THE UNIVERSITY OF QUEENSLAND

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EXPLORING THE ASSOCIATION BETWEEN MENTAL HEALTH AND DIABETES MELLITUS AMONG WOMEN, IN A DEVELOPED AND A DEVELOPING COUNTRY

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Abstract

Diabetes mellitus has been described as a disease involving multiple morbidities including physical and psychological conditions. People with diabetes are at greater risk of experiencing anxiety and depression than the general population. Recent longitudinal studies suggest that the association between depression and diabetes is reciprocal or bidirectional. However, relatively little is known about the possibility of anxiety as a risk factor for, or a consequence of, diabetes. A slightly increased risk of depression and anxiety in people with diabetes in developing countries relative to the developed countries has been suggested by previous studies; however, biases and methodological issues in these studies may limit the strength of the finding.

The investigations included in this thesis examine the relationships between depression and diabetes, and anxiety and diabetes, in a developed and in a developing country. The specific objectives were to examine whether: 1) depression symptoms are independent predictors of diabetes mellitus in Australian women; 2) anxiety symptoms are independent predictors of diabetes mellitus in Australian women; 3) the presence of diabetes mellitus is an independent predictor of depression and anxiety disorders in Australian women; 4) symptoms of depression and anxiety are associated with diabetes mellitus in Malaysian women; and 5) whether symptoms of depression and anxiety are associated with glycemic control in Malaysian women.

The data were taken from two studies; the first was conducted using longitudinal data (secondary) from the Mater-University of Queensland Study of Pregnancy (MUSP) study in Australia, and the second, using case-control data (primary) from Malaysia. Differences in the magnitude and strength of associations found in the Australian and Malaysian samples were examined.

MUSP comprised 6753 mothers who met the following three criteria: one or more singleton/ multiple birth children discharged alive from the hospital, after the birth, and the child was not adopted prior to discharge. The data were collected over 27 years after index pregnancy. In the Malaysian case-control study, a total of 1280 women aged 35 and above participated (case: 640, control: 640). The ‘case group’ was comprised of women who reported having Type 2 Diabetes Mellitus (T2DM) and the ‘control group’ comprised women without T2DM.

To test the hypothesis assessing the association between symptoms of depression and anxiety and the risk of diabetes, the observed proportion of women who reported a change in depression and anxiety symptoms between subsequent phases of the study, at 5-year and 14-year follow-up, was estimated. Depression and anxiety disorders were assessed via a self-report questionnaire and the CIDI-Auto. Potential confounding factors were selected using directed acyclic graphs (DAGs) and *priori* knowledge. Multivariate regression models were used to estimate the risk of relevant outcomes for each independent variable, with associations summarized as odds ratios (ORs) and 95% confidence intervals (CIs).

Regarding symptoms of depression and anxiety as risk factors for diabetes, the results of the adjusted prospective analyses showed that women with persistent depression and anxiety symptoms were more likely to report diabetes at the 21-year follow-up. The present analyses also indicated that almost one third of the women who reported depression symptoms continued to report these at the subsequent follow-up phase. Similarly almost half of the women who reported anxiety symptoms continued to report these at a subsequent follow-up phase. The cross-sectional analyses using the same variables (all measured at 21-years) showed no significant relationships between symptoms of depression and anxiety, and diabetes. The results of adjusted analyses showed that women with diabetes were at greater risk of reporting lifetime major depressive disorder and posttraumatic stress disorder.

The analyses of Malaysian data showed that women with diabetes were more likely to report symptoms of depression and anxiety compared with women without diabetes. The results of adjusted analyses showed that presence of diabetes, as well as duration of diabetes did not increase the odds of depression or anxiety symptoms. With regards to glycemic control, depression and anxiety symptoms were not significantly associated with poor glycemic control in women with diabetes.

Despite some limitations, the longitudinal study provides insight into the long-term bidirectional associations between depression and diabetes, and anxiety and diabetes. If the demonstrated longitudinal relationships with the exposures investigated in this study are causal, the temporal sequence and strength of these associations provide important implications for both prevention and treatment. However, the Malaysian case-control study and cross-sectional analyses of MUSP data suggest no relationship. Therefore, additional

well-designed studies, preferably longitudinal in nature, are needed to examine this relationship especially in developing countries where diabetes prevalence is escalating.

Modest evidence of an association or increased risk of mood disorders as a consequence of diabetes was detected in this study. While there are a number of component causes associated with the outcomes, the most interesting finding is arguably the fact that both represent component causes of each other.

Declaration by author

This thesis is composed of my original work, and contains no material previously published or written by another person except where due reference has been made in the text. I have clearly stated the contribution by others to jointly-authored works that I have included in my thesis.

I have clearly stated the contribution of others to my thesis as a whole, including statistical assistance, survey design, data analysis, significant technical procedures, professional editorial advice, and any other original research work used or reported in my thesis. The content of my thesis is the result of work I have carried out since the commencement of my research higher degree candidature and does not include a substantial part of work that has been submitted to qualify for the award of any other degree or diploma in any university or other tertiary institution. I have clearly stated which parts of my thesis, if any, have been submitted to qualify for another award.

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Publications during candidature

Publications arising from the literature review

1. **Hasan, S.S.,** Clavarino, A.M., Mamun, A.A., Kairuz, T. (2015). Incidence and risk of depression associated with diabetes in adults: evidence from longitudinal studies. *Community Ment Health J*, 51, 204–21.

2. **Hasan, S.S.,** Clavarino, A.M., Mamun, A.A., Kairuz, T. (2014). Incidence and risk of diabetes associated with depressive symptoms: evidence from longitudinal studies. *Diabetes Metab Syndr*, 8(2), 82-7.

3. **Hasan, S.S.,** Clavarino, A.M., Mamun, A.A., Doi, S.A.R, Kairuz, T. (2013). Population impact of depression either as a risk factor or consequence of type 2 diabetes in adults: a meta-analysis of longitudinal studies. *Asian J Psychiatr* 6(6), 460-72.

4. **Hasan, S.S.,** Clavarino, A.M., Mamun, A.A., Doi, S.A.R., Kairuz, T. Is anxiety a risk factor for the onset of type 2 diabetes mellitus in adults? Application of biased-adjusted method. *J Pharm Policy Pract* [Revised & Resubmitted].

5. **Hasan, S.S.,** Clavarino, A.M., Mamun, A.A., Kairuz, T (2015). A comparative drug utilization study of the treatment of diabetes in Malaysia and Australia. *Australas Med J, In Press.*

6. **Hasan, S.S.,** Clavarino, A.M., Mamun, A.A., Doi, S.A.R., Kairuz, T. The global distribution of comorbid depression and anxiety in people with diabetes: risk-adjusted estimates. *J Epidemiol* [Revised & Resubmitted].

Publications from the MUSP study

1. **Hasan, S.S.,** Clavarino, A.M., Mamun, A.A., Dingle, K., Kairuz, T. (2015). The validity of personality disturbance scale (DSSI/sAD) in women with diabetes; using longitudinal study. *Pers Individ Dif*, 72, 182-8.

2. **Hasan, S.S.,** Clavarino, A.M., Dingle, K., Mamun, A.A., Kairuz, T. (2015). Diabetes mellitus and the risk of depressive and anxiety disorders in Australian women: a longitudinal study. *J Womens Health*, *In Press*.

3. **Hasan, S.S.,** Clavarino, A.M., Dingle, K., Mamun, A.A., Kairuz, T. (2014). Psychological health and the risk of diabetes mellitus in Australian women: A 21-year prospective study. *J Womens Health*, 23(11), 912-9.

4. **Hasan, S.S.,** Clavarino, A.M., Mamun, A.A., Kairuz, T. (2013). A prospective study of anxiety symptoms and later-onset diabetes mellitus in women: evidence from a longitudinal study. *Australasian Epidemiologist* [Abstract] 20(2):82-3.

5. **Hasan, S.S.,** Clavarino, A.M., Mamun, A.A., Kairuz, T. Anxiety symptoms and the risk of diabetes mellitus in Australian women: evidence from 21-year follow-up. *Public Health J* [Revised & Resubmitted].

Publications arising from the Malaysian case-control study

6. **Hasan, S.S.,** Thiruchelvam K., Ahmed, S.I., Clavarino, A.M., Mamun, A.A., Kairuz, T. (2015). Relation between mental health-related variables and glycemic control in Malaysian women with type 2 diabetes mellitus. *Int J Diabetes Dev Ctries*, DOI: 10.1007/s13410-014-0250-7.

7. **Hasan, S.S.,** Thiruchelvam, K., Ahmed, S.I., Clavarino, A.M., Mamun, A.A., Kairuz, T. Psychological health and menopause-specific quality of life of Malaysian women with diabetes. *Asian J Psychiatr* [Revised & Resubmitted].

Presentations

1. **Hasan, S.S.,** Clavarino, A.M., Mamun, A.A., Abdullah, R., Kairuz, T. A comparative drug utilisation study of the treatment of diabetes in Malaysia and Australia. *National Medicines Symposium*, Brisbane, Queensland, 21 – 23 May, 2014.

2. **Hasan, S.S.,** Clavarino, A.M., Mamun, A.A., Kairuz, T. A prospective study of anxiety symptoms and later-onset diabetes mellitus in women: evidence from a longitudinal study. *Australasian Epidemiological Association Annual Scientific Meeting*, Brisbane, Queensland, 20 – 22 October, 2013.

Publications included in this thesis

The contribution of each author in the respective publications is reflected in terms of the following:

1. Study design (100%)
2. Wrote and edited the paper (100%)
3. Statistical analysis of data (100%)

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1. **Hasan, S.S.,** Clavarino, A.M., Mamun, A.A., Doi, S.A.R, Kairuz, T. The global distribution of comorbid depression and anxiety in people with diabetes: risk-adjusted estimates. *J Epidemiol* [Revised & Resubmitted].

Contributor	Statement of contribution
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Author 2 Clavarino AM	1. Study design (5%) 2. Wrote and edited paper (10%)
Author 3 Mamun AA	1. Wrote and edited paper (5%) 2. Statistical analysis of data (5%)
Author 4 Doi SAR	1. Study design (35%) 2. Wrote and edited paper (20%) 3. Statistical analysis of data (35%)
Author 5 Kairuz T	1. Study design (10%) 2. Wrote and edited paper (10%)

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1. **Hasan, S.S.,** Clavarino, A.M., Mamun, A.A., Kairuz, T. (2015). Incidence and risk of depression associated with diabetes in adults: evidence from longitudinal studies. *Community Ment Health J*, 51, 204–21.

2. **Hasan, S.S.,** Clavarino, A.M., Mamun, A.A., Kairuz, T. (2014). Incidence and risk of diabetes associated with depressive symptoms: evidence from longitudinal studies. *Diabetes Metab Syndr*, 8(2), 82-7.

3. **Hasan, S.S.,** Clavarino, A.M., Mamun, A.A., Doi, S.A.R., Kairuz, T. (2013). Population impact of depression either as a risk factor or consequence of type 2 diabetes in adults: a meta-analysis of longitudinal studies. *Asian J Psychiatr*, 6(6), 460-72.

4. **Hasan, S.S.,** Clavarino, A.M., Mamun, A.A., Doi, S.A.R., Kairuz, T. Is anxiety a risk factor for the onset of type 2 diabetes mellitus in adults? Application of biased-adjusted method. *J Pharm Policy Pract* [Revised & Resubmitted].

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Author 1 Hasan SS (Candidate)	1. Study design (60%) 2. Wrote the paper (60%) 3. Statistical analysis of data (60%)
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Author 4 Doi SAR	1. Study design (10%) 2. Wrote and edited paper (5%) 3. Statistical analysis of data (20%)
Author 5 Kairuz T	1. Study design (10%) 2. Wrote and edited paper (20%)

Publication citations – incorporated in Results (*Chapters 5 to 8*)

1. **Hasan, S.S.,** Clavarino, A.M., Mamun, A.A., Dingle, K., Kairuz, T. (2015). The validity of personality disturbance scale (DSSI/sAD) in women with diabetes; using longitudinal study. *Pers Individ Dif*, 72, 182-8.

2. **Hasan, S.S.,** Clavarino, A.M., Dingle, K., Mamun, A.A., Kairuz, T. (2015). Diabetes mellitus and the risk of depressive and anxiety disorders in Australian women: a longitudinal study. *J Womens Health*, *In Press*.

3. **Hasan, S.S.,** Clavarino, A.M., Dingle, K., Mamun, A.A., Kairuz, T. (2014). Psychological health and the risk of diabetes mellitus in Australian women: A 21-year prospective study. *J Womens Health*, 23(11), 912-9.

4. **Hasan, S.S.,** Clavarino, A.M., Mamun, A.A., Kairuz, T. Anxiety symptoms and the risk of diabetes mellitus in Australian women: evidence from 21-year follow-up. *Public Health J* [Revised & Resubmitted].

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Author 5 Dingle K	1. Study design (10%) 2. Wrote and edited paper (5%)

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1. **Hasan, S.S.,** Thiruchelvam, K., Ahmed, S.I., Clavarino, A.M., Mamun, A.A., Kairuz, T. (2015). Relation between mental health-related variables and glycemic control in Malaysian women with type 2 diabetes mellitus. *Int J Diabetes Dev Ctries*, DOI: 10.1007/s13410-014-0250-7.

2. **Hasan, S.S.,** Thiruchelvam, K., Ahmed, S.I., Clavarino, A.M., Mamun, A.A., Kairuz, T. Psychological health and menopause-specific quality of life of Malaysian women with diabetes. *Asian J Psychiatr* [Revised & Resubmitted].

Contributor	**Statement of contribution**
Author 1 Hasan SS (Candidate)	1. Study design (60%) 2. Wrote the paper (60%) 3. Statistical analysis of data (70%)
Author 2 Clavarino AM	1. Study design (10%) 2. Wrote and edited paper (10%)
Author 3 Mamun AA	1. Study design (5%) 2. Wrote and edited paper (10%) 3. Statistical analysis of data (10%)
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Contributions by others to the thesis

1. Therese Kairuz, my principal supervisor, provided substantial contribution to the formulation of research questions, preparation and submission of manuscripts, and editing of my thesis draft.

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Diabetes, depression, anxiety, disorders, symptoms, psychological health, mental health, Australia, Malaysia

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FoR code: 1117, Public Health and Health Services, 70%

FoR code: 1115 Pharmacology and Pharmaceutical Sciences, 30%

Table of Contents

Tables

Figures

List of Abbreviations

Terms	Explanation
ADA	American Diabetes Association
BMI	Body Mass Index
CES-D	Centre of Epidemiological Survey - Depression
CIDI	Composite International Diagnostic Interview
DAG	Directed Acyclic Graph
DSM	Diagnostic and Statistical Manual for Mental Disorders
DSSI/sAD	Delusions-Symptoms-States Inventory/States of Anxiety and Depression
HPA	Hypothalamus-Pituitary-Adrenal Axis
HR	Hazards Ratio
HRQoL	Health-related Quality of Life
IDF	International Diabetes Federation
MENQOL	Menopause-specific Quality of Life
MCS	Mental Composite Score
MH	Mental Health
MUSP	Mater-University of Queensland Study of Pregnancy
NHS	National Health Survey, Australia
NHMS	National Health & Morbidity Survey, Malaysia
NNEH	Number Needed to be Exposed for one additional person to be Harmed
OR	Odds Ratio
PCS	Physical Composite Score
QoL	Quality of Life
SAD	State of Anxiety and Depression
SF-36	Short Form Health Survey – 36
SF-12	Short Form Health Survey – 12
SDC	Standard Diagnostic Criteria
SRS	Self-report Scales
RD	Risk Difference
RR	Relative Risk
T2DM	Type 2 Diabetes Mellitus

T1DM	Type 1 Diabetes Mellitus
UN	United Nations
WHO	World Health Organization

Thesis overview

This PhD study is a quantitative study that uses a range of methods to investigate the association between anxiety and diabetes, and depression and diabetes, in women. The study methods included a systematic review, meta-analyses, and analyses of longitudinal and cross-sectional data. The PhD included data from two studies; the first comprised secondary data from the Mater-University of Queensland Study of Pregnancy (MUSP) longitudinal study in Australia, a developed country, and the second, case-control data (primary) were collected from Malaysia, a developing country, providing a comparison about associations between anxiety, depression and diabetes among women in these two nations. In both studies, data were comprised of women with and without diabetes and aged 35 and older, in Australia or Malaysia. Differences in the magnitude and strength of associations in the Australian and Malaysian samples were examined.

The thesis is divided into three main sections (background and methods, results, discussion), with the results section divided into two parts, as shown in **Figure 1**. The first section of the thesis covers general background, literature review and introduction (methods) to the Australian longitudinal study (MUSP) and a Malaysian case-control study. The second section (results) is divided into two parts. Part 1 presents the findings of the systematic review and meta-analyses. Part 2 discusses the results from the MUSP longitudinal study and the Malaysian case-control study. The final section is a general discussion followed by the conclusions that can be drawn from this PhD study.

Outline of chapters

Chapter 1 discusses the general literature regarding diabetes, depression, and anxiety and provides the theoretical framework. *Chapter 2* describes the methods and disusses the connection between theoretical framework and the methodology. The systematic review provided findings about the global burden of comorbid depression and anxiety in people with diabetes; it addressed a specific research question, and its findings have been incorporated into *Chapter 3*. Four meta-analyses then examined the following associations: depression and diabetes, and anxiety and diabetes. Descriptions of the meta-analyses and the respective key findings are included in *Chapter 4*; a random-effects model and a novel quality-effects model were used where relevant. Data analyses for the longitudinal Australian MUSP study and the case-control Malaysian study are described in the respective manuscripts which have been included in the Results section, *Chapters 5 to 10*.

