increases the ability to achieve glycaemic targets, researchers postulate that reduced self-management at least partly mediates this association between suboptimal glycaemic control

and depressive symptoms (Gonzalez et al., 2008; Schmitt, Bendig, et al., 2021; Schmitt, McSharry, et al., 2021; Van Tilburg et al., 2001).

Comorbid depression and T1D exacerbate the adverse health outcomes those with T1D are susceptible to. A meta-analysis by de Groot et al. (2001) demonstrated a consistent significant relationship between depression and numerous T1D-associated complications, including retinopathy, nephropathy, neuropathy, macrovascular complications and sexual dysfunction. Heightened severity of depressive symptoms was associated with greater acuteness or number of complications. Subsequent longitudinal studies support the findings from the meta-analysis (Kinder et al., 2002; Roy, Peng, et al., 2007; Roy, Roy, et al., 2007). Moreover, although there is minimal data specific to T1D, it appears that individuals with comorbid depression and T1D or T2D have a significantly higher risk of mortality compared to those without diabetes (van Dooren et al., 2013; Zhang et al., 2005).

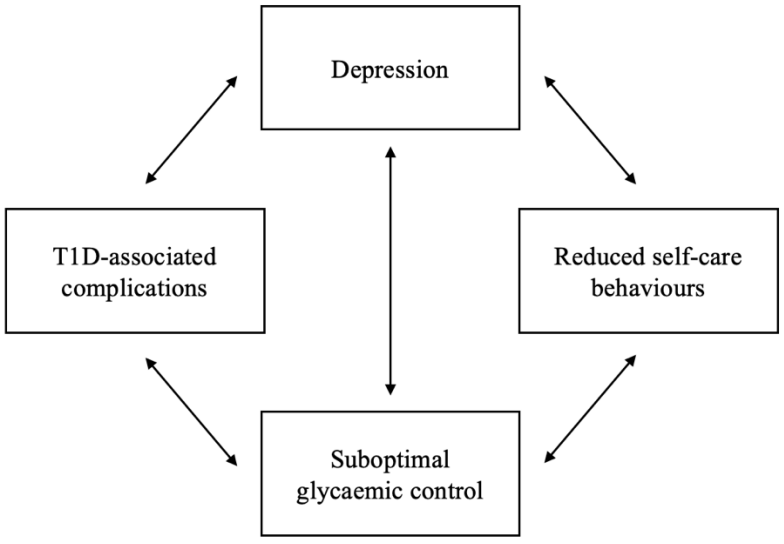
Unfortunately, the detrimental effects of depression and T1D extend beyond health consequences. For working-age individuals with T1D or T2D, depression may contribute to work performance difficulties and unemployment (Von Korff et al., 2005). Furthermore, comorbid depression and T1D are significantly associated with increased healthcare use and expenditures, even after adjusting for age, sex, ethnicity and other comorbidities (Ciechanowski et al., 2000; Egede et al., 2002). In fact, in 1996, it was estimated that among people with T1D, the total healthcare expenditures for those with depression were four and a half times greater than those without depression (Egede et al., 2002).

A growing body of literature exploring the association between T1D and depression has uncovered a complex, bidirectional relationship (Alzoubi et al., 2018). For instance, a recent meta-analysis by Nouwen et al. (2019) found that while depression increased the risk of microvascular and macrovascular complications, T1D-associated complications also

increased the risk of developing a depressive disorder. Although, the risks were disproportionate, and depression influenced the likelihood of developing complications more so than the risk of developing depression as a result of complications. The bidirectional relationship between depression and T1D also manifests as their ability to negatively impact each other. As described above, comorbid depression and T1D are associated with reduced adherence to management regimes, suboptimal glycaemic control, and increased risk of developing T1D-associated complications. Additionally, reduced self-management behaviours and glycaemic control can exacerbate depressive symptoms and may hinder response to treatment for depression, thereby creating a vicious cycle (see Figure 2) (Castellano-Guerrero et al., 2018; Lustman & Clouse, 2005).

Figure 2

Vicious Cycle Between Risk of Depression, Reduced Self-care Behaviours, Suboptimal Glycaemic Control and Risk of T1D-associated Complications



2.2 Anxiety

Along with depression, anxiety is one of the most common psychological conditions faced by individuals with T1D (Northam et al., 2005). Anxiety can be conceptualised as an adaptive, evolutionary emotion, serving as a threat detection system and narrowing one's attention to solve pressing tasks (Marks & Nesse, 1994). Nevertheless, anxiety can and often does become maladaptive in excess, leading to considerable distress and impairment in numerous aspects of functioning (Cassady & Johnson, 2002; Essau et al., 2014; Olatunji et al., 2007). Anxiety disorders typically present as anxious thoughts (for example, "what if I fail"), somatic symptoms (for example, shakiness, increased heart rate, and nausea) and dysfunctional behaviours (such as avoidance), although different anxiety disorder subtypes have distinct presentations (American Psychiatric Association, 2013; Grigsby et al., 2002). The most common anxiety disorders in individuals with T1D are general anxiety disorder, specific phobia (typically of needles), and fear of hypoglycaemia (Blevins et al., 2020; Garrett & Doherty, 2014; Grigsby et al., 2002).

2.2.1 Prevalence

Compared to depression, there is a paucity of research examining associations between anxiety and T1D. Nonetheless, the studies conducted suggest that anxiety is a common experience in patients with T1D (Collins et al., 2009; Grigsby et al., 2002; Janzen Claude et al., 2014; Lloyd et al., 2000; Maia et al., 2014; K. Smith et al., 2013). For example, a study of 110 people with T1D found that 60% reported anxiety symptoms, while 16.4% presented with an anxiety disorder (Maia et al., 2014). Unfortunately, similar to depression, it appears that those with diabetes (both T1D and T2D) may be at a greater risk of developing anxiety disorders compared to those without diabetes (Collins et al., 2009; Kendzor et al., 2014; K. Smith et al., 2013).

2.2.2 Impact

While the scientific community recognise that anxiety is prevalent amongst those with T1D, determining the impact of anxiety on health outcomes is less straightforward. Studies have demonstrated that in people with T1D, anxiety is associated with suboptimal diabetes self-management, increased blood glucose levels, T1D-associated complications and more severe pain from complications (Anderson et al., 2002; Gore et al., 2005; Kendzor et al., 2014; Lloyd et al., 2000; Nefs et al., 2019; Shaban et al., 2009). Additionally, as anxiety is an unpleasant experience, it can lead to avoidance of the anxiety-provoking object or situation. An example for those with T1D is mitigating their fear of hypoglycaemia by consciously increasing their blood glucose levels (Arend et al., 2019; Fidler et al., 2011; Lawton et al., 2013). However, Anderbro et al. (2015) noted that elevated anxiety symptoms in individuals with T1D were associated with improved glycaemic control and more frequent blood glucose monitoring. Perhaps anxiety regarding T1D-associated complications increases motivation to utilise health services and adhere to one's self-management regime, such as frequent blood glucose monitoring, to reduce their risk of complications (Eastin & Guinsler, 2006; Horenstein & Heimberg, 2020). In saying that, anxiety evidently has detrimental effects on T1D outcomes and psychological wellbeing.

Similar to depression, it is likely that T1D and anxiety have a bidirectional relationship, whereby each condition can negatively impact each other. As some of the most common anxieties of those with T1D can only emerge following diagnosis with T1D, such as fear of long-term complications associated with T1D, fear of needles from daily insulin injections, and fear of hypoglycaemia, it is reasonable to postulate that living with T1D leads to anxiety (Cemeroglu et al., 2015; de Groot et al., 2016; Snoek et al., 2000; Zambanini et al., 1999). However, anxiety symptoms can also impede T1D self-care behaviours, consequently

negatively affecting glycaemic control (Blevins et al., 2020; Castellano-Guerrero et al., 2018). In turn, this can increase levels of anxiety, demonstrating a similar vicious cycle.

2.3 Treatment

Effectively treating mental health conditions in individuals with T1D is imperative. Not only are people with T1D at greater risk of developing depression and anxiety than the general population, but the presence of these psychological conditions and T1D can act on each other to exacerbate their adverse outcomes on both physical and mental wellbeing.

Several studies have investigated the efficacy of treatments for anxiety and depression in patients with T1D, showing promising results. Studies utilising cognitive behavioural therapy, the most widely studied psychological intervention, have significantly reduced symptoms of depression and anxiety in individuals with T1D and T2D (C. Li et al., 2017; Lustman et al., 1998; Markowitz et al., 2012; Uchendu & Blake, 2017). Other psychotherapies such as group mindfulness-based cognitive therapy and blood glucose awareness training are also effective in reducing depressive and anxiety symptoms, with awareness training, in particular, reducing anxiety regarding hypoglycaemia (Cox et al., 2001; van Son et al., 2013). Finally, pharmacological approaches involving antidepressant medications significantly improved symptoms of depression in individuals with T1D and T2D (Baumeister et al., 2012; Lustman, Freedland, et al., 2000; Lustman et al., 1997; Williams et al., 2007).

Nevertheless, the current treatments available to individuals with T1D and comorbid depression and anxiety are inadequate and are often difficult to access. Psychotherapies such as cognitive behavioural therapy are time-intensive and require psychological expertise to deliver, making them tough to incorporate into routine diabetes care. Moreover, despite the

clear associations between depression, anxiety and glycaemic control, evidence that psychological or pharmacological interventions can improve glycaemic control are inconclusive (Winkley et al., 2006; Winkley et al., 2020). In fact, one study found that antidepressant nortriptyline increased blood glucose levels (Lustman et al., 1997). Taken together, there is a clear need for novel, accessible and cost and time-efficient approaches to treating mental health conditions in T1D.

A promising option for treating mental health conditions in individuals with T1D may be the use of probiotics. As mentioned in Chapter 1, research into possible environmental influences in the development and progression of T1D revealed an association between T1D and changes in gut microbiota composition (Harbison et al., 2018; Jamshidi et al., 2019). Additionally, albeit this will be discussed further in Chapter 3, the gut microbiota has shown to have crucial bottom-up influences on health, cognition and behaviour, and is implicated in depression and anxiety (Cryan & Dinan, 2012; Cryan et al., 2019; Jandhyala et al., 2015; Jiang et al., 2018; Sanada et al., 2020; Simpson et al., 2021; Q. Zhang et al., 2021). Probiotics, which can help restore the balance of the gut microbiota, may therefore have the capacity to improve psychological and physical health in individuals with T1D.

2.4 Summary

In sum, depression and anxiety are prevalent mental health conditions experienced by individuals with T1D, who are at a greater risk of developing these mental health conditions than those without T1D. Mental health disorders are especially problematic for people living with T1D, as higher rates of anxiety and depression are associated with higher rates of non-adherence, suboptimal glycaemic control and higher risk for life-threatening T1D-related complications. Although several psychological and pharmacological treatments exist for depression and anxiety, they are often unfeasible to implement in a busy clinical setting.

Therefore, the need for novel treatment approaches for depression and anxiety in individuals with T1D is paramount.

Chapter 3 Human Gut Microbiota & the Gut-Brain Axis

The concept that the gastrointestinal tract and the microbes that inhabit it are involved in human health has existed for centuries (Abernethy, 1826; Bested et al., 2013a; Johnson, 1827). In the 1800s and 1900s, conditions such as neurasthenia (similar to modern-day chronic fatigue syndrome), melancholia (an early concept of depression), and neuroses were attributed to colonic-derived toxins (Abbey & Garfinkel, 1991; Bested et al., 2013a; Kendler, 2020; Lane, 1912). While surgical removal of the colon emerged as a radical yet popular treatment choice, microbiologist Metchnikoff proposed one could instead "fight microbe with microbe" after noting age-related improvements in patients' health following lactic acid bacteria consumption (Abernethy, 1826; Bested et al., 2013a; Lane, 1913; Metchnikoff & Williams, 1912). Nonetheless, observations were primarily anecdotal and lacked robust empirical evidence, and the theory that the gut was influential in health was largely neglected for many decades (Bested et al., 2013a). However, the advent of modern genomic sequencing technologies and an increasing number of high-quality studies in recent years has dramatically enhanced our understanding of the structure and function of the gut microbiota in health and disease (Cryan et al., 2019; Gilbert et al., 2018). It is now evident that the gut microbiota is involved in many critical determinants of physical and mental health, and that gut bacteria may play a key role in enhancing human health (Cryan et al., 2019; Foster & McVey Neufeld, 2013; Jandhyala et al., 2015; Rhee et al., 2009; Rogers et al., 2016; Sekirov et al., 2010). In fact, the extensive metabolic capability and essential function of the gut microbiota in numerous aspects of physiology have motivated researchers to hail the gut microbiota as an organ in itself (Jandhyala et al., 2015; O'Hara & Shanahan, 2006).

This chapter provides a discussion on the influence of the gut microbiota on physical and mental health. Firstly, the acquisition and development of the human gut microbiota are

described, followed by a summary of the various factors that influence gut microbiota composition. The function of the gut microbiota in health and disease, including conditions such as T1D, is then outlined. Lastly, the gut-brain axis is introduced. With a particular focus on how the microbiota may contribute to depression and anxiety, the preclinical research elucidating communication pathways between the gut microbiota and the brain is briefly discussed.

3.1 Human Gut Microbiota

The term microbiome refers to all the microorganisms and their genetic material living in a particular environment, and microbiota represents all the living organisms forming the microbiome (Berg et al., 2020). Thus, the term gut microbiota refers specifically to the communities of microorganisms present throughout the gastrointestinal tract (Evrensel & Ceylan, 2015; Thursby & Juge, 2017). These dynamic and complex communities include bacteria, fungi, viruses, archaea and protozoans (Belkaid & Hand, 2014; Sekirov et al., 2010).

3.1.1 Composition and Development

The gut microbiota comprises trillions of organisms belonging to thousands of different species (Savage, 1977). Data from the Human Microbiome Project and Metagenome of the Human Intestinal Tract (MetaHIT) project provides the most comprehensive view of the composition of the human gut microbiome to date (Hugon et al., 2015; Li et al., 2014). The widely circulated estimate that there are ten times as many bacterial cells in the human body compared to human cells has been revised to be closer to a 1:1 ratio (Savage, 1977; Sender et al., 2016a, 2016b). Nonetheless, results from the Human Microbiome Project and MetaHIT project indicate there could be over 10 million non-redundant genes in the human

gut microbiome, highlighting the extensive functional capacity of the gut microbiota (Hugon et al., 2015; Li et al., 2014).

The understanding of the acquisition of the gut microbiota has advanced in past decades. It was widely accepted that the foetus and intrauterine environment were sterile, and consequently, colonisation of the gut microbiota occurred immediately ensuing birth (Grölund et al., 1999). However, evidence from recent studies using modern sequencing technologies have challenged this traditional view, with authors now proposing that neither the foetus, placenta, nor amniotic fluid is sterile, and development of the microbiota begins in the womb (Aagaard et al., 2014; Collado et al., 2016; Collado & Segata, 2020; Jiménez et al., 2008; Perez-Muñoz et al., 2017).

The infants' gut microbiota is largely shaped by the mode of delivery and further influenced by diet (i.e. breastmilk, formula or mixed feeding), hygiene levels and medication use (Dominguez-Bello et al., 2010; Grölund et al., 1999; Lee et al., 2015; Lozupone et al., 2012; Ma et al., 2020; Mackie et al., 1999; Penders et al., 2006; Stewart et al., 2018). The infant gut microbiota is initially low in diversity but promptly increases in complexity so that by around two and a half years of age, the gut microbiota resembles that of an adult (Thursby & Juge, 2017; Yatsunenko et al., 2012). This colonisation of the infant gut microbiota is not random or chaotic as previously described, with researchers observing distinct increments in bacterial diversity coinciding with life events such as the introduction of solid foods (Koenig et al., 2011; Stewart et al., 2018).

Researchers are uncertain as to what constitutes a healthy gut microbiota; however, suggest that optimal gut microbiota composition reflects ones' particular lifestyle and is, therefore, different for each individual (Rinninella et al., 2019; Schnorr et al., 2014). With that said, it appears that a healthy gut microbiota comprises functional diversity and

community stability (Lloyd-Price et al., 2016). Genomic studies demonstrate that microbiota with high gene counts are associated with a lower prevalence of metabolic disorders and obesity, whereas microbiota with low gene counts contain higher volumes of pro-inflammatory bacteria associated with inflammatory bowel disease (Joossens et al., 2011; Swidsinski et al., 2005). Studies have also revealed that individuals with T1D exhibit less diverse gut microbiotas than those without T1D, and, notably, such differences in microbiota diversity have been observed in infants prior to islet autoimmunity (Dedrick et al., 2020; Giongo et al., 2011; Kostic et al., 2015).

3.1.2 Variation in Gut Microbiota Composition

Gut microbiota composition is dynamic and varies over time and across populations. For instance, gut microbiota composition changes across one's lifespan (Odamaki et al., 2016; Stewart et al., 2018; Woodmansey et al., 2004; Xu et al., 2019; Yatsunenko et al., 2012). The microbiota also differs along the length of the gastrointestinal tract depending on the transit time of consumed products, nutrient and chemical gradients along the gut, presence of immunological markers, and the physical structure of the gut wall (Donaldson et al., 2016; Graf et al., 2015; Gu et al., 2013).

Along with intra-individual differences, gut microbiota composition varies considerably between individuals. Studies indicate it is likely each person has a unique gut microbiota (Dethlefsen & Relman, 2011; Jakobsson et al., 2010; Ley et al., 2006; Zoetendal et al., 2001). Genetics appears to play a role in gut microbiota structure, with the similarity in faecal bacteria composition in homozygotic twins being significantly higher than unrelated individuals, and a large-scale study noting presence of country-specific microbial signatures (Li et al., 2014; Zoetendal et al., 2001). The gut microbiota also changes depending on one's culture and whether someone is living in an urban or rural environment, with possible

underlying factors being differing cultural behaviours or diets, the standard of living, hygiene levels, and the availability and exposure to medicines and vaccinations (Knip & Siljander, 2016; Li et al., 2014; Tyakht et al., 2013; Yatsunenko et al., 2012).

Although the gut microbiota is relatively stable in adulthood, it is still vulnerable to disturbances by environmental factors. For instance, diet can substantially impact gut microbiota composition. There are significant differences in the gut microbiota between breastfed and formula-fed infants (Lee et al., 2015; Ma et al., 2020), plant-based diet and animal-based diets in adults (David et al., 2014), and between western and traditional or rural diets (De Filippo et al., 2010; Grzeskowiak et al., 2012; Schnorr et al., 2014; Yatsunenko et al., 2012). Likewise, ingestion of antibiotics consistently alters the composition of the gut microbiota, with studies noting antibiotic treatment significantly lowers bacterial diversity for up to four years post-treatment in adults with possibly further enduring effects in infants (Dethlefsen et al., 2008; Dethlefsen & Relman, 2011; El Aidy et al., 2013; Fouhy et al., 2012; Gasparrini et al., 2019; Gensollen et al., 2016; Jakobsson et al., 2010; Jernberg et al., 2007; Panda et al., 2014). Furthermore, albeit the majority of the evidence is preclinical, it appears that stress, including social, early life and physiological stress, also impacts gut microbiota composition (Bailey & Coe, 1999; Bailey et al., 2011; Golubeva et al., 2015; Karl et al., 2017; Murakami et al., 2017; O'Mahony et al., 2009).

3.1.3 The Role of Gut Microbiota in Health

The gut microbiota and humans have adaptively co-evolved over centuries to develop an intricate, symbiotic relationship (Ley et al., 2008; Moeller & Sanders, 2020). Crucial functions of the gut microbiota include shaping and reinforcing the gut epithelial barrier, regulating gut motility, syntheses of neurotransmitters and essential vitamins humans are incapable of producing, and metabolising nutrients from our diet (Barrett et al., 2012; Clarke

et al., 2013; den Besten et al., 2013; Husebye et al., 2001; LeBlanc et al., 2013; Martens et al., 2002; Natividad & Verdu, 2013; Reigstad et al., 2015; Sonnenburg et al., 2005). Furthermore, the gut microbiota protects against the over-representation of pathogenic bacteria while maintaining a healthy balance of different bacterial species, and is fundamental in development and modulation of the immune system (Bäumler & Sperandio, 2016; El Aidy et al., 2015; Fukuda et al., 2011; Gensollen et al., 2016; Kamada et al., 2013; Olszak et al., 2012).

An example of this essential relationship between the gut microbiota and the host is the colonic bacteria's ability to ferment complex carbohydrates the host cannot digest, resulting in the production of short-chain fatty acids (Flint et al., 2012; Macfarlane & Macfarlane, 2003). Along with acting as the primary energy source for the gastrointestinal epithelial cells, short-chain fatty acids are involved in promoting gut barrier integrity, regulating immune and inflammatory responses, modulating appetite, and has anti-cancer properties (Chambers et al., 2015; Corrêa-Oliveira et al., 2016; Morrison & Preston, 2016; Nakkarach et al., 2021; Scharlau et al., 2009; P. M. Smith et al., 2013).

3.1.4 The Role of Gut Microbiota in Disease

A consequence of the close symbiotic relationship between the gut microbiota and the host is that gut dysbiosis, an imbalance or dysregulation of gut microbiota composition, is implicated in the predisposition, initiation and progression of numerous disease-states (Carding et al., 2015; El Aidy et al., 2015). Dysbiosis may result from any of the factors described above that alter gut microbiota composition, such as antibiotic use, dietary or lifestyle changes, or parasitic infections. Gut dysbiosis is associated with numerous physiologically diverse disease-states, including, but not limited to, cystic fibrosis (Bruzzese et al., 2014), atherosclerosis (Karlsson et al., 2012), cardiovascular disease (Novakovic et al.,

2020), obesity (Ley et al., 2006), T2D (Gurung et al., 2020), colon cancer (Gao et al., 2015; Manichanh et al., 2006), Parkinson's disease (Petrov et al., 2017), Alzheimer's (Seo & Holtzman, 2019) and osteoporosis (Wang et al., 2017). Gut dysbiosis is also associated with several immune mediated inflammatory conditions including Crohn's disease (Frank et al., 2007), rheumatoid arthritis (Vaahtovuo et al., 2008), multiple sclerosis (Berer et al., 2011), and, notably, appears to have a role in development of T1D (Alkanani et al., 2015; Davis-Richardson et al., 2014; de Goffau et al., 2013; Harbison et al., 2018; Jamshidi et al., 2019; Kostic et al., 2015; Mejía-León et al., 2014; Murri et al., 2013). Moreover, several studies demonstrate that gut microbiota composition is significantly different in individuals with depression and anxiety compared to those without depression or anxiety (Jiang et al., 2015; Jiang et al., 2018; Sanada et al., 2020; Simpson et al., 2021; Q. Zhang et al., 2021).

The underlying mechanisms for the association between the gut microbiota and various disease-states are yet to be fully elucidated. Presently, the only consistent pattern of change in the gut microbiota is a decrement in functional diversity (Carding et al., 2015; Lloyd-Price et al., 2016). This likely reflects the complexity of the relationship between the gut microbiota, the individual and the particular health condition. Additionally, given most studies are cross-sectional, it is unclear whether gut dysbiosis contributes to disease, is a consequence of disease, or both.

