Psychoneuroimmunological Factors in Type 1 Diabetes: Characteristics and Consequences

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Use of infrastructure external to JCU

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Thesis Abstract

Type 1 diabetes is a serious chronic autoimmune disease that pervasively imposes itself into sufferers' lives without respite. While insulin is a treatment that aids to sustain life for those with the disease, it is not a cure, indeed presently, there is no cure. The direct and indirect physiological impact of type 1 diabetes is significant, degenerative, and ultimately for the vast majority of sufferers, life shortening. These include both acute and chronic complications that require a substantial and unceasing investment in self-care energies in order to prevent, monitor, and manage the multitude of ramifications they proffer. Additionally, the disease confers a significantly increased risk for psychopathology and neuropsychopathology. Anxiety, depression, and cognitive impairment across multiple domains, all have an increased prevalence in individuals with type 1 diabetes. There are a number of hypotheses as to why increased mind and brain disorders prevail that include factors relating to environmental, psychosocial and neurophysiological pathogenic mechanisms. While the specifics remain unclear, there is consensus that the biopsychosocial complexity of type 1 diabetes means that the pathogenic mechanisms underlying increased mind and brain comorbidities in the disease are likely to be heterogeneous and evanescent. This thesis presents a series of eleven studies that evaluate and describe the interrelationships between type 1 diabetes and a number of biopsychosocial characteristics, and their consequences. Psychosocial, psychological, cognitive, and immunoregulatory phenomena are explored throughout the thesis. A number of findings are presented across the eleven studies however, perhaps the most significant finding is that affective disorders (anxiety, depression, and comorbid anxiety-depression) are pervasively prevalent in children and adults with type 1 diabetes, and that the relationship between disordered affect and other psychosocial factors long considered ubiquitous such as increased stress and poor coping skills, differ in the disease compared to those without the condition. Moreover, the influence of affective disorders was shown to be pervasive, impacting cognitive function and inflammatory characteristics in type 1 diabetes to a far greater extent than no-type 1 diabetes controls. The influence of affective disorders was also shown to mediate the risk of diabetes-specific clinical factors such as metabolic control and complications. Ultimately, this thesis illustrates that psychopathological phenomena are a serious issue in type 1 diabetes that present a tangible impediment to general and diabetes-specific health and wellbeing. A far greater clinical investment is required to address this issue, and more research is needed to better understand the pathogenic mechanisms involved, and the consequences they produce.

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CHAPTER ONE: INTRODUCTION AND METHODS

Introduction

A number of studies have identified an increased risk for psychopathology and cognitive impairment in people with type 1 diabetes type 1 diabetes. However, the characteristics of this impairment and the mechanisms involved appear to be more controversial. The prevailing paradigms suggest that these and other central nervous system (CNS) disorders in type 1 diabetes are sequelae of the disease. This position argues that CNS disorders in type 1 diabetes occur primarily as a result of the psychological burden of living with a serious chronic disease and the physiological burden of long-term dysregulation to core biological function. These paradigms have excellent face-validity and compelling empirical evidence therefore, motivation to look beyond these paradigms to other possible influences has been lacking.

Numerous studies have explored the relationships between type 1 diabetes and a variety of psychosocial, psychological, and neuropsychological characteristics. These studies have investigated these phenomena in the context of their being sequelae of the disease as well as their relationship to disease-specific complications. While the general consensus in the literature is that type 1 diabetes is associated with a higher prevalence of psychosocial maladaptation, psychopathology, and cognitive impairment, there remains some dissent as to the strength, nature, and pathogenic mechanisms that contribute to these relationships. Furthermore, there has been little investigation of the multidimensional relationships that are inherent in these factors and the way in which they may relate to prevalence and presentation risk in a biopsychosocially complex chronic disease such as type 1 diabetes. Similarly, the literature is silent on the manner in which these complex interactions influence the risk of both acute and chronic diabetes complications and clinical risk factors that increase or mitigate the risk of these complications. Indeed, while there is evidence that factors such as maladaptive coping behaviours, depression, and impaired executive function, are related to poorer metabolic control and increased prevalence of serious complications such as cerebro- and cardio-vascular disease, retinopathy, nephropathy, and peripheral neuropathy; whether the relationships are direct, indirect, or unrelated even though comorbid, remains largely unclear.

Recently, the association between immunodysregulation and disorders of the CNS has received increasing attention. There is now a strong body of evidence that continues to grow, detailing the impact that dysregulation of neuroimmunology has on brain structure, neurological systems, and ultimately on central nervous system

function. This includes evidence for significant deleterious impacts on behaviour, cognition, and affect. A central feature of type 1 diabetes pathology is immune dysregulation. Indeed it is core to disease pathogenesis and to the challenges faced by researchers and clinicians working together for curative approaches such as transplantation. Given these facts, it is reasonable to propose that the inherent immunodysregulation that characterises autoimmune type 1 diabetes may also play a role in the increased central nervous system pathology risk associated with the disease. In broad context this position falls within the realm of psychoneuroimmunology (PNI): the study of the bidirectional influence that the mind, brain, immune system, and endocrine system have on each other's physiological structure, systems, and function.

People with type 1 diabetes are at significantly increased risk for a range of psychological, and neurobiological comorbidities. These extend from the psychosocial such as poorer coping and reduced quality of life, to the psychopathological such as mood, anxiety and eating disorders, and into the neuropsychological and neurobiological including impaired cognitive function, and a variety of neurodegenerative conditions resulting in dementia syndrome. The question of why there is an increased risk has, up to now, largely been explained by two paradigms: 1) that psychological disease burden leads to increased psychopathology, and; 2) clinical consequences of diabetes-related physiological dysregulation leads to increased neuropsychopathology.

Paradigm One: Psychological Disease Burden Leads to Maladaptive Coping and Stress Response Behaviours, and Psychopathology

The first paradigm suggests that the psychological disease burden of living with a serious chronic illness such as type 1 diabetes is a very stressful experience and can lead to the development of maladaptive coping behaviours resulting in an increased risk for psychopathology [1-3]. The added impress of living with type 1 diabetes has been shown to significantly reduce quality of life. Numerous studies from around the world have found evidence in support of this. In one Australian study, Hesketh and Colleagues [4] reported that adolescents with type 1 diabetes reported a quality of life equivalent to that reported by adolescents with cystic fibrosis and leukaemia. Findings such as this have prompted calls to introduce psychological screening as an element of the standard clinical protocols for patient management [4-6]. More recent investigations of quality of life and psychological wellbeing in type 1 diabetes in Australia has found that

significant numbers of patients with type 1 diabetes are experiencing anxiety, depression, and what has been termed "Diabetes Distress" [7-9]. Diabetes distress is a highly anxious emotional and behavioural reaction to diabetes, its management (injections, dietary management, finger pricks associated with blood testing), and/or other factors associated with the disease such as ruminations about the spectre of long-term complications, or the risk or experience of acute complications such as nocturnal hypoglycaemia or neuropathic pain [10, 11].

The suggestion that there is a high risk of psychological malaise in the face of life with a disease that requires 24-hour, seven days a week management; that is associated with severe acute and chronic physical complications, severe disability, and early mortality; and for which there is no cure; has both significant face validity and a voluminous store of empirical evidence. This paradigm has remained strong and well supported over time and continues to be well-evidenced by the literature.

Paradigm Two: Clinical Consequences Lead to Psychopathology

The second is the clinical consequences paradigm which argues that, long-term metabolic imbalance such as is a characteristic of type 1 diabetes, results in physiological dysregulation that eventually damages a variety of microvascular and other molecular mechanisms ultimately producing adverse outcomes in the body, including in the central nervous system. The result being impairment to neurological structures, systems, and ultimately functionality, in turn producing a host of identifiable pathology such as poor mental health, cognitive deficits, and neurodegenerative outcomes. There is strong evidence that type 1 diabetes is associated with an increased prevalence of these pathologies however, the full extent and nature of these associations remains unclear. Longitudinal studies such as that conducted by Northam et al., [12], suggests that young people diagnosed with type 1 diabetes show significant morphological and functional changes within a few years of diagnosis. This is supported by Dahlquist and Kallen [13] who found that children with type 1 diabetes performed significantly lower in school-based assessment tasks than their peers. Similar results are evident in the adult population with several studies showing that type 1 diabetes is associated with higher rates of psychopathology [14-17] and a higher prevalence and earlier onset of major cognitive disorder (dementia) [18-20].

Given the face validity of these arguments and the large body of empirical evidence that supports these paradigms, it would be futile to suggest that they are not well founded. However; recent advances in knowledge in the neurosciences along with increased understanding of the basic pathophysiology of type 1 diabetes leads to the possibility that these influences are not unique, and that other factors may also play an important role in mediating both the disease characteristics and consequences in the context of the structures, systems, and functional outputs of the central nervous system.

This thesis has three aims: 1) to describe the key psychosocial, psychological, and inflammatory biomarker characteristics in individuals with type 1 diabetes; 2) to compare the nature and prevalence of these characteristics in no-type 1 diabetes controls; and, 3) to explore and quantify the interrelationships between these factors, and the relationships between these factors and diabetes-specific clinical factors such as metabolic control, hyperglycaemia, complications, age of disease onset, and duration of illness. The question was asked: What is the relationship between type 1 diabetes and psychological wellbeing, and how and to what extent are psychosocial and psychopathological characteristics related to diabetes-specific factors such as aetiology, clinical measures, and both acute and chronic disease complications? It is envisaged that the knowledge obtained from exploring this question will progress to future research to investigate two key subsequent questions: 1) how can this knowledge help us to prevent complications, reduce mortality, and improve the quality-of-life of those who live with type 1 diabetes; and 2) how can this knowledge inform our efforts to prevent and/or cure type 1 diabetes?

An extensive protocol was engaged that provided for the collection of a significant and diverse volume of psychoneuroimmunological data from participants. Each participant spent time in face-to-face interview, assessment, and specimen collection activities. Participants also spent up to an hour more time completing a series of self-report questionnaires. The methods and measures used to collect the data, and the protocols used to process and analyse the blood specimens collected are presented in the methods section in this first chapter. The results of the study are presented in four chapters each focused in turn on the psychosocial, psychological, neuropsychological, and inflammatory areas investigated. Each chapter of the thesis contains an overarching chapter abstract followed by a series of studies relating to the chapter's topic. Each

individual study is presented with a study abstract, introduction and hypotheses, topic-specific results, and a discussion of the presented results.

In each chapter, correlation, chi-square, analysis of variance (or the non-parametric equivalent), and regression analysis has been used to evaluate the characteristics of the chapter-specific variables in participants with and without type 1 diabetes, as well as to evaluate the relationship between these variables and diabetes-specific clinical factors. Figure 1.1 provides a graphical representation of the structure and content flow.

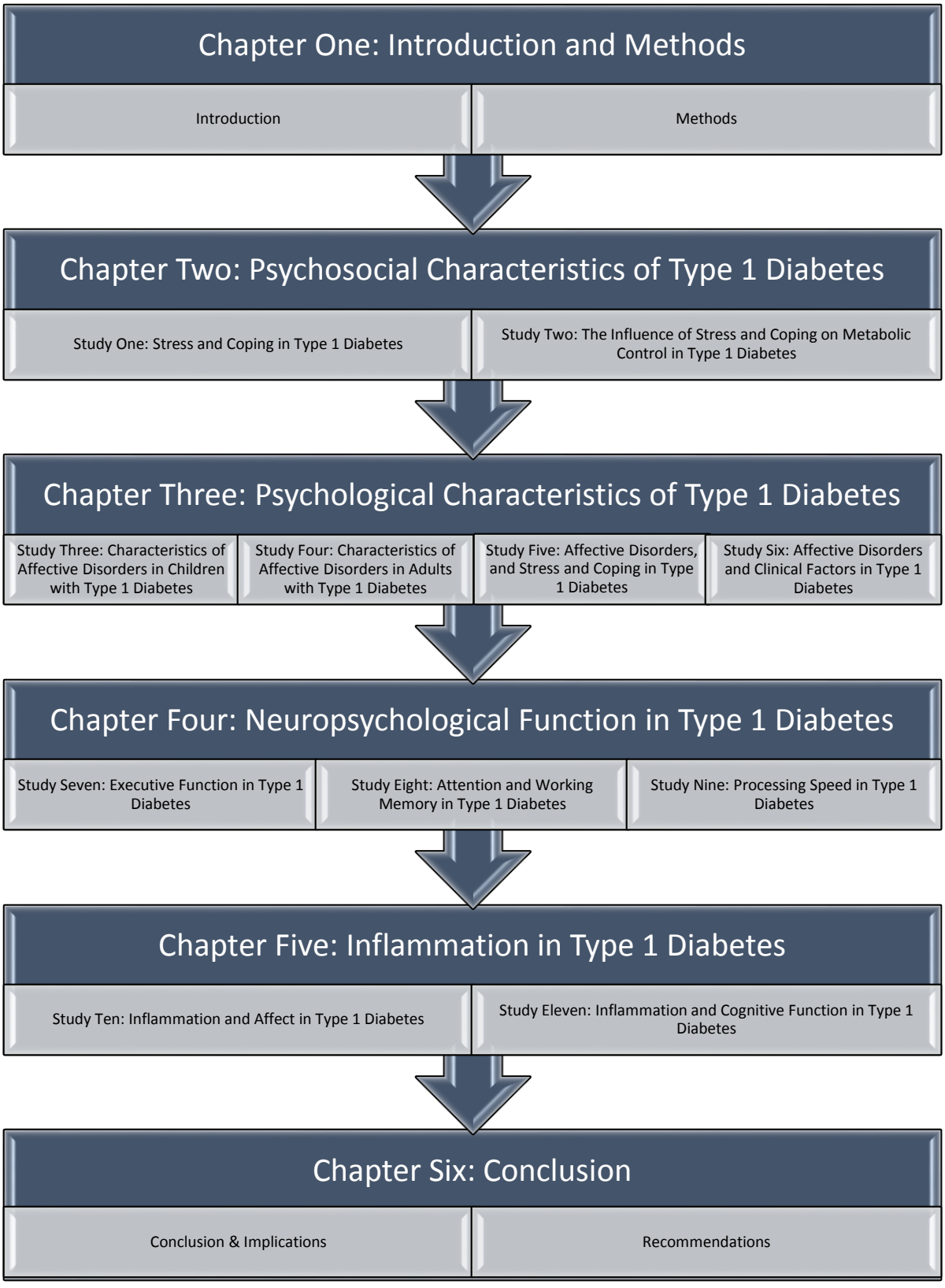

Figure 1.1. Structure and content of Thesis.

Methods

Ethical Considerations

Ethical approvals were obtained from the Human Research Ethics Committees from James Cook University (H3642 & H3693; appendix A & B), and Queensland Health, Cairns and Hinterland Health Service District (HREC/10/QCH/44-661; appendix C). In accordance with the National Statement on Ethical Conduct in Human Research, 2007 (Australia) (http://www.nhmrc.gov.au/publications/synopses/e72syn.htm), written informed consent was obtained from all participants.

Participant Recruitment

Participants aged 6-73 years were recruited through several community initiatives. Local media promotion in Townsville, Cairns, and the Atherton Tablelands regions of North and Far North Queensland provided an initial recruitment drive for participants with and without type 1 diabetes. The promotion took the form of editorial articles in the major newspaper of each location: Cairns Post, Townsville Bulletin, and the Atherton Advertiser. Local pharmacies assisted with recruitment by displaying posters and distributing flyers to their customers. The bulk of the participants with type 1 diabetes were recruited through several local General Medical Practices and the Cairns Base Hospital Diabetes Centre. Finally, participants were asked to promote awareness of the study to others within their family, friends, and wider community.

As some of the neuropsychological and psychometric measures were only valid for adults (16 years and over), participants were divided into two separate cohorts (child and adult). Child participants (under 18 years) were given the choice to only complete the age-validated self-report and parent-report components of the study if they wanted. Adolescent participants aged 16-18 years who chose to complete the self-report / parent-report components only, were included in the child cohort data set, while those completing the additional components were included in the adult cohort. In this way, a total of $N = 287$ participants were recruited into two separate cohorts (child, 6-18 years; and adult 16-73 years).

One hundred and eighty participants aged 16-73 years were recruited into an adult cohort and divided into two participant groups (type 1 diabetes $n = 73$; no-type 1 diabetes $n = 107$). The data from the adult cohort forms the basis of the analyses

reported in all of the studies of this Thesis with the exception of Study number three (Chapter 3). Study number three (Chapter 3) presents data analysis of the second cohort, which was comprised of *N* = 107 children (6-18 years) recruited into the study and also divided into two participant groups (type 1 diabetes *n* = 53; no-type 1 diabetes *n* = 54). Table 1.1 (adult) and Table 1.2 (children) present the details of the age and sex of participants in each cohort. Additional relevant participant data are presented in each individual study.

Table 1.1. *Mean Age and Sex of Adult Cohort Participants in Each Participant Group.*

Group	Total	Male		Female	
	M Age (range)	*n (% of group)*	*M* Age (range)	*n (% of group)*	*M* Age (range)
T1D (*n*= 73)	42 (16-73)	35 (48)	41 (16-67)	38 (52)	42 (16-73)
No-T1D (*n*= 107)	38 (16-73)	45 (42)	35 (16-73)	62 (58)	29 (16-65)
Total (*N*= 180)	39 (16-73)	80 (44)	38 (16-73)	100 (56)	40 (16-73)

Notes: 1. No sex differences between groups (χ^2= .394, *p*= .530); 2. No age differences between groups: Total group T1D= 42 ± 15 vs no-T1D= 38 ± 13, *F*(1,178)= 2.849, *p*= .093; males, T1D= 41 ± 16 vs no-T1D= 35 ± 14, *F*(1,78)= 3.038, *p*= .085; females, T1D= 42 ± 15 vs no-T1D= 40 ± 13, *F*(1,98)= .601, *p*= .440.

Table 1.2. *Mean Age and Sex of Child Cohort Participants in Each Participant Group.*

Group	Total	Male		Female	
	M Age (range)	*n (% of group)*	*M* Age (range)	*n (% of group)*	*M* Age (range)
T1D (*n*= 53)	12.3 (6-18)	30 (56.6)	12.0 (7-18)	23 (43.4)	12.9 (6-18)
NoT1D (*n*= 54)	12.7 (6-18)	18 (33.3)	13.3 (6-18)	36 (66.7)	12.4 (6-18)
Total (*N*= 107)	12.5 (6-18)	48 (44.9)	12.5 (6-18)	59 (55.1)	12.6 (6-18)

Notes: 1. No age differences (12.36 ±3.09 vs 12.70 ±3.94, (t(105)= .503, p= .616); 2. Sex difference (χ2 [continuity correction for 2x2 table]= 4.953, p= .02). 3. Mean duration of illness for type 1 diabetes group = 6.4yrs.

Protocol for Data Collection

Upon contact with the research team, an appointment was made and attended by participants at one of the locations used for data collection sessions. Sessions were held across North and Far North Queensland in locations in the Townsville, Cairns, and Atherton Tablelands regions. All recruitment and data collection was performed in

accordance with the guidelines and protocols set down and approved by the governing Human Research Ethics Committees overseeing the project.

Participants were provided with both verbal and written information about the study and participation requirements, and afforded opportunity to ask questions and discuss any concerns prior to agreeing or declining to take part. Written informed consent was obtained from all participants prior to taking part. Participants under the age of 18 years were asked to also provide written consent as well as have consent provided by their guardian.

An ethics requirement of the study was that participants had to give consent to each participation activity separately. Some participants elected to complete one element of the study but declined to complete others. For example, some participants declined to consent to blood collection however, consented to completing the self-report and interview sections of the study.

Participants underwent a clinical interview that included structured and unstructured components to obtain data on demographics, health, and psychopathology status, and had blood taken for biomarker analysis (participants unable or unwilling to give blood were asked to provide a saliva sample). The order in which these activities were undertaken was rotated to control for any impact it may have had on performance. Participants were given a collection of self-report questionnaires that assessed stress, coping, and affect, to take away and complete with provisions for them to return the completed self-reports by reply-paid post.

To control for assessment order effects, the order of participation was alternated between participants. Approximately half of all participants with and without type 1 diabetes had blood taken first and then underwent the interview portion of participation, while the other half underwent the protocol in reverse. Self-reports were taken home to complete immediately after attending the participation session.

Data Collection and Assessment Measures

A wide range of data was collected using self-report, clinical interview, and standardised neuropsychological testing. An extensive review process was undertaken to select the measures included. Inclusion criteria for measures covered five primary selection considerations. These were that all measures:

1. Be well validated and widely used, including across multiple language settings.

2. Be valid and reliable for the purpose of their inclusion in the study.
3. Have evidence of use within a similar participant group. IE: chronic illness, mental health, age comparable cohorts.
4. Be participant" friendly" in respect to the complexity of interface with the measure.
5. Were quantitative and used scoring and interpretation protocols that were consistent with data analysis requirements.

Table 1.3 shows the assessments used to collect the raw data that has been analysed and reported in this thesis.

Table 1.3. *Measures used to Collect Data reported in Thesis.*

Test Category	Domain	Test Name
Self-Report	Sociodemographic	Questions to elicit personal details and demography
	Personal perception of stress and coping self-efficacy	Rhode Island Stress and Coping (RISCI) [21]
	Cognitive and Behavioural Coping Strategies	Ways of Coping Questionnaire (WOCQ) [22]
	Recent experiences of stressful life events	Life Events Questionnaire (LEQ) [23]
	Anxiety and Depression in Children	Physiological Hyperarousal and Positive and Negative Affect Schedule for Children (PH-PANAS-C) [24, 25]
Clinical Interview	Medical History	Questions to elicit personal health history and current status
	Psychopathology symptoms	M.I.N.I International Neuropsychiatric Interview, English version, 6.0.0., DSM-IV (MINI600) [26]
Cognitive Assessment *	Executive Function	Tower of London Test * (TOLT) & Card Sort Test * (CST)
	Attention and Working Memory	n-Back Test *
	Processing Speed	Latency measures on the TOLT * and CST *
Biomarker	Cytokines	Blood collection via venepuncture: Serum collected for cytokine analysis.
Additional Medical History	Some participants authorised receipt of HbA1c history directly from medical providers. In these instances, data was obtained from medical records in accordance with ethics and informed consent provisions.	

Notes: * Cognitive function (neuropsychological performance) was measured using validated computer analogues of the TOLT, CST, and n-Back Test from the Colorado Assessments Tests (CATS) neuropsychological tests battery [27].

Demographic and Personal History (appendix D)

Personal and sociodemographic information was obtained using a combination of clinical interview and self-report. The clinical interview included questions about basic demographic information such as personal details, marital and family status, education and employment history, and household income.

Clinical Diagnostic Interview: Mini International Neuropsychiatric Interview English Version 6.0.0 (MINI600) (appendix E, F)

The MINI Screen and the MINI600 [26] are structured neuropsychiatric diagnostic interview tools that systematically assess patients for psychopathology according to diagnostic criteria set out in the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revised (DSM-IV-TR) [28] and International Statistical Classification of Diseases and Related Health Problems (ICD-10) [29]. The MINI600 screen was used to undertake a brief determination of the presence of symptoms of psychopathology with a particular emphasis on anxiety and depression disorders [26]. If the initial screen detected the presence of symptoms then the relevant sections of the full MINI600 was used to determine the presence of psychopathology according to the DSM-IV-TR and ICD-10 diagnostic criteria. The MINI600 has been used extensively in research and clinical practice and is translated into 30 languages. It has excellent validity and reliability and the structured format enhances the test-retest and inter-rater reliability allowing for improved standardisation of scoring. The psychometric properties of the MINI600 have been previously published [26, 30-32]. Positive results for anxiety and depression disorders were categorised into collective anxiety and depression subtypes for analyses. Table 1.4 describes the categories used to differentiate anxiety and depression psychopathology.

Table 1.4. *Categorisation of Clinical Anxiety and Depressive Disorders into Subtypes for Analysis.*

Category Label	Category Description #
Total Disordered Affect	All participants with a current clinical anxiety or depressive disorder
Anxiety	All participants with a current anxiety disorder and without a depressive disorder
Depression	All participants with a current depressive disorder and without an anxiety disorder
Comorbid Anxiety-Depression	All participants with both a current clinical anxiety and depressive disorder
Total Anxiety	All participants with a current clinical anxiety disorder. Derived by combining the anxiety group and the comorbid anxiety-depression group.
Total Depression	All participants with a current clinical depressive disorder. Derived by combining the depression group and the comorbid anxiety-depression group.

Notes: # All diagnoses are based on DSM-IV-TR and ICD-10 diagnostic guidelines as ascertained through MINI600 clinical diagnostic interview.

Neuropsychological Test Battery

All of the computerised testing versions used in this study are from the Colorado Assessments Tests (CATS) [27]. The CATS are a computerised neuropsychological test battery developed by Davis and colleagues from the University of Colorado, Colorado Springs [33]. CATS contains computer analogues of several of the most widely used neuropsychological tests.

Executive Function

CATS Tower of London test

The Tower of London Test (TOLT) was originally developed by Shallice [34] to investigate problem solving in subjects with damage to the frontal lobes. Numerous studies support the role of the frontal lobes and executive function in the ability to perform this test successfully [34-39]. Participants are required to move coloured beads in the window on the left (working area) so they match the arrangement of the coloured beads in the right window (goal position). A computerised version of the TOLT was used. Participants manipulate the beads using the computer mouse and are instructed to try to achieve the goal arrangement in as few moves as possible (Figure 1.2). The test arrangement used for this study contained trials with 3 beads and 3 pegs, 4 beads and 4 pegs, and 5 beads and 5 pegs. Trial initiation latency, total trial completion latency (processing speed), and the number of excess moves above optimal were assessed.

Figure 1.2. Screen shot from the Tower of London Test

CATS Card Sort Test

Additional executive function assessment was undertaken using a computerised card sorting task based on the Wisconsin Card Sort Test, which allows the user to design sorting tasks similar to those described by Vygotsky [(40)], Weigl [(41)], and Grant and Berg [(42)]. Card sorting tasks have been shown to be particularly sensitive to executive dysfunction and frontal lobe damage, but have also shown sensitivity to motor disorders, schizophrenia, chronic alcoholism, aging, and attention deficit disorder. The test used for this study was designed with four rule variations, and assessed initiation and completion latency (processing speed), correct responses and criterion runs (the ability to identify a rule and follow the rule in subsequent trials), incorrect responses/errors (both perseverative and non-perseverative), problem solving, inhibition, and set shifting / cognitive flexibility.

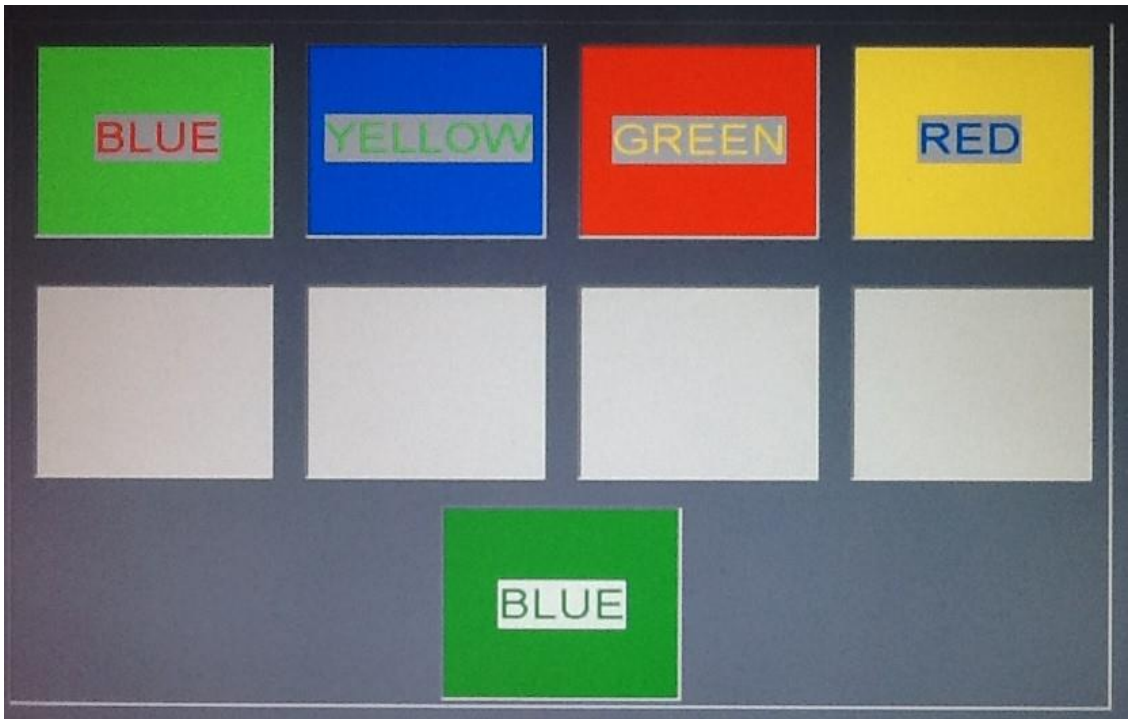

Figure 1.3. Screen shot from the Card Sort Test

Attention and Working Memory

CATS n-Back Test

The n-Back is a working memory task measuring attention and updating in executive control. The task requires the participant to monitor some dimension (EG: content, position, numerosity) of a temporally present sequence of items, responding to whether or not the currently presented item matches on the relevant dimension of an item that was previously presented. The match can be with an item presented either 1-back, 2-back, or 3-back according to the trial set instructions. The n-Back test measures attention and executive control of the updating of information in working memory [(43)].

In the n-Back task the participant is presented a series of stimuli at a constant rate. The task of the participant is to determine if the currently presented stimulus is similar (along some dimension) to one they have previously seen in the stream (usually one, two or three positions back). Match criteria can be dimensions like material, position on the screen, colour, or some combination. The presentation protocol for this study was a letter recognition sequence in which participants had to indicate whether a letter appearing on the screen was the same as the one presented on the screen either one, two, or three places prior (Figure 1.4). Letters were presented at a constant rate of

one every four seconds and results were scored for correct responses, correctly identifying a target stimuli, incorrect answers, and omissions (trials in which the participant does not respond in the allotted four second time window.

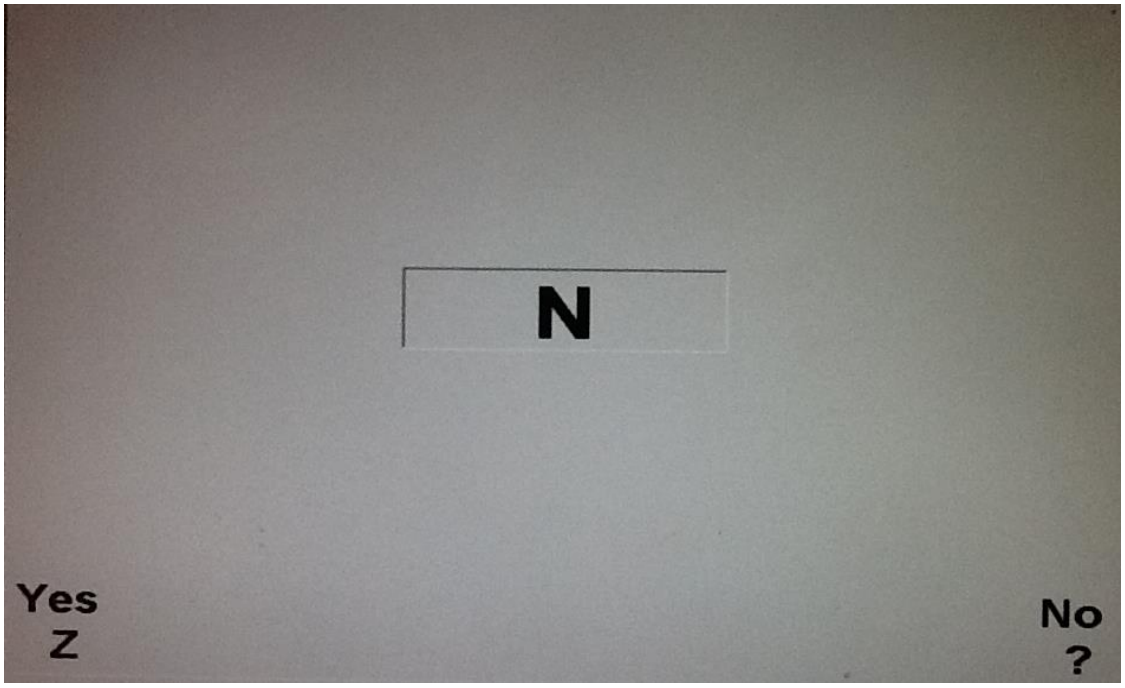

Figure 1.4. Screen shot from the n-Back Test

Blood Specimen Collection

Participants provided a blood specimen via venepuncture in the arm. Approximately 28ml of blood was collected from each participant.

Blood Glucose Levels / Metabolic Control

Participants were assessed for short, medium and long-term metabolic control. These data were used to assess the relationship between BGL and other variables.

Short-Term Blood Glucose Level (S-T BGL)

Short-term BGL was assessed using an Abbott, Accu-Check Personal Blood Glucose Metre. Short-term BGL was ascertained by taking participants' BGL at the commencement of the face-to-face component of assessment (interview and neuropsychological assessment), and again at the conclusion of this period (approximately 2 hours). These were taken via a finger prick test. The two results were then averaged to obtain a figure used as short-term BGL (S-T BGL $= \frac{BGL\ commencement + BGL\ conclusion}{2}$).

Medium-Term Blood Glucose Level / Metabolic Control (M-T BGL)

Medium-term BGLs or metabolic control were ascertained using glycosylated haemoglobin (HbA1c) results obtained for the period immediately preceding participation. HbA1c is regarded as the gold standard for assessing glycaemic control. According to the Royal Australian College of General Practitioners (RACGP) [44] HbA1c reflects the average blood glucose over the lifespan of the red blood cells containing it (approximately four months, or about 120 days), but primarily reflects the preceding six to eight weeks. Therefore, as a general guide, a test of HbA1c is considered to reflect the average percentage of glycosylated haemoglobin over approximately the previous three months. HbA1c results were obtained from patient records.

Long-Term Blood Glucose Level / Metabolic Control (L-T BGL)

Two longer-term measures of BGL were ascertained using a mean HbA1c over both one year and three years. Participants for whom at least one HbA1c measure for each six month period within the measurement timeframe were available, were included in the sample for these two long-term measures of metabolic control. Therefore, one year measures of long-term control included a range of three to five HbA1c records (immediate HbA1c + at least one additional HbA1c for each of the two, six month periods of the previous year), and three year measures of long-term control included a range of seven to 13 HbA1c records (immediate HbA1c + at least one additional HbA1c for each of the six, six month periods of the previous three years).

Self-Report Questionnaires

Demographic Questionnaire (appendix D)

Participants provided demographic information about personal circumstances, family, and medical history as already described.

Rhode Island Stress and Coping Inventory (RISCI) (appendix G)

Personal perceptions of stress and coping self-efficacy were assessed using the Rhode Island Stress and Coping Inventory (RISCI). The RISCI is a 12-item (Likert scale), two subfactor (stress and coping), self-report measure (appendix I). The RISCI subfactors measure respondents' personal perceptions of their present levels of stress (RISCI: stress), and the personal perceptions of how well the respondent is currently coping, also known as coping self-efficacy (RISCI: coping) [21]. The measure is

psychometrically sound [21] with both subfactors displaying excellent internal reliability (Cronbach's alphas stress = .85, coping = .87). The psychometric properties of the RISCI have been previously published [21, 23, 45].

Ways of Coping Questionnaire (WOCQ) (appendix H)

Derived from Lazarus' transactional model of stress [22], the Ways of Coping Questionnaire (WOCQ) is a 66-item, self-report measure of cognitive and behavioural strategies used to manage internal and/or external demands in specific stressful encounters (appendix J). Focusing on a recent specific stressor, participants use a Likert-type scale to indicate the extent to which they employed a range of strategies to help cope with the experience. The 66 items are divided into eight coping style subfactors: confrontive coping, distancing, self-controlling, seeking social support, accepting responsibility, escape avoidance, planful problem solving and positive reappraisal. The WOCQ is the most widely used psychometric measure of coping [46, 47], with all subfactors showing adequate to good reliability (Cronbach's alpha between .61 [distancing] and .79 [positive reappraisal]). The psychometric properties of the WOCQ have been previously published [22, 47, 48].

Life Events Questionnaire (LEQ) (appendix I)

Life stress data was collected using the 43-item Life Events Questionnaire (LEQ); a self-report checklist of social and familial experiences known to be highly stressful [23]. Adapted from the Social Readjustment Rating Scale (SRRS) [49], the LEQ ranks the 43 items identified as the most stressful commonly experienced life events and allocates a value that reflects the intensity, duration and accommodation necessary to navigate the event [50]. The psychometric properties of the LEQ have been previously published [23, 50] and suggest that the measure is not confounded by the effects of social desirability, carelessness or denial [23].

Family Inventory of Life Events and Changes (FILEC) (appendix J)

Life events data was collected using the Family Inventory of Life Events and Changes (FILEC) [51]. Participants were asked to indicate whether events such as marriage, divorce, death of a loved one, change of employment/school, or change in living arrangements, had been experienced by the immediate family (participant, parents and siblings) in the previous twelve months.

Physiological Hyperarousal and Positive and Negative Affect Schedule for Children (PH-PANAS-C) (appendix K)

The PH-PANAS-C, developed by Laurent and colleagues [24, 25, 52] is a self-report measure of positive (PA) and negative (NA) affect, and physiological hyperarousal (PH). The measure is a validated diagnostic tool based on the Tripartite Model of Anxiety and Depression Differentiation Model (TRAD) [53, 54]. The measure's psychometric properties have been previously published [24, 25, 52]. The measure was used to assess full-syndrome (FS) and subthreshold (St) anxiety, depression, and mixed-type anxiety-depression in participants aged 7-18 years. Using established cut-off scores on the PH-PANAS-C [52], FS AD was considered present if score profiles on the three scale subfactors accorded with diagnostic criteria (Table 1.3). St AD was considered present when two of the three diagnostic score criteria were met and the third subfactor score was within 10% of the diagnostic cut-off score.

Table 1.5. *Diagnostic Cut-Off Matrix for PH-PANAS-C.*

	Positive Affect (PA)	Negative Affect (NA)	Physiological Hyperarousal (PH)
Anxiety	≥ 38	≥ 37	≥ 40
Depression	≥ 33	≥ 37	≥ 35
Mixed Anxiety-Depression	≥ 33	≥ 37	≥ 40

Notes: Subthreshold disordered affect criteria: two factors with scores at diagnostic levels and one factor with a score within 10% of diagnostic level

Blood Collection Protocols

Blood was collected using standard venepuncture protocols for clean procedures. Each sample was left at room temperature for approximately 30 minutes in an upright position until the blood clotted in the tube. The 9ml specimen tubes were then centrifuged for 20 minutes at ≥1200 g at ambient temperature. The resulting serum supernatant was then transferred into clean 1.5ml aliquots and stored at -80^{c} until analysed.

Assessment of Serum Cytokine Concentrations

The serum concentrations of CRP, IL-6, IL-1β, IL-10, and TNF-α were measured using commercially available ELISA kits following the manufacturer's

instructions (eBioscience, San Diego, USA for CRP and R&D Systems, Minneapolis, USA for the remainder). The appropriate conditions for each assay were determined by sample titration. Based on these preliminary studies the following volumes and dilutions of serum were assayed: CRP (10uL of 1/50; #BMS288INST; high sensitivity ELISA), IL-6 (100uL neat; #DY206), IL-1β (100uL neat; #DY201), IL-10 (100uL neat; #DY208),TNF-α (100uL neat; #DY210).

Statistical Analysis

A range of statistical techniques were used to analyse the data. The specific techniques used for each component of the thesis is reported in the corresponding section of the appropriate chapter. All analysis was undertaken using SPSS v21.0.

Limitations

Limitations specific to each study are detailed in the "Limitations" subsection of the relevant study's "Discussion" section. Notwithstanding these specific limitations, there are several limitations that relate to the project more generally:

1. As a cross-sectional study, the present project was unable to assess the stability of results over time.
2. The adult sample of *N*=180 (type 1 diabetes *n*= 73; no-type 1 diabetes *n*=107) and the child sample of *N*=107 (type 1 diabetes *n*= 54; no-type 1 diabetes *n*=53) are relatively small samples and therefore the generalisability of these findings should be considered accordingly.
3. Undertaking community mental health research can attract individuals with mental health issues who feel they are unable to access services. These individuals may attend research programs in the hope of obtaining insight, assistance or referral for their problems. Control group prevalence rates of clinical levels of depression and anxiety are above the Australian population average and this may provide an explanation.
4. The study was undertaken in a regional and tropical location. Geographical factors and service accessibility factors may have influenced results in the within-groups analysis of diabetes-specific aetiological and clinical factors. For example, access to specialist services and allied health support services may have been more limited than what could be expected in a metropolitan setting

thereby influencing clinical outcomes and comorbid presentations in the participants with type 1 diabetes.

5. Self-report measures are known to create a moderated response set [55]. As such, it may be that self-reported symptoms and characteristics are more severe in participants than are reported in these results.
6. Further, there has been some suggestion that responses to somatic items in the self-reported assessment measures of affective disorder may relate more to disease-specific states rather than anxiety or depression symptoms in individuals with chronic illnesses [56]. In this way scores on the scales such as the Physiological Hyperarousal subscale of the PH-PANAS-C reported by case participants may indicate higher anxiety symptoms than are actually present (results presented for child participants in Chapter 3, Study 3). Recent research has refuted this argument [57], none-the-less it is a possible confound to results and should be considered.
7. Short-term BGL may be influenced by a variety of factors other than stress and coping including time of day, food intake and/or exercise prior to the test, and recent insulin dosage
8. Longer-term records of HbA1c results were difficult to obtain from all participants and therefore one the three year HbA1c data used are based on a relatively small sample size (*n*= 28 and *n*= 23 respectively). Adjusted R squared was used to assess the regression models in order to account for the small sample size.

CHAPTER TWO: PSYCHOSOCIAL DIMENSIONS OF TYPE 1 DIABETES

Chapter Abstract

Factors of stress and coping have been identified as mediators of wellbeing, psychological health, and the physiological outcomes of people with diabetes. This chapter presents two studies in which recent experiences of stressful life events, perceptions of stress, coping self-efficacy, and behavioural and cognitive coping strategies are evaluated in type 1 diabetes. Study one compares the characteristics of these factors to those of an age and sex balanced no-type 1 diabetes control group. The second study investigates the relationship between these stress and coping variables and both short and long-term metabolic control in type 1 diabetes. Results indicate that, participants with type 1 diabetes do not report themselves to be under any greater levels of stress than their no-type 1 diabetes peers, nor do they make use of strategies to manage stressful experiences that are significantly different. However, the results show that perceptions of stress, coping self-efficacy, and coping strategies used to manage stressful events, are predictive of both short and long-term metabolic control. The strongest predictors of metabolic control were shown to be coping strategies related to behaviours and ways of thinking that involve higher level, complex executive functions such as cognitive flexibility, planning, behavioural inhibition, and applying existing knowledge to solve new problems. The conclusion drawn from the results is that psychosocial factors associated with attitudes, behaviours, and self-beliefs are strong mediators of metabolic control in type 1 diabetes. These factors involve skills and psychological mechanics that are able to be readily learned and therefore the results provide support for the position that psychoeducation and psychosocial support mechanisms should be an integral element of primary diabetes care.

Aims and Hypotheses of Studies Presented in Chapter Two

Table 2.1. *Aims and Hypotheses of Studies Presented in Chapter Two.*

Study #	Aims	Hypotheses	Hypothesis Supported
1	To investigate the extent to which experiences of stressful life events, personal perceptions of stress, personal perceptions of coping ability, and the specific coping processes used to manage stressful events differed in individuals with type 1 diabetes compared to their no-type 1 diabetes peers.	1.1. Participants with type 1 diabetes would report more experiences of recent stressful life events;	No
		1.2. Participants with type 1 diabetes would a higher level of personal perceptions of stress and a lower personal perception of ability to cope with stress;	No
		1.3. Participants with type 1 diabetes would differ from no-type 1 diabetes participants in the specific coping strategies employed to deal with stressful experiences.	No
2	To evaluate the ability of perceptions of stress, coping self-efficacy, and the use of specific cognitive and behavioural coping strategies, to predict both short and long-term metabolic control in type 1 diabetes.	2.1. Participants' short-term blood glucose levels (BGL; average BGL during participation) would be predicted by personal perceptions of stress and coping self-efficacy;	Yes
		2.2. Participants' long-term metabolic control (mean HbA1c over three years) would be predicted by coping self-efficacy, and the specific behavioural and cognitive coping strategies used to manage challenges.	Yes

Study 1: Stress and Coping in Type 1 Diabetes

S1: Abstract

Background: The literature suggests that type 1 diabetes is associated with increased levels of stress and poorer coping skills related to disease-specific attitudes and behaviours. However, little research has been conducted to assess the broader more generic characteristics of stress and coping in type 1 diabetes relative to the general population. This study investigated non-disease-specific dimensions of stress and coping in adults with type 1 diabetes and compared them to non-type 1 diabetes controls.

Methods: A cross-sectional, case-control design was employed to assess sociodemographics, recent experiences of stressful life events, personal perceptions of stress, coping self-efficacy, and coping strategies employed to manage stressful experiences in n=51 participants with type 1 diabetes and n=79 without type 1 diabetes (N=130). A combination of self-report (Life Events Questionnaire [LEQ], Rhode Island Stress and Coping [RISCI], Ways of Coping Questionnaire [WOCQ]), and face-to-face interviews were used.

Results: After corrections for multiple comparisons, ANOVA results revealed no difference between the type 1 diabetes and no-type 1 diabetes participant groups in any of the eleven stress and coping variables assessed (recent experiences of stressful events, p= .007; perceptions of stress, p= .77; coping self-efficacy, p= .66; confrontive coping, p= .52; distancing, p= .80; self-controlling, p= .43; seeking social support, p= .40; accepting responsibility, p= .45; escape avoidance, p= .90; planful problem solving, p= .80; positive reappraisal, p= .70).

Conclusion: Type 1 diabetes does not appear to increase experiences of stressful life events, or the level of personally perceived stress when compared to healthy controls. Similarly, type 1 diabetes does not reduce personal perceptions of coping ability and is not related to changes in the coping strategies used to manage stressful events. These findings appear somewhat contradictory to previous research that has evidenced both high stress and significant maladaptive coping behaviours in type 1 diabetes case only studies.

Keywords: diabetes mellitus, type 1; stress; coping; stressful life events; anxiety; depression; psychopathology; clinical outcomes.

S1: Introduction

The disease burden model argues that living with type 1 diabetes carries the consequence of high loads of personal stress that are associated with living with the disease, its impact on quality-of-life, and the omnipresent spectre of both acute and chronic health complications [3]. When asked specifically about their disease, individuals with type 1 diabetes report high levels of stress attributed to the demanding management of the chronic illness and report that the disease impinges on every aspect of their life and the lives of their family and peers [1, 58-61]. Young people and adults alike with type 1 diabetes report a diminished quality-of-life significantly lower than their diabetes-free peers [4, 62, 63].

Stress and coping capacity are a major factor in managing type 1 diabetes and it is suggested that the major issues for long-term management of the disease are more likely to be moderated by psychosocial rather than medical factors [47]. Perceived stress, experiences of stressful life events, and maladaptive coping behaviours have all been associated with poorer outcomes in autoimmune-related chronic health conditions [64]. For example, Katon [65] identified that perceptions of stress and the coping strategies employed to deal with stressful events, were all associated with capacity for diabetes-related self-care behaviours.

The high level of psychological stress associated with type 1 diabetes has been associated with sufferers' perception of control and perceived predictability of the disease [3, 66]. Moreover, type 1 diabetes is commonly associated with maladaptive coping behaviours such as internalising, aggressive and delinquent behaviour, social isolation, fear of ostracism, alcohol and substance abuse, and other high risk behaviours [67-71]. These maladaptive behaviours have all been linked to poor self-care and an increased risk of complications.

Certain sociodemographic factors have been shown to both mediate stress, enhance ability to cope, and protect against the risk of poor mental and physical health and mortality [72]. For example, both low socioeconomic status and being single or living outside of a committed marriage-like relationship, have both been clearly linked to poorer health and increased mortality [72, 73]. In diabetes, being in a marriage or marriage-like relationship has been shown to be protective against stress and poor mental health and against the onset and progression of complications [74, 75].

While a number of studies have evidenced high levels of stress in type 1 diabetes populations, few stress and coping studies have been undertaken using a case-control design. Therefore the literature presents relatively little evidence as to whether the levels of stress identified in type 1 diabetes are in fact higher than it is in a comparative group of the population without type 1 diabetes. Furthermore, the majority of studies have examined stress and coping in a manner that only evaluates them in a diabetes-specific context. Few studies have reviewed stress and coping in type 1 diabetes within a global context.

The aim of this component of the project was to investigate the extent to which experiences of stressful life events, personal perceptions of stress, personal perceptions of coping ability (coping self-efficacy), and the specific coping processes used to manage stressful events, differed in individuals with type 1 diabetes compared to their no-type 1 diabetes peers. To explore this question, three corresponding hypotheses were forwarded. It was hypothesised that participants with type 1 diabetes would report more experiences of recent stressful life events, a higher level of personal perceptions of stress and a lower personal perception of ability to cope with stress, and that participants with type 1 diabetes would differ from no-type 1 diabetes participants in the specific coping strategies employed to deal with stressful experiences.

S1: Results

Participant data is reported in Table 1.1. Sociodemographic data for participants are reported in Table 2.2. The sociodemographic data shows that when the two groups were compared they differed significantly in two factors. Participants with type 1 diabetes had more of the group in a married or defacto relationship ($p = .002$) and more participants taking medications for conditions other than diabetes or mental illness ($p < .001$). More no-type 1 diabetes participants were living in low socioeconomic households however, the difference was not statistically significant ($p = .06$).

Table 2.2. *X^2 Tests of Independence for Group Comparisons of Demographic Variables.*

Demographic	T1D % (*n*)	No-T1D % (*n*)	χ^2 (*df*=1)#	*p*
Participant born in Australia	86.3 (44)	70.9 (56)	3.313	.069
Participant is married or defacto	68.6 (35)	39.2 (31)	9.565*	.002
Employed / not working by choice (home duties, ret'd)	98.0 (50)	94.9 (75)	.186	.666
Annual household income <$40,000 (low SES)	19.6 (10)	36.7 (29)	3.540	.060
Participant has post-secondary qualification	52.9 (27)	53.2 (42)	.000	1.000
Taking medication for conditions o/t diabetes and MI	45.1 (23)	10.1 (8)	18.991**	<.001
Participant taking mental health meds	13.7 (7)	6.3 (5)	1.237	.266
Family member diagnosed with mental illness	45.1 (23)	34.2 (27)	1.134	.287
Family member with type-1 diabetes	31.4 (16)	19.0 (15)	1.980	.159

Notes: # Continuity correction for 2 x 2 table used; * Significant at α< .01; ** Significant at α< .001.

Stress and Coping

Recent experiences of stressful life events was assessed by the Life Events Questionnaire (LEQ), Perceptions of stress and coping self-efficacy by the Rhode Island Stress and Coping Inventory (RISCI: stress, and RISCI: coping), and coping strategies were assessed by the eight subfactors of the Ways of Coping Questionnaire (WOCQ: confrontive coping [CC], distancing [D], self-controlling [SC], seeking social support [SSS], accepting responsibility [AR], escape avoidance [EA], planful problem solving [PPS], positive reappraisal [PR]). The subfactors of the RISCI and WOCQ were assessed for internal reliability prior to analysis (Table 2.3).

Table 2.3. *Cronbach's Alpha Reliability Statistics for RISCI and WOCQ Subfactors.*

Measure (# items)	Cronbach's α		
	T1D (Case)	No-T1D (Control)	Total Participants
RISCI: stress (7 items)	.921	.884	.899
RISCI: Coping Self-Efficacy (5 items)	.888	.925	.913
WOCQ: Confrontive Coping (6 items)	.436	.516	.556
WOCQ: Distancing (6 items)	.721	.563	.609
WOCQ: Self-Controlling (7 items)	.708	.569	.628
WOCQ: Seeking Social Support (6 items)	.767	.690	.720
WOCQ: Accepting Responsibility (4 items)	.467	.710	.644
WOCQ: Escape Avoidance (8 items)	.806	.733	.761
WOCQ: Planful Problem Solving (6 items)	.770	.699	.724
WOCQ: Positive Reappraisal (6 items)	.738	.718	.724

Univariate analysis of variance (ANOVA) was used to assess the between-groups differences in experiences of stressful life events (LEQ), perceptions of stress (RISCI stress subfactor), perceptions of coping ability (RISCI coping subfactor), and specific coping strategies used to manage stressful experiences (WOCQ subfactors). Age was included as a covariate in order to control for the effect of age on coping and stress. Correlational analysis of the 11 dependent variables showed a number of singularities and therefore univariate ANOVA was chosen over multivariate ANOVA. After applying Bonferroni corrections ($p \leq .005$ (α (.05) /11), the results of the ANOVAs revealed no significant variations between groups in any of the variables (Table 2.4).

Table 2.4. *Mean, Standard Deviation, and Results of Tests of Between-Subjects Effects (Univariate ANOVA) for WOCQ, LEQ, and RISCI.*

Dependent Variable	*M* (*SD*)		*F* (*df*)	*P*	n_p^2
	T1D	No-T1D			
LEQ: Stressful Life Events	101.00 (77.00)	142.99 (93.76)	7.55 (1,139)	.007	.052
RISCI: Perceived Stress	17.89 (6.68)	17.77 (6.27)	.088 (1,133)	.767	.001
RISCI: Coping Self-Efficacy	18.43 (3.21)	18.41 (4.15)	.199 (1,133)	.656	.001
WOCQ: Confrontive Coping	4.75 (2.90)	5.22 (3.23)	.422 (1,141)	.517	.003
WOCQ: Distancing	6.12 (3.69)	6.08 (4.24)	.066 (1,141)	.798	<.001
WOCQ: Self-Controlling	8.10 (4.23)	8.28 (3.89)	.616 (1,141)	.434	.004
WOCQ: Seeking Social Support	7.58 (4.44)	8.11 (3.86)	.704 (1,141)	.403	.005
WOCQ: Accepting Responsibility	2.69 (2.22)	3.15 (2.88)	.565 (1,141)	.454	.004
WOCQ: Escape Avoidance	6.37 (4.86)	6.42 (4.78)	.017 (1,141)	.896	<.001
WOCQ: Planful Problem Solving	9.17 (4.18)	9.30 (4.12)	.067 (1,141)	.796	<.001
WOCQ: Positive Reappraisal	7.31 (4.82)	6.70 (4.76)	.152 (1,141)	.697	.001

Notes: Bonferroni corrections applied to correct for multiple comparisons therefore results are only considered significant if $p \leq .005$ (α (.05) /11).

S1: Discussion

The present study investigated recent experiences of stressful life events, the level of perceived stress, coping self-efficacy, and the specific coping strategies used to manage stressful experiences in adults with type 1 diabetes compared to adults without the condition. No differences were found between participants with type 1 diabetes and those without in any of the assessed stress and coping variables. These results appear somewhat contradictory to previous research that has shown evidence that individuals with type 1 diabetes experience high levels of personal stress and display evidence of

poor or maladaptive coping behaviours [3, 64, 65]. However, this contradiction may have more to do with differences in methodology than any true contradiction in directly comparable data.

The present study employed a case-control design and therefore results are describing differences between participants with type 1 diabetes and those without rather than looking at stress and coping in a diabetes-only cohort. The diabetes literature has been criticised for its lack of case-control investigations which has impacted the translational capacity of the results [76]. This study addresses that concern.

Furthermore, previous studies have commonly used clinic visits to recruit and assess participants for factors such as perceived stress and coping behaviour. Clinic visits may be preceded by higher-stress events such as a specific health or disease management issue, and therefore these participants may be primed for higher perceived stress responses. Similarly, attendance to deal with such issues in clinic may impact perceptions of personal coping efficacy and impact responses accordingly. In contrast, the current study was conducted outside of clinic visits and assessments were completed in more relaxed and personally controlled circumstances. Additionally, the personal effort and commitment required by volunteers to participate in the present study outside of their regular clinic visit means that study participants may be a more resilient and organised sub-group than those who have participated in more opportunistic studies based around clinic visits.

H_1: Greater Experiences of Recent Stressful Life Events in Type 1 Diabetes

The first hypothesis that participants with type 1 diabetes would report higher experiences of recent stressful life events than participants without type 1 diabetes was not supported. The mean life events scores of the two groups show that the type 1 diabetes group had lower experiences of stressful life events than the participants in the no-type 1 diabetes group over the previous year. However, after Bonferroni corrections were applied to account for multiple analyses, these differences were not significant. Although the differences in life events between the groups was not significant, recent experiences of stressful life events was shown to be significantly related to group membership. The results of the rank order correlations showed that membership in the no-type 1 diabetes group was related to an increase in experiences of stressful life events in the previous year. Conversely, membership in the type 1 diabetes group was related to lower experiences of stressful life events in the same period.

These results are somewhat contradictory of previous research showing high rates of stress and associated disordered affect in type 1 diabetes compared to individuals without the condition [1, 8, 14]. This is an important consideration as individuals with type 1 diabetes are at significantly greater risk for mental health problems and the literature shows that stressful life events provide considerable influence on the onset and maintenance of a range of psychopathologies including both anxiety and depression [77-79]. Furthermore, stressful life events, by definition, place an inordinate amount of pressure on an individual's physical and psychological resources. As type 1 diabetes requires significant personal investment in managing the disease (food, exercise, medication, monitoring, personal grooming to protect from peripheral injury and infection), the presence of additional external stressors may have a disproportionate impact on health and psychological wellbeing. These results suggest that any increased stress and higher rates of psychopathology in type 1 diabetes may not be directly related to greater pressures from external experiences.

H_2: Perceptions of Higher Personal Stress and Perceptions of Lower Personal Ability to Cope in Type 1 Diabetes

Hypothesis two was not supported. Participants with type 1 diabetes did not perceive themselves to be under any greater personal stress than their no-type 1 diabetes peers, nor did they report a lower personal ability to cope. This also appears somewhat contradictory to previous research findings that individuals with type 1 diabetes report lower health-related quality-of-life and that their diabetes pervasively impacts across all facets of their life. Previous research that has asked specific questions about living with diabetes have shown that participants report high levels of perceived stress. Participants have directly attributed this high stress to the demands of living with the disease and the pressure and guilt felt by sufferers due the impact the illness has on their family and peers [1, 58-61]. The present results do not reflect these findings and instead suggest that, while people with type 1 diabetes may indicate that their disease is a burden when asked directly about the condition, they do not necessarily reflect this impact into the broader context of their general life. This is supported by the results showing that the participants with type 1 diabetes did not differ from the participants without type 1 diabetes in their own perceptions of their current ability to cope with their stress.

Psychological stress is considered to occur when events outstrip an individual's ability to establish an adequate degree of psychological defence to cope [80]. Participants

with type 1 diabetes did not consider their level of stress or their ability to cope to be any different to the way in which participants without type 1 diabetes perceived these factors. Therefore, the increased risk of outcomes generally attributed to stress and maladaptive coping such as anxiety, depression, and poor clinical outcomes that have been previously identified in type 1 diabetes may not be primarily mediated by personal perceptions of stress, or personal capacity to deal with psychological stressors. This has important ramifications for understanding the management of stress and psychological wellbeing in type 1 diabetes and requires additional research to fully elucidate the factors involved.

It is possible that the unremarkable self-reported personal perceptions of stress may not necessarily be a true indication of levels of stress in the type 1 diabetes participants. The chronic nature of the illness may result in sufferers becoming habituated to increased levels of personal stress and therefore they may not perceive personal stress in the same manner as those not living with a chronic disorder [81, 82]. Altered perceptions of stress may also be further exacerbated by neuropsychological sequelae common to type 1 diabetes [83].

Results may also indicate that participants were unwilling to disclose their true perceptions of stress and coping. This would fit with the literature in which there have been a high prevalence of maladaptive behaviours identified in participants with type 1 diabetes [70, 84] and may be an indication of disparities between the real and ideal self [85]. Maladaptive behaviours aimed at self-preservation often include denial and deception. The literature shows the prevalence of significant rates of anxiety and depression in type 1 diabetes [8, 14] and the presence of maladaptive coping processes would also explain the disparity between the comparatively unremarkable level of perceived stress and the high prevalence of affective psychopathology (see chapter 3). For example, maladaptive behaviours such as denial may be useful in minimising distress and thereby facilitate coping in the short-term [86]. An increased presence of anxiety in this cohort would support this explanation as denial- and deceit- driven behaviours are often a feature of anxiety disorders [8, 28, 87, 88]. Anxiety and depression are a major clinical feature of this type 1 diabetes cohort (see chapter 3).

Ultimately however, these results may well be reflective of genuinely unremarkable perceptions of stress and coping in participants with type 1 diabetes. The present study asked participants about general perceptions of stress and coping rather

than diabetes-specific perceptions. Having been asked about global perceptions of stress and coping, participants may negate the struggles of their condition and reflect more openly on other elements of their life such as work and family. The type 1 diabetes participant group had a higher level of the group living in committed marriage-like relationships and had a greater number of the group in households with a higher socioeconomic status than the no-type 1 diabetes group. This may be reflected in participant responses as both of these sociodemographic factors are protective against stress and conducive to psychological wellbeing [72-75].

In diabetes, being in a marriage or marriage-like relationship has been shown to be protective against poor mental health and against the onset and progression of complications. Close, supportive intimate partners provide a combination of psychological support, motivation to maintain health, and external pressure to conform to self-care protocols such as blood testing, regular visits to diabetes health care professionals, and maintaining a healthy diet and exercise program [74, 75]. Results may indicate that, outside of the direct elements of their disease, participants considered themselves to be secure, capable, and in control of managing their lives. Therefore, previous studies that have focused on diabetes-specific stress and coping may be indicative of personal perceptions of domain-specific efficacy rather than stress and coping in a global sense.

H_3: There would be Differences in the Coping Strategies Employed to Manage Stressful Experiences

Hypothesis three was not supported. The two participant groups did not differ in the strategies they used to cope with specific stressful events. In the eight coping strategies measured by the WOCQ, there was no difference between the two groups in the pattern or frequency of use of each specific process. Previous coping studies in type 1 diabetes have been specific about asking participants to respond based on diabetes-related stressors and the impact they have on lifestyle, psychological wellbeing, disease management, and clinical outcomes. In contrast, the present study explored global coping processes that are used in stressful situations across the spectrum of life events. Participants were asked to select any significantly stressful event they have had dealt with and only two type 1 diabetes participants chose to respond to a diabetes-specific stressful event. The majority of type 1 diabetes participants instead selected events that were similar to those selected by the no-type 1 diabetes participants including stressful

experiences around finances, relationships, living arrangements, employment, and study.