Depression and anxiety symptoms were assessed in all the phases of the MUSP study using the scale Delusions Symptoms-States Inventory: State of Anxiety and Depression (DSSI/sAD). Therefore, the DSSI/sAD was validated and the findings are included in *Chapter 5*. The association between *depression* symptoms and the risk of diabetes is examined in *Chapter 6*, and the association between *anxiety* symptoms and the risk of diabetes is discussed in *Chapter 7*. In *Chapter 8*, the association between *diabetes* and the risk of *mood disorders* (anxiety and depression) was examined. Relevant published/ submitted papers arising from this PhD have been included in the respective chapters.

Chapter 9 reports on the association between mental health (depression and anxiety) and diabetes, and *Chapter 10*, on the relation between mental health status and glycemic control in women with T2DM. Published/ submitted/ 'in press' papers are included in each of these chapters. The final chapter (*Chapter 11*) includes a general discussion of the findings, the causal pathways, strengths and limitations, implications of the findings, and general conclusions.

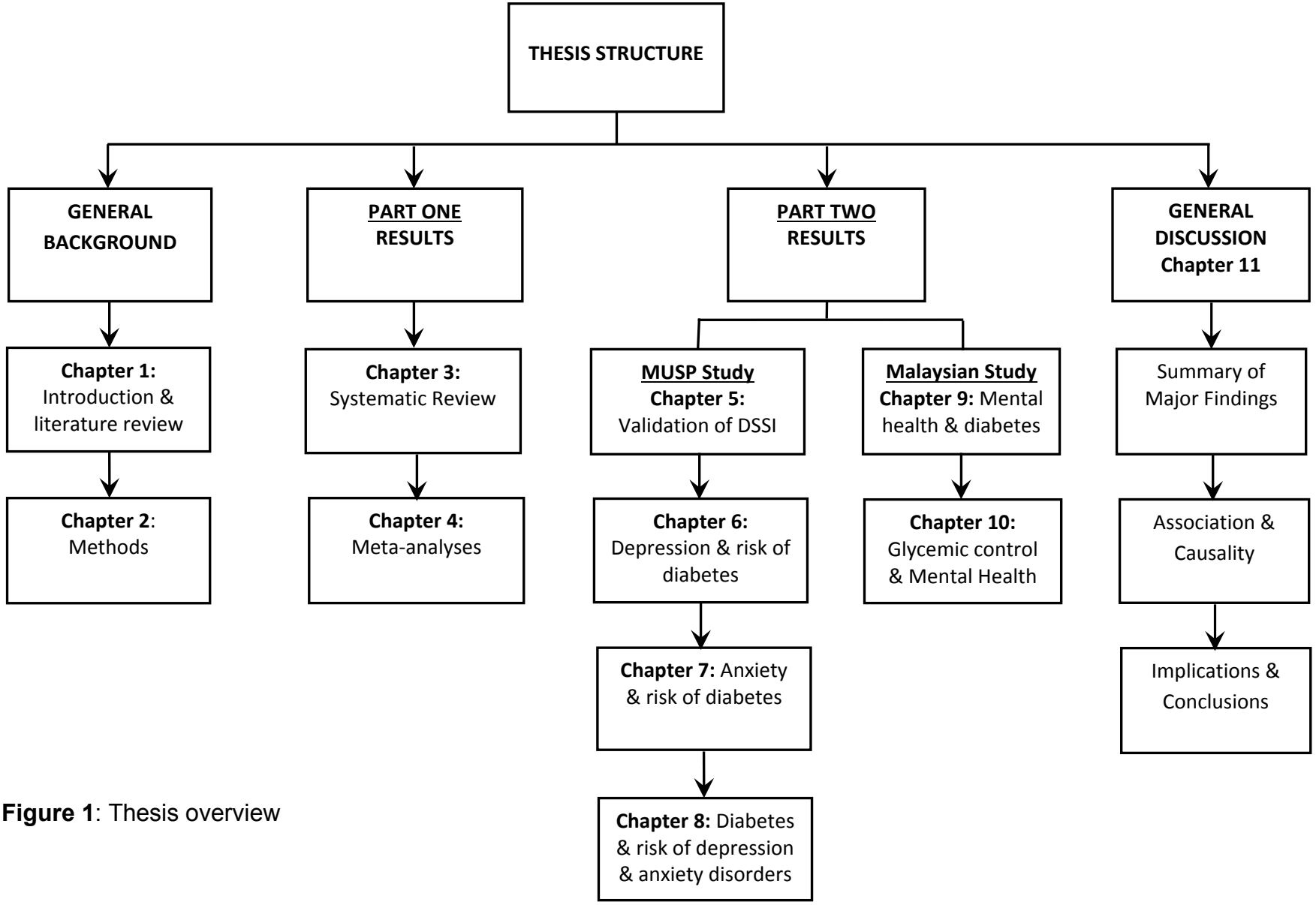

Figure 1: Thesis overview

CHAPTER 1

General Background

The prevalence and drug utilization research described in this chapter has been accepted for publication to the Australasian Medical Journal in the following form:

1. **Hasan, S.S.,** Clavarino, A.M., Mamun, A.A., Kairuz, T (2015). A comparative drug utilization study of the treatment of diabetes in Malaysia and Australia. *Australas Med J, In Press.*

The accepted, peer-reviewed manuscript in the pre-publication format provided by the publishers is attached as Appendix 1A.

1.1. Introduction

The prevalence of diabetes mellitus is increasing worldwide with estimates suggesting that 382 million (8.3% of adults) people were affected in 2013; by 2035 this number is projected to rise to 592 million (IDF, 2013). The predicted increase in patients with diabetes is 54%, at an annual growth of 2.2%, which is nearly twice the annual growth of the total world adult population (Shaw et al., 2010). According to the World Health Organization (WHO), diabetes is the 9th leading cause of death in the world contributing 1.26 million or 2.2%, of deaths (WHO, 2008). The International Diabetes Federation (IDF) estimated that 3.9 million deaths were caused by diabetes in 2010 which represents 6.8% of total global mortality (IDF, 2009). In 2010, approximately 1.9 million individuals aged 20 years and older were diagnosed with diabetes (CDC, 2011). Both the incidence and prevalence of diabetes are escalating particularly in developing and newly industrialized nations, and also among disadvantaged groups living in developed countries (Shaw et al., 2010).

About 80% of the total numbers of people with diabetes live in low- and middle-income countries with the majority aged between 40 and 59 years (IDF 2013). With more than 138 million people affected, the Western Pacific has more people with diabetes than any other region in the world (IDF 2013). The Western Pacific, which has 39 countries including Australia and Malaysia, also includes China, the country with highest prevalence of diabetes (9.6%) (IDF 2013). In developing countries, the majority of adults with diabetes are between 45 and 64 years old, whereas in developed countries the majority of adults with diabetes are 65 years and older (ADA, 2011; King et al., 1998). About 90% of all cases of diabetes in both developed and developing countries are type 2 diabetes mellitus (T2DM), which is primarily found in adults more than 30 years of age (Shaw et al., 2010). Globally, diabetes prevalence is similar in men and women, but after the age of 65 years diabetes is more prevalent in women (Wild et al., 2004). In developing countries such as China, Brazil, and Egypt, diabetes is more prevalent in women (Hu et al., 2001; Lin et al., 2008).

Diabetes mellitus has been described as a “complex chronic progressive disease,” which is defined as a disease involving multiple morbidities including physical and psychological conditions (Sevick et al., 2007). Depression and anxiety are two common co-morbid, modifiable mental health conditions associated with diabetes (Kessler et al., 1995; Smith

et al., 2013; WHO, 2000). It is reported that people with diabetes are at greater risk of reporting anxiety and depression compared to the general population (Anderson et al., 2001; Bouwman et al., 2010; Egede et al., 2002; Nichols et al., 2007), but this often remains unrecognized and thus is often untreated (Pouwer, 2009). A meta-analysis demonstrated that 11% of patients with diabetes had comorbid major depressive disorder (MDD) and 31% experienced significant depressive symptoms (Anderson et al., 2001). A systematic review reported that generalized anxiety disorder (GAD) was present in 14%, and elevated symptoms of anxiety in 40%, of patients with diabetes (Grigsby et al., 2002). The prevalence of depression and anxiety in women with diabetes was reported to be double that of men with diabetes (Ali et al., 2006; Clouse et al., 2003; Engum 2007; Grigsby et al., 2002). The association between depressive symptoms and diabetes was also stronger among women (Carnethon et al., 2003).

Recent meta-analyses of longitudinal studies suggest that the association between depression and diabetes is reciprocal or bidirectional (Mezuk et al., 2008; Rotella & Mannucci, 2013; Rotella & Mannucci, 2012). Regarding comorbid anxiety with diabetes, results from longitudinal studies are inconsistent (Atlantis et al., 2012; Edwards and Mezuk, 2012; Engum 2007). Although there is evidence regarding anxiety disorders and increased T2DM burden (Andrews et al., 1998), increased complications of diabetes with anxiety (Jonas et., 1997), poor glycemic control (Anderson et a., 2002), and reduced quality of life (QoL) (Mendlowicz and Stein, 2001), there has been little focus on the possibility of anxiety as a risk factor for later onset of T2DM. The findings of the only meta-analysis on this topic suggests that people with diabetes are more likely to have anxiety disorders or elevated anxiety symptoms compared with people who do not have diabetes (Smith et al., 2013). However, there is no meta-analysis investigating the development of diabetes associated with anxiety symptoms and/ or disorders.

The association between mental health conditions and diabetes can be described in terms of medications used for the treatment of diabetes and mental health conditions such as depression and anxiety. Treatment of diabetes is associated with improved glycemic control and reduced complications (Anderson et al., 2002; Lustman et al., 2000). Similarly treatment of mental health conditions not only improves the mental health status, but also improves glycemic control (Anderson et al., 2002; Lane et al., 1993). However, significant controversy exists over whether or not depression and anxiety in patients with diabetes is

associated with poorer glycemic control, with some studies reporting moderate to strong associations (Anderson et al., 2002; Eaton et al., 1992; Konen et al., 1996; Lustman et al., 2000; Mazze et al., 1984; van der Does et al., 1996), while others have found no association (Niemcryk et al., 1990; Viinamaki et al., 1995; Wilson et al., 1986).

This PhD study bridges a gap in the literature and examines the bidirectional association of depression and anxiety with diabetes, and also discusses possible causal pathways to explain these associations. It is important to examine these relationships in people with diabetes because co-morbid mental health conditions such as depression and anxiety may lead to increased diabetes severity, complications, work disability, increased use of medical services and substantially higher health care costs, poor QoL (Khowaja et al., 2007; Lin et al., 2010; Lin et al., 2009; Mosaku et al., 2008;) and poor glycemic control (Lustman et al., 2000).

1.2. Diabetes mellitus in developed and developing countries

Once a disease of developed countries, diabetes has now spread to every country in the world (Hu, 2011). Despite the increasing prevalence in developing nations, there are marked differences in prevalence between developed and developing countries. King et al. reported a 42% increase, from 51 to 72 million, in developed countries from 1995 to 2025; in comparison, the increase in developing countries is predicted to be 170%, from 84 to 228 million, during the same period (King et al., 1998). Between 2010 and 2030, the increase in the number of adults with diabetes in developed and developing countries is estimated to be approximately 20% and 69%, respectively (Shaw et al., 2010). In developing and developed countries, the majority of people with diabetes are reported to be in the age range of 40 to 64 years (King et al., 1998; Shaw et al., 2010).

1.2.1. Prevalence of diabetes in Australia – a developed country

The estimated resident population of Australia in September, 2013 was about 23.5 million (ABS, 2013), and is projected to increase to 48.3 million people by 2061 (ABS, 2013[a]). Approximately two-thirds (67%) of the population was in the working age group (15 – 64 years) (ABS, 2013b). The National Health Survey (NHS) is a series of regular population surveys conducted by the Australian Bureau of Statistics (ABS), and is designed to obtain information on a range of health-related issues (ABS, 2013). In 1995, the (second) NHS reported that 2.4% of Australians had been diagnosed with diabetes at some time during their lives (ABS, 1995). A little over ten years later, an estimated 4.6% of the population in

2011-12 (NHS) had been medically diagnosed with diabetes, excluding those with gestational diabetes mellitus (ABS, 2011-12). Despite the steady increase, the prevalence rate of diabetes in Australia is relatively low compared with North America and the Caribbean (10.2%), Middle East and North Africa (9.3%), and South East Asia (7.6%) (IDF, 2009). The prevalence of diabetes in Australia has increased steadily between 1995 and 2012, as shown in **Figure 1.1**.

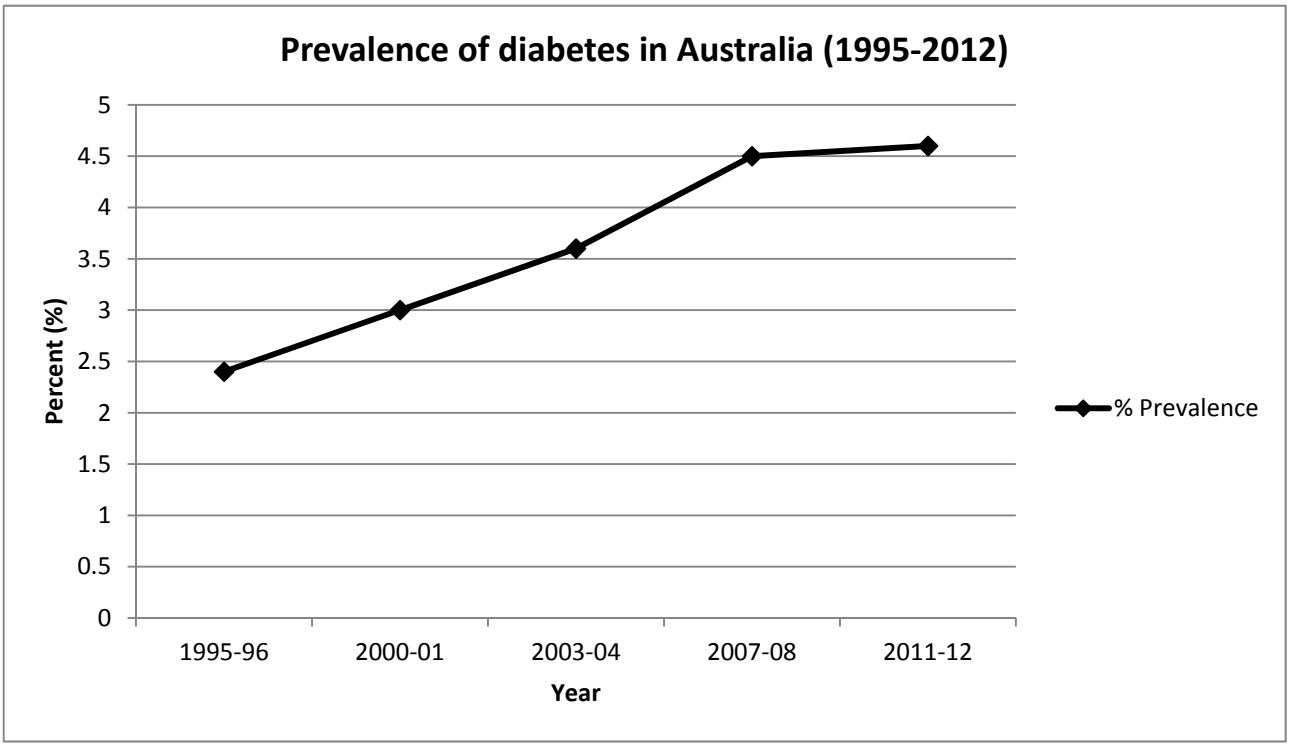

Figure 1.1: Source (ABS, 1995; ABS, 2008, ABS, 2011-12)

This rise in Australia was largely due to an increase in T2DM, from 1.1% in 1995 to 3.9% in 2011-12. The increase in the reporting of T2DM may be partly due to people finding out that the type of diabetes they had was T2DM, as the number of people whose type of diabetes was unknown decreased from 0.8% in 1995 to 0.1% in 2007-08 (ABS, 2007-8). The proportion of people with type 1 diabetes remained relatively stable over this period (ABS, 2007-8). Another reason for the increasing prevalence of diabetes prevalence is immigrants from high-risk diabetes countries; the age and sex standardized prevalence rate of diabetes among the immigrant population (3.0%) was higher than that of the Australian-born population (2.1%) (ABS, 2007-8; ABS, 1995).

Males aged 2 years and over accounted for just over five percent (5.1%) of all diabetes in 2011-12 (ABS, 2011-12), compared with 4.2% of females. The prevalence was highest

among those aged 75 to 84 years; this increased from 13% in 2007-08 to 17% in 2011-12) (ABS, 2007-8; ABS, 2011-12). Although the prevalence of diabetes is increasing, diabetes was not documented as one of the most commonly reported chronic conditions in Australia (ABS, 2007-8), which included predominantly cardiovascular related diseases.

1.2.2. Prevalence of diabetes in Malaysia – a developing country

Malaysia, a newly industrialized country, was among the top 10 countries worldwide for diabetes prevalence in 2010 and is predicted to remain in the top 10 until 2030 (Shaw et al., 2010). In Malaysia, nearly half the population lives to the age of 70 years and chronic diseases are the major cause of death, which is similar to high-income countries (WHO, 2008). In Malaysia, the National Health and Morbidity Survey (NHMS) is a nationwide survey of self-reported data that includes medicine use, dietary habits, various disease states, and demographics, and is published every ten years. The first NHMS was conducted in 1986 and was followed by NHMS II in 1996 and NHMS III in 2006. According to the NHMS, there was an increase of 80% in the prevalence of diabetes among those aged 30 years and older, from 8.3% (1996) (NHMS, 1996), to 14.9% in 2006 (Letchuman et al., 2010). The 200% increase in newly diagnosed cases of diabetes between 1996 (1.8%) (NHMS, 1996), and 2006 (5.4%) (Letchuman et al., 2010), is an indicator of the rising epidemic of diabetes in Malaysia. The overall projected prevalence, for the age group of 18 years and older, was 11.6% in 2006 (Letchuman et al., 2010); this figure reached the projected prevalence much earlier than predicted (Zaini, 2000). The prevalence increased dramatically to 22.9% and more than half (12.1%) were newly diagnosed (Wan Nazaimoon et al., 2013).