However, a picture of the gut microbiota's role in particular conditions, such as T1D, is emerging (Atkinson & Chervonsky, 2012; Bibbò et al., 2017; Davis-Richardson & Triplett, 2015; Knip & Honkanen, 2017; Knip & Siljander, 2016; Mishra et al., 2019; Zheng et al., 2018). Prospective studies show gut microbiota alterations precede the development of T1D (Davis-Richardson et al., 2014; Harbison et al., 2018; Vatanen et al., 2018). The gut microbiota contributes to the immune system's normal development, maturation and regulation in early postnatal life (Gensollen et al., 2016; Olszak et al., 2012). Consequently,

gut dysbiosis could induce abnormal immune function and contribute to autoimmunity (Mishra et al., 2019). Moreover, as described above, the gut microbiota augments gut wall integrity. Gut dysbiosis, on the other hand, is associated with increased intestinal permeability. Compromised intestinal lining can allow bacteria to leak into the bloodstream, triggering an immune response and chronic low-grade inflammation (Fukui, 2016; Isolauri et al., 2004). Numerous studies demonstrate that increased intestinal permeability is associated with T1D and that increased intestinal permeability is present before T1D onset (Bosi et al., 2006; Harbison et al., 2018; Lee et al., 2010; Li & Atkinson, 2015; Maffeis et al., 2016; Neu et al., 2005; Sapone et al., 2006; Vaarala et al., 2008; Visser et al., 2010). With the knowledge that pathogenesis of T1D involves immune-mediated destruction of pancreatic β-cells, authors theorise that gut dysbiosis contributes, either directly or indirectly, to the abnormal autoimmune response that leads to the development of T1D (Al Theyab et al., 2020; Atkinson & Chervonsky, 2012; Bibbò et al., 2017; Knip & Honkanen, 2017; Mishra et al., 2019; Morris et al., 2016; Neu et al., 2005). Although, further research is necessary to uncover exactly how the gut microbiota is implicated in T1D pathogenesis.

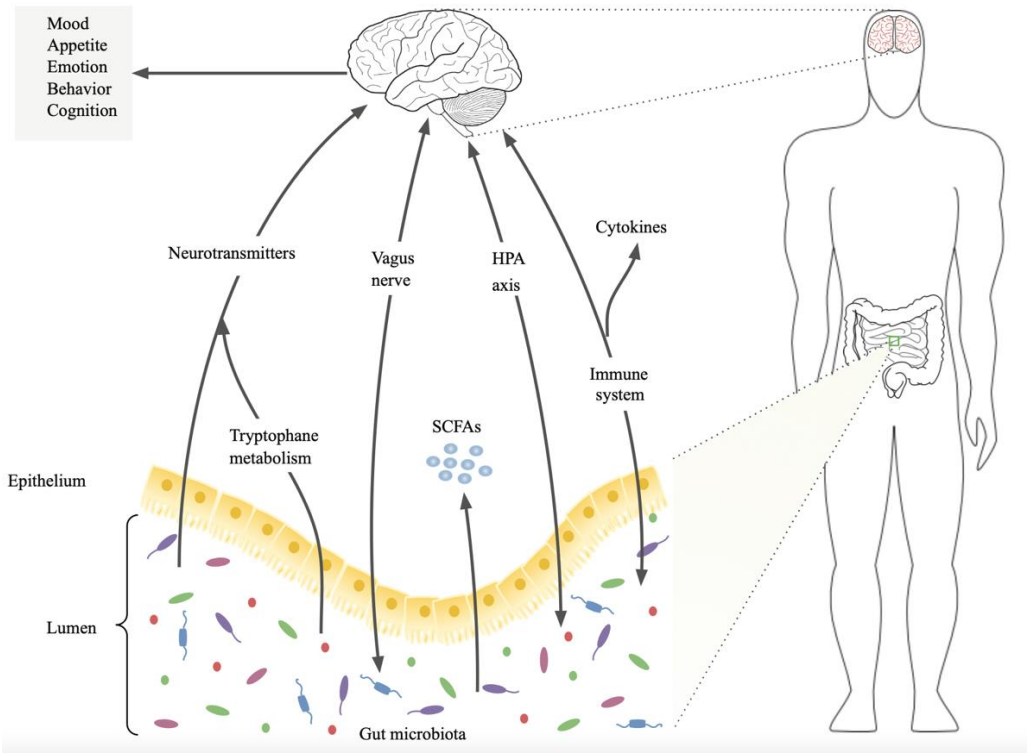
3.2 Gut-Brain Axis

The acceleration of research into the gut microbiota has also revealed a putative mechanism by which gut dysbiosis impacts mental health: the gut-brain axis (Cryan et al., 2019; Foster & McVey Neufeld, 2013; Rogers et al., 2016). The gut-brain axis is a bidirectional communication network between the central and enteric nervous systems (Carabotti et al., 2015; Cryan et al., 2019; Rogers et al., 2016). That is, the brain sends signals to the gastrointestinal tract, influencing functions such as motility, blood flow and visceral sensations such as pain or bloating, while the gut sends signals to the brain to influence mood, cognition and behaviour (Carabotti et al., 2015; Rhee et al., 2009). The

communication pathway exists through endocrine, metabolic, neural and immune routes (see Figure 3) (Carabotti et al., 2015; Collins et al., 2012; Foster & McVey Neufeld, 2013). Although communication between the gut and the brain is well-established, the scientific community have recently come to recognise the gut microbiota itself as a fundamental component in this relationship, prompting authors to retitle the model to the 'microbiota-gut-brain axis' (Collins et al., 2012; Cryan & Dinan, 2012; Cryan et al., 2019; Rhee et al., 2009; Rieder et al., 2017).

Figure 3

Bidirectional Communication Pathways of the Gut-Brain Axis



Note. From "Exploring the microbiota-gut-brain axis for mental disorders with knowledge graphs," by T. Liu, X. Pan, X. Wang, K. A. Feenstra, J. Heringa and Z. Huang, 2020, *Journal of Artificial Intelligence for Medical Sciences, 1*(3-4), p. 32 (https://doi.org/10.2991/jaims.d.201208.001).

Preclinical research, primarily using rodent models, has been instrumental in shaping our understanding of the gut-brain axis. Studies show that mice without gut microbiota (germ-free mice) display reduced anxiety-like and depressive behaviours compared to mice colonised with a microbiota (specific pathogen-free mice) (Heijtz et al., 2011; Neufeld et al., 2011; Zheng et al., 2016). Other studies demonstrate perturbation of the gut microbiota by pathogens, whether transient or chronic, is associated with increased anxiety- and depressive-like behaviours in mice (Bercik et al., 2010; Hoban et al., 2016; Lyte et al., 2006). Whereas administration of antimicrobials to specific pathogen-free mice, with an associated change in microbiota composition, reduced anxiety-like behaviours (Bercik, Denou, et al., 2011). Dispensing probiotic strains *Bifidobacterium longum* or *Bifidobacterium breve* also decreased anxiety-like behaviours in an innately anxious strain of mice, with effects similar to that of antidepressant escitalopram (Savignac et al., 2014). Interestingly, studies have demonstrated that transferring microbiota from mice or humans displaying anxiety-like and depressive behaviours to low anxiety mice led to an increased expression of these behaviours and associated changes in brain chemistry (Bercik, Denou, et al., 2011; Kelly et al., 2016; Zheng et al., 2016). The reverse trend is also true, whereby mice exhibited reduced anxiety-like behaviours following transfer of gut bacteria from low anxiety mice (Bercik, Denou, et al., 2011; Sudo et al., 2004). Furthermore, pathogen-infected mice exhibited memory dysfunction when exposed to a stressor; however, memory deficits were prevented when mice were treated daily with probiotics *Lactobacillus rhamnosus* and *Lactobacillus helveticus* (Gareau et al., 2011). These results imply that one's gut microbiota composition may contribute to the behavioural phenotype in depression and anxiety (American Psychiatric Association, 2013; Luczynski et al., 2016).

Although the exact mechanisms wherein the gut microbiota influences mood, cognition and behaviour in the host are not fully understood, preclinical experiments have

identified the vagus nerve, the hypothalamic-pituitary-adrenal (HPA) axis, immune cytokines, neurotransmitters, neurotrophic factors, and metabolites as important elements in the bidirectional communication network (Bercik, Park, et al., 2011; Bravo et al., 2011; Cryan et al., 2019; Sudo et al., 2004; Wikoff et al., 2009). For example, Sudo et al. (2004) demonstrated that germ-free mice had heightened activity of the HPA axis. This crucial neuroendocrine system regulates numerous body processes in response to stress, such as digestion, the immune system, energy storage and expenditure (Tsigos & Chrousos, 2002). The exaggerated stress response was entirely reversed when mice were supplemented with probiotic *Bifidobacterium infantis* and partially reversed when colonised by faecal microbiota of specific pathogen-free mice, when administered within an early timeframe (Sudo et al., 2004). Further experiments demonstrate gut microbiota composition is associated with the expression of hippocampal brain derived neurotropic factor (BDNF), an essential protein involved in neuroplasticity, memory and learning (Bercik, Denou, et al., 2011; Bercik et al., 2010; Calabrese et al., 2014; Hoban et al., 2016; Neufeld et al., 2011; Sudo et al., 2004). Additionally, the microbiota appears to be involved in neurotransmitter signalling by increasing production of serotonin and γ-Aminobutyric acid (GABA) and modulating expression of their receptors within the central nervous system (Barrett et al., 2012; Clarke et al., 2013; Cryan & Dinan, 2012; Reigstad et al., 2015; Yano et al., 2015). These findings are clinically meaningful given that HPA axis hyperactivity, reduced BDNF expression, and dysregulated serotonin and GABA signalling are all associated with depression and anxiety (Kraus et al., 2017; Martinowich et al., 2007; Möhler, 2012; Pariante & Lightman, 2008; Shimizu et al., 2003).

While the preclinical experiments described above are a modest selection of the burgeoning research base into the gut-brain axis, the results nonetheless provide significant implications. Firstly, evidence supports that altering the composition of the gut microbiota

can induce changes in brain chemistry, cognition and behaviour indicative of depression and anxiety, at least in mice (Bercik, Denou, et al., 2011; Bercik et al., 2010; Gareau et al., 2011; Kelly et al., 2016; Lyte et al., 2006; Sudo et al., 2004; Zheng et al., 2016). Secondly, restoration of the gut microbiota, particularly using probiotics, can normalise or prevent such changes (Bercik et al., 2010; Bravo et al., 2011; Desbonnet et al., 2010; Gareau et al., 2011; Savignac et al., 2014; Sudo et al., 2004). Probiotics, therefore, are positioned to be a potential alternative or adjuvant therapy for depression and anxiety via the gut-brain axis (Rhee et al., 2009; Rogers et al., 2016). However, caution should be exercised when extrapolating these conclusions from animals to humans, especially given that the normal inter-individual variation in gut microbiota composition observed in humans is negated in rodent models from being raised in highly controlled laboratory environments. The use of probiotics in humans to ameliorate symptoms of depression and anxiety and how they may benefit individuals with T1D will be discussed further in Chapter 4.

3.3 Summary

In summary, the exponential growth of research into gut microbiota in recent decades has vastly enhanced our understanding of its role in human health and disease. Research reveals the gut microbiota is involved in many critical determinants of health; immune system development and function, programming and regulation of neuroendocrine systems, protection against pathogens, producing vital nutrients and neurotransmitters, and, markedly, influencing mood, cognition and behaviour through the gut-brain axis. Therefore, it is unsurprising that gut dysbiosis is implicated in numerous health conditions, including T1D, depression and anxiety. Disturbances in gut microbiota composition result from environmental factors such as mode of birth, diet, exposure to antimicrobials, lifestyle, illness and stress. However, emerging research reveals that the consumption of probiotics can

stabilise these perturbations and either prevent or normalise the behavioural and neurochemical changes associated with gut dysbiosis. Consequently, probiotics may have the potential to offer meaningful improvements to health and wellbeing for individuals living with depression and anxiety and possibly also for individuals living with autoimmune mediated disorders such as T1D.

Chapter 4 Probiotics

As research into the gut microbiota and its function in physical and mental health grows, so too does the scientific community's interest and exploration into the use of probiotics. An increased curiosity in probiotics is paralleled amongst the general public, with Google trends demonstrating the search term "probiotics" grows in popularity each year (Kamiński et al., 2019). However, the concept of consuming bacteria to improve health is hardly a novel phenomenon, with references of ancient civilisations across the globe ingesting fermented food and drink in historical and religious texts, including Egyptian hieroglyphics, the Old Testament, and early sacred Hinduism books (Gasbarrini et al., 2016; Gogineni et al., 2013; Tamang et al., 2020; Tamime, 2002). Despite the longstanding anecdotal recognition that probiotic bacteria can benefit health, probiotics are only recently emerging as a potential empirically based treatment. Notably, accumulating evidence suggests that consumption of probiotics can improve mood, alter behaviour, and reduce the risk, progression and symptoms of disease, including T1D (Knip & Honkanen, 2017; Mishra et al., 2019; Vaghef-Mehrabany et al., 2020; Yang et al., 2019).

This chapter firstly defines probiotics and additional relevant terms, followed by an introduction to the possible therapeutic uses of probiotics. The effects of probiotics in mental health conditions such as depression and anxiety are examined, including possible reasons why some findings are inconsistent. The discussion then shifts to the therapeutic effects of probiotics in physical health, with a specific focus on how probiotics may benefit those with T1D. The possible mechanisms of action of probiotics in improving both mental and physical health outcomes are described. Finally, the therapeutic possibilities of probiotics are explored, particularly in how probiotics may ameliorate symptoms of depression and anxiety and improve clinical outcomes such as glycaemic control in individuals with T1D.

4.1 Introduction to Probiotics

4.1.1 Definitions

The scientific community define probiotics as "live organisms that, when administered in adequate amounts, confer a health benefit on the host" (Hill et al., 2014) (p. 507). Probiotic compounds are found naturally in fermented food and drink such as yogurt, kefir, kimchi or kombucha (Sanders et al., 2018). Probiotics are also developed for consumption in the form of capsules, tablets, or freeze-dried sachets and may be offered as single or multiple species (Havenaar et al., 1992). Most probiotics belong to the *Lactobacillus, Bifidobacterium* and *Saccharomyces* genera and examples of species and strains frequently used from these genera include *L. acidophilus, L. rhamnosus* GG, *L. acidophilus, B. bifidum, B. longum* and *S. boulardii* (Isolauri et al., 2004; Sanders et al., 2018). The term probiotic encompasses a magnitude of different microbes with diverse characteristics and metabolic activities, hence the importance of discussing probiotics effects using the correct nomenclature (Sanders et al., 2018).

An associated concept to probiotics is prebiotics. Prebiotics are non-digestible compounds that, when metabolised by microbes of the gut (including probiotic bacteria), induce changes in gut microbiota composition and activity that confer a benefit to host health (Bindels et al., 2015; Gibson et al., 2004; Gibson & Roberfroid, 1995; Slavin, 2013). Commonly utilised prebiotics include inulin and oligofructose, but prebiotics also occur naturally in some foods such as green vegetables, legumes and bananas, as well as human breastmilk (Bindels et al., 2015; Markowiak & Śliżewska, 2017). Prebiotics may be administered alongside probiotics, considered a synbiotic (Schrezenmeir & de Vrese, 2001). As alluded to by the name, synbiotics can create a synergistic effect whereby the prebiotic compound favours the growth and activity of the probiotic compound, essentially enhancing

the effect of the probiotic on host health (Markowiak & Śliżewska, 2017; Schrezenmeir & de Vrese, 2001). Therefore, prebiotics and synbiotics may constitute another approach to restore balance to the gut microbiota (Gibson et al., 2004).

4.1.2 Characteristics

All probiotics are unique. Even within the same species, different probiotic strains colonise distinct parts of the gastrointestinal tract, have contrasting immunologic effects, and diverse actions depending on the state of the gut microbiota (i.e. a healthy or dysbiotic state) (Isolauri et al., 2004; Sanders et al., 2018). Probiotics may also exert different effects when administered individually or in a mixture and may differ depending on the patient group (Fuller, 1992; Timmerman et al., 2004). Nevertheless, there are some properties probiotics must have in order to exert their effects on host physiology (Goldin & Gorbach, 1992). For instance, probiotics must firstly survive transit through the gastrointestinal tract, which involves being resistant to digestive enzymes, the low pH of the stomach, and bile, and also must adhere to the gut wall and proliferate (Goldin & Gorbach, 1992; Havenaar et al., 1992; Plaza-Diaz et al., 2019). Moreover, probiotics should display antimicrobial and immunogenic properties, for example inhibiting the growth of pathogenic bacteria by competitive exclusion or production of acids (Goldin & Gorbach, 1992; Havenaar et al., 1992; Plaza-Diaz et al., 2019; Tejero-Sariñena et al., 2012). Finally, probiotics must have the capacity to be efficiently produced and remain safe, stable and active during manufacture and storage (Lee, 2008; Plaza-Diaz et al., 2019).

4.1.3 Use of Probiotics

The primary use of probiotics is to alter the composition of the gut microbiota, namely by restoring the balance of bacteria and pathogens (Hemarajata & Versalovic, 2012).

As discussed in Chapter 3, gut microbiota composition and activity is implicated in numerous aspects of host health, including mood and behaviour via the gut-brain axis (Collins et al., 2012; Cryan & Dinan, 2012; Cryan et al., 2019). It is feasible, therefore, that manipulation of gut microbiota composition through the administration of probiotics could benefit host health (Park et al., 2018; Reid, 2016). That is, consumption of probiotics could lead to improvements in mood, ameliorate symptoms and reduce disease progression of those with health conditions, or act in a preventative manner and maintain health and wellbeing in healthy individuals.

The use of probiotics is well accepted in treating gastrointestinal conditions such as necrotising enterocolitis, inflammatory bowel disease, irritable bowel syndrome (IBS) and some diarrheal conditions (AlFaleh & Anabrees, 2014; Didari et al., 2015; Hempel et al., 2012; McFarland, 2007; McFarland & Dublin, 2008; Ritchie & Romanuk, 2012; X.-F. Zhang et al., 2021). Preliminary evidence suggests probiotics can also help treat or prevent more varied conditions, including allergic diseases, immune mediated inflammatory conditions, colon cancer, obesity, and mental health conditions (Eslami et al., 2019; Fuego et al., 2018; Li et al., 2019; Sales-Campos et al., 2019; Vaghef-Mehrabany et al., 2020; Wang et al., 2019; Wickens et al., 2018; Zajac et al., 2015). Importantly, accumulating evidence suggests that probiotics are generally safe, well-tolerated and well-accepted by diverse populations (Ahola et al., 2017; Crane et al., 2020; Salminen et al., 1998; Wallace & Milev, 2021).

4.2 Probiotics and Mental Health

Numerous studies investigating the effects of probiotic supplementation on symptoms of depression and anxiety in humans have found promising results. Firstly, it appears that probiotics can alleviate depressive symptoms in those with a diagnosis of depression. Akkasheh et al. (2016) demonstrated that consuming a probiotic capsule containing *L.*

acidophilus, *L. casei* and *B. bifidum* for eight weeks significantly reduced depressive symptoms in adults diagnosed with major depressive disorder (MDD), compared to placebo. Another study found that in patients diagnosed with MDD and IBS, supplementation with a probiotic tablet containing *B. coagulans* MTCC 5856 for 90 days significantly improved symptoms of depression and IBS compared to placebo (Majeed et al., 2018). Kazemi et al. (2019) found that probiotic supplementation with *L. helveticus* and *B. longum* for eight weeks led to a significant decrease in symptoms of depression in individuals with mild to moderate depression compared to both a prebiotic or placebo. In a prospective open-label trial, adults with treatment-resistant MDD displayed a significant improvement in depression when probiotic *Clostridium butyricum* MIYAIRI 588 was administered in combination with antidepressants for eight weeks (Miyaoka et al., 2018). Moreover, in an open-label pilot study, Wallace and Milev (2021) demonstrated that administration of probiotics *L. helveticus* R0052 and *B. longum* R0175 for eight weeks in individuals with treatment naive MDD significantly improved symptoms of depression and anxiety, including improving overall mood, anhedonia, and sleep quality.

The influence of probiotics on mood appears to benefit more than solely those with a diagnosis of depression. For example, Lew et al. (2019) noted that consumption of probiotic *L. plantarum* P8 for 12 weeks reduced symptoms of stress and anxiety in stressed adults compared to placebo. Although they did not observe any significant effects on symptoms of depression, the authors attributed this finding to the mild levels of depression in the sample. However, other studies involving healthy individuals have found that probiotic supplementation led to improvements in depression, anxiety and stress (Messaoudi et al., 2011; Mohammadi et al., 2016). Moreover, Steenbergen et al. (2015) demonstrated that administration of a multispecies probiotic in healthy individuals led to a significant reduction in reactivity to sad mood, a marker of psychological vulnerability that may increase the risk

of developing depression. Finally, studies have also demonstrated improvements in depressive and anxiety symptoms in various clinical samples, such as in individuals with pre-diabetes, multiple sclerosis, IBS, chronic fatigue, laryngeal cancer and those suffering from indigestion and abdominal pain (Kouchaki et al., 2017; Östlund-Lagerström et al., 2016; Pinto-Sanchez et al., 2017; Rao et al., 2009; Tay et al., 2020; Yang et al., 2016).

On the other hand, a number of studies investigating the effect of probiotics on mood have found non-significant results. For example, Chahwan et al. (2019) investigated the effect of a mixture of nine probiotic strains in individuals with depressive symptoms and found that all participants, regardless of whether the participant received probiotics or placebo, demonstrated improved symptoms of depression, anxiety and stress at any level of severity. However, they noted a greater reduction in reactivity to sad mood in the probiotic group than in the placebo. Kelly et al. (2017) found that supplementation with probiotic *L. rhamnosus* for eight weeks did not lead to any significant improvements in mood, anxiety, stress or sleep quality in healthy males compared to placebo. The authors also noted no significant differences between groups for cognitive measures or anti-inflammatory and HPA-reactivity markers. In a study of older adults, Östlund-Lagerström et al. (2016) found no significant effects of probiotic *L. reuteri* consumption on wellbeing, anxiety and stress. Finally, in a study involving individuals with at least moderate scores on mood measures and not concurrently taking psychotropic medications (i.e. antidepressants), the authors determined that consumption of probiotics *L. helveticus* and *B. longum* did not significantly alter symptoms of depression or anxiety compared to placebo (Romijn et al., 2017).

At present, evidence for the efficacy of probiotic supplementation to improve symptoms of depression and anxiety remains inconclusive (McKean et al., 2016; Ng et al., 2018; Vaghef-Mehrabany et al., 2020; Wallace & Milev, 2017; Yang et al., 2019). One likely reason for the discrepant findings is the marked heterogeneity between studies investigating

the effects of probiotics (Vaghef-Mehrabany et al., 2020). For example, the research described above utilised different probiotic strains, dosages, length of intervention, single or multiple strains, and examined different sample populations. Indeed, although multi-strain probiotics may provide a broader spectrum of action, one study demonstrated significant inhibition between probiotics when mixed, suggesting certain combinations may reduce probiotic efficacy (Chapman et al., 2012; Timmerman et al., 2004). Additionally, while some studies that found non-significant results from probiotic supplementation involved healthy adults (Gomi et al., 2018; Kelly et al., 2017; Östlund-Lagerström et al., 2016), Benton et al. (2007) noted that when analysing only those who initially scored in the bottom third of a scale measuring depressive symptoms, the probiotic led to a significant improvement in mood. There may therefore be a 'ceiling effect', whereby probiotics have a negligible effect in healthy individuals. Such discrepancies in the literature limit any firm conclusions regarding the efficacy of probiotics to alleviate symptoms of depression and anxiety. Further research is required to elucidate the necessary conditions in which probiotics can exert beneficial effects.

4.3 Probiotics in Physical Health

As well as reducing symptoms of depression and anxiety, probiotics have shown promise in alleviating physical symptoms in those with health conditions (Alipour et al., 2014; Dickerson et al., 2018; Yoon et al., 2014). For instance, Alipour et al. (2014) found that in patients with rheumatoid arthritis, probiotic supplementation with *L. casei* led to a significant decrease in disease symptom severity, tender and swollen joint counts, and concentrations of a marker of inflammation in the blood. Another study found that individuals with IBS who took a multispecies probiotic twice daily for four weeks were significantly more likely to experience substantial relief in symptoms, including an

improvement in abdominal pain and bloating, compared to placebo (Yoon et al., 2014). However, other studies have shown no improvement in symptoms, again likely due to the heterogeneous nature of the studies (Cremon et al., 2017; Dickerson et al., 2014).