Additionally, many of the previous studies of coping in diabetes have looked at maladaptive coping outcomes rather than coping processes or strategies. These studies have typically used dichotomous response methods to collect data about behavioural and physiological factors associated with poor coping skills, such as sleep and dietary hygiene, ability to concentrate, and changes in affect [84]. Items associated with these factors can also have an underlying physiological aetiology which, according to Holmes et al. [84], may skew reports of factors such as stress and coping within a type 1 diabetes cohort. The present results were derived from the Ways of Coping Questionnaire which uses a Likert-type scale to examine both positive and negative coping processes associated with social behaviours (EG: social isolation vs affiliation, confrontation vs. avoidance) and attitudes (EG: felt I did / did not have the ability to cope), rather than physiology-related reactions. The results suggest that the processes used to respond to stressful events do not differ between people with and without type 1 diabetes. Combined with previous findings, the research further suggests that the physiological and psychological indicators often associated with maladaptive coping mechanisms in type 1 diabetes may have an alternative origin unrelated to the psychosocial dimensions of coping.

Other Findings of Note

While there is evidence for increased disease-specific stress in type 1 diabetes, as a result of the increased stress from their disease, sufferers may perceive external stressors as "less than". In this way participants with type 1 diabetes may report globally referenced perceived stress to be lower than others who do not have a specific-chronic comparison by which other events are measured. Therefore, while individuals with type 1 diabetes may report that life with the condition is highly stressful when primed or prompted to actively consider the implications it has in their life; more general reports of perceptions of personal stress may not accurately reflect the actual level of stress they are experiencing. Therefore, disease-specific chronically elevated stress may retard sufferers' ability to perceive personal stress thereby rendering self-reported stress assessments as erroneous. This is further borne out by studies showing patients with type 1 diabetes exhibit impaired HPA axis function [89], and reduced heart-rate variability [90]. These alterations may ultimately result in an elevation of stress

physiology, a corresponding reduction in conscious awareness of the physiological arousal, a reduction in physiological capacity to deal with the increased stress demands, and an increased risk for comorbidities such as cardiovascular disease [91, 92], and anxiety-related disorders [93].

Clinical Considerations

The results suggest that participants with type 1 diabetes may be either unable or unwilling to disclose or recognise a number of symptoms associated with psychological disorder and personal levels of stress. This means that general practitioners, diabetes specialists, and diabetes educators may not be able to obtain accurate information about psychological wellbeing of patients in the normal course of a general clinic visit. To address this shortcoming, the inclusion of regular psychological health screenings by appropriately trained mental health professionals should be considered an essential adjunct to existing standard clinic visit protocols [8, 62].

Limitations

Stress and coping data were collected using self-report measures. This form of data collection is known to create a moderated response set [55] and it may be that the level of perceived stress is more severe and the coping strategies poorer, than reported.

Conclusion

The results of the present study suggest that adults with type 1 diabetes are not exposed to greater levels of stressful life events, do not perceive themselves to be under higher amounts of stress or to have less ability to cope with the demands of stress, and do not engage in coping processes that differ fundamentally to those employed by their no-type 1 diabetes peers. Further, the mean group scores of the life events questionnaire indicate that type 1 diabetes is negatively correlated to experiences of stressful life events. While these results may appear somewhat contradictory to findings from previous research, the present study differs to most previous studies in its focus and methodology and therefore the results are not directly comparable. Taken together, these results and those from previous studies provide a more detailed picture of the nature of stress and coping in type 1 diabetes.

A number of mechanisms may be involved in mediating these findings. It may be as it appears, that people with type 1 diabetes do not differ in their dimensions of stress and coping. Alternatively, it may be that maladaptive coping behaviours

associated with factors such as elevated rates of psychopathology in type 1 diabetes influence the preparedness of sufferers to disclose the reality of their situation, or impair personal capacity to identify their distress. In any event, the present findings provide additional insight into some of the psychosocial mechanisms that have been found to influence the quality-of -life of people with type 1 diabetes, as well as the functional capacity for disease self-management, complications risk, disability, and ultimately mortality. Further research is needed to ascertain the extent to which people with type 1 diabetes are impacted by factors of stress and coping. Of particular importance is the nature of experiences of stress, personal perceptions of ability to cope, and the character of the processes that are employed to manage stressful experience.

Study 2: The Influence of Stress and Coping on Metabolic Control in Type 1 Diabetes

S2: Abstract

Background: The literature suggests that stress and coping play an important role in diabetes management and clinical outcomes. The present study investigated the use of personal perceptions of stress (RISCI: stress), coping self-efficacy (RISCI: coping), and specific coping strategies (eight subfactors of the WOCQ), to predict both short and long-term metabolic control in adults with type 1 diabetes.

Methods: Self-reports were used to obtain information on participants' current perceptions of stress and coping self-efficacy, and recent (last three months) characteristic use of specific behavioural and cognitive coping strategies. Medical records were used to determine average metabolic control (HbA1c) for the preceding three years. Short-term blood glucose was measured by averaging the blood glucose results of two finger prick blood tests taken pre and post participation in the data collection protocol (approximately three hours).

Results: Multiple regression analysis found that perceived stress and coping self-efficacy significantly predicted 32.5% (adjusted *R* square) of the total variance in short-term metabolic control ($p < .01$). Perceived stress was a significant unique contributor to the model (beta = .43, $p < .01$). A five-factor model containing coping self-efficacy, and the coping strategies of self-controlling, planful problem solving, seeking social support, and positive reappraisal significantly predicted long-term metabolic control ($p = .03$), explaining 51.5% (adjusted *R* square) of the total variance in HbA1c over three years. No single predictor made a significant unique contribution to the long-term control prediction model suggesting considerable overlap between the items.

Conclusion: Levels of stress and coping self-efficacy are correlated to and predictive of short-term metabolic control with stress appearing to be of particular relevance to short-term blood glucose levels. Coping self-efficacy and the characteristic coping strategies used by adults with type 1 diabetes have a similarly significant relationship with and predictive value to long-term metabolic control. The influence of coping dimensions on long-term metabolic control appears to involve multiple variables and the manner in which they interact rather than any single factor making a significant unique contribution.

Keywords: diabetes mellitus, type 1; stress; coping; self-efficacy; metabolic control; glycaemic control; clinical outcomes.

S2: Introduction

The previous three decades have seen significant advances in knowledge of the relationship between improved diabetes management and complications risk, and in diabetes management techniques to assist in disease self-management practices and outcomes [94]. In spite of this improved knowledge and management capacity, research consistently shows sub-optimal metabolic control in type 1 diabetes cohorts, a high prevalence of acute and chronic complications, and a disparity between the knowledge of these risk factors and the behaviours undertaken by individuals with the disease in the day-to-day management of their condition.

Plack, Herpetz, and Petrak [95] state that "poor glycaemic control is prevalent in the majority of patients with diabetes" (p.131). According to Plack et al., [95] psychobehavioural variables are an important factor for understanding this issue as it is the actions of the patients themselves that are the most significant factor in determining treatment success. Devries, Snoek, and Heine [96] support this position stating that 25% of adults with type 1 diabetes have chronic poor glycaemic control and that psychosocial factors such as coping and motivation must be included in the raft of educational topics provided to patients. Moreover, Snoek [2] asserts that while psychosocial factors both impact on diabetes care and are impacted by the presence of the disease; the resolution of the stress and increased coping-load related to living with diabetes is more complicated than the perfunctory provision of education on disease management. Snoek [2] states that diabetes patients' health behaviours are largely determined by attitudes, illness beliefs, disease management self-efficacy, locus of control, and the underlying schemas about their disease that underscore these psychophenomena – all of which mediate the level of psychological stress perceived by patients.

Psychological stress occurs when the demand of our experiences exceed our capacity to present an appropriate level of psychological defences to cope [80]. In type 1 diabetes there are many physical, social and psychological factors that contribute to the level of stress experienced by sufferers. Psychosocially, self-efficacy beliefs and coping strategies are two areas that have been well established as contributing to the challenges of ongoing disease self-management, personal stress, and diabetes burnout [2, 97]. The evidence suggests that ultimately, the capacity to cope with the stressors of type 1 diabetes is linked to personal perceptions of control over the disease. This includes

individual beliefs about disease predictability, personal efficacy around perceived ability to exert personal control over the factors that will influence disease outcomes, and the strategies available to personally cope with the practical and psychological pressures of life with the disease [3, 66].

Self-efficacy and efficacy-related factors such as empowerment, motivation, health beliefs, coping and problem solving skills, and locus of control, are identified as among the most widely recognised factors that present a barrier to effective self-management in both type 1 and type 2 diabetes [98]. Internal psychological mechanisms such as self-efficacy are involved in motivational drive and therefore play a strong role in mediating behaviour choices. In type 1 diabetes, behavioural choices associated with disease management can have serious consequences for health and longevity. According to Rose et al., [97], self-efficacy and active coping behaviours are amongst the greatest predictors of the likelihood of achieving primary treatment goals (generally identified as the optimisation of metabolic control assessed by HbA1c levels).

In school-aged children with chronic illnesses such as type 1 diabetes, asthma, cystic fibrosis or seizure disorders, Mickley, Burkhart, and Siglar [99] argue that self-efficacy is not only essential in the management of chronic disease, but that disease self-efficacy is also an important factor in a child's normal development trajectory. While there is a scarcity of literature on psychosocial interventions in children with type 1 diabetes, Mickley et al. [99], are supported by Whitmore, Jaser, Guo, and Grey [100], who have proposed a conceptual model of childhood adaptation to type 1 diabetes in which self-management and coping self-efficacy sit alongside other factors such as familial functioning and social competence as important psychosocial influences on the level of adaptive success.

Self-efficacy and personal perceptions of ability to cope are foundational to the successful navigation of diabetes across all ages. Grey, Davidson, Boland, and Tamborlane [101], found that improvements to metabolic control in adolescents with type 1 diabetes were associated with coping skills training and that without the improvements in coping, other clinical mechanisms such as an intensification of management regimen may be counter-productive. In later adolescence Hanna et al. [102], found that self-efficacy was an important factor in diabetes management outcomes independent of other social factors such as living arrangements (with parents or

independently) or schooling status (still at school or finished / left high school). Yi-Frazer et al. [103], add support to the importance of coping self-efficacy with results from their study showing resilience – operationalised as a combination of self-efficacy, optimism, and self-esteem - is linked to reduced levels of distress and improved clinical outcomes in type 1 diabetes. Similarly, adult studies of diabetes management, chronic poor control, and factors contributing to optimised care, show that coping self-efficacy plays a significant role in type 1 diabetes and support its importance in improving and maintaining positive health and wellbeing outcomes in people with the disease. Krichbaum, Aarestad, and Buethe [104] found a clear relationship between coping self-efficacy and improved outcomes in type 1 diabetes. However, the majority of these studies have been undertaken in younger cohorts and do not account for potential mediating factors such as duration of illness [67, 69, 105, 106]. Hanson et al., [106] and Rassart et al., [107] both examined duration of illness in the context of illness coping in type 1 diabetes and identified that duration of illness was a mediator of illness adaptation [107] and of the coping behaviours selected [106].

External social and demographic factors can also play a significant role in moderating stress, coping capacity, and psychological wellbeing in type 1 diabetes. For example, low socioeconomic status is a major predictor of poor physical and mental health as well as early mortality [72]. Additionally, social factors such as intimate relationships are also indicated to be significant mediators of health and wellbeing in patients with type 1 diabetes. Living in a committed relationship has been found to mitigate the risk of poor mental health, complications onset, and mortality. Studies have evidenced that quality intimate relationships provide psychological support, motivation, and external pressure to conform to disease management and self-care requirements, all of which exert significant protective powers over the deleterious sequelae of type 1 diabetes [74, 75].

The aim of the present study was to evaluate the ability of perceptions of stress, coping self-efficacy, and the use of specific cognitive and behavioural coping strategies, to predict both short and long-term metabolic control in type 1 diabetes. To answer this question, two hypotheses were forwarded. It was hypothesised that participants' short-term blood glucose levels (BGL; average BGL during participation) would be predicted by personal perceptions of stress and coping self-efficacy. It was further hypothesised that participants' long-term metabolic control (mean HbA1c over three years) would be

predicted by coping self-efficacy, and the specific behavioural and cognitive coping strategies used to manage challenges. For more detail on BGL, see Chapter 1, "Methods" section, 'Blood Glucose Levels / Metabolic Control" subsection).

S2: Results

Participants' descriptive statistics are reported in Table 1.1. Demographic data for participants are reported in Table 2.2. The internal reliability, mean scores and standard deviations for the eight WOCQ subfactors, and the stress and coping subfactors of the RISCI are reported in Table 2.3, and Table 2.4. Diabetes-specific clinical data are reported in Table 2.5.

Table 2.5. *Type 1 Diabetes Group-Specific Clinical Characteristics.*

Type 1 Diabetes-Specific Clinical Data (*N*= 73)	% Group (*n*)	*M* (*SD*) age	Range
Mean age at diagnosis (years)	-	21.3yrs (14.4)	2 - 63
Mean duration of illness (years)	-	22.3yrs (15.4)	1 – 60
Participant using insulin pump **	23.3 (17)	40.4yrs (14.4)	16 - 64
≥1 severe hypoglycaemic events (lifetime)	46.6 (34)	42.7yrs (14.1)	16 - 65
Confirmed presence of complications	60.3 (44)	45.8yrs (13.7)	17 - 73
Confirmed presence of multiple complications	42.5 (31)	36.2 (15.7)	16 - 62
Additional diabetes meds (Eg: metformin)	6.8 (5)	59.4 (8.8)	46 - 67
	Median	*M* (*SD*) BGL	Range
Mean and median BGL during participation #	10.3	11.4 mmol/L (4.8)	5.1 – 27.5
Mean and median BGL variation during participation ##	-1.2	-1.0 mmol/L (4.2)	-10.3 - +10.4
Mean and median M-T HbA1c (*n*=58; see methods) * †	8.2	7.9% (1.6)	4.6 – 13.5
Mean and median L-T HbA1c (prev 1 year, *n*= 28) * †	8.1	8.0% (1.0)	5.5 – 10.1
Mean and median L-T HbA1c (prev 3 years; *n*= 23) * †	7.9	8.0% (1.0)	5.3 – 9.6

Notes: BGL = Blood Glucose Level; HbA1c = Glycated Haemoglobin; * Data based on smaller sample as indicated; ** vs injections, *n*=56, *M* age= 41.6, *SD*= 15.9, range= 16-73; # (BGL @ commencement of participation session + BGL @ conclusion of session) / 2; ## BGL @ commencement of participation session - BGL @ conclusion of session; † Optimal HbA1c <7 mmol/L.

Hierarchical multiple regression analysis was used to assess the ability of participants' personal perceptions of stress (RISCI: stress) and coping self-efficacy (RISCI: coping) to predict short-term BGL (S-T BGL). As age and duration of illness have been shown to mediate adaptation to illness and illness coping, these variables

were included at step 1 of the regression analysis to control for their influence [106-109]. Preliminary assumption testing was performed to confirm the suitability of the data for multiple regression analyses. Sample size, normality, linearity, multicolinearity, and homoscedasticity were all evaluated prior to conducting analysis, using assumption testing guidelines set out in Pallant (2011) [110], and Tabachnick and Fidell, (2007) [109]. Preliminary analyses showed that the sample size was adequate and that there were no violation of the assumptions of normality, linearity, multicolinearity, and homoscedasticity.

Analysis showed that age had a small significant correlation to coping self-efficacy (r = .153, p .038), but was not significantly correlated to personal perceptions of stress (r = -.062, p = .237), or S-T BGL (r = -.140, p .126). Duration of illness was significantly correlated to both coping self-efficacy (r = .418, p = .001), and personal perceptions of stress (r = -.266, p = .027), but not S-T BGL (r = -.198, p = .053). The two predictors were both significantly correlated to S-T BGL (personal perceptions of stress r = .556, p < .001; coping self-efficacy r = -.479, p < .001).

Age and duration of illness were entered into the hierarchical regression model at step 1. The two covariates were not a significant influence on the model, explaining only 4.0% of the total variance in participants' S-T BGL (R squared = .040, se of the estimate = 5.314, F (2, 48) = 1.009, p = .372). When age, duration of illness, personal perceptions of stress, and coping self-efficacy were all included in the model at step 2, the total model explained a statistically significant 41.6% of the total variance in participants' S-T BGL (R squared = 0.416, se of the estimate = 4.235, F (4, 46) = 8.190, p < .001).

Together, the two predictors (personal perceptions of stress and coping self-efficacy), explained a statistically significant 37.6% of the total variance in participants' S-T BGL (R square change = .376, F change (2, 46) = 14.791, p < .001). In the final model, neither age nor duration of illness made a statistically significant unique contribution to the prediction of participants'' S-T BGL (age: Beta = -.141, p = .307; duration of illness: Beta = .152, p = .317). Personal perceptions of stress, and coping self-efficacy both made a unique and statistically significant contribution to the prediction of S-T BGL in participants (personal perceptions of stress: Beta = .460, p < .001; coping self-efficacy: Beta = -.356, p = .009). There was considerable overlap

between the predictors as the total unique contribution by personal perceptions of stress was only 17.89% (semi-partial correlation coefficient = .423) of the total variance explained by the model, while coping self-efficacy was just 9.55% (semi-partial correlation coefficient = -.309).

Further hierarchical multiple regression analysis was undertaken to assess hypothesis two that long-term (L-T) metabolic control could be predicted by participants' coping self-efficacy, and the specific behavioural and cognitive coping strategies used to manage challenges, while again controlling for the influence of age and duration of illness [106-109]. Preliminary analyses again showed that the sample size was adequate, and that there were no violation of the assumptions of normality, linearity, multicolinearity, and homoscedasticity [109, 110]. To test the hypothesis a hierarchical multiple regression analysis was undertaken with age and duration of illness entered at step 1, and nine coping predictors entered into the model at step 2. The nine predictors entered at step 2 were coping self-efficacy (RISCI: coping), and the eight coping subfactors of the Ways of Coping Questionnaire (confrontive coping, distancing, self-controlling, seeking social support, accepting responsibility, escape avoidance, planful problem solving, and positive reappraisal).

Table 2.6., shows that coping self-efficacy, self-controlling, seeking social support, planful problem solving, and positive reappraisal, were all significantly correlated to participants' L-T metabolic control (average HbA1c levels over the preceding three years; see Chapter 1, "Methods" section). Of the two covariates entered at step 1, age had a small significant association with L-T metabolic control (r = -.399, p = .018), coping self-efficacy (r = .153, p = .038); and self-controlling (r = .181, p = .015), while duration of illness showed a moderate positive significant correlation to coping self-efficacy (r = .418, p = .001). All correlations of the predictors to age, duration of illness, and L-T metabolic control, and of age and duration of illness to L-T metabolic control, are presented in Table 2.6.

Age and duration of illness were not a significant influence on the model, jointly explaining 16.0% of the total variance in participants' L-T BGL (R squared = .160, se of the estimate = 1.283, F (2, 14) = 1.338, p = .294). When age, duration of illness, and the nine coping variables were all included in the model at step 2, the total model explained a significant 95.2% of the total variance in participants' L-T BGL (R squared = 0.952,

se of the estimate = .514, F (11, 5) = 8.978, p = .013). The nine coping variables together explained a statistically significant 79.1% of the total variance in participants' L-T BGL (R square change = .791, F change (9, 5) = 9.123, p = .013). In the final model, age, duration of illness, seeking social support, and escape avoidance made a statistically significant unique contribution to the model (Table 2.7).

Table 2.6. *Results of Pearson's Correlations of the Relationship between Long-Term Metabolic Control, Age, Coping Self-Efficacy, and the Eight Coping Strategies of the Ways of Coping Questionnaire (WOCQ) in Participants with Type 1 Diabetes.*

Coping Variables		L-T Met. Control	Age	Duration of Illness
L-T Metabolic Control (*n*= 23)	*r*	.	-.399*	-.195
	p	.	.018	.160
Age (*n*= 180)	*r*	-.399*	.	.
	p	.018	.	.
Duration of Illness	*r*	-.195	.	.
	p	.160	.	.
Coping Self-Efficacy (*n*= 130)	*r*	-.384*	.153*	.418***
	p	.047	.038	.001
Confrontive Coping (*n*= 144)	*r*	-.203	-.086	-.047
	p	.217	.153	.371
Distancing (*n*= 144)	*r*	-.146	-.072	-.116
	p	.288	.194	.209
Self-Controlling (*n*= 144)	*r*	-.521*	.181*	.159
	p	.016	.015	.132
Seeking Social Support (*n*= 144)	*r*	-.456*	.026	.155
	p	.033	.380	.139
Accepting Responsibility (*n*= 144)	*r*	-.170	-.098	.038
	p	.257	.121	.395
Escape Avoidance (*n*= 144)	*r*	.272	-.074	-.165
	p	.146	.190	.124
Planful Problem Solving (*n*= 144)	*r*	-.637*	.026	.108
	p	.003	.376	.226
Positive Reappraisal (*n*= 144)	*r*	-.581*	.134	.140
	p	.007	.055	.163

Notes: * Sig. at α= .05 level; ** Sig. at α= .01 level; *** Sig. at α= .001 level;

Table 2.7. *Beta Coefficients and Percentage of Unique Contribution to the Total Variance Explained by the Model for the Nine-Predictor Model of Long-Term Metabolic Control in Participants with Type 1 Diabetes.*

Model Predictors	Standardized Coefficients			Unique Cont. to Model	
	Beta	*t*	*p*	Semi-part. Cor. Co.	Unique % of Var.
Age	-.528	-4.212	.008	-.413	17.06
Duration of Illness	.444	3.231	.023	.317	10.05
RISCI: Coping Self-Efficacy	-.283	-2.378	.063	-.233	5.43
WOCQ: Confrontive Coping	-.133	-1.149	.302	-.113	1.24
WOCQ: Distancing	-.066	-.544	.610	-.053	.28
WOCQ: Self-Controlling	-.264	-2.020	.099	-.198	3.92
WOCQ: Seeking Soc. Support	-.303	-2.611	.048	-.256	6.55
WOCQ: Accepting Resp.	-.313	-2.415	.060	-.237	5.62
WOCQ: Escape Avoidance	.633	4.608	.006	.452	20.43
WOCQ: Planful Prob. Solving	-.190	-1.379	.226	-.135	1.82
WOCQ: Positive Reappraisal	-.103	-.734	.496	-.072	.52

The nine-predictor model was adjusted to include only those five predictors that showed significant correlations to L-T metabolic control (coping self-efficacy, self-controlling, planful problem solving, positive reappraisal, and seeking social support). Hierarchical regression analysis was then rerun with the resulting five-variable model and with age and duration of illness again entered at step 1 as covariates. Preliminary analyses again showed that the sample size was adequate, and that there were no violation of the assumptions of normality, linearity, multicolinearity, and homoscedasticity. As step 1 of the analysis was identical to that of the previous nine-predictor analysis, age and duration of illness once again did not significantly influence the model (see results at previous analysis above).

When age, duration of illness, and the five coping variables were all included in the model, the total model explained a statistically significant 73.5% of the total variance in participants' L-T BGL (*R* squared = 0.735, se of the estimate = .900, F (7, 9) = 3.561, p = .040). The five coping variables together explained a statistically significant 57.4% of the total variance in participants' L-T BGL (*R* square change = .574, *F* change (5, 9) = 3.896, p = .037). In the final model, no predictor made a statistically significant unique contribution to the model suggesting significant overlap between the variables. Beta values for all predictors in the final model are shown in Table 2.8.

Table 2.8. *Beta Coefficients, Correlation Coefficients, and Percentage of Unique Contribution to the Total Variance Explained by the Model for the Five-Predictor Model of Long-Term Metabolic Control in Participants with Type 1 Diabetes.*

Model Predictors	Standardized Coefficients			Unique Cont. to Model	
	Beta	*t*	*p*	Semi-part. Cor. Co.	Unique % of Var.
Age	-.465	-2.195	.056	-.377	14.21
Duration of Illness	.294	1.282	.232	.220	4.84
RISCI: Coping Self-Efficacy	-.255	-1.273	.235	-.219	4.80
WOCQ: Self-Controlling	-.135	-.655	.529	-.113	1.28
WOCQ: Seeking Social Support	-.289	-1.539	.158	-.264	6.97
WOCQ: Planful Prob. Solving	-.364	-1.588	.147	-.273	7.45
WOCQ: Positive Reappraisal	-.128	-.540	.602	-.093	.86

The results of the multiple regression analyses show that higher personal levels of stress and lower levels of coping self-efficacy are associated with, and predictive of, poor BGL in the short-term. Further, the results show that better metabolic control over the long-term is associated with higher levels of coping self-efficacy and the use of specific behavioural coping strategies that involve active problem solving, self-control, and social affiliation, and specific cognitive coping strategies that involve engaging positive cognitive reappraisal skills to help process challenging experiences.

S2: Discussion

The present study aimed to assess the capacity of perceptions of stress, coping self-efficacy, and the use of specific cognitive and behavioural coping strategies, to predict both short and long-term metabolic control in type 1 diabetes. The investigation builds on the initial assessment of stress and coping characteristics in type 1 diabetes presented in the first study of this chapter, and on the existing literature highlighting the continued high rates of sub-optimal metabolic control and associated clinical complications despite ever increasing improvement to both knowledge and capacity in regards to mitigating the risk factors for diabetes-related complications, disability, and early mortality [111-114]. While the literature clearly shows a relationship between disease-specific perceptions of stress, self-efficacy, and coping strategies and diabetes-specific clinical outcomes [1, 58-61]; these results show that broader perceptions of stress,

beliefs about personal ability to cope, and generalised behavioural and cognitive coping strategies are also predictive of clinical outcomes in the disease. These results show three important psychosocial factors that have the potential to impact significantly on diabetes management and clinical outcomes. Firstly, that an individual's stress levels will influence their short-term capacity to maintain good metabolic control. Secondly, that beliefs about personal ability to cope with stress – what is known as coping self-efficacy – has an impact on both short and long-term metabolic outcomes. Finally, these results show that the extent to which an individual uses positive behavioural and cognitive coping processes influences long-term metabolic control.

H_1: S-T BGL Predicted by Personal Perceptions of Stress and Coping Self-Efficacy

Hypothesis one that participants' short-term BGL would be predicted by the levels of personal perceptions of stress and coping self-efficacy was supported. Mean BGL during participation was positively correlated with increased perceptions of stress and negatively correlated with perceptions of coping ability. The levels of perceived stress and coping self-efficacy in participants was predictive of short-term BGL with results showing that participants who reported feeling less stressed and more able to cope had lower average blood sugar levels during participation in the study. This is consistent with the literature in which a number of studies have reported that clinical outcomes in type 1 diabetes are associated with feelings and beliefs about control and disease predictability [3, 66].

The assessment of stress in the present study used a self-reported level of stress to evaluate the level of stress participants perceived themselves to be under during the period of time in which they presented for participation in the study. Shalev [80] asserts that psychological stress occurs when the cognitive and emotional burdens of our environment exceed our capacity deal with them. The increased stress in some participants may have been directly related to participation in the study and the completion of "tests" or other performance tasks, or as a result of the common anxiety that is often associated with venepuncture. Stress can carry a physiological consequence of increased release of glucocorticoids which, in turn, may lead to elevated BGL in the short-term. In this way any performance anxiety, needle phobia, or an unrelated stressor may have contributed to an increased physiological stress response and a corresponding short-term spike in BGL in those participants affected.

Increased stress can also lead to behavioural strategies that result in increased short-term BGL. For example, stress may lead to overcompensating with carbohydrate intake due to appetite changes or specifically in preparation for participation in a stressful or challenging event. High stress loads can lead to impaired executive performance, and participants under increased stress may have been impaired in their ability to plan appropriately, prepare for, and manage, attendance for participation in the study, resulting in poor diabetes management during participation including "cutting corners" in dietary management leading to elevated BGL in the short-term.

The results of the present study support the assertion that internal psychological mechanisms such as perceived stress and self-efficacy have a role in mediating health behaviours and can have an immediate impact on diabetes-related clinical outcomes. According to Ahola and Groop [98], poorly valenced internal psychological mechanisms are among the most widely recognised barriers to effective self-management in diabetes. Coping self-efficacy involves an individual believing that they have the personal ability to maintain control, and find solutions to presented challenges. In the face of poor self-efficacy, individuals may lack sufficient motivation and empowerment to drive the behaviours required to meet the demands of the challenges they face. In type 1 diabetes, poor disease-related behavioural choices associated with feelings of stress and disempowerment, for whatever reason, can have serious consequences for both immediate health and longevity. Increased levels of personally perceived stress, combined with low levels of coping self-efficacy in type 1 diabetes appears to carry a corresponding and immediate cost to metabolic control.

H_2: L-T Metabolic Control Predicted by Coping Self-Efficacy, and Specific Behavioural and Cognitive Coping Strategies

Hypothesis two that long-term metabolic control would be predicted by coping self-efficacy, and the specific behavioural and cognitive coping strategies used to manage challenges was also supported. The results showed that long-term metabolic control is predicted by coping self-efficacy and by the characteristic use of a combination of coping behaviours involving planful problem solving, self-control, and social affiliation, and the positive cognitive reappraisal of challenges when they are faced. The regression model and associated correlations showed clearly that HbA1c levels over the three years preceding participation in the study were lower in participants who had higher levels of coping self-efficacy and made greater use of these

positive coping strategies. This result again supports the literature that argues clinical outcomes are associated with feelings and beliefs about control and disease predictability [3, 66].

The regression model showed that no single coping strategy contributed uniquely to the model to a statistically significant degree however, all predictors had either a strong or a high-moderate correlation to long-term metabolic control. This strong relationship without significant unique contributions to the model suggests a large overlap between the predictors and proposes that rather than individual coping strategies providing significant influence over clinical outcomes, it is the combination of self-efficacy, and positive behavioural and cognitive strategies that creates the personal circumstances that produce improved diabetes care outcomes. This appears sound given the identified predictors that were entered into the final five-predictor model.

Coping self-efficacy appears to be a foundational requirement to both short and long-term metabolic control. Krichbaum et al., [104] found a clear relationship between coping self-efficacy and improved outcomes in type 1 diabetes and according to Hanna et al. [102], the successful navigation of the challenge of long-term metabolic control in type 1 diabetes requires coping self-efficacy independent of other skills. Grey et al. [101] support this position, finding that coping skills training improved metabolic control in type 1 diabetes, while other clinical mechanisms such as intensifying treatment in the absence of psychosocial skills such as efficacy and coping strategies, could be counterproductive.

Poor glycaemic control is more prevalent than optimal control among patients with diabetes, and Plack et al. [95] argue that it is psychobehavioural inadequacies such as poor coping strategies that are the most significant factor in determining successful clinical outcomes. While no individual predictor made a statistically significant unique contribution to the prediction of long-term metabolic control, planful problem solving had the strongest correlation and made the largest unique predictive contribution to the model. Planful problem solving involves engaging in behaviours that are thought through, planned in advance, and based on previous experiences in which similar challenges were successfully overcome [22]. That planful problem solving would contribute to the prediction of long-term metabolic control is not surprising. The ability

to plan and then take action allows for potential challenges to be addressed in the planning stages and contingencies can be put in place to manage various eventualities when they arise. Moreover, the processes involved in planful problem solving are representative of high level executive functions. There is evidence that impaired executive functions are associated with type 1 diabetes [115-119] and with poorer metabolic control in those with the disease [120, 121].

Self-controlling coping behaviour strategies, similar to planful problem solving, involve contemplative action in which an individual acts in a rational, considered manner after careful deliberation of their options. According to Folkman and Lazarus [22], self-controlling behaviours are characterised by statements such as "I tried not to act too hastily or follow my first hunch" (WOCQ, Q: 35), "I tried not to burn my bridges, but leave things somewhat open (WOCQ, Q: 10)", and "I thought about how a person I admire would handle this situation and used it as a model" (WOCQ, Q: 63). Together planful problem solving and self-controlling coping result in rational, deliberate, and flexible behaviours that are based on sound objectives and sound evidence from the previous experiences of both self and others. As with planful problem solving, self-controlling behaviours are reliant on higher-order executive functions such as inhibition, and being able to apply existing knowledge to new situations in order to create solutions. Impairments in these areas of executive function have been identified in type 1 diabetes cohorts [116, 117, 122-124], and are known to be associated with reduced diabetes self-care behaviours and poorer clinical outcomes including elevated HbA1c [116, 118, 120, 125].

Planful problem solving and self-controlling coping both include tendencies to obtain advice or guidance (whether verbal or through observations) from others who have successfully navigated similar challenges. It comes as little surprise then that these two coping strategies are included in a predictive model alongside seeking social support as a third coping behaviour. As the name suggests, seeking social support is characterised by behaviours that engage social affiliation as a means of coping with challenge [22]. This engagement with others can take the form of either seeking advice and guidance from others, seeking help from others who are in a position of authority or who are better placed to resolve the issue (including seeking professional assistance), or it may involve seeking or accepting sympathy, support, or comfort in others such as intimate partners, family, friends, or support groups.

That seeking social support is a predictor of long-term metabolic control supports the existing literature that shows social factors such as intimate relationships, mediate health and wellbeing outcomes in type 1 diabetes. Stephens et al. [74] found that intimate spouses exerted significant influence over self-care behaviours such as dietary adherence. Moreover, the study by Stephens et al. [74] found that positive social encouragement was associated with better dietary adherence than negative social actions such as warning about complications risk. In a prospective study of spousal influence on quality-of-life and metabolic control in adults with insulin-treated diabetes, Trief et al. [75] found marriage quality prospectively predicted diabetes-related quality-of-life. These studies have shown evidence that quality social supports such as intimate relationships provide psychosocial support, encouragement, motivation, and external pressure to conform to disease management and self-care requirements. In turn, these factors exert significant protective power over the deleterious sequelae of type 1 diabetes [74, 75]. However, Trief and colleagues [75] found that marriage quality alone did not prospectively predict metabolic control. This supports the current results that show it is the combination of variables that predicted long-term metabolic control rather than any single dimension.

As three guiding behavioural principles for coping in the face of challenges; planful problem solving, self-controlling, and seeking social support offer strong and positive direction. The results show clearly that all three are significantly correlated to long-term metabolic control in type 1 diabetes. The characteristics of each also show considerable overlap in areas such as engaging help or advice from others or modelling the historically successful actions of others; and in the way in which all three strategies involve positive action that seeks resolution in a rational, measured, and flexible manner. It is therefore not surprising that no single strategy provided a significant unique contribution to the model. Much of type 1 diabetes management is self-directed and involves personal action on the part of the patient. Planful problem solving as a coping strategy involves characteristics that are the most directed towards immediate resolution and therefore, it is perhaps logical that this strategy, though not reaching individual significance, provided the greatest unique contribution to the model at 11.63% of the total variance explained (total variance explained by the model = 51.50%; adjusted for small sample size).

The final predictor in the model was positive reappraisal. Positive reappraisal is essentially a cognitive coping strategy based on the principals of positive cognitive reappraisal. According to Folkman and Lazarus [22] positive reappraisal involves cognitively reframing challenging experiences so that they are viewed in a more positive light. The positive reappraisal items in the WOCQ include statements such as "I changed or grew as person in a good way" (WOCQ, Q: 23); "I was inspired to do something creative" (WOCQ, Q: 20); "I came out of the experience better than when I went in" (WOCQ, Q: 30); and, "I rediscovered what was important in life" (WOCQ, Q: 38). The ability to frame challenges in a way that allows the individual to take something positive from the experience is a very beneficial coping strategy and when combined with strong coping self-efficacy, and positive behavioural strategies such as planful problem solving, self-control, and social affiliation, provides a powerful set of coping resources even in the face of significant challenge. The strength of this model and the associations between individual predictors and long-term metabolic control support the extant literature and add further weight to the argument for improved psychoeducation and psychosocial support mechanisms in type 1 diabetes care.

Clinical Considerations

The predictive power of the model supports the argument that diabetes patients' health behaviours are intimately entwined with their illness beliefs, attitudes, self-efficacy, locus of control, and the underlying schemas about their disease that underscore these psychophenomena [2]. The positive that comes from these results is that this model shows a clear relationship between specific positive coping strategies and improved metabolic control. Moreover, the specific behaviours and cognitive coping strategies identified have been successfully taught to patients within cognitive-behavioural frameworks in mental health and trauma environments and therefore, there is potential to help patients with type 1 diabetes to develop these skills. To the extent that short-term metabolic control may be mediated by stress, stress management psychoeducation and skills development (EG: breathing, visualisation, or mindfulness-based stress reduction) may provide the personal resources to assist with short-term metabolic control.

With as many as 25% of adults with type 1 diabetes having chronically poor glycaemic control [96], and the continued high rates of severe disability and early mortality from diabetes complications despite advances in diabetes management and

knowledge of complications prevention [94, 111-114]; the identification and implementation of effective programs to combat poor metabolic control is essential. These results support the existing calls for the inclusion of psychosocial skills training in the raft of educational topics already provided to patients with type 1 diabetes [96].

Limitations

As with the first study reported in this chapter, self-report data are known to create a moderated response set [55] and it may be that reported stress and coping characteristics are poorer than indicated. Short-term BGL may be influenced by a variety of factors other than stress and coping including time of day, food intake and/or exercise prior to the test, and recent insulin dosage. Longer-term records of HbA1c results were difficult to obtain from all participants and therefore the three year HbA1c data used are based on a relatively small sample size. Adjusted R squared was used to assess the regression models in order to account for the small sample size.

Conclusion

These results show that psychosocial dimensions have clear consequences for metabolic control in type 1 diabetes. Increased personal stress and reduced coping self-efficacy is correlated to and predictive of poorer short-term metabolic control. This was observed in the present study by the relationship between participants' average BGL during participation in the study and their self-reported levels of personal stress and perceived ability to cope. Modelling these relationships further highlighted that between the two predictors, it is stress more than coping self-efficacy that provides the greatest unique contribution to the prediction of short-term metabolic control. The reasons for an increased level of personal stress is likely to be heterogeneous and evanescent however, the impact on short-term BGL is clear. These results support the teaching of stress management skills to patients with type 1 diabetes as a core diabetes self-management practice. Numerous techniques can be employed for this purpose allowing for techniques to be selected based on patient preference. This is an important consideration as patient choice in treatment options has been shown to increase the likelihood of patient adherence [126-129].

When it comes to long-term metabolic control, the results show that coping self-efficacy and specific positive coping strategies predict outcomes. The results show that higher levels of coping self-efficacy combined with the use of positive coping strategies

that engage planful problem solving, self-control, social affiliation, and positive cognitive reappraisal have a beneficial impact on long-term metabolic control. Together these coping skills provide a strong foundation for establishing a sense of choice, personal control, stability, and predictability over one's circumstances – factors that have all been linked to improved outcomes in diabetes. Moreover, these coping mechanisms are strategies and skills that can be developed in patients and therefore, increased focus on teaching these psychosocial dimensions to patients with type 1 diabetes should be seen as a frontline diabetes care priority alongside existing care priorities such as insulin therapy, diet, exercise, and the care of peripheral physiology such as eyes, feet, kidneys, and the cardiovascular system. Ultimately, these findings highlight the importance of adequate psychological support and psychoeducation in diabetes care. The results of this study present a positive opportunity for informing clinical practice, diabetes management, and for improving metabolic control and reducing the known associated complications risk.

CHAPTER THREE: PSYCHOLOGICAL CHARACTERISTICS OF TYPE 1 DIABETES

Chapter Abstract

Psychopathology in type 1 diabetes is somewhat ubiquitous. The most prevalent mental health pathologies appear to be eating disorders, alcohol and substance use disorders, depression disorders, and anxiety disorders. This chapter investigates depression and anxiety (affective disorders) in type 1 diabetes. Results are presented in four separate studies (study 3-6). The first two studies describe the comparative prevalence of anxiety, depression, and comorbid anxiety-depression in a community sample of child (study 3), and adult (study 4) participants with type 1 diabetes compared to age and sex balanced no-type 1 diabetes controls. The third study (study 5) explores the comparative relationship between disordered affect and dimensions of stress and coping in adults from the same cohort. The final study of the chapter (study 6) investigates the relationship between disordered affect and diabetes-specific clinical factors such as short and long-term metabolic control, age of disease onset, duration of illness, experiences of severe hypoglycaemia, and diabetes-related complications. The results of the first two studies show that affective disorders are significantly more prevalent in both children and adults with type 1 diabetes compared to no-type 1 diabetes controls. Study three indicated that stress and coping relate to anxiety and depression differently in individuals with type 1 diabetes compared to those without the condition suggesting that disordered affect in type 1 diabetes may differ aetiologically. The final study indicated that affective disorders influence both metabolic control and complications risk in type 1 diabetes. Participants with an affective disorder were more than twice as likely to also have diabetes-related complications. Diabetes-specific clinical factors significantly predicted affective disorders in participants. Together the results of chapter three indicate that type 1 diabetes and disordered affect are strongly associated; that disordered affect has a deleterious influence on diabetes control and clinical outcomes, and; that the aetiological nature of affective disorders in type 1 diabetes may differ to that of the no-type 1 diabetes population.

Aims and Hypotheses of Studies Presented in Chapter Three

Table 3.1. *Aims and Hypotheses of Studies Presented in Chapter Three.*

Study #	Aims	Hypotheses	Hypothesis Supported
3	To assess and differentiate the levels of disordered affect in children with type 1 diabetes and to compare these results to their healthy peers.	3.1. Disordered affect would be more prevalent in participants with type 1 diabetes than controls at both full-syndrome (FS) and subthreshold (St) levels;	Yes
		3.2. When differentiated by type, anxiety would be more prevalent than depression in participants with type 1 diabetes.	Yes
4	To quantify and differentiate the prevalence and character of affective disorders in adults with type 1 diabetes compared to adults without type 1 diabetes	4.1. Compared to no-type 1 diabetes controls, participants with type 1 diabetes would have a higher prevalence of affective disorders;	Yes
		4.2. Anxiety would be more prevalent than depression in the participants with type 1 diabetes.	Yes
5	To assess the relationship between dimensions of stress and coping, alcohol and substance abuse, and affective disorders in participants with type 1 diabetes compared to no-type 1 diabetes participants.	5.1. Participants with type 1 diabetes would have a higher prevalence of clinically defined alcohol and substance abuse than participants with no-type 1 diabetes;	No
		5.2. Disordered affect would correlate differently with dimensions of stress and coping, and that alcohol and substance abuse would correlate differently with both disordered affect and dimensions of stress and coping, in participants with type 1 diabetes compared to participants with no-type 1 diabetes;	Yes
		5.3. That there would be a difference in the predictive characteristics of dimensions of stress and coping for both affective disorders and alcohol and substance abuse, between the type 1 diabetes and no-type 1 diabetes groups.	Yes
6	a. To evaluate the role of clinical and aetiological factors in the risk of anxiety and depression in adults with type 1 diabetes;	6.1. That age of onset, duration of illness, a history of severe hypoglycaemic events, long-term metabolic control, and the presence of complications predict the risk of affective disorder in adults with type 1 diabetes;	Yes
	b. To evaluate the relationship between affective disorders, and metabolic control and complications risk in adults with type 1 diabetes.	6.2. That short and long-term metabolic control would be poorer in participants with an affective disorder compared to participants without;	Partially
		6.3. That complications would be more prevalent in participants with disordered affect than in participants without.	Partially

Study 3: Differentiating Disordered Affect in Children and Adolescents with Type 1 Diabetes

The data presented in this study has been published:

Chapter and study #	Details of publication(s) on which study is based	Nature and extent of the intellectual input of each author, including the candidate
3-3	**Sinnamon, G. C. B.,** Caltabiano, M., & Baune, B. T. (2013). Differentiating Disordered Affect in Children and Adolescents with Type 1 Diabetes. *Journal of Affective Disorders, 147*(1-3): 51-58.	**Sinnamon** developed the research question, collected and analysed the data, and wrote the manuscript. Caltabiano and Baune advised on design, data collection, data analysis, and manuscript style and content. **Sinnamon** revised the manuscript with input from Caltabiano and Baune. **Sinnamon** produced the figures and tables.

S3: Abstract

Background: There is evidence for increased risk of affective disorders (AD) in adults with type 1 diabetes however, the prevalence and characteristics of AD in young people with the condition is unclear. Comorbid AD in type 1 diabetes is associated with deleterious self-management, sub-optimal clinical indicators, reduced quality-of-life, poorer physical health, increased complications, increased high risk behaviours in adolescence and young adulthood, and earlier mortality. The present study investigated the prevalence and character of AD in young people with type 1 diabetes.

Methods: The self-report PH-PANAS-C was employed in a cross-sectional, case-control design to identify and differentiate full-syndrome (FS) and subthreshold (St) levels of AD in 53 participants with type 1 diabetes (*M* age= 12.4 yrs; duration of illness *M*= 6.4yrs) and 54 age-balanced controls (*M* age= 12.7yrs; *N*= 107, 6-18yrs, *M* age= 12.5yrs).
Results: Case participants reported greater AD than controls. When differentiated, only anxiety was significantly more prevalent. Case participants reported less positive affect, and greater negative affect and autonomic arousal. Further, 1:3 case participants presented with St symptoms of AD.
Limitations: Self-report measures are known to produce moderated responses therefore symptoms may be more severe than reported. There has been some suggestion that responses to somatic items in the PH-PANAS-C may relate to diabetes-specific states rather than affect-related symptoms however, recent evidence has refuted this argument.

Conclusions: AD, particularly anxiety, represents a significant clinical concern in young people with type 1 diabetes both as a disorder in its own right and as a major impediment to primary care and management of the diabetes. The significant dominance of anxiety-related symptoms and prevalence of subthreshold presentation warrant further investigation.

Keywords: anxiety; depression; affective disorders; diabetes mellitus, type 1; comorbidity; Tripartite Model

S3: Introduction

Type 1 diabetes is a serious chronic autoimmune condition in which specialist care and rigorous self-management practices are essential to aide in the prevention of acute and chronic complications and reduce the risk of premature mortality [114]. The condition is associated with an increased risk of affective disorders (AD) in adults [17, 130]. AD in diabetes are, in turn, associated with reductions in self-care behaviours, significantly poorer clinical outcomes, a reduced quality-of-life, earlier and more severe onset of diabetes-related complications, and earlier mortality [130-134]. This relationship between disordered affect and type 1 diabetes has been contemplated for more than three Centuries, with Thomas Willis stating in the middle of the Seventeenth Century that both ".... nervous system juice [anxiety / worry / distress] and prolonged sorrow [depression] are important aetiological factors in diabetes" [135].

While the onset of type 1 diabetes may occur at any age, it is predominantly a condition with paediatric onset. However, the prevalence and characteristics of psychological impairment in children with type 1 diabetes are not well understood. The lack of knowledge concerning rates and characteristics of disordered affect in young people with type 1 diabetes presents a potentially significant shortcoming in treatment capacity as AD such as anxiety and depression are linked to poor outcomes right across the biopsychosocial spectrum.

Several depression symptoms are known to be associated with significant reductions in metabolic control [136], with symptoms such as lassitude, anhedonia, disordered eating, and sleep hygiene impacting on motivation and capacity to maintain important self-care practices. Similarly characteristics of depression such as impaired cognition can lead to mistakes and omissions in monitoring, treatment, and medication protocols, and ultimately a significantly increased health risk.

Heightened anxiety in children with type 1 diabetes also leads to poorer quality-of-life and physical health outcomes. Anxiety is associated with increased fear of diabetes-related events such as nocturnal hypoglycaemia or complications, and with poorer disease management such as deceptive or obsessive self-care and blood glucose monitoring behaviour [111, 130, 132, 137, 138]. Anxiety may also lead to distress specifically associated with individual elements of the care regimen such as insulin injections or finger pricks for blood glucose monitoring [139].

Biologically, changes in glucocorticoid levels, monoamine regulation, autonomic function, immunoregulation, and cognitive processing associated with anxiety and depression, have been associated with reduced capacity to feel blood glucose changes (hypoglycaemia risk), increased risk for cardiovascular and cerebrovascular events, impaired vision, balance and co-ordination leading to increased accident risk (a particular concern for adults and older adolescents who may be more independent and driving or otherwise self-managing transportation), and significant impairment in capacity for learning, memory, and general brain development [13, 140-145].

The general consequences of disordered affect in children and adolescents include reduced quality-of-life and significantly increased risk taking including high levels of illicit drug use, alcohol consumption, tobacco use and potentially dangerous physical and sexual behaviours [146]. While there is a noticeable dearth of literature on the topic specific to children and adolescents with type 1 diabetes [71]; the available literature does suggest that youth with type 1 diabetes show both low levels of quality-of-life [147-149] and increased levels of high risk behaviour [67-69, 71, 150]. For example, recent research has shown that adolescents and young adults with type 1 diabetes engage in illicit drug use at levels significantly higher than their peers [67, 69]. Lee and colleagues [67] found that 80% of adolescent and 72% of young adult respondents with type 1 diabetes in Australia reported using illicit drugs recreationally. This is well above the 30% level of recreational drug use reported by their peers [151]. Given the strong links between disordered affect, poor quality-of-life, and high risk behaviours, these findings offer some additional prima facie evidence of increased disordered affect in young people with type 1 diabetes.

Given the added impress of psychological factors on the developing individual with type 1 diabetes, it is important that the extent to which these factors are represented within young people living with the disease, and their presentation characteristics are elucidated. The current study aimed to assess and differentiate the levels of disordered affect in children with type 1 diabetes and to compare these results to their healthy peers. It was hypothesised that disordered affect would be more prevalent in participants with type 1 diabetes than controls at both full-syndrome (FS) and subthreshold (St) levels, and that when differentiated by type, anxiety would be more prevalent than depression in participants with type 1 diabetes.

S3: Results

Descriptive statistics of participants and demographic differences between groups are reported in Table 1.2. Family Inventory of Life Events results showed no difference of recent experiences of stressful life events between the type 1 diabetes case (*M*= 49.69 ±10.17) and no-type 1 diabetes control (*M*= 50.30 ±9.82) groups (*t*(105)= .314, *p*= .754).

Disordered Affect

The results of the PH-PANAS-C showed good to excellent internal reliability for the three factors (Cronbach's α PA= .92, NA= .85, PH= .87). The type 1 diabetes group had a greater prevalence of overall disordered affect and a higher prevalence of differentiated anxiety and mixed anxiety-depression at both FS and St levels. The type 1 diabetes group also had a higher prevalence of St depression however, the control group had a marginally higher prevalence of FS depression. Figure 3.1 shows the prevalence of disordered affect for participants in each group, while Figure 3.2 shows the prevalence of disordered affect differentiated into anxiety, depression and mixed anxiety-depression for each group.

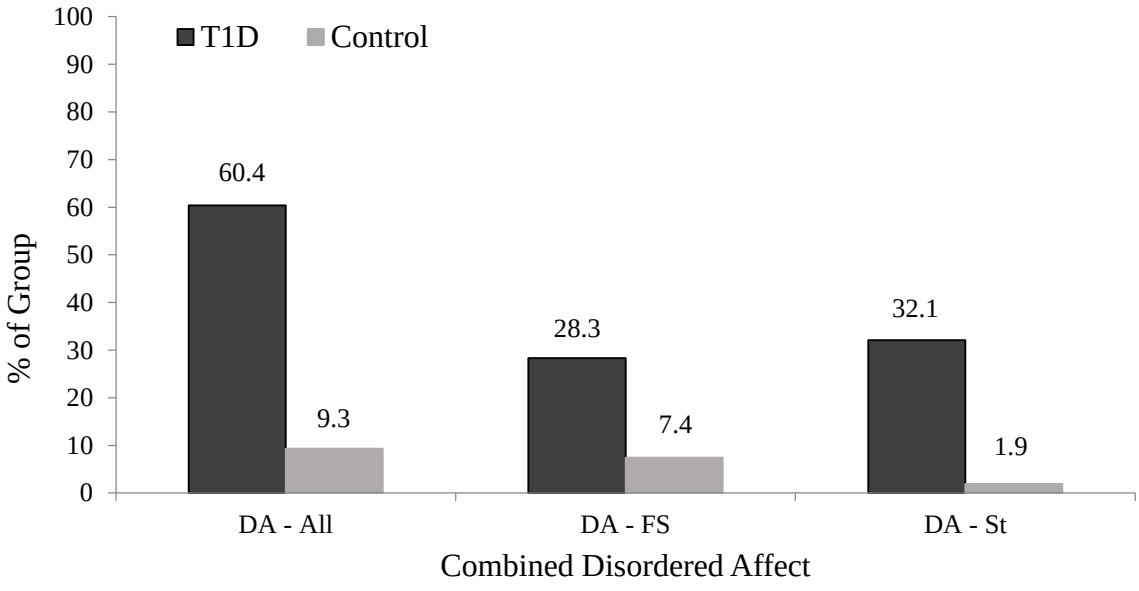

Figure 3.1. Percentage of participants in each group with undifferentiated disordered affect in total and categorized by full-syndrome and subthreshold symptom severity.

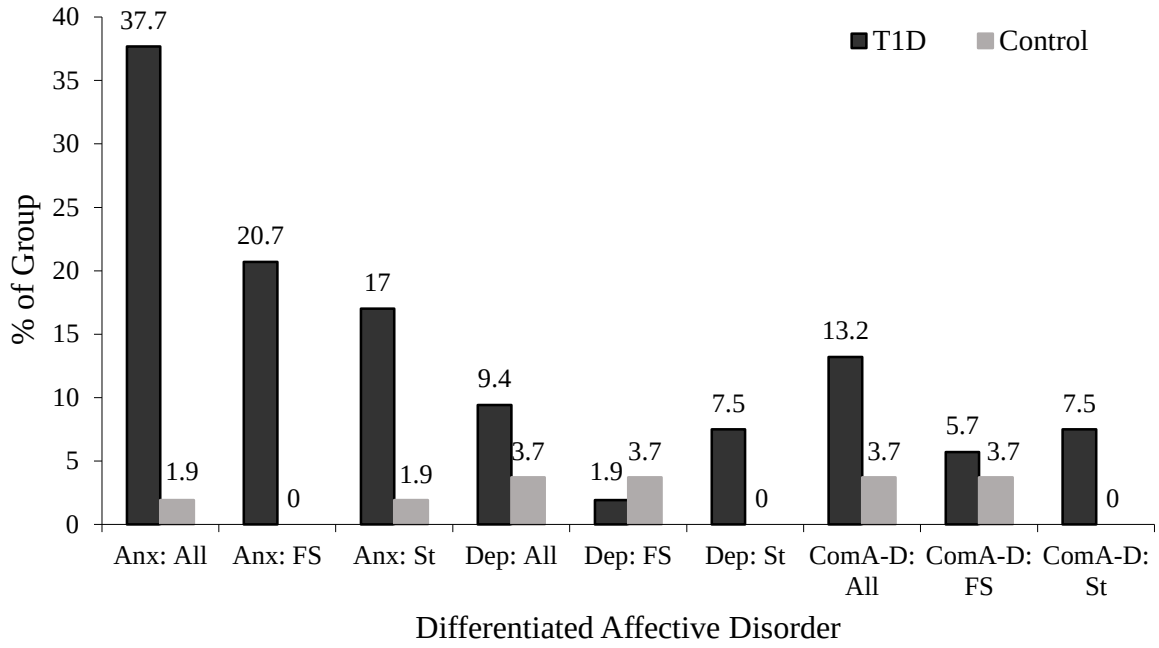

Figure 3.2. Percent of participants in each group with disordered affect differentiated into anxiety, depression and mixed anxiety-depression in total and at full-syndrome and subthreshold levels.

Chi-Square analysis was used to compare the levels of undifferentiated and differentiated disordered affect at both FS and St levels. Participants with type 1 diabetes had a significantly greater prevalence of undifferentiated disordered affect at both FS and St levels. When differentiated, only differences between the prevalence rates of FS and St anxiety disorder reached statistical significance (FS, 20.7% vs 0%, χ^2 [continuity correction]= 10.343, $p < .001$; St, 17% vs 1.9%, χ^2 [continuity correction]= 5.551, $p = .008$). All results are shown in Table 3.2.

Table 3.2. *Chi-Square Tests of Undifferentiated and Differentiated Disordered Affect at Full-Syndrome and Subthreshold Levels.*

Condition	Symptom Level	T1D (*N*=53)	No-T1D (*N*=54)	χ^2	*p*
		n (%)	*n* (%)		
Undifferentiated Disordered Affect	Total	32 (60.40)	5 (9.30)	28.678***	<.001
	FS	15 (28.30)	4 7.40)	6.629**	.005
	St*	17 (32.10)	1 (1.9)	15.368***	<.001
Anxiety Disorder	Total	20 (37.70)	1 (1.90)	19.619***	<.001
	FS	11 (20.70)	0 (0)	10.343***	<.001
	St*	9 (17.0)	1 (1.90)	5.551**	.008
Depression	Total	5 (9.40)	2 (3.70)	.652	.270
	FS	1 (1.90)	2 (3.70)	.000	1.000
	St*	4 (7.50)	0 (0)	2.396	.057
Mixed Anx-Dep	Total	7 (13.20)	2 (3.70)	2.024	.093
	FS	3 (5.70)	2 (3.70)	.000	.678
	St*	4 (7.50)	0 (0)	2.396	.057

Notes: St= subthreshold, FS= full-syndrome, χ^2 statistic shown is calculated with continuity correction for a 2x2 table, * Subthreshold symptom levels calculated as at least two factors at threshold and the third factor score within 10% of full-syndrome cut-off; ** Significant at $\alpha < .01$; *** Significant at $\alpha < .001$.

Symptom Characteristics and Severity

Between groups multivariate ANOVA of mean PA, NA, and PH scores was performed. Sex was added as a covariate to control for the age differences between the two groups. Parental personal perceptions of stress (RISCI: Stress) were included as a second covariate to control for the potential influence of parental stress on child affect. Results revealed a significant variance between the case and control group participants (Wilks' Lambda= .987, $F(3, 104) = 17.797$, $p = <.001$, $\eta_p^2 = .440$). Tests of between-subjects effects revealed significant differences between the groups across all three factors (Table 3.3).

Table 3.3. *Group Mean, Standard Deviation and Results of Between-Groups ANOVA Controlling for Sex Differences and Child-Related Parental Stress of Group PH-PANAS-C Subfactor Scores.*

Measure	Subfactors	No T1D (*n*=54)		T1D (*n*=53)		ANOVA (*df*= 1, 106)		
		M	*SD*	*M*	*SD*	*F*	*p*	η_p^2

PH-PANAS-C** (Child Self-Report)	PA / 75	56.07	12.99	44.70	10.78	12.748	.001*	.154
	NA / 75	23.37	8.29	32.55	7.80	18.922	<.001*	.213
	PH / 90	28.17	8.46	43.41	9.08	47.609	<.001*	.405

Notes: * Result is significant after Bonferroni correction applied for multiple analysis α= .017 (.05/3); ** PH-PANAS-C = Physiological Hyperarousal and Positive and Negative Affect Schedule for Children - child self-report of affect and physical symptoms of anxiety, depression, and mixed anxiety-depression.

S3: Discussion

The aim of the present study was to assess the differentiated incidence of affective disorders in children and adolescents with type 1 diabetes compared to non-type 1 diabetes controls. Using a cross-sectional, case-control design we identified that young people with type 1 diabetes have a higher prevalence of disordered affect at both FS and St levels than their peers. Given the plethora of risks associated with living with type 1 diabetes, the constant vigil required to manage the disease, and the neuropsychological impact type 1 diabetes may have, these findings are not unexpected.

Of primary interest is the finding that it is anxiety rather than depression that appears to be most represented in young people with type 1 diabetes. This study is one of the first to identify the differentiated nature of affective disorder in young people with type 1 diabetes and in doing so it is also one of the first to elucidate the extent to which anxiety may be a factor in the disease management and quality-of-life challenges faced by sufferers. With more than 60% of young people in the study showing levels of anxiety sufficient to potentially impair health care behaviours and quality-of-life, these results support the call for increased formal psychological care and support for young people with type 1 diabetes [(62)].

This is an important finding as psychological characteristics are important factors in type 1 diabetes management and control. The physiological responses to psychological stress are directly linked to hormonal and nervous system signals that can alter insulin sensitivity, demand, and secretion, and modify immune system regulation [(152-156)]. In this way the presence of psychological distress adds significant burden to managing metabolic control, placing additional challenges on the already arduous efforts to optimize HbA1c levels, reduce glucose variability, and proffer a quality-of-life with effective reductions in complications risk [(97)]. These factors add to the already significant burden that psychological impairment can place on fundamental physical,

social, emotional, behavioural and cognitive development throughout childhood and adolescence.

H_1: Increased Prevalence of Disordered Affect in Young People with Type 1 Diabetes

As predicted more participants with type 1 diabetes presented with disordered affect than controls. Over 60% of case participants were identified with symptoms of disordered affect compared to just 9% of controls. When defined by either FS or St threshold symptomology, the results showed that almost four times as many case participants presented with FS affective disorder than controls (28.3% vs 7.4%). This represents a major health concern as comorbid affective disorder in type 1 diabetes is associated with significantly elevated levels of disability and early mortality [157]. The data suggests that almost one third of young people with type 1 diabetes may be experiencing clinical levels of affective disorder at any given time and supports the suggestion that psychological screening and referral should be a part of clinical care and management procedures for type 1 diabetes [62, 158-160].

While the level of FS affective disorders is a significant issue, the level of St disordered affect is also of concern. As St disordered affect may still influence self-care behaviours and physiological regulation, they are therefore important clinical considerations. The results show that a further one third (32.1%) of participants with type 1 diabetes were experiencing a level of disordered affect severe enough to cause increased distress and changes to self-care motivation and behaviour but not sufficient for a diagnosis of either anxiety or depression. This group may remain undetected in a general psychological screening process unless St symptoms are specifically targeted with appropriately sensitive screening tools.

Early identification of St symptoms is recognised as important for early intervention aimed at preventing progression to FS disorder [161]. This finding highlights the importance of clinician awareness of the potential presence of psychological impairment when attending young people with type 1 diabetes. Further, St symptoms in childhood are associated with significant risk for the development of FS psychopathology in later life [161].

H_2: Anxiety most Prevalent Affective Disorder in Young People with Type 1 Diabetes

The second hypothesis, that anxiety would be more prevalent than depression in the participants with type 1 diabetes was also supported. Analysis showed that only differences in the rates of anxiety were statistically significant between groups with more case participants experiencing anxiety at both FS and St levels than their non-type 1 diabetes peers. While mixed anxiety-depression was also higher in the case group, it did not reach statistical significance. Interestingly, FS depression was marginally higher in the non-type 1 diabetes controls than it was in the type 1 diabetes group.