In Malaysia, the majority of people with diabetes are of Indian origin, followed by Malay and Chinese, with a high prevalence in people aged between 45 to 75 years of age (Letchuman et al., 2010). The prevalence of diabetes in Malaysia over nearly 30 years (1986 and 2013) is presented in **Figure 1.2**.

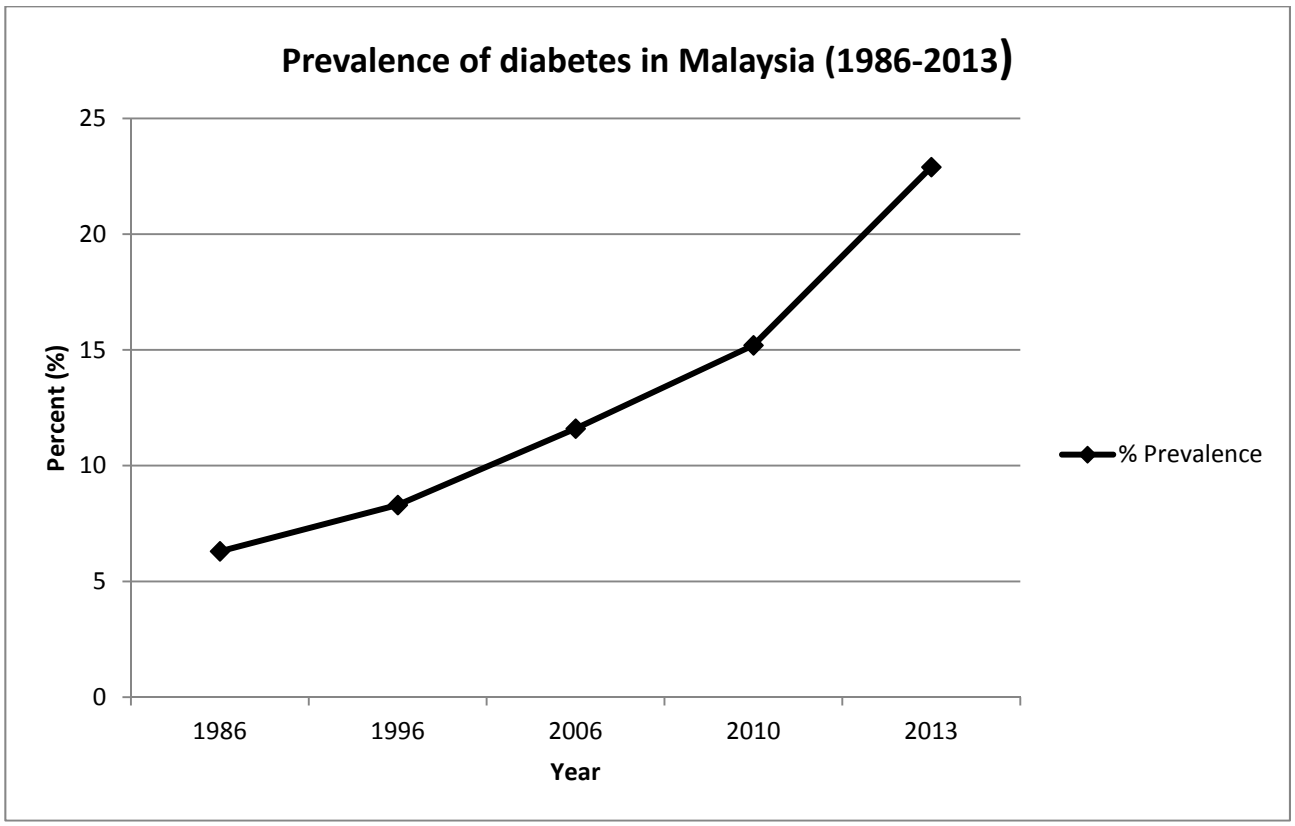

Figure 1.2: Source: NHMS, 1996; Letchuman et al., 2010; Rampal et al., 2010; Wan Nazaimoon et al., 2013

1.3. Association between diabetes and mental health conditions

People with diabetes are at higher risk of developing mental health conditions such as depression and anxiety (Anderson et al., 2001; Engum, 2007; Lin et al., 2008). Similarly, depression and anxiety also increase the risk of diabetes and several studies from developed countries suggest that an association between these mental health conditions (depression and anxiety) and diabetes is reciprocal or bidirectional in nature (Mezuk et al., 2008; Rotella & Mannucci, 2013; Rotella & Mannucci, 2012; Smith et al, 2013).

1.4. Association between depression and diabetes

Depression and diabetes are two serious medical conditions and health concerns that afflict millions of people worldwide (IDF, 2013; Mezuk et al., 2008). Multiple meta-analyses have suggested an association between depression and diabetes as bidirectional (Mezuk et al., 2008; Nouwen et al., 2010; Rotella & Mannucci, 2012; Rotella & Mannucci, 2013). The bidirectional association between diabetes and depression was first documented by Golden and colleagues who described the relationship as “modest” and “partially explained

by lifestyles" (Golden et al., 2008), and Eaton and colleagues were the first to report the results of an epidemiological study that confirmed this relationship (Eaton et al., 1996).

The bidirectional relationship between depression and diabetes can be elaborated with the help of two hypotheses. One hypothesis suggests that depression is a *consequence* of diabetes and may be a result of the burden of chronic disease or of biochemical changes that occur in diabetes (Kinder et al., 2002; Knol et al., 2007). Another hypothesis proposes depression as a *risk factor* for the development of diabetes which may be a consequence of a decline in health-maintenance behaviors among depressed persons (Barbour and Blumenthal, 2005; Golden et al., 2008; Katon et al., 2004; Kinder et al., 2002) or resulting from biochemical changes associated with depression (Bjorntorp, 2001; Knol et al., 2006).

1.4.1. Depression as a *risk factor* for diabetes

Previous studies have indicated that the risk of developing diabetes is elevated in persons who report high depressive symptoms and/ or clinical depression compared to those with fewer symptoms or without a clinical diagnosis (Rotella & Mannucci, 2013; Mezuk et al., 2008). However, some cohort studies found no effect of depressive symptoms on diabetes incidence (Saydah et al., 2003) or no overall association between depression and diabetes onset (van den Akker et al., 2004). Eaton et al. also found that major depressive disorder was associated with the onset of diabetes, but this was not the case for milder forms of depression or other psychiatric disorders (Eaton et al., 1996). In short, after controlling for demographic and clinical risk factors, most studies have shown that depression is an independent risk factor for the onset of diabetes (Rotella & Mannucci, 2013; Mezuk et al., 2008).

1.4.1.1. Possible risk mechanisms for the development of diabetes in people with depression

From a biological perspective, various mechanisms of how depression increases the risk of developing diabetes have been proposed (Danese et al., 2009; Tsigos et al., 2002; Vogelzangs et al., 2007). Detailed discussion on possible risk mechanisms are included in this PhD (*see appendix 4A and 4C*) and results section (*see Chapter 6*); this chapter discusses only two widely studied mechanisms, the hypothalamic–pituitary–adrenal-axis (HPA) dysregulation and pro-inflammatory cytokines.

1.4.1.1.1. Role of hypothalamic–pituitary–adrenal-axis (HPA) dysregulation

Depression is associated with physiological abnormalities, including increased activity of the HPA-axis and the sympathetic nervous system (Bjorntorp, 2001), resulting in increased cortisol release and increased release of the catecholamines (epinephrine and nor-epinephrine). The dysregulation of HPA axis is the most widely discussed biological explanation for the increased risk of diabetes as result of depression. This dysregulation can induce insulin resistance and contribute to diabetes risk (Golden, 2007).

Stress can mediate between symptoms of depression and diabetes by over-activating the HPA axis; this results in elevated cortisol levels, which stimulates glucose production, increases lipolysis and circulating free fatty acids, decreases insulin secretion from beta cells and decreases sensitivity to insulin (Bjorntorp, 2001; Ramasubbu, 2002; Weber-Hamann et al., 2002). It is postulated that a chronically high cortisol level, which is found in about 50% of depressed patients, results in obesity, insulin resistance and T2DM (Bjorntorp, 2001; Bjorntorp et al., 1999; Maes et al., 1991). Some studies have found evidence for this hypothesis (Bjorntorp et al., 1999; Weber-Hamann et al., 2002). A chronically elevated cortisol level increases the risk of developing metabolic syndrome, which increases the risk for developing diabetes (Bjorntorp, 2001; Knol et al., 2006). Metabolic syndrome is characterized by central adiposity or excess accumulation of abdominal fat, and insulin resistance, and has been reported in late-onset depression (Vogelzangs et al., 2007) and in persistent depression (Lehto et al., 2008). It is considered to be an important risk factor for the development of diabetes (Capuron et al., 2008).

Stressful situations have been shown to induce hyperglycemia in euglycemic animals (Surwit et al., 1992) and in humans with a genetic predisposition toward developing diabetes (Esposito-Del Puente et al., 1994). However, stress only precipitates clinical diabetes in persons predisposed to developing diabetes (Wales, 1995). This was confirmed by a study where depression scores were found to be associated with both diagnosed and undiagnosed diabetes (Holt et al., 2009).

Epinephrine generates responses in glucose and fat metabolism similar to those of cortisol (Genuth, 1998), possibly resulting in insulin resistance and diabetes. The credibility of this hypothesis is further strengthened by findings from other medical conditions that are accompanied by hypercortisolemia such as Cushing's syndrome, sleeping disorders, work stress and schizophrenia (Buckley & Schatzberg, 2005; Lundberg, 2005; Morris &

Grossman, 2002; Ryan et al., 2003); the hypothesis appears to be associated with an increased level of cortisol, an increased risk of diabetes and insulin resistance (Meisinger et al., 2005; Ryan et al., 2003).

1.4.1.1.2. Role of pro-inflammatory cytokines

The second most widely discussed explanation for the link between depression and diabetes involves the inflammatory response or dysregulation of the immune system (Howren et al., 2009; Valkanova et al., 2013). Both depression and diabetes are associated with increased C-reactive protein, TNF-α and pro-inflammatory cytokines (Au et al., 2014; Dentino et al., 1999; Kiecolt-Glaser & Glaser, 2002; Maes et al., 1997; Pradhan et al., 2001; Schmidt et al., 1999). However, disagreement between this assumption and the proposed hypothesis that cortisol inhibits inflammation and the immune response; whereas depression is correlated with both elevated cortisol and increased inflammatory markers. This apparent contradiction could be explained with the help of a finding that melancholic depressed patients had increased HPA axis activity and no signs of inflammation, whereas non-melancholic depressed patients did show signs of inflammation and normal HPA axis activity (Kaestner et al., 2005).

There is a growing body of evidence to support an association between inflammation and depression (Howren et al., 2009; Valkanova et al., 2013). The elevated levels of pro-inflammatory cytokines such as interleukin-6 (IL-6) and C-reactive protein (CRP) have been implicated in the pathophysiology of T2DM (Doyle et al., 2013; Stuart & Baune, 2012). Meta-analyses have also suggested an association between elevated level of CRP and increased risk of T2DM (Lee et al., 2009; Wang et al., 2013). The association of elevated CRP levels and depressive symptoms with a higher incidence of T2DM (Au et al., 2014), suggests that individual who have both depression and inflammation are at greater risk of developing diabetes, and both increased the risk of abdominal obesity, metabolic syndrome, and coronary heart disease (Ladwig et al., 2005; Valtonen et al., 2012).

The role of inflammatory mediators in the development of diabetes has been supported by at least two population-based studies (Ford, 2002; Schmidt et al., 1999). It is suggested that inflammation may be associated with oxidative damage and the release of free radicals (Paolisso et al., 1993a) that damage pancreatic β cells (Rabinovitch et al., 1992), thus limiting the release of insulin. The inflammatory process may inhibit insulin uptake (Paolisso et al., 1993b), a critical process in glucose regulation. Moreover, in cross-

sectional studies, inflammatory markers, including the cytokines interleukin-1β, and tumor necrosis factor-α (Appels et al., 2000) and C-reactive protein (Au et al., 2014; Dotevall et al., 2001), were found to be elevated in depressed persons. CRP has been linked to insulin resistance via obesity (Nakanishi et al., 2003), adipose tissue which is a main source of pro-inflammatory cytokines (Nakanishi et al., 2003), and impairment of endothelial permeability (Dehghan et al., 2007).

1.4.2. Depression as a *consequence* of diabetes

The presence of diabetes increases the risk for having a diagnosis of depression (Anderson et al., 2001; Eaton et al., 1996), and people with diabetes are more likely to have deficits in cognitive function (Wandell, 1999). Generally it is perceived that individuals experiencing diabetes-related complications and disability experience depression as a consequence of their disability (Nouwen et al., 2010; Talbot et al., 1999). Numerous prospective studies have investigated the association between diabetes and the risk of depression, although the findings are inconsistent (Engum, 2007; Golden et al., 2008; Mezuk et al., 2008; Nouwen et al., 2010; Rotella & Mannucci, 2012).

People with diabetes are more likely to suffer from depression and to rate their health worse than people without diabetes (Zhang et al., 2005). Diabetes is described as a "depressogenic" condition as it increases the risk of developing depression but there is only modest evidence to support this hypothesis (Mezuk et al., 2008). The competing risks for late-life depression, such as macro-vascular disease, and functional or cognitive decline, may mask this relationship (Gallo et al., 1994). However Golden and colleagues found that individuals with impaired fasting glucose and those with untreated diabetes had a reduced risk of incident depressive symptoms (Golden et al., 2008).

1.4.2.1. Possible risk mechanisms for developing depression in people with diabetes

Detailed discussion on possible risk mechanisms is included in the meta-analyses (*see appendix 4B and 4C*) and results section (*see Chapter 8*). When compared with depression resulting in diabetes, the association between existing diabetes and the onset of depression is weaker and is often conceptualized as having various possible indirect mechanisms. Cognition related to diabetes, such as perceived disability and awareness of having a chronic illness, may impose higher levels of psychological burden on people with diabetes, particularly in individuals with low levels of social support (Knol et al., 2007; Talbot & Nouwen, 2000). Biochemical changes associated with diabetes, such as arousal

of the nervous system, could account for an increased risk of depression in individuals with diabetes compared with those without the condition (Kinder et al., 2002; Knol et al, 2007).

1.5. Association between anxiety and diabetes

Anxiety is a common, co-morbid, modifiable condition experienced by individuals suffering from diabetes (Anderson et al., 2001; Grigsby et al., 2002; Smith et al., 2013). People with diabetes are at greater risk of suffering from anxiety than the general population (Grigsby et al., 2002; Shaban et al., 2006). Anxiety symptoms appear to be higher among patients with T2DM compared with those with T1DM (Hermanns et al., 2005). Among people with diabetes, women have significantly higher levels of anxiety than men and the prevalence is approximately double (Grigsby et al., 2002). The World Mental Health Survey conducted across 17 countries reported that the risk of anxiety disorders was higher among individuals with diabetes compared to those without (Lin et al., 2008).

1.5.1. Anxiety as a *risk factor* for diabetes

The findings from available longitudinal studies examining the association between anxiety and the risk of diabetes are inconsistent (Atlantis et al., 2012; Edwards & Mezuk, 2012; Engum, 2007). Anxiety has not been studied closely, unlike depression which is the most studied mental health condition associated with diabetes (Smith et al., 2013). There is evidence regarding anxiety disorders and increased T2DM burden (Andrews et al., 1998), increased complications (Jonas et al., 1997), poor glycemic control (Anderson et al., 2002), and reduced quality of life (Mendlowicz & Stein, 2001); however, there has been little focus on the possibility of anxiety as a risk factor for later onset T2DM. For example, there is no meta-analysis investigating the development of diabetes in relation to anxiety symptoms.

1.5.1.1. Possible risk mechanisms for the development diabetes in people with anxiety

Some studies suggest that anxiety and depression have different risk mechanisms, as anxiety is characterized by hypocortisolemia and up-regulation of glucocorticoid receptors, whereas, depression is generally characterized by hypercortisolemia and a decreased number of glucocorticoid receptors (Arborelius et al., 1999; Krystal et al., 2001).

A possible biological explanation for the increased risk of diabetes among people who have anxiety may be the chronic or recurrent stress which results in intermittent or sustained increase in levels of cortisol and adrenaline in vulnerable individuals (Dinan,

2004). Numerous studies have suggested that anxiety is associated with an up-regulation or dysregulation of the HPA axis resulting in elevated cortisol levels, which is also seen in depression; elevated cortisol can inhibit insulin function in a variety of ways (Chiodini et al., 2007; Ehlert et al., 2001; Merswolken et al., 2012; Steudte et al., 2011; Young et al., 2004). Anxiety disorders have been shown to be associated with obesity in various general population studies and it is possible for anxiety disorders to lead to weight gain (Gariepy et al., 2010). The HPA dysregulation is assumed to contribute to appetite dysregulation (Dallman et al., 2005; Torres & Nowson, 2007), increased appetite (Canetti et al., 2002) and subsequent weight gain in stressed individuals, and also to stimulate a craving for high-sugar and high fat foods (Adam & Epel, 2007; Nowson, 2007; Nieuwenhuizen & Rutters, 2008; Torres & Yannakoulia, 2008). In addition, a longitudinal study showed that people who developed anxiety or depression at one stage in their life were more likely to become obese than those in good mental health (Kivimäki et al., 2009).

