CHAPTER 1

INTRODUCTION

The prevalence of diabetes varies markedly among countries (Diabetes-Atlas 2008), and this is attributed to a combination of ethnic, cultural, environmental economic and social risk factors such as diet, level of obesity, physical activity and age distribution (Sanisoglu et al. 2006). Diabetes mellitus is not a single disorder and its definition depends on one’s perspective. From a medical perspective, it represents a series of metabolic conditions associated with hyperglycaemia and caused by defects in insulin secretion or insulin action.

Exposure to chronic hyperglycaemia may result in microvascular complications in the retina, kidney or peripheral nerves. Although these are characteristic of diabetes, they cannot be used to define the disorder because they take too long to manifest. The so-called macrovascular complications of diabetes (myocardial infarction, stroke, peripheral arterial disease) occur more commonly. It has been suggested that diabetes should be defined as ‘premature atherosclerosis with associated hyperglycaemia’, thereby emphasizing the clinical problems to which most patients succumb. A definition of diabetes from a societal perspective would include the burden that the disease places on health economies, in terms of both the costly treatment and the premature morbidity and mortality. From the individual patient’s perspective, diabetes is a lifelong condition requiring daily attention to diet, lifestyle and monitoring of blood or urine, and is
associated with varying degrees of anxiety and multiple visits to healthcare providers.

Diabetes mellitus is a severe metabolic disease that can have devastating effects on multiple organs in the body. In addition to well known hyperglycemia induced organ damage, diabetes type 2 may also contribute to the development of cognitive dysfunction. Type 2 diabetes patients have an increased incidence of Alzheimer's disease (Cukierman et al. 2005), increased incidence of vascular dementia (Strachan et al. 2008), and cognitive impairment without dementia. Type 2 diabetes is associated with decreases in psychomotor speed (Ryan et al. 2000), verbal memory (Elías et al. 1997), immediate recall, delayed recall (Grodstein et al. 2001), and verbal fluency (Arvanitakis et al. 2006).

The increasing incidence of diabetes mellitus in the industrialized world represents one of the most serious challenges faced by the medical profession today. Diabetes and its complications have been estimated to cost greater than $130 billion every year in the United States, and this figure is likely to grow as a sedentary lifestyle and aging population drive up the incidence and prevalence of disease (Hogan et al. 2002). The figures underscores the massive economic and social burden associated with diabetes and its complications, and clearly indicates the need for action.

Of the two types of diabetes, type 1 is the least common, accounting for 10% of total cases. It is characterized by insulin deficiency following selective destruction (usually mediated by the immune system) of insulin-producing beta cells in the pancreas, and its treatment involves administration of exogenous insulin. Type 2 diabetes is a heterogeneous group of disorders that involve impairment of the insulin-secretory response to glucose and insulin resistance (eg., decreased effectiveness of insulin in
stimulating glucose uptake by skeletal muscle and limiting hepatic glucose production). Type 2 diabetes accounts for 90% of all diagnosed cases of diabetes and usually presents in adults. Several options are available for the treatment of type 2 diabetes, including diet, exercise, oral antidiabetic agents, and insulin. However, the hallmark of type 2 diabetes is successive movement through oral treatments, with many patients ultimately requiring insulin as the disease progresses.

There has been considerable research addressing the situational variables that will influence when and where people will wish to think more effortfully about complex material and when and where they will be content to remain at a more superficial level of thinking. The notion of stable individual differences in a level of desire to seek out and engage in relatively complex cognitive activities was first discussed by Cacioppo and Petty (1982). In the past two decades or so, there has been considerable research into the personality side of this activity that is the identification and exploration of a concomitant trait. The initial Need for Cognition Scale (NCS) developed by (Cacioppo and Petty 1982), and its variations has been applied to samples representing various populations and they have been investigated with respect to their possible relations with other measures of individual differences. Need for cognition has been found to be weakly to moderately, but significantly, correlated with various social-personality measures including self-esteem and openness to experience.