Anxiety in type 1 diabetes is associated with a range of behaviours associated with increased health risk such as misuse of medications, high risk behaviours (eg, illicit drug use), and less interaction with, and disclosure to, diabetes specialists and other health care professionals [162, 163]. Further, anxiety is associated with poorer health outcomes including eating disorders, sexual dysfunction, cardiovascular disease, and increased hyperglycaemia [111, 164-166]. These results are supported by a number of Quality-of-life studies that have consistently identified anxiety characteristics in type 1 diabetes such as increased worry, catastrophising, diabetes distress, and phobic anxiety directed at specific factors such as injections, blood tests, and hypoglycaemia [9, 139, 159, 167, 168].

Clinical Implications

While further investigation is necessary, this result has important implications for the clinical management of type 1 diabetes in children and adolescents. Disease burden in the face of chronic illness is well known as a contributor to depression and anxiety in sufferers. In the case of diabetes however, the psychological consequences of disease burden are further exacerbated by physiological factors that may increase the risk of affective disorders. Even in the presence of chronic health problems worry can be a constructive problem-solving tool, creating the motivation to take action and seek a resolution however, when no solution is available the search for one can lead to feelings of failure, fear, and hopelessness which, in turn can lead to increased worry, distress, and catastrophising about the future [169]. In type 1 diabetes this conundrum is exacerbated when the anticipatory spectre of serious complications and early mortality risk is added to a child's awareness as they develop [170].

Furthermore, anxiety often creates a craving for control resulting in either obsessive or avoidance behaviours that may be general (GAD) or specific (phobia), leading to repetitive fears about a potential event (nocturnal hypoglycaemia, kidney disease) [170, 171]. This "over thinking" may lead to a range of maladaptive behavioural responses ranging from obsessive behaviours aimed at reducing the likelihood of the event to avoidance and denial as dissociative defence mechanisms [88].

Anxiety-related behaviours may be either disease-specific or generic and may include poor adherence to care plans, non-attendance at clinic visits or lack of co-operation during clinic visits, rejection of care assistance, obsessive care behaviours (such as over testing blood glucose levels), rebellion against dietary guidelines, self-harm, oppositional defiance, and high risk behaviours such as illicit drug use, alcohol and tobacco use, thrill seeking behaviours, and excessive and/or unprotected sexual activity [67-69, 71, 97, 111, 132, 137, 150, 155, 172].

Anxiety is also associated with potentially deadly physiological changes, many of which are also associated with type 1 diabetes. The comorbid presentation of these two conditions therefore represents a significantly amplified health risk. For example, both type 1 diabetes [173, 174] and anxiety [175, 176] are independently associated with autonomic dysregulation. This is linked to an amplification of the parasympathetic nervous system and a reduced ability to deal physiologically with intense emotional experience. Some of the associated underlying pathology includes basal hyperreactivity of corticotrophin releasing factor (CRF), hypothalamic-pituitary-adrenal (HPA) axis dysregulation, and hypercortisolaemia [177]. The impact on cardiovascular health is a major concern given the disproportionate mortality of individuals with type 1 diabetes from cardiovascular disease [114, 131, 178]. Recent figures show that 60% of people with diabetes in Australia suffer from some form of diagnosed cardiovascular disease [179, 180].

Additionally, while there is a significant base of literature dealing with the increased prevalence of depression in diabetes, there is a dearth of literature that addresses anxiety in the context of clinical presentation. Depression has been shown to be a significant issue in diabetes, particularly in type 2 diabetes where the increased prevalence can be attributed in large part to the associated obesity and inflammation that often characterises the presence of type 2 diabetes [181, 182]. This has led to depression becoming the primary focus of mental health awareness and care practices in diabetes management. This study has identified that anxiety is of potentially greater concern in

young people with type 1 diabetes than depression. It is therefore important that clinicians are made aware of the potential differences between the mental health profiles of type 1 and type 2 diabetes as well as those between adults and young people with the condition. Anecdotal evidence suggests that many clinicians are aware of the depression risk in diabetes and therefore may be predisposed towards interpreting affective malaise as depression related even when presentation points to anxiety oriented symptomology. The high rates of prescriptions for anti-depressants and the depression-focused mental health screening methods that appear to be employed most frequently within diabetes clinical environments provide additional support for this suggested bias [116, 183-187].

Limitations of the study

Self-report measures are known to create a moderated response set [55]. As such, it may be that symptoms are more severe in participants than were reported. Further, there has been some suggestion that responses to somatic items in the assessment measures may relate more to disease-specific states rather than affective disorder-specific symptoms in children with chronic illnesses [56]. In this way scores on the PH scale reported by case participants may indicate higher anxiety symptoms than are actually present. Recent research has refuted this argument [57], none-the-less it is a possible confound to results and should be considered.

Conclusion

There is little doubt that living with type 1 diabetes is a stressful experience and it is well documented that psychological stress can trigger anxiety and depression [153, 171, 188-191]. The spectre or actual presence of disease-related complications add additional stressors and therefore, children with type 1 diabetes have a confluence of factors that could account for the increased prevalence of disordered affect. In a challenging negative feedback loop young people with increased anxiety and depression are also prone to cognitive negativity bias and more severe psychological responses to trigger events, and may therefore exhibit biological stress responses to even seemingly pedestrian experiences [188-190]. These factors can all collude to produce significant impediments to successful diabetes control, reductions in complications risk, quality-of-life, and ultimately improved mortality.

These findings draw attention to two key issues: 1) the need for regular psychological screening that is sensitive enough to detect both clinical psychopathology and subthreshold indicators of distress, and can accurately differentiate anxiety and

depression in paediatric diabetes patients, and 2) the importance of psychological care as part of the diabetes management and education process. These data are an early indication of these issues and further study is required to better understand the dynamics involved.

Study 4: Anxiety and Depression Prevalence in Adults with Type 1 Diabetes

S4: Abstract

Background: Type 1 diabetes carries an increased risk for affective disorders (AD; depression and anxiety disorders). The literature is biased towards depression with few studies having systematically investigated the differentiated characteristics of anxiety and depression in the disease. AD has a significant negative impact on diabetes self-care, complications, disability, and mortality. This study quantified the prevalence and nature of AD in adults with type 1 diabetes.

Methods: Using the MINI600, depression, anxiety, and comorbid anxiety-depression disorders were clinically assessed in participants with (case; *n*=73) and without (control; *n*=107) type 1 diabetes (*N*= 180; 16–73 years).

Results: Case participants had a higher prevalence of clinical AD than controls ($p < .01$). When AD was differentiated into three broad sub-types of anxiety, depression, and comorbid anxiety-depression disorders, case participants had higher levels of all three sub-types compared to controls (anxiety $p = .01$; depression $p < .01$; anxiety-depression $p < .01$).

Limitations: As a cross-sectional study, the stability of these results over time couldn't be assessed. Control AD prevalence was above population average (25% vs ~20%). This may reflect unidentified regional variables influencing all results and this should be considered when generalizing the present results. However, group sociodemographic characteristics show higher risk factors in the controls compared to case participants that could also account for this increased prevalence (Control= lower SES $p<.004$; lower married/defacto $p<.005$).

Conclusions: Type 1 diabetes and ADs appear somewhat ubiquitous and this increased prevalence should be considered in clinical management planning and the self-care expectations placed on sufferers.

Keywords: anxiety; depression; affective disorders; diabetes mellitus, type 1; comorbidity; psychopathology.

S4: Introduction

People with type 1 diabetes are at a significantly increased risk for affective disorders (AD) [8, 16, 17, 130]. AD represent a significant impediment to chronic disease management [192, 193] and in type 1 diabetes have been associated with numerous deleterious outcomes including reductions in quality-of-life and self-care behaviours, poorer clinical measures, earlier and more severe onset of complications, and increased mortality [130, 133, 134, 180, 194, 195]. The successful management of type 1 diabetes requires a combination of primary care supervision and rigorous self-management. It is through this combination that sufferers reduce the risk of serious acute and chronic complications and prevent premature mortality [114].

In adults with type 1 diabetes, self-care practices are of particular importance as success in this process dictates, to a large degree, the ability to maintain long-term health and independence [196, 197]. Despite advances in the knowledge about complications risk factors and management practices in type 1 diabetes, sufferers consistently achieve sub-optimal metabolic control [198], and continue to experience significant levels of debilitating and life shortening complications [114, 199]. One explanation for continued suboptimal metabolic control is that as a group, individuals with type 1 diabetes have a high prevalence of psychological distress. Both depressive and anxious symptoms have been shown to have a significant impact on diabetes management, control, and prognosis [194, 196, 200]. Metabolic control, the primary predictor of complications risk in type 1 diabetes, is particularly sensitive to disordered affect [201-203].

Factors associated with depression such as loss of motivation, cognitive impairment, social withdrawal, sleep dysregulation and dietary inconsistency all collude to impair a patient's capacity to self-care and can lead to errors in medication dosage and in other essential self-moderated treatment and monitoring protocols. Depressive symptoms are associated with diabetes burnout in longer-term sufferers and has been linked to serious reductions in the quality of self-care and disease management adherence [2].

Similarly, anxiety-related factors have been shown to impact both quality-of-life and physiological wellbeing. In type 1 diabetes, increased anxiety symptoms are linked to poorer self-care behaviours, increased fear and worry about acute and long-term complications and reticence towards monitoring and treatment protocols [14, 196].

Excessive fear and worry is known to lead to a retardation of self-care behaviour and this outcome in type 1 diabetes, known as diabetes distress [204-206], is associated with poor disease self-management behaviours such as inconsistent, deceptive, or obsessional practices around diet, exercise and blood glucose monitoring [96, 207].

Ultimately, affective malady in patients with type 1 diabetes is related to changes in care practices and physiological and neuropsychological function that have a significant negative impact on diabetes outcomes. These include myriad biopsychosocial factors including reductions in general wellbeing and quality-of-life [208, 209], and impairments in the biological regulation of risk factors for acute diabetes complications such as a reduced capacity to recognise the onset of hypoglycaemia [208, 210]. Furthermore, AD are also associated with chronic and longer-term complications such as cardio- and cerebro- vascular disease [114, 211], microvascular disease impacting vital organs such as the eyes and kidneys, peripheral nerve disease [212], and cognitive impairments associated with learning, memory, executive function, and dementia risk [141, 213, 214].

While the literature shows a clear bias towards depression in diabetes, recent studies have begun to explore the prevalence and consequences of anxiety. In diabetes, anxiety studies are comparatively few in number relative to the volume of research on depression however, they suggest that anxiety may be highly prevalent and of significant clinical concern [8, 14]. The aim of the present study was to quantify and differentiate the prevalence and character of affective disorders in adults with type 1 diabetes compared to adults without type 1 diabetes using clinical diagnostic criteria as set out in the DSM-IV-TR [28], and ICD-10 [29]. It was hypothesised that compared to no-type 1 diabetes controls, participants with type 1 diabetes would have a higher prevalence of affective disorders. It was further predicted that anxiety would be more prevalent than depression in the participants with type 1 diabetes.

S4: Results

Table 3.4 shows the age and sex descriptive statistics for all participants. There were no age or sex differences between the groups (Table 3.4) however, group sociodemographic characteristics differed in three areas. The type 1 diabetes group had significantly more participants who were married or defacto (61.6% vs 39.3%, $\chi 2=$

7.839, *p*= .005), more participants who were taking medications for reasons other than diabetes or mental illness (T1D= 38.4% vs no-T1D= 15.0%, $\chi 2$= 11.633, *p*= .001), and a significantly lower number of participants from a low socioeconomic status household (17.8% vs 39.3%, $\chi 2$= 8.421, *p*= .004).

Table 3.4. *Mean Age and Sex of Participants in Each Participant Group.*

Group	Total	Male		Female	
	M Age (range)	*n (% of group)*	*M* Age (range)	*n (% of group)*	*M* Age (range)
T1D (*n*= 73)	42 (16-73)	35 (48)	41 (16-67)	38 (52)	42 (16-73)
No-T1D (*n*= 107)	38 (16-73)	45 (42)	35 (16-73)	62 (58)	29.01 (16-65)
Total (*N*= 180)	39 (16-73)	80 (44)	38 (16-73)	100 (56)	40 (16-73)

Notes: 1. No sex differences between groups (χ^2= .394, *p*= .530); 2. No age differences between groups: Total group T1D= 42 ± 15 vs no-T1D= 38 ± 13, *F*(1,178)= 2.849, *p*= .093; males, T1D= 41 ± 16 vs no-T1D= 35 ± 14, *F*(1,78)= 3.038, *p*= .085; females, T1D= 42 ± 15 vs no-T1D= 40 ± 13, *F*(1,98)= .601, *p*= .440.

Positive results for anxiety and depression were categorised into subtypes for analyses (Table 3.5).

Table 3.5. *Categorisation of Clinical Anxiety and Depressive Disorders for Analysis.*

Category Label	Category Description #
Total Disordered Affect	All participants with a current clinical anxiety or depressive disorder
Anxiety	All participants with a current anxiety disorder and without a depressive disorder
Depression	All participants with a current depressive disorder and without an anxiety disorder
Comorbid Anx-Dep	All participants with both a current clinical anxiety and depressive disorder
Total Anxiety	All participants with a current clinical anxiety disorder. Derived by combining the anxiety group and the comorbid anxiety-depression group.
Total Depression	All participants with a current clinical depressive disorder. Derived by combining the depression group and the comorbid anxiety-depression group.

Notes: # All Δ are based on DSM-IV-TR guidelines as ascertained through MINI600 clinical diagnostic interview.

Clinical Neuropsychiatric Assessment of Disordered Affect

The results of the MINI600 revealed several variations in prevalence of anxiety and depression between the case and control participants. Chi-square analysis revealed that case participants had a statistically significant greater overall prevalence of total

disordered affect than controls. When affective symptoms were differentiated into depressive disorders, anxiety disorders, and comorbid anxiety-depression disorders, analysis showed participants in the case group had a significantly higher prevalence of all three affective states (Table 3.6).

As comorbid anxiety-depression includes independent clinical levels of each condition, further analysis was undertaken to compare all anxiety and all depression between groups. The prevalence of anxiety and comorbid anxiety-depression was combined to assess total anxiety, and the prevalence of depression and comorbid anxiety-depression were combined to assess total depression. Chi-square analysis of total anxiety and total depression showed that participants with type 1 diabetes had a significantly higher prevalence of both total anxiety ($p < .001$) and total depression ($p < .001$) compared to participants without type 1 diabetes (Table 3.6).

Table 3.6. *Between-Groups Chi-Square Tests of Undifferentiated and Differentiated Disordered Affect in Type 1 and No-Type 1 Diabetes Participant Groups.*

χ^2 Between-Groups Comparison of Prevalence	T1D (*N*=73) % (*n*)	No-T1D (*N*=107) % (*n*)	χ^2 (*df*= 1) #	*p*
Undifferentiated Disordered Affect	71.2 (52)	25.2 (27)	35.440**	< .001
Anxiety only	21.9 (16)	7.5 (8)	6.632*	.010
Depression only	12.3 (9)	0.9 (1)	8.676*	.003
Comorbid Anxiety-Depression	37.00 (27)	16.8 (18)	8.365*	.004
Total Anxiety+	58.90 (43)	24.3 (26)	20.543**	< .001
Total Depression++	49.3 (36)	17.8 (19)	18.907**	< .001

Notes: # χ^2 statistic shown is calculated with continuity correction for a 2x2 table; * Sig. at $\alpha<.01$; ** Sig. at $\alpha<.001$; + Total anxiety= combination of anxiety only and comorbid anxiety-depression; ++ Total depression= combination of depression only and comorbid anxiety-depression.

Further chi-square analysis was undertaken to compare the prevalence of differentiated affect types within each participant group (Table 3.7). Results of within-groups analyses show that Comorbid anxiety-depression was more prevalent than either anxiety ($p = .001$) or depression ($p = .037$) in the type 1 diabetes group, while total anxiety was more prevalent than total depression in both groups (T1D $p=.012$; no-T1D $p < .001$).

Table 3.7. *Within-Groups Comparison of Prevalence Rates of Anxiety and Depression in the Type 1 Diabetes and No-Type 1 Diabetes Groups.*

χ^2 Within-Groups Comparison of	T1D (*N*=73)		No-T1D (*N*=107)	
Prevalence	χ^2 (*df*= 1) #	*p*	χ^2 (*df*= 1) #	*p*
Anxiety – Depression	1.606	.205	.000	1.000
Comorbid Anxiety-Depression – Anxiety	10.081**	.001	.691	.406
Comorbid Anxiety-Depression – Depression	4.351*	.037	.000	1.000
Total Anxiety+ – Total Depression++	6.346*	.012	57.743**	< .001

Notes: # χ^2 statistic shown is calculated with continuity correction for a 2x2 table; * Sig. at α<.01; ** Sig. at α<.001; + Total anxiety= combination of anxiety only and comorbid anxiety-depression; ++ Total depression= combination of depression only and comorbid anxiety-depression.

S4: Discussion

The aim of the present study was to assess the prevalence and character of disordered affect in adults with type 1 diabetes compared to their peers without the condition. Using a cross-sectional case-control design we identified that participants with type 1 diabetes had a significantly higher prevalence of anxiety and depressive disorders than participants without type 1 diabetes. This study is one of only a small number to clinically assess the differentiated prevalence of disordered affect in type 1 diabetes. In defining the prevalence of anxiety and depressive disorders at a clinical level and in highlighting the significantly high rates at which these conditions are experienced in sufferers, the study has helped to elucidate the extent to which these conditions may impact the challenges of disease management, metabolic control, quality-of-life, complications prevention, and morbidity.

With seven out of ten participants in the type 1 diabetes group presenting with clinical symptoms of a depressive and/or anxiety disorder, the results highlight the importance of the inclusion of psychological considerations in the ongoing care of sufferers. Diabetes health care professionals must take into account the high prevalence of anxiety and depression and the extent to which psychological stress can alter hormonal regulation and neural function which in turn impacts on insulin sensitivity and demand [152, 153, 156, 215, 216]. Furthermore, diabetes health care professionals must account for the psychological capacity of the individual to maintain personal responsibility for their health in the face of a disease whose course and prognosis is intimately dependent upon the success of self-management practices [154].

Type 1 diabetes under even the most ideal of circumstances has significant inherent challenges in the ongoing management of the disease. The added burden of psychological impairment amplifies these challenges by further reducing quality-of-life and complicating attempts to preserve metabolic control through hampering efforts to minimize glucose variability, maintain optimal HbA1c levels, and reduce complications risk [14, 217, 218]. This has been demonstrated in studies showing that affective disorder comorbidity in type 1 diabetes is correlated with a higher prevalence of medium to severe disability and earlier mortality [157]. These results further support the argument that psychological screening and ready access to professional mental health assistance should be an aspect of patient-focused clinical diabetes management.

These results were found despite the participants with type 1 diabetes having a higher prevalence of protective sociodemographic factors compared to the no-type 1 diabetes participants. Sociodemographic factors are known to influence the risk of mental illness. Type 1 diabetes participants had a higher percentage of the group who were either married or in a defacto relationship (61.6% vs 39.3%, p=.005), and a lower percentage of the group who were from a low socioeconomic status household (17.8% vs 39.3%, p=.004). Both of these factors are protective against the risk of mental and physical illness, and early mortality [72, 73]. Being in a committed relationship has been shown to have specific benefits to mental and physical health and wellbeing for people with diabetes [74, 219]. Given the type 1 diabetes group participants had a higher prevalence of these two economic and social protective factors, the results of the present study may be an underestimation of the true prevalence of affective disorders in the wider type 1 diabetes population.

H_1: Higher Prevalence of Affective Disorders in Type 1 Diabetes

As predicted participants with type 1 diabetes had a higher prevalence of disordered affect than participants with no-type 1 diabetes. Seventy percent of the type 1 diabetes group (71.2%) were identified as having clinical levels of disordered affect compared to 25.2 % of the no-type 1 diabetes group. The psychological burden of chronic disease is well documented and results in high rates of affective disorders and other psychopathology [17, 220, 221]. Moreover, individuals with type 1 diabetes have an increased risk burden for anxiety and depression due to disease factors that impact associated physiology such as autonomic regulation, systemic inflammation, and HPA axis function [175, 176, 211, 222].

Affective disorders in general and depression and anxiety independently, add a number of challenges to diabetes care both from the perspective of the individual's self-management capacities, and their ability and willingness to effectively engage with clinical care providers [14, 162]. The literature clearly highlights the detrimental impact of anxiety and depression on acute and long-term health and wellbeing in type 1 diabetes [192, 193], including earlier onset and more severe complications, disability, and increased mortality [130, 133, 134, 180, 194, 195].

While more investigation is necessary to further elucidate the full implications of such a high prevalence of disordered affect, these results have several important implications for the clinical management of type 1 diabetes. The psychological and physiological factors associated with affective disorders both present significant clinical implications in diabetes care [193]. Psychologically, disordered affect is associated with both alterations in conscious thought processes, as well as impairments to neurocognitive performance, both of which have a direct impact on emotion, motivation and behaviour. Physiologically, disordered affect is associated with a host of changes in areas such as autonomic function, HPA axis regulation, inflammation, and the vasculature, which increase the challenge of managing diabetes and increase the risk of a variety of complications. These complications include heart disease, stroke, peripheral vascular disease, peripheral nerve disease, macrovascular disease, and microvascular complications affecting organs such as the eyes and kidneys.

H2: Anxiety more Prevalent than Depression in Type 1 Diabetes

The second hypothesis, that anxiety would be more prevalent than depression in the participants with type 1 diabetes was also supported. Results show that six out of ten participants (58.9%) with type 1 diabetes presented to the investigators with clinical levels of an anxiety disorder compared to 24.3% of the participants without type 1 diabetes. Of the participants with type 1 diabetes who had clinical anxiety, two thirds (37% of total participants with type 1 diabetes) had anxiety comorbidly with depression while one third (21.9%) had a singular anxiety condition. These differentiated results are important as depression is generally considered a more pressing concern than anxiety and the psychological, psychiatric and psychosomatic literature concerning type 1 diabetes reflects a strong bias to that effect. More recent literature has begun to recognise anxiety characteristics as common in type 1 diabetes although the majority of studies relate to diabetes distress rather than clinically assessed anxiety disorder with

many studies clearly assessing depression and distress rather than depression and its clinical anxiety counterpart [105, 218, 223].

The literature that does deal with clinical anxiety suggests that anxiousness is both highly prevalent and related to deleterious outcomes or factors known to be associated with them [8, 204, 206]. Anxiety is associated with increased physiological hyperarousal as a result of upregulated activity in the hypothalamic-pituitary-adrenal (HPA) axis. The consequence of chronic activation of the HPA axis is ubiquitous to the outcomes found in chronic stress, the specifics of which are well documented and include increased risk for cardio- and cerebro- vascular disease as well as myriad other serious health conditions [152, 224, 225]. The results of the present study support the assertion that anxiety is highly prevalent in type 1 diabetes. Moreover, these results suggests that the severity of the anxiety being experienced by sufferers is perhaps greater than has been considered previously, and that the clinical consequences of such high levels of anxiety may be more significant than currently recognised.

The high level of anxiety identified in the present study is supported by recent research that has reported similar prevalence rates. Using the Hamilton Anxiety and Depression Scale (HADS) to assess anxiety and depression, de Ornelas Maia et al. [14], recently reported prevalence rates of 60% for anxiety and 52.4% for depression, in adult type 1 diabetes patients. These rates compare closely to the present study prevalence of 58.9% for anxiety and 49.3% for depression, and provides support for both a high rate of anxiety and a high rate of comorbid anxiety-depression in type 1 diabetes. Similarly, in a meta-analysis of 18 studies that assessed anxiety in diabetes, Grigsby et al. [16], reported a significant prevalence of anxiety in adults with type 1 diabetes. Results of the meta-analysis found a 14% prevalence rate of generalised anxiety, 27% subsyndromal symptoms of unspecified anxiety disorders, and 40% prevalence of elevated anxiety symptoms. The high prevalence of anxiety found in adults also appear to be reflected in young people with type 1 diabetes. Sinnamon et al. [8] reported a 50.9% prevalence of combined clinical and sub-clinical levels of anxiety symptoms (self-reported) in children and adolescents with the disease.

The results of the present study are supported by a number of quality-of-life and psychosocial studies that have found anxiety characteristics to be common in type 1 diabetes. Some of these include increased worry and distress (both general and diabetes-specific), negativity bias, catastrophising, and phobic anxiety directed at specific

diabetes management factors such as blood testing, complications screening, injections, and hypoglycaemia risk [168, 220, 226-228]. Further, in type 1 diabetes, anxiety is associated with several behaviours directly linked to poor health outcomes including high risk behaviours such as illicit drug and alcohol abuse, misuse of medications, poor medication and monitoring adherence, poor diet and exercise practices, reduced attendance at medical appointments, and inadequate communication and disclosure to health care professionals [67, 69, 162, 163].

Limitations of the study

As a cross-sectional study, the present project was unable to assess the stability of these results over time. Undertaking mental health research in a regional location often attracts individuals with mental health issues who feel they are unable to access services. These individuals attend research programs in the hope of obtaining insight, assistance or referral for their problems. Control group prevalence rates are above the Australian population average and this may provide an explanation.

Conclusion

While depression is presently the primary mental health focus in diabetes, the results of the present study suggests that anxiety may be a more prevalent concern in type 1 diabetes. Further, evidence suggests that anxiety may have a greater impact on glycaemic control than depression [221]. However, while the results show that anxiety is more prevalent than depression, both anxiety and depression were found to have a significant presence in individuals with type 1 diabetes. Perhaps of greater concern is that comorbid anxiety and depression were more prevalent than either condition individually. More research is needed to better understand the factors behind this finding.

Anxiety and depression manifest different motivations and behavioural outcomes however, the ultimate product of both conditions is that they result in poor self-care practices, a reduced quality-of-life, increased risk of complications and disability, and earlier mortality. The high prevalence of comorbid anxiety-depression in type 1 diabetes may increase this risk and has major implications for the management of both the patient and their health. Certainly self-care is further challenged, clinical implications are further exacerbated, health professional-patient communication is more complicated, and treatment plans more complex. More clinical research is needed to

evaluate the extent and nature of the increased risk and the implications that single and multiple mental health issues have on care practices and long-term health outcomes.

What is clear is that clinicians need to be aware of the nuances of both anxiety and depressive disorders and have access to resources that will allow accurate screening, and differential diagnosis of disordered affect. Moreover, clinicians and diabetes clinical centres, should have ready access to resources to support patients who present with these conditions. Accurate diagnoses, appropriate knowledge, and access to effective, evidence-based interventions to address disordered affect in patients with type 1 diabetes is essential.

Study 5: The Relationship between Disordered Affect and Dimensions of Stress and Coping in Type 1 Diabetes

S5: Abstract

Background: High levels of stress and maladaptive coping are associated with anxiety and depression prevalence in the general population. Whether the presence of type 1 diabetes moderates this relationship is unclear. This study investigated the relationship between affective disorders and personal perceptions of stress, coping self-efficacy, coping strategies, and alcohol and substance abuse in participants with and without type 1 diabetes.

Methods: Clinical diagnostic interview (MINI600), and self-report psychometrics were used to assess anxiety and depression, as well as experiences of stressful life events, perceptions of stress, coping self-efficacy, coping strategies, and alcohol and substance abuse status in N=180 participants with (n=73) and without (n=107) type 1 diabetes. The relational characteristics of dimensions of stress and coping, alcohol and substance abuse, and anxiety and depression were evaluated in participants with and without type 1 diabetes in order to compare relational variations between the groups.

Results: Dimensions of stress predicted affective disorders in participants with no-type 1 diabetes (p= .04) but not in the type 1 diabetes participants. The relationship between affective disorders and stress and coping differed between the two groups. In type 1 diabetes participants, only coping self-efficacy was significantly correlated to affective disorders (p=.04), while only seeking social support was related to affective disorders in the no-type 1 diabetes group (p < .01). In participants with type 1 diabetes, alcohol and substance abuse was significantly related to affective disorders (p= .04), and to the stress and coping variables of planful problem solving (p < .01), positive (cognitive) reappraisal (p= .03), seeking social support (p= .05), and recent experiences stressful life events (p= .05). Dimensions of stress and coping predicted alcohol and substance abuse in the type 1 diabetes group (p < .01), but not in the no-type 1 diabetes controls.

Conclusion: Stress and coping relate to anxiety and depression differently in individuals with type 1 diabetes compared to those without the condition suggesting that disordered affect in type 1 diabetes may differ aetiologically. Further research is needed to better understand these mechanisms.

Keywords: affective disorders; psychopathology; anxiety; depression; comorbidity; diabetes mellitus, type 1; stress; coping; life events; alcohol and substance abuse; clinical outcomes.

S5: Introduction

Research suggests that the prevalence of comorbid anxiety and depression disorders in type 1 diabetes is between two and six times higher than in otherwise healthy individuals [8, 14, 229, 230]. This is an important clinical consideration as psychological health is an important determinant of the wellbeing and physical health outcomes of sufferers [134, 207]. The increased prevalence of psychopathology in type 1 diabetes has been attributed historically to psychological disease burden [3]. Psychological disease burden refers to the deleterious consequences that arise due to the high load of stress and worry that occurs in the face of the ever-present burdens of managing type 1 diabetes and dealing with the constant spectre of acute and chronic complications, disability, and early mortality [3].

Research into quality-of-life and psychological disease burden have shown that individuals with type 1 diabetes report high levels of disease-specific stress that they attribute to the complex and unceasing vigil required to manage their disease. Sufferers report that living with a complex chronic condition like type 1 diabetes pervades every facet of their lives and impacts their own quality-of-life as well as that of family and friends [1, 58-61]. The capacity to cope with the stressors of type 1 diabetes are linked to both personal perceptions of control over the disease and ability to cope with the challenges it may present (coping self-efficacy), and the effectiveness of the cognitive and behavioural strategies used to address those challenges when they arise.

According to Shalev [80], stress and coping are important mediators of psychological wellbeing and when the capacity to deal psychologically with presenting stressors is exceeded, the worry, loss of control, and feelings of helplessness, can lead to anxiety and depression. In turn, anxiety and depression are both associated with poor levels of efficacy across cognitive, self-care, and health management domains and with the increased exhibition of maladaptive coping behaviours [231]. In type 1 diabetes, anxiety and depression have been associated with a range of behaviours linked to maladaptive coping such as alcohol and substance abuse, denial, deception, avoidance, social isolation, aggression, oppositional behaviours, and high risk activities [67-71]. Many of these behaviours not only provide a disadvantage to optimising glycaemic control, they can also present direct risks to both psychological and physical health and wellbeing. One such example is the excessive use of alcohol and other substances as a means of "dealing" with the stressors of diabetes and its associated challenges. Studies

have consistently found that people with type 1 diabetes use alcohol and other substances at rates significantly greater than their peers [67, 69, 151].

While stress, coping, and type 1 diabetes have been correlated in disease-specific contexts, the results presented in chapter two suggest that when examined in a more global context, stress and coping characteristics do not differ between those with type 1 diabetes and those without the condition. Therefore, it may be the case that while high prevalence rates of affective disorders exist in type 1 diabetes, they may not be associated with the traditional stress and coping factors that are characteristic of the "disease-burden" model, but rather are linked to factors that are as-yet-undetermined.

The aim of the this study was to assess the relationship between dimensions of stress and coping, alcohol and substance abuse, and affective disorders in participants with type 1 diabetes compared to no-type 1 diabetes participants. It was posited that, while the levels of stress, coping self-efficacy, and use of specific coping styles do not differ between those with and without type 1 diabetes, the relationship between these characteristics and affective disorders must differ given that rates of anxiety and depression are remarkably different between the two groups. Alcohol and substance abuse has been included as a variable as it is a globally recognised, non-diabetes-specific, maladaptive coping behaviour associated with both increased stress and with the increased prevalence of anxiety and depression [232, 233]. It was hypothesised that: 1) participants with type 1 diabetes would have a higher prevalence of clinically defined alcohol and substance abuse than participants with no-type 1 diabetes; 2) that disordered affect would correlate differently with dimensions of stress and coping, and that alcohol and substance abuse would correlate differently with both disordered affect and dimensions of stress and coping, in participants with type 1 diabetes compared to participants with no-type 1 diabetes, and; 3) that there would be a difference in the predictive characteristics of dimensions of stress and coping for both affective disorders and alcohol and substance abuse, between the type 1 diabetes and no-type 1 diabetes groups.

S5: Results

Participants' descriptive statistics are reported in Table 3.4, affect status statistics are reported in Table 3.6, demographic data is reported in Table 2.2, and descriptive statistics for dimensions of stress and coping for each participant group (and between-groups ANOVA results) are reported in Table 2.4. Results from the MINI600 clinical diagnostic interview (used to assess psychopathology in participants) were used to obtain information on clinically-derived alcohol and substance abuse rates in participants [28]. As already reported (Study 4, Table 3.6), the results of the MINI600 clinical interviews showed that participants with type 1 diabetes had a higher prevalence of affective disorders than participants without type 1 diabetes. Chi-square analysis revealed the increased prevalence was significant for total affective disorders, as well as for anxiety, depression, comorbid anxiety-depression individually (Table 3.6). Figure 3.3 shows the comparative prevalence of disordered affect and for alcohol and substance abuse between each participant group.

H_1: Higher Prevalence of Alcohol and Substance Abuse in Type 1 Diabetes

Chi-square analysis was conducted to evaluate the comparative prevalence of affective disorders in the type 1 diabetes and no-type 1 diabetes groups. The results of the analysis showed that, while more participants with type 1 diabetes were abusing alcohol and/or other substances compared to participants without type 1 diabetes (23.3%, *n*=17 vs 15%, *n*= 16), there was no statistically significant difference between the two participant groups (χ^2 [continuity correction] (1, 180)= 1.495, *p*= .221, *phi*= .106; Figure 3.3).

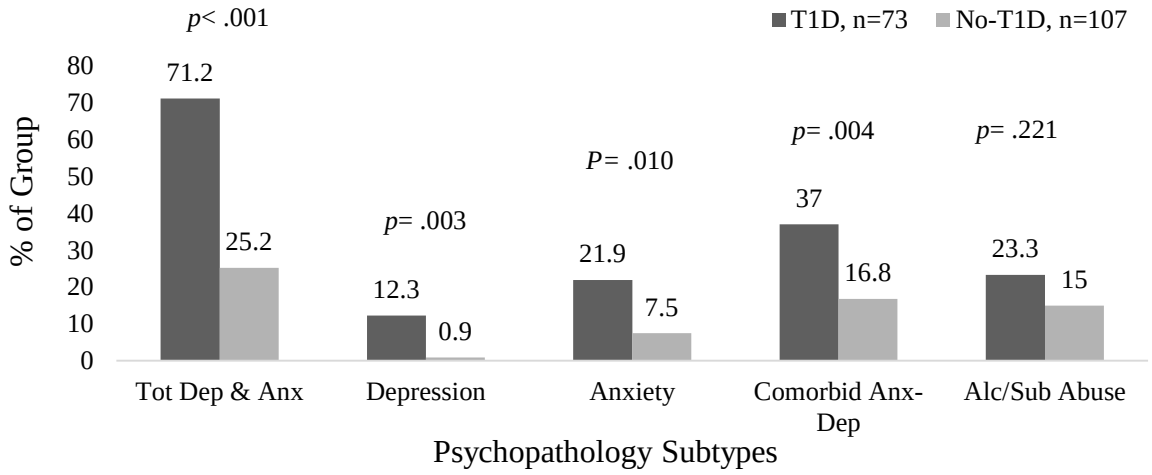

Figure 3.3. Prevalence of disordered affect and alcohol and substance abuse (as a percentage of group membership) in participants with type 1 diabetes compared to participants without type 1 diabetes. Note that participants with type 1 diabetes have statistically significant higher prevalence rates in all of the affect categories presented and that there is a higher rate of alcohol and substance abuse in the participants with type 1 diabetes although the between-groups difference did not reach statistical significance (χ^2).

Further chi-square analyses showed that alcohol and/or substance abuse was significantly associated with disordered affect in the type 1 diabetes group but not in the no-type type 1 diabetes group (Table 3.8). The results shown in Table 3.8 indicates that there is a difference in the relationship between alcohol and substance abuse and affect status in participants with type 1 diabetes compared to participants with no-type 1 diabetes.

Table 3.8. *Chi-Square Test Results of the Relationship between Alcohol and Substance Abuse, and Affective Disorders in Participants with and without Type 1 Diabetes.*

	Type 1 Diabetes (*n*= 73)				No-Type 1 Diabetes (*n*= 107)			
	% (*n*)	χ^2	*p*	*phi*	% (*n*)	χ^2	*p*	*phi*
Total Affect	21.9 (16)	4.301*	.038	.279	6.5 (7)	2.362	.124	.179

Notes: * Sig. at α< .05; Continuity correction for 2x2 table used.

H_2: Disordered Affect, Dimensions of Stress and Coping, and Alcohol and Substance Abuse would Correlate Differently in Type 1 Diabetes

Spearman's rank order correlations were used to assess the differences between the two groups in their relationships between affective disorders, alcohol and substance abuse, and dimensions of stress and coping. Spearman's correlations were used as they account for categorical data and they provide a more conservative estimate of the coefficient. Results of the analyses showed more significant relationships between the variables in the type 1 diabetes participants than in the no-type 1 diabetes group (Table 3.9). Table 3.9 shows that while there were a number of significant correlations (and intercorrelations for dimensions of stress and coping), no co-efficient was significant in both groups. In the type 1 diabetes group, affective disorder was significantly correlated to alcohol and substance abuse (*rho*= .279, *p*= .017), but not in the no-type 1 diabetes group (*rho*= .179, *p*= .065). In the type 1 diabetes participants affective disorder was also correlated to coping self-efficacy (*rho*= -.278, *p*= .042), while in the no-type 1 diabetes group, affective disorder was correlated to seeking social support (*rho*= .285, *p*= .006). In participants with type 1 diabetes, clinical levels of alcohol and substance abuse was significantly related to recent experiences of stressful life events (*rho*= .259, *p*= .054), and showed a significant negative correlation to seeking social support (*rho*= -.271, *p*= .052), planful problem solving (*rho*= 1.441, *p*= .001), and positive reappraisal (*rho*= -.305, *p*= .028). In the no-type 1 diabetes group alcohol and substance abuse was only related to distancing (*rho*= .282, *p*= .007).

In order to evaluate whether there was a statistically significant difference in these relationships, the correlation co-efficients (not the intercorrelations of dimensions of stress and coping), of the participants with type 1 diabetes were compared to the co-efficients of the no-type 1 diabetes participants. This was done by calculating the $z_{obtained}$ score from the corresponding $z_{observed}$ scores derived from converting the *r* co-efficients to their analogous *z* score [110]. Although a number of co-efficients differed between the two groups, when the co-efficients were evaluated, the group co-efficients only differed statistically in the relationship between alcohol and substance abuse and planful problem solving (Table 3.10).

Table 3.9. *Spearman's Rank Order Correlations and Intercorrelations of Dimensions of Stress and Coping, Affective Disorders, and Alcohol and Substance Abuse, in Participants with and without Type 1 Diabetes.*

		Type 1 Diabetes												
No-Type 1 Diabetes		Tot Affect	RISCI: stress	RISCI: coping	CC	D	SC	SSS	AR	EA	PPS	PR	LEQ	Alc/Sub Abuse
Tot Affect	*rho*		.205	-.278*	.154	-.092	-.016	.141	.009	.082	-.243	-.142	.065	.279*
	p		.137	.042	.277	.516	.908	.319	.949	.565	.082	.314	.635	.017
RISCI: stress	*rho*	.085		-.468***	.152	.073	.229	-.043	.280*	.390**	.058	.245	.236	-.069
	p	.445		< .001	.288	.609	.106	.767	.047	.005	.685	.083	.086	.618
RISCI: coping	*rho*	-.070	-.368***		-.090	.112	.081	.161	-.038	-.203	.249	.071	-.252	-.039
	p	.534	.001		.530	.433	.571	.260	.791	.152	.079	.621	.066	.780
CC	*rho*	-.018	-.211	-.068		.187	.448**	.633***	.363**	.357**	.205	.319*	.023	-.055
	p	.861	.062	.551		.185	.001	< .001	.008	.009	.146	.021	.869	.697
D	*rho*	-.070	.021	.086	.082		.477**	.037	.277*	.420**	.299*	.519***	.014	-.214
	p	.506	.854	.451	.438		< .001	.793	.047	.002	.031	< .001	.923	.127
SC	*rho*	.100	-.136	.191	.179	.387**		.190	.464***	.409**	.394**	.550***	.126	.013
	p	.345	.231	.091	.088	< .001		.178	.001	.003	.004	< .001	.373	.929
SSS	*rho*	.285**	-.104	.035	.236*	-.047	.292**		.085	.093	.231	.244	-.112	-.271
	p	.006	.360	.756	.023	.655	.005		.551	.511	.099	.082	.431	.052
AR	*rho*	.130	.006	-.138	.275**	.199	.321**	.153		.556***	.308*	.353**	.053	.070
	p	.218	.955	.224	.008	.057	.002	.144		< .001	.026	.010	.709	.621
EA	*rho*	.141	.051	-.142	.311**	.313**	.313**	.165	.552***		-.041	.207	.204	.132
	p	.180	.657	.212	.003	.002	.002	.115	< .001		.772	.142	.146	.350
PPS	*rho*	-.180	-.088	.314**	.211*	.411***	.391***	.270**	.134	.022		.622***	-.279*	-.441***
	p	.086	.440	.005	.043	< .001	< .001	.009	.202	.838		< .001	.045	.001
PR	*rho*	-.013	-.149	.162	.240*	.343**	.476***	.447***	.293**	.214*	.625***		.271	-.305*
	p	.903	.191	.155	.021	.001	< .001	< .001	.005	.041	< .001		.052	.028
LEQ	*rho*	.166	.206	-.099	.107	.089	.162	.292**	.093	.166	.107	.236*		.259
	p	.127	.063	.377	.341	.431	.149	.008	.408	.138	.342	.034		.054
Alc/Sub	*rho*	.179	.050	.023	.055	.282**	-.012	-.027	.136	.105	.095	.046	.070	
	p	.065	.655	.834	.602	.007	.910	.799	.198	.321	.368	.665	.523	

Notes: * Sig. at α= .05; ** Sig. at α= .01; *** Sig. at α= .001; Type 1 Diabetes Group = top of table; no-Type 1 Diabetes = bottom of table.

Table 3.10. *Tests of the Statistical Significance between Correlation Co-efficients of the Relationship between Affect and Dimensions of Stress, Affect and Alcohol/Substance Abuse, and Alcohol/Substance Abuse and Dimensions of Stress and Coping, in the Type 1 Diabetes Group Compared to the No-Type 1 Diabetes Group.*

	Affective Disorder							Alcohol and Substance Abuse						
	Type 1 Diabetes			No-Type 1 Diabetes			z_{obt}	Type 1 Diabetes			No-Type 1 Diabetes			z_{obt}
	r	*p*	z_1	*r*	*p*	z_2		*r*	*p*	z_1	*r*	*p*	z_2	
Total Affect	-	-	-	-	-	-	-	.279*	.017	.287	.179	.065	.181	.686
RISCI: stress	.205	.137	.208	.085	.445	.085	.796	-.069	.618	.069	.050	.655	.050	.123
RISCI: coping	-.278*	.042	.286	-.070	.534	.070	1.397	-.039	.780	.039	.023	.834	.023	.103
CC	.154	.277	.155	-.018	.861	.018	.886	-.055	.697	.055	.055	.602	.055	.000
D	-.092	.516	.092	-.070	.506	.070	.142	-.214	.127	.217	.282**	.007	.290	-.472
SC	-.016	.908	.016	.100	.345	.100	-.543	.013	.929	.013	-.012	.910	.012	.006
SSS	.141	.319	.142	.285**	.006	.293	-.977	-.271*	.052	.278	-.027	.799	.027	1.624
AR	.009	.949	.009	.130	.218	.131	-.789	.070	.621	.070	.136	.198	.137	-.433
EA	.082	.565	.082	.141	.18	.142	-.388	.132	.350	.133	.105	.321	.105	.181
PPS	-.243	.082	.248	-.180	.086	.182	.427	-.441**	.001	.474	.095	.368	.095	2.451#
PR	-.142	.314	.143	-.013	.903	.013	.841	-.305*	.028	.315	.046	.665	.046	1.740
LEQ	.065	.635	.065	.166	.127	.168	-.666	.259*	.054	.265	.070	.523	.070	1.261

Notes: * Sig. at α= .05; ** Sig. at α= .01; *** Sig. at α= .001. (WOCQ: confrontive coping [CC], distancing [D], self-controlling [SC], seeking social support [SSS], accepting responsibility [AR], escape avoidance [EA], planful problem solving [PPS], positive reappraisal [PR]).# Indicates significant statistical difference between correlation co-efficients of the groups: $-1.96 > z_{obt} > 1.96$; $z_{obt} = (z_1 - z_2) / \text{SQRT}((1 / (N_1 - 3)) + ((1 / (N_2 - 3)))$; Correlation co-efficient transformations to *z* from Table 11.1 in Pallant [110, p.142]

H_3: Difference in Predictive Characteristics of Dimensions of Stress and Coping for Affective Disorders and Alcohol and Substance Abuse, between Type 1 and no-Type 1 Diabetes Groups

Logistic regression was undertaken in order to assess the predictive characteristics of dimensions of stress and coping on disordered affect and alcohol and substance abuse in the type 1 diabetes and no-type 1 diabetes groups.

Affective Disorders

Logistic regression using all 11 dimensions of stress and coping in the model was assessed for its ability to predict affective disorders in the type 1 and no-type 1 diabetes groups. Previous analysis (study one, chapter two) of the 11 dimensions of stress and coping that were used in the full model showed that there was no difference in any of

variables ($p > .05$) with the exception of experiences of recent stressful life events ($p > .018$) for which the participants with type 1 diabetes reported significantly fewer events. However, after correcting for multiple comparisons, this difference did not reach the Bonferroni correction adjusted alpha level (α= .005) (Table 2.4). Figure 3.4 shows the strong similarities between the groups in all mean stress and coping profiles except recent experiences of stressful life events.

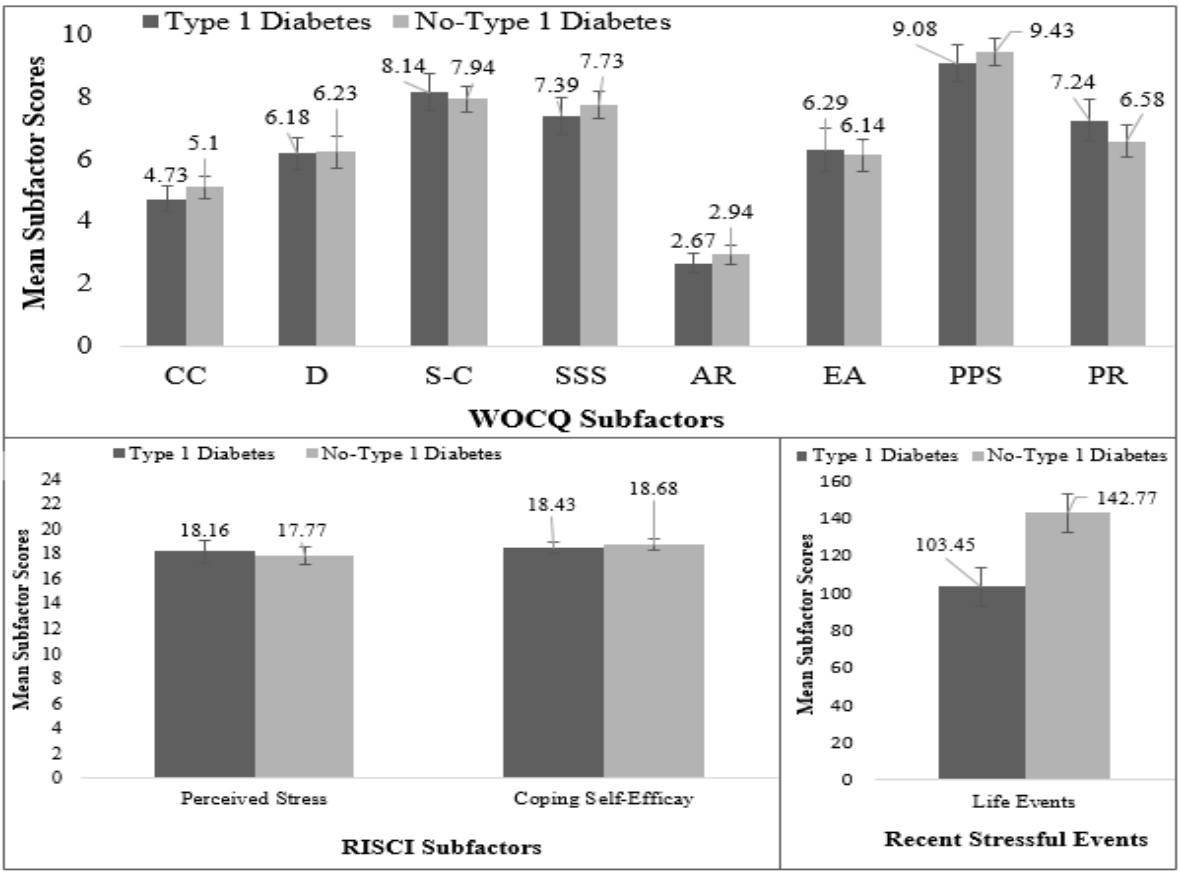

Figure 3.4. Mean coping strategy scores for all 11 stress and coping dimensions for participants with type 1 diabetes compared to participants without type 1 diabetes (wocq subfactors: confrontive coping [cc], distancing [d], self-controlling [s-c], seeking social support [sss], accepting responsibility [ar], escape avoidance [ea], planful problem solving [pps], positive reappraisal [pr]); All p> .05 except life events (p= .018).

Logistic regression analysis to evaluate the full model containing all 11 stress and coping variables as predictors of total disordered affect in the two groups showed that the

data was not a good fit to the model in participants with type 1 diabetes (χ^2 (11, 51)= 12.466, *p*= .330). No single predictor made a significant unique contribution to the model (Table 3.11). Correlational analysis showed that only coping self-efficacy was significantly correlated to total affect status (*rho*= -.278, *p*= .042), indicating that the presence of an affective disorder in type 1 diabetes is associated with lower levels of coping self-efficacy (Table 3.9).

The full model significantly predicted total disordered affect in participants without type 1 diabetes indicating that the data was a good fit to the model in this group (χ^2 (11, 79)= 20.337, *p*= .041). The model as a whole explained between 22.7% (Cox & Snell R square) and 39.6% (Nagelkerke R square) of the variance in affect status, and correctly classified 86.1% of cases. The model displayed 33.3% sensitivity, 95.5% specificity, with 57.1% positive predictive value, and 88.9% negative predictive value. Table 3.11 shows that three predictors were shown to provide a significant unique contribution to the total affect prediction model (seeking social support, Wald= 5.928, *p*= .015; planful problem solving, Wald= 3.894, *p*= .048; recent experiences of stressful life events, Wald= 3.947, *p*= .047). The most significant contribution to the model was made by seeking social support with an odds ratio of 1.465 indicating that participants without type 1 diabetes who did not use social affiliation behaviours to cope with stressful or challenging situations were almost 1½ times more likely to develop an affective disorder than those who did. Only seeking social support was correlated to total affect in participants without type 1 diabetes (*rho*= .285, *p*= .006) (Table 3.9).

Table 3.11. *Group-Specific Unique Contributions to the Total Affective Disorders Model Made by each Stress and Coping Predictor for both the Type 1 Diabetes and no-Type 1 Diabetes Groups.*

	Type 1 Diabetes								**No-Type 1 Diabetes**							
	B	*S.E.*	Wald	*df*	*p*	Exp(B)	95% C.I. for EXP(B)		*B*	*S.E.*	Wald	*df*	*p*	Exp(B)	95% C.I. for EXP(B)	
							Lo	Up							Lo	Up
LEQ	-.003	.008	.190	1	.663	.997	.981	1.012	.011	.005	3.947*	1	.047	1.011	1.000	1.022
Stress	.116	.078	2.201	1	.138	1.123	.963	1.309	-.053	.085	.385	1	.535	.949	.804	1.120
Coping	-.109	.149	.535	1	.465	.897	.669	1.201	-.003	.134	.000	1	.983	.997	.767	1.297
CC	.164	.200	.673	1	.412	1.178	.796	1.743	-.048	.144	.113	1	.737	.953	.719	1.263
D	.069	.153	.207	1	.649	1.072	.795	1.446	-.018	.124	.021	1	.884	.982	.771	1.251
SC	.015	.124	.015	1	.903	1.015	.797	1.293	-.023	.130	.033	1	.857	.977	.757	1.260
SSS	.115	.122	.883	1	.347	1.121	.883	1.424	.382	.157	5.928*	1	.015	1.465	1.077	1.993
AR	.108	.274	.156	1	.693	1.114	.652	1.904	.250	.170	2.162	1	.141	1.284	.920	1.792
EA	-.112	.160	.486	1	.486	.894	.653	1.224	-.020	.103	.037	1	.847	.980	.802	1.199
PPS	-.288	.173	2.770	1	.096	.749	.534	1.053	-.293	.148	3.894*	1	.048	.746	.558	.998
PR	-.080	.156	.259	1	.611	.924	.680	1.255	-.178	.130	1.884	1	.170	.837	.648	1.079
Con.	3.226	3.732	.747	1	.387	25.180	-	-	-2.480	3.294	.567	1	.452	.084	-	-

Notes: * Sig. at $\alpha < .05$

Alcohol and Substance Abuse

Logistic regression was again performed to assess the 11 dimensions of stress and coping model as a predictor of alcohol and substance abuse in the two participant groups. In the participants with type 1 diabetes, the data was shown to be a good fit for the model. The regression model containing all 11 stress and coping variables as predictors was statistically significant (χ^2 (11, 51)= 27.066, p= .004), explained between 41.2% (Cox & Snell R square) and 63.6% (Nagelkerke R square) of the variance in alcohol and substance abuse status, and correctly classified 90.2% of cases. The model displayed 72.7% sensitivity, 95.0% specificity, with an 80.0% positive predictive value, and 92.7% negative predictive value. When controlling for the other variables in the model, Table 3.12 shows that no single predictor made a significant unique contribution to the model. When the estimated odds ratios and their respective 95% confidence intervals were inspected, the model showed that accepting responsibility provided the strongest unique contribution to the model with an odds ratio of 2.133 suggesting that individuals in the type 1 diabetes

group who did not take personal responsibility were more than twice as likely to abuse alcohol or other substances (Table 3.12).

In participants with no-type 1 diabetes, the data was not a good fit for the model and the model did not significantly predictor alcohol and substance abuse in the group (χ^2 (11, 79)= 14.498, *p*= .183), and only explained between 17.3% (Cox & Snell R square) and 29.2% (Nagelkerke R square) of the variance in alcohol and substance abuse status. Table 3.12 shows that distancing provided a statistically significant unique contribution to the model (Distancing, Wald= 5.372, *p*= .020). The highest single contribution made to the model was accepting responsibility with an odds ratio of 1.331 (Table 3.12).

Table 3.12. *Group-Specific Unique Contributions to the Alcohol and Substance Abuse Model Made by each Stress and Coping Predictor for both the Type 1 Diabetes and no-Type 1 Diabetes Groups.*

	Type 1 Diabetes								**No-Type 1 Diabetes**							
	B	*S.E.*	Wald	*df*	*p*	Exp(B)	95% C.I. for EXP(B)		*B*	*S.E.*	Wald	*df*	*p*	Exp(B)	95% C.I. for EXP(B)	
							Lo	Up							Lo	Up
LEQ	.023	.013	3.062	1	.080	1.023	.997	1.050	.003	.004	.433	1	.510	1.003	.995	1.011
Stress	-.086	.118	.521	1	.470	.918	.728	1.158	.067	.068	.951	1	.329	1.069	.935	1.222
Coping	.280	.269	1.083	1	.298	1.323	.781	2.243	.140	.122	1.302	1	.254	1.150	.905	1.461
CC	.579	.430	1.812	1	.178	1.785	.768	4.149	.109	.125	.763	1	.383	1.115	.873	1.425
D	-.422	.291	2.110	1	.146	.656	.371	1.159	.205	.089	5.372*	1	.020	1.228	1.032	1.460
SC	.165	.197	.700	1	.403	1.179	.801	1.735	-.121	.121	.992	1	.319	.886	.699	1.124
SSS	-.570	.320	3.180	1	.075	.566	.302	1.058	.030	.110	.073	1	.787	1.030	.831	1.277
AR	.758	.473	2.569	1	.109	2.133	.845	5.387	.286	.156	3.381	1	.066	1.331	.981	1.807
EA	-.179	.189	.903	1	.342	.836	.578	1.210	-.060	.102	.344	1	.557	.942	.772	1.150
PPS	-.354	.278	1.612	1	.204	.702	.407	1.212	-.064	.127	.255	1	.614	.938	.731	1.204
PR	-.234	.248	.893	1	.345	.791	.487	1.286	-.078	.116	.451	1	.502	.925	.738	1.161
Con.	-2.167	5.626	.148	1	.700	.115			-6.687	3.430	3.800	1	.051	.001		

Notes: * Sig. at α< .05

S5: Discussion

The present study aimed to investigate the relationship between affective disorders, dimensions of stress and coping, and alcohol and substance abuse in a comparative analysis between participants with and without type 1 diabetes. This study builds on the findings thus far presented in this thesis showing that compared to those without type 1 diabetes, participants with type 1 diabetes do not differ in their levels of perceived stress, coping self-efficacy, or the coping strategies used to manage stressful or challenging experiences however; they do have a significantly higher prevalence of affective disorders. This is enigma in some respects as stress, poor coping skills, maladaptive coping behaviours, and affective disorders have been shown to be largely ubiquitous in the general population [8, 14, 234-236].

The results suggest that there were some basic differences between the two participant groups. In the type 1 diabetes group, stress and coping did not predict affective disorders however, they did in the no-type 1 diabetes group. Conversely, dimensions of stress and coping did predict alcohol and substance abuse disorders in the participants with type 1 diabetes, but not in the no-type 1 diabetes group. Interestingly, the same stress and coping variables that made a significant unique contribution to predicting affective disorders in the no-type 1 diabetes controls (planful problem solving, seeking social support, and positive reappraisal) were also significantly correlated to alcohol and substance abuse in the participants with type 1 diabetes.

H_1: Higher Prevalence of Alcohol and Substance Abuse in Type 1 Diabetes

Hypothesis one that alcohol and substance abuse would be more prevalent in participants with type 1 diabetes than in those with no-type 1 diabetes was not supported. The results showed that alcohol and substance abuse prevalence was higher in participants with type 1 diabetes (23.3% vs 15%) however, the variation between the groups was not statistically significant. The extant literature contradicts this finding. Recent research from around the world indicates that adolescents and young adults with type 1 diabetes may be abusing illicit drugs and alcohol at rates significantly greater than their no-type 1 diabetes peers [67-69, 71]. For example, Hart et al. [237] found that 172 (61%) of a cohort 281 participants with type 1 diabetes were abusing alcohol. Similarly, Lee et al. [67] identified

that illicit drug use in Australian adolescents and young adults with type 1 diabetes was as high as ~80%. This rate is around 2.5 times higher than the Australian national average use of illicit recreational drugs in these age groups of ~30% [151]. The results of the present study do not show such disparate rates between those with type 1 diabetes and those without however, this may be due to the higher mean age of the cohort, and use of a matched case-control design rather than the case-only, and case-population comparisons undertaken in other studies.

H_2: Disordered Affect, Dimensions of Stress and Coping, and Alcohol and Substance Abuse would Correlate Differently in Type 1 Diabetes

The second hypothesis that the relationship between affective disorders, dimensions of stress and coping, and alcohol and substance abuse, would differ between participants in the type 1 diabetes and no-type 1 diabetes groups was supported. Figure 3.5 illustrates the difference in the relational characteristics between the two groups.

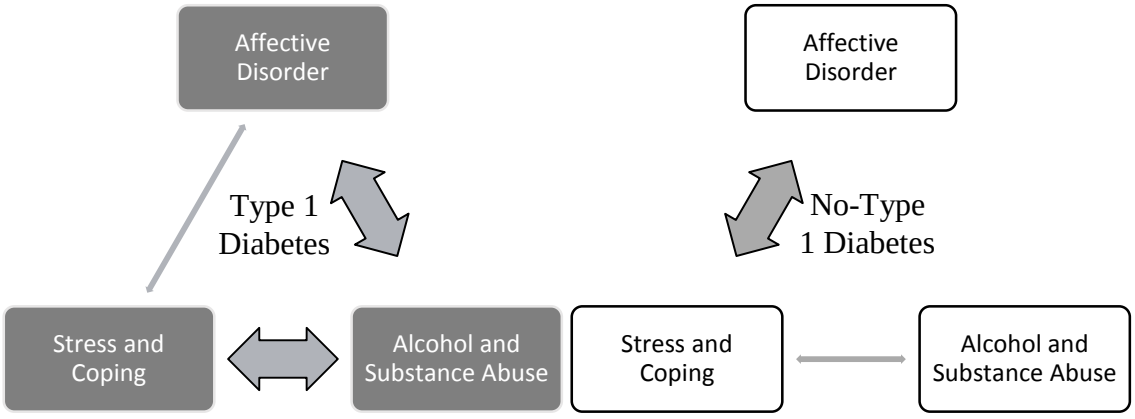

Figure 3.5. Comparative relationships between affective disorder, dimensions of stress and coping, and alcohol and substance abuse, in participants with type 1 diabetes and participants with no-type 1 diabetes.

In the type 1 diabetes group there were strong relational connections between alcohol and substance abuse and both stress and coping, and affective disorders. However, there was only limited association between dimensions of stress and coping and affective disorders. In contrast, the no-type 1 diabetes group showed strong connections between affective disorders and dimensions of stress and coping, and only a minor association between stress and coping and alcohol and substance abuse. Affective disorders were not related to alcohol and substance in the no-type 1 diabetes participants. As Figure 3.5 shows, the relational characteristics in the two groups are effectively opposite to one another. The extant literature shows a clear relationship between stress and coping, and affective disorders in the general population [234, 235, 238-240], and the results support these previous findings. The lack of correlation between stress and coping and affect in participants with type 1 diabetes suggests another as-yet-undetermined pathogenic mechanism may be presenting a stronger influence. Further research is needed to better understand this divergence in type 1 diabetes.