Interestingly, for individuals with diabetes, the advantages of probiotics may extend beyond symptom relief. Studies reveal that use of probiotics in individuals with T2D can lead to improved health outcomes, such as reduced HbA1c levels (Asemi, Zare, et al., 2013; Kasińska & Drzewoski, 2015; Kesika et al., 2019; Kocsis et al., 2020; Madempudi et al., 2019; Mahboobi et al., 2018; Tonucci et al., 2017; Wang et al., 2021). Probiotics may also protect against gestational diabetes (Asemi, Samimi, et al., 2013; Wickens et al., 2017).

Studies investigating the use of probiotics in individuals with T1D have found similarly encouraging results. Firstly, probiotics may protect against the development of T1D, after a study demonstrated that administration of probiotics to infants with the high-risk T1D genotype in the first month of life was associated with a reduction in islet autoimmunity (Uusitalo et al., 2016). Secondly, preliminary evidence suggests that consumption of probiotics may improve glycaemic control in those with T1D (Ahola et al., 2017; Groele et al., 2021; Zare Javid et al., 2020). For instance, Zare Javid et al. (2020) found that consumption of a synbiotic, including *L. sporogenes* GBI0-30 and two prebiotics, led to a significant reduction of HbA1c in individuals with T1D. This finding was accompanied by significantly lower concentrations of a marker of inflammation within the body. Another study noted that probiotic use in non-overweight individuals with T1D was associated with significantly more optimal glycaemic control (Ahola et al., 2017). However, it was a cross-sectional study, so conclusions regarding the direction of the association are limited. Moreover, Groele et al. (2021) noted that children with newly diagnosed T1D who consumed probiotics *L. rhamnosus* GG and *B. lactis* Bb12 for six months had lower HbA1c levels than those who had a placebo. The study was not powered for this outcome, however, so one must

be cautious in interpreting these results. Lastly, the administration of probiotics has been shown to reduce inflammation in those with T1D (Bianchini et al., 2020). Taken together, these findings suggest that probiotics may provide clinically meaningful therapeutic effects for those with T1D.

4.4 Probiotics Mechanisms of Action

The mechanisms of action through which probiotics exert an effect are yet to be fully elucidated (McFarland et al., 2018). Given that probiotics' effects are strain and mixture dependent, there is no single answer. Examples of actions demonstrated through research in some probiotic strains include competitive exclusion of pathogens, preventing bacterial adhesion to intestinal epithelial cells, secreting antimicrobial compounds, enhancing gut barrier integrity, production of neurotransmitters, and modulating the immune system (Bested et al., 2013b; Markowiak & Śliżewska, 2017; O'Toole & Cooney, 2008).

Authors propose that probiotics exert their effects on mood through the gut-brain axis, such as by increasing the availability of neurotransmitters serotonin and GABA. Serotonin is involved in regulating stress via the HPA axis, emotional processing, attention, appetite and sleep, and reduced serotonin levels are associated with depression (Colle et al., 2020; Hensler, 2010; Kraus et al., 2017; Merens et al., 2007). Probiotic bacteria can produce tryptophan, the precursor of serotonin, increasing serotonin availability (Valladares et al., 2013). Probiotics may also indirectly influence serotonin production through the fermentation of prebiotics, where by-products of this chemical process, short-chain fatty acids, have shown to increase serotonin synthesis in gut wall cells (Reigstad et al., 2015; Yano et al., 2015). Authors propose that increasing serotonin activity may improve mood by shifting appraisals of emotional stimuli to be more positive, as such appraisals tend to be negatively biased in individuals with depression (Beck, 1979; Cowen & Browning, 2015). Probiotics can also

synthesise and influence neurotransmission of another crucial neurotransmitter, GABA (Barrett et al., 2012; Bravo et al., 2011; Dhakal et al., 2012; Valenzuela et al., 2019; Yunes et al., 2016). GABA is an inhibitory neurotransmitter involved in numerous regulatory processes in the brain, and dysfunctional GABA signalling is linked to depression and anxiety (Cryan & Kaupmann, 2005; Cullinan et al., 2008; Lydiard, 2003; Möhler, 2012). Therefore, probiotics may improve symptoms of depression and anxiety through the gut-brain axis by upregulating the expression of critical neurotransmitters serotonin and GABA.

Probiotics may also confer their therapeutic effect on symptoms of depression and anxiety via an anti-inflammatory mechanism. Mounting evidence points towards a role of inflammation in mental health conditions such as depression and anxiety, with studies demonstrating inflammation is associated with diagnosis of depression, the severity of symptoms and an increased risk of not responding to treatment (Bercik et al., 2010; Dowlati et al., 2010; Köhler et al., 2014; Michopoulos et al., 2014; Miller et al., 2009; Miller & Raison, 2016; Osimo et al., 2019; Reichenberg et al., 2001; Suarez et al., 2003). Inflammation can impact mood and cognition by activating the HPA axis, reducing neurotransmitter availability, altering the metabolism of neurotransmitters and inducing changes in neuroplasticity (Cai et al., 2005; Hayley et al., 2005; Maes et al., 2011; Miller et al., 2009; Turnbull & Rivier, 1999; Zunszain et al., 2013). Researchers propose that systemic low-grade inflammation in those with depression is triggered by increased intestinal permeability, or a “leaky gut” (Maes et al., 2008; Maes et al., 2012; Maes et al., 2013; Simeonova et al., 2020). Increased gut permeability allows endotoxins to pass from the gastrointestinal tract into the bloodstream, initiating the body’s immune and inflammatory response (Fukui, 2016; Isolauri et al., 2004). Many probiotics function to enhance gut wall integrity, preventing endotoxins from leaking into the bloodstream, which in rodent models is associated with reduced inflammation and symptoms of depression and anxiety (Abildgaard

et al., 2017; Ait-Belgnaoui et al., 2012; Chen et al., 2019; Hsieh et al., 2015; Khailova et al., 2017; Mangell et al., 2002; Schultz et al., 2002; Stratiki et al., 2007; Zareie et al., 2006). Studies demonstrate that probiotic strains can also heighten concentrations of anti-inflammatory cytokines (O'Mahony et al., 2005; Pessi et al., 2000). Authors therefore propose that probiotics may improve symptoms of depression and anxiety by attenuating the chronic low-grade inflammation associated with increased intestinal permeability, thereby preventing changes in HPA-axis activity and neurotransmitter availability (Simeonova et al., 2020; Wallace & Milev, 2017).

Interestingly, albeit unsurprisingly, the immune regulating and anti-inflammatory effects of probiotics appears to benefit those with T1D as well as depression. A growing body of literature points towards increased intestinal permeability and its subsequent global immune response and inflammation as contributing to T1D development (Bosi et al., 2006; Harbison et al., 2018; Lee et al., 2010; Li & Atkinson, 2015; Maffeis et al., 2016; Neu et al., 2005; Sapone et al., 2006; Vaarala et al., 2008; Visser et al., 2010). Therefore, the administration of probiotics may inhibit the development and progression of T1D by maintaining gut wall integrity and preventing chronic low-grade inflammation (de Oliveira et al., 2017; Mishra et al., 2019). Indeed, preclinical studies have demonstrated that administering probiotics reduced intestinal permeability, led to changes in immune cytokine expression and delayed or inhibited the onset of T1D (Calcinaro et al., 2005; Kim et al., 2020; Matsuzaki et al., 1997; Valladares et al., 2010).

Probiotic-enhanced production of short-chain fatty acids may also be influential in protecting against and improving clinical outcomes of T1D. Short-chain fatty acids have essential functions in immune system regulation and inflammation (Corrêa-Oliveira et al., 2016; P. M. Smith et al., 2013). Production of short-chain fatty acids, particularly butyrate and acetate, appear to protect against the development of T1D in rodent models, possibly by

altering the activity of immune cells responsible for pancreatic β-cell destruction (Brown et al., 2011; Mariño et al., 2017; Tanca et al., 2018). Moreover, short-chain fatty acids can induce the production of a hormone that stimulates the secretion of insulin from β-cells, which authors suggest may be one way in which probiotic consumption leads to lower blood glucose levels (MacDonald et al., 2002; Mishra et al., 2019; Psichas et al., 2015; Tolhurst et al., 2012; Yadav et al., 2013). However, as depression and anxiety symptoms in those with T1D are associated with greater difficulties in reaching glycaemic targets, probiotics' influence on glycaemic control may be indirectly mediated by a reduction in depressive and anxiety symptoms (Lustman, Anderson, et al., 2000; Lustman & Clouse, 2005; Pouwer et al., 2010; Roy & Lloyd, 2012; Van Tilburg et al., 2001). Given that the implication of the gut microbiota in T1D is a relatively new concept, additional research is necessary to understand the mechanisms underlying the therapeutic effects of probiotics in people with T1D.

4.5 Therapeutic Potential of Probiotics

With the knowledge that gut dysbiosis is implicated in mental health conditions and T1D, probiotics are positioned as a potentially viable treatment option to ameliorate symptoms of depression and anxiety and improve health outcomes in individuals with T1D (He et al., 2015; Knip & Honkanen, 2017). Indeed, studies have demonstrated that in individuals with T2D, consumption of probiotics is associated with improved glycaemic control (Asemi, Zare, et al., 2013; Kasińska & Drzewoski, 2015; Kesika et al., 2019; Kocsis et al., 2020; Madempudi et al., 2019; Tonucci et al., 2017; Wang et al., 2021). Emerging evidence suggests probiotics could also lower HbA1c in those with T1D; however, these results remain preliminary, given that one study was cross-sectional and another was not powered to detect an effect in HbA1c (Ahola et al., 2017; Groele et al., 2021; Zare Javid et al., 2020). Further studies demonstrated that administering probiotics alongside supplements

improved depressive and anxiety symptoms in individuals with T2D, and probiotics alone improved mood in those with prediabetes (Raygan et al., 2019; Raygan et al., 2018; Tay et al., 2020). Despite the knowledge that depression and anxiety are more common in those with T1D than the general population and can lead to worse clinical outcomes, probiotics' capacity to improve symptoms of depression and anxiety have yet to be investigated in individuals with T1D (Roy & Lloyd, 2012; K. Smith et al., 2013). These findings and the limited research investigating the effects of probiotics on mental and physical health outcomes in adults with T1D leads to the question: can probiotics improve physical and mental health outcomes in individuals with T1D? Evidently, further research is required to investigate the therapeutic influence of probiotics in individuals with T1D.

4.6 Summary

To summarise, probiotics have the potential to improve host health by altering the composition and activity of the gut microbiota. Accumulating evidence suggests that consumption of probiotics may reduce symptoms of depression and anxiety in those diagnosed with depression and with physical health conditions, including those with pre-diabetes and T2D. Additionally, in a small number of studies probiotics also appear to improve health outcomes in those with diabetes, importantly improving glycaemic control. Although the exact mechanisms underlying probiotic effects are yet to be fully understood, authors propose probiotics can directly and indirectly increase the production of neurotransmitters, and have anti-inflammatory and immune-modulating activities. Despite some studies finding no significant improvement following consumption of probiotics, the findings discussed above are nevertheless promising and warrants further investigation into the therapeutic effects of probiotics in individuals with T1D.

Chapter 5 The Current Study

5.1 Rationale

T1D is a chronic, debilitating disorder of absolute insulin deficiency caused by autoimmune destruction of the insulin-producing pancreatic β-cells (Anderson & Bluestone, 2005; Daneman, 2006). Subsequently, to survive, those with T1D require lifelong insulin replacement. Insulin treatment, typically via daily injections or insulin pumps, is one crucial aspect of T1D management to maintain blood glucose levels within a narrow physiologic range (American Diabetes Association, 2013). Individuals with T1D are also advised to follow a strict, onerous self-management regime, including regular blood glucose monitoring to inform appropriate insulin dosage, monitoring physical activity and amount of carbohydrates consumed, and being aware of factors that may influence blood glucose levels such as illness or stress (American Diabetes Association, 2013; Franz et al., 2002). The challenging task of achieving blood glucose targets is pivotal in reducing the risk of numerous T1D-associated complications (Diabetes Control and Complications Trial Research Group, 1993; Nathan, 1993).

The burden of managing a demanding chronic condition in addition to the inevitable stressors of everyday life unequivocally takes a toll on psychological wellbeing. Individuals with T1D are vulnerable to mental health disorders such as depression and anxiety (Castellano-Guerrero et al., 2018; Grigsby et al., 2002; Janzen Claude et al., 2014; Lloyd et al., 2000; Maia et al., 2014; Pouwer et al., 2010). Studies reveal that those with T1D are at greater risk of developing depression and anxiety than the general population, and, in fact, the incidence of depression may be up to three times higher in those with T1D compared to those without (Anderson et al., 2001; Collins et al., 2009; Gendelman et al., 2009; Kendzor et al.,

2014; Poulsen & Pachana, 2012; Roy & Lloyd, 2012; K. Smith et al., 2013). An increased risk of depression and anxiety is particularly concerning for individuals with T1D as they are already susceptible to adverse health outcomes as a consequence of T1D, and these comorbidities can negatively influence each other (Daneman, 2005). Depression and anxiety are associated with reduced T1D self-management, suboptimal glycaemic control and poorer clinical outcomes of T1D-associated complications (Anderson et al., 2002; Arend et al., 2019; Ciechanowski et al., 2000; Gonzalez et al., 2008; Kendzor et al., 2014; Lustman, Anderson, et al., 2000; Nefs et al., 2019; Schmitt, McSharry, et al., 2021; Shaban et al., 2009; Van Tilburg et al., 2001). T1D-associated complications and suboptimal self-management and self-care behaviours can then worsen symptoms of depression and anxiety, creating a vicious cycle (Castellano-Guerrero et al., 2018; Lustman & Clouse, 2005; Nouwen et al., 2019).

Studies have yielded inconclusive evidence regarding the effectiveness and feasibility of current treatments for depression and anxiety in individuals with T1D. Common interventions for patients with T1D include psychotherapies such as cognitive behavioural therapy, group mindfulness-based therapy and blood glucose awareness training, as well as pharmacological treatment such as antidepressants (Cox et al., 2001; C. Li et al., 2017; Lustman et al., 1997; Lustman et al., 1998; Uchendu & Blake, 2017; van Son et al., 2013). Although studies have demonstrated reduced depressive and anxiety symptoms, there is no evidence to suggest these interventions can improve glycaemic control in adults with T1D (Winkley et al., 2006; Winkley et al., 2020). Additionally, psychotherapies, in particular, require time and cognitive load and are difficult to integrate into the already demanding daily lives of individuals with T1D and busy clinical settings. With the knowledge that the global incidence rate of T1D increases each year by 2-5%, developing cost and time-effective and

easily implementable approaches is imperative for the health and wellbeing of people with T1D (Derraik et al., 2012; Lipman et al., 2013; Mobasseri et al., 2020; Patterson et al., 2012).

A novel therapeutic approach to support psychological health in T1D may be probiotics (He et al., 2015; Knip & Honkanen, 2017). Landmark studies with mice demonstrated the existence of a gut-brain axis, a bidirectional communication network between the brain and the gut (Bercik, Denou, et al., 2011; Carabotti et al., 2015; Cryan et al., 2019; Rogers et al., 2016; Sudo et al., 2004). Recently, researchers have begun to appreciate the extent of the role of the gut microbiota in this relationship, whereby the microbiota itself has essential bottom-up influences in cognition, emotion and behaviour (Cryan et al., 2019; Foster & McVey Neufeld, 2013; Jandhyala et al., 2015; Rhee et al., 2009; Rogers et al., 2016; Sekirov et al., 2010). Trials investigating the influence of probiotics on depression and anxiety symptoms in various clinical populations such as patients with depression, chronic fatigue syndrome, multiple sclerosis, IBS, and laryngeal cancer have found promising results (Akkasheh et al., 2016; Kazemi et al., 2019; Kouchaki et al., 2017; Pinto-Sanchez et al., 2017; Rao et al., 2009; Wallace & Milev, 2021; Yang et al., 2016). Results can vary, however, with other studies showing no significant changes in depression or anxiety symptoms following probiotic supplementation (Chahwan et al., 2019; Kelly et al., 2017; Östlund-Lagerström et al., 2016; Romijn et al., 2017). This discrepancy in results may reflect a ‘ceiling effect’ in healthy individuals, or the heterogeneous nature of studies investigating probiotics, given that the probiotic strains, dosage, duration of intervention and sample population differ substantially across trials (Benton et al., 2007; Vaghef-Mehrabany et al., 2020).

Nevertheless, the use of probiotics may be especially pertinent in individuals with T1D. Studies reveal gut microbiota composition alterations in infancy may precede T1D development (Davis-Richardson et al., 2014; Harbison et al., 2018; Vatanen et al., 2018). Gut

microbiota dysbiosis is implicated in numerous determinants of health, including immune system development and function, which, along with increased gut permeability and reduced microbiota diversity, is common in people with T1D (Alkanani et al., 2015; de Goffau et al., 2013; Gensollen et al., 2016; Harbison et al., 2018; Jamshidi et al., 2019; Knip & Siljander, 2016; Mejía-León et al., 2014; Mishra et al., 2019; Murri et al., 2013; Olszak et al., 2012). Additionally, some of the risk factors identified for T1D, such as stress and early introduction of infant formula over breastmilk, reliably alters the gut microbiota composition (Bailey et al., 2011; Lee et al., 2015; Ma et al., 2020; Murakami et al., 2017; Uusitalo et al., 2016). Preclinical studies with rodent models of diabetes demonstrated that probiotics could delay or prevent T1D development and reduce symptoms of depression and anxiety (Bravo et al., 2011; Calcinaro et al., 2005; Desbonnet et al., 2008; Kim et al., 2020; Matsuzaki et al., 1997; Savignac et al., 2014; Sudo et al., 2004; Valladares et al., 2010). Furthering these advances, clinical trials in people living with T2D indicate probiotics may improve glycaemic control and improve symptoms of depression and anxiety (Kesika et al., 2019; Kocsis et al., 2020; Raygan et al., 2019; Raygan et al., 2018).

Despite the growing evidence to suggest probiotics can improve psychological and physical health outcomes in clinical populations, to the best of our knowledge, no prior studies have investigated probiotics' effects on mood and glycaemic control in people living with T1D. Therefore, the current study aims to address this gap in the literature and contribute to the burgeoning field of research regarding probiotics. The study is a double-blind, placebo-controlled, parallel-arm, randomised controlled trial in adults with T1D to explore the effects of probiotics on depression, anxiety and glycaemic control compared to placebo.

5.2 Aims

5.2.1 Primary Aims

The primary aim of this research is to examine the effect of probiotic supplementation compared to a placebo administered for 12 weeks on symptoms of depression and anxiety, and glycaemic control in adults with T1D in New Zealand.

5.2.2 Secondary Aims

1. To investigate the prevalence of depression, anxiety and stress in adults with T1D.
2. To investigate beliefs regarding probiotic supplementation in adults with T1D.

5.3 Hypotheses

1. Compared to placebo, probiotic use will reduce depression, anxiety and stress scores in adults with T1D across the 12-week intervention.
2. Compared to placebo, probiotic use will improve health-related quality of life in adults with T1D across the 12-week intervention.
3. Compared to placebo, probiotic use will improve glycaemic control in adults with T1D across the 12-week intervention.

Chapter 6 Methods

6.1 Design

The current study was a 1:1 randomised, double-blind, placebo-controlled, parallel-arm clinical trial, designed in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines (Schulz et al., 2010). We examined the effect of probiotic versus placebo supplementation on depression, anxiety and glycaemic control among adults with T1D in New Zealand.

6.2 Participants

6.2.1 Inclusion and Exclusion Criteria

Individuals were eligible to participate in the study if they had a diagnosis of T1D for at least one year, were 18 years or older, living in New Zealand, were able to understand, read and write English, and were able to provide informed consent.

Individuals were excluded from the study if they did not have T1D or if they received their T1D diagnosis less than one year prior to enrolment, had antibiotic or probiotic treatment within three months before enrolment, surgery in the previous three months, had a gastrointestinal infection within one month before enrolment, were taking strong immunosuppressant medications (e.g. chemotherapy), diagnosed with T1D with pancreatitis, or if they were pregnant or breastfeeding. Participant involvement in the study is displayed in Figure 4.

6.2.2 Recruitment

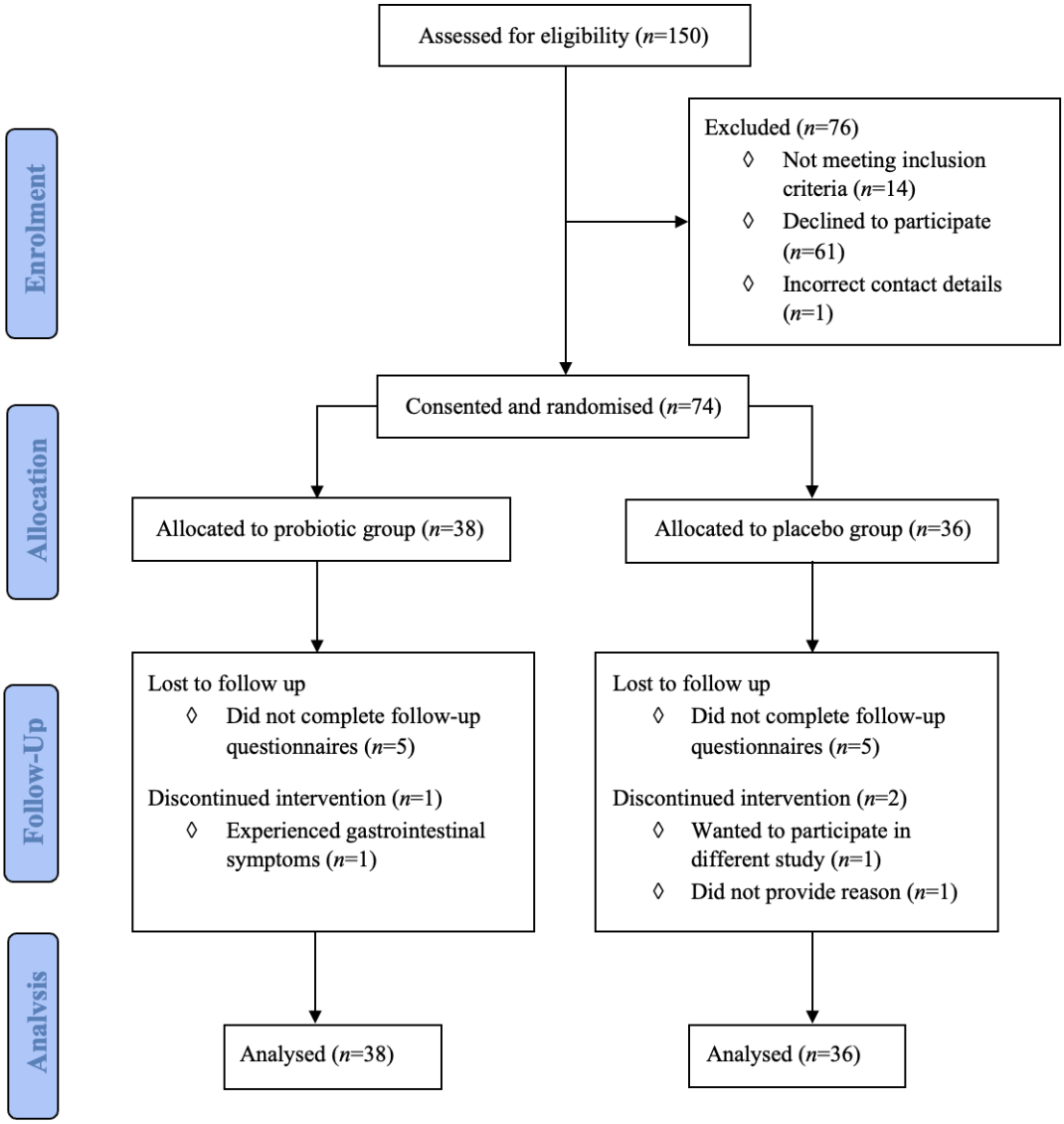
Participants were recruited through Waitematā District Health Board (DHB) diabetes outpatient clinics at North Shore and Waitakere Hospitals and through online Facebook support groups. Recruitment commenced 5th of May 2021 and concluded 16th of August 2021. An electronic version of the study flyer, accompanied by a letter describing the study, was distributed to eligible participants within the Waitematā DHB via email from the Diabetes team at two different time points during the recruitment period (see Appendix A and Appendix B). The researcher (Gabriella Browne) also recruited participants by attending diabetes outpatient clinics and Dose Adjustment for Normal Eating (DAFNE) courses and offering hard copies of the flyer to eligible participants. The electronic version of the flyer was also posted in various T1D support groups on Facebook; "Type 1 diabetes New Zealand", "Low Carb Diabetics NZ" and "Mount Albert Community". The flyer contained a link to the study website where participants could download and read the participant information sheet, provide informed consent, and complete the baseline questionnaires.