The association between anxiety and weight gain may also be explained by factors that share a relationship with both anxiety and weight gain. For example obesity and anxiety disorders are both partly heritable diseases (Hettema et al., 2001; Walley et al., 2009), and may share a common genetic basis (Gariepy et al., 2010). Factors such as negative events in childhood and personality traits such as neurocriticism, hypersensitivity to criticism and avoidant coping styles (Angst & Vollrath, 1991; Spira et al., 2004; Vink et al., 2008), can predispose individuals to anxiety and weight gain or obesity. In addition environmental endocrine-disrupting chemicals can affect hormonal homeostasis involved in weight and emotional regulation (Dallman et al., 2005; Elobeid & Allison, 2008; Torres & Nowson, 2007).

Mental health conditions are often comorbid with obesity and some have been found to lead to weight gain, such as mood disorders (Atlantis & Baker, 2008; Petry et al., 2008), eating disorders (Javaras, 2008; Picot & Lilenfeld, 2003), and personality disorders (Petry et al., 2008). Anxiety disorders tend to be co-morbid with depression (Alloy et al., 1990; Regier et al., 1990) and an estimated 85% of patients with depression have symptoms of anxiety (Beekman et al., 2000; Belzer & Schneier, 2004; Lenze et al., 2000; Mulsant & Reynolds, 1996); it is therefore possible that the comorbidity between depression and anxiety is the most important factor that increases the risk of developing diabetes.

Smoking, physical inactivity, pain and heavy drinking are significantly associated with a lifetime diagnosis of anxiety and these factors have also been shown to be associated with diabetes (Gerrits et al., 2012; Lin et al, 2008; Skilton et al., 2007; Strine et al., 2008).

1.5.2. Anxiety as a *consequence* of diabetes

Diabetes is a significant risk factor for depression and doubles the likelihood of co-morbid depression (Grigsby et al., 2002). Although there is evidence regarding anxiety disorders and increased diabetes complications (Collins et al., 2009; Jonas et al., 1997), poor glycemic control (Anderson et al., 2002), weight gain (Balhara & Sagar, 2011), and reduced quality of life (Mendlowicz & Stein, 2001), there has been little focus on the possibility of diabetes as a risk factor for the onset of anxiety disorders. Despite the fact that literature suggests anxiety is an important comorbid condition associated with diabetes, only one review examined the link between diabetes and the risk of developing anxiety (Smith et al., 2013). The review suggests that people with diabetes are more likely to have anxiety disorders or elevated anxiety symptoms compared with people who do not have diabetes (Smith et al., 2013). However, in a longitudinal study, Engum found that although elevated baseline anxiety symptoms were associated with an increased risk of developing diabetes, diabetes did not predict anxiety (Engum, 2007).

The psychosocial burden of a chronic disease such as diabetes may carry with it a risk of developing anxiety symptoms. Various studies have demonstrated that in people with diabetes, anxiety is significantly associated with diabetes complications (Collins et al., 2009; Fisher et al., 2008; Lloyd et al., 2000; Ludman et al., 2006), increased pain (Gore et al., 2005), engaging in unhealthy self-care behaviors (Collins et al., 2009; Lloyd et al., 2000), greater disability (Ludman et al., 2006), depression (Trento et al., 2011) and an increased Body Mass Index (BMI) (Balhara & Sagar 2011). However, many of these factors have also been shown to be associated with anxiety and anxiety disorders in the absence of diabetes. More studies should explore the association between diabetes and the risk of anxiety symptoms and/ or disorders and the role of other factors highlighted above.

1.6. Study aims and hypotheses

The hypotheses underpinning this PhD were that a bidirectional relationship exists between depression and diabetes, and between anxiety and diabetes. It was also hypothesized that similar associations between anxiety, depression and diabetes would be found among women in a developed and a developing country. The main aim of this study was to examine the bidirectional association between depression and diabetes, and anxiety and diabetes in women from both a developed and developing country. Australian data from Mater-University of Queensland Study of Pregnancy (MUSP) were used as this large birth cohort study provides a unique platform to examine longitudinal effects of depression and anxiety (Najman et al., 2005; Ware et al., 2006). By analyzing MUSP data, the prevalence of depression and anxiety in women with diabetes was estimated, and the bidirectional relationship of mental health conditions and diabetes in women was investigated. The same relationships in a developing country (Malaysia) were then also investigated using a case-control study.

In order to bridge the gap in the literature, specific objectives of this study were formulated and are stated below. It was conducted as two separate studies but which were linked through the questionnaires and the analyses.

1.6.1. Specific objectives of the study

1. To calculate the risk-adjusted global prevalence estimates of comorbid depression and anxiety in people with diabetes mellitus.

2. To summarize existing literature and synthesize findings on the association between depression and diabetes, and anxiety and diabetes in the form of meta-analyses.

3. To validate the personal disturbance scale (Delusions-Symptoms-States-Inventory/States of Anxiety and Depression) among women with diabetes using the MUSP dataset.

4. To investigate whether change in depression symptoms **(exposure)** was independently associated with the risk of diabetes mellitus, measured at 21-years post index pregnancy **(outcome)** in Australian women.

5. To investigate whether change in anxiety symptoms **(exposure)** was independently associated with the risk of diabetes mellitus, measured at 21-years post index pregnancy **(outcome)** in Australian women.

6. To investigate whether the presence of diabetes mellitus **(exposure)** was independently associated with the risk of depressive and anxiety disorders, measured at 27-years post index pregnancy **(outcome)** in Australian women.

7. To investigate whether symptoms of depression and anxiety were associated with diabetes mellitus in Malaysian women.

8. To investigate whether depression and anxiety symptoms were associated with glycemic control in Malaysian women.

1.6.2. Why Australia and Malaysia?

There were various reasons for collecting and analyzing data from a developed (Australia) and a developing (Malaysia) country in this study. It is suggested that between the years 2010 and 2030, the increase in the number of adults with diabetes in developing countries will be more than double compared to developed countries (Shaw et al., 2010). Malaysia is one of the most prominent developing, middle-income countries outside Europe as designated by the United Nation (UN) classification (UN, 2007), which excludes Australia, Canada, Japan, New Zealand, USA, Singapore, Hong Kong and Taiwan. It is a country in the developing world whose population characteristics are comparable to the Australian population. To facilitate comparison, the estimated and projected population for Australia and Malaysia are summarized in **Table 1.1**.

Table 1.1: The estimated and projected population of Australia and Malaysia

Country	Estimated Resident Population		Growth Rate	Projected Population	Rank 2050
	2010 (million)	2011 (million)	%	2050 (million)	
Australia	22	23	1.4	34	59
Malaysia	28	29	1.6	43	48

Source: (ABS, 2011; DSM, 2010)

Diabetes contributes substantially to public health issues in a high-income country such as Australia (0.24 million annual deaths), and a middle-income country, Malaysia (0.87 million annual deaths) (WHO, 2008). Australia was ranked 6th in the worldwide quality of life index, whereas Malaysia was the 51st country on the list (EIU, 2005). In terms of the human development index (HDI), Australia is categorized under 'very high' human development compared to 'high' for Malaysia (HDI, 2010).

About two-thirds of the population in both Australia and Malaysia are between 15 to 64 years of age. There were more people over the age of 65 years in Australia compared with Malaysia, while Malaysia had a greater number of younger people under 14 years (ABS, 2011). In Australia, the gender ratio at birth is approximately 100 females per 105 males. However, higher male mortality rates at a young age result in the ratio approaching 100 females per 100 males (ABS, 2011). The gender ratio of the total population for Australia was similar to Malaysia in 2011 (99.1 males per 100 females) (ABS, 2011). The age distribution of the Australian and Malaysian population respectively, is summarized in **Table 1.2**.

Table 1.2: The age standardized population of Australia and Malaysia

Country	2010			Median Age	2015			Median Age	LE
	0-14	15-64	>65		0-14	15-64	>65		
Australia	18.9	67.6	13.5	36.9	18.6	66.1	15.3	39.9	82.1
Malaysia	30.3	64.9	4.8	26.0	28.2	66.0	5.7	27.5	74.6

Source: (ABS, 2011; DSM, 2010); LE = Life Expectancy

1.6.3. Why is this study important?

During the process of compiling the literature review for this study, an increasing trend in the prevalence of people with diabetes in Malaysia and Australia was identified. A slightly increased risk of depression and anxiety in people with diabetes in developing countries relative to the developed countries has been suggested by previous studies (Aina and Susman, 2006; Bouwman et al., 2010; Collins et al., 2009; Lin et al., 2008); however, biases and methodological issues in these studies may limit the strength of the finding.

Women's role in society worldwide has expanded from the traditional carer role, to include provider, carer and member of the workforce. Therefore, women's health is an important issue in all countries, including Australia and Malaysia. No longitudinal or case-control studies have examined the association between modifiable mental health conditions (depression and anxiety) and diabetes in women in Malaysia and the current study examined this relationship. This study did not directly compare the data from Australia and Malaysia but examined differences in the strength and direction of the relationship between modifiable mental health conditions and diabetes in both countries.

CHAPTER 2

Methods

The methods used in Australian and Malaysian arms of the PhD study are described in the two sections that comprise this chapter. The chapter covers the major methods used in this thesis; further details, relevant to individual papers can be found in those individual papers attached in the results section.

2.1. The Mater-University of Queensland Study of Pregnancy (MUSP)

Data for the Australian arm of the PhD study (the 'developed country' arm) were obtained from a multidisciplinary study that represents Australia's largest longitudinal study of women's reproductive life from pre-birth pregnancy, to 27 years post birth, that is MUSP. This longitudinal study began in 1978-79 with a number of pilot studies. Full data collection commenced in January, 1981. All recruited women gave birth to at least one child at the Mater Misericordiae Mothers' Hospital which is one of the two major obstetric units in Brisbane, Australia. The study prospectively collected data across the reproductive life course of a large group of 6753 mothers.

2.1.1. Participants

Pregnant women attending their first clinic visit (at approximately 18 weeks' gestation) at the Mater Hospital were invited to participate in the study which was run over the three years between January 1981 and December 1983 (Najman et al., 2005; Ware et al., 2006). These women were re-interviewed at 3 to 5 days after delivery and their obstetric records were collected. Additional interviews were conducted when the children were 6 months, 5 years, 14 years, 21 years, and 27 years of age.

In this study, the dataset of 6753 mothers met three criteria: one or more singleton/ multiple birth children discharged alive from the hospital, after the birth, and the child was not adopted prior to discharge. Only data from the mother's cohort were used in this thesis. For completeness, however, methodological details associated with the complete sample are reported here.

2.1.2. Phases of the MUSP project

In the first interview (first clinic visit) data were obtained on the respondent's demographics characteristics, socio-economic status, family structure, and health conditions including

mental health, lifestyle and behaviours during pregnancy (Phase I). Data collection was undertaken using a 103-item questionnaire administered to mothers between the 3rd and 5th postpartum day, and four obstetricians extracted some 200 details potentially relevant to child development problems such as birth weight and evidence of abnormalities at birth (Phase II). The mother's past medical history is regarded as Phase III of the data collection, while details of the birth constituted Phase IV. Subsequently, in Phase V, a 103-item mailed questionnaire was completed at six months after delivery (Najman et al., 2005; Ware et al., 2006).

Phase VI was conducted five years after the birth, at which time mothers completed a 227-item self-administered questionnaire which included separate sections for the child and for themselves. Both mothers and children were then contacted for further information at 14 years after birth. At Phase VII, mothers were again asked to provide information regarding their family as well as themselves. In addition, a 141-item questionnaire was administered to the adolescents. For the 21-year follow-up (Phase VIII), comprehensive information was reported separately by the young adults and their mothers in relation to health, lifestyle, behavior and social factors.

In the Phase IX at 27-year postpartum, comprehensive information was gathered from young adults and their mothers in relation to their socio-demographic characterictics, financial situation, social history, reproductive health, general health, lifestyle, gambling behavior, exercise, sleep quality, relationship, well-being, mental health, food frequency and health related quality of life. For all the phases, ethical clearance was obtained from the University of Queensland and the Mater Hospital ethics committees.

2.1.3. Exposures and outcomes

An exposure may represent an actual exposure (e.g. depression or anxiety), a behavior (where one works or socializes), or an individual attribute (e.g. age, sex, race) (BES, 2013). The outcome refers to the disease state, event, behavior, or condition associated with health that is under investigation. An outcome in clinical or social research refers to the presence or absence of the health-related state or event (e.g. diabetes) (BES, 2013). In order to support a causal relationship between exposure and possible outcome, measuring intensity and duration of exposure is necessary. The validity of the study also depends on the quality of exposure and outcome measurements (BES, 2013). Assessment of exposures and outcome status can be performed using standard

diagnostic criteria as well as self-report scales. Unlike self-report scales, standard diagnostic criteria ensure consistent diagnosis of cases, regardless of where or when they were identified and who diagnosed the case. In this study, symptoms of depression, anxiety and diabetes were used as both exposures as well as outcomes to measure bidirectional associations.

2.1.4. Bidirectional association model

The bidirectional associations between depression and diabetes as well as anxiety and diabetes were examined (**Figure 2.1**):

1. Depression and anxiety symptoms as *risk factors* for diabetes.
2. Diabetes as a *risk factor* for depression and anxiety disorders.

2.1.4.1. Depression and anxiety symptoms as *risk factors* for diabetes

In this part of this study the association between changes in anxiety and depression symptoms and the risk of diabetes were examined for a cohort of women who were followed up at intervals over a 21-year period postpartum; it takes into account a range of potential confounding factors. Specifically, the association between changes in depression and anxiety symptoms measured between 5-year and 14-year follow-up while the risk of diabetes was measured at 21-year follow-up.

2.1.4.1.1. Measurement of depression and anxiety symptoms

Depression was assessed in all phases of the MUSP study using the Delusions Symptoms-States Inventory: State of Anxiety and Depression (DSSI/sAD) (Najman et al., 2005). The exposure was depression and anxiety symptoms measured at 5-years and 14-years after delivery; symptoms were assessed using the 14-item depression and anxiety subscales from the DSSI/sAD (Bedford and Foulds, 1978; Bedford and Deary, 1999; Najman et al., 2000).

One of the advantages of using the DSSI instrument is that it covers both depression and anxiety. The overall DSSI scale comprises 14 questions covering depression and anxiety. The DSSI anxiety subscale consists of seven items constructed to include the primary features of anxiety disorder. The seven items each for depression and anxiety, are scored using 5-point response options (1 = never, rarely, some of the time, most of the time, or 5 = all the time), these scores (reverse) are then summed (score range: 10 (all the time) – 50 (never)); the lower the score, the more depressed or anxious the person. Women are

classified as anxious or depressed when they score 4 or more, and as non-anxious or non-depressed when they score 4 or less out of a maximum 7 score (Bedford and Foulds, 1978).

The validity of the personal disturbance scale (DSSI/sAD) among women with diabetes using Mater-University of Queensland Study of Pregnancy (MUSP) cohort data was examined. Exploratory factor analysis and fit indices confirmed the hypothesized two-factor model of DSSI/sAD. As expected, the scale had poor discriminant validity and good convergent validity. DSSI/sAD demonstrated strong relationships with equivalent SF-36 & CES-D scales. DSSI/sAD was highly specific with low sensitivity, compared with the DSM IV.

2.1.4.1.2. Measurement of diabetes at 21-year follow-up

During data collection, the presence of diabetes was confirmed with a question to participants asking whether a health care professional had informed them that they have diabetes. Although pre-partum diabetes and gestational diabetes mellitus were identified as pre-pregnancy complications and an adverse pregnancy outcome in MUSP, the presence of postpartum diabetes was not determined among the participants in the initial phases of MUSP. The question about diabetes was first included in 21-year postpartum follow-up and it was retained in the 27-year follow-up questionnaire. In both phases, self-administered questionnaires were used to gather this information. Subsequently, each woman was asked, “Have you EVER been told by a doctor that you have diabetes (high blood sugars)?” A positive response to this question indicated that the woman had incident diabetes at some time during the 21 or 27-years after the index pregnancy.

A limitation in the MUSP study is that self-report diabetes was not confirmed against any standard diagnostic criteria. Another limitation is that women who were cared for at Mater hospital (MUSP study site) were not screened routinely for gestational diabetes at the time of recruitment (Callaway et al., 2007). However, it is beyond the scope of the present study, to address these limitations.

2.1.4.1.3. Adjustment for potential confounding

The conventional approaches of adjusting for potential confounders may introduce conditional associations and bias (Shrier et al., 2008). Directed Acyclic Graphs (DAGs) have been used in epidemiology to represent causal relations among variables, and they

have been used extensively to determine which variables are necessary to control for confounders (Vanderweele and Robins, 2007). In DAGs, possible confounders eventually resulted in the deletion of all the direct causal pathways between the exposure of interest (for example, depression or anxiety) and the outcome (for example, diabetes), and between the covariates and the outcome (Pearl, 2000). Potential confounding factors for each of the transition models (changes in depression and anxiety symptoms) were included from the most recent or relevant previous phase of MUSP; possible confounders in the current study were selected using *priori* knowledge as well as DAGs.