Alcohol and substance abuse in participants with type 1 diabetes was significantly associated with poorer use of positive coping strategies and with times of increased external stressors. Recent experiences of stressful life events, positive reappraisal, seeking social support, and planful problem solving were all significantly related to alcohol and substance abuse in participants with type 1 diabetes and not in the no-type 1 diabetes group. Increased experiences of stressful life events was also related to lower use of planful problem solving as a behavioural coping strategy in type 1 diabetes but not in the no-type 1 diabetes group. The association between increased alcohol and substance abuse, reduced use of planful problem solving strategies, and an increased experience of recent stressful life events may be an indication that the participants with type 1 diabetes were less able to engage with rational, considered, and well planned problem resolution processes in the face of external challenges.

The three positive coping strategy variables, along with are important elements of resilience and the association to alcohol and substance abuse may be indicative of poor resilience in the type 1 diabetes participants. Poor resilience has been linked to maladaptive and risk taking behaviours in type 1 diabetes [103, 241]. Together, these associations suggest

that participants with type 1 diabetes, when faced with increased stress and external challenge may be unable to use cognitive reframing to positively reappraise their circumstances nor to thoughtfully work through a solution to their problem. Moreover, the results support the current literature and indicate that, when faced with this scenario participants with type 1 diabetes are more likely to socially isolate themselves and seek out alcohol and/or other substances as a means of self-medicating or denial-avoidance behaviour [47, 62, 67, 68]. Seeking social support was negatively correlated to alcohol and substance abuse in the type 1 diabetes participant group. Seeking social support involves engaging with peers or professionals in order to obtain help or insight into your problem. The negative correlation suggests that individuals with type 1 diabetes do not seek help when faced with challenges but rather have a propensity to engage in maladaptive coping behaviours such as self-medication with alcohol or other drugs. This is consistent with the research showing a tendency for sufferers to self-isolate and not ask others for help [47, 62, 70, 242].

The difference in the relationship between affective disorders and alcohol and substance abuse in the two groups indicates that the rate of alcohol and substance abuse rises relative to the prevalence rates of anxiety and depression in the type 1 diabetes group but not in the no-type 1 diabetes group. This result may indicate that alcohol and substance use is utilised by type 1 diabetes participants as a means of self-medication for anxiety and depression disorders. Alcohol and substance abuse is indicative of maladaptive coping behaviour with self-medication behaviour being common in those with a propensity to socially isolate. Furthermore, it is characteristic of behaviours that attempt to mitigate against increased negative affect and anxiety without having to engage with others. This is supported by the results of the present study which found a relationship between alcohol and substance abuse and a significantly lower use of seeking social support as a coping strategy, and is consistent with the extant literature that shows that alcohol and other drug use in type 1 diabetes is significantly higher than in the no-type 1 diabetes population [67, 69, 151, 237]. High alcohol and/or substance use has been linked to increased risk of complications [243, 244], diabetes mismanagement [69], and significant impairments to glycaemic control and risk of ketoacidosis [67, 68].

Of the eleven dimensions of stress and coping that were assessed, only coping self-efficacy was significantly related to the prevalence of affective disorders in type 1 diabetes. There is evidence from the literature that indicates patients with chronic diseases use more avoidant coping styles [47], have a tendency to self-isolate, and are unwilling to ask for help [62]. These are characteristics of poor coping self-efficacy [2, 95, 103, 241]. The relationship between coping self-efficacy and affective disorder differed between the two groups with the relationship only reaching significance in the type 1 diabetes group. The result suggests that the greater the perceived ability to cope in participants with type 1 diabetes, the lower the prevalence rates of anxiety and depression disorders. This is consistent with the literature that has found perceptions of control and perceived disease predictability are both associated with psychological dimensions in type 1 diabetes [3, 66]. This relationship suggests that the more an individual with type 1 diabetes feels in control and able to cope, the more resilient they will be to episodes of anxiety and depression.

H_3: Difference in Predictive Characteristics of Dimensions of Stress and Coping for Affective Disorders and Alcohol and Substance Abuse, between Type 1 and no-Type 1 Diabetes Groups

Hypothesis three, that there would be a difference between the groups in the predictive characteristics of dimensions of stress and coping for both affective disorders and alcohol and substance abuse was supported. In the type 1 diabetes group, the data fit a predictive model with all 11 assessed dimensions of stress and coping as predictors of alcohol and substance abuse however, the data did not fit this model as a predictor of affective disorders. In the no-type 1 diabetes group, the opposite was true. The full model significantly predicted affective disorders but not alcohol and substance abuse.

Stress and coping have been shown to be strong mediators of psychological wellbeing with the literature indicating that when psychological capacity to manage presenting stressors is exceeded, disordered affect can result [80]. This is supported by the results in the no-type 1 diabetes group that showed experiences of stress, perceptions of stress, coping self-efficacy, and coping strategies, are predictive of disordered affect. However, participants with type 1 diabetes did not show this same predictive relationship but rather these same dimensions of stress and coping predicted alcohol and substance

abuse in the type 1 diabetes group – a known maladaptive coping behaviour associated with anxiety and depression disorders [67-71]. In the type 1 diabetes group affective disorders were significantly correlated to alcohol and substance abuse. These results suggest that when under increased stress, participants with type 1 diabetes may be lacking the psychological and physical coping skills to deal with the increased challenge, leading to higher use of maladaptive coping behaviours such as alcohol and substance abuse. This argument is supported by the results showing that poor coping self-efficacy was significantly correlated to disordered affect in the participants with type 1 diabetes. The lack of relationship between stress and coping and affective disorders in type 1 diabetes, despite the very high prevalence of disordered affect in sufferers, suggests that increased affective psychopathology in type 1 diabetes is not necessarily characteristic of the populist "disease-burden" paradigm, but rather may involve a different combination of pathogenic mechanisms that remain as-yet-undetermined.

Other Findings of Note

The lack of stress and coping indicators to support the higher prevalence of anxiety and depression may indicate one of two circumstances. Firstly, it may indicate inaccurate self-reported stress and coping strategies. This may be due to psychological habituation to higher baseline levels of stress [245], social desirability resulting in misleading responses by participants [246], denial [247], impaired capacity to make decisions [248], or factors relating to impression management [249]. These possible explanations are consistent with findings that maladaptive behaviours are more prevalent in sufferers of type diabetes than in the general population [250], and supports the higher prevalence of alcohol and substance abuse and the significant correlation between alcohol and substance abuse prevalence and affective disorders. The implications of psychological maladjustment for sufferers of type 1 diabetes include impaired cognitive function, reduced quality-of-life, poor self-care behaviours, low levels of adherence to medical treatment, poor glycaemic control, increased risk of complications and disability, and early mortality [113].

The second consideration is that factors other than psychological disease burden, stress, and poor coping, play a mediating role in anxiety and depression type 1 diabetes. Type 1 diabetes is associated with a number of physiological and neurophysiological

sequelae that have been independently linked to anxiety and depression including altered levels of neurotransmitters including serotonin, noradrenaline, and dopamine [251]. For example, research has identified that individuals with type 1 diabetes have decreased transmission of serotonin in the frontal lobes which may be associated with the pathophysiology of depression and anxiety disorders [252]. Further, a core characteristic of type 1 diabetes is immune dysfunction [64]. This dysfunction may impact on autonomic nervous system processes, increase neuroinflammation, and moderate physiological capacity to respond to stressful stimuli, all of which have been associated with depression and anxiety disorders [253]. Similarly, changes in autonomic function, HPA axis regulation, basal reactivity of CRF, and hypercortisolaemia are all sequelae of type 1 diabetes as well as physiological correlates of affective psychopathology [166, 175, 177].

Clinical Considerations

The results may suggest that participants with type 1 diabetes are either unable or unwilling to disclose or recognise a number of symptoms associated with psychological disorder and personal levels of stress. This means that general practitioners, diabetes specialists, and diabetes educators may not be able to obtain accurate information about psychological wellbeing of patients in the normal course of a general clinic visit. To address this shortcoming, the inclusion of regular psychological health screenings by appropriately trained mental health professionals should be considered an essential adjunct to existing standard clinic visit protocols [8, 62].

Limitations

Self-report data are known to create a moderated response set [55] and it may be that reported stress and coping characteristics are poorer than indicated.

Conclusion

The results show that while dimensions of stress and coping predict maladaptive behaviour such as alcohol and substance abuse in type 1 diabetes, they do not predict affective disorders. However, the results do show a clear relationship between coping self-efficacy and affective disorders in type 1 diabetes. This finding supports the extant literature that shows personal efficacy and perceptions of control play a role in psychological wellbeing in people with type 1 diabetes [2, 95, 96]. Furthermore the results

show that the relationship between stress and coping and affective disorders is markedly different in type 1 diabetes than in those without the condition. These results support the notion that anxiety and depression may have different mediating factors in people with type 1 diabetes compared to those without the disease, and that these different factors appear to play a stronger role in moderating anxiety and depression than the accepted psychosocial influences such as perceived stress and specific adaptive coping strategies.

The evidence is clear that many people with type 1 diabetes also battle with clinical levels of anxiety and depression. Life with type 1 diabetes is a difficult prospect with myriad factors requiring constant attention. This is made all the more difficult by the presence of psychological malady that is characterised by changes in mood, motivation, attention, and self-care adherence. The consequences of comorbid psychopathology on those with type 1 diabetes can be catastrophic with research showing a clear relationship with reduced quality-of-life, increased risk for poor health outcomes in the short and long-term, increased moderate to severe disability, and increased morbidity. What is less clear is the mechanisms by which psychopathology risk is increased in type 1 diabetes. While the historical paradigm has placed the blame on psychological disease-burden and the associated interplay between the stress created and the coping efficacy and resilience displayed; the results of the present study indicate that the nature of the relationship between type 1 diabetes and affective disorders, is perhaps not yet fully understood.

What appears clear from these results is that the relationship between affective disorders and stress and coping in type 1 diabetes does differ in character to that which exists in individuals without type 1 diabetes, and therefore suggests the existence of additional unique, disease-specific characteristics that remain as-yet-unknown. This is supported by the results showing the higher prevalence of anxiety and depression without a correspondingly higher presence of stress and maladaptive coping strategies that would usually be expected in studies of anxiety and depression in non-type 1 diabetes cohorts. Further research is needed to better understand the character and direction of these relationships.

Study 6: Disordered Affect and Clinical Outcomes in Type 1 Diabetes

S6: Abstract

Background: Research suggests that the majority of type 1 diabetes patients have poor metabolic control and that control is chronically poor in 25% of adults with the disease. Moreover, the literature shows a clear link to poor metabolic control and increased complications risk. One explanation for the ongoing challenges in diabetes glycaemic management may be the influence of the significant prevalence rates of anxiety and depression disorders. The present study investigated the relationship between anxiety and depression disorders, short and long-term metabolic control, and diabetes clinical and aetiological factors such as complications, age of onset, duration of illness, and severe hypoglycaemia.

Methods: Participants with type 1 diabetes (*N*= 73) with disordered affect (*n*= 52, anxiety *n*= 16, depression *n*= 9, mixed anxiety-depression *n*= 27), and without disordered affect (*n*= 21) were assessed for clinical and aetiological factors associated with type 1 diabetes. Relational analyses were undertaken to determine the nature of the association between these factors and disordered affect, as well as the ability to develop predictive models for risk of both poor clinical outcomes and disordered affect.

Results: Metabolic control (for description see Chapter 1, "Methods" section) in participants with and without an affective disorder were above levels considered optimal (short-term *M*= 12mm/l vs 10mmol/L; medium-term *M*= 8.2% vs 7.8%; long-term *Md*= 8.3% vs 7.6%). While short, medium and long-term metabolic control was poorer in participants with an affective disorder the differences were not significant (short *p*= .20; medium *p*= .45; long *p*= .24). Regression analysis found that age of onset, duration of illness, history of severe hypoglycaemic events, long-term metabolic control, and the presence of complications significantly predicted affective disorder in type 1 diabetes (*p*= .04) however, duration of illness was the only predictor to make a significant unique contribution to the model (*p*= .04). There was no significant relationship between disordered affect and complications (*p*= .25), and disordered affect did not significantly predict complications (*p*= .16) although the odds ratio of 2.078 showed that type 1 diabetes participants with an affective disorder were more than twice as likely to also have complications.

Conclusion: Affective disorder are associated with poorer glycaemic control and increased complications risk in type 1 diabetes although the strength of this influence was not strong enough to be significant in the present cohort. This relationship must be considered in the clinical management of type 1 diabetes.

Keywords: affective disorders; psychopathology; anxiety; depression; comorbidity; diabetes mellitus, type 1; clinical outcomes; metabolic control; glycaemic control.

S6: Introduction

Poor metabolic control in type 1 diabetes is the norm rather than the exception [95] with 25% of adults with the disease having chronically poor glycaemic control [96]. However, the challenge of maintaining optimal metabolic control falls largely outside of the purely biomedical management of the disease. Type 1 diabetes is primarily a disease of self-care, and Plack, Herpertz [95] argue that the most significant factor mediating treatment success is the actions of the patients themselves. Significant investment has been made in attempts to educate and motivate patients to improve self-care practices however, these efforts have often been implemented on the underlying assumption of psychological normalcy in diabetes patients, and have had little success in changing the widespread problem of poor glycaemic control. The high prevalence of anxiety and depression (affective disorders) in type 1 diabetes may provide some explanation for the lack success in improving metabolic control as both anxiety and depression have a significant impact on psychobehavioural and physiological function [7].

The psychological and physiological factors associated with affective disorders both present significant clinical implications in diabetes care [193]. Psychologically, disordered affect is associated with both alterations in conscious thought processes [254, 255], as well as impairments to neurocognitive performance [256, 257], both of which have a direct impact on emotion, motivation and behaviour [258]. Physiologically, disordered affect is associated with a host of changes in areas such as autonomic function, HPA axis regulation, inflammation, and the vasculature. In turn these changes increase the challenge of managing diabetes, have a bearing on metabolic control, and increase the risk of complications [173].

The psychological dimensions of anxiety and depression associated with poorer clinical outcomes ultimately stem from the behaviour that manifests as a result of disordered thinking, the associated increase in negative affect, and the manner in which these factors influence motivation. Anxiety is characterised by increased worry, negativity bias, and catastrophizing which drive and are driven by, increased experiences of fear, anger, hopelessness, guilt, and embarrassment. Worry is effectively an increased attentional focus on a particular issue or situation that is perceived as being problematic. According to Vervoort [169], in an appropriate context worry can enhance constructive problem-solving and create strong motivations to act for a resolution to a challenge. However, pathological worry is a feature of anxiety and when coupled with a

chronic illness and its associated challenges for which there is often no solution available, then the frenetic pursuit of resolution can readily lead to strong negatively valenced feelings such as failure, guilt, fear, anger, humiliation, hopelessness, and ultimately despair [169].

Strong, uncontrollable emotions and distorted thinking that is not able to be rationalized often results in feeling "out of control". This negative valence provides a strong motivator to engage in behaviours that are aimed at reducing these emotions and regaining some sense of control. In someone who is facing the challenges of type 1 diabetes through the distorted lens of anxiety, the spectre of complications, serious disability, and early mortality is likely to amplify these internal experiences, further overwhelming individuals and reducing their capacity to self-manage their disease [170]. In this way behaviour becomes motivated by the pursuit of avoiding the negative emotions as quickly as possible, though not necessarily in a manner that is the most beneficial to physical health objectives [8, 170, 171].

The physiological impact of anxiety also has potentially significant clinical implications. Of particular concern is the evidence showing that a number of the key deleterious impacts to physiology that are associated with anxiety are also independently associated to type 1 diabetes. For example, both conditions are linked to autonomic dysregulation and specifically an amplification of parasympathetic nervous system activation and a reduced autonomic response to intense emotional experience [173-176]. HPA axis dysregulation, hypercortisolaemia, and basal hyper-reactivity of CRF, are some of the core underlying physiological changes associated with these pathologies [166, 175, 177].

The pathological worry, cravings for control, and elevated HPA axis and autonomic nervous system activation that is characteristic of anxiety can lead to intentional behaviours that confound the success of diabetes management and metabolic control. In contrast, the psychology of depression can have a negative impact through a contrary effect in which intentional behaviour related to diabetes self-care and metabolic control is conspicuously absent. For example, poor adherence to medication protocols is (in part) due to a lack of motivation to perform the task and a lack of interest in the potential consequences of such an act of omission. This differs to the motivation in anxiety where this behaviour is more likely to be an act of denial or

avoidance due to fear and worry associated with diabetes or the specific act itself (eg; injecting). This difference in the motivational factors of anxiety versus depression is similar across all areas of the self-care and clinical management spectrum. The clinical challenge in the face of depression then is to be able to increase the intentional behaviours related to diabetes self-care whether in concert with the alleviation of depression symptoms or in spite of them, while in anxiety the aim is to reduce the worry and fear that are driving obsessional or avoidant intentional behaviours.

The consequences of the psychological symptoms of depression include reduced joy, increased sadness, anhedonia, lassitude, negative and self-destructive thoughts that are often the focus of intense rumination, and ongoing feelings of dread, guilt and worthlessness [259]. These symptoms all serve to significantly reduce the motivation to act in the pursuit of self-preservation. This is particularly evident when depression progresses to the point where suicide ideation becomes a feature. Given the impact of both depression and diabetes independently of one another, it is hardly surprising that comorbid diabetes-depression is also associated with significantly lower quality-of-life [217].

In the diabetes-specific context, depression is associated with increased health care utilization, poor medication and self-care adherence (blood testing, exercise, diet), poor metabolic control, and increased levels of social isolation [260, 261]. These diabetes-specific behavioural manifestations are important contributors to depression being associated with higher rates of advanced complications and mortality [132]. The lack of motivation and low levels of intentional behaviour in depression does not relate only to diabetes-specific behaviours but permeates across all facets of life. A potential generic high risk behaviour associated with depression is the propensity for individuals to self-medicate. The rates of high risk behaviours such as the abuse of alcohol, tobacco, and illicit drugs found in type 1 diabetes may be related to the high rates of depression and/or anxiety, as both disorder types are associated with increased alcohol and substance abuse [67-69, 71, 150].

This study had two aims: 1) to evaluate the role of clinical and aetiological factors in the risk of anxiety and depression in adults with type 1 diabetes, and; 2) to evaluate the relationship between affective disorders, and metabolic control and complications risk in adults with type 1 diabetes. Three hypotheses were forwarded. It

was hypothesised that age of onset, duration of illness, a history of severe hypoglycaemic events, long-term metabolic control, and the presence of complications predict the risk of affective disorder in adults with type 1 diabetes. It was further hypothesised that short and long-term metabolic control would be poorer in participants with an affective disorder compared to participants without. Finally it was hypothesised that complications would be more prevalent in participants with disordered affect than in participants without.

S6: Results

Participants' descriptive statistics are reported in Table 3.4, affect status statistics are reported in Table 3.6, and diabetes-specific clinical data for the type 1 diabetes group are reported in Table 2.5. Results from the MINI600 clinical diagnostic interview (used to assess psychopathology in participants) were used to obtain information on clinically-derived alcohol and substance abuse rates in participants. Results showed that 23.3% (*n*=17) of participants with type 1 diabetes were using alcohol and/or other substances to a level considered abusive in the one year period up to participation in the study [(28)].

H_1: Diabetes-Specific Aetiological and Clinical Factors Predict Affective Disorders

Direct logistic regression analysis was undertaken to test the first hypothesis that age of onset, duration of illness, a history of severe hypoglycaemic events, long-term metabolic control, and the presence of complications would predict the risk of affective disorder in adults with type 1 diabetes. The full model containing all five independent variables was statistically significant ($\chi 2$ (5, 23)= 11.443, p= .043), indicating that the data was a good fit for the model, and the model was able to differentiate between participants who had an affective disorder and those who did not. The full model explained between 39.2% (Cox and Snell *R* squared) and 55.4% (Nagelkerke *R* squared) of the variance in clinical affective disorder status, and correctly classified 82.6% of cases. The full model displayed 93.8% sensitivity, 57.1% specificity, 83.3% positive predictive value, and 80% negative predictive value. When controlling for the other variables in the model, Table 3.13 shows that duration of illness was the only predictor to make a unique significant contribution to the model (Wald= 4.329, *p*= .037). The strongest predictor of disordered affect was the presence of complications, with an odds

ratio of 12.697. This indicated that participants with diabetes-related complications are estimated by the model to be over 12½ times more likely to have a clinical anxiety or depression disorder than participants who do not have complications, although this should be considered with caution due to the small sample size – a point made clear by the large corresponding 95% CI shown in Table 3.13.

Table 3.13. *Type 1 Diabetes Group-Specific Unique Contributions to the Affective Disorders Model by each Clinical Characteristic.*

							EXP(B) 95% CI#	
	B	*SE*	Wald	*df*	*p*	Exp(*B*)	Lower	Upper
Age at diagnosis	-.188	.103	3.299	1	.069	.829	.677	1.015
Duration of illness	-.234	.112	4.329*	1	.037	.792	.635	.987
Diabetes-related complications	2.541	1.810	1.971	1	.160	12.697	.366	440.925
Severe hypo lifetime	.355	1.495	.056	1	.812	1.426	.076	26.717
Three year *M* HbA1c	.345	.561	.378	1	.538	1.412	.470	4.242
Constant	6.777	6.936	.955	1	.329	877.353		

Notes: # Odds ratios should be interpreted with caution due to the small sample size; * Sig. at $\alpha < .05$

H_2: Short-Term and Long-Term Metabolic Control Poorer in Participants with Affective Disorders

Analysis of variance was used to test the second hypothesis that short and long-term metabolic control would be poorer in participants with anxiety or depression compared to participants without disordered affect. Although participants with an affective disorder had a higher mean short-term BGL (*M*= 11.996 ±4.996, *n*= 50) than those without (*M*= 10.153 ±6.015, *n*= 19), univariate ANOVA revealed no significant difference in short-term blood glucose levels (BGL) between those with and without an affective disorder (F (1,67)= 1.672, p= .200, η_p^2= .024). Due to the small number of participants for whom long-term metabolic control data was available (1 year data *n*= 28, 3 year data *n*= 23), data was assessed using non-parametric ANOVA equivalent (Mann-Whitney U Test). Medium-term metabolic data was analysed using further ANOVA (*n*= 58).

Univariate ANOVA on HbA1c from the time of participation (a measure of approximately three-month metabolic control) showed higher mean HbA1c in type 1 diabetes participants with an affective disorder (*M*= 8.157 ±1.435, *n*= 42) than participants without (*M*= 7.831 ±1.549, *n*= 16), however the difference between the

groups did not reach significance (F (1,56)= .572, p= .453, η_p^2= .010). A Mann-Whitney U Test showed the same trend in long-term mean HbA1c levels again without the difference in groups reaching significance over both one year (participants with affective disorder *Md*= 8.150, *n*= 18; without affective disorder *Md*= 7.800, *n*= 10; *U*= 87.500, *z*= -.120, *p*= .904, *r*= .023), and three years (participants with affective disorder *Md*= 8.250, *n*= 16; without affective disorder *Md*= 7.600, *n*= 7; *U*= 38.500, *z*= -1.171, *p*= .242, *r*= .244).

Metabolic control recommendations state the optimal HbA1c level is <7.0% [262, 263] therefore, mean metabolic control was recoded into two categories to reflect whether participants metabolic control over the short, medium and long-term were at optimal (<7.0%) or suboptimal (>7.0%) levels. Chi-square test for independence indicated no significant difference in the relationship between the presence of disordered affect and metabolic control when nominally coded for optimal and suboptimal status in short-term BGL (<7.0%= 57.1% (*n*= 8), >7.0%= 76.4% (*n*= 42); χ^2 [continuity correction] (1,69)= 1.215, *p*= .270, *phi*= .173), three-month HbA1c (medium-term control <7.0%= 64.3% (*n*= 9), >7.0%= 75.0% (*n*= 33), χ^2 [continuity correction] (1,69)= .192, *p*= .661, *phi*= .103), or three year average HbA1c (long-term control <7.0%= 60.0% (*n*= 3), >7.0%= 72.2% (*n*= 13); Fischer's Exact Test *p*= .621 [2-sided]).

H_3: Complications more Prevalent in Participants with Affective Disorders

Chi-square analysis was used to evaluate the third hypothesis that complications would be more prevalent in participants with disordered affect than in participants without. Cell counts showed that 46.6% (*n*= 34/73) of the total group had both complications and disordered affect. This represented 65.4% (*n*= 34/52) of participants with an affective disorder and 77.3% (*n*= 34/44) of participants with complications (Table 3.14). However, the results of the chi-square test for independence indicated no significant relationship between the presence of clinical anxiety and depression disorders, and the presence of diabetes-related complications in participants with type 1 diabetes (χ^2 continuity correction (1,73)= 1.300, *p*= .254, *phi*= .164). Despite the relationship not reaching statistical significance, Table 3.14 there was a considerable difference between the number of participants in the total group that had both conditions compared to those with either an affective disorder without complications (24.7%, *n*=18/73), or complications without and affective disorder (13.7%, *n*= 10/73). Logistic regression revealed that affect status did not provide a unique predictive contribution to

the presence of complications in participants (Wald= 1.939, *p*= 164). While not significant, the odds ratio of 2.078 (95% CI= 0.742-5.817) indicates that type 1 diabetes participants with an affective disorder are more than twice as likely to have complications as those who don't.

Table 3.14. Chi-Square Test Results of the Relationship between Diabetes-Related Complications and Affective Disorders in Participants with Type 1 Diabetes.

			Complications		Total
			No	yes	
Affective Disorder	no	*N*	11	10	21
		% within Affective Disorder	52.4%	47.6%	100.0%
		% within Complications	37.9%	22.7%	28.8%
		% of Total	15.1%	13.7%	28.8%
	yes	*N*	18	34	52
		% within Affective Disorder	34.6%	65.4%	100.0%
		% within Complications	62.1%	77.3%	71.2%
		% of Total	24.7%	46.6%	71.2%
Total		*N*	29	44	73
		% within Affective Disorder	39.7%	60.3%	100.0%
		% within Complications	100.0%	100.0%	100.0%
		% of Total	39.7%	60.3%	100.0%

Notes: χ^2 continuity correction (1,73)= 1.300, *p*= .254, *phi*= .164

S6: Discussion

The present study aimed to investigate the relationship between disordered affect and clinical factors in type 1 diabetes. To do this the study evaluated the role of clinical and aetiological factors in the risk of anxiety and depression, and investigated the relationship between affective disorders, and metabolic control and complications risk in adults with type 1 diabetes. Three hypotheses were forwarded to investigate the relationship between affective disorders, metabolic control and diabetes-related complications. The results support a relationship between these factors however, analyses did not show these relationships to all be statistically significant and suggest that perhaps the relationship is more complex than a simple lineal association. These results build on the earlier studies of this chapter and on the existing wider literature that show high prevalence rates of anxiety and depression in type 1 diabetes [8, 14, 236, 264]. Affective disorders in type 1 diabetes have gained increasing attention in the face of

mounting evidence that the significant advancements in diabetes management knowledge and technology are failing to deliver on the anticipated improvements to metabolic control and complications reductions [111, 113, 114, 265]. These realisations have come on the back of evidence supporting the pivotal role of patient-driven psychobehavioural variables in mediating diabetes care outcomes [2, 95, 96].

H_1: Diabetes-Specific Aetiological and Clinical Factors Predict Affective Disorders

Hypothesis one that aetiological and clinical factors could predict anxiety and depression disorders in adults with type 1 diabetes was supported. Logistic regression showed the five-factor model of age at diagnosis, duration of illness, history of severe hypoglycaemia, long-term metabolic control, and the presence of diabetes-related complications was a significant predictor of disordered affect. This supports both the disease-burden and clinical consequences paradigms of neuropsychological sequelae in type 1 diabetes. These paradigms argue that living with the psychoemotional challenges of type 1 diabetes and the long-term dysregulation of core physiology that is central to the pathophysiology of the disease, both contribute to the increased risk of psychopathology [1-3, 173]. The influence of the predictor variables of the model that was tested can be explained through these paradigms.

Analysis of the first predictor in the model (age of onset) showed that the earlier an individual is diagnosed with type 1 diabetes, the greater the risk for affective disorders in adulthood. While the unique contribution to the model made by this variable was not significant, the nature of the relationship is cause for note. Type 1 diabetes is overwhelmingly a disease with a childhood onset [266, 267]. The Australian Institute of Health and Welfare estimate that the incidence of type 1 diabetes in children aged 0-14 years increased by around 10% between 2008 and 2013 [267]. If the incidence of type 1 diabetes continues to increase in children then the number of adults faced with comorbid type 1 diabetes and affective disorder will also increase accordingly [268]. This is concerning as the prevalence rates are already significant and any foreseeable growth will carry with it corresponding challenges in clinical care, complications risk, reductions in quality-of-life, and in the education and facilitation of self-care motivation and behaviours. Secondly, research presented in this thesis and supported by the wider body of literature show that considerable anxiety and depression onset in type 1 diabetes already occurs in young people with the disease. Greater disease prevalence will carry with it a parallel increase in early-onset psychopathology. As a public health issue, this

scenario represents a potentially significant increase in health care costs, health care service utilisation, and further disease-related reductions in productivity and an associated increase in social and familial burden.

The second predictor in the model (duration of illness) was the only predictor to make a statistically significant unique contribution to the model. The nature of the relationship indicated that, the longer participants have the disease, the lower the risk for affective disorders. This may be related to coping self-efficacy which is also known to increase with duration of illness and increased coping self-efficacy has been shown in this thesis to be related to lower rates of affective disorder (study five, chapter three). The small sample and effect sizes may also be influential in this result. One participant in the sample had a duration of illness of more than 60 years, and two more had durations in excess of 50 years. All three were also affective disorder free. This will have influenced the statistical outcome strongly. Interestingly, individuals with type 1 diabetes who live for 50 years or more with the condition have been shown to have less diabetes-related complications and comorbidities than those who do not despite no significant differences in long-term metabolic control, dietary adherence, or exercise practices [269]. This has only recently prompted research efforts to understand what mechanisms may be supporting resilience in these individuals.

The presence of complications provided the strongest unique predictive power with the model estimating that the risk of affective disorders is up to 12½ greater if participants have a diabetes-related complication such as retinopathy, nephropathy, or heart disease. The small sample size used to test the model means these estimates must be interpreted cautiously. None-the-less, the strong relationship between complications and affective disorders should be recognised and used to inform clinical activities with patients facing physical complications associated with their type 1 diabetes. The strength of this relationship is likely to be both psychological and physiological with both dimensions being seriously impacted by the presence of diabetes-related complications which, in large measure, are related to inflammation, micro and macro vascular disease, and neural degeneration and maladaptation. These three general areas of complications genesis can all have a significant impact on central nervous system function and associated cognitive, emotional, behavioural, and physiological outputs [3, 64, 166].

Having experienced at least one severe hypoglycaemic event was also a predictor in the model of affective disorders in type 1 diabetes. For the purposes of this study, a severe hypoglycaemic event was defined as an experience of a low blood sugar that was so severe as to cause seizure or loss of consciousness and that required assistance from a third party to treat. The literature shows that having experienced a severe hypoglycaemic event is associated with significant impairment to cognitive function [12, 270-274]. Cognitive impairment is, in turn, associated with both anxiety and depression disorders [275-277].

Any event that causes loss of consciousness or seizures is of concern to neurophysiological health and can lead to damage to neural function that may include an impact on affect regulation, HPA Axis function, and other key neurological mechanisms [272, 278]. Moreover, severe hypoglycaemia includes as a matter of course, a dangerous lowering of glucose provision to the brain. The brain uses a significant portion of all glucose consumed by the body and requires a regular supply for appropriate function and ultimately survival. Any disruption to the glucose supply to the brain can have potentially disastrous results including long-term or permanent damage to neurological function [279-281].

The final predictor in the model was long-term metabolic control, measured by the three year average of participants' HbA1c. The relationship between affect and metabolic control has been repeatedly reported in the literature [95, 96, 201-203]. Indeed, a conversation with the family members of almost anyone with type 1 diabetes will reward the listener with stories of mood swings and melancholy associated with poor glycaemic control. The long-term consequences of poor metabolic control relate to complications risks and neurological changes already discussed. There appears to be a bi-directional relationship between these factors in which poor metabolic control influences affect, and disordered affect has an influence on metabolic control. More research is needed to fully understand this relationship however, both the present results, and the extant literature, report a clear relationship between affect and metabolic control.

H_2: Short-Term and Long-Term Metabolic Control Poorer in Participants with Affective Disorders

The second hypothesis that short and long-term metabolic control would be poorer in participants with an affective disorder compared to participants without was only partially supported. All assessed metabolic control time periods (Short-term BGL over 3 hour period of participation, HbA1c at participation, and both 1 and 3 years mean HbA1c) showed that participants with an affective disorder had higher mean BGL than participants without an affective disorder. However, the variation between the two groups was not statistically significant and the effect sizes were small [(282)] for all of the metabolic control variables. The sample sizes for the groups in each analysis were quite small and this is likely to have had an influence on the statistical outcomes.

While the predominant message in the literature is that disordered affect and metabolic control are correlated, recent studies have begun to unpack this relationship with more sensitive and differentiated diagnostic tools. These studies, while still finding a relationship between metabolic control and affect, have found that the association is not as linear as previously reported and a number of other factors are covariates in the relationship. For example Zdunczyk and Sendela [(283)] found that in youth with type 1 diabetes, 18% of those with HbA1c <7.5% (optimal control) had depression symptoms, while 21% of those with HbA1c >7.5% (sub-optimal control) had depression symptoms. This is consistent with the results of the present study that show non-significant higher HbA1c in participants with an affective disorder compared to those without. However, a key finding of Zdunczyk and Sendela [(283)] was that, regardless of HbA1c levels, depression resulted in significantly reduced quality-of-life.

Emotional discord and other associated symptomology of disordered affect such as motivational change, can be experienced as a global state of psychological wellbeing (eg: unipolar depression or generalised anxiety disorder), or they can be stimuli-specific (eg: phobia, social anxiety, or agoraphobia). Strandberg and Graue [(284)] identified that diabetes distress in adults – a form of diabetes-specific disordered affect – was significantly related to long-term metabolic control (HbA1c) while clinical depression and anxiety were not. The differentiating of affective states in this way has not been a prominent feature in historical research in this area in type 1 diabetes. Much of the research presented in the literature rely on self-reported diagnostic tools which lack the specificity to differentiate between variations of clinical affective disorders as well as

between clinical disorder and psychological distress that features key elements of diagnostic criteria such as negative affect, worry, and rumination, but do not meet all criteria required for a clinical diagnosis under the DSM or ICD diagnostic guidelines [29, 259].

It may be that the prevalence of disordered affect in type 1 diabetes is mediated by factors that exist sufficient to influence onset outside of metabolic control. Even under these conditions, metabolic control may exert an influence on affect status however, the present study lacks sufficient sample size to have the statistical power to identify it. This is particularly relevant in metabolic control analysis as the long-term control of glycaemia tends to have a ceiling effect due to the acute impact that even relatively short periods of extreme poor control can have. If metabolic control is extremely elevated for even a few days, the result is diabetic ketoacidosis (DKA). DKA is a condition in which the burning of fat by the body to obtain a ready source of energy due to insulin deficiency results in an accumulation of ketones in the blood. If this situation is not remedied expediently, then acidosis eventuates and DKA is the end result [285]. DKA is an acute medical emergency that is the single largest cause of death in people with type 1 diabetes under the age 40 [286-288].

Given the majority of people with type 1 diabetes have poor metabolic control, and 1:4 have chronically poor metabolic control, it is expected that effect sizes would be small in comparison groups taken from general type 1 diabetes populations and therefore large sample sizes are needed to conduct a meaningful analysis of HbA1c variations. Ultimately the results show that, although not statistically significant, participants with type 1 diabetes who also have a comorbid affective disorder have poorer metabolic control across the short, medium and long term.

H_3: Complications more Prevalent in Participants with Affective Disorders

The third hypothesis that participants with disordered affect would have more complications than participants without was not fully supported. While a high portion of participants with complications also had an affective disorder (77.3%, *n*= 34/44), the relationship between the two conditions did not reach statistical significance and the effect size was small. However, despite not reaching statistical significance participants with an affective disorder were more than twice as likely to also have diabetes-related complications. This is an important indicator that affective disorders and complications

are related. The small effect size combined with the relatively small sample size are likely to have influenced the lack of statistical significance.

This finding is contrary to the literature that has consistently found a relationship between depression and anxiety and an increased risk of complications and mortality [132, 219, 289, 290]. For example, Trief and Xing [219] found that patients with type 1 diabetes who also had depression were significantly more likely to have one or more long-term diabetes-related complication, and in the previous three month period were more likely to have experienced acute diabetes complications such as severe hypoglycaemia (2:1) or DKA (3:1). Similarly, Chapman and Shuttleworth [290] found increased rates of anxiety and depression in patients with type 1 diabetes and peripheral neuropathy related Charcot complications. In a study of depression and mortality in type 1 diabetes, Kimbro and Mangione [289] found that patients with type 1 diabetes who were depressed had an overall mortality rate that was 49% higher than in those without depression. This result was identified after controlling for other variables such as age, sex, socioeconomic status, ethnicity, and the presence of other complications. In older patients (>65yrs) the increased mortality was 78%.

Clinical Considerations

While further investigation is necessary, these results have important implications for the clinical management of type 1 diabetes. Depression is characterised not only by negative affect but also by anhedonia; fatigue; poor sleep, diet, and exercise hygiene; and, social isolation [291, 292]. A reduced interest and motivation in areas such as self-care, long-term planning, and engagement with other people, can all contribute to poor acute health outcomes and an increased risk of long-term complications [265].

Furthermore, anxiety often creates a craving for control resulting in either obsessive or avoidance behaviours that may be general (GAD) or specific (phobia or diabetes distress) leading to repetitive fears about a potential event (nocturnal-hypoglycaemia, kidney disease), [170, 171]. This “over thinking” may lead to obsessive behaviours aimed at reducing the likelihood of the event or alternatively, it may lead to an engagement of maladaptive behaviours such as self-medication [293, 294], avoidance, or denial [88]. The outcome may be poor adherence to care plans, non-attendance at clinic visits, obsessive care behaviours such as over testing of BGL, or increased

affective difficulty leading to social isolation, depression, or disordered eating [97, 111, 137, 155, 172, 295, 296].

Conclusion

Both evidence and intuition suggest that living with chronic health conditions that are serious, highly demanding of time and both physical and psychological resources, and are ultimately incurable, extract a considerable toll on sufferers. Psychological disease burden places high loads of coping needs upon individuals. Those with type 1 diabetes must engage in and maintain the same general life responsibilities of the rest of the population as well as manage a significant level of healthcare responsibilities that cannot be delegated, and cannot be avoided, ignored, or placed in respite without the spectre of severe and life-threatening consequences. The evidence shows clearly that the burden of this ongoing demand is faced by many in the shadow of clinical psychopathology such as anxiety and depression. The consequences of these mental health conditions add yet more burden. These results show that the presence of anxiety and depression disorders are linked to poorer metabolic control and an increased prevalence of complications. Indeed, participants with an affective disorder are more than twice as likely to have diabetes-related complications as those without an anxiety or depression disorder. Further research is needed to better understand the full extent and the nature of the influence affective disorders have on type 1 diabetes clinical outcomes however, the present results make it clear that clinicians and researchers alike must pay more attention to the relationship between them.

CHAPTER FOUR: NEUROPSYCHOLOGICAL CHARACTERISTICS OF TYPE 1 DIABETES

Chapter Abstract

There is a general move away from global measures of IQ towards a recognition that domain-specific performance is more readily associated with both specific functional deficits as well as neuromorphological characteristics. In type 1 diabetes there is evidence for neuropsychological sequelae that manifests across multiple domains and can appear within a few years of diagnosis. However, the literature also presents conflicting results in which neuropsychological sequelae are not identified in type 1 diabetes even after periods of 20 years or more post-onset. This chapter presents a series of studies that describe the domain-specific neuropsychological characteristics of participants with type 1 diabetes and compares them to age and sex balanced peers without the disease. Executive function, attention and working memory, and processing speed, were assessed using computer analogues of the Wisconsin Card Sort Test (CST), The Tower of London Test (TOLT), and the n-Back Test (see Methods section). Additionally, in the type 1 diabetes participants, associations between the characteristics of neuropsychological function and disordered affect, disease aetiology, metabolic control, and diabetes-related complications were quantified and are presented. The specific results are shown and discussed in each individual study and together indicate that type 1 diabetes participants have characteristically impaired cognitive function however, different cognitive domains may be modulated by potentially different factors. Processing speed impairments appear to be a characteristic of type 1 diabetes and is significantly different in participants with the disease compared to controls, and is associated strongly with diabetes-related aetiology and clinical factors. However, attention and working memory, and executive function appear to be modulated by non-diabetes-specific antagonists. Performance in executive function did not differ between participants with and without type 1 diabetes however, within-groups differences in executive performance were affect-dependent and differed in characteristics between the participants with type 1 diabetes and without. Similar results were found for performance in attention and working memory. The conclusion drawn from the results is that type 1 diabetes does have an adverse impact on neuropsychological function both directly and due to the high prevalence rates of psychopathology that presents comorbidly with the disease. One factor that may provide further understanding of the pathogenics of cognitive dysfunction in type 1 diabetes is the increased appreciation of the high incidence of clinical anxiety and depression in patients and the impact this may exert on cognitive faculty.

Aims and Hypotheses of Studies Presented in Chapter Four

Table 4.1. *Aims and Hypotheses of Studies Presented in Chapter Four.*

Study #	Aims	Hypotheses	Hypothesis Supported
7	a. To investigate executive function, in adult participants with type 1 diabetes compared to controls;	7.1. Compared to age and sex balanced no-type 1 diabetes controls, participants with type 1 diabetes would perform more poorly on executive function tasks;	No
	b. To evaluate and compare the impact that disordered affect (anxiety, depression) has on this cognitive function	7.2. The presence of an affective disorder would influence executive function;	Yes
	c. To investigate the relationship between cognitive performance and diabetes-specific clinical and aetiological factors.	7.3. Diabetes-specific clinical and aetiological factors would be associated with executive function.	Yes
8	a. To evaluate the difference in attention and working memory between participants with type 1 diabetes and controls;	8.1. Compared to no-type 1 diabetes controls, participants with type 1 diabetes would perform more poorly on attention and working memory tasks;	Yes
	b. To evaluate and compare the influence of disordered affect on attention and working memory of participants;	8.2. The presence of an affective disorder would adversely influence attention and working memory performance;	Yes
	c. To assess the relationship between attention and working memory and diabetes-specific clinical and aetiological factors.	8.3. Diabetes-specific clinical and aetiological factors would be associated with attention and working memory performance.	Yes
9	a. To assess the difference in processing speed between participants with type 1 diabetes and no-type 1 diabetes controls;	9.1. It was hypothesized that compared to no-type 1 diabetes controls, participants with type 1 diabetes would have slower processing speed;	Yes
	b. To evaluate and compare the relationship between disordered affect and processing speed in participants;	9.2. Processing speed would be adversely influenced by the presence of an affective disorder;	Yes
	c. To identify any relationship between processing speed and diabetes-specific clinical and aetiological factors.	9.3. Processing speed would be associated with diabetes-specific clinical and aetiological factors.	Yes

Study 7: Executive Function in Type 1 Diabetes

S7: Abstract

Background: Executive function performance has been shown to be adversely impacted by type 1 diabetes. However, there is no consensus as to the extent and nature of the impact, or the pathogenic mechanics. The aim of the present study was to investigate executive function in adult participants with type 1 diabetes, and its association to anxiety and depression.

Methods: A cross-sectional, case-control, within-between designs model was used to evaluate executive function using computer analogues of the Wisconsin Card Sort Test (CST) and the Tower of London Test (TOLT) between age and sex balanced case (n=70) and control (n=73) participants (N=143). Psychopathology status was ascertained using the MINI International Neuropsychiatric Interview. The relationship between diabetes-specific aetiological and clinical factors, and executive function was also assessed in type 1 diabetes participants.

Results: Multivariate analysis showed no difference in executive function between participant groups (main effect: p= .73, η_p^2= .04; all individual measures p > .05). When the influence of affective disorder was controlled, there was still no difference between the groups. A comparison of the significance of the affect-controlled and uncontrolled MANOVA results showed that the influence of affective disorders significantly impacted six out of nine results (CST: correct responses, total errors; TOLT: excess moves 3, 4, & 5-ring trials, excess moves all conditions). Short-term metabolic control was significantly associated with performance on the TOLT (total excess moves r= .25, p= .04), and long-term metabolic control was significantly associated with performance on the CST (non-perseverative errors r= .59, p< .01; total errors r= .65, p< .01; category completions r= -.62, p< .01). A comparison of the correlation co-efficients with and without controlling for the influence of affective disorders showed that the presence of an affective disorder was a significant mediator of the relationship between executive function and metabolic control in participants with type 1 diabetes.

Conclusion: Affective pathology more than type 1 diabetes per se appears to adversely influence executive function in type 1 diabetes. While affect influences individuals with and without type 1 diabetes, the specific nature of the influence appears to differ.

Keywords: Diabetes Mellitus: Type 1; Neuropsychology; Cognition; Executive Function; Affective Disorder; Depression; Anxiety; Aetiology; Complications; Metabolic Control Glycaemic control.

S7: Introduction

There is emerging evidence that type 1 diabetes is associated with reductions in cognitive function [117]. This impact on cognition is known as type 1 diabetes-associated cognitive decline (T1DACD) [119]. The clinical features of cognitive impairment that have been most associated with diabetes include decreases in visual memory, information processing, planning, visuospatial construction, psychomotor efficiency and processing speed, sustained attention and working memory, and decreased executive function in tasks such cognitive flexibility, decision-making and problem solving by applying knowledge to a new situation [116, 117, 122-124, 297]. While these functional impairments have been identified, the mechanisms by which type 1 diabetes mediates neuropsychological performance remains largely unclear. What is clear is that, as a chronic medical condition, the successful navigation of a life lived with type 1 diabetes is highly self-care dependent and impairments to cognitive function has a negative influence on this capacity.

According to Thabit, Kyaw Tun, McDermott, and Sreenan [118], examples of successful self-care behaviours include medical treatment adherence; lifestyle management and making appropriate lifestyle choices; self-treating glycaemic changes through a combination of medication adjustment, diet, and exercise; and identifying when professional advice and assistance may be required. These behaviours are reliant on cognitive competency in areas such as planning, organisational skills, impulse control, and self-awareness, which are all primarily under the control of executive function [115, 116, 118]. Studies indicate that executive function may be impaired (impaired executive function or IEF) in type 1 diabetes even if other areas of cognition remain largely intact [118]. IEF, in particular compromised decision-making and problem solving, has been associated with poor treatment adherence and sub-optimal metabolic control in type 1 diabetes [116, 120, 125]. These factors in turn are associated with increased diabetes-related complications, increased hospitalisation rates, increased cost burden on both personal and public expenditure on healthcare, and greater mortality from both acute and chronic diabetes-related medical factors [116, 118, 119, 130].

While the pathogenics of IEF in type 1 diabetes remains unclear, both diabetes-specific factors and non-diabetes-specific antagonists have been speculated. Diabetes-specific factors include inflammation (see chapter 5); clinical factors such as reduced hypoglycaemia awareness [298], elevated HbA1c [120, 121], and cerebrovascular degeneration [299-301]; dysregulated neurotransmitter and catacholaminergic function [302,

[303]; and other possible contributory neuromorphology in areas such as the hippocampus [302, 304, 305]. The most widely speculated non-diabetes-specific antagonist contributing to poor decision-making and other factors of IEF is the high rate of comorbid depression and other psychopathologies in type 1 diabetes [116, 130].

This relationship between depression and IEF has been well reported in the literature [121, 306, 307]. For example, Cella et al., [306] identified that depressed patients performed more poorly than healthy controls in executive function tasks requiring flexible decision making. This was supported by neurobiological analysis of decision-making in depressed patients in which it was found that the intentional depletion of serotonin in otherwise healthy individuals, altered the decision-making process and was associated with a reduced capacity to predict reward [121]. Rogers et al [121], speculate that serotonin may therefore moderate decision-making in depressed individuals by modulating the processing of reward cues and thereby contributing to the onset and maintenance of anhedonia. Similarly van Randenborgh et al., [307] found that compared to healthy controls, depressed patients experienced greater levels of decisional conflict and tended to mediate their decision-making through depression-related processes such as low self-efficacy, poor concentration and focus, and rumination.

The purpose of this study was to investigate executive function, in adult participants with type 1 diabetes compared to no-type 1 diabetes controls, and to evaluate and compare the impact that disordered affect (anxiety, depression) has on this cognitive function. It was further aimed to investigate the relationship between cognitive performance and diabetes-specific clinical factors of duration of illness, age of onset, metabolic control, severe hypoglycaemic events, and the presence of diabetes-related complications. It was hypothesised that compared to age and sex balanced no-type 1 diabetes controls, participants with type 1 diabetes would perform more poorly on executive function tasks; that the presence of an affective disorder would influence executive function; and that diabetes-specific clinical and aetiological factors would be associated with executive function.

S7: Results

Descriptive analysis of group personal and demographic data confirmed that there were no differences between the participants in the type 1 diabetes and no-type 1 diabetes groups in age, sex, level of education, or employment characteristics.

Participants' descriptive statistics are reported in Table 1.1, demographic statistics are reported in Table 2.2, affect status statistics are reported in Table 3.6, and diabetes-specific clinical data for the type 1 diabetes group are reported in Table 2.5. The computerised analogues of the Wisconsin Card Sort Test (Card Sort Test or CST) and the Tower of London Test (TOLT) were used to assess executive function in participants.

H_1: Poorer Executive Function in Type 1 Diabetes

The first hypothesis was assessed by analysing the differences in executive function between participants in each of the two groups. Between-groups performance on the CST and TOLT were subjected to multivariate analysis of variance (MANOVA). No serious violations of the assumptions were noted. Multivariate analysis showed no difference in overall executive function between participants with type 1 diabetes compared to participants with no-type 1 diabetes (Wilk's Lambda= .962, F(8, 134)= .659, p= .727, η_p^2= .038). Individual analyses revealed no differences between the groups in any of the executive function performance measures of the CST or the TOLT (Table 4.2).

H_2: The Presence of an Affective Disorder would Influence Executive Function

Further analysis was undertaken to test the hypothesis that affect would moderate executive function. A second MANOVA was conducted, this time controlling for the presence of an affective disorder (anxiety, depression, comorbid anxiety-depression). No serious violations of the assumptions were noted. When the influence of the presence of an affective disorder was controlled, multivariate analysis again showed no difference in overall executive function between participants with type 1 diabetes compared to participants with no-type 1 diabetes (Wilk's Lambda= .975, F(8, 134)= .420, p= .908, η_p^2= .025). Individual analyses of the between-subjects effects also revealed no differences between the groups in any of the executive function performance measures of the CST or the TOLT (Table 4.2).

To evaluate the influence of the presence of an affective disorder on the group performances, an analysis of the statistical differences between the MANOVA results was undertaken. Individual between-subjects ANOVA *p* values were converted to *Q* values (where *Q* is the probability that the observed score is due to chance; $Q= 1 - p$), which were converted to *z* observed scores. The *z* observed scores for each of the corresponding MANOVA results where then analysed to deliver a *z obtained* value.

MANOVA results were considered significantly different if: $-1.96 > z_{obt} > 1.96$. Results indicated that the presence of an affective disorder had a significant influence on executive performance. The results of the MANOVA in six out of the nine measures of executive performance were significantly different when the influence of the presence of an affective disorder was controlled for (Table 4.2).

H_3: Diabetes-Specific Clinical and Aetiological Factors Correlated to Executive Function

To test the third hypothesis that diabetes-specific aetiology and clinical factors would be associated with executive function, correlation coefficients were calculated between the executive function performance variables of the CST and TOLT, and age of disease onset, duration of illness, hypoglycaemia history, metabolic control, and the presence of diabetes-related complications. Spearman's rank order correlation (*rho*) was used for analyses involving variables with non-parametric data and Pearson's (*r*) was used for all analyses involving parametric data. Results of the correlational analyses revealed that only metabolic control was significantly related to measures of executive function (Table 4.4).

Pearson's correlational analysis indicated that participants' short-term blood glucose level (average BGL during participation in study) was significantly correlated to the total number of excess moves made across all trials of the TOLT (r= .246, p= .042). Long-term metabolic control (average HbA1c over previous 36 months) was associated with the CST executive performance measures of total errors (r= .650, p= .001), non-perseverative errors (r= .594, p= .004), and the total number of categories completed (r= -.620, p= .002). Taken together, these four results indicate that both immediate blood glucose levels and long-term metabolic control may have an influence on planning and problem solving.

In order to evaluate whether affective disorders made a statistically significant impact on the results, partial correlations controlling for affect were undertaken. Any corresponding co-efficient pair from the affect-controlled and uncontrolled correlational analyses in which at least one co-efficient was statistically significant were then converted to *z*-scores and compared. This was done by calculating the $z_{obtained}$ score from the corresponding $z_{observed}$ scores derived from converting the *r* co-efficients to their analogous *z* score [110]. Nine co-efficients were significantly correlated across the controlled and uncontrolled analyses. In five of these nine, controlling for the influence

of affect changed the significance of the co-efficient (Table 4.4). Of these five coefficients, the statistical difference between four were shown to be significant (CST: non-perseverative error and medium-term HbA1c z_{obt} = -3.045, total errors and medium-term HbA1c z_{obt} = -3.752, category completions and medium-term HbA1c z_{obt} = -3.326; TOLT: excess moves – 4 ring and severe hypoglycaemia z_{obt} = -2.894; Table 4.4). The results indicate that affect mediates the relationship between diabetes-specific clinical outcomes and executive function.

Table 4.2. *Descriptive Statistics and Results of the MANOVA for Executive Function Task Performance in the Card Sort Test and Tower of London Test between Participants in the Type 1 Diabetes and No-Type 1 Diabetes Groups, With and Without Controlling for the Presence of an Affective Disorders and With Comparisons of the Statistical Significance of the Difference between the MANOVA Results.*

Executive Function Performance Variables	Type 1 Diabetes, *n*= 70		No-Type 1 Diabetes, *n*= 73		*MANOVA*			*MANOVA controlling for affect status*			Significance of the difference between MANOVA *p values* #		
	M	*SD*	*M*	*SD*	*F* (1,142)	*p*	η_p^2	*F* (1,142)	*p*	η_p^2	Z_1	Z_2	z_{obt}
CARD SORT TEST													
Correct responses	28.80	13.20	26.44	12.70	1.189	.277	.008	.357	.551	.003	0.592	0.128	3.882*
Perseverative errors	13.49	12.72	11.53	11.02	.964	.328	.007	1.332	.250	.009	0.445	0.674	-1.916
Non-perseverative errors	38.73	29.97	40.68	29.75	.153	.696	.001	.943	.333	.007	0.513	0.432	.678
Total errors	52.21	28.45	52.22	28.61	.000	.999	<.001	.283	.596	.002	3.09	0.243	23.820*
Category completions (max = 6)	3.41	2.31	4.30	7.01	1.014	.316	.007	.161	.689	.001	0.479	0.493	-.117
TOWER OF LONDON TEST													
Excess moves - 3 ring	5.57	8.44	5.36	6.62	.029	.866	<.001	.296	.588	.002	1.108	0.222	7.413*
Excess moves - 4 ring	1.83	2.60	1.60	2.40	.308	.580	.003	.007	.934	<.001	0.202	1.506	-10.910*
Excess moves - 5 ring	1.61	2.42	1.88	3.18	.320	.572	.002	.051	.821	<.001	0.181	0.919	-6.175*
Excess moves – total all conditions	9.01	9.17	8.69	8.01	.053	.818	.001	.216	.643	.002	0.908	0.366	4.535*

Notes: Effect size, small η_p^2= .01, medium η_p^2= .06, large η_p^2= .14 [(282)]. # Indicates significant statistical difference between *z* observed scores of the MANOVA *Q* values where *Q* (the probability that the observed score is due to chance)= 1 – *p*; z_{obt} (*z obtained*) = ($z_1 - z_2$) / SQRT ((1 / (N_1 – 3))+ ((1 / (N_2 – 3))); * Significant difference between MANOVA results: -1.96 > z_{obt} > 1.96.

Table 4.3. *Results of Correlations and Partial Correlations (Controlling for Affective Disorders) between Executive Function Performance on the Computer Analogues for the Wisconsin Card Sort, and Tower of London Tests, and Diabetes-Specific Clinical and Aetiological Factors.*

		Correlations							Partial Correlations: controlling for affective disorders						
		Aetiology		Metabolic Control			Severe Hypo.	Comp.	Aetiology		Metabolic Control			Severe Hypo.	Comp.
Executive Function Performance Variables		Age of onset	Illness duration	S-T	M-T	L-T			Age of onset	Illness duration	S-T	M-T	L-T		
Correct responses	*Cor*	.133	.116	-.156	-.194	.361	.036	-.008	-.021	-.040	-.138	.488*	.383	-.223	-.370
	p	.281	.350	.204	.151	.099	.775	.948	.929	.864	.550	.025	.086	.331	.098
Perseverative errors	*Cor*	-.001	.191	-.108	-.115	.047	-.026	-.164	-.208	.276	-.029	.175	.083	.140	-.161
	p	.996	.122	.381	.399	.834	.836	.176	.366	.226	.900	.447	.721	.545	.485
Non-perseverative errors	*Cor*	.113	-.047	.136	.011	.594**	.203	.133	.086	-.083	.306	.534*	.589**	.213	-.064
	p	.363	.705	.270	.935	.004	.108	.273	.710	.722	.177	.013	.005	.355	.784
Total errors	*Cor*	.117	.037	.093	-.040	.650**	.204	.148	-.004	.039	.309	.642**	.658**	.287	-.140
	p	.344	.767	.452	.768	.001	.105	.222	.987	.868	.173	.002	.001	.206	.544
Category completions	*Cor*	-.170	-.063	-.017	.097	-.620**	-.210	-.164	-.092	.012	-.155	-.627**	-.627**	-.115	.205
(max= 6)	*p*	.169	.611	.891	.477	.002	.095	.176	.690	.959	.502	.002	.002	.619	.373
Excess moves - 3 ring	*Cor*	-.054	-.027	.231	.221	-.022	.145	.143	-.006	.121	.050	.044	-.058	.129	.166
	p	.658	.826	.056	.096	.922	.244	.231	.981	.602	.828	.850	.804	.578	.473
Excess moves - 4 ring	*Cor*	.007	-.149	.140	.159	.028	-.067	.174	.299	-.194	.037	-.132	-.062	-.554**	.029
	p	.952	.223	.253	.234	.898	.591	.144	.188	.400	.872	.569	.789	.009	.900
Excess moves - 5 ring	*Cor*	-.124	-.168	-.048	-.131	-.024	.003	-.037	-.285	-.038	-.295	-.041	-.113	.025	-.045
	p	.312	.169	.694	.326	.914	.984	.760	.210	.869	.195	.859	.627	.915	.846
Excess moves – Total	*Cor*	-.076	-.106	.246*	.219	-.020	.141	.177	-.009	.068	-.009	.007	-.092	.018	.154
	p	.535	.386	.042	.099	.928	.258	.137	.970	.769	.968	.977	.691	.938	.506

Notes: * Sig. @ α = .05; ** Sig. @ α = .01; *** Sig. @ α = .001; S-T = Average BGL during participation; M-T = HbA1c most recent to participation; L-T = Average HbA1c over previous 36 months.

Table 4.4. *Tests of the Statistical Significance between Correlation Co-efficients of the Relationship between Executive Function and Diabetes-Specific Aetiological and Clinical Factors, before and after the Influence of Affective Psychopathology is Controlled.*

Executive Function Performance Variables	Diabetes Factor	Uncontrolled			Affect-Controlled			z_{obt}
		r	*p*	z_1	*r*	*p*	z_2	
CST								
Correct resp	M-T	-.194	.151	.197	.488*	.025	.534	-1.751
Non-Persev errors	M-T	.011	.935	.011	.534*	.013	.597	-3.045#
Non-Persev errors	L-T	.594**	.004	.685	.589**	.005	.678	.036
Total errors	M-T	-.040	.768	.040	.642**	.002	.762	-3.752#
Total errors	L-T	.650**	.001	.775	.658**	.001	.790	-.078
Category completions	M-T	.097	.477	.097	-.627**	.002	.737	-3.326#
Category completions	L-T	-.620**	.002	.725	-.627**	.002	.737	-.062
TOLT								
Excess moves - 4 ring	Sev Hypo	-.067	.591	.067	-.554**	.009	.624	-2.894#
Excess moves - total	S-T	.246*	.042	.251	-.009	.968	.009	1.257

Notes: : * Sig. @ α = .05; ** Sig. @ α = .01; *** Sig. @ α = .001; S-T = Average BGL during participation; M-T = HbA1c most recent to participation; L-T = Average HbA1c over previous 36 months; # Indicates significant statistical difference between correlation co-efficients of the groups: $-1.96 > z_{obt} > 1.96$; $z_{obt} = (z_1 - z_2) / \text{SQRT}((1 / (N_1 - 3)) + ((1 / (N_2 - 3)))$; Correlation co-efficient transformations to *z* from Table 11.1 in Pallant [110, p.142]

S7: Discussion

The present study investigated executive function in type 1 diabetes and the results indicate that IEF in participants was influenced more by the presence of an affective disorder (anxiety, depression, comorbid anxiety-depression) than the presence of type 1 diabetes per se. Furthermore, the results show that executive function is significantly associated with both short-term glycaemic control and longer-term HbA1c levels. These results support two of the three hypotheses forwarded and support the literature in as much as previous research shows strong evidence that AD influences executive function in studies of the general population [121, 256, 306, 307], and that executive function in type 1 diabetes is closely related to metabolic control [116, 120, 297, 299, 302, 308].

H_1: Poorer Executive Function in Type 1 Diabetes

The first hypothesis that participants with type 1 diabetes would perform more poorly on executive function tasks was not supported. When whole-of-group analysis was conducted, executive function task performance in the participants with type 1 diabetes did not differ compared to the participants with no-type 1 diabetes. This is at odds with the literature that generally shows increased IEF in type 1 diabetes [297, 302].

H_2: The Presence of an Affective Disorder would Influence Executive Function

Multivariate analysis controlling for the influence of affective disorders revealed no significant difference in executive function between participants with type 1 diabetes and no-type 1 diabetes controls. However, when the affect-controlled and uncontrolled MANOVA results were compared, the influence of disordered affect on the results was shown to be significant. These results indicate that while the difference between groups was not sufficient to reach statistical significance, there is a significant difference between the groups in the influence that affective disorders exert on executive performance.