6.2.3 Sample Size

To the best of our knowledge, there are no previous investigations on the effects of probiotic supplementation on mental and physical health outcomes in people with T1D. We therefore used the effect size from a comparable study by Akkasheh et al. (2016) for our sample size calculation, who examined the effects of probiotics on depression in patients with major depressive disorder. Using the G*Power (Faul et al., 2007) statistical power analysis programme, it was calculated that a sample of 72 participants was necessary to detect a large effect (Cohen's $d = 0.7$) in depression, using an independent samples t-test with 90% power and an alpha of .05. We increased the target sample size to 80, and therefore 40 participants in each arm to allow for attrition.

Figure 4

CONSORT Diagram of Participant Involvement in the Current Study



6.3 Randomisation

Randomisation was performed by the supplier of the probiotics and placebo capsules, Fonterra Co-operative Group Limited, prior to the delivery of the capsules to the University of Auckland. Randomisation was completed using a 1:1 allocation ratio so that 40 participants would receive the probiotic and 40 participants would receive the placebo. This

ensured that the study remained double-blind. The researchers were unblinded once data collection and the analyses had been completed.

6.4 Procedure

All participant data was recorded and securely stored electronically using the Research Electronic Data Capture (REDCap) application (Harris et al., 2009). Via the link on the study flyer, interested participants could access the study website, which contained further information and a direct link to the online eligibility questionnaire. After completing the eligibility questionnaire, eligible participants were directed to download and read the Participant Information Sheet and Consent Form (see Appendix C and Appendix D). Ineligible participants were unable to progress past the eligibility questionnaire. Participants who provided informed electronic consent were then asked to complete a series of baseline questionnaires (see Appendix E). Participants' sociodemographic and clinical information and beliefs surrounding probiotics were gathered. Additionally, participants completed questionnaires assessing psychological outcomes (depression, anxiety and stress), diabetes quality of life and diet. Participants' most recent HbA1c results were obtained through their medical records if recruited via the Waitematā DHB diabetes outpatient clinics or by the participants emailing a photo of their most recent laboratory results if recruited via Facebook. Reminder emails were sent to participants who did not complete the baseline questionnaires after providing informed consent or if they did not provide their HbA1c results.

The participants that completed the baseline questionnaires were sent a 12-week supply of probiotic or placebo capsules in a tracked courier bag to their home address, with accompanying instructions for usage and a capsule tracker (see Appendix F and Appendix G). All participants received a weekly email reminder to take the capsules daily. After the 12-week intervention, participants received the link to the online follow-up questionnaires via

email, which included a shorter version of the original sociodemographic and clinical information questionnaire, and the questionnaires measuring psychological outcomes, diabetes quality of life and diet. Upon completion of the follow-up questionnaires, a $30 Westfield voucher was sent to their home address as a *koha* to thank them for participating in the research. If participants had not completed the follow-up questionnaires after five days, they received three reminder emails in five-day intervals. If the participant still had not completed their follow-up questionnaires, one final reminder email was sent before allocating the participant as lost to follow-up.

6.5 Intervention

6.5.1 Probiotic Versus Placebo Capsules

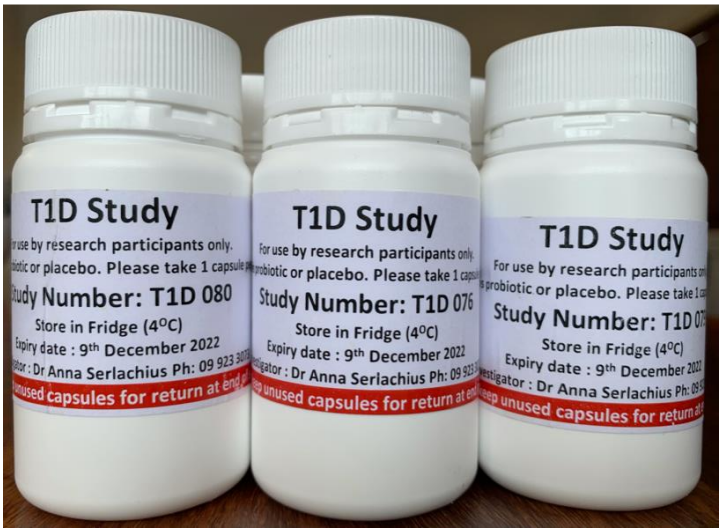
The probiotic capsules contained the probiotic strain *Lactobacillus rhamnosus* HN001 at a dose of 6 x 10^9 cfu/day. As no prior study has investigated the influence of probiotic consumption on mental health outcomes in adults with T1D, we chose this probiotic strain based on previous research that recommended *Lactobacillus* or *Bifidobacterium* bacterial strains be used for people with T1D (Groele et al., 2017; Mishra et al., 2019). This decision was also based on the knowledge that probiotics containing *Lactobacillus rhamnosus* have resulted in significant decreases in symptoms of depression and anxiety in a previous study by Mohammadi et al. (2016). The placebo capsules contained corn derived maltodextrin, which was chosen due to its' similarity in physical appearance and taste to the probiotic capsules and its safe use in individuals with T1D and T2D in prior randomised controlled trials (Dehghan et al., 2013; Ho et al., 2019; Zare Javid et al., 2020).

Fonterra Co-Operative Group Limited produced the probiotic and placebo capsules used in the study. The probiotic and placebo capsules were visually identical; however, the

placebo capsules did not contain any active ingredients. Both the probiotic and placebo were free of lactose, gluten, and animal products. Both the probiotic and placebo capsules were packaged in identical pre-labelled bottles except for the unique study number (001 to 080) (see Figure 5). Clear, brief instructions for usage were pre-printed on the bottle, while more thorough instructions were sent with the capsules along with a 12-week capsule tracker. Instructions included taking one capsule per day, not taking an extra capsule if participants missed a capsule on one day, and suggestions to help establish a routine to augment adherence.

Figure 5

Labelled Bottles of Capsules



6.5.2 Safety Monitoring Procedure

Probiotics have been safely administered and used in populations including pregnant women, infants, and adults with gestational diabetes, T2D and T1D (Kocsis et al., 2020; Slykerman et al., 2017; Uusitalo et al., 2016; Wickens et al., 2017; Zare Javid et al., 2020). Nevertheless, a safety monitoring protocol was developed prior to the study commencing and prior to seeking ethics and locality approval. The protocol stated that in the event that

participants experienced any adverse side effects that concerned them (e.g. bloating), it was the participants' responsibility to contact the research team to inform them of side effects. Participants were also encouraged to contact their GP or diabetes clinician if they were concerned about side effects. If participants contacted the research team with concerns about gastrointestinal symptoms, the participant would be advised to stop taking the capsules as a precaution. If requested by the participant or the participants' doctor, information regarding whether the participant was given the probiotic or placebo would be provided by Fonterra.

6.6 Outcome Variables

6.6.1 Depression, Anxiety and Stress (Primary Outcomes)

Depression, anxiety and stress was measured using the short version of the Depression, Anxiety and Stress Scale (DASS-21) (Lovibond & Lovibond, 1996). The brief, 21-item self-report questionnaire is widely used in clinical populations as a measure of depression, anxiety and stress, by assessing one's emotional experience in the past seven days. The scale is categorised into three subscales: depression, anxiety and stress, with seven items per subscale. Example items include "I felt that I had nothing to look forward to" from the depression subscale, "I felt scared without any good reason" from the anxiety subscale and "I found it hard to wind down" from the stress subscale. The items are rated on a 4-point Likert scale, with 0 = "*Did not apply to me at all*" ranging to 3 = "*Applied to me very much or most of the time*". The raw score from each subscale is multiplied by two, so possible scores range from 0 to 42 per subscale with higher scores indicating greater severity. The DASS-21 has demonstrated adequate construct validity and good convergent and discriminant validity compared to other validated measures of depression and anxiety in both clinical and non-clinical samples and across different ethnicities (Antony et al., 1998; Henry

& Crawford, 2005; Norton, 2007). The instrument also displays high internal consistency with a Cronbach's alpha of .93, indicating good reliability (Henry & Crawford, 2005). In the current study of adults with T1D, the DASS-21 displayed good internal consistency with a Cronbach's alpha of .92.

6.6.2 Quality of Life

Health-related quality of life was measured by the 15-item Diabetes Quality of Life scale (DQOL-15) (Burroughs et al., 2004). The scale was specifically designed for those with T1D or T2D to explore self-care behaviours, satisfaction with diabetes management, diabetes worry and social and occupational worry. Example items include "How satisfied are you with the amount of time it takes to manage your diabetes?" and "How often do you feel diabetes limits your career?". Items are measured on a 5-point Likert scale, with anchors corresponding to the content of each item. Possible scores range from 15 to 75, with a lower score indicating higher diabetes satisfaction. The questionnaire demonstrates adequate validity and reliability (Cronbach's alpha = .85). The Cronbach's alpha of the present study was calculated as .82.

6.6.3 Probiotic Knowledge and Beliefs

Probiotic knowledge and beliefs were assessed at baseline using a qualitative questionnaire on patient experience and use of probiotics (Chin-Lee et al., 2014). Items include "How familiar are you with the word 'probiotic'?" and "What was your reason for initially trying probiotics?". The questionnaire was tested for content validity and has been utilised in health care consumers recruited from a medical practice and pharmacy.

6.6.4 Glycaemic Control

HbA1c concentrations in the blood can be used to estimate average glycaemic control in the previous 90-120 days (Sacks, 2005). HbA1c, measured as millimoles per mol (mmol/mol), is collected routinely as part of standard diabetes care approximately every three to four months. Participants' HbA1c results were retrieved from their medical records if they were recruited through the Waitematā DHB, and participants were asked to email a photo of their HbA1c test results if they were recruited through Facebook. As diabetes outpatient appointments are typically every three to four months, we used participants' most recent HbA1c results prior to the onset of the intervention as the baseline measurement and their subsequent HbA1c score as the follow-up measurement. The follow-up HbA1c data were collected from September to December 2021.

6.7 Explanatory Variables

6.7.1 Diet

Participants' diet was assessed using the 4-item diet subscale of the Summary of Diabetes Self-care Activities Scale, which asks about participants eating patterns in the previous seven days (Toobert et al., 2000). Example items from the scale include "How many of the last seven days have you followed a healthful eating plan?" and "On how many of the last seven days did you eat high-fat foods such as red meat or full-fat dairy products?". Items are measured on a 7-point Likert scale, with "0" corresponding to zero days and "7" corresponding to seven days. The last two items are reversed scored before all scores are averaged, with a higher total score indicating a healthier eating pattern. The full scale has demonstrated adequate reliability and validity in patients with T1D and T2D (Toobert et al., 2000).

6.7.2 Sociodemographic and Clinical Variables

Relevant sociodemographic and clinical information was obtained from participants at baseline and follow-up. Participants were asked to provide their age, ethnicity, height and weight, as well as information regarding their level of education, occupation, living arrangements, and relationship status. Participants were also asked how long they have had T1D, what insulin treatment they use, and whether they use a continuous glucose monitor. They were also asked if they had any other medical conditions, taking any other medications or supplements, and were following a specific dietary plan (e.g. vegetarian).

6.8 Adherence to Intervention

Participants' adherence to the probiotic or placebo intervention was measured by the number of leftover capsules at the end of the 12-week period. Each bottle contained 105 capsules, including 21 extra capsules. The follow-up questionnaires contained a question asking, "Did you have any leftover capsules? If yes, how many?". Participants were also asked to record the date they began taking the capsules and the date they completed the follow-up questionnaires. The number of leftover capsules was determined based on when the participant began taking the capsules and when they completed the follow-up questionnaires. The number of leftover capsules reported by the participant was measured against the expected number of capsules the participant would have if they took one capsule per day from their start date to the date the follow-up questionnaires were completed. We determined that participants were adherent when the difference in reported and expected leftover capsules were ten or less.

6.9 Statistical Analysis

Data were analysed using IBM SPSS Statistics Version 23. Statistical significance was defined as $p \leq .05$. Data were screened for errors and exceptional outliers prior to being tested for violations of statistical assumptions. The normality of distribution assumption was checked for all continuous variables using Kolmogorov-Smirnov tests, skew and kurtosis values and visual assessment of histograms. The central limit theorem states that a normal distribution can be assumed in large samples regardless of the sample distribution (Field, 2013). Therefore, despite some outcome variables violating the normality assumption (depression, anxiety and diet scores), with the current study's sample size being greater than 30, it is acceptable to use parametric tests. Nonetheless, some analyses were replicated using non-parametric tests to confer greater confidence in the results. All other statistical assumptions (e.g. homogeneity of variance, independence, homoscedasticity and multicollinearity) were assessed and met.

Differences in participant demographics, clinical characteristics and psychosocial outcome measures at baseline were compared between the intervention (probiotic) and control (placebo) groups. Independent samples t-tests were conducted to compare continuous variables, and for variables that did not meet normality assumptions, non-parametric Mann-Whitney U tests were used. Given the results between the parametric and non-parametric tests were unchanged, only the parametric tests were reported for clarity and coherence. Categorical variables were compared using Pearson chi-square tests, and in the instances where cell frequencies totalled less than five, Fisher's exact test statistics were reported. Differences between those who completed the intervention and those lost to follow up were examined using independent samples t-tests.

Correlational analyses were performed to explore the relationships between HbA1c and psychosocial outcome measures at baseline. As half of the variables violated the normality assumption for these baseline analyses, for simplicity and clarity, non-parametric Spearman's Rho correlation coefficients were reported for all variables. Participants' probiotic knowledge and beliefs at baseline were analysed via descriptive statistics.

A series of 2 (group) x 2 (time) mixed-model analyses of variance tests (ANOVAs) were performed to test Hypotheses 1-3 and establish any differences in measures of mental health, quality of life and glycaemic control between participants allocated to the probiotic intervention and placebo control group from baseline to the 12-week follow-up. Although ANOVAs are regarded as robust to violations of the normality assumption, non-parametric Mann-Whitney U and Wilcoxon signed-rank tests were conducted for the non-normally distributed variables to provide confidence in the results of the parametric tests.

Additional ANOVAs were performed within specific sub-groups to investigate whether more severe self-reported symptoms of depression, anxiety and stress and adherence to the intervention impacted the results. The study employed intention-to-treat analyses, whereby all participants were included in the analyses irrespective of whether or not they adhered to the intervention (probiotics or placebo).

6.10 Ethics and Trial Registration

Ethical approval was granted by the Health and Disability Ethics Committee (HDEC) on the 8th of March 2021 (Reference number: 19/NTB/206/AM01). Locality approval was granted by the Waitematā District Health Board on 4th August 2020 (see Appendix H). The study was prospectively registered on the Australian and New Zealand Clinical Trials Registry (Trial ID: ACTRN12620000294954).

Chapter 7 Results

This chapter describes the results of the current study. Firstly, demographic information, clinical characteristics and psychosocial outcome measures of participants at baseline are presented, including comparisons between the intervention (probiotic) and control (placebo) group. Secondly, correlational analyses of HbA1c and psychosocial outcome measures at baseline are displayed, followed by a summary of participants beliefs and knowledge about probiotics. Next, the results of the main analyses testing the study's hypotheses are demonstrated, that is, whether the probiotic intervention can improve measures of mental health, quality of life, and glycaemic control. Lastly, exploratory analyses examining if higher baseline scores of depression, anxiety and stress and adherence to the intervention had an impact on the results are presented.

7.1 Sample Characteristics at Baseline

7.1.1 Demographics

A total of 74 adults with T1D met the eligibility criteria, consented to participate, completed the baseline questionnaires and were randomised to receive either the probiotic (intervention group) or placebo (control group). Of those 74 participants, 61 (82.4%) completed the follow-up questionnaires. Ten participants were lost to follow up, and three participants requested to withdraw from the study. However, as the current study employs the intention-to-treat approach, all participants who were randomised were included in the analyses despite missing data. There were no significant differences in baseline variables between those who completed the intervention and those lost to follow up.

Table 1 displays the demographic information of the study sample collected at baseline. Participants were between 19 and 75 years of age, with an overall mean age of 43.95 years (*SD* = 15.33). Reflecting the global incidence rate of T1D, the majority of the sample identified as New Zealand European (87.5%), with a lesser proportion identifying as Māori (5.4%), Samoan (1.4%), Chinese (1.4%), Indian (1.4%) and other (10.8%). A greater proportion of females participated in the study (59.5%) compared to males (40.5%). Most participants reported being in a relationship (87.8%) and living with others (95.9%). The study sample was highly educated, with 36.5% completing an undergraduate degree and 23% completing a postgraduate degree. There were no significant differences in demographic variables between the intervention and control groups at baseline.

Table 1

Demographic Variables of Study Sample

Demographic variable	**Probiotic** (n=38)	**Placebo** (n=36)	**Total sample** (n=74)	**Test statistic** *t* or x^2	***df***	***p***
Gender				1.298	1	.255
Female	25 (65.8%)	19 (52.8%)	44 (59.5%)			
Male	13 (34.2%)	17 (47.2%)	30 (40.5%)			
Age in years *M(SD)*	43.76 (15.97)	44.14 (14.84)	43.95 (15.33)	-.105	72	.917
Ethnicity [a]						
European	32 (84.2%)	33 (91.7%)	65 (87.5%)			.481
Māori	2 (5.3%)	2 (5.6%)	4 (5.4%)			1.00
Samoan	0 (0%)	1 (2.8%)	1 (1.4%)			.486
Chinese	0 (0%)	1 (2.8%)	1 (1.4%)			.486
Indian	0 (0%)	1 (2.8%)	1 (1.4%)			.486
Other	6 (15.8%)	2 (5.6%)	8 (10.8)			.263
Level of education				7.186	4	.126
Did not complete high school	4 (10.5%)	0 (0%)	4 (5.4%)			
Completed high school	5 (13.2%)	11 (30.6%)	16 (21.6%)			
Started undergraduate degree	5 (13.2%)	5 (13.9%)	10 (13.5%)			
Completed undergraduate degree	16 (42.1%)	11 (30.6%)	27 (36.5%)			
Completed postgraduate degree	8 (21.1%)	9 (25%)	17 (23%)			
Living arrangements [a]						.610
Living alone	1 (2.6%)	2 (5.6%)	3 (4.1%)			
Living with friends/family	37 (97.4%)	34 (94.4%)	71 (95.9%)			
Relationship status [a]						.732
Single	4 (10.5%)	5 (13.9%)	9 (12.2%)			
In a relationship	34 (89.5%)	31 (86.1%)	65 (87.8%)			

[a] Fisher's exact test used

7.1.2 Clinical characteristics

The clinical characteristics of the study sample were also collected at baseline, presented in Table 2. The time since diagnosis with T1D ranged between 12 months and 64 years, with 19.81 years (*SD* = 13.96) representing the study sample's average length of time living with T1D. Sixty-eight per cent of the participants reported using insulin injections as their mode of insulin delivery compared to 32% using an insulin pump, and just over half of the participants used a continuous glucose monitor (56%). While the majority of participants did not have a comorbid diagnosis (58%), 65% of the sample reported taking other medications alongside insulin. Although most participants did not follow any dietary plan (67.5%), of the nine participants who selected 'other', seven reported that they followed a low carbohydrate diet. There were no significant differences in clinical characteristics between the intervention and control groups at baseline.

Table 2

Clinical Variables of Study Sample at Baseline

Clinical variable	Probiotic (*n*=38)	Placebo (*n*=36)	Total sample (*n*=74)	Test statistic *t* or x^2	*df*	*p*
BMI *M(SD)*	27.59 (5.50)	25.88 (4.24)	26.76 (4.97)	1.493	72	.140
Time with T1D in years *M(SD)*	22.40 (15.21)	17.08 (12.16)	19.81 (13.96)	1.659	72	.101
Insulin regimen				.693	1	.405
Injections	24 (63.2%)	26 (72.2%)	50 (67.5%)			
Pump	14 (36.8%)	10 (27.8%)	24 (32.4%)			
Using a continuous glucose monitor				.001	1	.980
Yes	21 (55.3%)	20 (55.6%)	41 (55.4%)			
No	17 (44.7%)	16 (44.4%)	33 (44.6%)			
Other medical conditions				.188	1	.665
Yes	15 (39.5%)	16 (44.4%)	31 (41.9%)			
No	23 (60.5%)	20 (55.6%)	43 (58.1%)			
Currently taking other medications				.433	1	.510
Yes	26 (68.4%)	22 (61.1%)	48 (64.9%)			
No	12 (31.6%)	14 (38.9%)	26 (35.1%)			
Dietary plan [a]						
No dietary plan	26 (68.4%)	24 (66.7%)	50 (67.5%)			1.00
Vegetarian	2 (5.3%)	2 (5.6%)	4 (5.4%)			1.00
Vegan	0 (0%)	1 (2.8%)	1 (1.4%)			.486
Gluten Free	0 (0%)	2 (5.6%)	2 (2.7%)			.233
Paleo/high protein	3 (7.9%)	3 (8.3%)	6 (8.1%)			1.00
Low Fat	2 (5.3%)	1 (2.8%)	3 (4.1%)			1.00
Other	5 (13.2%)	4 (11.1%)	9 (12.2%)			1.00
HbA1c (mmol/mol) *M(SD)*	62.61 (16.40)	63.67 (17.01)	63.10 (16.57)	-.267	69	.790
Diabetes self-care – diet *M(SD)*	4.17 (1.52)	3.83 (1.60)	4.01 (1.56)	.932	72	.354

[a] Fisher's exact test used

7.1.3 Psychosocial Outcome Measures

Results from psychosocial questionnaires assessing depression, anxiety, stress and diabetes quality of life (QOL) administered at baseline are displayed in Table 3. At baseline, the sample had normal (low) levels of depression (between 0-9), normal (low) to mild levels of anxiety (normal = 0-6 and mild = 7-9), and mild levels of stress (between 11-18), based on the DASS classifications where higher scores indicate higher severity. Despite the overall sample displaying relatively low levels of depression, anxiety and stress, according to the DASS cut off scores, 10.8%, 12.2% and 1.4% of participants scored as either "severe" or "extremely severe" on the depression, anxiety or stress subscales, respectively (detailed in Table 4).