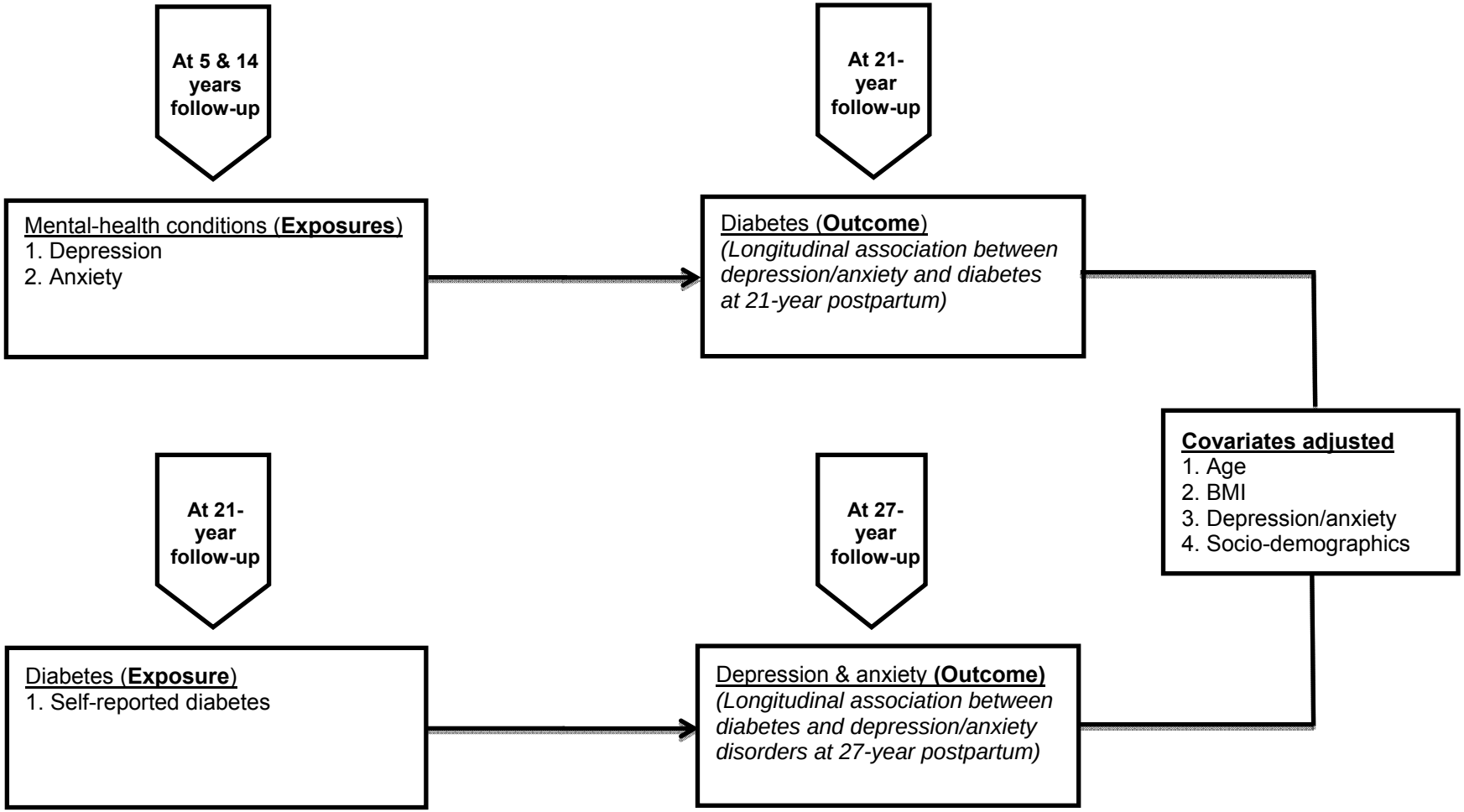

Figure 2.1: Bidirectional association models – using Mater-University Study of Pregnany data

2.1.4.1.4. Analytical strategy

To test the hypothesis assessing the association between symptoms of depression and anxiety and the risk of diabetes, the observed proportion of women who reported a change in depression and anxiety symptoms between subsequent phases of the study, that is the 5-year and 14-year follow-ups was estimated. In this study, diabetes was the dependent variable at 21-years, and a change in depression and anxiety symptoms (i.e. transitions) from the previous two phases (at 5 and 14-year follow-ups), was the main predictor. The possible transitions that could occur during the period from the 5-year follow-up (FU) (origin state) to the 14-year FU (destination state) were classified into four categories, based on a cut-off of 4 or more symptoms (Mamun et al., 2009). The details are included in the respective manuscripts (*Chapter 6 and 7*). To assess the robustness of the analytical strategy, sensitivity analyses were also performed using the transitions during the post-delivery period of 3 to 5 days (origin state) to the 6-month FU (destination state). They were classified into the same four categories used in the main analysis.

2.1.4.2. Diabetes as a *risk factor* for depression and anxiety disorders

I examined the association between diabetes at the 21-year follow-up and the risk of depression and anxiety disorders at the 27-year follow-up, using longitudinal data on women collected via the Composite International Diagnostic Interview (CIDI). Previous studies investigating the association between diabetes and depression and/ or anxiety are not conclusive and have several deficiencies, such as cross-sectional study design (Mezuk et al., 2008; Smith et al., 2013). Despite the fact that the literature suggests anxiety is an important comorbid condition associated with diabetes, only one review published in 2013 examined the link between diabetes and the risk of anxiety (Smith et al., 2013).

To examine diabetes as a risk factor for depression and anxiety disorders, a cohort of 6753 women was used. It was considered important to exclude women who had experienced previous cases of anxiety, depression or comorbid depression and anxiety at the 21-year follow-up, and thus data from a total of 6472 women were included in the final analysis.

2.1.4.2.1. Measurement of exposure – diabetes mellitus at 21-years

The exposure in the analyses was information regarding self-reported diabetes mellitus in 21 years after the index pregnancy; data in this phase were collected using a self-administered questionnaire as described above.

2.1.4.2.2. Measurement of outcomes – depressive and anxiety disorders at 27-year

At the 27-year follow-up, data on mood disorders were extracted from a computerized structured interview of depressive and anxiety symptoms using the World Health Organization-World Mental Health-Composite International Diagnostic Interview-CAPI Modularization Program (WHO WMH-CIDI CAPI: Version: 21.1.3) (WHO, 2004). This instrument assesses current and lifetime prevalence of mental health disorders according to Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) diagnoses. The CIDI summary outcomes (any depressive or anxiety disorder) were calculated as a positive diagnosis across a range of DSM IV diagnoses. Three categories were used to define duration of (any) depressive or anxiety disorders: lifetime, 12-month and 30-day periods.

2.1.5. Analyses of data

The aim of the present investigation was to examine diabetes as a risk factor for, or consequence of, depression and anxiety in women. The data were analyzed using the IBM Statistical Package for Social Sciences (SPSS) ® version 22 and STATA IC ® version 12, with a significance level of ≤ 0.05. Descriptive statistics were initially used to examine the percentages, frequencies, means and standard deviations. Cross-tabulation, Chi-Square test, and Student *t* test were used to examine the pattern of prevalence of diabetes, and prevalence of symptoms of depression and anxiety in women with diabetes. They were also used to compare the characteristics of those women who did and did not provide information about diabetes or depressive/anxiety disorders.

In the next step, multiple logistic regression models were developed to test the association between symptoms of depression and anxiety and the subsequent development of diabetes mellitus, after adjustment for other potential confounding variables. Detailed information about the construction of the prediction model for each specific dependent variable is given the Methods sections of the relevant manuscripts, which have been incorporated into Chapters 6 to 8 of this thesis The following paragraphs provide general information about the statistical analyses used in this study and describe how the issue of loss to follow-up was addressed using multiple imputations to assess the validity and generalizability of the findings of the present study.

2.1.6. Prediction models

The prediction of diabetes, depression and anxiety incidence primarily employed logistic regression and odds ratios (ORs). A direct causal relationship among the variables used in

the analyses is not claimed; rather, the aim has been to establish whether symptoms of depression and anxiety in postpartum phase tend to be independently associated with increased risk of diabetes onset and *vice versa*.

In most instances, logistic regression was applied when the dependent variable comprised a dichotomous outcome, such as the presence or absence of diabetes at 21-year follow-up. In order to illustrate the model, let Y denote the measurement of a dichotomous outcome, presence or absence of diabetes at 21-year or presence or absence of depressive and anxiety disorders at 27-year. Then Y = 0 if the woman was *not* associated with diabetes/depression/anxiety and Y = 1 if the woman was associated with diabetes/depression/anxiety. Values x_1 through x_n symbolize additional explanatory variables, which may be either dichotomous or continuous. The unified model for a dichotomous variable is:

$$\text{Logit } (Y) = b_0 + b_1x_1 + b_2x_2 + \ldots\ldots\ b_nx_n$$

Logistic regression generates results as an odds ratio (95% confidence interval) for each predictor. For instance, all other characteristics being equal, an odds ratio would estimate how much more or less likely a man would be to become a diabetic or depressed or anxious, compared with a woman (Leyland and Goldstein, 2001). In a rare condition (prevalence < 10%), the odds ratio approximates the relative risk, such as the proportion of women with diabetes, in this study.

In the present study, the prediction models are based on odds ratios (95% confidence intervals) obtained from logistic regression. Simple binomial logistic regression was used when the outcome was dichotomous (diabetes: yes/no). When the outcome comprised three or more values (glycemic control: normal, mild, moderate, poor), the analyses were carried out using multinomial logistic regression (Leyland and Goldstein, 2001).

2.1.7. Multivariate adjusted prediction models

In order to achieve the most parsimonious model that correctly predicts the category of outcome for individual cases, a model should be created that includes all independent variables that appear to be associated with the outcome variable (Field, 2005). A stepwise regression process was used to enter variables into the model, in the order chosen by the investigator or by the logistic regression software after each coefficient is added or

deleted. To examine the model diagnostics, likelihood-ratio tests (Cohen, 2003; Dupont, 2002) were used to find the model by which the outcome variable is best predicted by a set of several independent variables.

2.1.8. Investigation of missing data

Loss to follow-up or attrition over the follow-up phases from the original cohort has been a common feature in almost all population-based cohort studies, and was so in MUSP. While the cohort began with 6753 mothers and their offspring, at the 21-year follow-up only 54% provided information regarding the diagnosis of diabetes mellitus. At 27-year follow-up, the number further decreased to 3330 for those who provided information about depressive and anxiety disorders. Missing data due to attrition or loss to follow-up and item non-response inevitably will lead to lower study power and less precise, possibly biased, estimates (Criqui, 1979; Miettinen, 1985).

Little and Rubin defined the process for dealing with missing values, or non-response (Little and Rubin, 1987); non-response or missingness is of three types. The first one is defined as missing completely at random (MCAR) if the missingness is independent of both outcome and independent variables. The second one is missing at random (MAR) if, condition on the independent variable, the missingness is independent of the outcome variable. ‘Missing at random’ means that the probability of the data being missing may depend on observed values (Schafer, 1999). Finally, missing not at random (MNAR) is the most serious type as the non-response is associated with the outcome (Little and Rubin, 1987).

In the current study, there are two possible effects associated with MNAR; if loss to follow-up was greater in those exposed to depression or anxiety measured at 5-year and 14-year and the outcome of interest was truly more common among those lost, the findings would underestimate the true association. The apparent OR would be less than estimated for the complete cohort if the follow-up in the exposed group was only 50% while that in the unexposed group was 100%. On the other hand, if those who developed the outcome of interest, i.e. development of diabetes, were less likely to drop out of subsequent follow-ups than individuals who did not, then the risk would have been overestimated.

Complementary tests were conducted to examine the possible effects of loss to follow-up on the validity of the results. These tests were conducted to assess the association

between each exposure variable at the early phases (depression and anxiety at 5-year and 14-year) of follow-up with losses to the sample at the 21-year follow-up. Analyses show that those excluded because of missing data or loss to follow-up were more likely to be young when they gave birth (aged between 13 and 19 years), to have one change in marital status, to have been consistently poor, to have not completed secondary schooling, to have a low BMI, and to be depressed or anxious.

2.1.8.1. Multiple imputations

Multiple imputations were carried out to adjust for missing data (Sterne et al., 2009). Results of the analyses of the complete datasets were combined using Rubin's rules (described above) and performed in Stata IC version 12.0 (Stata Corporation, College Station, TX, USA). The relationship between 'missingness' (yes *vs* no) and the predictor variables was assessed using logistic regression. In general, it is recommended to impute more than the percentage of missing data (Simpson et al., 2007). An imputation model was devised using the recommendations of Van Buuren et al. (van Buuren et al., 1999). The model included all of the predictor variables excluding the outcome. The data on covariates were assumed to be 'missing at random'.

The imputation model was used to generate sets of imputed values for the missing data points thus creating complete datasets. Data were imputed from the posterior predictive distribution of the missing data given the observed data. The posterior predictive distribution of the data was assumed to be multivariate normal, so that all of the predictor variables (categorical and continuous) were assumed to be normally distributed (Simpson et al., 2007). The results from the regression modelling of the different datasets were combined using the rules given by Rubin to produce a multiple imputation estimate (Rubin, 1987). Methods used in the Malaysian (developing country) arm of the study are described in the following section.

2.2. The Malaysian Case-Control Study

2.2.1. Study design and participants

For the 'developing country' arm of the PhD, I conducted a case-control study in Malaysia among women aged 35 or older, with and without known Type 2 Diabetes Mellitus (T2DM). The case-control study involved women with diabetes matched to women without T2DM in the same age range. A frequency matching technique was used to match

participants on ‘cell’ instead of ‘individual’ basis. The frequency matching was conducted using two conditions: presence or absence of diabetes and aged 35 years or more. The frequency matching was completed in two steps. In the first step, only women aged ≥ 35 who attended outpatient clinics for the management of T2DM and who had a known diagnosis of T2DM were selected (cases). In the second step, cases were matched with controls; these were women were aged ≥ 35 years, with no known diagnosis of T2DM. The control participants were healthy friends or unrelated family members (no blood relation) of women with type 2 diabetes.

Patients belonging to any ethnic group and who had Malaysian citizenship were included in this study. Women diagnosed with diabetes before the pregnancy, gestational diabetes mellitus that was diagnosed during the pregnancy, and T1DM were excluded from analysis.

2.2.2. Development of study questionnaire

A questionnaire for self-administration in Malaysia consisting of 111 questions was developed for this study. The questions covered factors such as: background (9 questions), medical and pregnancy history (7 questions), lifestyle (11 questions), reproductive health (33 questions), mental health (27 questions), sleep quality (9 questions), quality of life (10 questions) and physical ad clinical measurements (5 quetions). Of the 111 questions, 86 (78%) questions were used from MUSP questionnaire that was administered at 27-year follow-up and were used without any changes to elicit information about quality of life, mental health, sleep quality; 20 (18%) questions were desgined to explore socio-demographic factors and were MUSP questions that had been modified for the Malaysian context; and 5 (4%) were new questions that explored physical and clinical parameters.

The English version of the complete questionnaire, designed by the candidate and used for primary data collection in Malaysia (March 2012 to January 2013), and can be found at the end of this thesis as Appendix 5A. It is important to mention that only questions relevant to the PhD study objectives were analyzed and included in the findings; these included questions which related to socio-demographics, presence or absence of chronic conditions (e.g. diabetes) and mental health. The specific questionnaire used to identify symptoms of depression and anxiety, was validated separately and the findings are incorporated in Chapter 5 of this thesis.

2.2.3. Validation of the study questionnaire

2.2.3.1. Content validation

The questionnaire developed for use in Malaysia was written in English as this was the language used in the MUSP study questionnaire and was the version subjected to content validation. Panellists for content validation were selected according to the *Standards for Educational and Psychological Testing*, which emphasizes the necessity of relevant training, experience, and qualifications in selecting content experts to review instruments (AERA, 2002). A widely accepted method of measuring content validity developed by Lawshe was used to assess how essential each question is (Lawshe, 1975). Ratings for each question were entered into a spreadsheet, and the content validity ratio (CVR) was calculated for each question based on the formula developed by Lawsche:

$$CVR = (n_e - N / 2) / (N / 2)$$

Where: n_e= number of panellists (jurors) indicating "essential" and N= total number of panellists. This formula yields values which range from +1 to -1; positive values indicate that at least half the panelists rated the item as essential. The overall mean content validation index of the study questionnaire was found to be +0.81.

2.2.3.2. Face validation

For face validity, questionnaires were then distributed to individuals who were not expert in testing instrument design and construction and their feedback and comments were incorporated into the final version of questionnaire.

2.2.4. Translation of questionnaire

Translation of the questionnaire was conceptual as stipulated by the WHO (PTAI, 2012). The validated English version of the questionnaire was translated into Bahasa Malaysia (the official language of Malaysia) using a forward-back translation process performed by two native speakers. The Bahasa Malaysia version was then again translated into English by two English language teachers. The reason for translating the questionnaire into Bahasa Malaysia was that the majority of Malaysian citizens can speak and understand Bahasa Malaysia. Reasons for not translating the questionnaire into Chinese or Tamil languages included a scarcity of resources, lack of funding, and trained translators.

2.2.5. Feasibility, reliability and piloting of the instruments

In the final step, the questionnaire (English and Bahasa Malaysia version) was pre-tested and piloted on 30 women with and 30 women without T2DM, the target population. The feasibility and reliability of the instruments in the questionnaires were investigated. The Cronbach alpha values for the main instruments that were incorporated into the questionnaire (DSSI, CES-D-10 and SF-12) were found to be more than 0.70 for both the English and the Bahasa Malaysia versions which show that items included in the questionnaire were internally consistent.

2.2.6. Sampling sites

There are thirteen states and three federal territories that constitute the total Malaysian territory, which is further divided into 2 areas: West and East Malaysia. West Malaysia is mainly populated by three ethnic groups namely, Malay, Chinese and Indian. Indigenous inhabitants such as Iban, Melanau, and Bedayu are found mainly in East Malaysia, which is comprised of the states Sabah and Sarawak. Due to budget and time constraints, sampling for this PhD was restricted to West Malaysia. Three Medication Therapy Adherence Clinics (MTACs), two hospitals (Hospital Putrajaya and Hospital Tuanku Jaa'far Seremban) and one Health Clinic (Health Clinic, Seremban) in West Malaysia were selected as primary sampling sites.