Participants with type 1 diabetes showed a greater difference in performance when affect was controlled than the no-type 1 diabetes controls. The groups differed in CST performance on measures of correct responses and the total number of errors made, and in TOLT performance on all measures of performance evaluated. These results suggest that affect influences decision making, problem solving, planning, and visuospatial skills differently in type 1 diabetes. Error rates and correct responses in the CST are indicators of complex executive processes including problem solving, decision making, inhibition, and perseveration, while the differences in performance on the TOLT reflect general executive function as well as specific processes of problem

solving, planning, and visuospatial skills. The literature supports the presence of deficits in problem-solving and associated executive functions in type 1 diabetes [116, 119, 125, 299] and the relationship between executive deficits and affective disorders [276].

H_3: Diabetes-Specific Clinical and Aetiological Factors Correlated to Executive Function

Hypothesis three that executive function would be associated with aetiological and clinical factors of type 1 diabetes was supported. Executive function was significantly correlated to both short-term glycaemic control (average BGL during participation in the study), and to long-term metabolic control (average HbA1c over previous 36 months). These results are in line with previous findings that IEF was associated with hyperglycaemia [115, 120, 299, 302]. Average BGL during participation was associated with the number of moves taken to reach a solution in the TOLT with the results indicating that higher BGLs adversely impacted participants' ability to find the most efficient solution to the problem. The strongest association was shown in the relationship between executive function and long-term metabolic control. Three-year average HbA1c was significantly correlated to executive function measures in the CST requiring general problem solving and cognitive set maintenance (non-perseverative errors, total errors made, and less category completions).

Factors such as hypoglycaemia and complications have been associated with cognitive function in several studies [302], and have been found to have no relationship in others [299]. The results of the present study showed no relationship between these clinical factors and executive function. Given the inconclusive nature of the evidence presented in the extant literature, more research is needed to better elucidate the relational qualities of these important type 1 diabetes considerations.

Several other aetiological and clinical factors have been associated with executive function including age of onset and duration of illness [308], however, hyperglycaemia is one of the most consistently identified correlates [120, 302]. What is less clear is the direction of the relationship between hyperglycaemia and executive function. While there is a general consensus that the association is likely to be bi-directional, McNally and Rohan [120] used structural equation modelling to investigate this relationship and found that the data best fit a model in which executive function mediated glycaemic control via the mechanism of treatment adherence. According to McNally and Rohan [120], IEF reduces adherence to optimal diabetes management

behaviours which, in turn, results in poorer glycaemic/metabolic control. Figure 4.1 shows the two alternate models tested by McNally and Rohan [120].

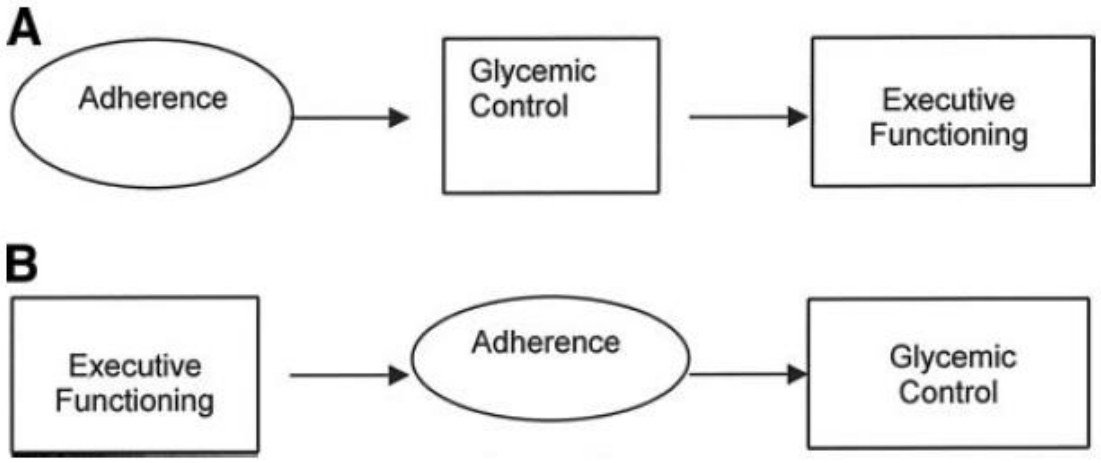

Figure 4.1. Hypothesised alternate models of the relationship between executive functioning, treatment adherence, and glycaemic control. A: Glycaemic control mediating the relationship between adherence and executive functioning. B: Adherence mediates the relationship between executive functioning and glycaemic control.

Given the strong and consistent associations between IEF and hyperglycaemia, executive function capacity is an important clinical consideration. The research shows that patients with better competency in executive functions are more likely to demonstrate greater adherence to diabetes management best practices which consequently relates to better glycaemic control [120]. Improved glycaemic control is ultimately related to reduced complications risk and lower rates of premature mortality [309-311].

The presence of an affective disorder was shown to be a significant mediator of the relationship between executive function and metabolic control. The correlation co-efficients between medium-term metabolic control and non-perseverative errors, total errors, and the number of categories completed in the CST were significantly different when affect was controlled. Similarly, when affect was controlled, there was a significant difference between history of severe hypoglycaemia and moves to completion in the TOLT.

Affect may have a more pronounced impact on executive function in type 1 diabetes due to the compounding effects that the comorbid presentation of the two conditions has on pathophysiological characteristics [302], including affect-related and

diabetes-specific HPA-Axis alterations [89, 93, 240], and the accumulative effect of the chronic glycaemic upregulation that is associated with type 1 diabetes [14, 95, 284]. The results support previous findings that show that anxiety and depression are major influences on cognitive function [121, 276, 306, 307]. However, few studies of cognition in type 1 diabetes have included an analysis of executive function that evaluates or controls for the influence of disordered affect. Given the high level of affective disorders in type 1 diabetes and the influence they have on cognition, this is somewhat surprising [8, 14, 130, 219, 268, 283, 284]. More research is needed to account for the role affective disorders play in the overall pathogenic mechanics of IEF in type 1 diabetes.

Conclusion

The primary findings of the study were that 1) Affective pathology more than type 1 diabetes per se appears to adversely impact executive function in type 1 diabetes; 2) that the nature of the relationship between affect and executive function appears to differ in type 1 diabetes, and; 3) that executive function is significantly associated with both short and long-term glycaemic control. These results do not directly support the extant literature that reports a direct relationship between type 1 diabetes and executive dysfunction [119, 120, 124, 297, 302], but rather supports the relationship as indirect and mediated by the influences of affective pathology such as anxiety and depression disorders. These results do however support the overwhelming bulk of the literature that evidences the consistent relationship between executive function and hyperglycaemia across age and aetiological boundaries [115, 119, 120, 299, 302]. While the dyadic relationships between type 1 diabetes, executive function, and affect are well documented, further research is needed to further understand the triarchic relationship between these factors.

Study 8: Attention and Working Memory in Type 1 Diabetes

S8: Abstract

Background: Type 1 diabetes has an adverse impact on attention and working memory (AWM). While several aetiological and clinical factors have been proposed as mediating factors, the understanding of the pathogenic mechanisms of impaired AWM in type 1 diabetes remains incomplete. Further, the influence of affective disorders on AWM performance in type 1 diabetes has not been well documented. The present study investigated AWM, and its relationship to these factors in adults with type 1 diabetes.

Methods: AWM performance was assessed using a computer analogue of the n-Back Test. Psychopathology status was ascertained using the MINI International Neuropsychiatric Interview. A mixed-methods, case-control design was used to assess the differences in performance between the type 1 diabetes case (n= 70) and no-type 1 diabetes control (n= 73) groups. The relationship between diabetes-specific aetiological and clinical factors, and AWM was also assessed in the type 1 diabetes participants. Within-groups comparisons of these factors between affect-controlled and uncontrolled analyses conditions were also conducted.

Results: Cognitive load had a significant impact on performance in both groups (p= <.01, η_p^2= .54) however, there was no difference between the groups in overall performance across cognitive load conditions (F(1, 139)= 1.57, p= .21, η_p^2= .01). Participants with type 1 diabetes missed more target stimuli as cognitive load increased (p= .03, η_p^2= .03). Type 1 diabetes participants performed more poorly than controls under higher cognitive load cognitions, in both a general comparison and when the influence of affect was controlled (uncontrolled MANOVA: 3-back miss target p= .02, η_p^2= .04; affect-controlled MANOVA: 3-back miss target p= .01, η_p^2= .05; 3-back omit target p= .02, η_p^2= .04, 3-back accuracy p= .02, η_p^2= .04, omit target all conditions p= .05, η_p^2= .03). In the type 1 diabetes group, a comparison of MANOVA results with and without controlling for the influence of affective disorders revealed that affective disorders significantly influenced 16 out of 18 AWM variables assessed across all cognitive load conditions ($-1.96 > z_{obt} > 1.96$). Correlations between AWM, and diabetes-specific clinical and aetiological factors revealed that, age of onset, short-term glycaemic control, HbA1c, hypoglycaemia, and complications were significantly associated with multiple measures of AWM ($p < .05$). Co-efficients were significantly influenced by the presence of an affective disorder.

Conclusion: Type 1 diabetes is associated with reduced AWM function, and the added presence of an affective disorder appears to lend further challenges to performance capacity. Impaired AWM is significantly associated with aetiology and deleterious clinical outcomes.

Keywords: Diabetes Mellitus, Type 1; Attention and Working Memory; Neuropsychology; Cognition; Comorbidity; Anxiety; Depression; Affect; Psychopathology; Glycaemic Control; Metabolic Control; HbA1c; Aetiology; Complications; Hypoglycaemia.

S8: Introduction

The heavy reliance on self-care practices for successful health outcomes means that impairments to any personal capacity to identify, monitor, manage, and engage in ongoing, consistent, and flexible disease management behaviours can result in serious deleterious consequences. Functional impairments to attention and working memory can have a negative impact on these capabilities by increasing the risk of self-care disease mismanagement behaviours through errors and omissions in monitoring, medication, and important health supporting practices such as diet management, exercise, and engagement with healthcare professionals [115, 119, 299, 305, 312].

Attention and working memory have been proposed to have a multi-dimensional operating structure in which several distinct components engage across a similar number of distinct neurological locations [313-317]. This functional complexity makes performance in this domain highly susceptible to influence from by a number of factors and has been consistently identified as impaired in type 1 diabetes [116, 119, 297, 305]. For example Sato and Morishita [117] found that patients with type 1 diabetes exhibit a number of similar cognitive impairments to that found in dementia. Similarly, Rustad et al. [116] found evidence for reduced working memory in type 1 diabetes that was in turn associated with poorer clinical outcomes.

Lin et al. [297] identified reduced performance in both attention and working memory in youth with type 1 diabetes within about a decade of diagnosis, while Cato and colleagues [318] identified deficits within about two years of diagnosis in children with the disease. These deficits were associated with clinical and aetiological factors. According to Lin et al. [297], working memory was associated with a history of both hypoglycaemia and hyperglycaemia, while attention was related to earlier age of disease onset. There is also some indication of an accumulatory affect with the presence of any combination of these factors (EG: hyper/hypo-glycaemia, early disease onset) being associated with a comparatively poorer performance [297]. Similarly, Brismar et al. [308] found that disease duration and age of onset were the most significant predictors of impaired cognitive function, including attention and working memory, in adults with type 1 diabetes.

While attention and working memory performance is multi-faceted, performance in this domain is particularly important to executive function. Executive functions such as planning, organising, cognitive set maintenance, inhibition and cognitive flexibility, require the ability to attend to the task at hand and to the information relevant to that task. Successful executive performance also requires a good working memory in order

to maintain awareness of the task-specific information such as rules or materials components, and to update these rules and components lists in line with set shift. As with executive function, attention and working memory deficits are also characteristic of affective disorders [116, 256, 306], and therefore the cognitive deficits identified in type 1 diabetes may be indicative of, or influenced by, an increased prevalence of disordered affect [8, 116, 130]. However, despite both impaired cognition and disordered affect being significant sequelae in type 1 diabetes, there is a dearth of literature that focuses on the two conditions in combination in this patient group.

In the present study attention and working memory performance was assessed in participants with type 1 diabetes and compared with age and sex balanced no-type 1 diabetes controls. The aim of the study was to evaluate the difference in attention and working memory performance between the participant groups, to evaluate and compare the influence of disordered affect on attention and working memory of participants, and to assess the relationship between attention and working memory and diabetes-specific clinical and aetiological factors such as age of onset, duration of illness, hypoglycaemia history, metabolic control, and the presence of diabetes-related complications. It was hypothesized that compared to no-type 1 diabetes controls, participants with type 1 diabetes would perform more poorly on attention and working memory tasks; that the presence of an affective disorder would adversely influence attention and working memory performance; and that diabetes-specific clinical and aetiological factors would be associated with attention and working memory performance.

S8: Results

Descriptive analysis of group personal and demographic data confirmed that there were no differences between the participants in the type 1 diabetes and no-type 1 diabetes groups in age, sex, level of education, or employment characteristics. Participants' descriptive statistics are reported in Table 1.1, demographic statistics are reported in Table 2.2, affect status statistics are reported in Table 3.6, and diabetes-specific clinical data for the type 1 diabetes group are reported in Table 2.5. A computer analogue of the n-Back Test was used to assess attention and working memory in participants.

H_1: Poorer Attention and Working Memory in Type 1 Diabetes

Attention and working memory performance was compared between participants in the type 1 diabetes and no-type 1 diabetes groups by analysing the differences between participants in each of the two groups.

Effect of Increased Cognitive Demand on Performance

Mixed-model ANOVA was used to evaluate the group differences in performance across the three n-back cognitive load trial conditions. Differences in performances between the groups and within the groups were assessed for measures of the number of hits on a target stimuli (Hits), the number of times a target stimuli was missed (Misses), the number of times a participant failed to provide a response in the allotted four second response window given for each trial (Omissions), and for the total accuracy of responses across all trials in each of the three cognitive load conditions (Total Accuracy).

Analysis of Hits revealed no significant interaction effect between cognitive load and participant group (Wilk's Lambda= .984, $F(2, 138)= 1.124$, $p= .328$, $\eta_p^2= .016$). There was a significant main effect for cognitive load and Hits with both groups showing a substantial decrease in the number of target stimuli hit as the cognitive demand of the task increased (Wilk's Lambda= .377, $F(2, 138)= 114.035$, $p= <.001$, $\eta_p^2= .623$; Figure 4.2). The between-groups analysis of performance difference indicated no significant difference in the impact of cognitive load on Hits during the n-Back task performance in the two groups ($F(1, 139)= .024$, $p= .878$, $\eta_p^2= <.001$).

Analysis of misses revealed no significant interaction between cognitive load and participant group (Wilk's Lambda= .978, $F(2, 138)= 1.587$, $p= .208$, $\eta_p^2= .022$). There was a significant main effect for cognitive load on Misses with both groups showing a substantial increase in the number of target stimuli missed as the cognitive demand of the task increased (Wilk's Lambda= .553, $F(2, 138)= 55.732$, $p= <.001$, $\eta_p^2= .447$; Figure 4.2). Between-groups comparison indicated that increased cognitive load had a significantly greater impact on the number of target stimuli missed during the n-Back task performance in the participants with type 1 diabetes ($F(1, 139)= 4.752$, $p= .031$, $\eta_p^2= .033$).

There was no significant interaction between cognitive load and participants groups for Omissions (Wilk's Lambda= .984, $F(2, 138)= 1.098$, $p= .337$, $\eta_p^2= .016$) however, there was a main effect for the impact of cognitive load with both groups making significantly more omissions as the cognitive demand of the task increased

(Wilk's Lambda= .865, $F(2, 138)= 10.736$, $p= <.001$, $\eta_p^2= .135$; Figure 4.2). There was no significant difference between the groups in the number of omissions made as cognitive load increased ($F(1, 139)= 2.490$, $p= .117$, $\eta_p^2= .018$).

There was no significant interaction between cognitive load and participant group for Total Accuracy (Wilk's Lambda= .992, $F(2, 138)= .564$, $p= .570$, $\eta_p^2= .008$). Both groups showed a substantial reduction in attention and working memory total response accuracy as the cognitive load increased (Wilk's Lambda= .460, $F(2, 138)= 81.014$, $p= <.001$, $\eta_p^2= .540$; Figure 4.2). The main effect comparing the performance between the two groups was not significant ($F(1, 139)= 1.573$, $p= .212$, $\eta_p^2= .011$) indicating that the groups did not differ in their total accuracy of responses across the three cognitive load trial conditions of the n-back test. Results and descriptive statistics for the attention and working memory measures of performance during increased cognitive load are shown in Table 4.5.

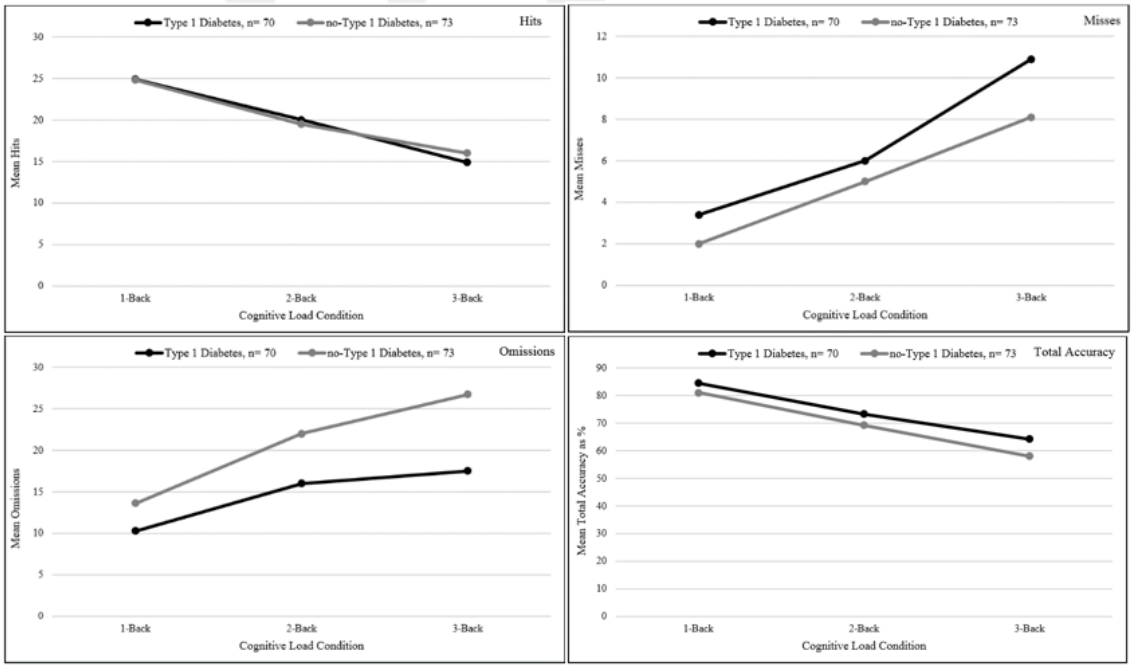

Figure 4.2. The trend of performance in attention and working memory tasks in participants with type 1 diabetes compared to participants with no-type 1 diabetes as cognitive load increased during the completion of the n-Back Test.

Individual Measures: Attention and Working Memory Performance

Multivariate analysis (MANOVA) was used to assess the differences in overall attention and working memory performance as well as the individual differences

between groups of the specific attention and working measures assessed by the n-Back. No serious violations of the assumptions were noted. Multivariate analysis showed no difference in overall attention and working memory performance between participants with type 1 diabetes compared to participants with no-type 1 diabetes (Wilk's Lambda= .881, $F(13, 127)= 1.320$, $p= .209$, $\eta_p^2= .119$). Individual analyses revealed that participants with type 1 diabetes missed significantly more target stimuli in the highest cognitive load condition than the no-type 1 diabetes participants (3-Back misses, $F(1,140)= 5.447$, $p= .021$, $\eta^2= .038$). There were no other significant differences in performance on the individual attention and working memory measures (Table 4.6).

H_2: Affective Disorders Adversely Influence Attention and Working Memory

Further analysis was undertaken to test the hypothesis that affect would adversely moderate attention and working memory performance.

Influence of Affective Psychopathology on Increased Cognitive Demand

To assess the influence of affect on performance across the three n-Back cognitive load trial conditions, mixed-model ANOVA was again run on the number of hits, misses, omissions, and on total accuracy, this time controlling for the influence of the presence of an affective disorder (anxiety, depression, comorbid anxiety-depression).

When the influence of affective psychopathology was controlled, analysis of Hits revealed no significant interaction between cognitive load and participant group (Wilk's Lambda= .986, $F(2, 137)= .982$, $p= .377$, $\eta_p^2= .014$). There was a significant main effect for cognitive load and Hits with both groups showing a substantial decrease in the number of target stimuli hit as the cognitive demand of the task increased (Wilk's Lambda= .598, $F(2, 138)= 46.080$, $p= <.001$, $\eta_p^2= .402$). The between-groups analysis of performance difference indicated no significant difference between the groups in the impact of cognitive load on Hits when the influence of affect is controlled ($F(1, 138)= .001$, $p= .972$, $\eta_p^2= <.001$).

Affect-controlled analysis of misses revealed no significant interaction between cognitive load and participant group (Wilk's Lambda= .978, $F(2, 137)= 1.545$, $p= .217$, $\eta_p^2= .022$). There was a significant main effect for cognitive load on Misses with both groups showing a substantial increase in the number of target stimuli missed as the cognitive demand of the task increased (Wilk's Lambda= .716, $F(2, 138)= 27.207$, $p= <.001$, $\eta_p^2= .284$). Cognitive load had a significantly greater impact on the number of

target stimuli missed during the n-Back task performance in the participants with type 1 diabetes ($F(1, 138)= 6.506$, $p= .012$, $\eta_p^2= .045$).

There was no significant interaction between cognitive load and participant group for Omissions (Wilk's Lambda= .962, $F(2, 137)= 2.738$, $p= .068$, $\eta_p^2= .038$), nor was there a significant main effect for omissions (Wilk's Lambda= .986, $F(2, 137)= .983$, $p= .377$, $\eta_p^2= .014$). However, when the influence of affect was controlled, participants with type 1 diabetes performed significantly better than the no-type 1 diabetes control group in the number of omissions made during the n-Back task. Participants without type 1 diabetes failed to make a response within the time allotted significantly more often as cognitive load increased compared to the participants with type 1 diabetes ($F(1, 138)= 4.019$, $p= .047$, $\eta_p^2= .028$).

There was no significant interaction between cognitive load and participant group for Total Accuracy in the affect-controlled analysis (Wilk's Lambda= .970, $F(2, 137)= 2.085$, $p= .128$, $\eta_p^2= .030$), however there was a significant main effect for total accuracy with both groups showing substantially reduced total response accuracy as cognitive load increased (Wilk's Lambda= .738, $F(2, 137)= 24.346$, $p= <.001$, $\eta_p^2= .262$). The main effect comparing total accuracy performance between the two groups was not significant ($F(1, 138)= 2.986$, $p= .086$, $\eta_p^2= .021$) indicating that the groups did not differ in their total accuracy of responses across the three cognitive load trial conditions. A comparison of performance across the three cognitive load conditions between participants with and without and affective disorder is shown in Figure 4.3. Results and descriptive statistics for the affective disorder-controlled repeated-measures analyses are shown in Table 4.6.

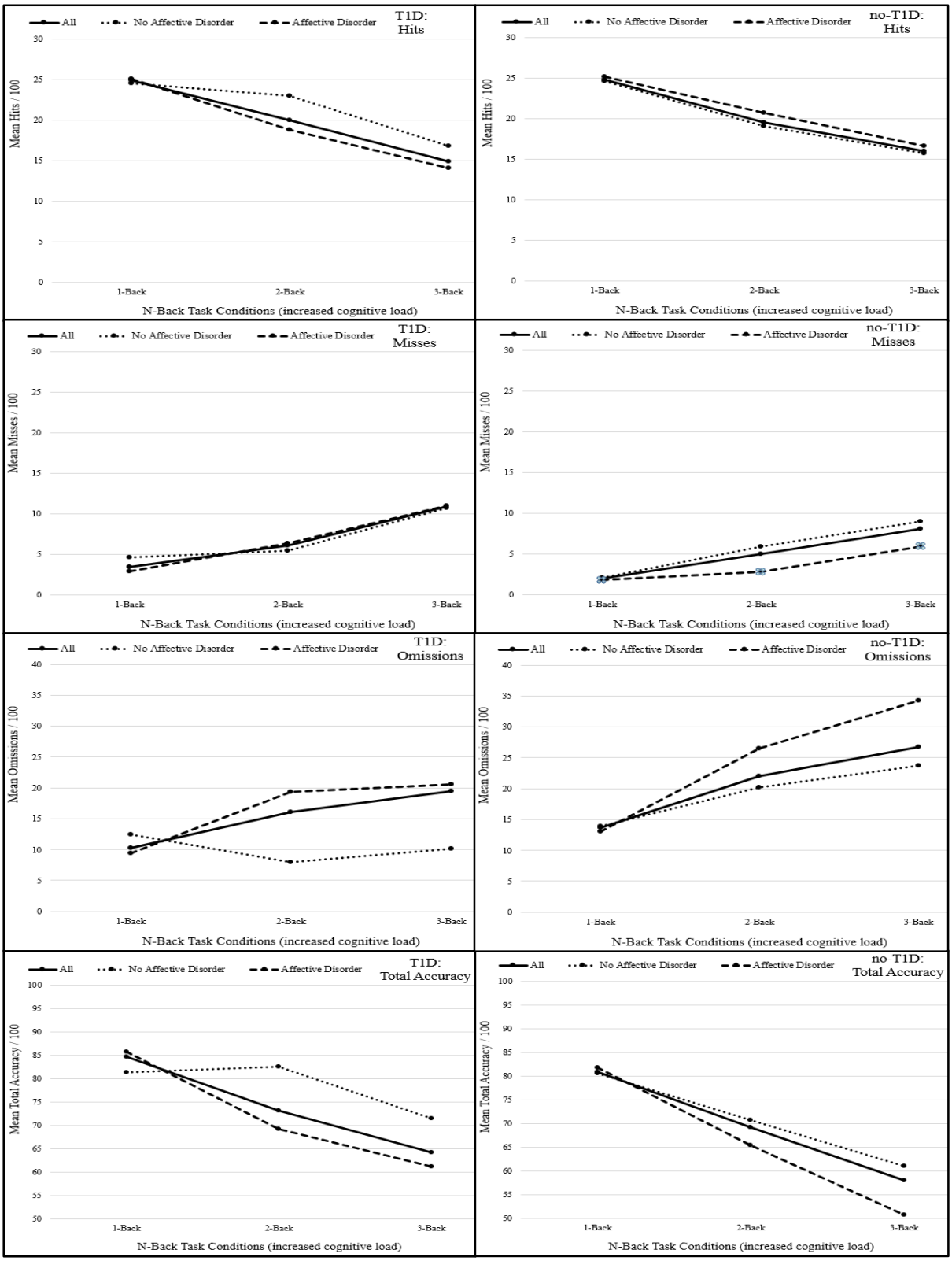

Figure 4.3. Comparison of attention and working memory performance in participants with and without an affective disorder in the type 1 and no-type 1 diabetes groups, across the three cognitive load conditions of the n-Back Test.

Table 4.5. *Descriptive Statistics and Results of the Mixed-Model Repeated-Measures ANOVA for Attention and Working Memory over Increased Cognitive Load Conditions in the n-Back Test between Participants in the Type 1 Diabetes and No-Type 1 Diabetes Groups, With and Without Controlling for the Presence of an Affective Disorders and With Comparisons of the Statistical Significance of the Difference between the ANOVA Results.*

	Type 1 Diabetes, *n*= 70			No-Type 1 Diabetes, *n*= 73			Mixed-Model ANOVA			Mixed-Model ANOVA controlling for affect status			Significance of the difference between MANOVA *p values (Q)* #		
	M (SD)			*M (SD)*			*F* (1,138)	*p*	η_p^2	*F* (1,138)	*p*	η_p^2	Z_1	Z_2	z_{obt}
	1	*2*	*3*	*1*	*2*	*3*									
Hits	24.88	20.03	14.88	24.79	19.53	15.95	.024	.878	<.001	.001	.972	<.001	1.165	1.911	-6.197**
	(6.98)	(8.22)	(6.80)	(6.67)	(9.06)	(7.12)									
Misses	3.40	6.04	10.90	1.99	4.97	8.10	4.752*	.031	.033	6.506*	.012	.045	1.866	2.257	-3.248**
	(6.48)	(5.78)	(7.00)	(3.29)	(6.77)	(7.20)									
Omissions	10.31	16.03	17.54	13.64	22.00	26.73	2.490	.117	.018	4.019	.047	.028	1.19	1.675	-4.029**
	(17.13)	(23.79)	(27.75)	(22.01)	(29.98)	(33.34)									
Total Accuracy	84.47	73.16	64.18	80.95	69.19	58.03	1.573	.212	.011	2.986	.086	.021	0.8	1.366	-4.702**
	(18.84)	(23.35)	(21.95)	(24.58)	(28.04)	(27.62)									

Notes: * Sig. @ $\alpha = .05$; Effect size, small $\eta^2 = .01$, medium $\eta^2 = .06$, large $\eta^2 = .14$ (282). # Indicates significant statistical difference between *z* observed scores of the MANOVA *Q* values where *Q* (the probability that the observed score is due to chance)= $1 - p$; z_{obt} (*z* obtained) = $(z_1 - z_2)$ / SQRT $((1 / (N_1 - 3)) + ((1 / (N_2 - 3)))$; ** Significant difference between MANOVA results: $-1.96 > z_{obt} > 1.96$.

Influence of Affective Psychopathology on Individual Measures of Attention and Working Memory Performance

A second MANOVA controlling for the presence of an affective disorder was conducted. No serious violations of the assumptions were noted. When the influence of affective psychopathology was controlled, multivariate analysis showed no main difference in overall attention and working memory performance between participants with type 1 diabetes compared to participants with no-type 1 diabetes (Wilk's Lambda= .854, $F(13, 126)= 1.663$, $p= .077$, $\eta_p^2= .146$). Analyses of the between-subjects effects revealed four measures that were significantly different between the two groups.

Controlling for affect, participants with type 1 diabetes had a greater number of misses in the higher cognitive load condition (3-back misses, $F(1, 139)= 6.753$, $p= .010$, $\eta_p^2= .047$). In contrast, participants with type 1 diabetes made significantly fewer errors of omission in the highest cognitive load condition (3-back omissions, $F(1, 139)= 5.756$, $p= .018$, $\eta_p^2= .040$), had a significantly lower rate of total omissions (All conditions total omissions, $F(1, 139)= 4.019$, $p= .047$, $\eta_p^2= .028$), and had a significantly higher level of total accuracy in the highest cognitive load condition (3-back total accuracy, $F(1, 139)= 5.206$, $p= .024$, $\eta_p^2= .036$; Table 4.5).

Tests of the Statistical Difference between ANOVA Results

To evaluate whether the presence of an affective disorder substantially moderated repeated-measures performance over increasing cognitive demand, or the individual performance results on the individual measures, an analysis of the statistical differences between the uncontrolled ANOVA and affect-controlled ANOVA results was performed. The *p* values of the individual between-subjects tests were converted to *Q* values (where *Q* is the probability that the observed score is due to chance; $Q= 1 - p$), which were then converted to $z_{observed}$ scores. The $z_{observed}$ scores for each of the corresponding MANOVA results were analysed to deliver a $z_{obtained}$ value. Both the mixed-methods ANOVA and the MANOVA results were considered significantly different if: $-1.96 > z_{obt} > 1.96$. Results indicated that the presence of an affective disorder had a significant influence on attention and working memory. All four repeated-measures, and 12 out of the 14 individual performance results were found to be significantly different when the influence of the presence of an affective disorder was statistically controlled (Table 4.5 and Table 4.6).

Table 4.6. *Descriptive Statistics and Results of the MANOVA for Attention and Working Memory in the n-Back Test between Participants in the Type 1 Diabetes and No-Type 1 Diabetes Groups, With and Without Controlling for the Presence of an Affective Disorders and With Comparisons of the Statistical Significance of the Difference between the MANOVA Results.*

	Type 1 Diabetes, *n*= 70		No-Type 1 Diabetes, *n*= 73		*MANOVA*			*MANOVA controlling for affect status*			Significance of the difference between MANOVA *p values (Q)* [#]		
	M	*SD*	*M*	*SD*	*F* (1,140)	*p*	η_p^2	*F* (1,140)	*p*	η_p^2	Z_1	Z_2	z_{obt}
1-Back: Hit	24.88	6.979	24.79	6.67	.006	.939	.000	.012	.911	.000	1.546	1.347	1.647
1-Back: Miss	3.40	6.481	1.99	3.29	2.712	.102	.019	3.746	.055	.026	1.27	1.598	-2.744**
1-Back: Total Omissions	10.31	17.13	13.64	22.01	.998	.319	.007	.480	.489	.003	0.47	0.028	3.698**
1-Back: Total Accuracy / 100	84.47	18.841	80.95	24.58	.904	.343	.006	.335	.564	.002	0.404	0.161	2.033**
2-Back: Hit	20.03	8.221	19.53	9.06	.115	.735	.001	.369	.544	.003	0.628	0.111	4.326**
2-Back: Miss	6.04	5.783	4.97	6.77	1.014	.316	.007	1.726	.191	.012	0.479	0.874	-3.305**
2-Back: Total Omissions	16.03	23.79	22.00	29.98	1.700	.194	.012	3.718	.056	.026	0.863	1.59	-6.083**
2-Back: Total Accuracy / 100	73.16	23.348	69.19	28.04	.828	.364	.006	2.696	.103	.019	0.348	1.265	-7.672**
3-Back: Hit	14.88	6.799	15.95	7.12	.819	.367	.006	.304	.582	.002	0.34	0.207	1.113
3-Back: Miss	10.90	6.995	8.10	7.20	5.477*	.021	.038	6.753*	.010	.047	2.034	2.33	-2.477**
3-Back: Total Omissions	17.54	27.75	26.73	33.34	3.134	.079	.022	5.756*	.018	.040	1.412	2.097	-5.731**
3-Back: Total Accuracy / 100	64.18	21.948	58.03	27.62	2.122	.147	.015	5.206*	.024	.036	1.049	1.977	-7.764**
All Conditions: Total Omissions	43.88	56.61	62.37	79.68	2.490	.117	.018	4.019*	.047	.028	1.19	1.675	-4.058**
All conditions Total Accuracy as %	74	18	69	24	1.774	.185	.013	3.441	.066	.024	0.896	1.506	-5.104**

Notes: * Sig. @ α = .05; Effect size, small η_p^2= .01, medium η_p^2= .06, large η_p^2= .14 [(282)]. # Indicates significant statistical difference between *z* observed scores of the MANOVA *Q* values where *Q* (the probability that the observed score is due to chance)= 1 – *p*; z_{obt} (*z* obtained) = (z_1 – z_2) / SQRT ((1 / (N_1 – 3))+ ((1 / (N_2 – 3))); * Significant difference between MANOVA results: -1.96 > z_{obt} > 1.96.

H_3: Diabetes-Specific Clinical and Aetiological Factors Correlated to Attention and Working Memory

To test the third hypothesis that diabetes-specific aetiology and clinical factors would be associated with attention and working memory performance, correlation coefficients were calculated between the n-back attention and working memory performance variables and age of disease onset, duration of illness, hypoglycaemia history, metabolic control, and the presence of diabetes-related complications (Table 4.7). Spearman's rank order correlation (*rho*) was used for analyses involving variables with non-parametric data and Pearson's (*r*) was used for all analyses involving only parametric data. Results revealed that both aetiology and clinical factors were significantly related to measures of attention and working memory performance. All diabetes-specific factors with the exception of duration of illness were significantly correlated to measures of attention and working memory performance (Table 4.7).

In order to evaluate whether affective disorders made a statistically significant impact on the results, partial correlations controlling for affect were undertaken. Any corresponding co-efficient pair from the affect-controlled and uncontrolled correlational analyses in which at least one co-efficient was statistically significant were converted to *z*-scores and compared. This was done by calculating the $z_{obtained}$ score from the corresponding $z_{observed}$ scores derived from converting the *r* co-efficients to their analogous *z* score [(110)]. When affect was controlled, the number of significant co-efficients reduced by 43%, from 30 to 17. Table 4.8 shows several coefficients were significant in the affect controlled condition that were not significant in the uncontrolled analysis.

Six co-efficients were identified as having a statistically significant difference between the uncontrolled and affect-controlled analyses. Table 4.8 shows the comparative evaluation of the affect-controlled and uncontrolled co-efficients, and shows that affect had a significant influence on the relationship between attention and working memory and diabetes-specific factors across low, moderate, and high cognitive load conditions (1-back missed target and medium-term HbA1c z_{obt} = -2.182; 1-back total omitted targets and complications z_{obt} = -4.250; 1-back total accuracy and complications z_{obt} = -3.720; 2-back missed target and age of onset z_{obt} = -2.068; 3-back hit target and medium-term HbA1c z_{obt} = -2.037; 3-back total accuracy and severe hypoglycaemia z_{obt} = -2.369).

Table 4.7. *Results of Correlations and Partial Correlations (Controlling for Affective Disorders) between Attention and Working Memory Performance on the n-Back Test, and Diabetes-Specific Clinical and Aetiological Factors.*

Attention and Working Memory Performance Variables		Correlations							Partial Correlations: controlling for affective disorders						
		Aetiology		Metabolic Control			Severe Hypo.	Comp.	Aetiology		Metabolic Control			Severe Hypo.	Comp.
		Age of onset	Illness duration	S-T	M-T	L-T			Age of onset	Illness duration	S-T	M-T	L-T		
1-Back: Hit	*Cor*	-.014	.124	-.275*	-.266*	-.526*	.082	-.062	-.145	.290	-.214	-.386	-.624**	-.140	.021
	p	.909	.322	.025	.048	.012	.524	.614	.531	.202	.352	.084	.003	.545	.929
1-Back: Miss	*Cor*	.159	.017	.003	.114	.393	-.055	.009	.179	-.163	.064	.489*	.538**	.018	-.203
	p	.202	.894	.980	.405	.071	.670	.943	.438	.482	.782	.024	.012	.937	.378
1-Back: Total Omissions	*Cor*	-.147	-.074	.248*	.260	-.025	-.071	-.015	.054	-.309	-.295	.244	.059	-.315	-.682***
	p	.240	.556	.045	.053	.911	.581	.901	.818	.173	.194	.286	.800	.164	.001
1-Back: Total number	*Cor*	.001	.090	-.247*	-.286*	-.224	.166	-.014	-.136	.324	.104	-.452*	-.373	.190	.623**
correct / 100	*p*	.991	.471	.045	.033	.317	.194	.911	.556	.151	.655	.040	.096	.408	.003
2-Back: Hit	*Cor*	-.062	-.072	-.314*	-.067	-.377	-.159	-.335**	-.423	.409	-.356	-.339	-.395	-.238	-.157
	p	.621	.565	.010	.625	.084	.212	.005	.056	.065	.113	.133	.076	.300	.495
2-Back: Miss	*Cor*	.212	.131	.237	-.098	.225	-.015	.155	.546**	-.349	.256	.239	.235	.029	.032
	p	.088	.295	.056	.473	.315	.908	.208	.010	.121	.262	.296	.306	.900	.889
2-Back: Total Omissions	*Cor*	-.202	.059	.191	.223	.307	.272*	.269*	-.001	-.210	.235	.215	.317	.356	.223
	p	.105	.640	.124	.099	.165	.031	.026	.998	.362	.305	.349	.162	.114	.332
2-Back: Total number	*Cor*	.007	-.092	-.254*	-.172	-.378	-.172	-.404**	-.187	.338	-.248	-.290	-.382	-.368	-.195
correct / 100	*p*	.954	.463	.040	.206	.083	.177	.001	.417	.134	.278	.203	.088	.100	.396
3-Back: Hit	*Cor*	-.125	-.047	-.330**	-.095	-.490*	-.161	-.245*	-.211	.083	-.352	-.451*	-.535**	-.211	-.195
	p	.316	.705	.007	.485	.020	.207	.044	.359	.721	.118	.040	.012	.358	.397
3-Back: Miss	*Cor*	.169	.165	.019	-.142	.231	.102	-.015	.204	.005	.135	.329	.233	.084	.092
	p	.176	.186	.881	.297	.301	.424	.901	.374	.981	.559	.145	.309	.717	.691
3-Back: Total Omissions	*Cor*	-.263*	-.048	.298*	.309*	.448*	.104	.220	-.018	-.062	.502*	.301	.551**	.296	.230
	p	.033	.701	.015	.021	.037	.417	.072	.939	.791	.020	.185	.010	.193	.316
3-Back: Total number	*Cor*	.035	-.022	-.350**	-.274*	-.519*	-.173	-.318**	-.074	.177	-.426*	-.368	-.581**	-.458*	-.220
correct / 100	*p*	.778	.860	.004	.041	.013	.175	.008	.750	.444	.054	.101	.006	.037	.338
All conditions: Total	*Cor*	-.169	-.001	.307*	.327*	.397	.052	.227	.011	-.276	.288	.375	.495*	.253	.001
Omissions	*p*	.175	.992	.012	.014	.068	.683	.063	.964	.225	.205	.094	.022	.268	.996
All conditions Total	*Cor*	.018	-.039	-.341**	-.286*	-.474*	-.058	-.331**	-.173	.360	-.249	-.462*	-.561**	-.286	.060
accuracy as a %	*p*	.887	.758	.005	.032	.026	.653	.006	.454	.109	.276	.035	.008	.209	.795

Notes: * Sig. @ α = .05; ** Sig. @ α = .01; *** Sig. @ α = .001; S-T = Average BGL during participation; M-T = HbA1c most recent to participation; L-T = Average HbA1c over previous 36 months.

Table 4.8. *Tests of the Statistical Significance between Correlation Co-efficients of the Relationship between Attention and Working Memory and Diabetes-Specific Aetiological and Clinical Factors, before and after the Influence of Affective Psychopathology is Controlled.*

		Uncontrolled			**Affect-Controlled**			
	Diabetes Factor	*r*	*p*	z_1	*r*	*p*	z_2	z_{obt}
1-Back: Hit	S-T	-.275*	.025	.282	-.214	.352	.217	.338
1-Back: Hit	M-T	-.266*	.048	.272	-.386	.084	.408	-.707
1-Back: Hit	L-T	-.526*	.012	.585	-.624**	.003	.732	-.764
1-Back: Miss	M-T	.114	.405	.115	.489*	.024	.535	-2.182#
1-Back: Miss	L-T	.393	.071	.416	.538**	.012	.602	-.966
1-Back: Total Omissions	S-T	.248*	.045	.253	-.295	.194	.304	-.265
1-Back: Total Omissions	M-T	.260	.053	.266	.244	.286	.249	.088
1-Back: Total Omissions	Comp.	-.015	.901	.015	-.682***	.001	.833	-4.250#
1-Back: Total number correct / 100	S-T	-.247*	.045	.253	.104	.655	.104	.774
1-Back: Total number correct / 100	M-T	-.286*	.033	.295	-.452*	.040	.487	-.998
1-Back: Total number correct / 100	Comp.	-.014	.911	.014	.623**	.003	.730	-3.720#
2-Back: Hit	S-T	-.314*	.010	.325	-.356	.113	.373	-.249
2-Back: Hit	Comp.	-.335**	.005	.348	-.157	.495	.158	.987
2-Back: Miss	Age of onset	.212	.088	.215	.546**	.010	.613	-2.068#
2-Back: Total Omissions	Sev Hypo	.272*	.031	.279	.356	.114	.373	-.488
2-Back: Total Omissions	Comp.	.269*	.026	.276	.223	.332	.227	.255
2-Back: Total number correct / 100	S-T	-.254*	.040	.260	-.248	.278	.253	.036
2-Back: Total number correct / 100	Comp.	-.404***	.001	.428	-.195	.396	.198	1.195
3-Back: Hit	S-T	-.330**	.007	.343	-.352	.118	.368	-.130
3-Back: Hit	M-T	-.095	.485	.095	-.451*	.040	.487	-2.037#
3-Back: Hit	L-T	-.490*	.020	.536	-.535**	.012	.597	-.317
3-Back: Hit	Comp.	-.245*	.044	.250	-.195	.397	.198	.270

3-Back: Total Omissions	Age of onset	-.263*	.033	.269	-.018	.939	.018	1.304
3-Back: Total Omissions	S-T	.298*	.015	.308	.502*	.020	.551	-1.263
3-Back: Total Omissions	M-T	.309*	.021	.319	.301	.185	.311	.042
3-Back: Total Omissions	L-T	.448*	.037	.482	.551**	.010	.620	-.717
3-Back: Total number correct / 100	S-T	-.350**	.004	.365	-.426*	.054	.455	-.468
3-Back: Total number correct / 100	M-T	-.274*	.041	.281	-.368	.101	.508	-1.180
3-Back: Total number correct / 100	L-T	-.519*	.013	.575	-.581**	.006	.664	-.462
3-Back: Total number correct / 100	Sev Hypo	-.173	.175	.175	-.458*	.037	.631	-2.369#
3-Back: Total number correct / 100	Comp.	-.318**	.008	.330	-.220	.338	.224	.551
All conditions: Total Omissions	S-T	.307*	.012	.318	.288	.205	.232	.447
All conditions: Total Omissions	M-T	.327*	.014	.341	.375	.094	.394	-.275
All conditions: Total Omissions	L-T	.397	.068	.578	.495*	.022	.543	.182
All conditions Total accuracy as a %	S-T	-.341**	.005	.355	-.249	.276	.254	.525
All conditions Total accuracy as a %	M-T	-.286*	.032	.294	-.462*	.035	.500	-1.070
All conditions Total accuracy as a %	L-T	-.474*	.026	.516	-.561**	.008	.635	-.618
All conditions Total accuracy as a %	Comp.	-.331**	.006	.344	.060	.795	.060	1.476

Notes: : * Sig. @ α = .05; ** Sig. @ α = .01; *** Sig. @ α = .001; S-T = Average BGL during participation; M-T = HbA1c most recent to participation; L-T = Average HbA1c over previous 36 months; # Indicates significant statistical difference between correlation co-efficients of the groups: $-1.96 > z_{obt} > 1.96$; $z_{obt} = (z_1 - z_2) / \text{SQRT}((1 / (N_1 - 3)) + ((1 / (N_2 - 3)))$; Correlation co-efficient transformations to *z* from Table 11.1 in Pallant [110, p.142]

S8: Discussion

The present study investigated attention and working memory in type 1 diabetes compared to no-type 1 diabetes controls. In support of the three hypotheses, the results show that attention and working memory was poorer in participants with type 1 diabetes, affect status was identified as a significant mediator of attention and working memory performance, and diabetes-specific aetiological and clinical factors were found to be significantly associated with attention and working memory performance. These results are consistent with the extant literature and highlights the importance of providing focused attention in the clinical and health education settings to the psychological and neuropsychological wellbeing of patients with type 1 diabetes.

H_1: Poorer Attention and Working Memory in Type 1 Diabetes

The results show that participants with type 1 diabetes did not differ to no-type 1 diabetes controls in their overall level of performance accuracy across the three trial sets of the n-Back task (total correct selections). However, individual comparative analyses of each attention and working memory measure included in the study, revealed that participants with type 1 diabetes missed significantly more target stimuli than controls in trials involving an increased level of cognitive demand (3-back). Type 1 diabetes participants also did worse compared to controls in the higher-cognitive demand trial conditions when the comparison was made between participants from each group who had an affective disorder. Compared to controls, participants with type 1 diabetes missed significantly more target stimuli in the high cognitive demand trial conditions.

The key finding in these results is that the identified deficits were related to a lack of recognition of important (target) data when it was presented. A reduced capacity to attend to key details represents a serious challenge to self-care and disease management practices. In type 1 diabetes, errors of this nature may translate into potentially disastrous outcomes such as errors or omissions in blood glucose monitoring, dosage mistakes in insulin delivery, caloric and insulin dose correction miscalculations, and poor planning for medical or dietary needs when away from close access to assistance [115, 119, 299, 305, 312].

Brands et al., [299] found that cognitive decline in type 1 diabetes is associated with the presence of microvascular complications. While the whole of brain function is susceptible to vascular pathology, attention and working memory may be particularly vulnerable as it is theorised to have a multi-dimensional operating structure engaging

numerous unique components across similarly numerous neurological locales [313-317]. This neurosystemic and functional complexity makes psychophysiological interaction in this domain extremely vulnerable to vascular pathologies and any number of other pathophysiological characteristics affecting the brain in type 1 diabetes including inflammation, advanced glycated endproducts (AGEs), and insulin resistance, [116, 117, 119, 297, 305, 319].

H_2: Affective Disorders Adversely Influence Attention and Working Memory

The second hypothesis that affective disorders would adversely influence attention and working memory was supported. Interestingly, within-groups comparisons of affect-specific sub-groups showed that compared to participants without an affective disorder, anxious and depressed participants in both the type 1 diabetes and no-type 1 diabetes groups performed better under low cognitive demand conditions. However, in-line with the stated hypothesis, type 1 diabetes participants then proceeded to perform significantly worse under higher cognitive demand conditions.

This is consistent with the performance-arousal theory posited by the Yerkes-Dodson Law [320] and later applied to the cognitive demands of learning by John Sweller [321], that suggests performance exists on an arousal/cognitive load Bell Curve in which arousal and/or low cognitive demand or familiar tasks improve performance however, the arousal/cognitive demand-performance relationship reaches a zenith and subsequently performance declines as arousal and/or cognitive demand continues to increase (Figure 4.10).

This is an important consideration as the impaired glucose regulation and processing mechanisms inherent to type 1 diabetes may result in a greater arousal / cognitive load imposition being placed on those with the disease. Research has shown that increased arousal and increased cognitive load result in a significant increase in the brain's glucose needs. For example, McNay et al. [322] found that glucose demand in the brain under elevated cognitive load conditions increased by as much as 32% in rodent models. This trend was also found in human studies in which cognitive tasks of increased complexity led to accelerated glucose depletion in the periphery [323].

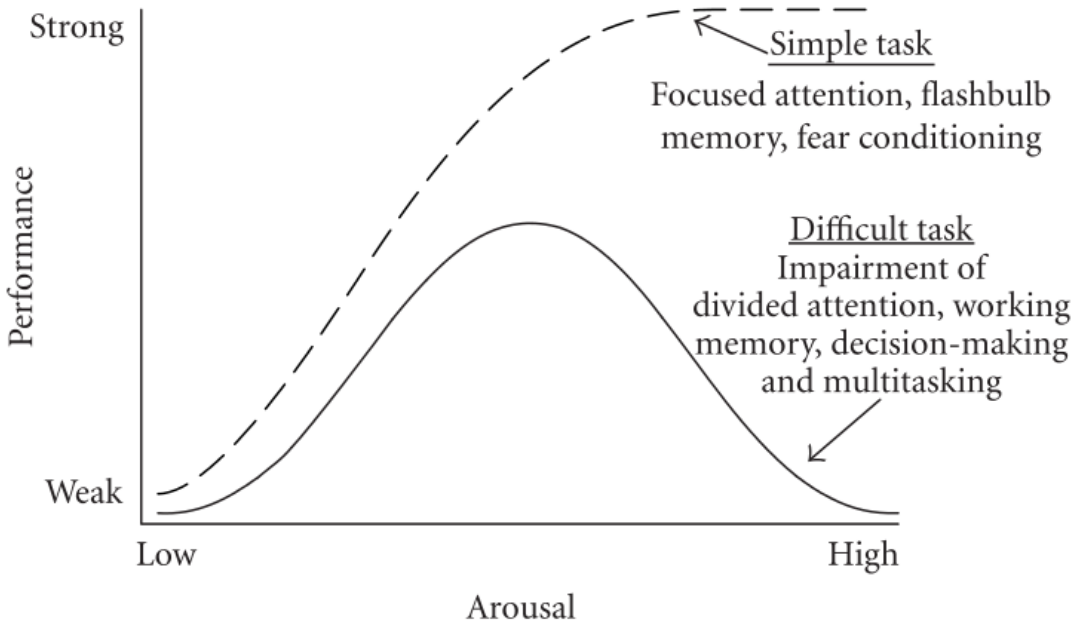

Figure 4.4. The original Yerkes-Dodson Law bell curve of the relationship between arousal/cognitive load and performance [320].

Despite both impaired cognition and disordered affect being significant sequelae in type 1 diabetes, and despite the voluminous extant literature on the relationship between the two, there remains a dearth of literature that focuses on the two conditions in combination in type 1 diabetes. Attention and working memory deficits are common characteristics affective disorders [116, 256, 276, 306], and therefore, given the high prevalence rates of affective psychopathology in type 1 diabetes [8, 14, 116, 130, 284] it is a logical outcome to find evidence that supports the existence of a triarchic relationship. Although, more research is needed to understand the nature of the relationship.

H_3: Diabetes-Specific Clinical and Aetiological Factors Correlated to Attention and Working Memory

The final hypothesis that diabetes-specific aetiology and clinical factors would be associated with measures of attention and working memory was supported. Age of onset, short-term glycaemic control, HbA1c, hypoglycaemia, and complications were all significantly associated with measures of attention and working memory. This supports the existing literature that has consistently found a relationship between attention and working memory and diabetes-specific factors such as age of onset and disease duration, hyperglycaemia, hypoglycaemia, and the presence of other diabetes-related complications such as microvascular disease and neuropathy [116, 119, 120, 297, 299, 302, 308, 318]. For example, Brismar et al., [308] found that

disease duration and age of onset were the most significant predictors of impaired cognitive function, including attention and working memory, in adults with type 1 diabetes. Brands et al. [299], Kodl and Seaquist [302], and Tonoli et al. [119], have also identified multiple associations between attention and working memory, and both clinical and aetiological factors in adults with the disease.

Similarly, Cato et al. [318], Lin et al. [297], and McNally et al. [120], have all identified attention and working memory impairments in younger people with type 1 diabetes that were associated with aetiology and clinical outcomes including age of onset, duration of illness, and both hyperglycaemia and hypoglycaemia. These deficits are being identified within a few years of diagnosis and while factors such as establishing optimal glycaemic control appear to attenuate some of the performance deficits, longitudinal evaluation ultimately shows a progressive decline in function over time [297]. While a progressive decline in cognition is expected as part of the later aging process, it is of serious concern when it is being quantified in children and charted over the course of development through to early adulthood. Identifying these relationships is an important clinical factor as evidence is emerging that there is an accumulatory effect in that two or more clinical and aetiological factors co-presenting is associated with greater attention and working memory deficits [297].

Attention and working memory performance is particularly important to executive function. Executive functions such as planning, organising, cognitive set maintenance, inhibition, and cognitive flexibility, require attendance, retrieval and operational engagement with information, the ability to maintain awareness of the task-specific information such as rules or materials components, and to update these rules and components lists in line with set shift or situational fluidity. Glycaemic control (both short-term and long-term) was associated with attention and working memory measures across both low and high cognitive demand conditions. This pervasive relationship means that hyperglycaemia may be an adverse influence on attention and working memory, and by extension executive function performance, even under relatively pedestrian cognitive conditions. By contrast, age of onset, hypoglycaemia, and the presence of diabetes-related complications, were all associated with measures of attention and working memory under the higher cognitive demand parameters of the 2-back and 3-back trial conditions. However, in these higher demand conditions, there were multiple associations across measures of attention and working memory and this may produce an accumulatory effect as was reported by Lin et al. [297].

Conclusion

These results suggest that attention and working memory performance is associated with a number of diabetes-specific factors related to both short and long-term health and wellbeing. While type 1 diabetes has an adverse influence on attention and working memory the results of the present study indicates that the added presence of an affective disorder appears to lend further challenges to performance capacity. The present study supports previous findings that 1) attention and working memory is impaired in type 1 diabetes; 2) that affective psychopathology has an adverse influence on attention and working memory; and 3) that attention and working memory is associated with diabetes-specific aetiology and clinical factors. These results directly support the extant literature on these factors and extends the existing knowledge through establishing preliminary evidence for a triarchic role between type 1 diabetes, affective psychopathology and cognitive dysfunction. This is an important advance in the field of type 1 diabetes as the extant literature deals largely with these phenomena in a dyadic segmented manner that belies the interconnectedness and likely multi-directional nature of the three components. Further study is needed to further elucidate the characteristics of the relationship between these constituents.

Study 9: Processing Speed in Type 1 Diabetes

S9: Abstract

Background: Processing speed is an integral component of cognition and one of the most consistently identified deficit cognitive processes in type 1 diabetes. Optimal executive function, and other cognitive processes rely on fast and efficient information processing speed and in its absence may become significantly impaired. The present study investigated processing speed in adults with type 1 diabetes compared to age and sex balanced controls. The relationship between processing speed and affective disorders, and diabetes-specific aetiological and clinical factors was also assessed.

Methods: Processing speed measures on computer analogues of the Wisconsin Card Sort Test (CST) and the Tower of London Test (TOLT) were used to assess performance in participants with type 1 diabetes (n=70), and without (n=73). The presence of anxiety and depression was ascertained using the MINI International Neuropsychiatric Interview. The relationship between processing speed and diabetes-specific aetiological and clinical factors, and the influence of affective disorders on these factors was also assessed.

Results: Participants with type 1 diabetes showed significantly slower processing speed compared to controls across measures of both initiation and completion in the CST and TOLT. The presence of an affective disorder had only a minor influence on processing speed in type 1 diabetes participants, and more measures of processing speed were associated with type 1 diabetes status than with affective disorder status. Initiation and completion measures of processing speed were significantly associated with diabetes-specific aetiological and clinical factors (DSACF) of age of disease onset, duration of illness, short-term glycaemic control, medium and long-term HbA1c, hypoglycaemic history, and diabetes-related complications. However, affect was a significant mediator of these relationships. When affect was controlled, the number of significant relationships between processing speed and DSACF reduced by 94% from 49 to three.

Conclusion: Poor processing speed performance is associated with type 1 diabetes and is strongly related to DSACF. The presence of affective psychopathology appears to have less influence on processing speed than it does on other cognitive domains such as executive function and attention and working memory. More research is need to fully elucidate the extent and nature of processing speed deficits in type 1 diabetes.

Keywords: Diabetes Mellitus: Type 1; Neuropsychology; Cognition; Processing Speed; Executive Function; Affective Disorder; Depression; Anxiety; Aetiology; Complications; Metabolic Control; Glycaemic control.

S9: Introduction

Type 1 diabetes is a serious multifactorial metabolic disease that, due to its complex and pervasive pathophysiological mechanics, can result in a host of potentially devastating sequelae. Amongst the most commonly recognised and experienced are degenerative disorders of the vasculature and peripheral nervous systems such as retinopathy, cardiovascular disease, nephropathy, cerebrovascular disease, autonomic dysfunction, peripheral neuropathy, dermatological syndromes, and immune dysregulation [117, 302, 304, 324-327]. A no less potentially devastating, though far less well acknowledged sequelae of type 1 diabetes is complications of the central nervous system (CNS) [124, 299, 302]. An appreciation of the relationship between central neural processes and diabetes is not a new phenomenon. Thomas Willis wrote of diabetes in 1684 "Nervous system juice and prolonged sorrow are important aetiological factors in type 1 diabetes" [135]. Modern recognition of neuropsychological impairment has been identified in the literature for almost a century [328-332] although it has remained largely a secondary consideration in the scope of type 1 diabetes treatment and complications screening.

Impairments to cognitive performance are an example of these CNS sequelae [118, 299, 302]. The most common impairments to cognition identified in type 1 diabetes are global measures of intellectual functioning [297], memory [333], attention and working memory [305], executive function [116, 119], and processing speed [124, 299, 305]. Processing speed is an integral component of almost all cognitive function and is perhaps one of the most consistently identified deficit cognitive processes in type 1 diabetes [119, 302]. Optimal executive function, attention, working memory, and other cognitive processes rely on fast and efficient information processing speed and in its absence may become significantly impaired as a secondary consequence to the deficit speeds at which information is processed. For example, performance levels in both executive function and attention and working memory, collectively and independently, are often correlated to reductions in processing speed [122-124, 297].

Processing speed is thought to pervasively impede cognitive performance via the mechanisms of time limitations and simultaneity [334]. According to Salthouse [334] suboptimal processing speeds impair cognition as cognitive tasks cannot be executed with the appropriate temporal resolution (time limitations), and because the temporal resolution is inadequate, component processes of the whole cognitive task are not available when they are required by other elements of the cognitive task (simultaneity).

In essence time limitations impair sequential performance parameters, while the absence of simultaneity impairs spatial resolution.

Numerous factors have been associated with processing speed decline in type 1 diabetes, including vascular degeneration, Abeta/tau-dependent pathological alterations, the presence of other diabetes-related complications, age of disease onset, duration of illness, poor metabolic control, and hypoglycaemia [115, 117, 119, 120, 302, 308]. Moreover, type 1 diabetes has been linked to a number of specific neurodegenerative and neuromorphological sequelae that are characteristic of an accelerated aging process in the brain [117, 119, 302, 335, 336]. However, in spite of the large and increasing body of literature addressing CNS sequelae and specifically cognitive dysfunction in type 1 diabetes, there remains an absence of consensus as to the pathogenic mechanics that determine and moderate cognitive alteration in the disease.

What is clear is that impaired cognitive function is both clearly linked to poor clinical outcomes and to behavioural risk factors that may contribute to the onset and progression of diabetes-related complications and ultimately early mortality [116, 118-120, 302]. For example, impaired decision making processes such as an inability to apply existing knowledge to solve new problems, reduced ability to set-shift, poor recall, and reduced capacity for sustained attention and working memory, may all have a significant impact on self-care behaviours such as medication regimen adherence, blood glucose monitoring, or maintaining a healthy diet and exercise program [116, 118, 120]. Processing speed underpins the efficiency of almost all cognitive processes, and specific factors of processing speed such as initiation are particularly integral to the higher-order executive function tasks such as set-shifting and inhibition. Therefore, impaired processing speed is a cause for significant concern in the context of a life lived under the cloud of a serious, life threatening disease such as type 1 diabetes, where day-to-day decisions made about disease self-management carry the portent of deadly consequence.

In the present study, processing speed during executive function tasks was assessed in adult participants with type 1 diabetes and compared to age and sex balanced no-type 1 diabetes controls. The aim of the study was to assess the difference in processing speed between the groups, to evaluate and compare the relationship between disordered affect and processing speed in participants, and to identify any relationship between processing speed and diabetes-specific aetiological and clinical factors such as age of onset, duration of illness, hypoglycaemia history, metabolic

control, and the presence of diabetes-related complications. It was hypothesized that compared to no-type 1 diabetes controls, participants with type 1 diabetes would have slower processing speed, that processing speed would be adversely influenced by the presence of an affective disorder, and that processing speed would be associated with diabetes-specific clinical and aetiological factors.