Table 3

Psychosocial Outcomes at Baseline

Outcome variable	**Probiotic** (*n*=38)	**Placebo** (*n*=36)	**Total sample** (*n*=74)	**Test statistic** *t* or x^2	***df***	***p***
Depression score *M(SD)*	7.95 (9.11)	7.11 (7.98)	7.54 (8.53)	.419	72	.676
Anxiety score *M(SD)*	7.63 (8.11)	6.17 (5.56)	6.92 (6.98)	.902	72	.370
Stress score *M(SD)*	12.16 (6.92)	11.28 (8.4)	11.73 (7.55)	.499	72	.620
Diabetes QOL *M(SD)*	36.92 (9.64)	36.50 (7.97)	36.72 (8.81)	.204	72	.839

Table 4

DASS Cut Off Scores for Depression, Anxiety and Stress in the Study Sample at Baseline

DASS score cut off	Depression	Anxiety	Stress
Normal	49 (66.2%)	44 (59.5%)	35 (47.3%)
Mild	10 (13.5%)	12 (16.2%)	27 (36.5%)
Moderate	7 (9.5%)	9 (12.2%)	11 (14.9%)
Severe	4 (5.4%)	3 (4.1%)	1 (1.4%)
Extremely severe	4 (5.4%)	6 (8.1%)	0 (0%)

7.2 Associations Between HbA1c and Psychosocial Outcome Measures

Correlational analyses were conducted to investigate relationships between glycaemic control and measures of wellbeing and self-care at baseline. As half of the variables violated the normality assumption, Spearman's Rho tests were performed to determine the size and direction of the linear relationships between HbA1c levels and diet, health-related quality of life, depression, anxiety and stress scores.

Table 5 demonstrates that HbA1c was positively correlated with DASS depression scores, indicating that increased self-reported symptoms of depression were associated with reduced glycaemic control, $r_s = .233$, $p = .05$, two-tailed, $n = 71$. HbA1c was also positively correlated with anxiety scores, however, this relationship was non-significant, $r_s = .213$, $p = .074$, two-tailed, $n = 71$. HbA1c was weakly associated with diet, diabetes quality of life and stress scores.

Notably, diabetes quality of life was strongly positively correlated with depression, $r_s = .586$, $p < .001$, two-tailed, $n = 74$, anxiety, $r_s = .594$, $p < .001$, two-tailed, $n = 74$ and stress, $r_s = .507$, $p < .001$, two-tailed, $n = 74$. Given a lower score on the diabetes quality of life scale

indicates greater diabetes satisfaction, these findings suggest that increased self-reported symptoms of depression, anxiety and stress was associated with reduced diabetes satisfaction.

Table 5

Correlation Matrix of Psychological and Clinical Variables at Baseline

	1.	2.	3.	4.	5.	6.
1. HbA1c (mmol/mol) [a]	-					
2. Diet [b]	-.190	-				
3. Diabetes QOL [b]	.002	-.233*	-			
4. Depression score [b]	.233*	-.244*	.568**	-		
5. Anxiety score [b]	.213	-.110	.594**	.641**	-	
6. Stress score [b]	.042	-.288*	.507**	.632**	.599**	-

[a] $n = 71$

[b] $n = 74$

* $p < .05$, ** $p < .01$.

7.3 Probiotic knowledge and beliefs

Descriptive statistics were generated to explore the knowledge and beliefs regarding probiotic supplementation in adults with T1D at baseline. The majority of the sample were at least somewhat familiar with the word probiotic (98.7%), with only one participant reporting they had never heard the word before (see Figure 6). Figure 7 showcases the wide range of mediums where participants learnt of probiotics, with the most commonly reported avenue being the internet (37.8%), followed by a pharmacist (29.7%) and a family member (23%).

Figure 6

Participants' Reported Familiarity with the Word 'Probiotic'

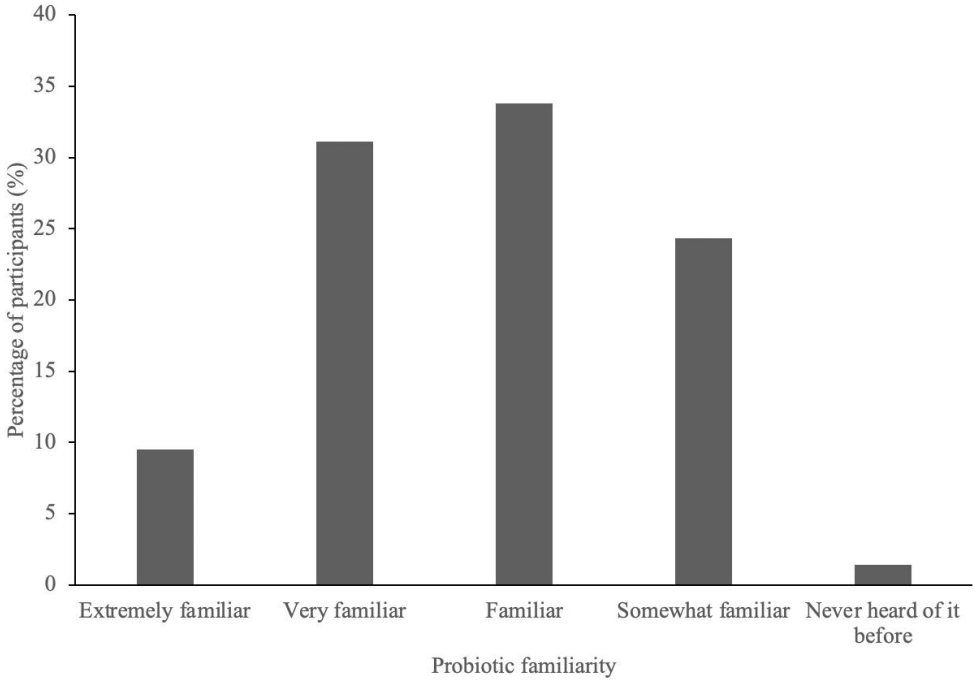
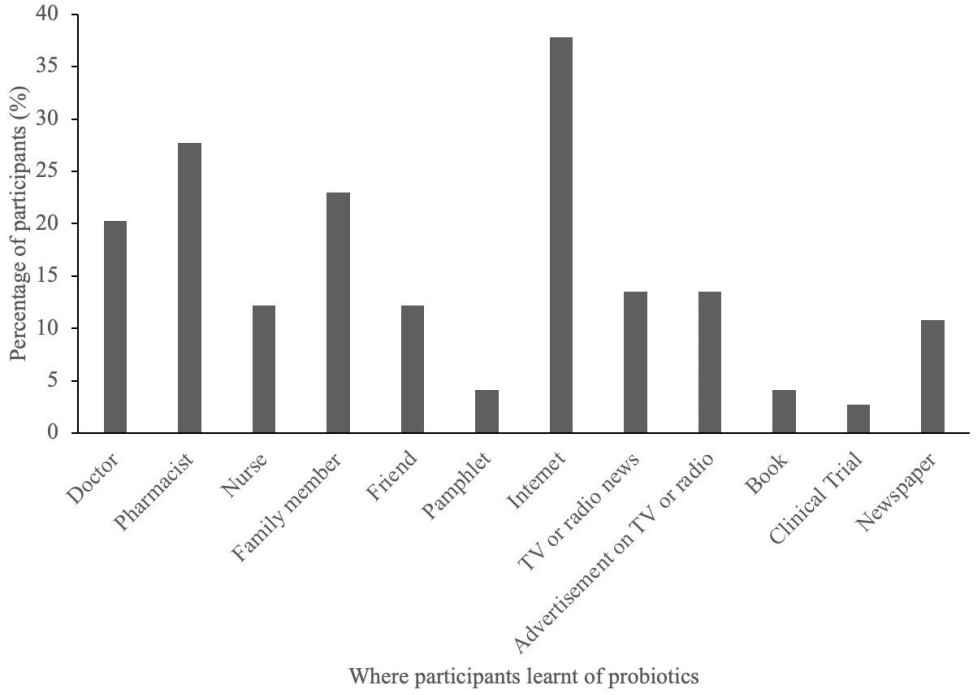


Figure 7

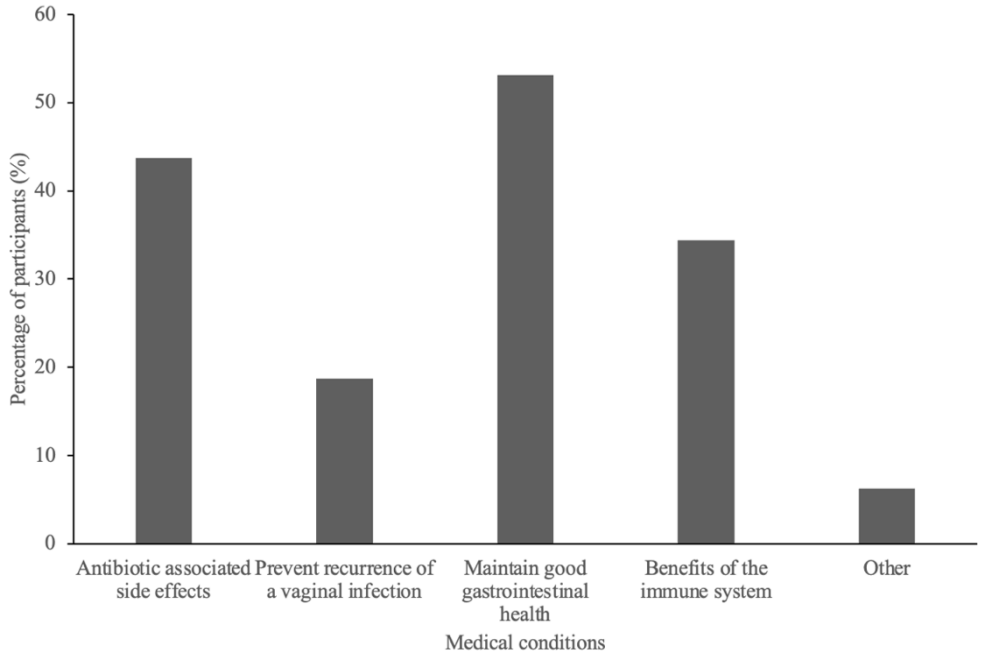
Where Participants Learnt of Probiotics



Despite most of the sample being acquainted with the word probiotic, just 32 of the total 74 participants (43.2%) at baseline reported having used a probiotic food or supplement to obtain health benefits. Females were more likely to have previously tried probiotics than males, with 50% of females reporting they had used probiotics in comparison to 33.3% of males. When those who had tried probiotics were asked for what medical conditions they took probiotics for, the most common answer was to maintain good gastrointestinal health (17 participants), followed by antibiotic associated side effects (14 participants), displayed in Figure 8. No participants reported using probiotics for chronic diarrhoea, chronic constipation, inflammatory bowel disease, IBS, or allergic skin conditions, and were therefore omitted from the graph. The two participants who answered 'other' stated that they were advised to take probiotics with or after a course of antibiotics.

Figure 8

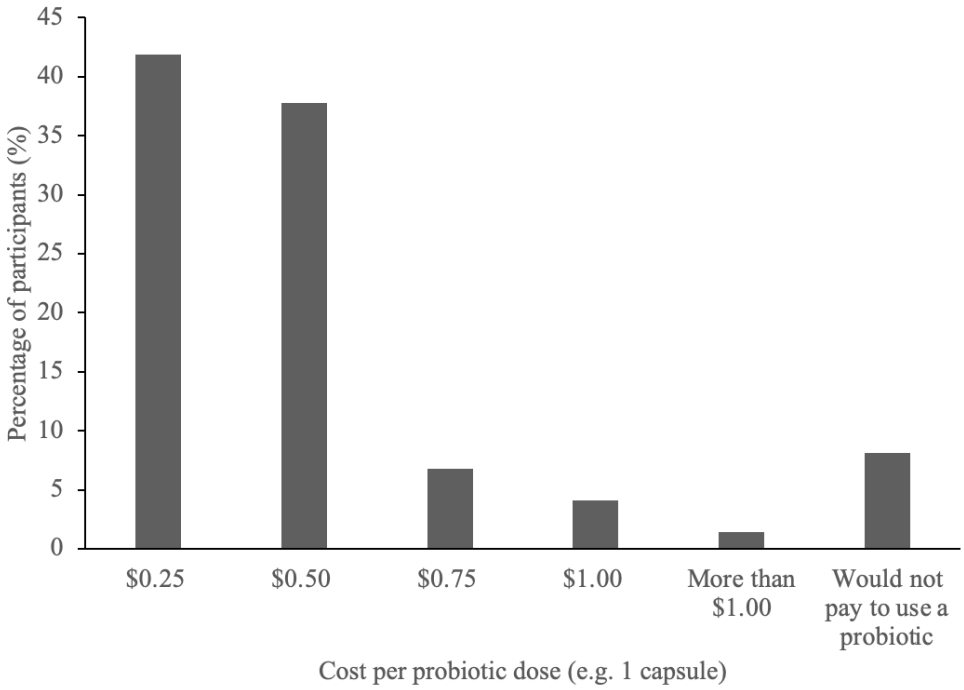
The Medical Conditions Participants Reported Trying Probiotics for



Of the 42 people who reported not having used a probiotic food or supplement to obtain health benefits, after being offered a definition of probiotics, 39 (92.9%) expressed they would consider taking them in the future. In saying that, the majority of the full sample (87.8%) expressed that they would not be prepared to pay more than 50c per probiotic dose (i.e. capsule) if they were to buy probiotics (see Figure 9).

Figure 9

Cost per Probiotic Dose that Participants Report Being Willing to Pay



7.4 Main Analyses

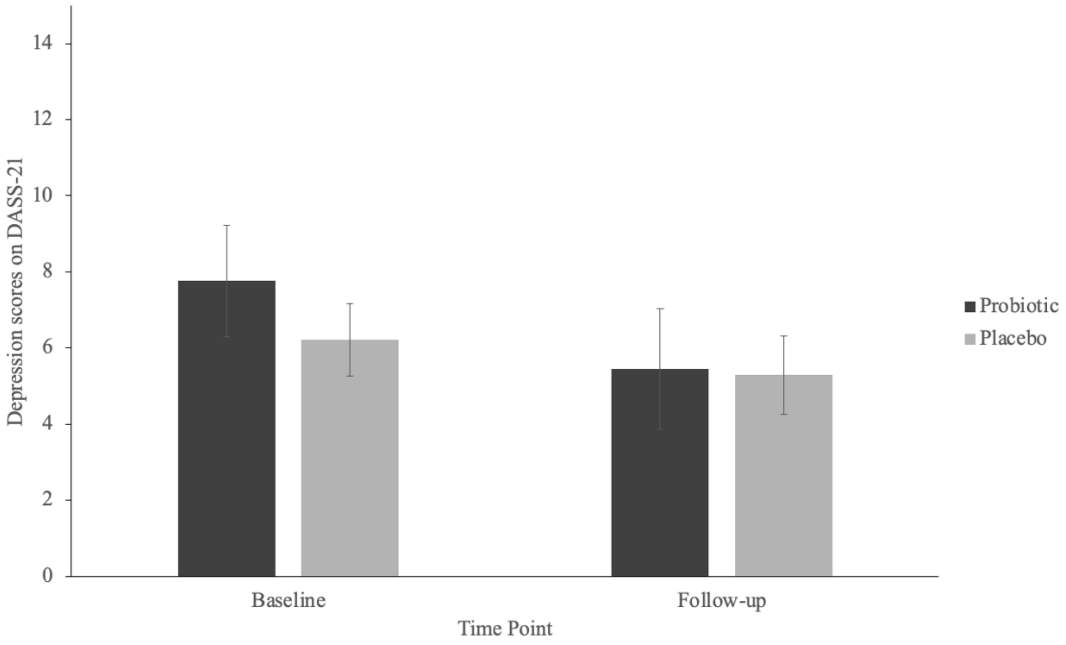
7.4.1 Hypothesis 1. Exploring the Effect of Probiotics on Depression, Anxiety and Stress

Three 2 (time: baseline, 12-week follow-up) x 2 (group: probiotic, placebo) mixed ANOVAs were conducted to test the hypothesis that participants allocated to the probiotic intervention group would demonstrate improvements in depression, anxiety and stress from baseline to 12-weeks follow-up, compared to those in the placebo control group.

The first mixed ANOVA exploring the effects on the depression subscale of the DASS revealed no significant main effect of time, $F(1, 59) = 3.55$, $p = .065$, $\eta_p^2 = .056$, indicating that irrespective of group allocation, there was no significant change in depression scores over time. The main effect of group allocation was also non-significant, $F(1, 59) = .285$, $p = .596$, $\eta_p^2 = .005$, signifying that there was no difference in depression scores between participants in the intervention or control group for either time point. There was also no significant interaction effect between time and group allocation, $F(1, 59) = .638$, $p = .428$, $\eta_p^2 = .011$. These results are displayed in Figure 10.

Figure 10

Depression Scores of Participants Allocated to Probiotic and Placebo Group at Baseline and 12-weeks Follow-up



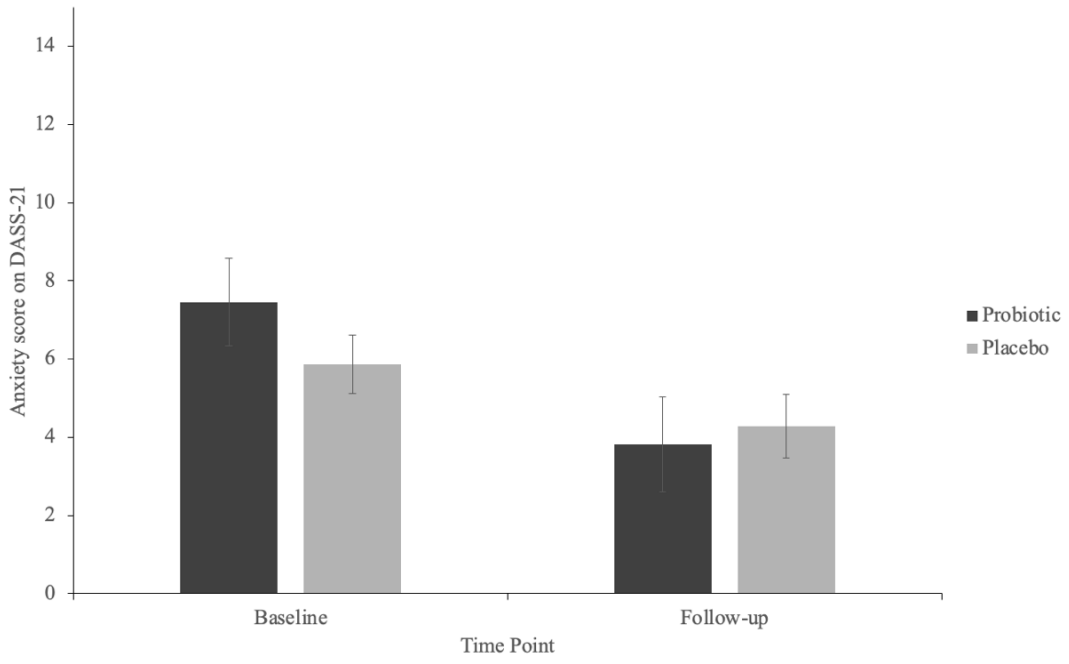
Note. Bars represent estimated marginal means, and error bars represent standard errors.

Due to minor violations of the normality assumption in the depression subscale of the DASS, Wilcoxon signed-rank and Mann-Whitney U tests were performed to provide confidence in the results of the mixed ANOVA. The Wilcoxon signed-rank test revealed no significant change in depression scores between baseline (*Mdn* = 4) and 12-weeks follow-up (*Mdn* = 4) for the probiotic group, $T = 132.5$, $z = -1.37$, $p = .170$, $r = -.239$, supporting the findings of the mixed ANOVA. Similarly, the Mann-Whitney U test found no significant difference in depression scores between participants in the probiotic group (*Mdn* = 4, $n = 33$) and the placebo group (*Mdn* = 2, $n = 28$) at the 12-week follow-up, $U = 398$, $z = -9.45$, $p = .345$, $r = 1.21$.

The second mixed ANOVA exploring the effects on the anxiety subscale of the DASS revealed a significant main effect of time, $F(1, 59) = 13.014$, $p = .001$, $\eta_p^2 = .181$, indicating that irrespective of group allocation, anxiety scores decreased across time from baseline ($M = 6.92$, $SD = 6.98$) to the 12-week follow-up ($M = 4.03$, $SD = 4.26$). No significant main effect was found for group allocation, $F(1, 59) = .218$, $p = .642$, $\eta_p^2 = .004$, indicating there were no difference in anxiety scores between participants in the intervention or control group irrespective of time point. Moreover, no significant interaction effect between time and group allocation was reported, $F(1, 59) = 2.046$, $p = .158$, $\eta_p^2 = .034$. The results are exhibited in Figure 11Figure 11.

Figure 11

Anxiety Scores of Participants Allocated to Probiotic and Placebo Group at Baseline and 12-weeks Follow-up



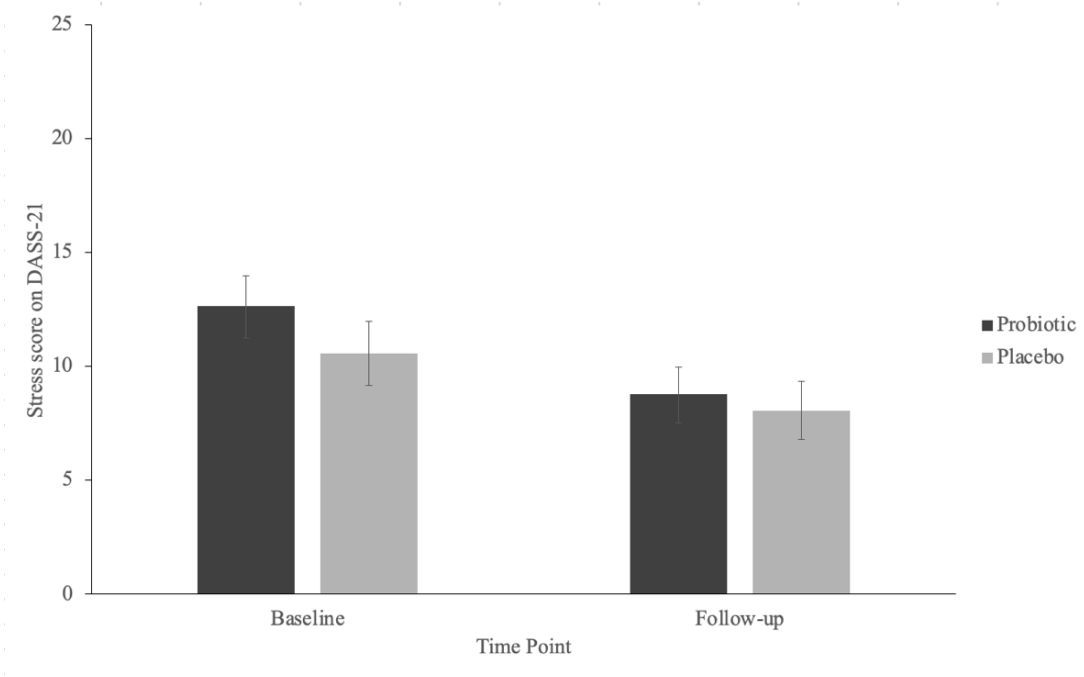
Note. Bars represent estimated marginal means, and error bars represent standard errors.

Given minor violations of the normality assumption for the anxiety scores, Wilcoxon signed-rank and Mann-Whitney U tests were performed to provide confidence in the results of the mixed ANOVA. The Wilcoxon signed-rank test found a significant reduction in anxiety scores between baseline (*Mdn* = 6, *n* = 38) and 12-week follow-up (*Mdn* = 2, *n* = 33) in the probiotic group, *T* = 40, *z* = -3.469, *p* = .001, *r* = .604. However, no difference was found for participants in the placebo group, *T* = 52, *z* = -1.465, *p* = .143, *r* = .277. In line with the mixed ANOVA, the Mann-Whitney U test also found no significant difference in anxiety scores at the 12-week follow-up between participants in the probiotic group (*Mdn* = 2, *n* = 33) and the placebo group (*Mdn* = 2, *n* = 28), *U* = 452.5, *z* = -1.41, *p* = .888, *r* = .181.