Non probability-based design was used to select the sampling sites. Recruitment was initially started in Hospital Putrajaya where the majority of the patients were of Malay origin. Therefore, to select a sample that included all three ethnic groups, sampling was extended to the Seremban region to include patients of Chinese and Indian ethnicity.

2.2.7. Sample size and sampling procedure

Sample size was calculated based on three factors; prevalence of diabetes in women (p), margin of error (2.5%) and 95% confidence interval (Z-value). The prevalence of diabetes in Malaysian women in 2012 was extrapolated and estimated as 11.82% (Shaw et al., 2010); this estimation was made based on the prevalence of diabetes in Malaysian women in 2010 and 2030, i.e. 11.6% and 13.8%, respectively (Shaw et al., 2010). Assuming a 2.5% margin of error, a 95% confidence interval and using the extrapolated prevalence in 2012, a sample size of 640 was estimated (See Appendix 6A for details). This sample size was estimated for women with diabetes (i.e. cases). To match the frequency of cases in

same age range, 640 controls were selected. Therefore, a total of 1280 women were approached to participate in this case-control study.

To achieve the required sample size, a systematic random sampling technique was applied. In this sampling process, every k^{th} was selected where k = N/n. The sampling process started with a randomly chosen woman, from 1 to k. The patient list provided by clinics at the start of the study had about 1310 women with diabetes. The k was calculated as:

N = 1310 students and we want to sample n = 640 patients.
k = N/n = 1310/640 = 2.

The subsequent sampling of every second patient from the target population on the MTAC occurred, and the women were systematically invited to participate. The example of sampling process is presented below.

MRN	Name	Age	Sampling
131	Mrs. XXX	41	-
156	Miss. YYY	48	Selected
165	Mrs. KKK	39	-
182	Miss. GGG	52	Selected

Note: MRN = Medical Record Number

Those who meet the inclusion criteria then proceeded to complete the questionnaire under the guidance of research assistants. The research assistants had been trained and briefed by the PhD candidate about the data collection process, with clear instructions not to lead the respondents in their answers but to assist when clarification was required. Data collection from the three sampling sites started in March 2012 and was completed in January 2013. After the data were collected, I merged and analyzed the data as described below.

2.2.8. Ethics approval

The study was conducted according to the principles expressed in the Declaration of Helsinki, and was approved by the Ethics Committee at the School of Pharmacy, The University of Queensland (Reg. No. 2011/14) and International Medical University Research and Ethics Committee (Project ID. No. B01/09-Res (04)2012). The study was

also registered with the National Medical Research Registry (NMRR), Ministry of Health Malaysia (Research ID: 12444).

2.2.9. Measurement of T2DM

Data on T2DM were collected through the self-administered questionnaire, where women were asked “Have you EVER been told by a doctor that you have diabetes (high blood sugars)?” with response options “yes” or “no.” Subjects were categorized as having T2DM if they had been told by a physician they had diabetes. The presence of T2DM in the selected clinics was identified according to two criteria: A fasting plasma glucose (FPG) greater than or equal to 7.0 mmol/l, and random plasma glucose (RPG) greater than or equal to 11.1 mmol/l. Women diagnosed with type 1 diabetes were excluded. Information was confirmed by accessing patients’ medical records.

2.2.10. Measurement of depression and anxiety

2.2.10.1. Delusions-Symptoms-States Inventory/ States of Anxiety & Depression

The information about the presence of depression and anxiety symptoms was measured using the Delusions-Symptoms-States Inventory/States of Anxiety and Depression (DSSI/sAD). The DSSI/sAD contains 14 symptoms; 7 for depression and 7 for anxiety. Participants in this study were classified as anxious or depressed when they scored 4 or more and as non-anxious or non-depressed when they scored 4 or less, out of a maximum score of 7.

2.2.10.2. The Center for Epidemiological Studies Depression (CES-10)

The information about the presence of depression was also measured using a brief self-report screening tool, Center for Epidemiological Studies Depression 10 Scale (CES-D 10) (Radloff, 1978). It has been shown to have reliability and validity comparable to the standard 20-item CES-D instrument and is considered a good instrument for screening depression in older adults (Irwin et al., 1999), and patients with T2DM (Swenson et al., 2008). The CES-D 10 uses a zero-to-three response scale, with total symptom severity scores ranging from 0 (no depression) to 30 (severe depression) (Brockington, 1996). Participants in this study were categorized as depressed if they scored 11 or more on the CES-D 10 scale. The CESD is one of the most commonly used scales in people with diabetes and has been validated to use among people with diabetes (Roy et al., 2012).

The reliability of the CES-D was investigated and the Cronbach alpha value was found to be 0.78.

2.2.11. Measurement of covariates

The potential confounders and risk factors were identified on the basis of their association with outcomes and on the basis of *a priori* knowledge (Mezuk et al., 2008; Smith et al., 2013). The covariates measured in this part of the study included: body mass index (BMI) (kg/m^2), comorbidities or medical conditions other than T2DM, and socio-demographic information (age, ethnicity, education, monthly, marital status). Menopausal status was identified as pre-menopausal, peri-menopausal or post-menopausal. Menopause-specific QoL (MENQOL) was measured using a validated MENQOL instrument (Hasan et al., 2013).

2.2.12. Analyses of data

The aim of this part of the investigation was to examine the association between depression and diabetes, anxiety and diabetes in Malaysian women. I analyzed the data using the IBM Statistical Package for Social Sciences (SPSS) ® version 22 and STATA IC ® version 12, with a significance level of ≤ 0.05. Descriptive statistics were initially used to examine the percentages, frequencies, means and standard deviations. Cross-tabulation, Chi-Square test, and Student *t* test were used to examine the pattern of prevalence of diabetes, and prevalence of symptoms of depression and anxiety in women with diabetes.

In the next step, multiple logistic regression models were developed to test the association between symptoms of depression and anxiety, and diabetes mellitus, after adjustment for other potential confounding variables. Detailed information about the construction of the model for each specific dependent variable is given the Methods section of the relevant manuscripts and which have been incorporated into the Results section of this thesis (*Chapters 9 & 10*). The following paragraphs provide general information about the statistical analyses used in this part of the study.

2.2.13. Association models

The prediction of diabetes, depression and anxiety incidence primarily employed logistic regression and odds ratios (ORs). A direct causal relationship among the variables used in the analyses was not claimed; rather, the aim was to establish whether symptoms of depression and anxiety tend to be independently associated with diabetes.

In this investigation, the models were based on odds ratios (95% confidence intervals) obtained from logistic regression. Simple binomial logistic regression was used when the outcome was dichotomous (diabetes: yes/no). When the outcome comprised three or more values (glycemic control: normal, mild, moderate, poor), the analyses were carried out using multinomial logistic regression. The objective of logistic regression was to define the most parsimonious model that correctly predicts the category of outcome for individual cases. Multiple logistic regressions were then used to further assess the relationship, after adjustment for other potential confounding variables. A series of models are presented, that were adjusted the potential confounders so that readers can see the effect of factors that may have confounded this association.

RESULTS

PART 1

SYSTEMATIC REVIEW AND META-ANALYSES

CHAPTER 3

The global distribution of comorbid depression and anxiety in people with diabetes: risk-adjusted estimates

The first objective of this thesis was to calculate the risk-adjusted global prevalence estimates of comorbid depression and anxiety in people with diabetes mellitus. The global prevalence estimates via risk adjustment were calculated; the methods, results and findings were compiled into a manuscript that has been revised and resubmitted for publication, and forms the basis for this chapter. The formal citation for the resubmitted work:

1. **Hasan, S.S.,** Clavarino, A.M., Mamun, A.A., Doi, S.A.R., Kairuz, T. The global distribution of comorbid depression and anxiety in people with diabetes: risk-adjusted estimates. *J Epidemiol* [Revised & Resubmitted].

The global distribution of comorbid depression and anxiety in people with diabetes mellitus: risk-adjusted estimates

Abstract

Background: Previous reports suffer from the problem that they simply pooled data using aggregate means or standard meta-analytic method. The aim of the current study was to re-estimate the point prevalence of comorbid depression and anxiety in people with diabetes.

Methods: The estimates were calculated using recently introduced Directly Standardized Effect Estimate (DSE) method, which gives corrected risk-adjusted estimates for the population of interests. Reported are global and regional burden of prevalence, presented as risk-adjusted prevalence estimates with 95% confidence intervals (CI).

Results: Globally, the burden of comorbid depression was higher than the burden of anxiety (23.36% vs. 17.58%) symptoms and/or disorder in people with diabetes. There was a higher burden of comorbid depression in people living in developing regions (26.32%), in women (15.41%) and when assessed by self-report scales (22.66%). The burden of anxiety was higher in developed regions in people with T2DM (20.15%) and when assessed by self-report scales (20.75%). No statistically significant differences were seen due to gross heterogeneity across countries.

Conclusions: There are wide-ranging differences in studies in developed and developing regions, regarding the burden of comorbid depression and of anxiety among people with diabetes and both conditions affect approximately a fifth of the diabetic population.

Keywords: Prevalence, depression, anxiety, diabetes, comorbid

INTRODUCTION

Worldwide estimates of prevalence of depression and anxiety among people with diabetes seem to vary by diabetes type and where the study was conducted, including whether countries were developed or developing.[1-3] These two conditions are mental health-related co-morbidities in people with diabetes,[4] and their prevalence has been summarised in a number of systematic reviews.[5-8] A meta-analysis published in 2001 reported that 11% of patients with diabetes had comorbid major depressive disorder (MDD) and 31% experienced significant depressive symptoms.[6] Another meta-analysis published in 2006, reported that the prevalence of clinical depression was significantly higher among patients with diabetes (17.6%) compared to those without diabetes (9.8%).[5]

Both studies reported that the prevalence of depression in women with diabetes was double that of men with diabetes; they also estimated that the prevalence in people with diabetes was nearly twice that of people without diabetes.[5,6] The only meta-analysis on prevalence of anxiety was published in 2002 by Grigsby *et al.,* who reported that generalized anxiety disorder (GAD) was present in 14% of patients with diabetes; however, elevated symptoms of anxiety were found in 40% of patients with diabetes who had participated in clinical studies.[7]

These previous reports suffer from the problem that they simply pooled data using aggregate means or standard meta-analytic methods,[5-7] which are inappropriate given that we are not seeking a common underlying estimate and therefore this approach could lead to biased prevalence estimates. What is actually more meaningful is a standardized rate and the directly standardized rate (DSR) is one of the most commonly used methods of standardization in epidemiologic studies,[9-11] but its use is limited to rates. Doi and colleagues recently introduced a directly standardized effect estimate (DSE) which can be used to standardize any effect size against the size of population at risk.[9] The aim of the current study was to re-estimate the point prevalence of comorbid depression and anxiety in people with diabetes using the DSE method which gives corrected risk adjusted estimates for the population of interests.[9] We also stratified the estimates by type of region (developed vs. developing), type of diabetes (T1DM vs. T2DM), type of measurement (self-report vs. standard criteria), and gender (males vs. females).

METHODS

The databases PubMed, EMBASE, and PSYCINFO were systematically searched to identify relevant studies published between 2000 and 2014. The reason was to include more articles. Additional articles were sourced from the reference lists of relevant review articles and original research studies. Keywords included original terms and synonyms related to diabetes, depression, and anxiety, and critical review were conducted by the principal investigator. The search strategy involved using the explode command with a search under the MeSH terms, for example 'depression/ anxiety', 'depressive/anxiety disorder', 'major depressive disorder' and 'dysthymic disorder' combined with 'diabetes mellitus' or 'type 2 diabetes mellitus'. This was supplemented with a keyword search of the terms 'depression/ anxiety', 'depressive/anxiety disorder', and 'depressive/ anxiety symptoms' combined using Boolean operators with 'diabetes' and 'diabetes mellitus'. We categorised the countries into developed and developing using the United Nation (UN) classification.[12] Developing world includes countries outside Europe, excluding Australia, Canada, Japan, New Zealand, USA, Singapore, Hong Kong and Taiwan.

Studies eligible for inclusion in this paper were required to assess diabetes mellitus type 1 (T1DM) and/ or type 2 (T2DM) in an adult population with no limit on age. Studies were included only if they had a sample size ≥ 30, were published or available in English, and if a current estimate of proportion with depression or anxiety was available either through self-reports diagnostic criteria. Included studies utilized both standard diagnostic criteria (SDC) as well as Self-report Scales (SRS) to measure these disorders and their symptoms. Standard criteria comprised structured or semi-structured interviews that were based on the Diagnostic and Statistical Manual of Mental Disorders (DSM). Elevated symptoms were assessed using self-report measures such as the Beck Depression Inventory, or the Hospital Anxiety and Depression Scale.

Selection criteria were not restricted to studies comparing occurrence of depression and/ or anxiety disorders or elevated symptoms (using a clinically significant cut-off) in people with diabetes. Because there were many controlled studies that reported prevalence of depression and anxiety in a non-diabetic group, prevalence in the latter studies was taken from the diabetic arm only. For studies that presented graded relationships such as low, medium, or

high depressive symptoms, only the prevalence for the highest category was selected. Studies where the type of diabetes, was not specified were included as T2DM because the ages of populations recruited suggested they would be predominantly subjects with T2DM.

The quality of the included studies was rated independently by the authors using criteria that include adequacy of the description of groups (type 1 and type 2 diabetes mellitus, diabetes mellitus, type 1 and type 2 diabetes mellitus with depression/ anxiety, control without depression/ anxiety and control with depression/ anxiety), control for confounding variables, and representativeness of sampling.

Statistical analysis

Each study was examined for information regarding events of comorbid depression and anxiety in people with diabetes. For studies that reported events separately by gender (males vs. females), type of assessment (self-report scales vs. standard diagnostic criteria), and type of diabetes (T1DM vs. T2DM), events were extracted and burden of depression and anxiety within these subgroups were calculated.

In addition to comorbid depression and anxiety disorders, data on depression and anxiety symptoms as well as specific anxiety disorders were extracted (GAD, panic disorder, phobias, and PTSD).

The country-specific prevalence of comorbid depression and anxiety was then used to pool the burden of these disorders in specific broad populations using the DSE approach.[9] This process involves adjustment for different sizes of populations at risk when computing summary measures across populations with diabetes. The population size at risk was the prevalence of diabetes across the different countries in the world obtained from the International Diabetes Federation.[13] Sensitivity analysis was also conducted by publication years in order to explore potential heterogeneity.

This approach is similar to direct standardization using the diabetes subpopulation size to adjust prevalence estimates such that larger populations contribute more to the pooled estimate for a region than smaller populations.[9] Thus the DSE is a type of direct standardization and can be calculated as:

$$\mathrm{DSE} = \frac{\sum\left(w_j^{\alpha} \times \mathrm{ES}_j\right)}{\sum w_j^{\alpha}}$$

where the weight is defined as described by Doi *et al*. (2014) and *j* indexes the sub-populations and ES_j is the subpopulation effect estimate of interest (the double

arcsine square root transformed proportion in this study with results back transformed for reporting).[9] This weighted averaging procedure does not use inverse variance weights and thus is not a meta-analysis.[9] For countries where more than one study was available, a single estimate was obtained through standard meta-analysis thus ensuring that each country provided a single estimate. This meta-analysis (within country) was conducted using an inverse variance quasi likelihood based alternative (IVhet) to the random effects model, also recently introduced by Doi and colleagues.[14] Data were analysed using STATA 12 (StataCorp LP, TX, USA), MetaXL 2.0 (EpiGear International Pty Ltd), and Microsoft Excel. Linear regression analysis was used to examine trend of prevalence between 2000 and 2013.

RESULTS

The 103 studies selected for review generated 103 datasets of which 71 examined prevalence of depression in people with diabetes, and 32 examined prevalence of anxiety in people with diabetes. Of the 71 studies assessing prevalence of depression in people with diabetes, 37 studies were from developed and 34 from developing countries. Similarly, to estimate the prevalence of anxiety in people with diabetes, a comprehensive review was conducted on 17 studies from developed and 15 studies from developing countries, as shown in (*see supplementary file*).

Burden of depression

Global: The burden of comorbid depression symptoms and/or disorder in people with diabetes was 23.36%, and was similar to the burden of symptoms only at 24.50% and the burden of any depressive disorder at 22.27% (Table 1).

Developed: The burden of comorbid depression in T1DM and T2DM was similar (13.47 vs 17.9%). Subgroups by standard diagnostic criteria (21.70%) or female gender (12.92%) made up a greater burden than self-reports and males respectively (Table 1). The sensitivity analysis by publication years presented a declining trend in the prevalence of depression where prevalence was lowest in recent years (2010 onwards).

Developing: Trends were similar to developed nations except that self-reports demonstrated exaggerated estimates of burden (Table 1). The prevalence was higher in recent years (2010 onwards) compared to prevalence between 2000 and 2009.

Burden of anxiety

Global: The burden of comorbid anxiety symptoms or disorder in people with

diabetes was lower than that of depression (17.58%), the burden of symptoms was 20.16% and the burden of any anxiety disorder was 7.11% (Table 1).

Developed: The burden of comorbid anxiety in people with T1DM (17.00%) was similar to T2DM (20.15%) (Table 1). Again, subgroups by female gender and self-reports made up a higher burden than male gender and standard criteria respectively (Table 1). The prevalence was highest between 2005 and 2009, and almost same in other two groups (2000-2004 and 2010-2014).