S9: Results

Descriptive analysis of group personal and demographic data confirmed that there were no differences between the participants in the type 1 diabetes and no-type 1 diabetes groups in age, sex, level of education, or employment characteristics. Participants' descriptive statistics are reported in Table 1.1, demographic statistics are reported in Table 2.2, affect status statistics are reported in Table 3.6, and diabetes-specific clinical data for the type 1 diabetes group are reported in Table 2.5. Computer analogues of the Wisconsin Card Sort Test (CST), and Tower of London Test (TOLT), were used to assess processing speed during executive function tasks.

H_1: Slower Processing Speed in Type 1 Diabetes

Processing speed associated with both cognitive initiation and total completion time during executive function tasks was compared between participants in the type 1 diabetes and no-type 1 diabetes groups by analysing the differences between participants in each of the two groups. Multivariate analysis of variance (MANOVA) was used to assess the between-groups processing speed performance on the CST and TOLT. Initial assumption testing revealed no serious violations. The data showed a high number of generally moderate correlations between performance measures across both participant groups (result not shown), and therefore task initiation and completion processing speed performance variables were included in the same multivariate analysis model [109, 110].

Results of the MANOVA showed no difference in the main effects of processing speed between participants with type 1 diabetes compared to participants with no-type 1 diabetes (Wilk's Lambda= .787, $F(18, 103)= 1.546$, $p= .089$, $\eta_p^2= .213$). Individual analyses showed that 12 of the 18 measures of processing speed performance across cognitive initiation and completion in both the CST and TOLT were significantly different. In all cases participants with type 1 diabetes demonstrated slower rates of processing speed than the no-type 1 diabetes control participants. When Bonferroni

adjustments were made to the alpha level to account for multiple comparisons [109, 110], only three measures met the adjusted significance level (adjusted α= .003; TOLT: 3-ring average pick-up time (initiation), F (1, 121)= 11.276, p= .001, η_p^2= .086; TOLT: total average pick-up time (initiation), F (1, 121)= 9.081, p= .003, η_p^2= .070; TOLT: 3-ring average total trial time (completion), F (1, 121)= 10.077, p= .002, η_p^2= .077). Although Bonferroni adjustments rendered a number of results not significant, several of these results had a moderate or higher effect size ($\eta_p^2 \geq .06$) and therefore are still noteworthy (TOLT: all conditions average total pick-up (initiation), F (1, 121)= 8.434, p= .004, η_p^2= .066; CST: criterion run average total trial time (completion), F (1, 121)= 7.220, p= .008, η_p^2= .057; CST: perseveration errors total latency (completion), F (1, 121)= 8.408, p= .004, η_p^2= .065; TOLT: 5-ring average total trial time (completion), F (1, 121)= 7.754, p= .006, η_p^2= .061; TOLT: all conditions total average trial time (completion), F (1, 121)= 8.797, p= .004, η_p^2= .068; Table 4.9).

H_2: Processing Speed Adversely Influenced Affective Disorders

To test the second hypothesis that processing speed would be adversely influenced by the presence of a current affective disorder, a second MANOVA was conducted, this time controlling for the presence of an affective disorder. Again, no serious violations of the assumptions were noted. When the influence of the presence of an affective disorder was controlled, multivariate analysis again showed no difference in overall processing speed between participants with type 1 diabetes compared to participants with no-type 1 diabetes (Wilk's Lambda= .833, F(18, 102)= 1.133, p= .332, η_p^2= .167). Individual analyses of the between-subjects effects showed a smaller, though still substantial number of individual measures (10 out of 18) were significantly different between the groups. Participants with type 1 diabetes continued to have significantly slower processing speeds across measures of both cognitive initiation and completion on the CST and TOLT when the influence of affect was controlled. When Bonferroni corrections were applied none of the results reached the adjusted alpha level (Bonferroni adjusted α= .003). Only one of the measures had an effect size that was moderate or above and therefore, despite the Bonferroni correction impacting significance, remained noteworthy (TOLT: 3-ring average pick up (F(1, 121)= 6.974, p= .009, η_p^2= .055; Table 4.9).

To evaluate the influence of the presence of an affective disorder on the group performances, an analysis of the statistical differences between the MANOVA results

was undertaken. Individual between-subjects ANOVA *p* values were converted to *Q* values (where *Q* is the probability that the observed score is due to chance; $Q = 1 - p$), which were converted to $z_{observed}$ scores. The $z_{observed}$ scores for each of the corresponding MANOVA results where then analysed to deliver a $z_{obtained}$ value. MANOVA results were considered significantly different if: $-1.96 > z_{obt} > 1.96$. Results indicated that 13 out of the 18 processing speed measures was found to be statistically significantly different between the uncontrolled and affect-controlled MANOVAs. This indicates that the presence of an affective disorder had a significant adverse influence on processing speed performance (Table 4.9).

Table 4.9. *Descriptive Statistics and Results of the MANOVA for Processing Speed Performance in the Card Sort Test and Tower of London Test between Participants in the Type 1 Diabetes and No-Type 1 Diabetes Groups, With and Without Controlling for the Presence of an Affective Disorders and With Comparisons of the Statistical Significance of the Difference between the MANOVA Results.*

	Type 1 Diabetes, *n*= 61		No-Type 1 Diabetes, *n*= 61		*MANOVA*			*MANOVA controlling for affect status*			Significance of the difference between MANOVA *p values (Q)* [#]		
	M	*SD*	*M*	*SD*	*F* (1,122)	*p*	η_p^2	*F* (1,122)	*p*	η_p^2	z_1	z_2	z_{obt}
Cognitive Initiation Latency													
CST: Correct avge cog lat	2866.77	1743.93	2484.07	1805.39	1.418	.236	.012	1.510*	.222	.013	0.719	0.765	-0.355
CST: Perseveration avge cog lat	3172.39	2363.22	2444.15	1944.86	3.454	.066	.028	2.832	.095	.023	1.506	1.311	1.504
CST: Non-perseveration avge cog lat	4142.82	3606.50	3395.95	2076.03	1.965	.164	.016	2.969	.087	.024	0.978	1.359	-2.939#
CST: Error avge cog lat	3814.61	2969.82	3076.98	1815.27	2.740	.101	.022	3.244	.074	.027	1.221	1.447	-1.743
ST: Criterion run avge cog lat	1785.46	1215.09	1401.21	671.92	4.672*	.033	.037	2.657	.106	.022	1.838	1.248	4.551#
TOLT: Avge pick up - 3 ring	3.30	1.52	2.52	.99	11.276***	.001	.086	6.974**	.009	.055	3.09	2.366	5.585#
TOLT: Avge pick up - 4 ring	3.03	1.30	2.57	1.19	4.308*	.040	.035	2.658	.106	.022	1.751	1.248	3.880#
TOLT: Avge pick up - 5 ring	2.82	1.01	2.33	.84	8.434**	.004	.066	5.688*	.019	.046	2.652	2.075	4.451#
TOLT: Avge pick up – Total	3.05	1.16	2.47	.97	9.081**	.003	.070	5.759*	.018	.046	2.748	2.097	5.022#
Total Completion Latency													
CST: Correct avge tot lat	5072.72	3284.87	4107.56	2832.94	3.020	.085	.025	1.840	.177	.015	1.372	0.927	3.433#
CST: Perseveration avge tot lat	5859.80	4498.38	3910.07	2710.23	8.408**	.004	.065	5.582*	.020	.045	2.652	2.054	4.613#
CST: Non-perseveration avge tot lat	6970.80	4926.03	5734.97	4328.45	2.167	.144	.018	2.579	.111	.021	1.063	1.221	-1.219
CST: Error avge tot lat	6680.49	4276.45	5208.67	3875.29	3.968*	.049	.032	3.565	.061	.029	1.654	1.546	0.833
CST: Criterion run avge tot lat	3274.87	2369.19	2387.87	1016.99	7.220**	.008	.057	4.000*	.048	.033	2.409	1.665	5.739#
TOLT: Avge tot time - 3 ring	5.29	2.13	4.24	1.48	10.077**	.002	.077	6.502*	.012	.052	2.878	2.257	4.790#
TOLT: Avge tot time - 4 ring	4.80	1.80	4.00	1.65	6.594*	.011	.052	4.710*	.032	.038	2.29	1.852	3.379#
TOLT: Avge tot time - 5 ring	4.46	1.45	3.74	1.40	7.754**	.006	.061	5.323*	.023	.043	2.512	1.995	3.988#
TOLT: Avge tot time - Total	4.85	1.71	4.00	1.45	8.797**	.004	.068	5.999*	.016	.048	2.652	2.144	3.919#

Notes: * Sig. @ α = .05; ** Sig. @ α = .01; *** Sig. @ α = .001; Effect size, small η_p^2= .01, medium η_p^2= .06, large η_p^2= .14 [(282)]. # Indicates significant statistical difference between *z* observed scores of the MANOVA *Q* values where *Q* (the probability that the observed score is due to chance)= 1 – *p*; z_{obt} (*z* obtained) = ($z_1 - z_2$) / SQRT ((1 / (N_1 – 3))+ ((1 / (N_2 – 3))); Significant difference between MANOVA results when: -1.96 > z_{obt} > 1.96.

To further investigate the relationship between processing speed, type 1 diabetes, and affective disorders, further correlational analyses were undertaken on the group as a whole, and on the type 1 diabetes and no-type 1 diabetes groups independently. In an all participants analysis, the relationship between processing speed and both affect status and type 1 diabetes was evaluated. The results of the whole-of-group analysis indicated that more measures of processing speed were correlated to type 1 diabetes status than to affect status (Table 4.10).

When the co-efficients were compared, the z_{obt} scores showed that there was no statistically significant difference between the correlation co-efficients of the relationship between processing speed and type 1 diabetes status compared to those of processing speed and affect status (for all co-efficients: $-1.96 < z_{obt} < 1.96$; Table 4.10). This suggests that although processing speed has more statistically significant relationships with type 1 diabetes status than with affective status, the comparative difference between the relationships is not statistically significant.

The relationship between processing speed and affect was then correlated independently in participants with and without type 1 diabetes, and again the significant correlations in were compared in order to identify whether the relationship between processing speed and affect was significantly different in the two groups. Correlations in the two participant groups showed that there were no significant relationships between processing speed and affect status in participants with type 1 diabetes, while there were three significant associations found in the participants with no-type 1 diabetes (Table 4.11). In the no-type 1 diabetes participants the presence of an affective disorder was significantly associated with measures of cognitive initiation (CST: criterion run average cognitive latency, *rho*= .313, *p*= .012; perseveration average cognitive latency *rho*= .303, *p*= .011), as well as with total trial completion time (CST: perseveration average total trial time, *rho*= .272, *p*= .023; Table 4.11). When the co-efficients were compared between the two groups, the z_{obt} scores showed that there was a statistically significant difference between the type 1 diabetes and no-type 1 diabetes groups in both cognitive initiation (criterion run average cognitive latency $z_{obt} = 2.202$) and total completion time (perseveration average total trial time $z_{obt} = 2.387$). This result indicates that the relationship between processing speed in these measures of executive task performance and disordered affect differed in participants with type 1 diabetes compared to participants without the disease (Table 4.12).

Table 4.10. *Results of Whole-of-Group Spearman's Rank Order Correlational Analyses of the Relationship between Processing Speed and both Type 1 Diabetes, and Affect Status, including Tests of the Statistical Significance of the Difference between the Significant Co-efficients.*

	Type 1 Diabetes Status			Affective Disorder			z_{obt}
	rho	*p*	z_1	*rho*	*p*	z_2	
CST							
Correct avge cog lat	.137	.102	-	.088	.298	-	-
Correct avge tot lat	.187*	.025	.189	.177*	.034	.179	.059
Perseveration avge cog lat	.168*	.049	.170	.112	.189	.112	.339
Perseveration avge tot lat	.236**	.005	.241	.170*	.045	.172	.404
Non-perseveration avge cog lat	.072	.395	-	.067	.424	-	-
Non-perseveration avge tot lat	.156	.062	-	.135	.108	-	-
Error avge cog lat	.104	.218	-	.078	.354	-	-
Error avge tot lat	.211*	.011	.214	.166*	.047	.168	.269
Criterion run avge cog lat	.161	.072	-	.140	.118	-	-
Criterion run avge tot lat	.208*	.019	.211	.181*	.042	.183	.164
TOLT							
Avge pick up - 3 ring	.272***	<.001	.279	.153	.067	.154	.731
Avge pick up - 4 ring	.242**	.004	.247	.093	.270	.093	.901
Avge pick up - 5 ring	.245**	.003	.250	.110	.191	.110	.819
Avge pick up - Total	.280***	<.001	.288	.122	.146	.123	.965
Avge tot time - 3 ring	.274***	<.001	.281	.167*	.046	.168	.661
Avge tot time - 4 ring	.275***	<.001	.282	.106	.206	.106	1.030
Avge tot time - 5 ring	.287***	<.001	.296	.148	.077	.149	.860
Avge tot time - Total	.287***	<.001	.296	.140	.094	.141	.907

Notes: N= 143; * Sig. @ α = .05; ** Sig. @ α = .01; *** Sig. @ α = .001; z_{obt} considered significant if: $-1.96 > z_{obt} > 1.96$; $z_{obt} = (z_1 - z_2) / \text{SQRT}((1 / (N_1 - 3)) + ((1 / (N_2 - 3)))$; Spearman's *rho* transformations to *z* from Table 11.1 in Pallant (p.142) [110].

Table 4.11. *Results of Spearman's Rank Order Correlational Analyses of the Relationship between Processing Speed during Executive Function Task Performance and Affect Status in Participants with Type 1 Diabetes and Participants with no-Type 1 Diabetes.*

	Affective Disorder			
	Type 1 Diabetes, *N*=70		No-Type 1 Diabetes, *N*=73	
CST	*rho*	*p*	*rho*	*p*
Correct avge cog lat	-.060	.620	.142	.230
Correct avge tot lat	.170	.160	.082	.491
Perseveration avge cog lat	-.189	.119	.303*	.011
Perseveration avge tot lat	-.051	.680	.272*	.023
Non-perseveration avge cog lat	-.004	.974	.088	.461
Non-perseveration avge tot lat	.139	.253	.009	.942
Error avge cog lat	-.023	.852	.118	.321
Error avge tot lat	.159	.189	.049	.682
Criterion run avge cog lat	-.101	.436	.313*	.012
Criterion run avge tot lat	.026	.839	.232	.065
TOLT				
Avge pick up - 3 ring	-.014	.911	.112	.349
Avge pick up - 4 ring	-.055	.649	.059	.623
Avge pick up - 5 ring	.011	.926	.025	.832
Avge pick up - Total	-.001	.995	.045	.708
Avge tot time - 3 ring	.026	.827	.101	.396
Avge tot time - 4 ring	-.038	.751	.044	.714
Avge tot time - 5 ring	.034	.779	.056	.641
Avge tot time - Total	.009	.940	.062	.605

Notes: * Sig. @ α = .05

Table 4.12. *Tests of the Statistical Significance of the Difference between Significant Correlation Co-efficients of the Relationship between Affect Status and Processing Speed during Executive Function Tasks Performance in Participants with Type 1 Diabetes compared to participants with no-Type 1 Diabetes.*

Co-efficient for Affective Disorders and:	Type 1 Diabetes			No-Type 1 Diabetes			z_{obt}
	rho	*p*	z_1	*rho*	*p*	z_2	
Criterion run avge cog lat	-.101	.436	.101	.313	.012	.503	2.202*
Perseveration avge cog lat	-.189	.119	.388	.303	.011	.495	.617
Perseveration avge tot lat	-.051	.680	.051	.272	.023	.465	2.387*

Notes: * Indicates significant statistical difference between correlation co-efficients of the groups: -1.96 > z_{obt} > 1.96; $z_{obt} = (z_1 - z_2) / \text{SQRT}((1 / (N_1 - 3)) + ((1 / (N_2 - 3)))$; Spearman's *rho* transformations to *z* from Table 11.1 in Pallant (p.142) [110].

H_3: Processing Speed Associated with Diabetes-Specific Clinical and Aetiological Factors

To test the third hypothesis that processing speed would be associated with diabetes-specific aetiology and clinical factors, correlation coefficients were calculated between processing speed measures and age of disease onset, duration of illness, metabolic control, hypoglycaemia history, and the presence of diabetes-related complications (Table 4.13 and 4.14). Results of the correlational analyses revealed that both aetiology and clinical factors were significantly related to numerous measures of processing speed during executive function task performance in both task initiation and task total time-to-completion conditions.

Correlational analysis of diabetes aetiological factors indicated that both age of onset and duration of illness were significantly correlated to measures of processing speed in both cognitive initiation and total trial completion times (Table 4.13 and 4.14). Age of disease onset was significantly associated with cognitive initiation in trials resulting in a selection error (CST: errors average cognitive latency), and in the highest cognitive load conditions of the TOLT (5-ring average pick-up time). Age of onset was also associated with total trial completion times during the highest cognitive load conditions of the TOLT (5-ring average total time). Duration of illness was found to be significantly related to every cognitive initiation measure on both the CST and TOLT, with every total trial completion time measure on the TOLT, and with the CST total trial completion measures of non-perseverative errors and criterion run average total latencies (Table 4.13 and 4.14). Short, medium and long-term metabolic control were all significantly correlated to measures of cognitive initiation. Medium-term metabolic control was also significantly correlated to total trial completion times on both the CST and TOLT. No significant associations were found between processing speed and hypoglycaemia history. Diabetes-related complications were significantly correlated to every processing speed measure of cognitive initiation and of total trial completion time on the TOLT, and with poorer total trial completion times in CST measures of correct selection responses, criterion run correct selection responses, and non-perseverative error responses. (Table 4.13 and 4.14).

When the influence of affective disorders was controlled, the number of significant correlation co-efficients reduced by 94%, from 49 in the uncontrolled analysis to three in the affect-controlled analysis (Table 4.13 and 4.14). When the corresponding co-efficients were compared using their $z_{obtained}$ $^{(110)}$ value, none of the

co-efficient pairs showed a statistically significant difference between them (Table 4.14 and 4.15). These results indicate that processing speed is associated with numerous type 1 diabetes-specific factors related to both short and longer-term health and wellbeing, and that affect is a substantial mediator of the significance of this relationship.

Table 4.13. *Results of Correlations and Partial Correlations (Controlling for Affective Disorders) between Processing Speed Performance on the Computer Analogues for the Wisconsin Card Sort, and Diabetes-Specific Clinical and Aetiological Factors.*

Attention and Working Memory Performance Variables		Correlations							Partial Correlations: controlling for affective disorders						
		Aetiology		Metabolic Control			Severe Hypo.	Comp.	Aetiology		Metabolic Control			Severe Hypo.	Comp.
		Age of onset	Illness duration	S-T	M-T	L-T			Age of onset	Illness duration	S-T	M-T	L-T		
CST															
Correct avge cog lat	*Cor*	.119	.382***	-.083	-.336*	-.154	.065	.125	.013	.228	.132	-.226	-.100	.177	-.080
	p	.337	.001	.501	.011	.494	.608	.303	.961	.363	.603	.367	.693	.483	.754
Correct avge tot lat	*Cor*	.048	.232	-.009	-.366**	.064	.196	.287*	-.018	.219	.074	-.058	.088	.046	-.223
	p	.698	.059	.944	.005	.778	.121	.016	.944	.383	.772	.818	.728	.856	.373
Perseveration avge cog lat	*Cor*	.049	.245*	-.251*	-.295*	-.251	-.074	.128	.215	.088	.095	-.207	-.099	-.069	-.064
	p	.695	.048	.040	.027	.259	.562	.293	.392	.728	.707	.410	.696	.787	.800
Perseveration avge tot lat	*Cor*	-.019	.187	-.236	-.298*	-.084	.079	.160	.034	.184	.062	-.111	.015	.019	-.221
	p	.879	.132	.055	.025	.709	.536	.189	.895	.466	.808	.660	.954	.939	.378
Non-perseveration avge	*Cor*	.236*	.249*	-.136	-.420***	-.454*	-.060	.136	.481*	-.140	.021	-.384	-.337	-.030	.090
cog lat	*p*	.054	.042	.269	.001	.034	.637	.260	.043	.581	.933	.115	.172	.905	.721
Non-perseveration avge	*Cor*	.151	.243*	-.105	-.430***	-.319	.114	.268*	.446	-.080	-.021	-.236	-.178	-.110	-.023
tot lat	*p*	.222	.047	.394	.001	.147	.368	.025	.064	.751	.936	.346	.481	.663	.927
Error avge cog lat	*Cor*	.243*	.244*	-.156	-.424***	-.432*	-.048	.135	.463*	-.107	.049	-.400	-.326	-.070	.097
	p	.048	.046	.203	.001	.045	.705	.265	.053	.672	.848	.100	.187	.783	.703
Error avge tot lat	*Cor*	.152	.224	-.138	-.420***	-.277	.147	.233	.380	-.027	-.007	-.246	-.160	-.125	-.046
	p	.219	.068	.263	.001	.211	.248	.053	.120	.916	.979	.325	.526	.620	.857
Criterion run avge cog lat	*Cor*	.045	.420***	-.128	-.353*	-.246	.003	.207	.081	.248	.273	-.197	-.159	.090	.153
	p	.732	.001	.325	.012	.310	.981	.106	.750	.321	.272	.433	.528	.724	.544
Criterion run avge tot lat	*Cor*	-.001	.409***	-.193	-.216	.238	.064	.263*	.140	.200	-.205	.270	.275	-.246	.093
	p	.995	.001	.137	.133	.326	.636	.039	.578	.426	.416	.278	.269	.325	.714

Notes: * Sig. @ α = .05; ** Sig. @ α = .01; *** Sig. @ α = .001; S-T = Average BGL during participation; M-T = HbA1c most recent to participation; L-T = Average HbA1c over previous 36 months.

Table 4.14. *Results of Correlations and Partial Correlations (Controlling for Affective Disorders) between Processing Speed Performance on the Computer Analogues for the Tower of London Tests, and Diabetes-Specific Clinical and Aetiological Factors.*

Attention and Working Memory Performance Variables		Correlations							Partial Correlations: controlling for affective disorders						
		Aetiology		Metabolic Control			Severe Hypo.	Comp.	Aetiology		Metabolic Control			Severe Hypo.	Comp.
		Age of onset	Illness duration	S-T	M-T	L-T			Age of onset	Illness duration	S-T	M-T	L-T		
TOLT															
Avge pick up - 3 ring	*Cor*	.102	.471**	.002	-.255	.085	.009	.349**	-.043	.426	.286	.063	.116	.269	.127
	p	.408	<.001	.984	.055	.706	.943	.003	.865	.078	.249	.803	.647	.281	.616
Avge pick up - 4 ring	*Cor*	.135	.341**	-.031	-.324*	.285	-.093	.336**	-.319	.676**	-.062	.220	.307	.006	.362
	p	.274	.004	.802	.014	.199	.462	.004	.197	.002	.808	.381	.216	.980	.140
Avge pick up - 5 ring	*Cor*	.258*	.324**	.048	-.314*	-.051	-.111	.370**	.211	.263	.284	-.057	-.162	-.095	.507*
	p	.034	.007	.698	.017	.822	.379	.002	.400	.292	.254	.823	.520	.707	.032
Avge pick up - Total	*Cor*	.169	.424***	.004	-.323*	.121	-.070	.373***	-.056	.528*	.221	.085	.105	.106	.356
	p	.168	<.001	.977	.014	.592	.581	.001	.826	.024	.378	.736	.679	.676	.147
Avge tot time - 3 ring	*Cor*	.149	.423***	.034	-.305*	.031	.011	.360**	.088	.267	.338	.160	.134	.230	.104
	p	.224	<.001	.783	.021	.889	.933	.002	.727	.284	.170	.525	.595	.358	.682
Avge tot time - 4 ring	*Cor*	.169	.403***	-.067	-.282*	.245	-.114	.301*	-.101	.387	-.038	.422	.375	-.145	.051
	p	.168	.001	.587	.034	.272	.365	.011	.691	.113	.882	.081	.125	.567	.839
Avge tot time - 5 ring	*Cor*	.249*	.334**	-.014	-.347**	.017	-.086	.321**	.205	.256	.085	.182	.026	-.144	.350
	p	.040	.005	.908	.008	.941	.495	.006	.415	.306	.736	.469	.918	.569	.154
Avge tot time - Total	*Cor*	.192	.412***	-.013	-.322*	.106	-.077	.338**	.065	.333	.166	.275	.201	.012	.168
	p	.116	<.001	.913	.015	.639	.541	.004	.797	.177	.509	.270	.424	.962	.504

Notes: * Sig. @ α = .05; ** Sig. @ α = .01; *** Sig. @ α = .001; S-T = Average BGL during participation; M-T = HbA1c most recent to participation; L-T = Average HbA1c over previous 36 months.

Table 4.15. *Tests of the Statistical Significance between Correlation Co-efficients of the Relationship between Processing Speed and Diabetes-Specific Aetiological and Clinical Factors, before and after the Influence of Affective Psychopathology is Controlled.*

		Uncontrolled			**Affect-Controlled**			
	Diabetes Factor	*r*	*p*	z_1	*r*	*p*	z_2	z_{obt}
CST								
Correct avge cog lat	Illness duration	.382***	.001	.402	.228	.363	.232	.883
Correct avge cog lat	M-T	-.336*	.011	.349	-.226	.367	.230	.618
Correct avge tot lat	M-T	-.366**	.005	.384	-.058	.818	.058	1.694
Correct avge tot lat	Comp.	.287*	.016	.296	-.223	.373	.227	.359
Perseveration avge cog lat	Illness duration	.245*	.048	.250	.088	.728	.088	.842
Perseveration avge cog lat	S-T	-.251*	.040	.256	.095	.707	.095	.837
Perseveration avge cog lat	M-T	-.295*	.027	.304	-.207	.410	.210	.488
Perseveration avge tot lat	M-T	-.298*	.025	.308	-.111	.660	.111	1.024
Non-perseveration avge cog lat	Age of onset	.236*	.054	.240	.481*	.043	.525	-1.481
Non-perseveration avge cog lat	Illness duration	.249*	.042	.254	-.140	581	.141	.587
Non-perseveration avge cog lat	M-T	-.420***	.001	.448	-.384	.115	.405	.223
Non-perseveration avge cog lat	L-T	-.454*	.034	.492	-.337	.172	.350	.738
Non-perseveration avge tot lat	Illness duration	.243*	.047	.462	-.080	.751	.080	1.985
Non-perseveration avge tot lat	M-T	-.430***	.001	.460	-.236	.346	.240	1.143
Non-perseveration avge tot lat	Comp.	.268*	.025	.275	-.023	.927	.023	1.309
Error avge cog lat	Age of onset	.243*	.048	.248	.463*	.053	.501	-1.315
Error avge cog lat	Illness duration	.244*	.046	.249	-.107	.672	.107	.738
Error avge cog lat	M-T	-.424***	.001	.453	-.400	.100	.424	.151
Error avge cog lat	L-T	-.432*	.045	.462	-.326	.187	.338	.644
Error avge tot lat	M-T	-.420***	.001	.448	-.246	.325	.251	1.024
Criterion run avge cog lat	Illness duration	.420***	.001	.448	.248	.321	.253	1.013
Criterion run avge cog lat	M-T	-.353*	.012	.368	-.197	.433	.200	.873
Criterion run avge tot lat	Illness duration	.409***	.001	.435	.200	.426	.203	1.206
Criterion run avge tot lat	Comp.	.263*	.039	.268	.093	.714	.093	.909

Notes: : * Sig. @ α = .05; ** Sig. @ α = .01; *** Sig. @ α = .001; S-T = Average BGL during participation; M-T = HbA1c most recent to participation; L-T = Average HbA1c over previous 36 months; # Indicates significant statistical difference between correlation co-efficients of the groups: $-1.96 > z_{obt} > 1.96$; $z_{obt} = (z_1 - z_2) / \text{SQRT}((1 / (N_1 - 3)) + ((1 / (N_2 - 3)))$; Correlation co-efficient transformations to *z* from Table 11.1 in Pallant (p.142) [110].

Table 4.16. *Tests of the Statistical Significance between Correlation Co-efficients of the Relationship between Processing Speed and Diabetes-Specific Aetiological and Clinical Factors, before and after the Influence of Affective Psychopathology is Controlled.*

		Uncontrolled			**Affect-Controlled**			
	Diabetes Factor	*r*	*p*	z_1	*r*	*p*	z_2	z_{obt}
TOLT								
Avge pick up - 3 ring	Illness duration	.471**	<.001	.512	.426	.078	.456	.291
Avge pick up - 3 ring	Comp.	.349**	.003	.364	.127	.616	.128	1.226
Avge pick up - 4 ring	Illness duration	.341**	.004	.355	.002	.263	.002	1.834
Avge pick up - 4 ring	M-T	-.324*	.014	.336	.381	-.057	.401	-.338
Avge pick up - 4 ring	Comp.	.336**	.004	.349	.362	.140	.378	-.151
Avge pick up - 5 ring	Age of onset	.258*	.034	.264	.211	.400	.214	.260
Avge pick up - 5 ring	Illness duration	.324**	.007	.336	.263	.292	.269	.348
Avge pick up - 5 ring	M-T	-.314*	.017	.325	-.057	.823	.057	1.393
Avge pick up - 5 ring	Comp.	.370**	.002	.388	.507*	.032	.559	-.889
Avge pick up - Total	Illness duration	.424***	<.001	.453	.528*	.024	.588	-.701
Avge pick up – Total	M-T	-.323*	.014	.227	.085	.736	.085	.738
Avge pick up - Total	Comp.	.373***	.001	.280	.356	.147	.372	-.478
Avge tot time - 3 ring	Illness duration	.423***	<.001	.452	.267	.284	.273	.930
Avge tot time - 3 ring	M-T	-.305*	.021	.325	.160	.525	.161	.852
Avge tot time - 3 ring	Comp.	.360**	.002	.377	.104	.682	.104	1.419
Avge tot time - 4 ring	Illness duration	.403***	.001	.428	.387	.113	.409	.099
Avge tot time - 4 ring	M-T	-.282*	.034	.290	.422	.081	.450	-.831
Avge tot time - 4 ring	Comp.	.301*	.011	.311	.051	.839	.051	1.351
Avge tot time - 5 ring	Age of onset	.249*	.040	.254	.205	.415	.208	.239
Avge tot time - 5 ring	Illness duration	.334**	.005	.347	.256	.306	.262	.442
Avge tot time - 5 ring	M-T	-.347**	.008	.362	.182	.469	.184	.925
Avge tot time - 5 ring	Comp.	.321**	.006	.333	.350	.154	.365	-.166
Avge tot time - Total	Illness duration	.412***	<.001	.439	.333	.177	.346	.483
Avge tot time – Total	M-T	-.322*	.015	.334	.275	.270	.282	.270
Avge tot time - Total	Comp.	.338**	.004	.352	.168	.504	.170	.946

Notes: : * Sig. @ α = .05; ** Sig. @ α = .01; *** Sig. @ α = .001; S-T = Average BGL during participation; M-T = HbA1c most recent to participation; L-T = Average HbA1c over previous 36 months; # Indicates significant statistical difference between correlation co-efficients of the groups: $-1.96 > z_{obt} > 1.96$; $z_{obt} = (z_1 - z_2) / \text{SQRT}((1 / (N_1 - 3)) + ((1 / (N_2 - 3)))$; Correlation co-efficient transformations to *z* from Table 11.1 in Pallant (p.142) [110].

S9: Discussion

The present study supports the extant literature that documents a clear relationship between type 1 diabetes and deficits in information processing speeds, and between processing speed and diabetes-specific aetiology and clinical factors [116, 119, 299, 302, 305, 308]. The extent of the association between processing speed and type 1 diabetes is a concern given the underlying importance of processing speed to cognition in general, and to higher-level cognition such as attention, working memory, and executive function specifically. The results show a clear pattern of deficits in processing speed during executive function task performance in type 1 diabetes, and support all of the hypotheses forwarded that 1) participants with type 1 diabetes would have slower processing speed, 2) processing speed would be adversely influenced by the presence of an affective disorder, and 3) processing speed would be associated with diabetes-specific clinical and aetiological factors. These results build on the extant literature and provide further argument for the investigation of the triarchic relationship between type 1 diabetes, neurocognitive impairment, and affective psychopathology.

H_1: Slower Processing Speed in Type 1 Diabetes

The results support the first hypothesis that participants with type 1 diabetes would have slower processing speeds during executive function tasks compared to no-type 1 diabetes controls. Participants with type 1 diabetes showed significantly slower processing speed compared to controls across measures of both initiation and completion. Processing speed is arguably the most consistently identified cognitive impairment in type 1 diabetes [119, 124, 299, 302, 305], and is foundationally important to the functional competence of all other cognitive processes due to processing limitations brought about by the limited time and simultaneity mechanisms [334]. Optimal cognitive processing in areas such as executive function, and working memory, rely on fast and efficient information processing. In the absence of adequate speed and efficiency, cognitive function degrades and may become significantly impaired as a secondary consequence to the deficit speeds at which information is processed. According to Salthouse [334], cognitive performance is corrupted when information processing speed is slow because the cognitive processes involved cannot be executed in the required time (time limitations), and because the outcomes of the early or initial processes are no longer available when the secondary or later processes require them (simultaneity). This has been demonstrated in a number studies, for example, Brown et al., [122] found that

35% of the variance in executive function and spatial working memory were related to processing speed in older adults. Similar results were found in infants by Cuevas and Bell [123]. In a longitudinal study of *N*=201 infants with evaluations commencing at five months of age and extending to 48 months, Cuevas and Bell [123] identified that infants with greater processing speed showed consistently higher executive function at 24, 36 and 48 months of age compared to infants with less efficient processing.

The pattern of deficit speed illustrated by the results shows that type 1 diabetes appears to effect processing speed across a consistent and widespread collection of operational neural systems. Processing was shown to be slower in both task initiation and task completion measures across multiple executive functions. This supports the general and diabetes-specific literature on the pathogenic characteristics of both processing speed and processing speed performance degradation that identify microvascular pathophysiology and white matter morphology as central causal mechanisms [116-119, 124, 300, 302, 333, 337, 338]. These physiological correlates are most often pervasive in nature and therefore support the widespread, systemic nature of processing speed deficits [337, 338].

H2: Processing Speed Adversely Influenced Affective Disorders

The results of the present study support the second hypothesis and suggest that type 1 diabetes may be a greater influence on processing speed than the presence of an affective disorder. More measures of processing speed during executive function task performance were significantly associated to type 1 diabetes then were correlated to the presence of an affective disorder. This differs to the findings from the previous two studies presented in this chapter, in which results suggested that executive function and attention and working memory performance may be more influenced by the high prevalence of affective disorders rather than type 1 diabetes per se. Moreover, processing speed was influenced by affect in controls more strongly than in participants with type 1 diabetes.

The relationship between processing speed and type 1 diabetes makes sense from a pathogenic standpoint as a number of the pathophysiological mechanisms that have been identified in general population studies as being associated with processing speed, have also been identified as pathophysiological features of type 1 diabetes. Most notably are the microvascular pathophysiology and white matter morphology already detailed. Further, pathophysiological correlates include the potential role of Abeta/tau-

dependent and independent pathological alterations [117]; AGEs and in particular the AGE receptor's (RAGE) involvement in neurodegenerative changes in white matter, myelination, and to a lesser extent gray matter [302, 339, 340]; alterations to gene expression of the CNS that impact molecular and functional performance in neurons [341]; insulin resistance/desensitization and its role in the promotion of β-Amyloid intracellular neurofibrillary tangles and extracellular plaques [302, 342]; inflammatory dysregulation [319]; and an accelerated concentration of the combinatory forces involved in neurodegeneration typically found in the course of aging [117, 119, 302, 335, 336].

H_3: Processing Speed Associated with Diabetes-Specific Clinical and Aetiological Factors

Both initiation and completion processing speed measures were associated with age of disease onset, duration of illness, short-term glycaemic control, medium and long-term HbA1c, hypoglycaemic history, and the confirmed presence of diabetes-related complications. These results support the third hypothesis that processing speed would be associated with diabetes-specific aetiology and clinical factors. Given the correlation to type 1 diabetes in general, it is perhaps not surprising that processing speed was also correlated to factors known to be associated with an amplified expression of the pathophysiologic characteristics of the disease. The diabetologic factors known or theorised to be associated with processing speed deficits are the same degenerative and accumulative factors causally linked to clinical outcomes such as complications onset, or consequentially linked to aetiology and clinical characteristics such as hyper and hypoglycaemia, age of disease onset, or duration of illness [89, 117, 120, 297, 300, 302, 319, 339, 340]

The results clearly link poor processing speed to poor clinical outcomes and to increased clinical and aetiological risk factors [116, 118-120, 302]. The specific pathogenic mechanisms may be heterogeneous and physiologically complex however, the functional implications of impaired processing speed and the potential impact on diabetes management and self-care behaviours is relatively straight forward. The functional implications of processing speed deficits on clinical diabetes care behaviours can be explained within the principals of the limited time and simultaneity mechanisms espoused by Salthouse [334]. In essence, reduced processing speeds prevent information from being accessed, shared between operational neural components, interpreted, and made appropriately available when needed. This absence of information and process

capacity results in executive dysfunction in areas such as impaired decision making processes (EG: an inability to apply knowledge to new situations to solve problems), reduced inhibitory capacity, inability to set-shift (resulting in decisional errors such as perseveration), poor working memory update capacity, and a reduced capacity for sustained attention and working memory. The diabetes-specific behavioural consequences may include lack of glycaemic awareness resulting in increased risk for diabetic ketoacidosis or iatrogenic hypoglycaemia; inconsistent health checks and complications screening; and serious lapses in adherence to medication schedules, blood glucose monitoring, and appropriate diet and exercise practices [116, 118, 120]. Several studies including the one by McNally et al., [120] have evidenced this link and shown that impaired cognitive function such as processing speed, is closely associated with reduced adherence to diabetes care practices, and poorer clinical outcomes (see Figure 4.1).

Conclusion

Given the significant crossover between the independently identified pathophysiological mechanisms of impaired processing speed and type 1 diabetes CNS sequelae, the results showing an association between the two factors is not surprising. There is a voluminous and steadily increasing body of literature that consistently shows that the CNS pathophysiology of type 1 diabetes is antithesis to the physiological conditions inherent in optimal information processing speed performance. Although the literature shows evidence that affective psychopathology is also associated with impaired processing speed, these results suggest that the relationship between processing speed and type 1 diabetes is such that the added presence of anxiety and/or depression disorders has little added influence. In the present cohort at least, the presence of affective psychopathology appears to have less influence in type 1 diabetes than controls. Ultimately this study supports the position that processing speed is adversely impacted by type 1 diabetes and is strongly related to diabetes-specific aetiology and clinical factors. Further research is need to fully elucidate the extent and nature of processing speed deficits in type 1 diabetes.

CHAPTER FIVE: INFLAMMATORY CHARACTERISTICS IN TYPE 1 DIABETES

Chapter Abstract

Inflammation has been identified as a feature of type 1 diabetes although its determinants remain largely unelucidated. While inflammation increases during disease onset, it appears to stabilise soon thereafter and remain as a low-level chronic inflammatory state. The evidence suggests that this chronic low-level inflammatory condition is a contributory factor in vascular and other diabetes-related complications. Low-level chronic inflammation has also been implicated in psychological and neuropsychological pathology, including affective disorders and cognitive impairment. Given both chronic low-level inflammation and an increased prevalence of affective disorders are ubiquitous in type 1 diabetes, there is speculation that there is a corollary between the two conditions. This chapter presents the findings from two studies that investigated inflammation (CRP, IL-1β, IL-6, TNF-α) in type 1 diabetes. The first study (study ten) investigated the relationship between inflammation and affective disorders. The second study (study eleven) investigated the relationship between inflammation and cognitive function, and the influence that affective disorders exert on this relationship. Detailed results are presented in each study. Taken together the results indicate that inflammation is related to both affective disorders and cognitive function, that there is a difference in this relationship between participants with type 1 diabetes and participants with no-type 1 diabetes, and that the relationship between inflammation and cognitive function is significantly mediated by affective disorders. The results also indicate that inflammation is significantly associated with metabolic control in type 1 diabetes. The high degree of within-groups variations in the levels of inflammation are likely to have influenced the results of some of the statistical analyses and highlighted the challenges associated with attempts to make use of low-grade chronic inflammation as clinical biomarkers. The conclusion drawn from the results is that while inflammation appears to be related to affective disorders, cognitive function, and diabetes-specific clinical outcomes, the lack of within-groups uniformity that seem to be a factor of low-level inflammation, presents substantial challenges for the clinical application of low-grade chronic inflammation as biomarkers of pathology. Moreover, inflammation appears to relate differently to psychopathology in type 1 diabetes. Further research is required to better understand the nature of this difference.

Aims and Hypotheses of Studies Presented in Chapter Three

Table 5.1. *Aims and Hypotheses of Studies Presented in Chapter Five.*

Study #	Aims	Hypotheses	Hypothesis Supported
10	a. Compare the levels of circulating pro-inflammatory cytokines in the serum of participants with type 1 diabetes compared to no-type 1 diabetes participants;	10.1. Participants with type 1 diabetes would have a higher level of CRP, IL-1β, IL-6, and TNF-α (inflammatory biomarkers) compared to participants with no-type 1 diabetes;	No
	b. Evaluate the capacity of inflammatory biomarkers to predict disordered affect in participants with type 1 diabetes compared to those without type 1 diabetes;	10.2. The relationship between inflammation and affective disorders would differ between the case and control groups;	Yes
		10.3. There would be a difference in the strength of inflammatory biomarkers to predict affective disorders between the case and control groups;	Yes
	c. Assess the relationship between inflammation and diabetes-related complications and metabolic control.	10.4. Inflammatory biomarkers would predict complications and metabolic control in case participants.	Partially
11	To assess the relationship between the levels of circulating pro-inflammatory cytokines and cognitive function in participants with type 1 diabetes and compare them to age and sex balanced no-type 1 diabetes controls.	11.1. Inflammatory biomarkers would be associated with executive function, attention and working memory, and processing speed;	Yes
		11.2. The presence of an affective disorder (anxiety and/or depression disorders) would mediate the relationship between cognition and inflammation;	Yes
		11.3. The relationship between inflammation and cognition, and the mediating role of affective disorders on the relationship will differ in participants with type 1 diabetes compared to participants with no-type 1 diabetes.	Yes

Study 10: Inflammation in Type 1 Diabetes

S10: Abstract

Background: Low-level, chronically upregulated inflammation and an increased prevalence of disordered affect have both been identified independently as characteristic of type 1 diabetes. A relationship between inflammation and affect has also been identified although this relationship is not conclusive with studies finding both for and against an association between the two factors. The present study investigated the relationship between inflammation and affective disorders in adults with type 1 diabetes.

Methods: A cross-sectional, case-control, within-between designs model was used to evaluate the relationship between type 1 diabetes, inflammation, and affective disorders. Inflammation and the influence of affective disorders on inflammation was compared in participants with type 1 diabetes (n=59), and no-type 1 diabetes controls (n=57). Associations between inflammation, complications, and metabolic control were also assessed. Inflammation was identified by the circulating (serum) levels of CRP, IL-1β, IL-6, and TNF-α. The presence of an affective disorder was ascertained using the MINI International Neuropsychiatric Interview.

Results: There was no between-groups difference in the circulating levels of inflammatory biomarkers in both the uncontrolled and affect-controlled analyses (CRP, IL-1β, IL-6, TNF-α, $p > .05$). There was a significant difference in the influence of affective disorders on inflammation in the type 1 diabetes participants compared to controls (CRP, IL-1β, IL-6, TNF-α uncontrolled vs affect-controlled ANOVA comparison = $-1.96 > z_{obt} > 1.96$). Logistic regression showed that inflammation predicted affective disorders in controls (p= .04) but not in type 1 diabetes (p= .28). In participants with type 1 diabetes, there was a significant negative correlation between metabolic control and inflammation (IL-1β, p< .01; IL-6, p< .01; TNF-α, p< .01), and a regression model using all four biomarkers was a significant predictor of long-term metabolic control (p= .02). Complications were not correlated to any inflammatory biomarkers and logistic regression showed the four biomarkers model did not predict complications.

Conclusion: While inflammation is related to long-term metabolic control in type 1 diabetes, the relationship between inflammation and affect appears to differ in type 1 diabetes compared to those without the condition. Further research is needed to fully understand the impact of inflammation on mental health in type 1 diabetes.

Keywords: inflammation; cytokines; biomarkers; diabetes mellitus, type 1; IL-1β; IL-6; TNF-α; CRP; Affective Disorders, Mood, Anxiety, Depression; Comorbidity; HbA1c; Metabolic Control; Glycaemic Control; Complications

S10: Introduction

Inflammation has been identified as a feature of type 1 diabetes [343]. While its determinants remain largely unelucidated [344], inflammatory dysregulation has been shown to play a role in the pathogenesis of the disease [345-347]. Inflammation increases during onset of the disease however, the level of inflammation does not appear to increase with progression of the illness, and instead remains as a low-level chronic inflammatory state [348]. There is strong evidence that this chronic low-level inflammation is a contributory factor in the risk for vascular and other diabetes-related complications [349, 350]. As a result Reis et al., [348] suggest that the inflammation-related functional changes that are associated with diabetes complications may therefore occur within the first few years post-onset even though overt signs of their presence may not be visible until much later.

Upregulated inflammation is a characteristic of type 1 diabetes even in patients with good metabolic control, with several studies showing higher levels of pro-inflammatory cytokines in people with type 1 diabetes compared to controls. Snell-Bergeon et al. [351] found that regardless of metabolic control, participants with type 1 diabetes had higher levels of interleukin-6 (IL-6) compared to those without type 1 diabetes. Furthermore, C-reactive protein (CRP) was found to be higher in participants with sub-optimal metabolic control (HbA1c $\geq$7.2%) compared to controls and participants with type 1 diabetes who had HbA1c <7.2% [351]. Both IL-6 and CRP are markers of systemic inflammation and the results of Snell-Bergeon et al. [351] indicate elevated and physiology-wide inflammation in type 1 diabetes.

IL-6 dysregulation has been shown to significantly contribute to the pathogenesis of a number of illnesses in humans including autoimmune diseases and cancer [352]. Chronic dysregulation of this cytokine is a major concern as it is associated with a significant risk for comorbidities in type 1 diabetes and circulating levels of both CRP and IL-6 have been associated with diabetes-related complications such as cardiovascular disease, nephropathy, and proliferative retinopathy [343, 349, 350, 353]. The targeting of IL-6 as an intervention for related illnesses has gained support and there is presently a strong research program aimed at developing and testing potential anti-IL-6 treatments for use in autoimmune disease, inflammatory conditions, and cancers [352, 354].

A number of other cytokines have been identified in the inflammatory response that ultimately contributes to β-cell death and the onset of type 1 diabetes [355-357]. These cytokines act in concert to influence β-cell death [355] and to effect gene activation that results in expression that is either protective or deleterious to β-cell survival [356, 357]. Two prominent cytokines identified in this process are interleukin-1 beta (IL-1β) and tumour necrosis factor-alpha (TNF-α).

CRP is an acute phase protein [358] that upregulates in the blood in response to an increase in IL-6 circulation and has been identified as a broad-spectrum indicator of inflammation in the body [359, 360]. In comparison, IL-1β, IL-6, and TNF-α are immune-modulating cytokines that are secreted by specific immune cells and carry local messages between cells [358]. The circulating levels of IL-6, IL-1β, and TNF-α have been shown to have a number of specific negative impacts on physiological function. For example, upregulated circulation of IL-6, IL-1β, and TNF-α are associated with changes to hepatic growth hormone release and the associated function of the insulin-like growth factor I gene (IGF-I)) in human in vitro and mouse in vivo models [361, 362]. These cytokines are associated with almost all common diabetes-related complications highlighting the central role of inflammation in both the pathogenesis of type 1 diabetes as well as the most common sequelae of the disease [344, 353, 354, 362-365].

Inflammation has also been associated with mental health [358, 366-368]. IL-1β, IL-6, and TNF-α all have a role in brain function with studies in human and animal models showing that these cytokines are involved in a range of psychological functions including monoaminergic, dopaminergic and glutamatergic pathways, HPA Axis, NMDA-mediated transmission, and glucocorticoid-related activation, to name a few [358, 369, 370]. However, the use of low-level chronic inflammation as a biomarker of mental or other illness in humans is problematic [358, 369]. This is important as circulating baseline levels of these biomarkers in non-pathological human populations are often too low to be readily detectable [371]. High levels of circulating cytokines are generally reflective of an acute pathogenic response and are not necessarily indicative of chronic or trait elevation [372].

There are a number of complexities associated with the attempted use of biomarkers as predictive or diagnostic features in psychiatric conditions in humans [358]. Research results in this field are far from consistent with findings that show associations between inflammation and depression or other psychiatric illness ranging from very

strong to non-existent, and in some instances inflammation has been negatively associated with depression subtypes [358, 369, 373-375]. According to Lopresti eta l., [358], there are a number of factors that may contribute to this including a lack of sensitivity and specificity in any single biomarker; significant inconsistencies with specimen collection, preparation, storage, and measurement protocols; and a lack of understanding and appreciation of patient variables such as age, sex, medication interaction, menstrual cycle effects, circadian variability, BMI, and lifestyle factors such as alcohol and smoking. Moreover, Lotrich [370] asserts that while inflammatory cytokines may trigger and be associated with psychiatric disturbance such as major depression in humans, and elicit behaviours that can be considered homologous to depression in animals, there is mounting evidence that this may well be the case only in a subtype of illness and not be a representative feature of all depression. Therefore assessments of inflammation and depression that do not account for the potential for a subtypology may confound the argument.

Rodent models are used extensively to investigate inflammation as brain and other tissue concentrations of biomarkers can be scrutinised directly and provide a more robust measure of localised cytokine regulation under specific circumstances [376]. In animal models, IL-1β, IL-6, and TNF-α have been linked to myriad pathogenic processes including those involving the central nervous system [370, 376]. For example, in mouse models IL-1β has been linked to cognitive function [377-379]; TNF-α with signalling in the central nervous system related to both neurotoxic and neuroprotective states [380], as well as anxiety and depression behaviours [381]. Both IL-1β and IL-6 have been implicated in animal models of thalamic function [382], and IL-6 has been shown to be involved in brain-mediated control of glucagon secretion, but only in response to a stress-based stimuli such as epinephrine [383]. In the brain, inflammation is further associated with numerous function and pathology, including those associated with glutamatergic systems [384], long-term potentiation and NMDA-mediated transmission [370, 385], dopaminergic mechanisms [386, 387], and monoaminergic pathways [388, 389].

In humans and animal models, IL-6, IL-1β, and TNF-α have all been closely associated with mood regulation and mood related behaviours [367, 390, 391] with strong evidence showing that dysregulation of IL-6, IL-1β, and TNF-α, are all associated with increases in negative affect [367, 390-392]. Human studies have shown that increased circulating IL-6, IL-1β, and TNF-α have been consistently observed in depressed but

otherwise healthy individuals [366, 391-393], and depression remittance through antidepressant treatments corresponds with a normalising of serum levels of these cytokines [394-396].

Results presented in this thesis and in the wider literature show that anxiety and depression disorders are a significant comorbidity in type 1 diabetes (chapter three) [8, 14, 397-399]. Given that type 1 diabetes is characterised by low-level chronic inflammation, and inflammation is associated with increased risk for affective disorders, there appears to be a strong case that these factors are also correlated in those with the disease. Therefore, the high rates of affective disorders in type 1 diabetes may be mediated to some extent by the characteristic presence of chronic inflammation. However, because chronic low-level inflammation is a consistent characteristic across all sufferers, and appears largely independent of other factors such as glycaemic control, duration of illness, and the presence of complications, inflammatory biomarkers may not be a reliable indicator of disordered affect in type 1 diabetes in the same manner that it is in animal models and in some no-type 1 diabetes populations. Moreover, if type 1 diabetes inflammation is at a low-level, then despite its chronic nature, the clinical utility of inflammatory biomarkers to be effective as predictive and diagnostic indicators based on these low-level increases in circulating inflammatory concentrations (compared to normal) may be limited, and research-based investigation may prove challenging without considerable sampling due to the likelihood of large within-groups variations (individual differences) and small effect sizes between groups.

To test this assertion, the present study aimed to compare the levels of circulating pro-inflammatory cytokines in the serum of participants with type 1 diabetes compared to no-type 1 diabetes participants; to evaluate the capacity of inflammatory biomarkers to predict disordered affect in participants with type 1 diabetes compared to those without type 1 diabetes; and to assess the relationship between inflammation and diabetes-related complications and metabolic control. Four hypotheses were tested. It was hypothesised that: 1) participants with type 1 diabetes (case) would have a higher level of CRP, IL-1β, IL-6, and TNF-α (inflammatory biomarkers) compared to participants with no-type 1 diabetes (controls); 2) that the relationship between inflammation and affective disorders would differ between the case and control groups; 3) that there would be a difference in the strength of inflammatory biomarkers to predict

affective disorders between the case and control groups, and; 4) Inflammatory biomarkers would predict complications and metabolic control in case participants.

S10: Results

Descriptive analysis of group personal and demographic data confirmed that there were no differences between the participants in the type 1 diabetes and no-type 1 diabetes groups in age, sex, level of education, or employment characteristics. Participants' descriptive statistics are reported in Table 1.1, demographic statistics are reported in Table 2.2, affect status statistics are reported in Table 3.6, and diabetes-specific clinical data for the type 1 diabetes group are reported in Table 2.5. Correlations between inflammatory biomarkers and affective disorders (affect status) for participants with and without type 1 diabetes were assessed using Spearman's rank order correlations (Table 5.2).

Table 5.2 shows that circulating levels of IL-1β, IL-6, and TNF-α were highly correlated in both the participants with type 1 diabetes and in those without the condition. However, results also show that the level of CRP was not correlated to any of the other biomarkers in either group. Correlations among the affect status variables showed that only anxiety and depression were not correlated in the type 1 diabetes participants. In participants with no-type 1 diabetes anxiety and comorbid anxiety-depression were not correlated, and depression was not correlated to any other affect variable (Table 5.2). Contrary to the literature, affect status and inflammatory biomarkers were not correlated in either group (Table 5.2) [366, 367, 390, 392-394, 396].

Mean serum levels of CRP, IL-1β, IL-6, and TNF-α were obtained for all participants based on group membership and affect status. As CRP was not correlated to any of the other biomarkers and IL-1β, IL-6, and TNF-α were all strongly correlated to each other (Table 5.2), the mean serum levels for CRP were presented separately and IL-1β, IL-6 and TNF-α mean serum levels were presented together (Figure 5.1). These curves are descriptive only with the statistical analyses to be presented within the individual hypotheses results.

Table 5.2. *Spearman's Rank Order Correlations of Serum Concentrations of Inflammatory Biomarkers (CRP, IL-1β, IL-6, TNF-α) and Affect Status (Total Affect, Comorbid Anxiety-Depression, Anxiety Disorders, Depression Disorders) in Participants with and without Type 1 Diabetes.*

		Type 1 Diabetes				
No-Type 1 Diabetes		Tot Affect	CRP	IL-1β	IL-6	TNF-α
Tot Affect	*rho*		-.044	-.042	-.142	-.110
	p		.743	.755	.285	.408
CRP	*rho*	.213		-.215	-.119	-.184
	p	.111		.102	.369	.162
IL-1β	*rho*	-.001	-.116		.903***	.941***
	p	.993	.389		<.001	<.001
IL-6	*rho*	.057	.045	.934***		.914***
	p	.674	.740	<.001		<.001
TNF-α	*rho*	-.012	.004	.926***	.952***	
	p	.929	.974	<.001	<.001	

Notes: * Sig. at α= .05 level; ** Sig. at α= .01 level; *** Sig. at α= .001 level; Type 1 Diabetes Group = top of table); no-Type 1 Diabetes = bottom of table.

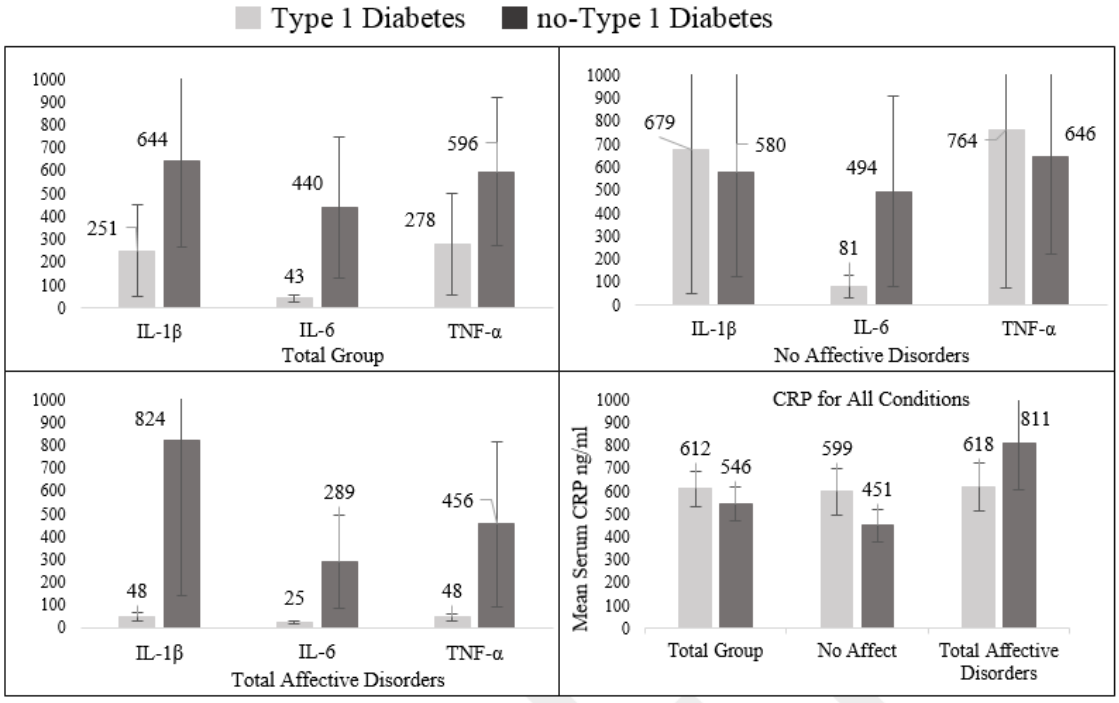

Figure 5.1. Mean (SE bars) serum levels of CRP, IL-1β, IL-6, and TNF-α for all participants by group membership and affect status. IL-1β, IL-6, and TNF-α volume in pg/ml; CRP volume in ng/ml; Total Group: Type 1 Diabetes n= 59, No-Type 1 Diabetes n= 57; No Affective Disorders: Type 1 Diabetes n= 19, No-Type 1 Diabetes n= 42; Total Affective Disorders: Type 1 Diabetes n= 40, No-Type 1 Diabetes n= 15.

H_1: Higher Inflammation in Case Group Compared to Controls

As the inflammatory biomarkers were very highly correlated (>.9; Table 5.2), univariate analysis of variance (ANOVA) was used to assess the between-groups differences in circulating inflammatory biomarkers. No serious violations of the assumptions were noted. ANOVA revealed no difference in the level of circulating biomarkers for CRP, IL-1β, IL-6, or TNF-α between participants in the case and control groups (Table 5.3).

H_2: The Relationship between Affective Disorders and Inflammation Different in Type 1 Diabetes

A second series of ANOVA was conducted, this time controlling for the presence of an affective disorder (anxiety disorders, depression disorders, comorbid anxiety-depression disorders). No serious violations of the assumptions were noted. When the influence of the presence of an affective disorder was controlled, ANOVA again showed no difference in the level of circulating biomarkers for CRP, IL-1β, IL-6, or TNF-α between the case and control groups (Table 5.3).

To evaluate the influence of the presence of an affective disorder on the group levels of inflammation, an analysis of the statistical differences between the ANOVA results was undertaken. Individual between-subjects ANOVA *p* values were converted to *Q* values (where *Q* is the probability that the observed score is due to chance; $Q= 1 – p$), which were converted to $z_{observed}$ scores (z_1 and z_2). The $z_{observed}$ scores for each of the corresponding ANOVA results where then analysed to deliver a $z_{obtained}$ value (z_{obt}). ANOVA results were considered significantly different if: $-1.96 > z_{obt} > 1.96$. ANOVA results for all four biomarker comparisons were significantly different when the influence of the presence of an affective disorder was controlled, indicating that the presence of an affective disorder had a significantly different influence on the level of circulating CRP, IL-1β, IL-6, and TNF-α in participants with type 1 diabetes compared to controls (Table 5.3).

Table 5.3. *Descriptive Statistics and Results of the univariate ANOVA for Inflammatory Biomarkers between Participants in the Type 1 Diabetes and No-Type 1 Diabetes Groups, With and Without Controlling for the Presence of an Affective Disorders and With Comparisons of the Statistical Significance of the Difference between the ANOVA Results.*

	Type 1 Diabetes, *n*= 59		No-Type 1 Diabetes, *n*= 57		ANOVA (*df*= 1,116)			ANOVA controlling for affect (*df*= 1,116)			Significance of the difference between ANOVA *p values* [#]		
	M	*SD*	*M*	*SD*	*F*	*p*	η_p^2	*F*	*p*	η_p^2	z_1	z_2	z_{obt}
CRP	611.85	599.77	546.10	575.30	.363	.548	.003	.004	.951	<.001	0.121	1.655	-11.833[#]
IL-1β	251.22	1552.85	644.24	2838.90	.864	.355	.008	.411	.523	.004	0.372	0.058	2.422[#]
IL-6	42.95	128.46	440.37	2331.22	1.710	.194	.015	1.061	.305	.009	0.863	0.51	2.723[#]
TNF-α	278.38	1713.96	596.17	2451.88	.658	.419	.006	.080	.778	.001	0.204	0.765	-4.327[#]

Notes: Effect size, small η_p^2= .01, medium η_p^2= .06, large η_p^2= .14 [(282)]. # Indicates significant statistical difference between *z* observed scores of the ANOVA *Q* values where *Q* (the probability that the observed score is due to chance)= 1 – *p*; z_{obt} (*z* obtained) = ($z_1 - z_2$) / SQRT ((1 / (N_1 – 3))+ ((1 / (N_2 – 3))); Significant difference between MANOVA results: -1.96 > z_{obt} > 1.96.

Within-groups analyses were undertaken to compare inflammation in participants with an affective disorder compared to participants without an affective disorder in the participants with type 1 diabetes and no-type 1 diabetes. Within-groups results were then compared to evaluate whether there was a significant difference between the groups in the interactions between inflammation and affect. Figure 5.2 shows the comparative levels of each biomarker based on affect status, in the participants with type 1 diabetes and without type 1 diabetes.