The third mixed ANOVA explored the effects of the stress subscale of the DASS, and found a significant main effect of time, $F(1, 59) = 10.808$, $p = .002$, $\eta_p^2 = .155$, indicating that stress scores decreased over time between baseline (*M* = 11.73, *SD* = 7.55) and 12-week follow-up (*M* = 8.46, *SD* = 6.72) irrespective of group allocation. The main effect of group allocation was non-significant, $F(1, 59) = .821$, $p = .368$, $\eta_p^2 = .014$, signifying there was no difference in stress scores between groups regardless of time point. There was also no main interaction effect between time and group allocation, $F(1, 59) = .505$, $p = .480$, $\eta_p^2 = .008$. These results are displayed in Figure 12.

Figure 12

Stress Scores of Participants Allocated to Probiotic and Placebo Group at Baseline and 12-weeks Follow-up.



Note. Bars represent estimated marginal means, and error bars represent standard errors.

In summary, Hypothesis 1 was not supported. Results from the mixed ANOVAs and non-parametric tests suggest the probiotic intervention did not significantly improve depression, anxiety and stress scores of participants from baseline to 12-week follow-up compared to those in the placebo control group. Instead, the results suggest that anxiety and stress decreased over time between baseline and 12-week follow up, irrespective of whether participants were randomised to the probiotic or placebo group.

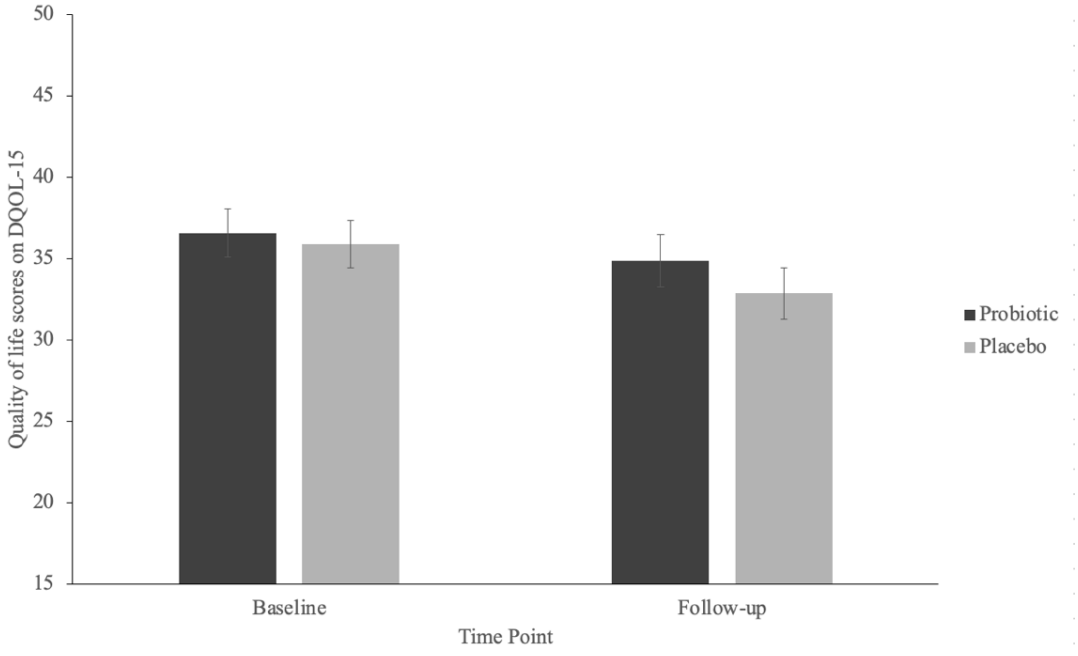
7.4.2 Hypothesis 2. Exploring the Effect of Probiotics on Quality of Life

A 2 (time: baseline, 12-week follow-up) x 2 (group: probiotic, placebo) mixed ANOVA was conducted to investigate the hypothesis that adults in the probiotic intervention

group would display improved health-related quality of life from baseline to 12-week follow-up compared to those in the placebo control group. The mixed ANOVA revealed a significant main effect of time $F(1, 59) = 11.492$, $p = .001$, $\eta_p^2 = .163$, indicating that regardless of group allocation, participants reported improved quality of life between baseline to follow-up. There was no significant main group effect, $F(1, 59) = .437$, $p = .511$, $\eta_p^2 = .007$, in which there was no difference in quality of life scores between groups irrespective of time point. The main interaction effect between time and group allocation was also non-significant, $F(1, 59) = .920$, $p = .342$, $\eta_p^2 = .015$. The results are exhibited in Figure 13.

Figure 13

Quality of Life Scores of Participants Allocated to Probiotic and Placebo Group at Baseline and 12-weeks Follow-up



Note. Bars represent estimated marginal means, and error bars represent standard errors.

The results do not support Hypothesis 2. While participants' quality of life significantly improved over time from baseline to 12-week follow-up irrespective of group

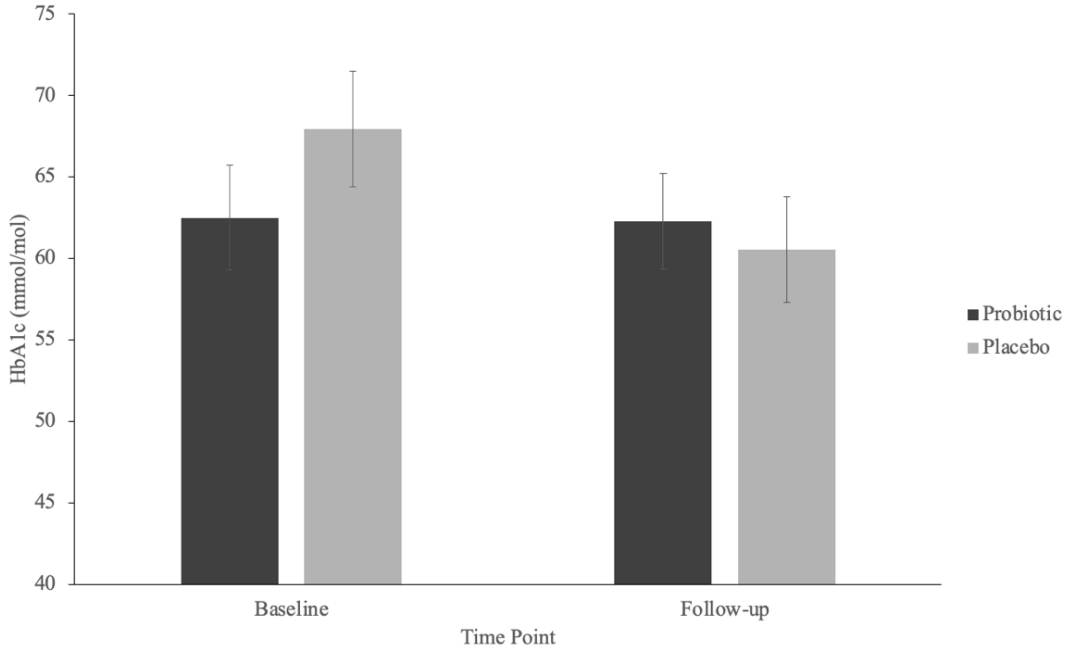
allocation, the results of the mixed ANOVA indicate that the probiotic intervention did not significantly improve quality of life scores from baseline to follow-up compared to placebo.

7.4.3 Hypothesis 3. Exploring the Effect of Probiotics on HbA1c

A 2 (time: baseline, 12-week follow-up) x 2 (group: probiotic, placebo) mixed ANOVA was conducted to test the hypothesis that those randomised to the probiotic intervention would exhibit lower HbA1c levels from baseline to 12-week follow-up compared to those in the placebo group. The mixed ANOVA revealed a significant main effect of time, $F(1, 49) = 5.393$, $p = .024$, $\eta_p^2 = .099$, indicating that irrespective of group allocation, participants' HbA1c lowered over time from baseline ($M = 63.10$, $SD = 16.572$) to the 12-week follow up ($M = 61.29$, $SD = 15.33$). No significant main effect of group allocation was found, $F(1, 49) = .190$, $p = .665$, $\eta_p^2 = .004$, indicating there was no significant difference in HbA1c levels between participants in the intervention or control group regardless of time point. There was, however, a significant main interaction effect between time and group allocation, $F(1, 49) = 4.803$, $p = .033$, $\eta_p^2 = .089$, indicating there was a greater reduction in HbA1c results over time in the placebo group compared to the probiotic group. These results are displayed in Figure 14.

Figure 14

HbA1c Levels of Participants Allocated to Probiotic and Placebo Group at Baseline and 12-weeks Follow-up



Note. Bars represent estimated marginal means, and error bars represent standard errors.

In summary, Hypothesis 3 was not supported. The results of the mixed ANOVA suggest that the probiotic intervention did not significantly improve (i.e. reduce) HbA1c levels between baseline and follow up compared to the placebo. Instead, both the probiotic and placebo groups displayed improved HbA1c levels across time. Moreover, even though there were no significant differences between the groups at either time point, the placebo group displayed a significantly greater improvement in HbA1c levels compared to the probiotic group between baseline and follow-up.

7.5 Further Exploratory Analyses

7.5.1 Participants with Moderate to Extremely Severe Levels of Depression, Anxiety and Stress

Further analyses were conducted to explore whether the probiotic intervention offered greater improvements in mental health outcomes for individuals who scored more severely on the depression, anxiety and stress subscales of the DASS. The series of 2 (time: baseline, 12-week follow-up) x 2 (group: probiotic, placebo) mixed ANOVAs investigating the effectiveness of the intervention on depression, anxiety and stress subscales of the DASS of Hypothesis 1 were replicated solely including individuals who scored as moderate, severe or extremely severe on the corresponding subscale.

The mixed ANOVAs involving participants who scored more severely on each of the DASS subscales revealed only one finding divergent from the main analyses of Hypothesis 1. When the full sample is considered, the mixed ANOVA found no significant main effects for time, group allocation or interaction effect between time and group allocation for depression scores. However, when analysing participants who scored at least moderately on the depression subscale (probiotic group $n = 8$, placebo group $n = 7$), the mixed ANOVA revealed a significant main effect of time $F(1, 10) = 21.931$, $p = .001$, $\eta_p^2 = .687$. Therefore, irrespective of the group allocation, the participants who scored at least moderately on the depression subscale displayed significantly improved depression scores between baseline ($M = 22.13$, $SD = 5.78$) and 12-week follow-up ($M = 10.83$, $SD = 5.81$).

Due to the depression and anxiety subscales minor violations of the normality assumption, non-parametric tests were conducted to provide confidence in the results of the replicated mixed ANOVAs and found comparable results. Although the Wilcoxon signed-

rank test for the depression subscale revealed a significant change in depression scores from baseline to follow up in the probiotic group, $T = 0$, $z = -2.38$, $p = .017$, $r = -.901$, which is in line with the replicated mixed ANOVA, the change was non-significant in the placebo group, $T = 0$, $z = -1.826$, $p = .068$, $r = -.913$. The Mann Whitney U test revealed no significant difference in depression scores of those who scored at least moderately between the probiotic group ($Mdn = 10$, $n = 7$) and the placebo group ($Mdn = 10$, $n = 5$) at the 12-week follow up, $U = 16.0$, $p = .876$, $r = .071$.

The results of the original analyses remaining essentially unchanged suggest the probiotic intervention offered no additional benefit over the placebo to individuals who scored more severely on the DASS subscales compared to those who scored as normal or mild. However, the subgroup sample sizes are small and, therefore, are underpowered to detect such an effect.

7.5.2 Adherence

To examine whether self-reported adherence impacted the results, the main analyses investigating the influence of the probiotic intervention on mental health, quality of life and glycaemic control outcomes from Hypotheses 1 to 3 were replicated solely including participants who were considered adherent (i.e. had less than 10 capsules remaining). Thus, a series of 2 (time: baseline, 12-week follow-up) x 2 (group: probiotic, placebo) mixed ANOVAs were conducted to explore if those allocated to the probiotic group displayed improved depression, anxiety and stress scores, elevated diabetes quality of life scores, and reduced HbA1c levels compared to those in the placebo group, among participants classed as adherent (probiotic group $n = 25$, placebo group $n = 26$). Non-parametric tests were also replicated in non-normally distributed variables to verify the findings.

With one exception, there were no different outcomes of the original analyses when replicated in participants considered adherent. The only result varying from the main findings was the previously significant main interaction effect between time and group allocation for HbA1c results from baseline to follow-up in the placebo group became non-significant when the mixed ANOVA was performed only including participants considered adherent (probiotic group $n = 19$, placebo group $n = 20$), $F(1, 37) = 3.706$, $p = .062$, $\eta_p^2 = .091$.

Chapter 8 Discussion

The current study's primary aim was to examine the effect of probiotic supplementation on mental health outcomes and glycaemic control over 12-weeks in a sample of adults with T1D in New Zealand. The study also aimed to investigate the prevalence of depression, anxiety and stress within this sample and explore the participants beliefs and knowledge of probiotics. This chapter begins with a summary of the study's main findings before discussing the results in the context of existing literature. Next, the study's strengths and limitations are described, followed by a commentary on the theoretical and clinical implications of the results. Lastly, possible pathways for future research is explored.

8.1 Summary of Findings

The current study demonstrates that probiotic supplementation did not improve symptoms of depression, anxiety or stress, health-related quality of life (DQOL), or glycaemic control in this sample of adults with T1D. There were no significant differences in depression, anxiety, stress and quality of life scores between the probiotic and placebo group at either time point. Rather, participants in both the probiotic and placebo group displayed a significant reduction (i.e. improvement) in anxiety, stress and quality of life scores from baseline to the 12-week follow-up. Depression scores also decreased over time for both groups, but this did not reach levels of statistical significance. Probiotic supplementation did not offer any additional benefit to individuals with more severe self-reported symptoms of depression, anxiety or stress, except that this subgroup displayed a significant improvement in depression scores over the 12 weeks, irrespective of group allocation. Participants' HbA1c levels did not significantly differ between the probiotic and placebo group at either time point; however, similar to the mental health outcomes, both groups displayed a significant

improvement in HbA1c levels over the 12-week intervention. Intriguingly, the placebo group demonstrated a more significant reduction in HbA1c levels over time compared to the probiotic group. However, when the analyses were replicated among participants considered adherent, the interaction effect became non-significant.

At baseline, the sample displayed relatively low depression, anxiety and stress levels and appeared to be satisfied with their diabetes management. Unsurprisingly, measures of health-related quality of life were strongly correlated with depression, anxiety, stress and diet scores, whereby more severe symptoms of depression, anxiety, stress, and a less optimal diet were associated with greater diabetes dissatisfaction. However, unexpectedly, HbA1c was only weakly associated with any measures of psychosocial functioning.

The majority of the sample was at least somewhat familiar with probiotics. Participants reported learning about probiotics through varied sources, with the internet, pharmacists and family members being among the most common answers. Just below half of the sample had previously tried probiotics to obtain health benefits, including maintaining good gastrointestinal health, combatting antibiotic-associated side effects, and benefitting the immune system. Of those who had not tried probiotics before, 92.9% reported that they would consider taking them in the future.

8.2 Interpretation of Findings in Context of Existing Literature

8.2.1 Influence of Probiotics on Psychological Health

In contrast to the study's hypotheses, the probiotic group did not demonstrate greater improvements in depression, anxiety, stress and quality of life compared to the placebo group. Although research into the beneficial effects of probiotics is growing, the literature base is still in its infancy. Thus, evidence supporting the use of probiotics to improve mental

health outcomes remains inconclusive (Romijn & Rucklidge, 2015; Vaghef-Mehrabany et al., 2020). Subsequently, the findings of the current study are both consistent with and conflicting with existing literature, with studies similarly demonstrating that probiotics do not impact symptoms of depression, anxiety and stress compared to placebo (Chahwan et al., 2019; Gomi et al., 2018; Kelly et al., 2017; Östlund-Lagerström et al., 2016; Roman et al., 2018; Romijn et al., 2017; Rudzki et al., 2019), as well as studies finding significant improvements (Akkasheh et al., 2016; Kazemi et al., 2019; Lew et al., 2019; Mohammadi et al., 2016; Slykerman et al., 2017; Wallace & Milev, 2021).

One possible reason for the non-significant findings is the probiotic itself, whereby the probiotic strain utilised in the study, *Lactobacillus rhamnosus* HN001 at a dose of 6 x 10^9 cfu/day, may not confer mental health benefits in individuals with T1D. Because probiotics effects are strain-specific, and may further differ depending on dose, length of intervention and combination of probiotic strains, the substantial heterogeneity of existing studies investigating the influence of probiotics on mental health hinders the ability to ascertain what probiotics under what conditions can improve mood and wellbeing (Vaghef-Mehrabany et al., 2020). At present, only two other studies investigating probiotics' effect on mental health have utilised *L. rhamnosus* HN001 exclusively. Slykerman et al. (2017) found that supplementation of *L. rhamnosus* HN001 at 6 x 10^9 cfu per day to women during pregnancy and six months after delivery if breastfeeding led to significantly lower depression and anxiety scores compared to those in the placebo group. However, a limitation of this study was that depression and anxiety were measured retrospectively. In another study, Tay et al. (2020) found that in individuals with pre-diabetes, the consumption of *L. rhamnosus* HN001 at 6 x 10^9 cfu daily for 12 weeks paired with intermittent fasting led to significant improvements in mental health measures compared to placebo. Although these findings conflict with that of the current study, the distinctive methodology of each study prevents

straightforward comparisons between them. Therefore, the non-significant results of the current study may still indicate that *L. rhamnosus* HN001 cannot improve mental health in individuals with T1D or, perhaps, is insufficient as a standalone treatment.

An alternative explanation for the non-significant results may be due to the participants' gut microbiota characteristics. Fuller (1992) posits that a positive response from a probiotic firstly requires the presence of harmful microbes, a lack of the probiotic bacteria in the microbiota naturally, or the gut is in dysbiosis. Moreover, preclinical research on the gut-brain axis suggests that gut microbiota composition may have direct influences on the expression of depressive and anxiety symptoms. With the knowledge that microbiota composition varies considerably between individuals and is impacted by numerous factors across the lifespan, perhaps the participants in the current study did not meet such compositional conditions to see a positive effect of probiotic consumption. Indeed, the literature supports the use of multi-strain over single-strain probiotics for improving symptoms of depression and anxiety; possibly due to synergistic interactions between strains, a higher concentration of probiotic strains, or a higher chance of participants obtaining probiotics that were lacking from the gut microbiota (Nikbakht et al., 2018; Timmerman et al., 2004). Utilising only one probiotic strain in the current study may have limited the scope of beneficial effects that probiotics can confer to mental health and led to non-significant results. Furthermore, because the gut microbiota increases in complexity and is more susceptible to change during infancy, it may be easier to manipulate microbiota composition using probiotics early in life rather than adulthood when the gut microbiota is established and more stable. In which case, probiotics may only provide finite benefits to adults. Nevertheless, the previous studies investigating *L. rhamnosus* HN001 noted improvements in mood regardless of participants' pre-existing gut microbiota composition (Slykerman et al., 2017; Tay et al., 2020).

Another contributing factor to the study's null findings may be the low levels of psychopathology in the sample. Measures of mental health were relatively mild at baseline, with 20.3%, 24.4% and 16.3% of the sample experiencing moderate to extremely severe symptoms of depression, anxiety and stress, respectively. These numbers were unexpected, given that the literature indicates that individuals with T1D are more likely to experience symptoms of depression and anxiety compared to those without T1D (Roy & Lloyd, 2012; K. Smith et al., 2013). With little room for improvement at baseline, any beneficial effects of probiotics would be difficult to detect. Perhaps, probiotics offer negligible improvements to mental health in healthy individuals (i.e. non-depressed and non-anxious), similar to the limited beneficial effect of antidepressants in healthy populations (Serretti et al., 2010). Previous studies exploring the influence of probiotics on mental health outcomes have also raised this concern of a 'ceiling effect' leading to non-significant results (Benton et al., 2007; Kelly et al., 2017; Lew et al., 2019). Notably, a meta-analysis by Ng et al. (2018) demonstrated that while the overall effect of probiotics on mood was non-significant, they noted a significant improvement when analysing only the studies involving participants with depression or anxiety. Although the current study performed subgroup analyses with participants reporting moderate to extremely severe symptoms of depression, anxiety and stress, the sample size of each group were small and underpowered to detect any genuine improvements, highlighting a limitation of the study.

Confounding factors, such as diet and physical activity, may also have impacted the results. While participants indicated how frequently they ate healthily or followed their eating plan, this did not specify what foods they consumed during the intervention nor if their diet significantly changed. The literature demonstrates that diet and physical activity can influence mental health outcomes (Hallgren et al., 2020; Harvey et al., 2018; Y. Li et al., 2017; Ströhle, 2008). In fact, increasing physical activity is emerging as an alternative

treatment for depression, exhibiting benefits comparable to antidepressants (Dinas et al., 2011; Nyström et al., 2015). In addition, research demonstrates that physical activity, and diet, in particular, are significantly associated with gut microbiota composition and activity (David et al., 2014; De Filippo et al., 2010; Ortiz-Alvarez et al., 2020). For instance, prebiotics, which promotes the growth and activity of specific probiotic strains and confers health benefits, are found in numerous everyday food items such as bananas, berries and oats (Markowiak & Śliżewska, 2017). Consequently, a change in participants' diet and level of physical activity could have impacted results by directly influencing mood or, as per the gut-brain axis model, indirectly shaping mood by changing microbiota composition and activity.

One should also consider the study's findings in light of the socio-political context in which the data was collected. The majority of the follow-up data was collected while New Zealand was in COVID-19 Alert Levels 3 or 4 'lockdown', a time that heavily limited people's movements and social interactions to mitigate the spread of the virus. Auckland city, where most participants resided, was particularly impacted with restrictions extending considerably longer than the remainder of the country. Unsurprisingly, lockdowns negatively impact psychological wellbeing, with New Zealand cohort studies demonstrating depression, anxiety and stress levels during the 2020 lockdown were significantly greater than population norms (Every-Palmer et al., 2020; Gasteiger et al., 2021). Entering Level 4 lockdown mid-intervention imparts a significant yet unavoidable confounding factor to the study and may have prevented improvements in mood following probiotic supplementation. With that said, one might have expected participants' depression, anxiety and stress scores to worsen or remain stable, whereas participants reported improvements in mood irrespective of group allocation.

Indeed, although this study found no significant differences in mental health outcomes between the probiotic and placebo groups, participants across both the probiotic and placebo

groups demonstrated reductions in symptoms of depression, anxiety and stress. These findings are consistent with previous placebo-controlled probiotic studies that observed improvements in mental health outcomes irrespective of group allocation (Chahwan et al., 2019; Roman et al., 2018). The universal improvements may have resulted from statistical confounders, including regression towards the mean or a repeated assessment effect (Andrade, 2012). However, given that participants were encouraged to take the capsule at the same time each day to create a routine, perhaps the daily activity of preparing and consuming a capsule alleviated symptoms of depression, anxiety and stress, regardless of whether they took the probiotic or placebo. This notion is in line with research indicating routines and engaging in planned activities can ease symptoms of depression (Cuijpers et al., 2007; Ekers et al., 2014).