Developing: Again, self-reports were associated with a much higher burden of anxiety than standard criteria. The sensitivity analysis by publication years showed an increasing trend in the prevalence of anxiety where prevalence was highest in years between 2010 and 2014.

DISCUSSION

Our findings suggest that about one in eight people with diabetes living in developed region and one in four people with diabetes living in developing region are likely to experience depression symptoms. We also notice that depression and anxiety demonstrate a greater burden in females with diabetes and by self-reports. The burden of depression in people with diabetes tended to be lower in developed regions compared to developing regions. However, the reverse trend was seen for anxiety, being higher in developed regions than developing regions, in people with T2DM. Baxter and colleagues also suggested that anxiety was more common in general population living in high income regions compared to low or middle income regions.[15]

Unlike the previous reviews,[5-7] one of the strengths of this study is the use of standardised prevalence estimates. Previous estimates seem to have been biased upwards and for instance the reported 40% prevalence of comorbid anxiety in people with diabetes,[7] was revised downwards to 20% in this study (Table 2).

This study was based on self-report scales and thus their validity is of paramount importance. This does not seem to pose a problem because these scales used for screening for depression and anxiety have been shown to be reliable and valid,[16] and are often employed in epidemiological surveys such as those investigated in this study. However the diagnosis of diabetes is also important and again it has been shown in a meta-analysis that depression prevalence varies little across

assessments by either blood glucose measures, physician diagnosis or patient self-report.[17]

Regarding gender, our findings suggest that about one in eight females with diabetes living in developed region and one in six females with diabetes living in developing region are likely to report depression. This is consistent with the reports from earlier studies.[5,6] Similarly the gender difference in prevalence between females and males has been previously reported.[7] Even in the general population, women are more likely to experience mood disorders compared to men,[18] so this is not unexpected.

The overall burden of any anxiety disorder in people with diabetes was within the range of 12% to 21% reported for the general population.[19-21] Depression was however found to be higher (23%) compared to the general population (10%).[5] Finally prevalence of the GAD found in developed regions is comparable to the 3–4% observed in community studies in the US.[22,23] Since this burden is within or close to the range of estimates reported for the general population, there is a possibility that the burden can be explained by factors other than diabetes per se that share a relationship with both diabetes and depression or anxiety. For instance obesity has been shown to be associated with the former condition as well as with diabetes.[24,25]

Co-morbid depression and anxiety disorders and elevated symptoms in people with diabetes have been shown to be associated with increased diabetes complications,[1] worsened blood glucose levels,[26,27] and reduced quality of life.[28] This is of particular concern to developing regions where resources to address depression and anxiety are not adequate.[29] Indeed it has been reported that about 35% to 50% of serious cases in developed countries and about 76% to 85% in less-developed countries received no treatment in the 12 months preceding the interview.[30]

There were limited number of studies using standard criteria to diagnose depression and anxiety disorders. It is possible that some estimates and confidence intervals may be unstable because of the small number of subjects used in the calculations, and there is a concern about variability in the methods used to identify cases of depression and anxiety. Various self-report scales were used to measure depression and anxiety symptoms, and even in studies that employed the same scales, different threshold scores were used.

We had samples from variety of settings including primary, secondary and community settings. Patients with diabetes recruited from a secondary-care setting are likely to differ from those selected from primary-care and population settings with regard to disease stage and severity.[31] No statistically significant differences were seen due to gross heterogeneity across countries. Despite these limitations, this review presents significant findings regarding standardized prevalence of comorbid mental health conditions in people with diabetes living in different types of countries.

The association between depression and diabetes, and anxiety and diabetes may have deleterious impact on public and individual health. Once depression or anxiety develops, it can represent a barrier to glycaemic control.[32] Unfortunately, both conditions often remain unrecognized and thus untreated.[33] The burden of depression found in this study is higher in people with diabetes than in general population. However the burden of anxiety seems to be similar in diabetes as in the general population. The burden of comorbid depression and anxiety tended to be higher in people with diabetes living in developing region compared to developed region, and in females relative to males with diabetes. The above findings that people with diabetes are at higher risk of having depression and anxiety should alert clinicians to screen and treat anxiety and depression in people with diabetes.

Conflicts of interest

The authors declare they have no conflict of interest with respect to this research study and paper.

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Table 1: The standardized prevalence estimates of comorbid depression and anxiety in people with diabetes, by developed and developing countries

Region	Variable	Prevalence of depression (%)			Prevalence of anxiety (%)		
			95% CI			95% CI	
		ES	LCI	UCI	ES	LCI	UCI
Global	Symptoms or disorder	23.36	5.03	49.72	17.58	4.22	37.44
	Symptoms	24.50	5.27	51.86	20.16	5.17	41.68
	Any disorder	22.27	3.13	51.98	7.11	1.04	17.87
Developed	T2DM + T1DM	13.58	1.61	32.37	15.46	2.63	36.17
	T2DM	13.47	1.10	36.42	20.15	8.57	35.09
	T1DM	17.90	1.00	51.33	17.00	1.00	42.80
	Self-report	14.53	3.27	30.85	22.26	4.49	48.39
	Standard criteria	21.70	3.20	66.20	11.72	2.60	25.23
	Male	6.55	2.94	24.94	17.50	1.60	42.20
	Female	12.92	1.00	38.68	23.30	14.90	32.90
Developing	T2DM	26.32	1.00	64.93	18.19	2.15	44.90
	Self-report	30.79	9.64	57.51	19.24	2.72	45.71
	Standard criteria	2.20	2.00	52.20	2.50	0.70	5.10
	Male	10.30	0.20	28.80	8.27	1.27	41.16
	Female	17.90	4.70	36.30	15.21	1.20	50.99

Note: DSE = Directly Standardised Effect Estimate, DM = diabetes mellitus

Table 2: Comparison of comorbid depression and anxiety in people with diabetes in percentage, reported by different studies

Variables	Global Burden *(risk adjustment)*	Burden in developed regions *(risk adjustment)*	Burden in developing regions *(risk adjustment)*	Gavard et al., 1993 – *Burden (proportion)*	Anderson et al., 2001 – *Burden (aggregate mean)*	Grigsby et al., 2002 – *Burden (aggregate mean)*	Ali et al., 2006 – *Burden (Meta-analysis)*
Depressive symptoms	24.50	14.53	30.79	26.0	31.0	-	17.60
Any depressive disorder	22.27	21.70	2.20	-	-		-
Anxiety symptoms	20.16	22.26	19.24	-	-	39.60	-
Any anxiety disorder	7.11	11.72	2.50	-	-	14.00	-
GAD	8.76	5.41	12.10	-	-	13.50	-
PTSD	2.30	3.10	1.50	-	-	1.20	-
Any phobia	9.82	13.27	6.37	-	-	10.10	-

Note: GAD = Generalised Anxiety Disorder; PTSD = Post-Traumatic Stress Disorder

CHAPTER 4

Meta-analyses

The second objective of this thesis was to summarize existing literature and synthesize findings on the association between depression and diabetes, and anxiety and diabetes in the form of meta-analyses. As part of this chapter, four meta-analyses were completed. The major findings of these meta-analyses are presented in this chapter, which also includes an overview of statistical methods and a description of a novel approach, namely a quality-effects model. The full-text papers are attached at the end of the thesis (Appendices 4A to 4D). Three formal citations for the published work are:

Appendix 4A

1. **Hasan, S.S.,** Clavarino, A.M., Mamun, A.A., Kairuz, T. (2014). Incidence and risk of diabetes associated with depressive symptoms: evidence from longitudinal studies. *Diabetes Metab Syndr*, 8(2), 82-7.

Appendix 4B

2. **Hasan, S.S.,** Clavarino, A.M., Mamun, A.A., Kairuz, T. (2015). Incidence and risk of depression associated with diabetes in adults: evidence from longitudinal studies. *Community Ment Health J*, 51(2), 204-10.

Appendix 4C

3. **Hasan, S.S.,** Clavarino, A.M., Mamun, A.A., Doi, S.A.R., Kairuz, T. (2013). Population impact of depression either as a risk factor or consequence of T2DM in adults: a meta-analysis of longitudinal studies. *Asian J Psychiatr*, 6(6), 460-72.

One other manuscript included in this chapter has been revised and submitted for publication:

Appendix 4D

4. **Hasan, S.S.,** Clavarino, A.M., Mamun, A.A., Doi, S.A.R., Kairuz, T. Is anxiety a risk factor for the onset of T2DM mellitus in adults? Application of biased-adjusted method. *J Pharm Policy Pract* [Revised & Resubmitted].

4.1. Introduction

The findings of a recent meta-analysis suggest that people with diabetes are more likely to have anxiety disorders or elevated anxiety symptoms compared with people who do not have diabetes (Smith et al. 2013). However, there are no meta-analyses investigating anxiety symptoms as a risk factor for the development of diabetes. A bidirectional relationship between depression and diabetes has been demonstrated (Knol et al., 2006; Mezuk et al., 2008; Smith et al., 2013), although the findings of previous meta-analyses are far from conclusive because of several deficiencies. For example, absolute risk and incidence measures were not computed because most of the longitudinal studies neither presented data in a four-fold table form nor supplied adequate information to calculate cumulative incidence proportion (CIP) (i.e. raw numbers of incident diabetes by risk category). The overall aim of the four reviews was to examine the relationship between depression and diabetes and anxiety and diabetes by conducting bias-adjusted (quality effects) meta-analyses of longitudinal studies; this was performed in addition to use of the conventional random-effects model.

4.2. Methods

The following electronic databases were searched for each review: MEDLINE (1950 to July, 2013); EMBASE (1980 to July, 2013); CINAHL (1982 to July 2013); PsycINFO (1880 – July 2013). After identifying possible papers, titles and abstracts were screened to select relevant studies. The full texts of selected studies were then examined to determine whether the studies met the inclusion criteria. To locate additional relevant papers, the list of references in identified studies was also examined. When multiple publications from the same study population were available, only the most recent publication was included.

4.2.1. Eligibility criteria

Eligibility criteria were based on study type and population attributes. Regarding study type, the following were included: studies that investigated the association, comorbidity and/or coexisting prevalence of diabetes and depression or anxiety, and/or depressive or anxiety symptoms, in adults with diabetes mellitus. In the meta-analyses all studies that longitudinally examined the relationship between depression and diabetes, and anxiety and diabetes, were examined. Studies that focused on efficacy of treatment, comorbidities, or included other psychiatric conditions were excluded; studies that only examined gestational diabetes mellitus were also excluded.

4.2.2. Data abstraction

Data extracted from the studies included the name of the first author; publication year; study design; follow-up time in years; number of subjects in the analysis; gender and age of subjects; method of depression and anxiety assessment; method of diabetes assessment; binary point estimates and time-to-event (survival) analysis estimates with 95% CI (adjusted for the largest number of confounders); and number of confounders that were adjusted for in the analyses. The method of assessment of diabetes was either based on self-report or clinical diagnosis based on blood glucose levels or based on the diagnosis of diabetes from administrative data (drug consumption or hospitalization). Depression and anxiety were based either on a diagnosis by a psychiatrist (using Diagnosis and Statistical Manual (DSM) criteria) or the assessment of depressive or anxiety symptoms was by self-administered questionnaire.

4.2.3. Quality assessment

The studies were carefully weighed against a quality checklist to estimate a quality index that served to rank studies in terms of safe-guards against bias. Quality was assessed using a study-specific modification of the quality criteria of observational studies published by Shamliyan and colleagues (Shamliyan et al., 2010). The rank of studies by the univariate quality score was then used in the bias-adjustment model to discount studies at higher risk of bias. This method does not quantify bias and there is no imputation of effect sizes in relation to bias parameters.

4.2.4. Statistical analyses

Four-fold cells (2 X 2 tables; exposure yes/no *versus* outcome yes/no) were imputed for all binary point estimates using the reconstruction method proposed by Pietrantonj (Pietrantonj, 2006). Studies using time-to-event estimates (hazard ratios) were presented separately, as 2 x 2 table reconstruction was not possible for studies using time-to-event estimates. The four-fold cells were used to compute relative risk (RR), risk difference (RD) and CIP. Binary point estimates and time-to-event estimates were not combined as done by others (Knol et al., 2006; Mezuk et al., 2008). All odds ratios (ORs) were converted to Relative Risks (RRs) so that interpretation was uniform.

For studies that presented graded relationships such as low, medium, or high depressive or anxiety symptoms, only the estimate for the highest category was selected. Heterogeneity was evaluated using the Cochran's *Q* heterogeneity test (*Q* test) and a related metric, the I^2. A p-value of 0.10 was used as the cut-off point for heterogeneity;

therefore a related metric I^2 was also reported (I^2 = (Q – df) / Q × 100%). Pooled results were calculated via the statistical methods mentioned previously.

The first and second meta-analyses (*Appendices 4A and 4B*) examined depression as a risk factor for diabetes, and depression as a consequence of diabetes, using the random-effects (RE) model, a traditional method used for meta-analysis. However, this estimate is known to underestimate the statistical error and be overconfident in results (Doi, 2014). The other problem with the RE model is that it introduces other errors (Knol et al., 2006). In particular, the methodology in the RE model is flawed because, even in standard meta-analyses, there is a lack of interpretation of a RE summary (Alkhalaf et al., 2011). Peto referred to the use of RE model in meta-analyses as "wrong" because it answers a question that is "abstruse and uninteresting" (Peto, 1987). Moreover, use of the RE model requires strong assumptions that are unlikely to be valid in practice. It is, nevertheless, commonly used when heterogeneity between studies exists (Fleiss & Gross, 1991). Therefore, the third meta-analysis to examine the bidirectional relationship between depression and diabetes (*Appendix 4C*), was completed using a bias-adjusted approach with the quality-effects model.

In the meta-analysis to examine anxiety as a risk factor for diabetes, the asymmetry of the RR was investigated to determine the impact of any excess risk (e.g. anxiety) on diabetes incidence, and whether RR for the positive outcome (diabetes) differed substantially from the RR for its negative complement, that is, no-diabetes. In addition, the risk difference (RD) at two year follow-up was also computed by estimating the events based on the yearly incidence rate of the complementary outcome in each study. For studies which had a duration of more than two years, the yearly incidence rate (IR) was estimated as IR = -[ln (1 – CI_t)/t] where CI_t is the cumulative incidence proportion of events at the end of the study and *t* is the duration of follow-up (Suissa et al. 2012)**.** The two year cumulative incidence was then computed as $1 - e^{-IR(2)}$. From a pooled RD, the number needed to be exposed for one additional person to be harmed (NNEH) at two years was computed (reciprocal of pooled RD).

4.2.5. Sensitivity analyses

To assess the robustness of the meta-analyses, sensitivity analyses were performed by modifying the selection criteria and then examining the effect of the variously modified selection criteria on the pooled results. For example selection by self-report versus clinical assessment of depression and diabetes was examined, by regional differences (United

States versus non-United States), by length of follow-up period, and by number of confounders adjusted for in the analyses. The follow-up period was classified into <10 years and ≥10 years for depression predicting diabetes, and ≤5 years and >5 years for diabetes predicting depression. A funnel plot was used to examine the existence of publication bias through visual inspection for asymmetry and was considered asymmetrical if the intercept of Egger's regression line deviated from zero with $p < 0.10$. When the funnel plot was found to be asymmetric, additional analyses for publication bias were performed using the Duval and Tweedie non-parametric "Trim and Fill" method of accounting for missing studies in meta-analysis (Duval & Tweedie, 2000). All imputations were done assuming random error only. The meta-analysis was re-run to arrive at a pooled estimate that corrects somewhat for publication bias. All analyses were conducted using Microsoft Excel and MetaXL software version 2.0 (MetaXL, 2013).

4.3. Key findings

4.3.1. Meta-analysis 1: Depression as a *risk factor* for diabetes mellitus

The search yielded 850 unique abstracts from MEDLINE, 180 unique abstracts from EMBASE/CINAHL, and 230 from PsycINFO. After removal of duplication and applying the eligibility criteria, 96 relevant papers were examined for further consideration. Of these, 80 studies were excluded for reasons such as failing to remove prevalent cases of diabetes at baseline and insufficient data to generate pooled effect sizes. Studies that examined the association of antidepressant use and DM were also excluded (Egberts et al., 1997; Kivimaki et al., 2010; Knol et al., 2009). A total of 16 articles were then included in the review; these provided 16 datasets.

Three studies used the same sample (Arroyo et al., 2004; Pan et al., 2010; Saydah et al., 2003); however, two of these were retained: the most recent publication by Pan et al. (Pan et al., 2010), and Saydah et al. (Saydah et al., 2003) who had used a different risk estimate, (Hazards Ratios (HRs)), in the earlier (2003) publication; they were thus different analyses. However, for estimating CIP and IR, these studies were not included so as to avoid over-inflation of the sample. There were two studies published by Golden et al., in 2004 (Golden et al., 2004), and 2008 (Golden et al., 2008), where they had used the same sample, and only the most recent was retained. Among studies assessing depression predicting diabetes, four-fold cells were reconstructed and used to compute CIP from ORs (4 studies) or RR (4 studies). The data presented by Kumari et al. (Kumari et al., 2004) was insufficient to compute a four-fold cell and the study was excluded. The reconstructed

CIP was then used to compute RR and RD for meta-analysis while original effect sizes (HRs) were presented separately.

Nine studies reported their findings in the form of binary point estimates. However, only eight studies that presented complete data to formulate four-fold cell were used to calculate CIP and RR. Of these eight studies, six studies reported statistically significant associations; increasing risk of incident diabetes as a result of depression was present. A significant heterogeneity was present, with a pooled RR of 1.67 (95% CI: 1.30 – 2.15) (**Figure 4.3.1.1**) for studies examining depression as a risk factor of diabetes.