With the rapid rise in the number of older persons suffering from dementia and the associated care burden, there is an increasing interest in maintaining cognitive health in later life. The public health impact is obvious. A delay in the onset of dementia would lead to its reduced prevalence (Sloane et al. 2002), it would be important to examine factors influencing change in cognitive function over time (Gallo 1995).
Recently, there has been a growing emphasis on the identification of risk factors and development of primary prevention strategies for promoting cognitive health (Centers for Disease Control and Prevention and Alzheimer's Association 2007 and Hendrie et al. 2006).

There is accumulating evidence that health or lifestyle behaviours contribute to cognitive function. Studies suggest that positive health behaviors, such as higher levels of physical activity (Anstey and Christensen 2000; Rockwood and Middleton 2007), healthy diet, especially vegetable consumption (Kang et al. 2005; Morris et al. 2006), non-smoking (Anstey et al. 2007; Reitz et al. 2007), and moderate alcohol drinking (Lang et al. 2004) are associated with a decreased risk of cognitive decline, cognitive impairment and dementia. Moreover, social activity, an increasingly recognized type of leisure activity, contributes to better cognitive function (Karp 2006; Hsu 2007; Scarmeas and Stern 1995). Given that multiple lifestyle behaviours may affect cognitive ability in older adults, it is important to examine these potentially modifiable factors together. Moreover, different lifestyle factors may share common pathways in engendering protection against cognitive decline and dementia (Fratiglioni et al. 2004). Early evidence of significant interactions between lifestyle factors, such as exercise, diet, and social engagement, in predicting cognitive function using animal models has underscored the need for more research (Kramer and Erickson 2002).

The benefits of tight blood glucose control in delaying or preventing the complications of diabetes have been well documented. The Wisconsin Epidemiological Study of Diabetic Retinopathy (Klein et al. 1995), for example, has shown a significant correlation between increased serum glycosylated hemoglobin (HbA1c) values and the incidence or progression of diabetic complications in both types of diabetes, including
proliferative retinopathy (P < 0.001), lower-extremity amputation (P < 0.01 to P < 0.005), ischemic heart disease (P < 0.05), and all-cause mortality (P < 0.005). These data are supported by the findings of several other epidemiologic and interventional studies (Khaw et al. 2001).

Skyler et al. (1996) modelled the outcomes of the Diabetes Control and Complications Trial (DCCT) in patients with type 1 diabetes by comparing changes in HbA$_{1c}$ values with the relative risk of various diabetic complications. For each 1% increase in HbA$_{1c}$, (beginning at 6.0%), the relative risk was found to range from a low of 1.5 for all diabetic complications at an HbA$_{1c}$ of 7.0% to a high of 20 for progression of retinopathy at an HbA$_{1c}$ 12.0%. Therefore, tight glycaemic control would appear to be a valuable public health measure in terms of both health outcomes and economic burden. The American Diabetes Association (ADA) has established a target HbA$_{1c}$ value of 7.0% for all persons with diabetes. This target is based on consistent epidemiologic data linking elevated blood glucose levels with the development and progression of diabetic complications. However, other evidence has suggested that an even lower blood glucose threshold may be necessary to prevent development of diabetic microangiopathy (Reichard et al. 1993). On the basis of this information, the American Association of Clinical Endocrinologists (AACE) recommended a more aggressive HbA$_{1c}$ target of 6.5% (Feld et al. 2002).