However, a more feasible explanation may be that the positive expectations of probiotics held by participants led to the improvements in mental health outcomes and quality of life rather than the probiotic itself. In other words, the 'placebo effect'. The placebo effect exerts powerful influences on health outcomes, clearly exemplified by a study by Bingel et al. (2011) investigating the influence of expectations on the efficacy of an opioid drug at reducing pain. When the authors created positive expectations that the drug would help reduce pain, participants reported more significant pain reduction than when the researchers provided no expectations. The current sample was well acquainted with the word probiotic, and those that had tried probiotics in the past reported taking them for health benefits such as maintaining good gastrointestinal health, reducing antibiotic-associated side effects and benefitting the immune system. Consequently, perhaps participants' beliefs that probiotics can benefit health and alleviate symptoms of depression, anxiety and stress led to the reported improvements in mood, regardless of whether they consumed the probiotic or placebo. This concept is consistent with previous studies exploring the efficacy of antidepressants in

reducing symptoms of depression and anxiety, whereby participants report improvements in mood despite consuming a placebo (Rief et al., 2009). A future study may benefit from including items in the baseline questionnaires that measure probiotic treatment expectations and control for them in the analyses.

8.2.2 Influence of Probiotics on Glycaemic Control

Contrary to what was hypothesised, probiotic supplementation did not improve glycaemic control compared to placebo. In contrast, both the probiotic and placebo group displayed a significant reduction in HbA1c levels over the 12-week intervention. In fact, the placebo group displayed a greater reduction in HbA1c levels across the intervention compared to the probiotic group. However, there were no differences between groups when analysing the participants who were considered adherent, suggesting it was a chance finding.

Many of the possible explanations why probiotics did not impact mood in this study may also explain why probiotics did not influence glycaemic control. For instance, the probiotic used in the study, *L. rhamnosus* HN001, at a dose of 6 x 10^9 cfu/day, may not have the capacity to exert effects on glycaemic control. This is in line with Tay et al., 2020, who found probiotic supplementation with *L. rhamnosus* HN001 paired with intermittent fasting did not significantly decrease HbA1c levels in individuals with pre-diabetes compared to placebo. However, these findings conflict with the promising results from Wickens et al., 2017, who discovered that *L. rhamnosus* HN001 supplementation was associated with lower rates of gestational diabetes in older women and women with a history of gestational diabetes, compared to placebo. The current study's non-significant findings in mood and glycaemic control following *L. rhamnosus* HN001 supplementation is consistent with theories of probiotics' mechanisms of action, which postulate that probiotics impact both

physical and psychological health via common anti-inflammatory and immune system regulating mechanisms (Mishra et al., 2019; Wallace & Milev, 2017).

Confounding factors may have contributed to the non-significant findings. As discussed previously, the types of foods consumed and one's level of physical activity can impact gut microbiota composition, possibly impacting probiotics' effect on HbA1c levels. However, a shift in diet, engaging in physical activity and other everyday experiences such as illness and life stress can also influence blood glucose levels directly (American Diabetes Association, 2013). Consequently, a change in any of the factors listed above may have undermined probiotics' influence on glycaemic control in the current study. Moreover, entering the lockdown midway through the intervention likely amplified these confounding factors.

Another consideration is that glycaemic control may not have improved due to the probiotics' lack of effect on symptoms of depression and anxiety. The current study revealed that HbA1c was associated with depression scores, although not with anxiety and stress scores, possibly due to the low level of psychopathology in the current sample. These findings contrast with existing literature that demonstrates clear correlations between suboptimal glycaemic control and symptoms of depression and anxiety (Anderson et al., 2002; Lustman, Anderson, et al., 2000; Pouwer et al., 2010; Shaban et al., 2009; Van Tilburg et al., 2001). Authors suggest these associations are at least partly mediated by reduced T1D self-management, including missing medical appointments, lower adherence to dietary recommendations, and infrequent blood glucose monitoring (Gonzalez et al., 2008; Schmitt, McSharry, et al., 2021; Van Tilburg et al., 2001). In saying that, systematic reviews demonstrate that despite these associations, there is no evidence to suggest pharmacological or psychological interventions that reduce symptoms of depression and anxiety can improve glycaemic control, which aligns with our results (Winkley et al., 2006; Winkley et al., 2020).

Interestingly, participants across both the probiotic and placebo group displayed significantly reduced HbA1c levels. Tay et al. (2020) similarly demonstrated that while there were no significant differences in HbA1c levels between the probiotic or placebo group, both groups demonstrated significantly improved glycaemic control at follow-up. However, participants in Tay's study also engaged in intermittent fasting, which may explain their findings. Despite the unfavourable outcomes of lockdowns, paradoxically, the lockdown in New Zealand may have led to the universal improvement in glycaemic control in the current study. Retrospective studies worldwide have demonstrated that being in lockdown was associated with improved glycaemic control in adults with T1D (Aragona et al., 2020; Capaldo et al., 2020; Fernández et al., 2020; Prabhu Navis et al., 2021). It is, therefore, possible that the lockdown in New Zealand may have led to lower HbA1c levels by facilitating a more regular lifestyle, more consistent mealtimes including fewer carbohydrates, more time to engage in self-care (including blood glucose monitoring), and longer sleep duration. Hence, the lockdown may have fostered participants' optimal glycaemic control.

An alternative explanation for the overall improvement in glycaemic control across the intervention is the participant's positive expectations of probiotics. Indeed, researchers claim treatment expectations and the placebo effect are not limited to subjective self-reported symptoms and can influence objective physiological outcomes (Crum et al., 2011; Crum & Langer, 2007; Leibowitz et al., 2019). In which case, the reduction of HbA1c levels may have resulted from the positive beliefs of probiotics held by participants rather than the probiotic intervention itself.

8.3 Strengths and Limitations

Acknowledging the current study's strengths and limitations is another important aspect when evaluating the results. As discussed above, one of the study's limitations is the low psychopathology of the sample at baseline, which was unexpected in a sample of adults living with T1D. With the majority of participants scoring under the cut-off for depression, anxiety and stress, probiotics were unlikely to provide further benefits to mental health. This may have been due to self-selection bias, whereby participants who volunteered for the study were more health-conscious and likely to engage in health-promoting behaviours than the general T1D population, resulting in the overall low levels of depression and anxiety symptoms at baseline (Young et al., 2020). Consequently, self-selection bias may have undermined the probiotics' effects. A related limitation of the current study was that target sample size was calculated based on a probiotic study that included participants with major depressive disorder, expecting our sample to have moderate to high levels of depression and anxiety at baseline. Therefore, it is unlikely the study was powered to find an effect. Future probiotic studies could increase the likelihood of detecting an effect by using the DASS-21 to assess eligibility for the study and only involving participants who score at least moderately on the questionnaire at baseline.

Another limitation of the present study is the lack of an objective measure of adherence to the intervention, which is two-fold. Firstly, adherence was measured using self-report, which is subject to biases such as socially desirable responding and recall bias (Adams et al., 1999; Pannucci & Wilkins, 2010). Secondly, determining whether participants were considered adherent or not was also based on an arbitrary cut off value decided by the researchers. Nonetheless, the necessary dose, length and consistency of probiotic supplementation to achieve health benefits is still unknown, so currently, no objective

recommendations exist. While the study endeavoured to reduce these biases, alternative measures of adherence may provide greater confidence in the findings. For instance, authors have found electronic monitoring (capsule bottle caps that record time and date when opened) to be more sensitive to non-adherence than self-report (Arnsten et al., 2001; Riekert & Rand, 2002). Another option to measure adherence could have involved obtaining faecal samples from participants to examine gut microbiota composition for the presence of the probiotic bacteria. However, this method has its own caveats, as not only is it invasive for participants and may have deterred initial participation in the study, but it is not an accurate measure for gut microbiota composition, nor does probiotics necessarily change faecal microbiota composition (Kristensen et al., 2016; Tang et al., 2020; Zoetendal et al., 2002).

Attrition comprises another limitation of the current study. Attrition, which includes a loss to follow up and participant withdrawal, is a concern in clinical trials as it may introduce bias and threaten validity (Nunan et al., 2018). According to the study's power calculation, a sample size of 72 was required to detect an effect. Therefore, while the study's sample size of 74 participants surpassed this number, it did not allow for much attrition. Although authors suggest a loss to follow-up of below 20% is acceptable, rates above 5% may still introduce varying levels of bias (Fergusson et al., 2002). Hence, the attrition rate of 17.5% in the current study is satisfactory but represents a potential source of bias. Attempts to reduce attrition included offering a *koha* after completing the intervention and conducting the study remotely to reduce barriers to participation. However, the only form of communication between participants and the researchers was via email. Future studies would benefit from collecting other modes of communication, such as personal and work phone numbers, to increase regular communication with participants to reduce attrition.

Despite these limitations, the study also comprises many strengths. Firstly, the study is novel; this is the first randomised placebo-controlled trial investigating the effects of

probiotics on symptoms of depression and anxiety and glycaemic control in adults with T1D. Therefore, despite finding non-significant results, this study provides a novel contribution to the growing understanding of the role of probiotics in mental and physical health, particularly in those with T1D.

Another strength of the current study is the study's robust design. The double-blind, randomised, placebo-controlled trial design reduces the introduction of bias (e.g. channelling bias, selection bias and researcher bias), thereby strengthening the validity of the results. Moreover, the researchers conducted the study remotely. This strategy expanded the sample pool to the whole of New Zealand and significantly reduced typical barriers to participation by omitting the need to take time out of one's day to travel to appointments or collect the capsules. Finally, utilising one probiotic strain rather than a combination provided the opportunity to assess the strain-specific effects and contributes to insight regarding what probiotic strains exert clinically meaningful effects.

Lastly, the study's incorporation of intention-to-treat analysis represents a further key strength. The intention-to-treat approach involves analysing all participants once randomised despite loss to follow up and reduces biases resulting from non-random attrition (Armijo-Olivo et al., 2009). The intention-to-treat approach accounts for realistic behaviours and unexpected events and is, therefore, more reflective of real-life treatment effects than studies performed in highly controlled laboratory environments, even though the effects are considered more conservative (Gupta, 2011). For this reason, the intention-to-treat approach also helps retain participants in the study and limit attrition due to non-adherence. For example, if a participant intentionally or unintentionally stops taking the capsules as a result of being admitted to a hospital or other significant life events, they can remain in the study and their data are included in the analyses.

8.4 Implications

The study's findings extend current knowledge of the gut-brain axis as a theoretical framework depicting how probiotics may impact mood, cognition and behaviour. Researchers theorise that manipulating gut microbiota composition (e.g., administering probiotics) may influence gut-brain axis activity and subsequently impact mental health. The current study's results suggest that the probiotic *L. rhamnosus* HN001 cannot improve symptoms of depression, anxiety and stress or glycaemic control in adults with T1D. These findings do not necessarily disprove the theory that enhancing gut microbiota composition can improve physical and mental health outcomes via the gut-brain axis. Instead, it may signify that probiotics cannot alter gut microbiota composition to the extent that it affects gut-brain axis activity to improve psychological or physical health outcomes in adults with T1D, or, simply, that supplementation with probiotic strain *L. rhamnosus* HN001 cannot do so. Alternatively, perhaps probiotics only confer benefits to mental health in individuals living with T1D who are also diagnosed with depression and anxiety, which is implicated with gut dysbiosis. The gut-brain axis is a useful framework for conceptualising the putative mechanisms underlying associations between probiotics and mental and physical health outcomes, but further research is required to validate this theory and ascertain whether it can be applied to those with chronic health conditions such as T1D.

Living with T1D incurs a significant burden on wellbeing. People with T1D are asked to adhere to a strict, lifelong self-management regime involving numerous daily decisions to maintain blood glucose levels within a specified range. Moreover, probiotics are expensive. With insufficient evidence at present to suggest probiotics can make meaningful changes to the mood and glycaemic control of individuals with T1D, it would be ill-considered to encourage people to take them as part of their already demanding self-management routine.

This does not rule out the possibility of utilising probiotics in the future to improve mental health and glycaemic control. However, currently, there is too much conflicting evidence and uncertainty regarding the probiotic strain, dose, combination, and what population can benefit from probiotics. It is imperative that further high-quality studies, including randomised placebo-controlled trials, are performed to ascertain whether probiotic supplementation can improve mental health and glycaemic control in individuals with T1D before endorsing it as part of standard care.

8.5 Future Directions

While considering the existing literature, the insights gained from the current study encourages possible avenues of future research. Firstly, further randomised placebo-controlled studies investigating probiotics' effects on mental health outcomes and glycaemic control are required to build on the current study results. Specifically, additional studies utilising *L. rhamnosus* HN001 are necessary to validate the results of this current study. Moreover, studies using different probiotic strains, individually and in varying combinations, doses and lengths of intervention, are required to ascertain under what conditions probiotics can be effective (or ineffective). These insights can help guide further research and the optimal use of probiotics clinically.

Additionally, addressing one of the study's main limitations, further probiotic studies investigating the impact on mental health outcomes would benefit from using cut-off scores for depression or anxiety as inclusion criteria. That is, only recruiting individuals with depression or anxiety. Depression and anxiety are associated with detriments in psychosocial, occupational and physiological functioning, with further implications to health for individuals with T1D due to the challenging daily task of maintaining optimal glycaemic control.

Probiotics could, therefore, provide the greatest impact on health and wellbeing in these populations.

Under a similar rationale, a future study could address another limitation by measuring participants' expectations of probiotic supplementation prior to the intervention. Including this measure would provide the opportunity to explore whether positive expectations of probiotics are associated with improvements in mood and glycaemic control, essentially evaluating the extent of the placebo effect.

Finally, the probiotic literature would benefit from studies exploring probiotics' mechanisms of action in addition to their effects. Studies exploring the effects of probiotics largely overlook their mechanisms of action, and this study is no exception. Even if the current study observed the hypothesised effects, there would not be an objective way to determine the cause of the results. According to probiotics' hypothesised mechanisms of action for physical and mental health effects, future studies could incorporate measuring biomarkers of inflammation or immune-system activity and neurotransmitter levels before and after consuming probiotics.

8.6 Conclusion

In conclusion, T1D is a chronic, debilitating condition that incurs a significant cognitive, emotional and behavioural burden to those living with T1D. The challenging task of maintaining optimal glycaemic control and the increased likelihood of experiencing depressive and anxiety symptoms compared to the general population represent critical concerns among those with T1D, particularly as they can negatively impact each other. Probiotics are a potential therapeutic approach to improving both mental health and glycaemic control in individuals with T1D via altering the composition and activity of the gut

microbiota and gut-brain axis. This study, addressing a gap in the literature, has enhanced the current understanding of probiotics for mental health and glycaemic control in adults with T1D. The present study found no beneficial effects of the probiotic *L. rhamnosus* HN001 on mental health outcomes and HbA1c levels compared to placebo, so cannot recommend the probiotic used in this study to improve health and wellbeing in adults with T1D. Further studies are integral to verify and build on these findings. The literature on the use of probiotics to improve mental and physical health is still foundational, and many questions remain regarding their application in clinical populations such as T1D.

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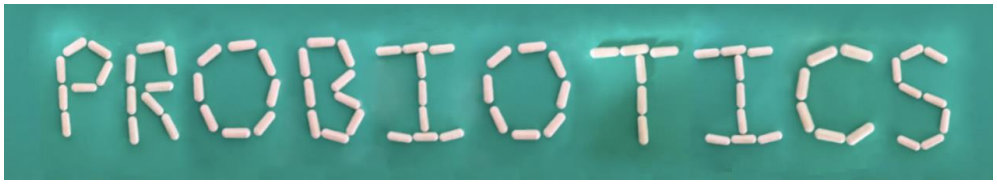
Appendices

Appendix A

Study Flyer

THE UNIVERSITY OF AUCKLAND
Te Whare Wānanga o Tāmaki Makaurau
NEW ZEALAND

MEDICAL AND HEALTH SCIENCES
SCHOOL OF MEDICINE



CAN PROBIOTICS INCREASE WELLBEING IN ADULTS WITH TYPE 1 DIABETES?

We are looking for people aged 18 years and older with type 1 diabetes to take part in a study exploring whether taking probiotics can improve wellbeing. Probiotics have been shown to be helpful for things like allergy, digestion and mental wellbeing in other patient populations and we want to explore whether it would be beneficial for people with type 1 diabetes.

Participating will mean completing a questionnaire at two time points and taking a capsule every day for 12 weeks. This capsule will contain either probiotics or a placebo (no active ingredients) and you will have an equal chance (50:50) of receiving a probiotic or a placebo. Participants will receive a $30 Westfield voucher as a thank you for your time.

If you are interested in participating, you may click on the link to our website, which has more information about the study and the link to begin the online questionnaires. Alternatively, you may contact us (see below).

https://gbro566.wixsite.com/probioticsstudy

FOR MORE INFORMATION OR IF YOU WOULD LIKE TO TAKE PART, PLEASE CONTACT:

GABY BROWNE (MHLTHPSYC STUDENT) gbro566@aucklanduni.ac.nz

DR ANNA SERLACHIUS (LEAD INVESTIGATOR) a.serlachius@auckland.ac.nz OR 09 923 3073

Approved by Health and Disability Ethics Committee.
Reference no: 19/NTB/206/AM01

Appendix B

Recruitment Letter

Waitemata District Health Board
Best Care for Everyone

DIABETES SERVICE

Diabetes Clinic
North Shore Hospital Campus
124 Shakespeare Rd, Takapuna 0622
Private Bag 93-503, Takapuna 0740
Telephone: 09 486 8920 Ext: 2505
Email: diabetess@waitematadhb.govt.nz

Diabetes Clinic
Waitakere Hospital Campus
55-75 Lincoln Rd, Henderson 0610
Private Bag 93-115, Henderson 0650
Telephone: 09 839 0000

Kia Ora,

RE: Invitation to participate in a study investigating whether probiotics can improve wellbeing in patients with type 1 diabetes

The University of Auckland, in collaboration with the Diabetes service at WDHB, are conducting a study to investigate if probiotics could improve wellbeing in patients with type 1 diabetes. Probiotics can be helpful for allergy, digestion and mental wellbeing in various patient populations, and we are exploring whether probiotics would benefit the wellbeing of people with type 1 diabetes. The study was granted ethics approval from the Human Disability Ethics Committee (ref. number 19/NTB/206/AM01).

You are invited to participate in the study if you are 18 years of age or older, have been diagnosed with type 1 diabetes for at least one year, live in Auckland, and have not had surgery or antibiotic or probiotic treatment in the past three months.

The study involves taking a capsule every day for 12 weeks, which will be posted to their home address. Participants will be randomised into two groups; those in one group will receive capsules containing probiotics, and those in the other group will receive capsules containing a placebo (no active ingredients). There is an equal chance of receiving the probiotic or the placebo. Participants will also be asked to complete two sets of online questionnaires, one at the beginning of the study and one at the end of the 12-week intervention, which will take about 20 minutes each to complete. As a thank you for their time, all participants will receive a $30 Westfield voucher after the study.

If you are interested in learning more or participating in this study, you may click on the link below to our website.

https://gbro566.wixsite.com/probioticsstudy

Through the website, you may download and read the participant information sheet and click on a link that will direct you to a brief questionnaire to check if you are eligible to participate in the study. If eligible, you can then provide consent to participate.

After providing consent, participants can then complete the initial questionnaires. Once they have been completed, the researcher will send the capsules, which should arrive within ten days. At the end of the 12 weeks, participants will be sent an email that contains another link for the online follow-up questionnaires. Some participants may also be invited to attend a focus group or interview to discuss their views on taking probiotics at the end of the intervention.

Appendices

If you have any questions about the study, please do not hesitate to contact the student researcher, Gaby Browne, by emailing gbro566@aucklanduni.ac.nz.

Best wishes,

Dr Simon Young
Clinical Director Diabetes Service
Simon.young@waitematadhb.govt.nz

Dr Anna Serlachius
Senior Lecturer
Department of Psychological Medicine
University of Auckland
a.serlachius@auckland.ac.nz

Appendix C

Participant Information Sheet

Participant Information Sheet

MEDICAL AND HEALTH SCIENCES

Department of Psychological Medicine
Faculty of Medical and Health Sciences
Level 12, Support Building
Auckland City Hospital
Park Road, Grafton
Auckland, New Zealand
Phone: +64 9 373 7599 x 84938

Study title:	Probiotics and Wellbeing in Adults with Type 1 Diabetes		
Locality:	Auckland, New Zealand	Ethics committee ref.:	19/NTB/206/AM01
Lead investigator:	Dr Anna Serlachius	Contact phone number:	+64 9 923 3073

You are invited to take part in a study investigating the effect of probiotics on wellbeing in adults with type 1 diabetes (T1D). Whether or not you take part is your choice. If you don't want to take part, you don't have to give a reason, and it won't affect the care you receive. If you do want to take part now, but change your mind later, you can pull out of the study at any time.

This Participant Information Sheet will help you decide if you'd like to take part. It sets out why we are doing the study, what your participation would involve, what the benefits and risks to you might be, and what would happen after the study ends. We will go through this information with you and answer any questions you may have. You do not have to decide today whether or not you will participate in this study. Before you decide you may want to talk about the study with other people, such as family, whānau, friends, or healthcare providers. Please feel free to do this.

If you agree to take part in this study, you will be asked to sign the Consent Form following this document. You will be given a copy of both the Participant Information Sheet and the Consent Form to keep.

This document is 3 pages long. Please make sure you have read and understood all the pages.

WHAT IS THE PURPOSE OF THE STUDY?

The purpose of this study is to investigate the effect of probiotics on wellbeing in adults with T1D. We wish to examine whether probiotics might improve mood and quality of life for participants in this study. Probiotics are good bacteria like the ones we have in our gut. They occur naturally in some foods but can also be taken as a capsule. Other studies have shown that probiotics can be helpful for things like allergy, digestion and mental wellbeing.

This study will randomly allocate you to receive either placebo or probiotic capsules. Both you and the researchers won't know if you have the placebo or the probiotic.

This research is funded by the Department of Psychological Medicine at the University of Auckland as part of a Masters in Health Psychology thesis conducted by student researcher Gaby Browne. She is being supervised by Dr Anna Serlachius and co-supervised Dr Rebecca Slykermann and Dr Rinki Murphy. Dr Simon Young is a co-investigator.

WHAT WILL MY PARTICIPATION IN THE STUDY INVOLVE?

You have been chosen to participate because you have type 1 diabetes. We wish to explore whether taking probiotics is helpful for improving things like mental wellbeing and glycaemic control (HbA1c) in adults with type 1 diabetes.

If you choose to participate in this study you will be randomised into either the placebo or the probiotic group. You will have an equal chance (50:50) of being in either group. Group allocations have been generated by a statistician and placed in a sealed envelope.

You will then complete a questionnaire which will take approximately 30 minutes. Following completion of the questionnaire, you will be given a bottle of capsules and asked to take one capsule each day for the next 12 weeks. The capsules will need to be refrigerated for the duration of the study (12 weeks).

During the 12-week period you will receive a text message every two weeks reminding you to take your capsules.

At the end of this study we will send you a link to complete the same questionnaire which will take approximately 30 minutes.

Some health information will also be collected via the questionnaires you complete (e.g. your current insulin regimen) and your HbA1c will be collected by accessing your health records.

This research is expected to finish by early-2022 and you can request a summary of the research findings.

WHAT ARE THE POSSIBLE BENEFITS AND RISKS OF THIS STUDY?

This intervention is considered low risk and any possible risks are minimal. The probiotic we are using is Lactobacillus rhamnosus HN001. This probiotic has been safely used in studies with pregnant women and babies. Both the probiotic and placebo capsules are lactose free, gluten free and contain no animal products.

If you experience any side-effects (e.g. mild bloating) it is your responsibility to contact the researchers. We will advise you to contact your GP or diabetes team if you are concerned and we will advise you to stop taking the capsules as a precautionary measure.

As part of the study we will also be measuring your mood and wellbeing. If your scores indicate you have low mood and may be depressed we will send you a letter advising you to speak to your GP or diabetes team if you require support. We will also send you links to free mental health services in the community.

The possible direct benefits of this study include improvement in mood and wellbeing. Additionally, this study may help to improve your HbA1c levels. Future benefits of this study include gaining knowledge in an under-researched area which could lead to improved treatment for patients with T1D.

Regardless of whether you participate in the study, this will not change the care you normally receive for your diabetes.

WHO PAYS FOR THE STUDY?