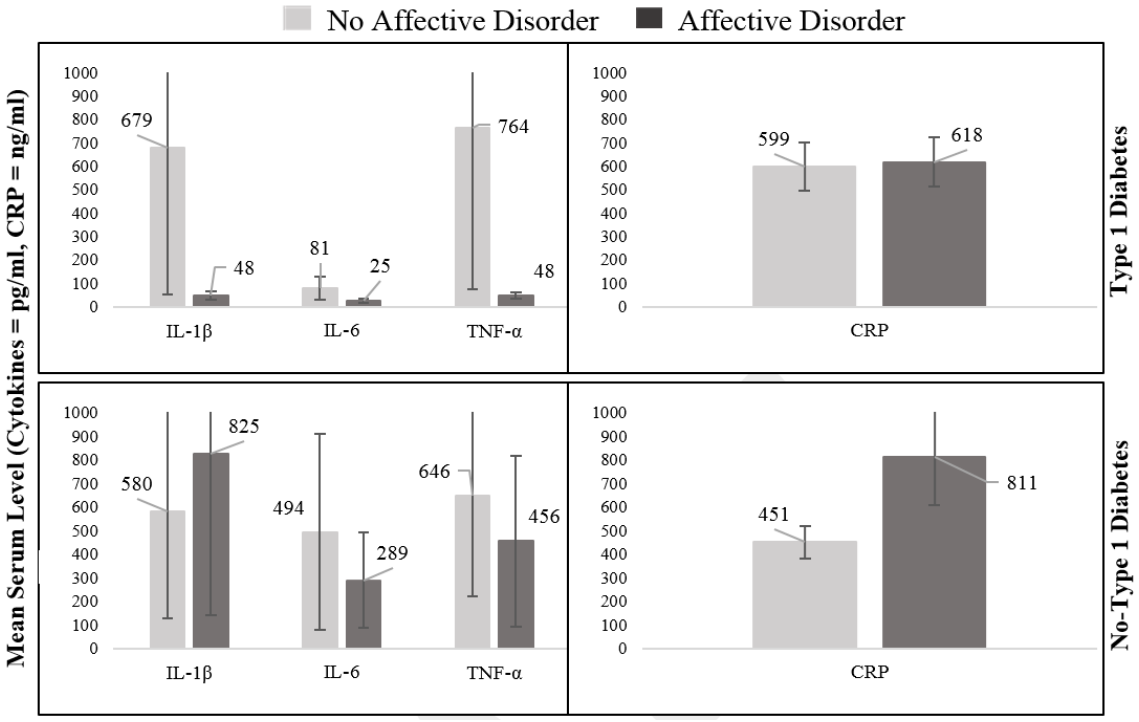

Figure 5.2. Comparison of mean levels of inflammatory biomarkers in serum of participants with type 1 diabetes and without type 1 diabetes, with and without an affective disorder. Type 1 diabetes: no affective disorder n= 19; affective disorder n= 40; no-Type 1 diabetes: no affective disorder n= 42; affective disorder n= 15.

ANOVA results showed no statistically significant differences in the level of circulating CRP, IL-1β, IL-6, or TNF-α between type 1 diabetes participants with and without an affective disorder (Table 5.4). In participants with no-type 1 diabetes, there was a significant difference in the level of CRP indicating that no-type 1 diabetes control participants with an affective disorder had significantly higher circulating levels of CRP ($F(1, 115)= 4.219$, $p= .042$, $r= .264$; Table 5.4). Table 5.4 shows that the mean level of circulating biomarkers were substantially different between comparison groups in both the type 1 diabetes and no-type 1 diabetes groups. However, the within-groups variances were quite large and this will have influenced the statistical outcomes.

The z_{obt} values for the comparison of the ANOVA results between groups showed that the influence of affect on peripheral levels of CRP (z_{obt} = -2.999) and IL-6 (z_{obt} = 6.246) was greater in control participants compared to the participants with type 1 diabetes (Table 5.4).

Table 5.4. *Descriptive Statistics and Results of ANOVA for Inflammatory Biomarkers between Participants in the Type 1 Diabetes and No-Type 1 Diabetes Groups, With and Without an Affective Disorder, and With Comparisons of the Statistical Significance of the Difference between the ANOVA Results.*

	Type 1 Diabetes, *N*= 59				ANOVA			No-Type 1 Diabetes *N*= 57				ANOVA			Significance of the difference between ANOVA *p values* [#]		
	No-Affective Disorder, *n*= 19		Affective Disorder *n*= 40		(*df*= 1,115)			No-Affective Disorder, *n*= 42		Affective Disorder, *n*= 15		(*df*= 1,115)					
	M	*SD*	*M*	*SD*	*F*	*p*	*r*	*M*	*SD*	*M*	*SD*	*F*	*p*	*r*	z_1	z_2	z_{obt}
CRP	599.07	454.58	617.92	662.93	0.013	.908	.017	451.43	456.71	811.18	781.57	4.219	.042	.264	1.329	1.728	-2.999[#]
IL-1β	678.88	2730.30	48.08	118.84	0.980	.324	.161	579.88	2934.71	824.63	2639.62	0.127	.722	.057	0.457	0.589	-0.992
IL-6	81.14	213.54	24.81	49.47	0.015	.903	.182	494.43	2683.42	289.01	785.54	0.171	.680	.054	1.299	0.468	6.246[#]
TNF-α	763.50	3013.23	47.95	95.70	1.476	.227	.166	646.36	2744.05	455.63	1402.38	0.090	.765	.048	0.749	0.722	0.203

Notes: Effect size, small *r*= .10, medium *r*= .30, large *r*= .50 [(282)]. # Indicates significant statistical difference between *z* observed scores of the ANOVA *Q* values where *Q* (the probability that the observed score is due to chance)= 1 – *p*; z_{obt} (*z* obtained) = ($z_1 - z_2$) / SQRT ((1 / (N_1 – 3))+ ((1 / (N_2 – 3))); Significant difference between MANOVA results: -1.96 > z_{obt} > 1.96.

H3: Difference in ability of Inflammation to Predict Affective Disorders

Logistic regression was undertaken to evaluate the ability of inflammatory biomarkers to predict affective disorders in the case and control groups. An evaluation of the full model containing CRP, IL-1β, IL-6, and TNF-α, showed that the model was not a significant predictor of affective disorders in the participants with type 1 diabetes (χ^2 (4, 59)= 5.125, *p*= .275). In the type 1 diabetes group, no single biomarker made a significant unique contribution to the model Table 5.5. In the no-type 1 diabetes control participants, the model significantly predicted affective disorders (χ^2 (4, 57)= 11.849, *p*= .019), explained between 18.8% (Cox & Snell R square) and 27.4% (Nagelkerke R square) of the variance in affect status, and correctly classified 82.5% of cases. Table 5.5 shows that CRP made a significant unique contribution to the model (Wald= 4.262, *p*= .039), and that the odds ratios for all four biomarkers were similar (all ExpB= ~1.000).

Table 5.5. *Results of Logistic Regression Evaluating CRP, IL-1β, IL-6, and TNF-α as Predictors of Affective Disorders in Participants with and without Type 1 Diabetes.*

	B	*S.E.*	Wald	*df*	*p*	Exp(B)	95% C.I. for EXP(B)	
							Lo	Up
Type 1 Diabetes								
CRP	.000	.000	.074	1	.786	1.000	.999	1.001
IL-1β	.010	.007	2.040	1	.153	1.011	.996	1.025
IL-6	-.005	.008	.433	1	.511	.995	.980	1.010
TNF-α	-.010	.007	2.100	1	.147	.990	.978	1.003
Const.	1.070	.489	4.786	1	.029	2.917		
No-Type 1 Diabetes								
CRP	.001	.001	4.262*	1	.039	1.001	1.000	1.002
IL-1β	.006	.004	2.585	1	.108	1.006	.999	1.014
IL-6	.003	.004	.475	1	.491	1.003	.994	1.012
TNF-α	-.010	.007	2.023	1	.155	.990	.976	1.004
Const.	-1.735	.499	12.069	1	.001	.176		

Notes: * Sig. at α= .05 level

H4: Inflammation would Predict Complications and Metabolic Control

Correlational analysis was undertaken to evaluate the relationship between inflammation and diabetes-related complications and metabolic control in participants with type 1 diabetes. Results revealed significant negative correlations between long-term metabolic control and the peripheral biomarkers for IL-1β (*r*= -.569, *p*= .009), IL-6 (*r*= -.636, *p*= .003), and TNF-α (*r*= -.636, *p*= .003), indicating that higher long-term HbA1c is associated with lower circulating peripheral inflammation (Table 5.6).

Table 5.6. *Correlations of Serum Concentrations of Inflammatory Biomarkers (CRP, IL-1β, IL-6, TNF-α), Metabolic Control, and Diabetes-Related Complications in Participants with Type 1 Diabetes. Biomarker Intercorrelations are presented in Table 5.2.*

		CRP	IL-1β	IL-6	TNF-α
S-T Metabolic Control [#], *n*= 56	*r*	.152	-.063	-.043	-.069
	p	.263	.647	.755	.616
M-T Metabolic Control [##], *n*= 49	*r*	.110	.131	.072	.128
	p	.453	.370	.621	.382
L-T Metabolic Control [###], *n*= 20	*r*	.129	-.569**	-.636**	-.626**
	p	.588	.009	.003	.003
Complications, *n*= 59	*rho*	.106	.044	.091	.024
	p	.423	.743	.492	.855

Notes: * Sig. at α= .01; [#] Average BGL during participation (approx. 3 hrs); [##] HbA1c at participation (approx. 3 month average); [###] average HbA1c over previous 36 months.

Diabetes-Related Complications

Due to a high degree of multicolinearity, biomarkers were not appropriate for multivariate analysis or multiple regression therefore, to test the associations between complications and inflammation, analysis was undertaken using One-Way ANOVA and logistic regression. Descriptive statistics showed participants with complications had lower IL-1β and TNF-α, higher CRP, compared to participants without complications. Figure 5.4 shows the comparative levels of peripheral biomarkers in those with and without complications.

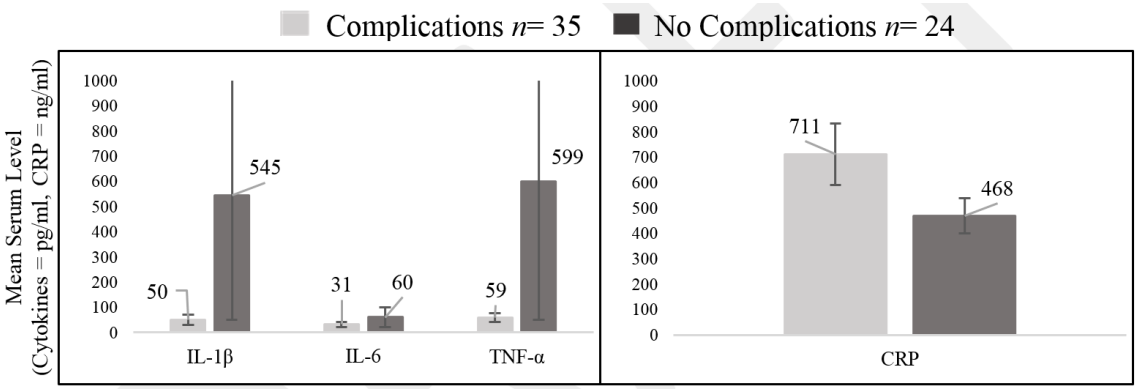

Figure 5.3. Mean inflammatory biomarker levels in type 1 diabetes participants with and without diabetes-related complications.

Despite a difference in mean biomarker levels between participants with and without complications, the results of the ANOVA indicated that the differences in the levels of CRP, IL-1β, IL-6 and TNF-α were not statistically significant (Table 5.7). Further investigation of the results revealed large standard deviations in most groups which will have affected the power and had an impact on the statistical outcome.

Table 5.7. *Mean Serum Concentrations, Standard Deviations, and Results of One-Way ANOVA of CRP, IL-1β, IL-6, and TNF-α for Type 1 Diabetes Participants with and without Diabetes-related Complications.*

Biomarker	Complications. (*n*= 35)		No Complications (*n*= 24)		One-Way ANOVA (*df*= 1,58)		
	M	*SD*	*M*	*SD*	*F*	*p*	η_p^2
CRP	711	715	468	339	2.395	.127	.040
IL-1β	50	119	545	2431	1.455	.233	.025
IL-6	31	53	60	192	.736	.394	.013
TNF-α	59	104	599	2685	1.422	.238	.024

Notes: Effect size, small η_p^2= .01, medium η_p^2= .06, large η_p^2= .14 [(282)].

CRP, IL-1β, IL-6 and TNF-α were entered into a logistical regression model to test their ability to predict diabetes-related complications (EG: cardiovascular disease, peripheral vascular disease, neuropathy, retinopathy, nephropathy). Analysis revealed that the predictive ability of the model was not significant (χ^2 (4, 59)= 6.035, *p*= .197), and no single predictor made a significant unique contribution to the model Table 5.8.

Table 5.8. *Group-Specific Unique Contributions to the Diabetes-Related Complications Model Made by each Inflammatory Biomarker for the Type 1 Diabetes Group.*

Complications Model	*B*	*S.E.*	Wald	*df*	*p*	Exp(B)	95% C.I. for EXP(B)	
							Lo	Up
CRP	.001	.001	2.388	1	.122	1.001	1.000	1.002
IL-1β	-.005	.007	.599	1	.439	.995	.982	1.008
IL-6	.010	.009	1.301	1	.254	1.010	.993	1.028
TNF-α	.003	.006	.304	1	.581	1.003	.991	1.016
Constant	-.323	.481	.451	1	.502	.724		

Metabolic Control

Logistic regression was again used to evaluate the predictive relationship between inflammation and short, medium, and long-term metabolic control. Metabolic control data was recoded into categorical sub-groups of optimal control (BGL / HbA1c < 7.1%) and suboptimal control (BGL / HbA1c ≥ 7.1%). Once recoded, the three new categorical metabolic control variables were entered as dependent variables into separate regression models.

Results showed that the model was not a significant predictor of either short or medium-term metabolic control (S-T: χ^2 (4, 56)= 2.830, *p*= .587; M-T: χ^2 (4, 49)= 6.573, *p*= .160), and no single predictor made a significant unique contribution to either model (Table 5.8). The inflammatory biomarker model did significantly predict long-term metabolic (χ^2 (4, 20)= 12.301, *p*= .015). The model as a whole explained between 45.9% (Cox & Snell R square) and 72.6% (Nagelkerke R square) of the variance in long-term metabolic control and correctly classified 95.0% of cases. The results indicated the model was had a sensitivity of 100%, specificity of 75.0%, a positive predictive value of 94.1%, and a negative predictive value of 100%. Table 5.9 shows that no single biomarker made a significant unique contribution to the model, and that the odds ratios for all four biomarkers were similar.

Table 5.9. *Group-Specific Unique Contributions to the Short-Term Metabolic Control Model Made by each Inflammatory Biomarker for the Type 1 Diabetes Group.*

		B	*S.E.*	Wald	*df*	*p*	Exp(B)	95% C.I. for EXP(B)	
								Lo	Up
S-T	CRP	.000	.001	.330	1	.566	1.000	.999	1.002
	IL-1β	.011	.008	1.735	1	.188	1.011	.995	1.028
	IL-6	-.002	.009	.044	1	.833	.998	.981	1.015
	TNF-α	-.010	.008	1.590	1	.207	.990	.975	1.005
	Constant	1.268	.573	4.895	1	.027	3.552		
M-T	CRP	.001	.001	.926	1	.336	1.001	.999	1.003
	IL-1β	-.008	.007	1.208	1	.272	.992	.978	1.006
	IL-6	-.011	.009	1.525	1	.217	.989	.972	1.006
	TNF-α	.008	.007	1.586	1	.208	1.008	.995	1.021
	Constant	1.088	.615	3.131	1	.077	2.969		
L-T	CRP	.009	.010	.786	1	.375	1.009	.990	1.028
	IL-1β	.028	.037	.568	1	.451	1.028	.956	1.106
	IL-6	-.187	.173	1.170	1	.279	.829	.591	1.164
	TNF-α	.048	.071	.454	1	.500	1.049	.913	1.204
	Constant	1.387	1.672	.688	1	.407	4.003		

S10: Discussion

The present study sought to compare the levels of circulating pro-inflammatory cytokines (CRP, IL-1β, IL-6, and TNF-α) in the serum of participants with and without type 1 diabetes, to compare the relationship between these biomarkers and affective disorders in the two groups, and to evaluate the relationship between inflammation and both diabetes-related complications and metabolic control. These results build on the existing literature that details 1) inflammation as an aspect of the pathogenic processes of type 1 diabetes, and low-level chronic inflammation as a post-onset characteristic of the disease; 2) a relationship between inflammation and affective disorders in otherwise healthy individuals, and; 3) a high prevalence of affective disorders in type 1 diabetes. The extrapolated argument being that inflammation and affective disorders should therefore be related in type 1 diabetes. However, due to the characteristically elevated inflammation in type 1 diabetes, the revelation of this relationship may be difficult. It was therefore posited that while relational variations in low-level chronic inflammation may be detectable in the tissue of humans and in animal models of pathology, including

type 1 diabetes; it may prove more challenging to replicate this in the circulating levels of inflammatory biomarkers in human type 1 diabetes populations due to the existing immune-dysregulation characteristics of the disease.

This is not to say that chronic low-level inflammatory mechanisms may not influence disordered affect or other pathogenic processes in type 1 diabetes, but only that detection of this relationship may prove more challenging without very large population sampling due to the likely small effect sizes involved. This assertion was generally supported with the results showing several differences between comparison groups during analysis however, none of these variations were shown to be significant in participants with type 1 diabetes. Small effect and sample sizes, large within-groups variations, and the elevated baseline levels (levels in participants without psychopathology) of the biomarkers may have all influenced these results and further research is needed to clarify the relationship between inflammation and affective disorders in type 1 diabetes.

Initial correlational analysis showed that the cytokine biomarkers were all highly positively correlated in both participants with and without type 1 diabetes. These results are in line with the literature as numerous studies have shown that peripheral circulating concentrations of IL-1β, IL-6, and TNF-α are consistently correlated in animal and human models in healthy samples as well as across a diverse range of pathologies [358, 369, 370, 390, 391, 393, 400]. The lack of correlation between the cytokines and CRP is contrary to previous studies that have consistently found associations between inflammatory cytokines, particularly IL-6, and CRP [344, 353, 400]. Of particular note was the finding that affective disorders did not correlate to a biomarker in either group. This was not unexpected in the type 1 diabetes group as the chronic low-level elevation that presents in type 1 diabetes may effectively rule out any corollary to other conditions associated with low-level chronic elevation (such as affective disorders) in the group. Based on the inconsistent findings of the relationship between circulating biomarkers and affect in human studies that are presented in the extant literature, the lack of correlation in the participants with no-type 1 diabetes was also perhaps not surprising [369, 370, 373, 390].

H_1: Higher Inflammation in Case Group Compared to Controls

Hypothesis one that participants with type 1 diabetes would have higher levels of inflammation than controls was not supported. Initial descriptive analysis of inflammation in participants showed that only CRP was higher in the case group, with

the mean levels of IL-1β, IL-6, and TNF-α all lower in the case group compared to controls. No differences between the groups were found to be significant when subjected to analysis. The literature has consistently shown upregulated CRP and inflammatory cytokines in both humans and animal models [344, 351, 401]. Only CRP was higher in participants with type 1 diabetes and therefore these results generally contradict what would be expected based on the existing literature. The small sample size combined with small effect size is likely to have had an impact on this result.

There is limited comparative literature that examines general concentrations of circulating inflammation in human type 1 diabetes cohorts. Most type 1 diabetes studies in the literature have evaluated inflammation in humans either within the parameters of pathogenesis of the disease [348, 356, 402, 403], or in the context of additional pathology such as microvascular complications [343, 349, 404] cardiovascular disease [343, 349, 405], nephropathy [350], or proliferative retinopathy [353]. These are chronic inflammatory conditions and are potentially more likely to show variations in associated biomarkers than might otherwise be found. Other studies that have identified regionally-specific inflammatory upregulation have been undertaken in animal models and human post-mortem evaluations. In these forms of investigation it is possible to perform specific analysis of inflammation or other phenomena in targeted organs such as the brain, pancreas, kidneys, and selected locations within the vascular apparatus such as the heart or arteries [406-414]. While such studies have been used to make a case for a corresponding level of circulating inflammatory biomarkers, several studies have shown this process of animal-to-human or organ/tissue-to-circulation extrapolation to be a complex issue that is hampered by a number of translational challenges [358, 415, 416].

Despite several mitigating factors, these results are somewhat contrary to the literature that report higher levels of inflammation in type 1 diabetes than in healthy comparison populations [351, 401, 404, 417]. For example, IL-6, a cytokine that has been shown to be consistently higher in type 1 diabetes in both humans and in animal models [348, 401, 402], was lower in the type 1 diabetes participants. Results of the present study showed that, compared to the corresponding control group, IL-6 was ten times lower in the type 1 diabetes group, six times lower in the type 1 diabetes group without an affective disorder, and 11 times lower in the type 1 diabetes group with an affective disorder. This result is somewhat controversial and not explicable in the context of the present understanding of inflammatory pathogenics in type 1 diabetes.

H_2: The Relationship between Affective Disorders and Inflammation Different in Type 1 Diabetes

ANOVA controlling for affective disorders showed no significant differences in inflammation between the case and control groups for CRP, IL-1β, IL-6, or TNF-α. However, when the results of the affect-controlled ANOVA were compared to those of the uncontrolled ANOVA, analyses showed that there was a statically significant difference in results for all four inflammatory biomarkers. This suggests that inflammation and affect have a different relationship in type 1 diabetes compared to controls, and supports the second hypothesis that affective disorders would influence inflammation differently in participants with type 1 diabetes compared to no-type 1 diabetes controls.

The results of the within-groups ANOVAs supported this assertion, showing that control but not case participants had a significant difference in inflammation between the participants with and without an affective disorder. Control participants with an affective disorder had almost 50% higher levels of circulating CRP than controls without an affective disorder. In contrast, the level of CRP did not differ between case participants with and without an affective disorder. The levels of IL-1β were also contrasted in the case and control groups. Though not significant, IL-1β was higher in affect disordered control participants and lower in affect disordered case participants, when compared to their corresponding group participants without an affective disorder. When the within-groups ANOVA results were compared between the groups, results showed that there was a significant difference between the groups in the influence of affective disorders on the levels of CRP and IL-6. Results indicated that the influence of affective disorders on the level of CRP and IL-6 was greater in control participants compared to the participants with type 1 diabetes. This supports the literature that reports low-grade inflammatory characteristics in type 1 diabetes [344, 354, 362]. When inflammation has been associated with affective disorder, it has been linked to similar low-grade inflammatory characteristics as those associated with type 1 diabetes [358, 366-368] and therefore, inflammatory markers associated with affective disorders may be masked in type 1 diabetes as a result of existing dysregulation.

These results show that there was a difference in the affect-inflammation relationship in type 1 diabetes compared to controls, however, the relationship also appears to be somewhat complex and has substantial within-groups variation. The high

degree of variation of inflammation levels within the groups supports the present argument that the use of biomarkers of low-level chronic inflammation for the clinical differentiation of affective pathology in type 1 diabetes presently lacks sufficient utility to be reliable [358]. This also reflects current opinion in the literature that suggests similar challenges in general populations [358, 370, 390]. Recent reviews of the literature have concluded that, while inflammatory biomarkers have the potential to be beneficial in the prediction and diagnosis of pathology, current inconsistencies with detection and assay sensitivity, research methodologies, sampling sizes, and a poor understanding of the impact on inflammatory biomarkers of patient variables, are presenting considerable challenges. Moreover, these complexities are hampering any meaningful general comparison of the results in the current literature [344, 358, 369, 370, 373, 390]. In type 1 diabetes, this is further exacerbated by the high reliance on animal models to extrapolate potential condition-relevant factors for humans [358, 376].

H_3: Difference in ability of Inflammation to Predict Affective Disorders

Hypothesis three that there would be a difference in the capacity for inflammatory biomarkers to predict affective disorders between the type 1 diabetes and no-type 1 diabetes groups was supported. A predictive model containing CRP, IL-1β, IL-6, and TNF-α significantly predicted affective disorders in the no-type 1 diabetes control participants but not in the participants with type 1 diabetes. In the control group, CRP made a significant unique contribution to the model however, odds ratios suggested that there was little difference in the contributions made by each predictor variable. There is a scarcity of studies that have investigated the relationship between inflammation and affect in type 1 diabetes. Numerous studies have explored this relationship in type 2 diabetes and have consistently found a relationship [181, 368, 418-424]. Inflammation in type 2 diabetes is characteristically higher than in type 1 diabetes with several factors contributing to the inflammatory state including age, obesity, and a sedentary lifestyle. Studies that have investigated the relationship in type 1 diabetes have found only limited evidence for a relationship. For example, Hood et al., [222] examined the link between depression and inflammation in youth with diabetes and found only apolipoprotein B (apoB) to be significantly related to depression. Ultimately these results show that inflammation may not have as good utility as a predictive mechanism in type 1 diabetes due to the existent chronic inflammatory characteristics that are inherent in the disease.

H_4: Inflammation would Predict Complications and Metabolic Control

The final hypothesis that inflammatory biomarkers would predict diabetes-related complications and metabolic control in participants with type 1 diabetes was partially supported. The four inflammatory biomarkers did not predict diabetes-related complications. However, results indicated that the biomarkers did predict long-term metabolic control (participants' three-year average HbA1c), with the model correctly classifying 95% of cases and explaining between 45.9% and 72.6% of the variance in long-term metabolism.

Previous research by Snell-Bergeon et al., [351] found that CRP was significantly associated with poorer metabolic control. The results of the present study did not indicate that either CRP or any of the inflammatory cytokines in the model were significantly correlated to long-term metabolic control, nor were they indicated as providing a significant unique contribution to the prediction of long-term metabolic control. Rather, the model as a whole was a significant predictor of metabolic control. There is an absence of literature on the relationship between inflammation and metabolic control. The present study and the study by Snell-Bergeon et al. [351] are the only recent studies identified that have investigated metabolic control and inflammation independently of major pathology such as heart, kidney, or liver disease in type 1 diabetes. While both inflammation and metabolic control are consistently discussed in the literature, few studies investigate the direct relationship between the two variables. Further research is need to better understand the nature and direction of this association.

Although inflammation did not predict diabetes-related complications in the present study, there is clear evidence in the literature that inflammation is associated with a number of specific diabetes-related complications and that the association has been quantified in both humans and in animal models [349, 404, 406, 425-432]. For example, Devaraj et al. [404], and Schram et al. [349], identified an association between inflammation and microvascular complications; Kanter and Bornfeldt [428] showed a clear relationship between inflammation and atherosclerosis risk; Dong et al. [425] showed a link between inflammation and heart disease; Lin et al. [429], and Lopes-Virella et al. [430] showed an association between inflammation and nephropathy; and Schram et al. [349], and Lopes-Virella et al. [430], demonstrated an association between inflammation and retinopathy. However, these studies are often undertaken under conditions in which participants are in acute-phase inflammatory response to complications-related issues

such as immediately post-cardiac event, during late or end-stage renal failure, while receiving treatment for a foot ulcer or other open wound, or measures are taken in tissue post-mortem in either humans or animal models. In these circumstances it is acute response rather than low-level chronic inflammation that is likely being measured. Moreover, the homogenous nature of the samples in these studies (IE: all cardiac/renal/ulcer patients) generally provide a more concise capacity to evaluate direct complication-related inflammation. The present cohort, while consisting of a high level of group members with a diabetes-related complication, were represented by a variety of complications types further divided into an array of severity and stages of progression. The present cohort was also a community sample rather than a targeted clinical sample and all participants were sufficiently well controlled and physically able to attend and participate in the study, and to complete self-reports unaided.

Conclusion

On balance the literature provides support for a relationship between disordered affect and higher activation of the inflammatory response system however, there have been a number of studies that have found no relationship between inflammation and affect [370, 374, 433], with a small number going further and reporting reduced levels of inflammation [370, 375]. These contrary findings have provided evidence to support a subtype of affective disorder that is related to inflammation while other subtypes may not be inflammation related [370]. Further research is needed to investigate the tripartite relationship between type 1 diabetes, affective disorders, and inflammation in order to ascertain whether: A) the lack of association between affect and inflammation is a consequence of the universally increased inflammatory characteristics of the disease serving to mask any corollary between them, or B) affective disorder in type 1 diabetes is influenced by factors other than inflammation and could potentially be considered as a unique subtype of disordered affect.

The results present conflicting evidence in that some biomarkers of inflammation were shown to be lower (though not significantly) in participants with type 1 diabetes compared to controls, and what's more, in type 1 diabetes participants with an affective disorder, the levels of some biomarkers were even lower again. These results highlight the complexities involved in the potential clinical use of peripheral biomarkers in any forum other than acute-phase response. Presently, the sensitivity and specificity of biomarkers at the lower-end of the "abnormally regulated" spectrum lack

the utility to be of clear diagnostic or predictive value [358]. This is even more apparent in autoimmune conditions such as type 1 diabetes in which low-level inflammation may be a characteristic feature of the condition. What is clear from the results is that there was a difference in the relationship between affective disorders and inflammation in participants with type 1 diabetes compared to the no-type 1 diabetes controls. The presence of an affective disorder does not appear to uniformly influence inflammation across individuals with type 1 diabetes and those without the disease. More research is needed to understand this difference and to ascertain the implications for people living with the disease.

Study 11: Inflammation and Cognitive Function in Type 1 Diabetes

S11: Abstract

Background: Inflammation, cognitive impairment, and affective disorders have been independently associated with type 1 diabetes however, what is less clear is the relationship between these factors within the disease. The present study investigated inflammation and cognitive function in type 1 diabetes, and the influence of affective disorders on their association.

Methods: Relationships between inflammation (CRP, IL-1β, IL-6, TNF-α), affective disorders, and cognitive function in the domains of executive function, attention and working memory (AWM), and processing speed, were assessed and compared in participants with type 1 diabetes (Case; *n*= 70), and no-type 1 diabetes (Controls; *n*= 73).

Results: IL-1β, IL-6 and TNF-α were significantly associated with executive function in case participants only. CRP was significantly correlated to attention and working memory in both groups. CRP, IL-1β, IL-6, and TNF-α, were all significantly associated with processing speed across measures of both initiation and completion in control participants only. When the influence of affective disorders was controlled, inflammation was not related to measures of executive function or AWM in either participant group however, CRP was significantly correlated to both initiation and completion speeds in case participants, and to completion speeds only in the control group. There were no statistically significant differences between the affect-controlled and uncontrolled correlation co-efficients in either group. When affect-controlled and uncontrolled co-efficients were compared between groups, there was a statistically significant difference in the uncontrolled co-efficient for CRP and perseveration error total trial time (processing speed) and affect-controlled co-efficient for CRP and perseveration error initiation time (processing speed; $-1.96 > z_{obt} > 1.96$). When inflammation was controlled, ANOVA results showed no difference between the case and control groups in any measures of executive function or AWM performance. However, case participants performed significantly poorer than controls in 12 out of 18 measures of processing speed across both initiation and total trial completion speeds. When the inflammation-controlled ANOVA results were compared to the uncontrolled ANOVA results originally presented in chapter four (Tables 4.1, 4.3, 4.4, 4.6), there were statistically significant differences between 5 out 9 executive function DVs, 13 out of 18 AWM DVs, and 7 out of 18 processing speed DVs.

Conclusion: Inflammation is significantly related to cognitive function, and the presence of an affective disorder has a substantial influence on this relationship. Furthermore, the influence of inflammation on cognitive performance differs markedly in type 1 diabetes compared to those without the condition. More research is needed to further elucidate the factors behind this difference.

Keywords: inflammation; cytokines; diabetes mellitus, type 1; IL-1β; IL-6; TNF-α; CRP; cognitive function; executive function; attention and working memory; processing speed; affective disorders; depression; anxiety; psychopathology.

S11: Introduction

Cognitive impairment is a biopsychosocially disabling condition that most often has an insidious, degenerative presentation. Its association to type 1 diabetes is well established in the extant literature, and numerous pathogenic mechanisms in both general populations and in type 1 diabetes-specific populations have been expounded [117, 124, 299, 302, 335, 337, 392, 434]. However, a consensus on the pathophysiology and causal influences of cognitive impairment in type 1 diabetes remains elusive. What appears most likely is that the pathogenics of impaired cognition in type 1 diabetes are heterogeneous and subject to individual differences in bioecology. What does appear clear is that a chronic low-level inflammatory state such as that which is inherent to type 1 diabetes, is a significant contributor to a myriad of the neuropathophysiological sequelae in both type 1 diabetes and in general populations that have been linked to decremental cognitive performance.

Cognitive impairment in type 1 diabetes is analogous to a process of accelerated aging [435, 436], and the disease carries with it an increased risk for dementia syndrome [117, 302, 335]. The inflammatory characteristics in these conditions are similar in that they all follow a process of chronic low-level inflammation that has been identified in the periphery [222, 437-441], as well as in animal models [407-409, 427, 428, 432, 435], and in the human CNS in post-mortem investigations [434, 442]. The link between cognitive decline and systemic inflammation was first identified four decades ago during post-mortem investigations of the brains of dementia patients [442]. Since that time, numerous studies have reported an association between inflammation and cognition. In particular the pro-inflammatory biomarkers of C-Reactive Protein (CRP), Interleukin-1beta (IL-1β), Interleukin-6 (IL-6), and Tumour Necrosis Factor-alpha (TNF-α) have been associated with impaired cognitive function, cognitive decline, and dementia [434, 438, 443-445]. While a large number of inflammation-related biomarkers have been associated with cognitive function, these four signalling proteins have become key measures of inflammation in many contexts, including peripheral biomarker studies and in localised explant tissue analysis [434, 438, 445-448].

Inflammatory biomarkers have been reported as chronically upregulated in type 1 diabetes, including in those with optimal glycaemic control [351], and postulated to be one of the mechanisms involved in the pathogenics of cognitive impairment in the disease [302, 319, 436, 449, 450]. The cytokine model of cognitive function supports this

position [392] however, some controversy exists over the specific nature of inflammatory dominance in biomarker upregulation associated with cognitive impairment [434]. While the association between inflammation and cognition is commonly reported [436, 451-453], some studies have reported a failure to find any relationship [452, 454]. In type 1 diabetes, the direct relationship between inflammation and cognition is even less clear. While inflammation in type 1 diabetes has been linked to both the neuropathophysiological sequelae, and to some of the clinical factors associated with cognitive impairment and decremental cognitive performance [351, 404, 449, 455], there is relatively little literature on the direct relationship between inflammation and cognition in type 1 diabetes populations, and whether this relationship differs to that found in the general population of similar age and sex.

The aim of the present study was to assess the relationship between the levels of circulating pro-inflammatory cytokines and cognitive function in participants with type 1 diabetes and compare them to age and sex balanced no-type 1 diabetes controls. It was hypothesised that inflammatory biomarkers would be associated with executive function, attention and working memory, and processing speed; that the presence of an affective disorder (anxiety and/or depression disorders) would mediate the relationship between cognition and inflammation; and that both the relationship between inflammation and cognition, and the mediating role of affective disorders on the relationship will differ in participants with type 1 diabetes compared to participants with no-type 1 diabetes.

S11: Results

Descriptive analysis of group personal and demographic data confirmed that there were no differences between the participants in the type 1 diabetes and no-type 1 diabetes groups in age, sex, level of education, or employment characteristics. Participants' descriptive statistics are reported in Table 1.1, demographic statistics are reported in Table 2.2, affect status statistics are reported in Table 3.6, and diabetes-specific clinical data for the type 1 diabetes group are reported in Table 2.5. Intercorrelations between inflammatory biomarkers appear in Table 5.2 and show strong relationships between circulating levels of IL-1β, IL-6, and TNF-α in participants with and without type 1 diabetes. Circulating CRP was not correlated to any other biomarkers in either participant group. The high level of correlation between biomarkers

makes them unsuited to multivariate statistical manipulation so where applicable, univariate analysis or logistical regression was used in place of multivariate analysis and multiple regression.

Cognitive performance in the domains of executive function, attention and working memory, and processing speed, was assessed using computer analogues of the Wisconsin Card Sort Test (CST; executive function and processing speed), Tower of London Test (TOLT; executive function and processing speed), and the n-Back Test (attention and working memory). Group performance descriptive statistics are reported in Tables 4.2 (executive function), 4.4 (attention and working memory), and 4.7 (processing speed).

To test the hypotheses, the data was subjected to several analyses. Bivariate correlations were undertaken to assess the direct relationship between cognitive performance and inflammation. Partial correlations were then run in order to control for the influence of affective disorder on the relationship between cognition and inflammation. The correlation co-efficients found to be significant from the two sets of analyses were tested to ascertain whether there was a statistically significant difference between the corresponding co-efficients. Between-groups co-efficients were also compared to assess any difference in the interaction effects of inflammation and affective disorders on cognitive function in the type 1 diabetes case compared to no-type 1 diabetes control groups. Following the correlational analyses, ANOVAs were conducted, using CRP, IL-1β, IL-6, and TNF-α as covariates in order to control for the influence of inflammation on cognitive performance.

H_1: Inflammatory biomarkers would be associated with cognitive performance

Correlations were undertaken to assess the direct relationship between inflammation and executive function (CST and TOLT), attention and working memory (n-Back), and processing speed (CST and TOLT) in each participant group.

Executive Function

In participants with type 1 diabetes, the results showed that there was a significant negative relationship between correct responses on the CST and both IL-1β (*rho*= -.298, *p*= .025), and TNF-α (*rho*= -.262, *p*= .049). CST errors of perseveration were negatively associated with IL-1β (*rho*= -.257, *p*= .053; Table 5.10). There was no

relationship between any of the executive function measures and CRP, IL-1β, IL-6, or TNF-α in the no-type 1 diabetes control group (Table 5.10).

Attention and Working Memory

In participants with type 1 diabetes, CRP was associated with measures of attention and working memory during both low and high cognitive demand (1-back missed target, *rho*= .266, *p*= .049; 1-back total correct responses, *rho*= .368, *p*= .006; 3-back hits on target, *rho*= -.264, *p*= .051; 3-back total correct responses, *rho*= -.319, *p*= .017; All conditions total omissions, *rho*= .357, *p*= .007; All conditions total % correct, *rho*= -.373, *p*= .005; Table 5.10). In the no-type 1 diabetes group, CRP was correlated to attention and working memory performance during moderate cognitive demand (2-back hits on target, *rho*= .295, *p*= .038; 2-back missed target, *rho*= -.358, *p*= .011; Table 5.11). IL-1β, IL-6, and TNF-α were not associated with any measures of attention and working memory performance in either participant group (Table 5.11).

Processing Speed

None of the inflammatory biomarkers in participants with type 1 diabetes were associated with processing speed performance (Table 5.12). In the no-type 1 diabetes participants, CRP, IL-1β, IL-6, and TNF-α, were all significantly associated with processing speed across measures of both initiation and completion. CRP was found to be significantly associated with task initiation and completion speeds on trials involving a perseverative error responses (CST: perseveration average cognitive latency, *rho*= .299, *p*= .037; perseveration average total latency, *rho*= .373, *p*= .008). IL-1β was associated with completion speed on trials involving a correct response on the CST (correct average total latency, *rho*= .283, *p*= .047). IL-6 was associated with completion speed on CST trials involving both correct and incorrect responses (correct responses average total latency, *rho*= .374, *p*= .007; non-perseverative error responses average total latency, *rho*= .311, *p*= .028; Total error responses average total latency, *rho*= .330, *p*= .019; criterion run average total latency, *rho*= .343, *p*= .024). Finally, TNF-α was also involved in trial completion processing speed (criterion run average total latency, *rho*= .329, *p*= .031; Table 5.12).

H_2: Affect Influences the Relationship between Inflammation and Cognition

Partial correlation analysis controlling for the presence of an affective disorder, was undertaken in order to evaluate the role of affect in mediating the association between inflammation and cognitive function.

Executive Function

Results of the partial correlational analyses showed that when the influence of affective disorders was controlled, there were no associations between executive function and inflammation in either participant group (Table 5.10). This is different to the results of the uncontrolled correlation in which several relationships were significant across both groups, indicating that affect has a mediating influence on the relationship between inflammation and executive function in individuals with and without type 1 diabetes.

Attention and Working Memory

When the influence of affect was controlled, there were no significant relationships between any measure of attention and working memory in either participant group. Table 5.11 shows that numerous co-efficients are different in both groups from the uncontrolled to the affect-controlled correlations suggesting that affect exerts a substantial mediating influence on the relationship between attention and working memory performance and inflammation (Table 5.11).

Processing Speed

Several significant relationships were indicated between processing speed and inflammation when affect was controlled. In the type 1 diabetes group, CRP was significantly associated with both trial initiation speed and total trial completion speed during a run of consecutively correct responses (CST: criterion run average cognitive latency, r= .410, p= .003; criterion run average total latency, r= .462, p= .001). These co-efficients were not significant in the uncontrolled analysis. In the no-type 1 diabetes group, CRP was also significantly correlated to both initiation and completion processing speed (CST: correct response average total latency, r= .317, p= .046; perseveration error average cognitive latency, r= .312, p= .050; and perseveration error average total latency, r= .371, p= .018). However, six completion speed co-efficients that were significant in the uncontrolled analyses failed to reach significance when the influence of affect was controlled. These co-efficients were across IL-1β (correct total latency), IL-6 (correct total latency, non-perseveration error total latency, error response total latency, criterion run total latency), and TNF-α (criterion run total latency). The change in these co-efficients indicates that affective disorders have a considerable role in mediating how inflammation impacts processing speed performance in total task completion processes and suggest that affect is a potentially stronger mediator of the

relationship between processing speed and inflammation in no-type 1 diabetes participants than in the participants with type 1 diabetes (Table 5.12).

In order to evaluate whether there was a statistically significant difference in performance when the influence of affect was controlled, the correlation co-efficients of the uncontrolled analyses were compared to the co-efficients of the affect-controlled analyses in each group. This was done by calculating the $z_{obtained}$ score from the corresponding $z_{observed}$ scores derived from converting the *r* co-efficients to their analogous *z* score [110]. Although a number of co-efficients were different in the uncontrolled and affect-controlled conditions, when the uncontrolled and affect-controlled co-efficients were evaluated within each group, no co-efficient from either participant group was statistically different to its twin (Table 5.13). This suggests that statistically, affect does not have a significant influence on the relationship between cognitive performance and inflammation in participants with or without type 1 diabetes.

Table 5.10. *Results of Correlational Analyses of the Relationship between Measures of Executive Function CRP, IL-1β, IL-6, and TNF-α.*

EXECUTIVE FUNCTION		**Uncontrolled**								**Affect-Controlled**							
		Type 1 Diabetes, *n*= 57				No-Type 1 Diabetes, *n*= 50				Type 1 Diabetes, *df*= 54				No-Type 1 Diabetes, *df*= 47			
		CRP	IL1-β	CRP	TNF-α	CRP	IL1-β	IL-6	TNF-α	CRP	IL1-β	CRP	TNF-α	CRP	IL1-β	IL-6	TNF-α
CST																	
Correct responses	*r*	.187	-.298*	-.128	-.262*	-.018	.033	.035	-.003	.231	-.040	-.116	-.039	-.022	-.107	-.110	-.105
	p	.163	.025	.343	.049	.902	.821	.811	.982	.087	.770	.395	.775	.883	.462	.453	.471
Perseverative errors	*r*	.104	-.257*	-.171	-.149	-.007	.052	.072	.132	.087	-.088	-.144	-.082	-.050	-.050	-.039	.035
	p	.440	.053	.203	.270	.963	.718	.618	.360	.522	.517	.290	.546	.732	.732	.793	.811
Non-perseverative errors	*r*	.210	.057	.069	.052	.043	.102	.088	.038	.037	.216	.153	.217	.189	-.111	-.114	-.111
	p	.118	.676	.611	.699	.766	.480	.544	.791	.787	.111	.261	.108	.193	.447	.434	.450
Total errors	*r*	.176	-.048	-.071	-.050	.059	.043	.054	.018	.080	.184	.091	.188	.183	-.137	-.136	-.104
	p	.189	.722	.599	.715	.684	.766	.710	.903	.556	.175	.503	.165	.209	.347	.351	.475
Category comp (max = 6)	*r*	-.193	.129	.101	.137	-.006	-.021	-.039	.010	-.091	-.159	-.048	-.161	-.039	.044	.036	.024
	p	.150	.337	.455	.309	.967	.884	.788	.947	.504	.242	.724	.237	.788	.765	.805	.868
TOLT																	
Excess moves - 3 ring	*r*	.094	-.009	.026	-.077	.185	-.037	.008	-.058	-.080	-.062	-.014	-.063	.221	-.192	-.183	-.123
	p	.478	.948	.844	.563	.198	.798	.954	.690	.556	.652	.917	.643	.126	.185	.207	.398
Excess moves - 4 ring	*r*	.239	.026	.119	.078	-.021	-.062	-.031	-.035	.009	-.001	.062	-.002	-.062	.047	.020	-.050
	p	.069	.846	.370	.555	.883	.669	.832	.809	.949	.995	.649	.987	.674	.746	.892	.732
Excess moves - 5 ring	*r*	-.131	-.077	-.125	-.082	-.110	-.155	-.229	-.193	.005	.040	.011	.042	-.022	-.048	-.084	-.099
	p	.322	.562	.345	.538	.447	.283	.110	.180	.970	.769	.936	.759	.882	.741	.565	.501
Excess moves – all cond	*r*	.078	.004	.040	-.025	.023	.001	-.027	-.058	-.073	-.048	.003	-.050	.137	-.161	-.174	-.150
	p	.556	.977	.763	.852	.876	.993	.852	.687	.592	.723	.985	.715	.348	.269	.231	.304

Notes: * Sig. @ α = .05; ** Sig. @ α = .01; # Uncontrolled = Bivariate correlations; ## Affect-Controlled = Partial correlations controlling for the presence of an anxiety, depression or comorbid anxiety-depression disorder.

Table 5.11. *Correlational Analyses of the Relationship between Measures of Attention and Working Memory and CRP, IL-1β, IL-6, and TNF-α.*

ATTENTION & WORKING MEMORY		**Uncontrolled**								**Affect-Controlled**							
		Type 1 Diabetes, *n*= 57				No-Type 1 Diabetes, *n*= 50				Type 1 Diabetes, *df*= 54				No-Type 1 Diabetes, *df*= 47			
		CRP	IL1-β	CRP	TNF-α	CRP	IL1-β	IL-6	TNF-α	CRP	IL1-β	CRP	TNF-α	CRP	IL1-β	IL-6	TNF-α
1-Back: Hit	*r*	-.253	.155	.124	.223	.009	.072	.069	.082	-.120	.099	.150	.102	.008	.115	.129	.114
	p	.062	.259	.367	.102	.949	.621	.633	.571	.387	.476	.280	.465	.954	.433	.376	.435
1-Back: Miss	*r*	.266*	-.115	-.036	-.155	-.075	-.140	-.155	-.179	.121	-.087	-.137	-.089	-.069	-.120	-.122	-.076
	p	.049	.403	.791	.258	.604	.334	.282	.214	.382	.532	.322	.524	.639	.410	.405	.603
1-Back: Total Omissions	*r*	.244	-.198	-.190	-.247	-.049	-.173	-.137	-.115	.145	-.105	-.127	-.108	.022	-.073	-.089	-.093
	p	.073	.148	.165	.069	.735	.228	.342	.428	.294	.449	.359	.437	.880	.620	.543	.523
1-Back: Tot num cor / 100	*r*	.368**	-.188	-.123	-.230	-.016	-.219	-.181	-.206	-.167	.125	.158	.128	-.013	.109	.128	.121
	p	.006	.170	.370	.091	.910	.127	.209	.151	.228	.366	.254	.356	.932	.456	.380	.408
2-Back: Hit	*r*	-.215	-.015	-.066	.073	.295*	-.102	-.064	-.089	-.221	.106	.062	.108	.166	.040	.078	.127
	p	.115	.911	.633	.597	.038	.483	.658	.540	.108	.446	.657	.438	.253	.787	.593	.383
2-Back: Miss	*r*	-.075	.034	-.036	-.036	-.358*	.163	.056	.078	-.092	-.091	-.057	-.097	-.238	.108	.070	-.026
	p	.584	.807	.795	.795	.011	.257	.699	.592	.508	.511	.683	.487	.100	.461	.633	.858
2-Back: Total Omissions	*r*	.249	.025	.060	-.041	.103	-.235	-.138	-.144	.189	-.042	-.023	-.041	.043	-.157	-.172	-.143
	p	.067	.857	.664	.768	.475	.101	.341	.320	.170	.761	.867	.768	.767	.281	.238	.328
2-Back: Tot num cor / 100	*r*	-.259	-.026	-.094	.044	.171	.060	.049	.071	-.177	.061	.039	.061	.037	.149	.179	.170
	p	.056	.851	.497	.749	.234	.680	.733	.624	.201	.660	.781	.661	.801	.306	.219	.243
3-Back: Hit	*r*	-.264*	-.015	-.074	.052	.113	-.032	-.027	-.114	-.156	.132	.134	.131	.003	.024	.060	.121
	p	.051	.912	.593	.708	.433	.826	.850	.430	.259	.340	.335	.344	.984	.868	.680	.408
3-Back: Miss	*r*	-.041	-.042	-.108	-.050	-.242	.165	.078	.212	-.075	-.056	-.097	-.055	-.232	.159	.142	.055
	p	.768	.759	.433	.718	.090	.251	.589	.139	.591	.686	.484	.691	.108	.274	.330	.706
3-Back: Total Omissions	*r*	.248	-.022	.070	-.046	.162	-.178	-.068	-.054	.193	-.041	-.003	-.039	.168	-.192	-.211	-.180
	p	.067	.873	.612	.738	.262	.216	.640	.711	.161	.771	.985	.779	.249	.186	.146	.217
3-Back: Tot num cor / 100	*r*	-.319*	-.081	-.160	.009	-.010	.239	.196	.234	-.187	.073	.051	.073	-.105	.210	.252	.245
	p	.017	.556	.244	.946	.947	.094	.173	.103	.177	.599	.715	.601	.471	.147	.081	.090
All Cond: Total Omissions	*r*	.357**	-.141	-.063	-.175	.114	-.222	-.115	-.097	.209	-.068	-.050	-.068	.091	-.158	-.176	-.154
	p	.007	.304	.650	.201	.431	.121	.427	.502	.129	.624	.718	.626	.535	.277	.226	.291
All cond: Tot cor as a %	*r*	-.373**	.130	.041	.200	.058	.174	.154	.196	-.204	.099	.093	.099	-.028	.170	.203	.195
	p	.005	.344	.766	.143	.689	.227	.285	.173	.138	.478	.506	.475	.848	.242	.161	.179

Notes: * Sig. @ α = .05; ** Sig. @ α = .01; # Uncontrolled = Bivariate correlations; ## Affect-Controlled = Partial correlations controlling for the presence of an anxiety, depression or comorbid anxiety-depression disorder.

Table 5.12. *Results of the Correlational Analyses of the Relationship between Measures of Processing Speed and CRP, IL-1β, IL-6, and TNF-α.*

PROCESSING SPEED		**Uncontrolled[#]**								**Affect-Controlled[##]**							
		Type 1 Diabetes, *n*= 57				No-Type 1 Diabetes, *n*= 50				Type 1 Diabetes, *df*= 54				No-Type 1 Diabetes, *df*= 47			
		CRP	IL1-β	IL-6	TNF-α	CRP	IL1-β	IL-6	TNF-α	CRP	IL1-β	IL-6	TNF-α	CRP	IL1-β	IL-6	TNF-α
CST																	
Correct avge cog lat	*r*	.068	.112	.129	.191	.172	.184	.233	.179	.221	-.067	-.088	-.064	.262	-.001	-.014	-.065
	p	.614	.407	.338	.155	.233	.200	.104	.214	.126	.648	.550	.660	.103	.995	.930	.692
Correct avge tot lat	*r*	.104	-.022	-.015	.002	.228	.283*	.374**	.263	.202	-.059	-.105	-.057	.317*	.032	.026	-.009
	p	.442	.869	.914	.988	.111	.047	.007	.065	.165	.685	.471	.696	.046	.846	.872	.956
Perseveration avge cog lat	*r*	-.040	-.051	.089	.050	.299*	.054	.114	.129	.045	-.019	-.002	-.017	.312*	.005	.003	-.015
	p	.769	.704	.512	.709	.037	.715	.437	.379	.757	.897	.988	.908	.050	.975	.987	.926
Perseveration avge tot lat	*r*	-.002	-.050	.094	.029	.373**	.136	.225	.219	.157	-.058	-.068	-.054	.371*	.045	.055	.053
	p	.990	.709	.485	.830	.008	.352	.121	.130	.283	.690	.642	.710	.018	.782	.738	.747
Non-perseveration avge cog lat	*r*	.029	.119	.143	.168	-.013	.136	.164	.162	.064	-.095	-.069	-.099	-.054	.025	.006	-.068
	p	.831	.379	.290	.211	.931	.347	.256	.260	.662	.516	.638	.499	.742	.878	.973	.678
Non-perseveration avge tot lat	*r*	.093	.057	.084	.084	.091	.245	.311*	.258	.207	-.100	-.095	-.101	.231	.057	.043	-.007
	p	.493	.672	.536	.533	.531	.087	.028	.070	.153	.493	.516	.489	.151	.725	.792	.967
Error avge cog lat	*r*	.011	.135	.198	.215	.058	.172	.204	.189	.065	-.086	-.056	-.089	.021	.035	.022	-.047
	p	.936	.317	.140	.109	.691	.232	.156	.188	.657	.556	.704	.545	.896	.830	.893	.773
Error avge tot lat	*r*	.061	.055	.104	.099	.194	.240	.330*	.247	.210	-.095	-.093	-.094	.255	.062	.052	.008
	p	.653	.683	.442	.464	.176	.094	.019	.083	.147	.517	.527	.520	.113	.705	.749	.960
Criterion run avge cog lat	*r*	.125	-.140	-.015	-.056	.226	.183	.238	.245	.410**	-.107	-.121	-.105	.042	.092	.094	.013
	p	.386	.333	.917	.698	.144	.240	.124	.113	.003	.463	.407	.472	.798	.570	.565	.937
Criterion run avge tot lat	*r*	.189	-.144	-.043	-.114	.283	.274	.343*	.329*	.462***	-.109	-.145	-.106	.152	.130	.138	.092
	p	.189	.318	.765	.432	.066	.075	.024	.031	.001	.457	.321	.467	.351	.423	.396	.573
TOLT																	
Avge pick up - 3 ring	*r*	.133	-.073	-.080	-.062	.023	.129	.137	.062	.255	-.148	-.197	-.143	.137	.026	.017	.021
	p	.318	.588	.549	.644	.877	.378	.348	.674	.077	.311	.175	.326	.399	.872	.916	.897
Avge pick up - 4 ring	*r*	.037	-.089	-.048	-.080	-.085	.059	.057	.000	.191	-.140	-.174	-.133	.054	.104	.095	.088
	p	.782	.509	.720	.552	.561	.686	.699	.999	.189	.338	.231	.362	.743	.525	.560	.590
Avge pick up - 5 ring	*r*	-.071	.103	.144	.090	-.132	.124	.089	.026	.051	-.138	-.085	-.135	.024	.227	.199	.137
	p	.598	.441	.280	.500	.364	.394	.545	.859	.729	.346	.561	.355	.885	.159	.218	.399
Avge pick up - Total	*r*	.050	-.022	.008	-.015	-.081	.149	.124	.057	.204	-.160	-.181	-.155	.071	.116	.102	.083
	p	.709	.871	.951	.913	.576	.303	.389	.696	.159	.271	.213	.287	.663	.475	.531	.611
Avge tot time - 3 ring	*r*	.117	-.044	-.050	-.051	.037	.153	.148	.051	.221	-.196	-.236	-.192	.235	.022	.017	.038
	p	.382	.742	.710	.705	.799	.294	.309	.725	.127	.177	.103	.186	.144	.893	.918	.818
Avge tot time - 4 ring	*r*	.080	-.139	-.110	-.127	-.112	.100	.101	.025	.250	-.195	-.241	-.189	.026	.116	.108	.089
	p	.550	.298	.413	.343	.445	.494	.488	.864	.084	.179	.095	.193	.875	.477	.508	.583
Avge tot time - 5 ring	*r*	-.063	.043	.041	.017	-.124	.131	.107	.036	.127	-.191	-.165	-.187	.067	.192	.178	.143
	p	.636	.750	.758	.901	.398	.368	.466	.807	.385	.188	.258	.198	.679	.235	.273	.377
Avge tot time - Total	*r*	.069	-.061	-.051	-.064	-.087	.113	.097	.012	.218	-.205	-.231	-.200	.114	.114	.105	.092
	p	.609	.647	.705	.632	.552	.442	.508	.934	.133	.157	.110	.168	.484	.482	.521	.571

Notes: * Sig. @ α = .05; ** Sig. @ α = .01; *** Sig. @ α = .001; # Uncontrolled = Bivariate correlations; ## Affect-Controlled = Partial correlations controlling for the presence of anxiety and/or depression.

Table 5.13. *Tests of the Statistical Significance between Correlation Co-efficients of the Relationship between Inflammation (CRP, IL-1β, IL-6, and TNF-α) and Cognitive Function, before and after the Influence of Affective Psychopathology is Controlled in the Type 1 Diabetes Group, and the no-type 1 Diabetes Group.*

Type 1 Diabetes, *n*= 57		**Uncontrolled**			**Affect-Controlled**			
	Infl. Bio.	*r*	*p*	z_1	*r*	*p*	z_2	z_{obt}
EXEC. Fx								
Correct resp	IL-1β	-.298	.025	.307	-.040	.770	.040	1.338
Correct resp	TNF-α	-.262	.049	.268	-.039	.775	.039	1.148
Persev errors	IL-1β	-.257	.053	.264	-.088	.517	.088	.882
ATT. & WM								
1-back: miss	CRP	.266	.049	.272	.121	.382	.122	.752
1-back total cor.	CRP	.368	.006	.386	-.167	.228	.169	1.088
3-back hit	CRP	-.264	.051	.272	-.156	.259	.570	-1.494
3-back total cor.	CRP	-.319	.017	.331	-.187	.177	.179	.762
All cond: tot omit	CRP	.357	.007	.373	.209	.129	.130	1.218
All cond: tot % acc	CRP	-.373	.005	.392	-.204	.138	.207	.927
PROC. SPEED								
Crit run avg cog lat	CRP	.125	.386	.126	.410	.003	.436	-1.554
Crit run avg tot lat	CRP	.189	.189	.191	.462	.001	.500	-1.549
No-Type 1 Diabetes, *n*= 50								
EXEC. Fx		No significant co-efficients						
ATT. & WM								
2-back: hit	CRP	.295	.038	.304	.166	.253	.168	.682
2-back: miss	CRP	-.358	.011	.374	-.238	.100	.243	.657
PROC. SPEED								
Cor avg tot lat	IL-1β	.283	.047	.291	.032	.846	.032	1.298
Cor avg tot lat	IL-6	.374	.007	.391	.026	.872	.026	1.830
Cor avg tot lat	CRP	.228	.111	.232	.317	.046	.328	-.481
Pers avg cog lat	CRP	.299	.037	.309	.312	.050	.323	-.070
Pers avg tot lat	CRP	.373	.008	.392	.371	.018	.389	.015
Non-pers avg tot lat	IL-6	.311	.028	.322	.043	.792	.043	1.399
Error avg tot lat	IL-6	.330	.019	.343	.052	.749	.052	1.459
Crit run avg tot lat	IL-6	.343	.024	.358	.138	.396	.139	1.098
Crit run avg tot lat	TNF-α	.329	.031	.342	.092	.573	.092	1.253

Notes: * Indicates significant statistical difference between correlation co-efficients of the groups: $-1.96 > z_{obt} > 1.96$; $z_{obt} = (z_1 - z_2) / \text{SQRT}((1 / (N_1 - 3)) + ((1 / (N_2 - 3)))$; Correlation co-efficient transformations to *z* from Table 11.1 in Pallant [110, p.142]

H_3: The Influence of Inflammation on Cognitive Performance would differ in Type 1 Diabetes

The results of the correlation analyses between cognitive function and inflammation in each group were compared to assess the statistical difference between the relationships in each group. This was again done by calculating the $z_{obtained}$ score from the corresponding $z_{observed}$ scores derived from converting the *r* co-efficients to their analogous *z* score [110]. Only co-efficient pairs in which one co-efficient was statistically significant were subjected to the z_{obt} comparison. This was conducted in both an affect-controlled and affect-uncontrolled condition to also assess the influence of affective disorders on the transaction. In the affect-uncontrolled condition, the z_{obt} scores from each converted co-efficient pair indicated that only one co-efficient pair between the groups was statistically different to each other. The relationship between CRP and the total time taken to complete a trial in which a perseverative error was made was significantly stronger in no-type 1 diabetes participants (CST: CRP and perseveration error, z_1= .002, z_2= .392, z_{obt}= -2.026; Table 5.14). In the affect-controlled condition, the z_{obt} scores indicated again that only one pair of co-efficients were statistically different between the groups. In the affect-controlled condition, only the speed of task initiation during trials in which a perseverative error was made was statistically different between the groups with participants without type 1 diabetes showing a stronger relationship for this measure (CST: CRP and perseveration error average cognitive latency, z_1= .045, z_2= .323, z_{obt}= -2.090; Table 5.14).