Cognitive dysfunction and dementia are becoming increasingly prevalent in ageing western populations. The estimated prevalence of dementia at the age of 65 years is approximately 0.5% (Breteler et al. 1992), at the age of 75 years it is 4% and at the age of 85 years it has risen to 23% (Juva et al. 1993). Milder forms of cognitive dysfunction may be even more common (Koivisto et al. 1995). Also the prevalence of non-insulin-dependent diabetes mellitus (NID diabetes mellitus), which accounts for
nearly all cases of diabetes in the elderly, increases rapidly with aging, doubling or tripling every ten years after the age of 40 years (Harris et al. 1987, Ohlsson et al. 1987 and Laakso et al. 1991). The concept of glucose intolerance includes also an intermediate category between normality and diabetes, so called impaired glucose tolerance (IGT). In elderly western populations, the prevalence of NID Diabetes mellitus has been estimated to be 10-19% and prevalence of IGT 14-23%, giving an overall prevalence figure of approximately 30-40% for glucose intolerance (Mykken et al. 1990). Glucose intolerance is associated with increased mortality and morbidity, including cerebrovascular disease (Pye et al. 1987). Hyperinsulinemia as a result of peripheral insulin resistance is one of the most important risk factors for NID diabetes Mellitus, and it has also been associated with increased morbidity. Hyperinsulinemia has been associated with atherosclerosis and other risk factors for lacunar infarcts, thereby possibly affecting cognitive function.

In previous studies, NID diabetes mellitus has been associated frequently with impaired cognitive function, mainly with impaired verbal memory (Strachan et al. 1997a). Most of these studies were small case-control studies, which can severely limit the generalization of the results obtained. There is also preliminary evidence that hyperinsulinemia would be associated with cognitive dysfunction (Kalmijn et al. 1995). Since hyperinsulinemia is major risk factor for NID diabetes mellitus (Stern 1991 and 1995), the possibility arises that frequently reported memory dysfunction could be present already in subjects in the prediabetic phase. Abnormal glucose and insulin metabolism have been reported in patients with Alzheimer disease (Craft et al. 1993), which is the major dementing disease in Caucasian populations (Van Duijn 1996). There is also evidence that late onset Alzheimer's disease is associated with cerebrovascular
changes (Blennow et al. 1991 and Brun et al. 1986). Therefore, the role of glucose intolerance and hyperinsulinemia may be of significance with respect to cognitive dysfunction and Alzheimer's disease. This series of studies was conducted in order to elucidate the association of glucose intolerance and hyperinsulinemia with cognitive function and Alzheimer disease.

1.1 ADHERENCE AND OUTCOMES

Diabetic patients are faced with a demanding set of lifestyle changes that necessitate satisfactory adherence in order to slow the progression of diabetic complications. In chronic diseases in general, adherence to treatment recommendations has been found to be an important factor in medical outcomes (Dunbar-Jacob 2001). A meta-analysis spanning thirty years of research on patient adherence and treatment outcomes in various diseases found that adhering to the prescribed treatment plan reduced the risk of a poor outcome by 26% (Dimatteo, Giordani, Lepper and Croghan, 2002). Additionally, the authors concluded that the adherence-outcome relationship was stronger for chronic diseases than for acute diseases. Adhering to a medication regimen and lifestyle changes like diet and exercise can be challenging for patients who are experiencing symptoms associated with their illness. However, failing to make these lifestyle changes may result in worsening symptoms and possibly hospitalization.

Since the early 1970’s, it has been recognized that conditions characterized by abnormalities in the supply of glucose to the brain, such as diabetes, are likely to affect cognitive performance (Anthony and Niaz 1982). To date, the precise mechanism by which diabetes may cause cognitive dysfunction is unclear (Brandt and Folstein 2002). Also unclear is the extent and type of cognitive impairment associated with diabetes as
distinct from impairment associated with other conditions frequently seen in older people with diabetes (Brandt 2002). Moreover, the implications of any such cognitive deficits for diabetes self management activities are yet to be established.

1.2 IMPAIRED COGNITIVE FUNCTIONING AND DIABETIC MANAGEMENT

The above review suggests that there may be modest cognitive deficits associated with diabetes among the elderly. Therefore, health care providers for older people with diabetes should be aware of the possibility that their elderly patients are more likely to have cognitive deficits compared to elderly people without diabetes.