You will not incur any financial costs due to participation in this study. Upon completion of this study you will receive a koha ($30 Westfield voucher) as a thank you for your time and participation.

WHAT IF SOMETHING GOES WRONG?

If you were injured in this study, you would be eligible **to apply** for compensation from ACC just as you would be if you were injured in an accident at work or at home. This does not mean that your claim will automatically be accepted. You will have to lodge a claim with ACC, which may take some time to assess. If your claim is accepted, you will receive funding to assist in your recovery.

If you have private health or life insurance, you may wish to check with your insurer that taking part in this study won't affect your cover.

WHAT ARE MY RIGHTS

Your participation in this study is entirely voluntary. You are free to decline to participate and may withdraw from the study at any time without giving a reason. If you choose not to participate, or you

participate and chose to withdraw at a later stage, this will in no way affect your access to current or future health care.

You have the right to access information about you that we have collected as part of this study. You will be informed of any new information about adverse or beneficial effects related to this study that may have an impact on your health. To ensure privacy and confidentiality, all participants in this study will be assigned a numeric code, which corresponds with their responses on the questionnaires and their health information. Any publications or reports arising from this study will only report findings on a group level and your participation will not be identifiable in these publications.

WHAT HAPPENS AFTER THE STUDY OR IF I CHANGE MY MIND?

Information collected from the study will be stored in a locked cabinet on University of Auckland premises during the study, by the Principal Investigator Dr Serlachius. Data generated in this study will be available for use in future research, however this data will be de-identified and only used for research purposes.

All electronic information will be password protected. After the study has been completed, all data will be destroyed by a disposal company that provides security for confidential documents.

We intend to publish the findings from this study in peer-reviewed scientific journals and in academic conferences, as well as present the findings to the diabetes team involved in caring for you. All of the data will be de-identified and report only aggregate results (e.g. group means). You will also be provided with a summary of the results of the study if you wish.

WHO DO I CONTACT FOR MORE INFORMATION OR IF I HAVE CONCERNS?

If you have any questions, concerns or complaints about the study at any stage, you can contact:

Dr Anna Serlachius, Supervisor/ Lead Investigator
Phone: +64 9 923 3073
Email: a.serlachius@auckland.ac.nz

Gaby Browne, MHealthPsyc candidate in the Department of Psychological Medicine
Email: gbro566@aucklanduni.ac.nz

If you want to talk to someone who isn't involved with the study, you can contact an independent health and disability advocate on:

Phone: 0800 555 050
Fax: 0800 2 SUPPORT (0800 2787 7678)
Email: advocacy@advocacy.org.nz
Website: https://www.advocacy.org.nz/

You can also contact the health and disability ethics committee (HDEC) that approved this study on:

Phone: 0800 4 ETHICS
Email: hdecs@moh.govt.nz

If you require Māori cultural support talk to your whānau in the first instance. Alternatively, you may contact the administrator for He Kamaka Waiora (Māori Health Team) by telephoning 09 486 8324 ext 2324

If you have any questions or complaints about the study, you may contact the Auckland and Waitematā District Health Boards Maori Research Committee or Maori Research Advisor by phoning 09 4868920 ext 3204.

If you are worried about something to do with your diabetes, please call your doctor or nurse as normal.

Endocrine 24-hour Cell Phone: 021 974 804 or 631-0790 and follow prompts or direct line 29140.

Appendix D

Consent Form

Confidential

Participant Information Sheet and Consent Form

This section contains the Participant Information Sheet and Consent Form. The Participant Information Sheet provides information about the study. Please make sure you have read and understood everything. Please ask questions if you are unsure about anything.

Whether or not you take part is your choice. If you don't want to take part, you don't have to give a reason and you can exit the page. If you do want to take part now, but change your mind later, you can pull out of the study at any time.

If you have any questions or concerns about the study you may contact one of the researchers, Gaby Browne, via email at gbro566@aucklanduni.ac.nz at any stage.

If you haven't already, please download and read the attached Participant Information Sheet to find out more about this study.

[Attachment: "Participant Information Sheet.pdf"]

Consent Form

Department of Psychological Medicine
Faculty of Medical and Health Sciences
Building 507, Level 3
22-30 Park Road, Grafton
Auckland, New Zealand

Please read the following statements:

- I have read and understood the Participant Information Sheet.
- I have been given sufficient time to consider whether or not to participate in this study.
- I have had the opportunity to use a legal representative, whānau/family support or a friend to help me ask questions and understand the study.
- I am satisfied with the answers I have been given regarding the study and I have a copy of this consent form and information sheet.
- I understand that taking part in this study is voluntary (my choice) and that I may withdraw from the study at any time without this affecting my medical care.
- I consent to the research staff collecting and processing my information, including information about my health (e.g. HbA1c).
- I consent to research staff informing my health practitioner that I am taking part in this study.
- I agree to an approved auditor appointed by the New Zealand Health and Disability Ethic Committees, or any relevant regulatory authority or their approved representative reviewing my relevant medical records for the sole purpose of checking the accuracy of the information recorded for the study.
- I understand that my participation in this study is confidential and that no material, which could identify me personally, will be used in any reports on this study.
- I understand the compensation provisions in case of injury during the study.
- I know who to contact if I have any questions about the study in general.
- I understand my responsibilities as a study participant.

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Do you agree with the above statements and wish to participate in this study?	◯ Yes ◯ No

You clicked 'No' to consenting to the study.Either go back to the previous question and click 'Yes', or click 'No' and your study involvement will end and you can close this window.

Would you like to receive a summary of the study findings?	◯ Yes ◯ No
Would you like to be contacted about future research?	◯ Yes ◯ No

PLEASE NOTE: Your email address will only be used to send you the link to the online questionnaires, reminders to complete the intervention and the study findings.
Your mailing address will only be used to send you the probiotics or placebo and the koha ($30 Westfield voucher) on completion of this study.

These details will be kept strictly confidential.

Please fill in your email address:	_____
Please fill in your mailing address: (Street number and name, Suburb and postcode, City)	_____

Declaration by participant:

I hereby consent to take part in this study.

Participant name: (first and last name)	_____
Signature:	_____
Date of signature:	_____

Appendix E

Baseline Questionnaires

Confidential

Background Information

This initial questionnaire asks for some background information and information about your type 1 diabetes.

All the information you give us is confidential and only used for research purposes.

If you have any concerns about a question or the study, please do not hesitate to ask the researcher at gbro566@aucklanduni.ac.nz.

There are no right or wrong answers to these questions. Please choose the response that best fits you and your circumstances.

Today's date	_____
What is your age?	_____
What is your gender?	◯ Female ◯ Male ◯ Gender diverse
What is your weight (in kg)?	_____
What is your height (in cm)?	_____
Which ethnic group do you belong to? Please select more than one if applicable.	☐ New Zealand European ☐ Māori ☐ Samoan ☐ Cook Island Māori ☐ Tongan ☐ Niuean ☐ Chinese ☐ Indian ☐ Other
Are you currently in school/studying?	◯ Yes ◯ No
Please indicate your level of education.	◯ Did not complete high-school ◯ Completed high-school ◯ Started undergraduate degree ◯ Completed undergraduate degree (e.g. Bachelors) ◯ Completed postgraduate degree (e.g. Masters)
What is your occupation?	_____
What are your living arrangements?	◯ Living alone ◯ Living with family, partner or friends

Appendices

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What is your marital/relationship status?	◯ Single ◯ In a relationship
How long have you had type 1 diabetes? Please indicate months or years.	_____
What current insulin regimen are you on?	_____ (e.g. Injections or insulin pump)
Do you currently use a continuous glucose monitor (CGM)?	◯ Yes ◯ No
Do you have any other medical conditions?	◯ Yes ◯ No
What is(are) the other medical condition(s)?	_____
Are you taking any other medications and/or supplements?	◯ Yes ◯ No
Please list any other medications and/or supplements you may take.	_____
Do you follow any of the following dietary plans/ways of eating? Please select more than one if applicable.	☐ Vegetarian ☐ Vegan ☐ Gluten Free ☐ Dairy Free ☐ Nut free ☐ Paleo or high protein ☐ Low fat ☐ None of the above ☐ Other
What other dietary plan(s) do you follow?	_____

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Beliefs about Probiotics

This questionnaire asks you about your prior beliefs about probiotics. Please complete the following questions to the best of your ability. There are no right or wrong answers.

If you have any questions you may contact the researcher at gbro566@aucklanduni.ac.nz.

How familiar are you with the word "probiotic"?	◯ Extremely familiar - know what the term means, what probiotics are used for and comfortable explaining to other people ◯ Very familiar - know what the term means and what probiotics are used for ◯ Familiar - know what the term means ◯ Somewhat familiar - heard of the term before ◯ Never heard of it before
How did you learn about probiotics? Check all that apply	☐ Doctor ☐ Pharmacist ☐ Nurse ☐ Family member ☐ Friend ☐ Pamphlet ☐ Internet ☐ TV or Radio news ☐ Advertisement on TV or radio ☐ Book ☐ Clinical Trial ☐ Newspaper
Have you ever used a probiotic food or supplement to obtain health benefits? For your reference, the definition of "probiotics" that we will be using is: "live microorganisms, that when ingested, may produce health benefits."	◯ Yes ◯ No
Knowing what probiotics are, would you ever consider using them in the future?	◯ Yes ◯ No
Major concerns that I have about probiotics include... Select all that may apply.	☐ Cost ☐ Side effects ☐ Effectiveness ☐ Attitude of health care professionals towards the therapy ☐ Other
As you selected 'other', please state any other concerns you have about probiotics.	_____
Was the probiotic used as a food or a supplement?	◯ Food ◯ Supplement ◯ Both

Appendices

Confidential

What organisms are/were in the probiotic you took?	◯ Yeast (ie, Saccharomyces) ◯ Bacteria - Lactobacillus ◯ Bacteria - Bifidobacteria ◯ Bacteria - Bacillus ◯ Mixed bacterial species ◯ Mixed bacteria and yeast ◯ Do not know
Who or what made you want to try probiotics? Please pick the answer that best fits your opinion, or you may select 'other' to write your own response.	☐ Physician ☐ Pharmacist ☐ Nurse ☐ Family member ☐ Friend ☐ Health-food store clerk ☐ Alternative care provider or clinic (ie, Naturopath, chiropractor, etc.) ☐ Magazine or book ☐ Internet ☐ Advertisement on TV or radio ☐ Other
As you selected 'other', please state who or what made you want to try probiotics.	_____
For what medical condition(s) do/did you take probiotics?	☐ Antibiotic-associated side effects (diarrhea, abdominal discomfort, gas, yeast infection) ☐ Chronic diarrhea ☐ Chronic constipation ☐ Inflammatory bowel disease ☐ Irritable bowel syndrome ☐ Allergic skin conditions (ie, eczema) ☐ Prevent recurrence of vaginal infection (yeast or bacterial vaginitis) ☐ Maintain good gastrointestinal health ☐ Benefits of the immune system ☐ Other
As you selected 'other', please state what other medical condition(s) you do/did take probiotics for.	_____
What was your reason for initially trying probiotics?	☐ Dissatisfaction with standard medications ☐ Attempt to avoid side effects of standard medications ☐ Desperation to do something and feel in control ☐ Positive experiences by others ☐ Lack of other alternatives ☐ To complement other therapies ☐ Other
As you selected 'other', please state your reason for initially trying probiotics.	_____
Were probiotics beneficial to you?	◯ Yes ◯ No ◯ Not sure
Does your physician know you take or have taken probiotics?	◯ Yes ◯ No

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Why does your physician not know about your current or past use of probiotics?	◯ Forgot to tell my physician ◯ Afraid I would be reprimanded by my physician ◯ Did not think it was important ◯ It was none of my physician's business
How did your physician respond?	◯ Positively ◯ Negatively ◯ Neutrally ◯ Could not tell

Finally, we want to know about your opinions on probiotics and their use.

If you were to use probiotics, which formulations would you prefer?	◯ Incorporated into food (i.e. yogurt) ◯ Capsule or tablet ◯ Liquid ◯ Powder
If you were to buy probiotics, how much would you be willing to pay for these products?	◯ $0.25/dose (e.g. 1 capsule) ◯ $0.50/dose ◯ $0.75/dose ◯ $1.00/dose ◯ More than $1.00/dose ◯ I would never pay to use a probiotic
If you were to buy probiotics, please pick the area where you would like to buy these products.	◯ Pharmacy ◯ Doctor's office ◯ Grocery store ◯ Health food store ◯ Internet ◯ Other
As you selected 'other', please indicate what location you would prefer to buy probiotics.	_____

Please rate the following scenarios on probiotics.

If I was prescribed antibiotics...

	Strongly disagree	Disagree	Neutral	Agree	Strongly agree
... I would be willing to take probiotics starting from the beginning of the antibiotic treatment and up to 4 weeks afterwards.	◯	◯	◯	◯	◯
...I would be willing to take probiotics starting from the beginning of the antibiotic treatment and up to 2 weeks afterwards.	◯	◯	◯	◯	◯

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...I would be willing to take probiotics starting from the beginning of the antibiotic treatment only up until the antibiotic treatment ends.	○	○	○	○	○

Where would you go to learn more about probiotics?
Please rank your answer with 1 being the first option you would use to 7 as your last option.

	1 (First Choice)	2	3	4	5	6	7 (Last Choice)
Doctor	○	○	○	○	○	○	○
Pharmacist	○	○	○	○	○	○	○
Internet	○	○	○	○	○	○	○
Family or friend	○	○	○	○	○	○	○
Alternative health care provider or clinic	○	○	○	○	○	○	○
Other	○	○	○	○	○	○	○
Not interested in learning more	○	○	○	○	○	○	○

Confidential

Stress and Wellbeing Questionnaire

Please read each statement and select a number 0, 1, 2, 3 which indicates how much the statement applied to you over the past week.

There are no right or wrong answers. Do not spend too much time on any statement.

If you have any questions you may contact the researcher at gbro566@aucklanduni.ac.nz.

		Did not apply to me at all (0)	Applied to me to some degree, or some of the time (1)	Applied to me to a considerable degree or a good part of the time (2)	Applied to me very much or most of the time (3)
1)	I found it hard to wind down	○	○	○	○
2)	I was aware of dryness of my mouth	○	○	○	○
3)	I couldn't seem to experience any positive feeling at all	○	○	○	○
4)	I experienced breathing difficulty (e.g. excessively rapid breathing, breathlessness in the absence of physical exertion)	○	○	○	○
5)	I found it difficult to work up the initiative to do things	○	○	○	○
6)	I tended to over-react to situations	○	○	○	○
7)	I experienced trembling (e.g. in the hands)	○	○	○	○
8)	I felt that I was using a lot of nervous energy	○	○	○	○
9)	I was worried about situations in which I might panic and make a fool of myself	○	○	○	○
10)	I felt that I had nothing to look forward to	○	○	○	○
11)	I found myself getting agitated	○	○	○	○
12)	I found it difficult to relax	○	○	○	○
13)	I felt down-hearted and blue	○	○	○	○
14)	I was intolerant of anything that kept me from getting on with what I was doing	○	○	○	○
15)	I felt I was close to panic	○	○	○	○
16)	I was unable to become enthusiastic about anything	○	○	○	○
17)					

Confidential

	I felt I wasn't worth much as a person	○	○	○	○
18)	I felt that I was rather touchy	○	○	○	○
19)	I was aware of the action of my heart in the absence of physical exertion (e.g. sense of heart rate increase, heart missing a beat)	○	○	○	○
20)	I felt scared without any good reason	○	○	○	○
21)	I felt that life was meaningless	○	○	○	○

Confidential

Diabetes Quality of Life

This questionnaire asks about your quality of life. Please select the most appropriate response for you for each question.

If you have any questions you may contact the researcher at gbro566@aucklanduni.ac.nz.

1) How satisfied are you with your current diabetes treatment?

◯ Very satisfied (1) ◯ Moderately satisfied (2) ◯ Neither (3) ◯ Moderately dissatisfied (4) ◯ Very dissatisfied (5)

2) How satisfied are you with the amount of time it takes to manage your diabetes?

◯ Very satisfied (1) ◯ Moderately satisfied (2) ◯ Neither (3) ◯ Moderately dissatisfied (4) ◯ Very dissatisfied (5)

3) How often do you find that you eat something you shouldn't rather than tell someone that you have diabetes?

◯ Never (1) ◯ Very seldom (2) ◯ Sometimes (3) ◯ Often (4) ◯ All the time (5)

4) How often do you worry about whether you will miss work?

◯ Never (1) ◯ Very seldom (2) ◯ Sometimes (3) ◯ Often (4) ◯ All the time (5)

5) How satisfied are you with the time it takes to determine your sugar level?

◯ Very satisfied (1) ◯ Moderately satisfied (2) ◯ Neither (3) ◯ Moderately dissatisfied (4) ◯ Very dissatisfied (5)

6) How satisfied are you with the time you spend exercising?

◯ Very satisfied (1) ◯ Moderately satisfied (2) ◯ Neither (3) ◯ Moderately dissatisfied (4) ◯ Very dissatisfied (5)

7) How often do you have a bad night's sleep because of diabetes?

◯ Never (1) ◯ Very seldom (2) ◯ Sometimes (3) ◯ Often (4) ◯ All the time (5)

8) How satisfied are you with your sex life?

◯ Very satisfied (1) ◯ Moderately satisfied (2) ◯ Neither (3) ◯ Moderately dissatisfied (4) ◯ Very dissatisfied (5)

9) How often do you feel diabetes limits your career?

◯ Never (1) ◯ Very seldom (2) ◯ Sometimes (3) ◯ Often (4) ◯ All the time (5)

10) How often do you have pain because of the treatment for your diabetes?

◯ Never (1) ◯ Very seldom (2) ◯ Sometimes (3) ◯ Often (4) ◯ All the time (5)

Confidential

11) How satisfied are you with the burden your diabetes is placing on your family?

◯ Very satisfied (1) ◯ Moderately satisfied (2) ◯ Neither (3) ◯ Moderately dissatisfied (4) ◯ Very dissatisfied (5)

12) How often do you feel physically ill?

◯ Never (1) ◯ Very seldom (2) ◯ Sometimes (3) ◯ Often (4) ◯ All the time (5)

13) How often do you worry about whether you will pass out?

◯ Never (1) ◯ Very seldom (2) ◯ Sometimes (3) ◯ Often (4) ◯ All the time (5)

14) How satisfied are you with time spent getting check-ups for your diabetes?

◯ Very satisfied (1) ◯ Moderately satisfied (2) ◯ Neither (3) ◯ Moderately dissatisfied (4) ◯ Very dissatisfied (5)

15) How satisfied are you with your knowledge about your diabetes?

◯ Very satisfied (1) ◯ Moderately satisfied (2) ◯ Neither (3) ◯ Moderately dissatisfied (4) ◯ Very dissatisfied (5)

Confidential

Diabetes Self-Care -Diet

This is the final questionnaire.

The questions below ask you about your diabetes self-care activities during the past 7 days. If you were sick during the past 7 days please think back to the last 7 days that you were not sick.

If you have any questions you may contact the researcher at gbro566@aucklanduni.ac.nz.

		0 Days	1 Day	2 Days	3 Days	4 Days	5 Days	6 Days	7 Days
1)	How many of the last seven days have you followed a healthful eating plan?	○	○	○	○	○	○	○	○
2)	On average, over the past month, how many days per week have you followed your eating plan?	○	○	○	○	○	○	○	○
3)	On how many of the last seven days did you eat five or more servings of fruit and vegetables?	○	○	○	○	○	○	○	○
4)	On how many of the last seven days did you eat high fat foods such as red meat or full-fat dairy products?	○	○	○	○	○	○	○	○

Appendix F

Capsule Instructions

Thank you for participating in the *Probiotics and Wellbeing Study*. Please find enclosed your capsules.

Instructions for capsules:

- Start taking the capsules from today. Please note todays date:

  _____

  (We will ask you at the end of the 12-week intervention the date you began taking the capsules).
- Take one capsule a day
- If you miss a day, no problem just start again the next day - do not take more than one a day
- Capsules are best stored in the fridge once opened

You can take the capsules at any time of the day. We suggest you take the capsules at the same time each day to create a routine, for example with breakfast. We have included a capsule tracker that you may want to use to help remember to take them each day. You may also find creating an alert on your phone or storing the capsules in a visible area in the fridge helpful.

If you have any questions, feel free to contact Gaby Browne at gbro566@aucklanduni.ac.nz

Appendix G

Capsule Tracker

Probiotics and Wellbeing Study – Capsule Diary

WEEK 1	Day 1 Today's date: _____						
WEEK 2							
WEEK 3							
WEEK 4							
WEEK 5							
WEEK 6							Half way!

WEEK 7							
WEEK 8							
WEEK 9							
WEEK 10							
WEEK 11							
WEEK 12							Final Day 12-week intervention completed! ☺

Appendix H

Ethics Committee Approval Letter

Health and Disability Ethics Committees
Ministry of Health
133 Molesworth Street
PO Box 5013
Wellington
6011

0800 4 ETHICS
hdecs@health.govt.nz

08 March 2021

Dr Anna Serlachius
Department Psychological Medicine
Auckland University
Private Bag 92019, Victoria Street West
Auckland 1142

Dear Dr Serlachius,

Re:	**Ethics ref:**	**19/NTB/206/AM01**
	Study title:	Probiotics and mental health: a randomized controlled trial of probiotics in adults with type 1 diabetes

I am pleased to advise that this amendment has been ***approved*** by the Northern B Health and Disability Ethics Committee. This decision was made through the HDEC Expedited Review pathway.

Please don't hesitate to contact the HDEC secretariat for further information. We wish you all the best for your study.

Yours sincerely,

Mrs Kate O'Connor
Chairperson
Northern B Health and Disability Ethics Committee

Encl: appendix A: documents submitted
appendix B: statement of compliance and list of members

Appendices

Appendix A
Documents submitted and approved

Document	Version	Date
Protocol: Updated protocol	3	24 February 2021
PIS/CF: Updated PIS/CF	3	24 February 2021
updated flyer	3	24 February 2021
Survey/questionnaire: Updated baseline questionnaires	3	24 February 2021
Survey/questionnaire: Updated follow-up questionnaires	3	24 February 2021
Post Approval Form	AM01	24 February 2021

Appendices

Appendix B
Statement of compliance and list of members

Statement of compliance

The Northern B Health and Disability Ethics Committee:

- is constituted in accordance with its Terms of Reference
- operates in accordance with the *Standard Operating Procedures for Health and Disability Ethics Committees*, and with the principles of international good clinical practice (GCP)
- is approved by the Health Research Council of New Zealand's Ethics Committee for the purposes of section 25(1)(c) of the Health Research Council Act 1990
- is registered (number 00008715) with the US Department of Health and Human Services' Office for Human Research Protection (OHRP).

List of members

Name	*Category*	*Appointed*	*Term Expires*
Mr John Hancock	Lay (the law)	14/12/2015	14/12/2018
Dr Nora Lynch	Non-lay (health/disability service provision)	19/03/2019	19/03/2026
Miss Tangihaere Macfarlane	Lay (consumer/community perspectives)	20/05/2017	20/05/2020
Mrs Kate O'Connor	Lay (ethical/moral reasoning)	14/12/2015	14/12/2018
Mrs Stephanie Pollard	Non-lay (intervention studies)	01/07/2015	01/07/2018
Mrs Leesa Russell	Non-lay (intervention studies), Non-lay (observational studies)	14/12/2015	14/12/2018
Ms Susan Sherrard	Lay (consumer/community perspectives)	19/03/2019	19/03/2022
Mrs Jane Wylie	Non-lay (intervention studies)	20/05/2017	20/05/2020

Unless members resign, vacate or are removed from their office, every member of HDEC shall continue in office until their successor comes into office (HDEC Terms of Reference)

http://www.ethics.health.govt.nz