Table 5.14. *Tests of the Statistical Significance between Significant Correlation Co-efficients of the Relationship between Inflammation (CRP, IL-1β, IL-6, and TNF-α) and Cognitive Function before and after Controlling for the Presence of an Affective Disorder (Uncontrolled / affect-controlled), in the Type 1 Diabetes Group Compared to the no-Type 1 Diabetes Group*

Uncontrolled	Inflam. Bio.	**Type 1 Diabetes, *n*= 57**			**No-Type 1 Diabetes, *n*= 50**			
		rho	*p*	z_1	*rho*	*p*	z_2	z_{obt}
EXECUTIVE FUNCTION								
CST: cor. resp.	IL-1β	-.298	.025	.307	.033	.821	.033	1.437
CST: cor. resp.	TNF-α	-.262	.049	.268	-.003	.982	.003	1.389
CST: persev. err.	IL-1β	-.257	.053	.264	.052	.718	.052	1.112
ATT & WK MEM								
1-back: miss	CRP	.266	.049	.272	-.075	.604	.075	1.014
1-back total cor.	CRP	.368	.006	.386	-.016	.910	.016	1.904
2-back: hit	CRP	-.215	.115	.218	.295	.038	.304	-.443
2-back: miss	CRP	-.075	.584	.075	-.358	.011	.374	-1.539
3-back hit	CRP	-.264	.051		.113	.433		
3-back total cor.	CRP	-.319	.017	.331	-.010	.947	.010	1.652
All cond: tot omit	CRP	.357	.007	.373	.114	.431	.313	.309
All cond: tot % acc	CRP	-.373	.005	.392	.058	.689	.058	1.719
PROCESSING SPEED								
CST: cor tot lat	IL-1β	-.022	.869	.022	.283	.047	.291	-1.398
CST: cor tot lat	IL-6	-.015	.914	.015	.374	.007	.391	-1.954
CST: persev cog lat	CRP	-.040	.769	.040	.299	.037	.309	-1.398
CST: persev tot lat	CRP	-.002	.990	.002	.373	.008	.392	-2.026#
CST: non-persev tot lat	IL-6	.084	.533	.084	.311	.028	.322	-1.237
CST: Errors tot lat	IL-6	.104	.442	.104	.330	.019	.343	-1.242
CST: crit run tot lat	IL-6	-.043	.765	.043	.343	.024	.357	-1.632
CST: crit run tot lat	TNF-α	-.114	.432	.114	.329	.031	.342	-1.185
Affect-Controlled								
EXECUTIVE FUNCTION		No significant correlations						
ATT & WK MEM		No significant correlations						
PROCESSING SPEED								
CST: correct resp total latency	CRP	.202	.165	.205	.317	.046	.328	-.925
CST: persev error cognit latency	CRP	.045	.757	.045	.312	.050	.323	-2.090*
CST: persev error total latency	CRP	.157	.283	.158	.371	.018	.159	-.008

Notes: Uncontrolled = Bivariate correlations; Affect-Controlled = Partial correlations controlling for the presence of an anxiety and/or depression; # Indicates significant statistical difference between correlation co-efficients of the groups: $-1.96 > z_{obt} > 1.96$; $z_{obt} = (z_1 - z_2) / \text{SQRT}((1 / (N_1 - 3)) + ((1 / (N_2 - 3)))$; Correlation co-efficient transformations to *z* from Table 11.1 in Pallant [110, p.142].

To further evaluate the significance of the difference in the influence of inflammation on cognitive performance in participants with and without type 1 diabetes, between-groups ANOVA of executive function, attention and working memory, and processing speed, while controlling for the influence of inflammation was conducted. Results indicated that there were no statistically significant differences between the groups in executive function (Table 5.15) or attention and working memory performance (Table 5.16 and 5.17) when the influence of inflammation was controlled. However, 12 out of the 18 processing speed variables compared were significantly different between the participants with type 1 diabetes and the no-type 1 diabetes controls (Table 5.18). Table 5.18 shows that 11 of these were also significantly different when inflammatory effects were not controlled. In addition, one variable (initiation during trials resulting in a perseverative error) was significant when inflammation was controlled but not when it was uncontrolled (CST: perseverative errors average cognitive latency, $F(1,91)= 3.824$, $p= .054$, $\eta_p^2= .043$ vs $F(1,122)= 3.450$, $p= .066$, $\eta_p^2= .028$), and one variable (trial completion speed in trials resulting in any error) was significant when inflammation was not controlled but not when it was controlled (CST: error average total latency, $F(1,91)= 2.030$, $p= .158$, $\eta_p^2= .023$ vs $F(1,122)= 3.970$, $p= .049$, $\eta_p^2= .032$).

To evaluate whether inflammation substantially moderated comparative cognitive performance between the groups, the statistical significance of the difference between the ANOVA results was assessed. *Q* values (where *Q* is the probability that the observed score is due to chance; $Q= 1 – p$), were converted to $z_{observed}$ scores and the corresponding $z_{observed}$ scores for each of the ANOVA results were analysed to deliver a $z_{obtained}$ value (z_{obt}). The difference between the ANOVA results were considered significant if: $-1.96 > z_{obt} > 1.96$. Results indicated that inflammation had a significant influence on executive function with the difference between five out of nine executive function performance variables' *p* values showing a statistically significant difference between them (Table 5.15). Attention and working memory comparisons showed a similar pattern with several variables showing statistically significant differences between the ANOVA results of uncontrolled cognitive function and inflammation-controlled cognitive function between the groups. All four repeated-measures (performance trends over increased cognitive demand conditions), and nine out of the 14 individual variables performance results for measures of attention and working memory were found to be significantly different when inflammation was statistically

controlled (Table 5.16 and 5.17). When the inflammation-controlled and uncontrolled ANOVA results for processing speed were compared the differences between seven out of 18 variables were shown to be statistically significant (Table 5.18). Taken together, these results suggest that the influence of inflammation on cognitive function across the domains for executive function, attention and working memory, and processing speed differs in type 1 diabetes compared to individuals without the disease.

Table 5.15. *Descriptive Statistics and Results of the ANOVA for Executive Function Task Performance in the Card Sort Test and Tower of London Test between Participants in the Type 1 Diabetes and No-Type 1 Diabetes Groups, With and Without Controlling for the Influence of Inflammation, and With Comparisons of the Statistical Significance of the Difference between the ANOVA Results.*

EXECUTIVE FUNCTION	Type 1 Diabetes, *n*= 57		No-Type 1 Diabetes, *n*= 50		*ANOVA With ctrl for Inflam*			*Original unctrld ANOVA from Chapter 4 (Table 4.1)*			Sig of diff b/tw *p* values		
	M	*SD*	*M*	*SD*	*F* (1,106)	*p*	η_p^2	*F* (1,142)	*p*	η_p^2	Z_1	Z_2	z_{obt}
CST													
Correct responses	29.81	13.59	26.14	12.21	1.422	.236	.014	1.189	.277	.008	0.719	0.592	0.980
Perseverative errors	14.35	13.23	11.42	10.74	1.413	.237	.014	.964	.328	.007	0.716	0.445	2.037#
Non-perseverative errors	38.61	29.42	41.62	30.76	.757	.386	.007	.153	.696	.001	0.29	0.513	-1.676
Total errors	52.96	27.93	53.04	28.893	.165	.686	.002	<.000	.999	<.001	0.485	3.09	-19.581#
Category completions (max = 6)	3.32	2.26	4.64	8.33	.980	.325	.010	1.014	.316	.007	0.454	0.479	-0.188
TOLT													
Excess moves - 3 ring	6.33	9.172	5.42	6.943	.252	.617	.002	.029	.866	<.001	0.298	1.107	-6.081#
Excess moves - 4 ring	1.63	2.093	1.58	2.251	.023	.880	.000	.308	.580	.003	1.175	0.202	7.314#
Excess moves - 5 ring	1.49	2.494	2.02	3.548	1.184	.279	.012	.320	.572	.002	0.586	0.181	3.044#
Excess moves – total all cond	9.46	9.646	8.80	8.485	.066	.797	.001	.053	.818	.001	0.831	0.908	-0.579

Notes: Mean and standard deviations for ANOVA results for original executive function analysis appear in Table 4.1; Effect size, small η_p^2= .01, medium η_p^2= .06, large η_p^2= .14 [(282)]. # Indicates significant statistical difference between *z* observed scores of the ANOVA *Q* values where *Q* (the probability that the observed score is due to chance)= 1 – *p*; z_{obt} (*z* obtained) = (z_1 – z_2) / SQRT ((1 / (N_1 – 3))+ ((1 / (N_2 – 3))); Significant difference between MANOVA results: -1.96 > z_{obt} > 1.96.

Table 5.16. *Descriptive Statistics and Results of the Mixed-Model Repeated-Measures ANOVA for Attention and Working Memory over Increased Cognitive Load Conditions in the n-Back Test between Participants in the Type 1 Diabetes and No-Type 1 Diabetes Groups, With and Without Controlling for the Influence of Inflammation, and With Comparisons of the Statistical Significance of the Difference between the ANOVA Results.*

ATTENTION AND WORKING MEMORY	Type 1 Diabetes, *n*= 55 *M* (*SD*)			No-Type 1 Diabetes, *n*= 50 *M* (*SD*)			Repeated-Measures ANOVA Ctrl for Inflammation			Original Mixed-Model ANOVA - No control (Ch. 4, Table 4.3)			Sig of diff b/tw *p* values		
	1	*2*	*3*	*1*	*2*	*3*	*F* (1,105)	*p*	η_p^2	*F* (1,138)	*p*	η_p^2	Z_1	Z_2	z_{obt}
Hits	25.04	19.91	15.56	25.68	19.60	15.94	.003	.955	<.001	.024	.878	<.001	1.700	1.165	4.126#
	(6.32)	(7.53)	(6.02)	(5.93)	(9.44)	(7.73)									
Misses	2.96	5.67	10.55	1.70	5.54	8.56	1.952	.165	.019	4.752*	.031	.033	.974	1.866	-6.880#
	(5.47)	(4.94)	(6.48)	(2.71)	(7.28)	(7.68)									
Omissions	11.89	18.22	17.07	12.44	19.96	24.48	.959	.330	.010	2.490	.117	.018	.440	1.190	-5.785#
	(18.50)	(25.41)	(26.58)	(22.70)	(29.49)	(31.65)									
Total Accuracy	83.58	71.27	64.60	83.66	70.32	59.26	.627	.430	.006	1.573	.212	.011	.176	.800	-4.813#
	(20.10)	(24.08)	(20.96)	(23.71)	(27.84)	(26.49)									

Notes: Mean and standard deviations for ANOVA results for between-subjects and between subjects with control for affect appear in Table 4.3; Effect size, small η_p^2= .01, medium η_p^2= .06, large η_p^2= .14 [(282)]. # Indicates significant statistical difference between *z* observed scores of the MANOVA *Q* values where *Q* (the probability that the observed score is due to chance)= 1 – *p*; z_{obt} (*z* obtained) = $(z_1 - z_2)$ / SQRT ((1 / (N_1 – 3))+ ((1 / (N_2 – 3))); Significant difference between MANOVA results: -1.96 > z_{obt} > 1.96.

Table 5.17. *Descriptive Statistics and Results of the MANOVA for Attention and Working Memory Task Performance in then-Back Test between Participants in the Type 1 Diabetes and No-Type 1 Diabetes Groups, With and Without Controlling for the Influence of Inflammation, and With Comparisons of the Statistical Significance of the Difference between the MANOVA Results.*

ATTENTION AND WORKING MEMORY	Type 1 Diabetes, *n*= 50		No-Type 1 Diabetes, *n*= 55		ANOVA Ctrl for inflammation			ANOVA No control (Ch. 4, Table 4.4)			Sig of diff b/tw *p* values		
	M	*SD*	*M*	*SD*	*F* (1,105)	*p*	η_p^2	*F* (1,142)	*p*	η_p^2	z_1	z_2	z_{obt}
1-Back: Hit	25.04	6.319	25.68	5.933	.120	.730	.001	.006	.939	.000	0.613	1.546	-7.196#
1-Back: Miss	2.96	5.467	1.70	2.705	1.701	.195	.017	2.712	.102	.019	0.86	1.27	-3.162#
1-Back: Total Omit	11.89	18.501	12.44	22.696	.078	.781	.001	.998	.319	.007	0.776	0.47	2.360#
1-Back: Total Acc / 100	83.58	20.103	83.66	23.705	.032	.858	.000	.904	.343	.006	1.071	0.404	5.145#
2-Back: Hit	19.91	7.526	19.60	9.442	.069	.794	.001	.115	.735	.001	0.82	0.628	1.481
2-Back: Miss	5.67	4.944	5.54	7.276	.080	.778	.001	1.014	.316	.007	0.765	0.479	2.206#
2-Back: Total Omit	18.22	25.407	19.96	29.487	.300	.585	.003	1.700	.194	.012	0.215	0.863	-4.998#
2-Back: Total Acc / 100	71.27	24.084	70.32	27.835	.162	.688	.002	.828	.364	.006	0.49	0.348	1.095
3-Back: Hit	15.56	6.021	15.94	7.731	.026	.873	.000	.819	.367	.006	0.141	0.34	-1.535
3-Back: Miss	10.55	6.475	8.56	7.675	2.667	.106	.026	5.477*	.021	.038	1.248	2.034	-6.062#
3-Back: Total Omit	17.07	26.577	24.48	31.653	2.614	.109	.026	3.134	.079	.022	1.232	1.412	-1.388
3-Back: Total Acc / 100	35.56	21.022	40.76	26.500	2.239	.138	.022	2.122	.147	.015	1.089	1.049	0.309
All Cond: Total Omit	47.18	60.11	56.88	77.64	.959	.330	.010	2.490	.117	.018	0.44	1.19	-5.785#
All Cond: Tot Acc as %	73.15	18.54	71.08	23.90	.627	.431	.006	1.774	.185	.013	0.174	0.896	-5.569#

Notes: Mean and standard deviations for ANOVA results for between-subjects and between subjects with control for affect appear in Table 4.4; Effect size, small η_p^2= .01, medium η_p^2= .06, large η_p^2= .14 [(282)]. # Indicates significant statistical difference between *z* observed scores of the MANOVA *Q* values where *Q* (the probability that the observed score is due to chance)= 1 – *p*; z_{obt} (*z* obtained) = ($z_1 - z_2$) / SQRT ((1 / (N_1 – 3))+ ((1 / (N_2 – 3))); Significant difference between MANOVA results: -1.96 > z_{obt} > 1.96.

Table 5.18. *Descriptive Statistics and Results of the MANOVA for Processing Speed Performance in the Card Sort Test and Tower of London Test between Participants in the Type 1 Diabetes and No-Type 1 Diabetes Groups, With and Without Controlling for the Influence of Inflammation, and With Comparisons of the Statistical Significance of the Difference between the MANOVA Results.*

PROCESSING SPEED	Type 1 Diabetes, *n*= 50		No-Type 1 Diabetes, *n*= 41		ANOVA controlling for inflammation			ANOVA original no control from Ch. 4 (Table 4.6)			Sig of diff b/tw *p* values		
	M	*SD*	*M*	*SD*	*F* (1,91)	*p*	η_p^2	*F* (1,122)	*p*	η_p^2	z_1	z_2	z_{obt}
Cognitive Initiation Latency													
CST: Correct avge cog lat	2994.44	1822.24	2479.68	2033.23	1.033	.312	.012	1.42	.236	.012	0.49	0.719	-1.766
CST: Pers avge cog lat	3306.72	2410.88	2341.59	1814.81	3.824*	.054	.043	3.45	.066	.028	1.607	1.506	0.779
CST: Non-pers avg cog lat	4323.26	3601.00	3565.68	2173.98	1.361	.247	.016	1.98	.164	.016	0.684	0.978	-2.268$^{\#}$
CST: Error avg cog lat	3988.10	2903.66	3127.15	1814.49	2.636	.108	.030	2.74	.101	.022	1.237	1.276	-0.301
ST: Crit run avg cog lat	1924.82	1259.21	1378.78	731.11	5.547*	.021	.061	4.67*	.033	.037	2.034	1.838	1.512
TOLT: Avg pick up - 3	3.39352	1.51	2.50	1.04	9.392**	.003	.099	11.28***	.001	.086	2.748	3.09	-2.638$^{\#}$
TOLT: Avg pick up - 4	3.08084	1.24	2.50	1.19	4.986*	.028	.055	4.31*	.040	.035	1.911	1.751	1.234
TOLT: Avg pick up - 5	2.87724	.95	2.28	.87	10.851***	.001	.113	8.43**	.004	.066	3.09	2.652	3.378$^{\#}$
TOLT: Avg pick up – Tot	3.11720	1.10	2.42	1.00	9.670**	.003	.102	9.08**	.003	.070	2.748	2.748	0.000
Total Completion Latency													
CST: Correct avge tot lat	5355.76	3490.61	4176.07	3243.39	2.074	.154	.024	3.02	.085	.025	1.019	1.372	-2.723$^{\#}$
CST: Pers avge tot lat	5946.06	4553.24	3759.71	2516.81	6.720**	.011	.073	8.41**	.004	.065	2.29	2.652	-2.792$^{\#}$
CST: Non-pers avg tot lat	7272.70	5131.72	6202.32	4973.50	.743	.391	.009	2.17	.144	.018	0.277	1.063	-6.062$^{\#}$
CST: Error avg tot lat	6912.10	4430.93	5456.73	4399.50	2.030	.158	.023	3.97*	.049	.032	1.003	1.655	-5.029$^{\#}$
CST: Crit run avg tot lat	3535.40	2497.68	2370.59	1130.44	7.156**	.009	.078	7.22**	.008	.057	2.366	2.409	-0.332
TOLT: Avg tot time – 3	5.50076	2.15	4.24	1.49	9.612**	.003	.102	10.08**	.002	.077	2.748	2.878	-1.003
TOLT: Avg tot time – 4	4.93608	1.84	3.88	1.68	7.902**	.006	.085	6.59*	.011	.052	2.512	2.29	1.712
TOLT: Avg tot time - 5	4.57342	1.39	3.67	1.50	9.670**	.003	.102	7.75**	.006	.061	2.748	2.512	1.820
TOLT: Avg tot time - Tot	5.00356	1.70	3.94	1.50	9.768**	.002	.103	8.80**	.004	.068	2.878	2.652	1.743

Notes: * Sig. @ α = .05; ** Sig. @ α = .01; *** Sig. @ α = .001; Mean and standard deviations for ANOVA results for between-subjects and between subjects with control for affect appear in Table 4.6; Effect size, small η_p^2= .01, medium η_p^2= .06, large η_p^2= .14 $^{(282)}$. # Indicates significant statistical difference between *z* observed scores of the MANOVA *Q* values where *Q* (the probability that the observed score is due to chance)= 1 – *p*; z_{obt} (*z* obtained) = ($z_1 - z_2$) / SQRT ((1 / (N_1 – 3))+ ((1 / (N_2 – 3))); Significant difference between MANOVA results when: -1.96 > z_{obt} > 1.96.

S11: Discussion

The present study investigated the relationship between cognitive function and inflammation in adults with type 1 diabetes. The results indicated that inflammation was associated with a number of measures of cognition across executive function, attention and working memory, and processing speed. Results also showed that affect mediates the influence of inflammation on cognitive function, with cognitive performance having a weaker relationship to cognitive function in the domains of executive function and attention and working memory when the influence of affect is controlled. However, this was not the case in the domain of processing speed where affect appeared to have a weaker influence on the relationship between inflammation and cognition than it did in the other two domains. These results support the extant literature that broadly reports similarly directional associations between these variables, and shows that inflammation is associated with impairments in cognitive tasks requiring attention, working memory, set-shifting / cognitive flexibility, rule / set-maintenance, complex problem solving, inhibition, planning, and visuospatial problem solving. Finally, the results also indicate that the relationship between cognitive function and inflammation has some variation in character in type 1 diabetes compared to the general population which require further elucidation. One interesting difference between the groups was the finding that, in participants with type 1 diabetes, some measures of executive function showed improved performance related to increased markers of systemic inflammation.

H_1: Inflammatory biomarkers would be associated with cognitive performance

The first hypothesis that inflammatory biomarkers would be associated with cognitive performance was supported with numerous variables measuring cognitive performance across executive function, attention and working memory, and processing speed showing associations with CRP, IL-1β, IL-6, or TNF-α.

In the executive function domain, inflammation was correlated to performance in participants with type 1 diabetes but not in participants with no-type 1 diabetes. In the type 1 diabetes group, increased circulating IL-1β and TNF-α were associated with poorer overall problem solving on the CST. The CST requires complex cognitive processing including the ability to think abstractly, selectively attend to perceptual information, maintain cognitive set / rules, integrate new information, inhibit responses, and set-shift as new information is applied to solving problems. This finding is consistent with the literature that has shown that elevated inflammatory biomarkers

including IL-1β and TNF-α are associated with cognitive impairment across multiple domains including executive function [441, 456, 457].

Interestingly and somewhat contradictory was the finding that increased IL-1β was also associated with lower rates of perseveration in participants with type 1 diabetes. This association has not been previously reported in the literature. One possible explanation is that increased cytokines are associated with sickness behaviours, sickness-related negative affect, and the general physiological feelings of illness (eg: lethargy, nausea, aches) within the body [366, 458]. For an individual with type 1 diabetes, illness carries an increased risk of negative outcome [459] and an amplification of feelings of illness and illness behaviours [460]. Moreover, in type 1 diabetes, these feelings are often associated with diabetes-related care factors such as hyper or hypoglycaemia, or other diabetes-care factors such as an infected insulin pump cannula site, or peripheral surface infection [461, 462]. These circumstances require specific, timely, and accurate responses such as insulin adjustment, measured caloric intake, cannula site changes, and appropriate wound management and antibiotic treatment. Therefore, improvements in some cognitive function may be a possible type 1 diabetes-specific adaptation to sickness feelings associated with illness and injury events that represent a higher acute health risk to those with the disease. If this adaptation were to occur, it may include an increased focus on recognising cues associated with a required behavioural change and reductions in perseveration as has been identified in these results.

While, IL-1β, IL-6, and TNF-α were not significantly related to attention and working memory performance in either participant group, The correlation between CRP and attention and working memory performance was statistically significant in n-Back Test task trials across low, medium, and high cognitive demand conditions in both groups. Increased CRP in the participants with type 1 diabetes was directly associated with poorer performance results across measures of correct and missed target selection, target selection accuracy, and trial response omissions in trials with both low (1-back) and high (3-back) cognitive demand. In the participants without type 1diabetes CRP was associated with the number of successful target selections made (both hits and misses) during tasks with a moderate (2-back) cognitive demand. Impairments to attention and working memory performance have been consistently associated with increased inflammation in studies of cognitive impairment associated with dementia and

aging [441, 463, 464] however, there is an absence of literature on inflammation and attention and working memory in type 1 diabetes.

Unlike measures of performance in executive function and attention and working memory, processing speed performance did not correlate to inflammation in the participants with type 1 diabetes. However, in the no-type 1 diabetes participants, CRP, IL-1β, IL-6, and TNF-α were all significantly correlated to processing speed across initiation (CRP), and trial completion measures (CRP, IL-1β, IL-6, TNF-α). Chronic low-grade elevation of these markers have been consistently associated with cognitive decline in both normal aging and in pathology such as dementia, lupus, and type 2 diabetes [441, 454, 457, 465-467]. In the no-type 1 diabetes participants, slower processing speeds were related to impaired problem solving abilities. This was highlighted across several measures of executive performance including increased rates of both perseveration and non-perseveration errors, poorer general problem solving skills, less criterion consecutively correct trial responses, and fewer category completions. This result is not surprising given that the extant literature consistently shows a strong relationship between inflammation and processing speed in general populations [441, 454, 468].

With the exception of the correlation between improved perseveration and increased levels of circulating CRP in the participants with type 1 diabetes, these results are consistent with the literature that shows numerous studies reporting reduced cognitive performance associated with increased inflammation across general populations as well as in targeted populations based on various health conditions including type 2 diabetes and metabolic syndrome, vascular diseases, neurodegenerative disorders, and in post-operative patients [386, 456, 469-477]. The lack of literature dealing specifically with type 1 diabetes and the relationship between cognition and inflammation is of concern and requires redressing.

H_2: Affect Influences the Relationship between Inflammation and Cognition

The results support the second hypothesis that affect would influence the relationship between inflammation and cognition. When the influence of affect was controlled, there was no correlation between inflammation and any of the variables measuring executive function or attention and working memory, in either the participants with type 1 diabetes or in the no-type 1 diabetes controls. This is

substantially different to the results of the uncontrolled correlational analyses between these factors in which numerous inflammation-cognition co-efficients were significantly related across the two participant groups. These differences in relational outcomes suggests that affect exerts a substantial mediating influence on the relationship between inflammation and both executive function, and attention and working memory performance. There is significant evidence that affect, inflammation, and cognitive function are closely associated [434, 438, 443-445]. The present results support the extant literature and show that the impact of affect and inflammation on cognitive performance may not be readily excisable from one another.

There were several significant relationships between processing speed and inflammation when the influence of affect was controlled and when the influence of affect remained uncontrolled. However, a number of the significant relationships in the controlled and uncontrolled analyses differed. In the uncontrolled condition there were no significant correlations in the type 1 diabetes participants while in the affect-controlled analyses both initiation and trial completion processing speeds were significantly associated with CRP. There was a high prevalence of anxiety in the participants with type 1 diabetes (Table 3.6), and this may have resulted in a compensatory increase in processing speed in the group. With this increase controlled, the relationship between inflammation and performance may be more apparent. This position fits with the performance-arousal theory forwarded by the Yerkes-Dodson Law [320] in which arousal can improve performance in low cognitive demand and when arousal does not exceed a zenith point at which further arousal decreases performance (Figure 4.11). This principal was applied to learning and problem solving by John Sweller [321], and would explain how anxiety may improve response speed under conditions such as those imposed by the CST.

In the no-type 1 diabetes group, CRP was also significantly correlated to initiation and trial completion however, six co-efficients that were significant in the uncontrolled analyses were no longer significant when the influence of affect was controlled. These co-efficients related to correlations between variables measuring trial completion speeds and IL-1β, IL-6, and TNF-α. The difference in the results of the uncontrolled and affect-controlled correlational analyses suggest that affect has a substantial role in mediating the relationship between inflammation and processing speed performance.

The results further indicate that affect is possibly a stronger mediator of the inflammation-processing speed relationship in participants with no-type 1 diabetes than in those with type 1 diabetes. This is supported by the extant literature that shows evidence in support of microvascular pathophysiology as the primary progenitor for impairments to processing speed in type 1 diabetes [116-119, 124, 300, 302, 333, 337, 338]. As microvascular pathophysiology is generally pervasive, processing speed deficits resulting from these physiological correlates are likely to crossover any specific systemic or homologous relational boundaries [337, 338].

Analysis of the statistical difference between the correlations in the affect-controlled and uncontrolled conditions showed no statistically significant differences between any of the corresponding co-efficients (Table 5.13). This is an important result as it suggests that while affect-mediation of the relationship between inflammation and cognition is present, the influence is not statistically significant. The close relationship between inflammation and affective disorders may be a factor in this lack of statistical significance as the presence of one implies the likely presence of the other. The results support the call for more research into the triarchic relationship between affect, inflammation, and cognition.

H_3: The Influence of Inflammation on Cognitive Performance would differ in Type 1 Diabetes

The third hypothesis that the relationship between inflammation and cognition would differ between participants with type 1 diabetes compared to participants with no-type 1 diabetes, was supported. The results indicated that the relationship between inflammation and cognition does not directly correspond between type 1 diabetes and the general population.

Comparative analysis of the correlation co-efficients for the relationship between cognition and inflammation between the type 1 diabetes and no-type 1 diabetes groups indicated that there was a statistically significant difference between the co-efficients of the groups for CRP and the executive function measure of perseveration when affect was not controlled. When the affect-controlled co-efficients were compared, there was a significant difference between the groups for CRP and the processing speed measure of initiation during perseveration trials. In both instances, the relationship was stronger in participants with no-type 1 diabetes. This supports the other

presented findings that showed no significant relationships in the type 1 diabetes participants between processing speed and inflammation and an improved performance in perseveration associated with higher levels of CRP.

ANOVA results showed that, when the influence of inflammation was controlled, the groups did not differ in executive function or attention and working memory performance. However, when processing speed was compared while controlling for inflammation, 12 out of the 18 measures of performance were significantly different between the two groups. In all 12 measures that were different, participants with type 1 diabetes performed more poorly than their no-type 1 diabetes peers. These results were similar to those obtained when ANOVA were undertaken between the groups without controlling for inflammation. However, when controlled and uncontrolled ANOVA results were directly compared to assess for the statistical difference between *p* values (z_{obt}), the analyses indicated substantial variations in the influence of inflammation between the two groups in executive function, attention and working memory, and processing speed.

In measures of executive function performance, five out of nine measures had significantly different *p* values between the inflammation-controlled and inflammation-uncontrolled ANOVAs. These results show that there was a marked variation in the influence of inflammation between the two groups across measures of performance in tasks requiring complex executive processes including inhibition and set-shifting (perseveration error rates); set-maintenance, applying information to new situations, and problem solving (CST error rates); and planning and visuospatial problem solving skills (TOLT excess moves). The results support the literature that shows neurological changes in type 1 diabetes mirror those observed in aging and are generally pervasive in nature [435, 436]. The central executive, while characterised by operational performance in the frontal region, is not a unitary system, but rather is systemic in nature and comprised of functional connectivity between multiple brain regions. Therefore, a systemic influence such as inflammation may result in more pervasively observable impairments.

In measures of attention and working memory, between-groups ANOVA comparisons of inflammation-controlled and inflammation-uncontrolled analyses showed several significant differences in results. In the repeated-measures comparison of performance across increased cognitive load conditions, the ANOVA results of all

four measures of performance (hits, misses, omissions, accuracy) were significantly different in the inflammation-controlled analysis compared to the inflammation-uncontrolled analysis. These results indicate that inflammation had a substantially different influence on the ability to manage attention and working memory performance under increasing cognitive demand in participants with type 1 diabetes compared to their no-type 1 diabetes peers. Nine out of 14 variables were significantly different when the ANOVA results for individual performance measures in the inflammation-controlled versus uncontrolled conditions were compared. The differences were across low, medium, and high cognitive demand trial conditions, and included rates of successful target selection (hits), unsuccessful target selection (misses), missed trials (omissions), and measures of total task accuracy (accuracy). These results suggest again that inflammation has a markedly different influence on attention and working memory performance in participants with type 1 diabetes compared to their no-type 1 diabetes peers.

The comparison of inflammation-controlled and uncontrolled ANOVA results for processing speed performance shows a similar level of difference to that observed in the executive function, and attention and working memory domains. Seven out of 18 performance measures of processing speed showed a statistically significant difference between the ANOVA results obtained in the between-groups comparisons made without controlling for the influence of inflammation in comparison to those obtained when inflammation was controlled. The influence of inflammation on processing speed performance between the two groups was significantly different in both speed of cognitive initiation as well as that of total completion times in CST trials in which there were both errors and correct selections. In tasks of the TOLT, in which executive processes of planning, inhibition, set-maintenance, and visuospatial problem solving were required, there were significant differences in measures of task completion speeds but no differences in task initiation speeds.

The substantial number of significant differences in *p* values between ANOVA results in the inflammation-controlled and inflammation-uncontrolled conditions suggests that inflammation mediates cognitive performance differently in type 1 diabetes. This evidence was not apparent from a direct between-groups ANOVA in either the inflammation controlled or inflammation-uncontrolled condition. Similarly, this was not evident from the correlational evaluations. The relationship between

cognition and inflammation appears to be somewhat complex and the extant literature provides no opportunity for a direct comparison of these results in type 1 diabetes cohorts. As there is no comparative literature against which to evaluate the present results, further study is needed to ascertain the nature of the difference in influence that inflammation appears to have in type 1 diabetes.

Conclusion

The present results are among the first to attempt to describe the characteristics of the relationship between inflammation and cognitive function in type 1 diabetes, and to identify that there are substantial differences in this relationship in individuals with type 1 diabetes compared to those without the condition. Moreover, the present study provides evidence that affect influences inflammation in type 1 diabetes and therefore, any studies of cognition must take into account the influence of both inflammation and the affective state of participants. Finally, the results provide further support for the need for more research into the triarchic relationship between cognition, affect, and inflammation in type 1 diabetes. Diabetes is a complex and attention-intensive self-managed disease. Those living with type 1 diabetes must consider a complex interplay of treatment, environment, and behaviour several times each day in order to plan, manage, and successfully navigate a life lived with the disease. Diabetes-related acute complications such as hyperglycaemia, hypoglycaemia, and infections related to injection/cannulation sites, can result in serious and potentially fatal consequences if not addressed correctly and expediently. These events in type 1 diabetes are notoriously unforgiving if treatment mistakes are made and therefore, a high level of consistent cognitive performance is essential to successful disease management. Similarly, repeated mistakes and poor planning and decision making are associated with increased deleterious clinical outcomes and chronic diabetes-related complications, which are in turn associated with higher rates of disability and early mortality. These results indicate that inflammation is a strong influence on cognitive function in type 1 diabetes however, there remains a substantial gap in knowledge about the nature of this influence. Further study is essential in order to further elucidate the characteristics and nature of the inflammation-cognition relationship in type 1 diabetes. Finally, further clinical investigation is required to develop methods of early identification, and treatments that will be effective in helping to prevent, arrest, and manage cognitive impairment associated with type 1 diabetes.

CHAPTER SIX: CONCLUSION

Introduction

This thesis was predicated on the question: *"What is the relationship between type 1 diabetes and psychological wellbeing, and how and to what extent are psychosocial and psychopathological characteristics related to diabetes-specific factors such as aetiology, clinical measures, and both acute and chronic disease complications?"* In answering this question the project described the psychosocial, psychological, and inflammatory biomarker features of individuals with type 1 diabetes and compared the prevalence and relational characteristics of these features in type 1 diabetes to age and sex balanced controls with no-type 1 diabetes; explored the interrelationships between these factors in type 1 diabetes compared to no-type 1 diabetes controls, and; quantified the relationships between these factors and diabetes-specific aetiological and clinical factors such as age of disease onset, duration of illness, metabolic control, hypoglycaemia, and complications.

While recognising the validated position of the existing psychological and neuropsychological health paradigms of type 1 diabetes described in chapter 1, this study was conducted with the consideration that these paradigms may not tell the "whole story" and that there may be as-yet-unespoused pathogenic mechanisms that underpin elements of mental health risk and decremental cognitive performance characteristics in type 1 diabetes.

Some of the results presented in this thesis support features of the existing paradigms, while other results present evidence of characteristics and interactions that suggest alternative explanations may be warranted. While the thesis presents a large volume of data from across the psychoneuroimmunological spectrum in answer to the hypotheses forwarded in each of the 11 individual studies, it invariably creates more questions than it answers. Regardless of the theoretical framework, the results illustrate that type 1 diabetes has a significant impact on the psychological wellbeing and neuropsychological function of those who live with the disease, and that in turn, psychological wellbeing and neuropsychological function are associated with adverse clinical outcomes such as suboptimal metabolic control and complications. The results also indicate that the relationship between type 1 diabetes, psychological health, and neuropsychological function, is somewhat complex, and differs in type 1 diabetes compared to the broader population.

By necessity, the results in the preceding chapters have been presented in a lineal manner. What the project has illustrated is that the factors that contribute to, and

are impacted by, psychological wellbeing and neuropsychological function in type 1 diabetes, interact in a far more complex way than a simple lineal exposition of the data can portray. Therefore, while the studies presented attempt to reflect the complexity of these interactions, the ultimate conclusion of this thesis is that unless a detailed and broad investigation of associated factors is undertaken, it is very easy to misinterpret relational characteristics and between-groups variations when it comes to type 1 diabetes.

This chapter concludes the thesis by synthesising some of these complexities and providing an evidence-based conclusion, though containing some thoughtful speculation, as to their meaning, character, and consequence. Finally, limitations are discussed and recommendations for future research provided.

Conclusions from Empirical Findings

Synthesising the empirical findings from the eleven studies presented in the thesis, the following section reports the key conclusions drawn.

Psychosocial Conclusions

The level of recent experiences of stressful life events, perceived stress, coping self-efficacy, and the profile of the pattern of coping strategies used to deal with stressful life events did not differ in type 1 diabetes. Participants with type 1 diabetes self-reported no difference in levels of these psychosocial factors compared to that reported by participants without type 1 diabetes (study one, chapter two). This was somewhat surprising given the literature consistently reports increased stress, poorer coping-self-efficacy, and lower use of positive coping strategies and a corresponding increased use of poor coping strategies, in type 1 diabetes [1, 58-61].

The majority of reports in the literature report on these factors as they relate directly to disease-specific factors. In contrast, the present study reported on perceived stress in a global context, with assessment items making reference to general events, experiences, behaviours, and thought processes. The conclusion drawn is that while type 1 diabetes is a pervasive illness, those living with the illness can differentiate between the impact of the disease on their lives, and their interactions with and influences of, their broader environment.

This is an important distinction as it suggests that factors such as social support, the ability to use positive cognitive reappraisal, and having a broader purpose that can be a focus for motivation, planning, and behavioural direction, could be powerful mitigants against some of the most deleterious factors related to poor disease outcomes and psychological wellbeing. This position is supported by several results. It was reported in chapter two that in type 1 diabetes, personal perceptions of stress and coping self-efficacy were predictive of short-term metabolic control, and that long-term metabolic control was predicted by coping self-efficacy and the extent to which individuals with type 1 diabetes used positively valenced coping strategies. Specifically, these coping strategies involved self-controlled behaviours, planful and directed problem solving, social affiliation, and the ability to engage positive cognitive reappraisal processes to reframe stressful experiences (study two, chapter two). Moreover, in type 1 diabetes, lower levels of coping self-efficacy were significantly associated with a reduced presence of affective disorders, and planful and directed problem solving and the use of positive cognitive reappraisal when faced with stressful experiences, were associated with lower prevalence rates of alcohol and substance abuse disorders (study five, chapter three).

Psychological Conclusions

The characteristics of affective disorders in type 1 diabetes were significantly different. Stress and coping factors significantly predicted affective disorders in controls but did not predict them in type 1 diabetes, while stress and coping factors predicted alcohol and substance abuse in type 1 diabetes but not in controls (study five, chapter three). The conclusion drawn is that while affective disorders are significantly more prevalent in type 1 diabetes (study three and four, chapter three), their aetiology appears to differ. Affective disorders have been consistently associated with stress and coping [8, 14, 80, 234-236] however, these results suggest that in type 1 diabetes, affective disorders may have a different pathogenic influence. Only coping self-efficacy was associated to affective disorders in type 1 diabetes. The direction of the relationship warrants greater scrutiny. It is possible that poorer coping self-efficacy leads to greater psychological despair as has been found in stress studies [80] and therefore is a contributor to the pathogenesis of affective disorders. However, if this were the case, participants with type 1 diabetes and an affective disorder should have reported greater levels of perceived stress and experiences of stressful life events to correspond to the perceived

inability to cope. Instead, these were not reported as being higher in type 1 diabetes, in fact, experiences of recent stressful life events were lower in type 1 diabetes, and only Bonferroni corrections of the alpha level prevented the result from reaching significance (study one, chapter two). Considering these results, it could be logically concluded that the reduced coping self-efficacy is a product of the negative influence of disordered affect in type 1 diabetes (hopelessness, anhedonia, lassitude, worry, panic, worthlessness, etc). In this way, the results indicate that the presence of an affective disorder in type 1 diabetes, has a deleterious impact on coping self-efficacy.

Moreover, the results indicate that, once affective disorders are present in type 1 diabetes, they are associated with deleterious outcomes and maladaptive behaviours. In the type 1 diabetes group, the presence of an affective disorder was significantly associated with increased alcohol and substance abuse disorders – a known maladaptive behaviour associated with disordered affect (study five, chapter three) [232, 233], and was associated with higher (though not statistically significant) blood glucose levels in the short, medium, and longer term. Affective disorders were also significant influences on cognitive function in type 1 diabetes participants. The influence of affective disorders on cognition significantly differed to the influence exerted on participants with no-type 1 diabetes in executive function, attention and working memory, and processing speed (study seven, eight, and nine, chapter four). The influence of affective disorders on inflammation was also significantly different in type 1 diabetes with the influence of affective disorders on the level of circulating CRP, IL-1β, IL-6, and TNF-α all being significantly different in type 1 diabetes.

The conclusion of these results is that affective disorders are a significant deleterious factor in type 1 diabetes, pervasively influencing both psychological and physiological factors. The results suggest that this is a complex interaction that requires further investigation as the factors influenced by disordered affect were also shown to be related to poorer diabetes specific-outcomes, and in a circular feedback; affective disorders were significantly predicted by diabetes-specific factors. Duration of illness and the presence of complications provided the most influence on the prediction of disordered affect. The results showing that the presence of complications increases the risk of an affective disorder by more than 12½ times (study six, chapter three).

Neuropsychological Conclusions

The influence of type 1 diabetes on cognition was varied across the domains of executive function, attention and working memory, and processing speed. There were no differences between the type 1 diabetes and no-type 1 diabetes groups in executive function. There were only minimal differences (2 out of 18 DVs) in attention and working memory performance in type 1 diabetes. However, performance in processing speed was significantly different in type 1 diabetes compared to participants with no-type 1 diabetes in 12 out of 18 DVs. This supports the extant literature that shows processing speed as the most significant and consistently impaired cognitive domain in type 1 diabetes [119, 124, 299, 302, 305]. What is perhaps one of the most significant findings of this thesis is the remarkable and pervasive influence that disordered affect has on functional and clinical outcomes in type 1 diabetes. As discussed already (Psychological Conclusions), affective disorders were significantly influential in cognitive function across multiple domains. Moreover, when the influence of disordered affect on cognition in type 1 diabetes is compared to its influence on those without type 1 diabetes, the difference between the groups was striking.

The conclusions drawn from these results are 1) that, while factors associated with type 1 diabetes influence cognitive function, the influence of affective disorders appears to be a significant mediator of this influence, and; 2) the influence of affective disorders on cognitive function is significantly greater in type 1 diabetes.

The preceding chapters present a plethora of evidence to support this conclusion (study seven, eight, and nine, chapter four). The key evidence being the results of the ANOVAs for hypothesis two in studies seven (executive function), eight (attention and working memory), and nine (processing speed). The results together support the first conclusion, showing that when the influence of affective disorders were controlled there was a substantial reduction in the number of cognitive performance measures that were significantly different in type 1 diabetes. This was most marked in the domain of processing speed where the number of significant DVs went from 12 out of 18 in the uncontrolled analyses, to zero. The results supporting the second conclusion presented striking evidence to illustrate the remarkable difference in the influence of affective disorders on cognitive function in type 1 diabetes. Comparisons in the domain of executive function (study seven, chapter four) showed that affective disorders had a significantly greater influence on performance in six out of the nine executive function

performance measures. Similarly, in the domain of attention and working memory, the influence of affective disorders was significantly greater in type 1 diabetes in 16 out of the 18 attention and working memory performance measures. This included all four measures of performance across increased cognitive demand conditions, and 12 out of 14 individual performance measures (study eight, chapter four). Finally, in the domain of processing speed, the influence of affective disorders on cognitive function was significantly greater in type 1 diabetes in 13 out of the 18 measures of attention and working memory performance. This included measures of performance across both cognitive initiation speed as well as total task completion speed (study nine, chapter four).

Cognitive function was also significantly associated with diabetes-specific aetiological and clinical factors (study seven, eight, and nine, chapter four). Executive function measures were significantly related to both short-term and long-term metabolic control; attention and working memory measures of both cognitive initiation and total task completion, were correlated with age of onset, short, medium, and long-term metabolic control, hypoglycaemic history, and complications, and; measures of processing speed were correlated with age of onset, duration of illness, short, medium and long-term metabolic control, hypoglycaemia history, and complications. When correlations were re-evaluated, this time while controlling for the influence of disordered affect, the difference in the influence of affect between the groups was remarkable with numerous significant differences across domains.

The conclusion drawn from these results is that while multiple measures of cognitive function were significantly correlated to diabetes-specific aetiological and clinical factors, the influence of affective disorders significantly mediates this relationship.

Once again, the evidence supporting this conclusion is substantial. When the influence of affective disorders was controlled, short-term metabolic control was no longer significantly correlated to executive function, long-term metabolic control remained significantly correlated to executive function, and the relationships between executive function and medium-term metabolic control, and hypoglycaemia history became significant. When the statistical difference between the uncontrolled and affective disorders-controlled co-efficients was evaluated, the co-efficients for executive

function and short-term metabolic control, medium-term metabolic control, and hypoglycaemic history were all significantly different (study seven, chapter four). Controlling for affective disorders reduced the number of significant co-efficients between measures of attention and working memory and diabetes-specific factors by 43% from 30 to 17. When the statistical difference between the uncontrolled and affective disorders-controlled co-efficients was evaluated, the co-efficients for attention and working memory, and age of onset, medium-term metabolic control, hypoglycaemic history, and complications, were all significantly different (study eight, chapter four). Finally, analysis of the correlation co-efficients between measures of processing speed and diabetes-specific factors revealed that the number of significant co-efficients reduced by 94% when re-evaluated while controlling for affective disorders (from 49 to just 3). However, while controlling for affective disorders substantially altered the number of significant co-efficients, there were no statistically significant differences between co-efficients in the uncontrolled and affective-disorder controlled conditions (study nine, chapter four).

Inflammation Conclusions

While a low-grade inflammatory state is considered characteristic of type 1 diabetes, the results did not support this position (study ten, chapter five). Instead, the results showed no significant difference between CRP, IL-1β, IL-6, or TNF-α, in type 1 diabetes compared to controls. When affect was controlled, the difference between inflammatory biomarkers in type 1 diabetes remained non-significant. However, when the affect-controlled between-groups comparisons were compared to the uncontrolled comparisons, the results revealed that affective disorders significantly influenced all four inflammatory biomarkers differently in type 1 diabetes. This was reflected in the findings that inflammation did not predict affective disorders in the participants with type 1 diabetes, however, inflammation was a significant predictor of affective disorders in control participants (study ten, chapter five). The within-groups variations of the levels of CRP, IL-1β, IL-6, and TNF-α, in the groups were problematic for statistical analysis and this inconsistency highlights the challenges inherent in the use of measures of low-grade inflammation as clinically-relevant biomarkers.

When inflammation was correlated to cognition the results showed that inflammation was significantly correlated with executive function in type 1 diabetes but not in controls; attention and working memory was significantly correlated to

inflammation in both type 1 diabetes and controls; and processing speed was not correlated to inflammation in type 1 diabetes, but was significantly correlated to inflammation in the control group (study eleven, chapter five).

Affect significantly influenced the relationship between executive function and inflammation in the type 1 diabetes group with affect-controlled analysis showing no significant relationships between them. This is substantially different to the uncontrolled analysis that showed several significant co-efficients. There was no change in the control group. In the affect-controlled analysis of the correlation between measures of attention and working memory and inflammation, no co-efficients were found to be significant. This was a marked change from the uncontrolled analysis. The affective-disorder-controlled correlations between processing speed and inflammation showed a several significant relationships in both the type 1 diabetes group and controls. When the statistical difference between the uncontrolled and affective disorder-controlled co-efficients was evaluated, the results showed that no co-efficients in either group were significantly different (study eleven, chapter five).

The conclusion drawn from these results is that while there appears to be a relationship between cognitive function, affective disorders, and inflammation, and this relationship appears to differ in type 1 diabetes compared to controls; the within-groups variations in the level of CRP, IL-1β, IL-6, and TNF-α created challenges in statistical analysis that were such that the sample size was not sufficient to draw meaningful conclusions from the present results. This has been a consistent conclusion drawn in the literature when attempts have been made to use biomarkers of low-grade inflammation to investigate clinical factors [358, 370, 390, 415, 416], and has been a particular criticism in type 1 diabetes research of mental health [358]. This is further supported by the findings that inflammation was not a significant predictor of affective disorders in the type 1 diabetes group but was a significant predictor of affective disorder in controls (study ten, chapter five).

Inflammation predicted long-term metabolic control but did not predict complications (study ten, chapter five). This is somewhat contradictory as a large percentage of diabetes-related complications are of a sort that means inflammatory factors are generally characteristic. Again, the conclusion is that the sample size was not sufficient to overcome some of the challenges presented by the data.

Ultimately, inflammation is well documented in respect to its associations to type 1 diabetes, affective disorders, and cognitive function [358, 366-368] [344, 353, 354, 362-365]. However, just as there have been numerous studies supporting these relationships, there have been several studies that have found contradictory results [358, 369, 373-375]. In accord with this, Lotrich [370] and others have presented evidence that inflammation may only be associated with a specific subtype of psychological illness and not a representative characteristic of all, and therefore, assessments of inflammation and depression that do not account for the potential for a subtypology may confound the argument. While significantly more research is needed to explore this hypothesis, it must be considered in the context of the results presented in this thesis. Moreover, the variable of affective disorders in this thesis is comprised of participants with depression disorders, anxiety disorders, and comorbid anxiety-depression disorders. While depression has been associated with inflammation, the potential for a non-inflammatory sub-type not withstanding, the high proportion of anxiety disorders that are represented in the type 1 diabetes participants compared to depression disorders, may also be an influence on the observed levels of CRP, IL-1β, IL-6, and TNF-α.

Theoretical Implications

The lack of relationship between stress and coping and affective disorders in type 1 diabetes, despite the very high prevalence of disordered affect in sufferers, suggests that increased affective psychopathology in type 1 diabetes is not necessarily characteristic of the populist "disease-burden" paradigm, but rather may involve a different combination of pathogenic mechanisms that remain as-yet-undetermined. What appears clear from these results is that the relationship between affective disorders and stress and coping in type 1 diabetes does differ in character to that which exists in individuals without type 1 diabetes, and therefore suggests the existence of additional unique, disease-specific characteristics that remain as-yet-unknown. This is supported by the results showing the higher prevalence of anxiety and depression without a correspondingly higher presence of stress and maladaptive coping strategies that would usually be expected in studies of anxiety and depression in non-type 1 diabetes cohorts. Further research is needed to better understand the character and direction of these relationships.

Clinical Implications and Recommendations

The results of this thesis have several key implications for the clinical management of type 1 diabetes.

1. The results suggest that participants with type 1 diabetes may be either unable to recognise or unwilling to disclose a number of symptoms associated with psychological disorder and personal levels of stress. A number of mechanisms may be involved in mediating these findings. The maladaptive coping behaviours associated with factors such as elevated rates of psychopathology in type 1 diabetes may influence the preparedness of sufferers to disclose the reality of their situation, or may impair personal capacity to identify their distress. This means that general practitioners, diabetes specialists, and diabetes educators may not be able to obtain accurate information about psychological wellbeing of patients in the normal course of a general clinic visit. To address this shortcoming, the inclusion of regular psychological health screenings by appropriately trained mental health professionals should be considered an essential adjunct to existing standard clinic visit protocols [8, 62].
2. Twenty-five percent of adults with type 1 diabetes have chronically poor metabolic control [96]. The identification and implementation of effective programs to combat poor metabolic control is essential [94, 111-114].
3. Type 1 diabetes patients' health behaviours are intimately entwined with their illness beliefs, attitudes, self-efficacy, locus of control, and the underlying schemas about their disease that underscore these psychophenomena [2].
4. Achieving better metabolic control is related to the characteristic use of a combination of positively valenced coping behaviours involving planful problem solving, self-control, and social affiliation, and the ability to use positive cognitive reappraisal to reframe challenging experiences when they are faced. This result supports the literature that shows clinical outcomes are associated with feelings and beliefs about control and disease predictability [3, 66].
5. Moreover, these coping mechanisms are strategies and skills that can be developed in patients and therefore, increased focus on teaching these psychosocial dimensions to patients with type 1 diabetes should be seen as a frontline diabetes care priority

alongside existing care priorities such as insulin therapy, diet, exercise, and the care of peripheral physiology such as eyes, feet, kidneys, and the cardiovascular system.

6. Psychobehavioural inadequacies such as poor coping self-efficacy are the most significant factors in determining successful clinical outcomes [95]. The results show that coping self-efficacy is foundational to both short and long-term metabolic control, and that there is a clear relationship between coping self-efficacy and improved clinical outcomes [104]. Optimal metabolic control in the long-term is dependent upon good coping self-efficacy independent of any other skills or knowledge [102]. The literature supports this finding and shows that coping skills training significantly improves metabolic control in type 1 diabetes, while other clinical mechanisms, such as intensifying treatment or attempting to modify behaviour, in the absence of psychosocial skills such as efficacy and coping strategies, can be counterproductive [101].
7. These results support the existing calls for the inclusion of psychosocial skills training in the raft of educational topics already provided to patients with type 1 diabetes [96]. Stress management skills should be taught to patients with type 1 diabetes as a core diabetes self-management practice. Numerous techniques can be employed for this purpose allowing for techniques to be selected based on patient preference. This is an important consideration as patient choice in treatment options has been shown to increase the likelihood of patient adherence [126-129].
8. The greater the perceived ability to cope in participants with type 1 diabetes, the lower the prevalence rates of anxiety and depression disorders. This is consistent with the literature that has found perceptions of control and perceived disease predictability are both associated with psychological dimensions in type 1 diabetes [3, 66]. This relationship suggests that the more an individual with type 1 diabetes feels in control and able to cope, the more resilient they will be to episodes of anxiety and depression.
9. Of the participants in the study, one third of young people with type 1 diabetes were experiencing clinical levels of affective disorder, while in adults with type 1 diabetes the prevalence of affective disorders was more than 70%. A further one third of child participants had a level of disordered affect severe enough to cause increased distress and changes to self-care, motivation, and behaviour, but not sufficient for a diagnosis of either anxiety or depression. This group may remain undetected in a general psychological screening process unless subthreshold

symptoms are specifically targeted with appropriately sensitive screening tools. Subthreshold symptoms in childhood are associated with significant risk for the development of full syndrome psychopathology in later life [161], and early identification of subthreshold symptoms is recognized as important for early intervention aimed at preventing progression to full syndrome disorder [161]. This supports the suggestion that psychological screening and referral should be a part of the standard clinical care and management procedures for type 1 diabetes [62, 158-160].

10. While depression is presently the primary mental health focus in diabetes, the results presented in this thesis indicate that anxiety may be a more prevalent concern in type 1 diabetes. Anecdotal evidence suggests that many clinicians are aware of the depression risk in diabetes and therefore may be predisposed towards interpreting affective symptoms as depression related even when presentation points to anxiety. The high rates of prescriptions for anti-depressants and the depression-focused mental health screening methods that appear to be employed most frequently within diabetes clinical environments provide additional support for this suggested bias [116, 183-187]. Further, evidence suggests that anxiety may also have a greater impact on glycaemic control than depression [221]. However, while the results show that anxiety is more prevalent than depression, both anxiety and depression were found to have a significant presence in individuals with type 1 diabetes. Comorbid anxiety and depression was shown to be a significantly prevalent affective combination in both children and adults. What is clear from the results is that clinicians need to be aware of the nuances of both anxiety and depressive disorders and have access to resources that will allow accurate screening, and differential diagnosis of disordered affect. Moreover, clinicians and diabetes clinical centres, should have ready access to resources to support patients who present with these conditions. Accurate diagnoses, appropriate knowledge, and access to effective, evidence-based interventions to address disordered affect in patients with type 1 diabetes is essential. These results further support the argument that psychological screening and ready access to professional mental health assistance should be an aspect of patient-focused clinical diabetes management.
11. The extant literature shows a clear relationship between stress and coping, and affective disorders in the general population [234, 235, 238-240], and the results support these previous findings. The lack of correlation between stress and coping and affect in participants with type 1 diabetes suggests another as-yet-undetermined

pathogenic mechanism may be presenting a stronger influence. Further research is needed to better understand this divergence in type 1 diabetes.

12. Alcohol and substance abuse in participants with type 1 diabetes was significantly associated with poorer use of positive coping strategies and with times of increased external stressors. The association between increased alcohol and substance abuse, reduced use of planful problem solving strategies, and an increased experience of recent stressful life events may be an indication that the participants with type 1 diabetes were less able to engage with rational, considered, and well planned problem resolution processes in the face of external challenges, and instead were more likely to engage maladaptive coping behaviours such as using alcohol or other substances.
13. The results support the extant literature and show a bi-directional relationship between affective disorders and metabolic control in type 1 diabetes in which poor metabolic control influences affect, and disordered affect has an influence on metabolic control.
14. Poorer cognitive function in type 1 diabetes is associated with poorer clinical outcomes. Importantly, the relationship between cognitive function and affect is heavily mediated by the presence of affective disorders.

Critical Reflections

As is appropriate for a study of this nature, the results present more questions than answers. Cross-sectional studies cannot provide evidence of stability, progression, or decremental functioning over time and these characteristics are essential to understanding the nature of disease and disease sequelae in type 1 diabetes. Therefore, prospective, longitudinal investigations are ultimately necessary to further elucidate on the nature and character of many of the results reported in this thesis. This was appreciated at the outset, and the objective of this study was to use a cross-sectional design – a design more suited to a time-sensitive project such as a PhD thesis – to establish information about comparative variations in presentation between type 1 diabetes and controls, and to identify associations between these factors and diabetes-specific outcomes. This had the ultimate objective of being able to inform future research and reinforce or inform changes to clinical practices. None-the-less, this is an overall limitation to the results obtained and should moderate any interpretation of the data.

The information collected represents a broad cross-section of data and as such, required an extensive battery of measures and time to collect, process, score, interpret and enter into the database. This meant that the sample size was limited by the time restrictions of the PhD project. While the objective of the project was to gather a breadth of data from a single participant group, the resulting relatively small number of participants should be considered when evaluating the generalisability of the results. The impact of the smaller sample size is potentially more relevant to the results that were not-significant, as the smaller sample size may have influenced effect sizes.

Generalisability may have also been impacted by the regional characteristics of the sample. It has been suggested by some that participant samples obtained from regional locations may have unique characteristics that differentiate their results from the equivalent measures obtained from other geographically located population centres[478]. This is a risk factor of data collection that is restricted to any single unique region[478]. While the results presented in this thesis should be considered in light of this; data collection and analysis has been conducted following recommendations set out by the literature as best practice for improving generalisability[479].

Moreover, the regional centres of Cairns and Townsville are well serviced, modern cities with excellent medical facilities and specifically, clinical diabetes services. However, specialist services and illness management resources, while available through both world class public and private clinical practices, may be less accessible due to travel or staffing limitations. Therefore, these factors have the capacity to potentially impact patient outcomes and therefore the study findings, and subsequently the generalisability of these results. Given that the participants live in a tropical region, factors such as heat and humidity may also have influenced results and therefore generalisability. Heat and humidity have been found to impact several areas of diabetes management [480-482] including affect[483-485], wound healing[486, 487], and blood glucose stability[480, 488].

The psychoneuroimmunological factors, and the diabetes-specific clinical and aetiological components, included in the study, have been presented lineally in the thesis. However, these factors are more likely to be related in a three-dimensional, multi-directional manner. Substantial time was spent considering the best format to present the data to try and reflect this. As the objective was to present data from

across the psychoneuroimmunological spectrum it was ultimately decided to present the results in the manner ultimately reported in this thesis. This provides an insight into some of the characteristics of these variables. Those well-versed in the subject matter will be able to identify further multi-faceted relational connections from this presentation of the data however, further research will be required to understand the extent, nature, and direction of these relationships.

Recommendations for Future Research

1. The complexity of the interrelationships between the variables highlights the importance of conducting more detailed, multifarious analysis. This will require a substantially larger sample and would benefit from multi-regional participation in order to control for the potential confounds from a single location recruitment (as described earlier in this section). To get the best outcomes, future research should include longitudinal measures.
2. Further research is needed to ascertain the extent to which people with type 1 diabetes are impacted by factors of stress and coping. Of particular importance is the nature of experiences of stress, personal perceptions of ability to cope, and the character of the processes that are employed to manage stressful experience. Future research should also investigate the extent to which perceptions of stress, coping self-efficacy, coping strategies, and maladaptive coping behaviours, relate to diabetes-specific experiences or whether they are global in nature.
3. More research is needed to better understand the factors behind the high prevalence of disordered affect in type 1 diabetes. The nature of the progression of disordered affect from childhood to adulthood is a particular issue that requires focused longitudinal evaluation. Anxiety and depression should be investigated to better understand the common and unique pathogenic factors associated with their presentation in type 1 diabetes, and to distinguish the common and unique consequences of their presence.
4. Cognitive impairment in type 1 diabetes appears to be domain-dependent, and sensitive to a number of factors including affect and inflammation. Future research should investigate the pathogenic mechanisms of impaired cognitive function in type 1 diabetes, account for the role affective disorders and inflammation play in mediating cognition, and further elucidate the impact of cognitive impairment on diabetes clinical outcomes. Furthermore, while the dyadic relationships between

type 1 diabetes, executive function, affective disorders, and inflammation have been documented (although their remains some conflicting evidence), further research is needed to further understand the more complex multidimensional relationships between these factors. This includes a better understanding of the directional characteristics of these relationships and the extent to which these factors are trait characteristics, sequelae, or pathogenically associated with both type 1 diabetes as well as diabetes-specific aetiological and clinical factors.

5. Inflammation is a characteristic of type 1 diabetes however, its role in type 1 diabetes sequelae remains unclear. Further research is needed to provide a clearer understanding of the nature of the role that inflammation plays in type 1 diabetes-related complications, comorbidities, and clinical outcomes.
6. Psychosocial, psychological, and neuropsychological phenomena have been implicated in poor diabetes-specific outcomes, and in the quality and length of life for people with type 1 diabetes. Interventions and changes to clinical management protocols such as, psychoeducation, stress management, coping skills, and regular psychological screening and neuropsychological assessment, are necessary to help mitigate the deleterious impact these factors can have. Research into clinical management best practices, and the efficacy of psychoeducation and other targeted interventions and skills development programs need to be conducted in order to establish the most effective way to improve diabetes-related outcomes, psychological health and wellbeing, neuropsychological function, quality-of-life, and ultimately mortality.

Concluding Statement

Type 1 diabetes is a complex autoimmune disease that is amongst the most self-care intensive of the high risk chronic illnesses. The disease offers no opportunity for respite and sufferers face the prospect of serious and life threatening acute and chronic complications. Despite advances in disease management practices and assistive technologies, and despite significant advances in knowledge about the relationship between good management, and complications and mortality risk; more individuals with the disease continue to have suboptimal disease management indicators such as metabolic control, and more than one in four adults have chronically poor control of their condition. This thesis has explored, evaluated, and described a number of psychosocial, psychological, neuropsychological, and inflammatory characteristics of

type 1 diabetes. The results show that a life lived with type 1 diabetes carries with it substantial challenges that both impact, and are impacted by, the aetiological and clinical characteristics of the disease.

Those living with type 1 diabetes must traverse a complex gauntlet of treatment, environment, and associated behaviour choices several times each day in order to plan, manage, and successfully navigate a life lived with the disease. Type 1 diabetes is notoriously unforgiving; repeated treatment mistakes, poor planning and decision making, low motivation, poor attention to detail, and avoidant behaviours associated with disease management and related self-care, are associated with increased deleterious clinical outcomes and decremental physical health. Acute and chronic complications result in significant imposition. The portent or actual reality of serious consequences are a constant companion, and if not managed correctly, expediently, and consistently, can result in significant disability and ultimately premature morbidity.

As the results presented in this thesis attest, psychosocial, psychological, and neuropsychological factors are intimately involved in mediating the mental and physical capacity to successfully deal with the challenges of type 1 diabetes. Despite a substantial body of evidence supporting the importance of these factors, there remains a limited application of purposeful mental health services as an integrated feature of primary type 1 diabetes care. More research is needed to provide the critical mass of evidence required to move governments and institutional diabetes healthcare agencies to provide these necessary psychological resources. This thesis set out to investigate some of the core aspects of the psychoneuroimmunological profile of type 1 diabetes. A substantial volume of information to this effect has been presented and the results provide a number of important findings that add to the extant literature. Ultimately, type 1 diabetes is an enigma, and while this thesis has contributed pieces to the puzzle, the complexity and multidimensionality of the disease continues to present far more questions than we have yet to find answers.

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