Diabetes management is the term used for patient-centered diabetes care in which it is recognized that patients are responsible for carrying out the day to day activities that form most of the diabetes regimen (Assisib and Marmot 2005). Recognition of the central role of people with diabetes in their own care is exemplified in the increasing emphasis on patient empowerment in diabetes care (Yeung, Sophie and Fischer, 2009)

Sinclair et al. assessed 396 people with diabetes (5% had type 1 diabetes) and 393 without diabetes who were matched for sex and age. All participants were at least 65 years old. Two tests of cognitive function were used: the Mini Mental State Examination ‘MMSE” Clock Drawing Test (Folstein 2002). The MMSE is a widely used screening measure for dementia, and a score of 23 or less out of 30s an indication of cognitive impairment.
The focus of my research, diabetes and cognition, is a field that has grown considerably since I started working on the present thesis. The growth has been both quantitative and qualitative, such that high-quality studies are now published at about the same rate per month as they were published per year in the late 90’s. As the quality and volume of publications increases, so does the amount of unanswered research questions? An answer to the question “does diabetes affect cognitive performance?” gives rise to more detailed questions, such as “are the effects differential across cognitive domains?” and “does disease severity matter?” The answers to these questions in turn give rise to even more detailed or specific questions. In the present doctoral thesis, I attempt to give a brief summary of some of the questions that have been answered by me and others and point to some questions that have yet to be answered.

In this study, we evaluate the evidence of cognitive dysfunctioning in diabetic patients with respect to many key issues like: metabolic characteristics, socio demographic data, cardiovascular events, dietary modifications, lifestyle modification, and knowledge of disease, medication and duration of diabetes. The evidence includes contradictory findings about the cognitive decline associated with diabetes, and therefore the implications for diabetes management with regard to cognitive functioning are not always clear. In addition, there has been remarkable little research that directly addresses the possible impact of cognitive functioning in diabetes management.

Much has been researched about diet and dementia, but primarily from retrospective and observational studies. However, significant randomized controlled trials that could provide prospective data on the role of a specific diet and the risks of cognitive impairment have not often been successfully carried out, for a number of reasons. Achieving change in the
intake of major nutrients for large numbers of people and sustaining that change for the years required to assess a change is a very challenging task. It requires changing the food supply and the provision of the education necessary to establish and maintain adherence to the new dietary prescription. Furthermore, establishing a control group that is not influenced significantly by an ever-changing supply of foodstuffs in the modern global market is a further challenge. Finally, the measurement of changes in the various components of mental function with well-established evaluation techniques and tools is still a developing science. When one considers obtaining funding for such an effort, organizations with sufficient resources or commitment to fund such a study limited to governmental sources. Few manufacturers are willing to pay for studies other than with their own products. Yet, there have been good studies that have attempted to bridge the gap between what is desirable and what is practical (Nash et al. 2006).

Many cognitive skills decline with age, but the magnitude of the age differences varies across functional domains (Horn 1986). Executive functions (EF) that comprise goal setting, planning, and coordinating multiple tasks while storing information, shifting between stimulus and response sets, and deployment of attentional resources are among the most age-sensitive cognitive skills (Hultsch et al. 1992; West 1996). One of the important contributors to age-related vulnerability of EF is vascular risk. Vascular health declines with age (Fleg 1986) and clinical, epidemiological, and experimental findings indicate that increasing vascular risk and overt cardiovascular disease have a significant negative impact on EF (Apter et al. 1951; Elias et al. 2003, 2004; Waldstein et al. 2008).

Among the brief cognitive tests that have been proposed as a screening measure for dementia and cognitive impairment in either research settings or particular clinical situations, the Mini-Mental State Examination
(MMSE) (Folstein et al. 1975) is one of the most frequently used and extensively studied with regard to precision and accuracy (Aevarsson et al. 2000, Cossa et al. 1999).

1.3 OBJECTIVES OF THE PRESENT STUDY

The proposed study attempted to answer the following questions in order to contribute to better diabetes management:

1) The relationship of socio demographic characteristics, life style factors and metabolic characteristics of diabetic patients related to cognitive dysfunctioning and management of diabetes.

2) The impact of knowledge of diabetes and its management due to decline in cognitive dysfunction.