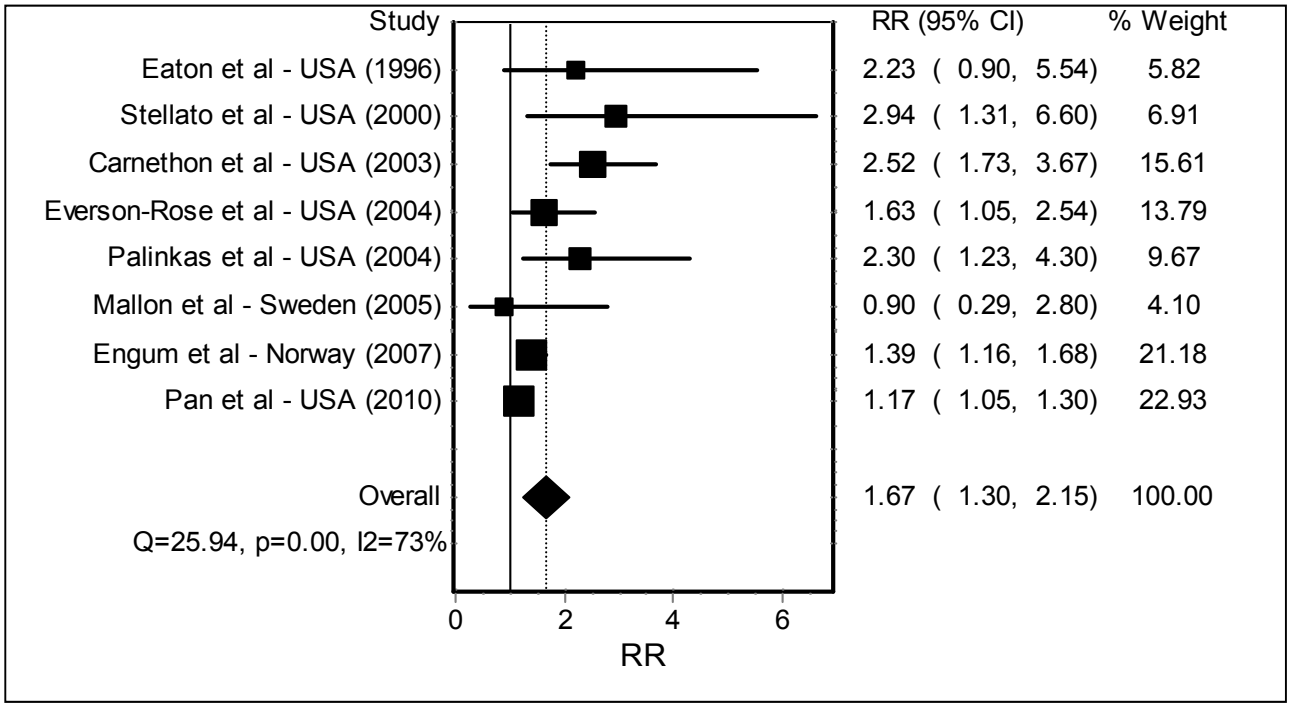

Figure 4.3.1.1: Random-effects forest plot showing the risk of diabetes for individual studies using self-report questionnaires, diagnostic criteria, and all studies combined; studies using reconstructed Relative Ratios. Bars and diamonds indicate 95% CIs. RR = Relative Risk

For eight studies that presented their findings in the form of hazard ratios, there were four studies in which the association was statistically significant and where increasing risk was evident. The pooled hazard ratio was 1.45 (95% CI: 1.12 – 1.87) and there was an evidence of heterogeneity (**Figure 4.3.1.2**).

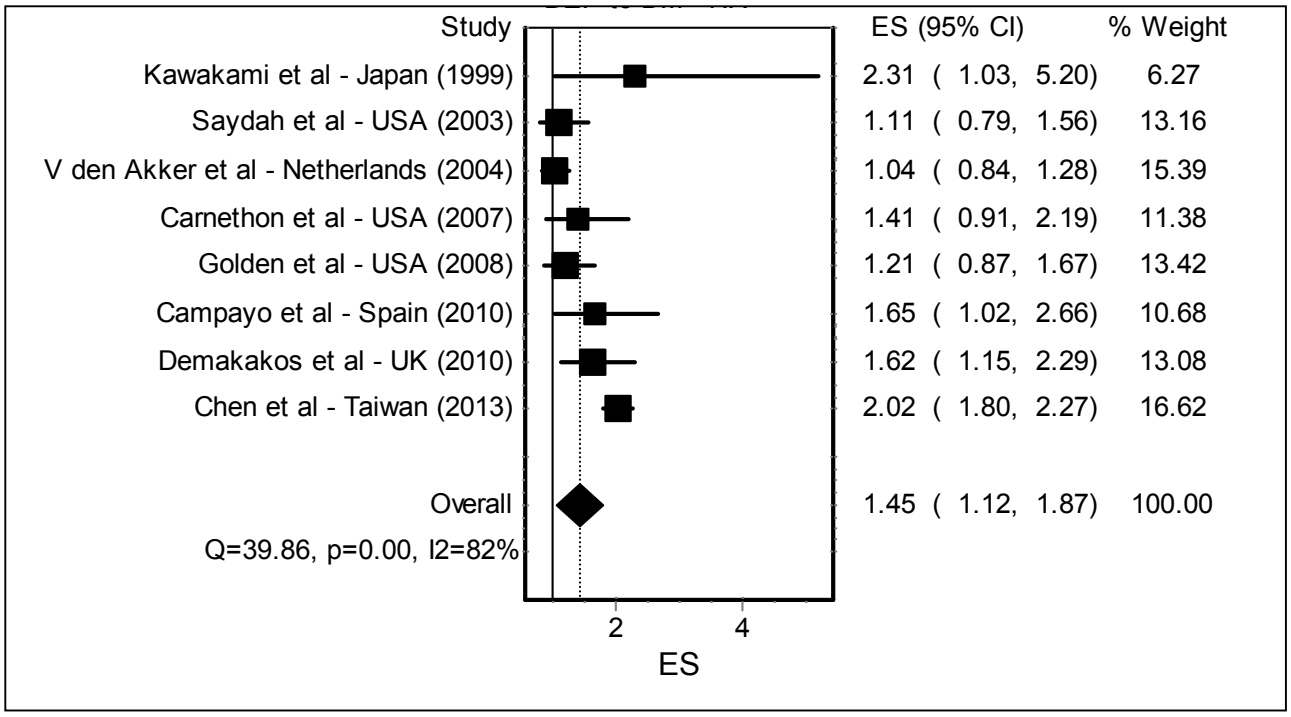

Figure 4.3.1.2: Random-effects forest plot showing the risk of diabetes for individual studies using self-report questionnaires, diagnostic criteria, and all studies combined; studies using HRs. Bars and diamonds indicate 95% CIs. Effect Size (ES) = HR (Hazard Ratios)

Studies with <10 years follow-up (RR: 1.98), those adjusted for ≤5 confounders (RR: 2.20), and conducted in the US (RR: 1.92) showed significantly higher risk of incident diabetes than studies with ≥ 10 years of follow-up (RR: 1.52), adjusted for >5 confounders (RR: 1.24) and conducted outside the US (RR: 1.37). The funnel plot revealed gross asymmetry, as most of the studies reported higher relative risks on one side of the line representing the most precise relative risk. The Egger's test for publication bias also suggested asymmetry (intercept 0.449; p = 0.025). Using the Trim and Fill method to impute missing studies, three dummy studies were added and the revised estimate was 1.26 (95% CI: 1.02 – 1.57).

4.3.2. Meta-analysis 2: Depression as a *consequence* of diabetes

The aim of the second review was to examine the relationship between diabetes and incident depression by conducting a meta-analysis of longitudinal studies using random-effects models, and extensive review and synthesis of the data. A total of 16 studies were included in this review; 11 assessing diabetes and incident depression using binary point and five studies using time-to-event estimates. Among the 11 studies assessing diabetes predicting depression, four-fold cells were reconstructed and used to compute CIP from ORs (10 studies) or RR (1 study). The reconstructed CIP was then used to compute RR and CIP for meta-analysis while original effect sizes (HRs) were used for studies that

reported time-to-event estimates and presented separately. For details on quantitative synthesis, please refer to the original paper attached at the end of the thesis (Appendix 3b)

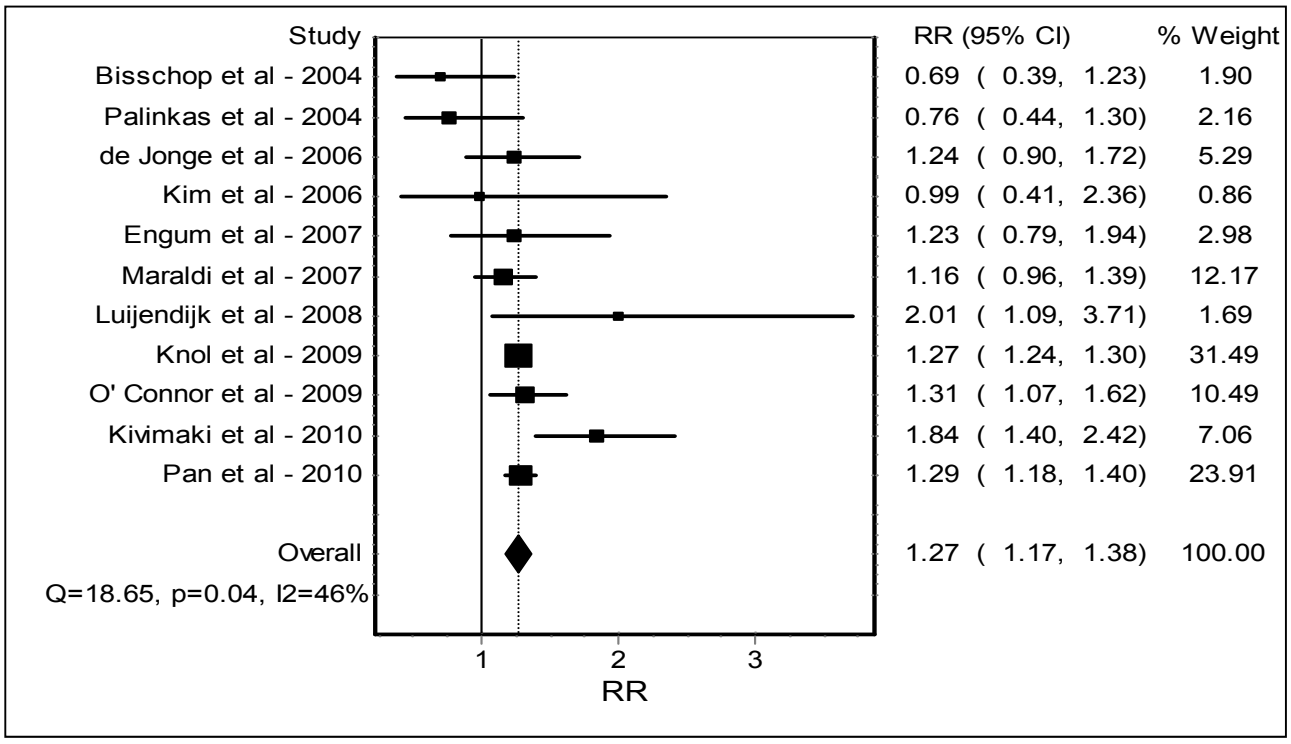

Figure 4.3.2.1: Random-effects forest plot showing the risk of depression for individual studies using self-report questionnaires, diagnostic criteria, and all studies combined; studies using reconstructed Relative Ratios. Bars and diamonds indicate 95% CIs. RR = Relative Risk

The 16 longitudinal studies assessing depression as a consequence of diabetes provided 16 datasets. Eleven studies that reported their findings using binary point estimates and provided sufficient data to formulate four-fold cell were used to reconstruct RR and CIP. In six studies the association was not statistically significant but increasing risk of incident depression as a result of diabetes was present in most cases. For RR, significant heterogeneity was present, with a pooled RR of 1.27 (95% CI: 1.17 – 1.38) (**Figure 4.3.2.1**). Only five studies reported time-to-event (survival) estimates but there was significant heterogeneity. The five studies generated a pooled HR of 1.23 (95% CI: 1.08 – 1.40) (**Figure 4.3.2.2**).

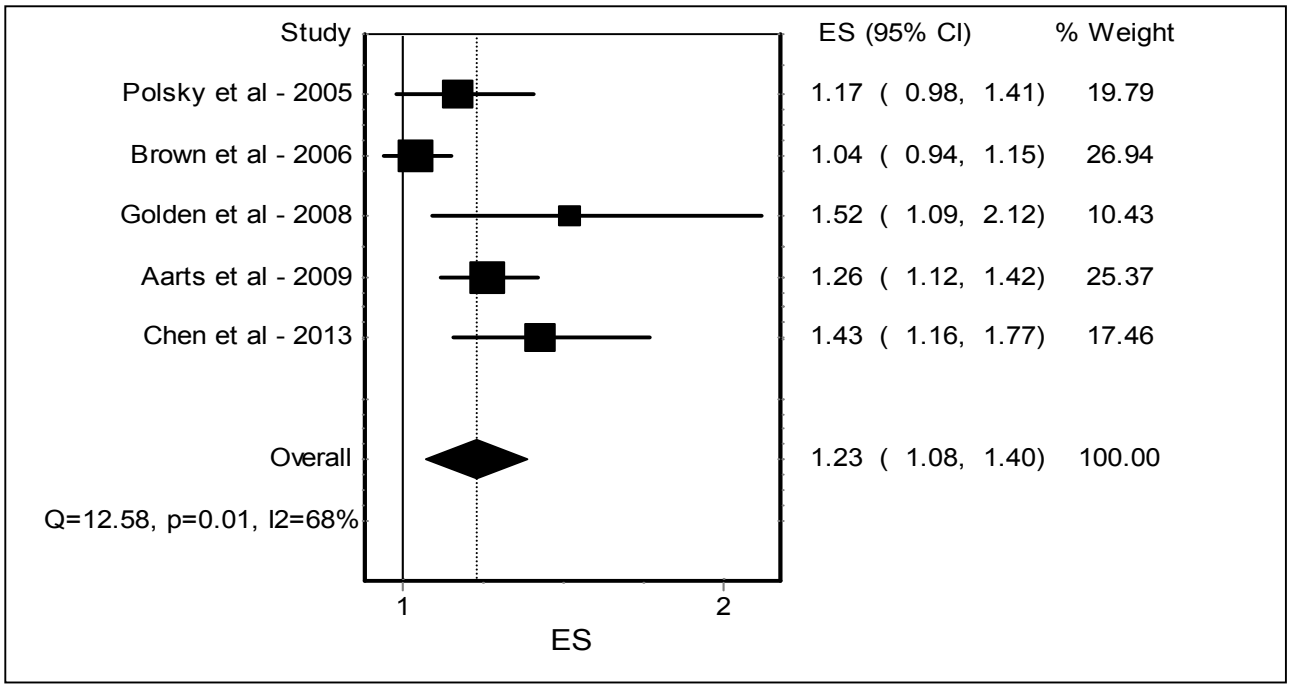

Figure 4.3.2.2: Random-effects forest plot showing the risk of depression for individual studies using self-report questionnaires, diagnostic criteria, and all studies combined; studies using hazards ratios. Bars and diamonds indicate 95% CIs. ES = Effect Size (hazards ratio)

In the sensitivity analysis, non-US studies (RR: 1.33, 95% CI: 1.09 – 1.64), studies that adjusted for less than 5 confounders (RR: 1.22, 95% CI: 1.05 – 1.43), and studies ≤ 5 years of follow-up (RR: 1.54, 95% CI: 1.16 – 2.04) produced a significantly higher relative risk than studies conducted in the US (RR: 1.24, 95% CI: 1.13 – 1.37), studies that adjusted for 5 or more confounders (RR: 1.22, 95% CI: 1.05 – 1.43), and studies with more than 5 years of follow-up (RR: 1.25, 95% CI: 1.17 – 1.33). The funnel plot was reasonably asymmetrical and Egger's test for publication bias also suggested asymmetry (intercept = 0.243, p= 0.001) for studies using binary point estimates. However 'Trim and Fill' method used to impute missing studies did not result in additional dummy studies.

For studies using time-to-event, the funnel plot revealed gross asymmetry, as most of the studies reported higher relative risks on one side of the line representing the most precise relative risk. The Egger's test for publication bias also suggested asymmetry. The Trim and Fill method resulted in two dummy studies being added and the revised estimate was 1.14 (95% CI: 1.00–1.30).

4.3.3. Meta-analysis 3: Bidirectional association between depression and diabetes

The third meta-analysis examined the bidirectional association between diabetes and depression using a bias-adjusted approach with quality-effects model. A total of 29 articles were included in this review; 15 assessing depression and incident diabetes and 14

examining diabetes and incident depression (**Figure 4.3.3.1**). Of these 29 studies, four studies examined both depression predicting diabetes and diabetes predicting depression and were retained for analysis: (Palinkas et al. (Palinkas et al., 2004), Engum (Engum, 2007), Golden et al. (Golden et al., 2008), Pan et al. (Pan et al., 2010)).

Among studies assessing depression predicting diabetes, four-fold cells were reconstructed and used to compute CIP from ORs (4 studies) or RR (4 studies). Similarly CIP was reconstructed from 9 studies examining diabetes predicting depression. The reconstructed CIP was then used to compute RR for meta-analysis while original effect sizes (HRs) were used for studies that reported time-to-event estimates and presented separately.

4.3.3.1. Depression as a *risk factor* for diabetes mellitus

Nine studies reported their findings in the form of binary point estimates. However, only eight studies presented complete data to formulate four-fold cells and were used to reconstruct CIP and RR. Of these eight studies, only two studies reported statistically insignificant associations; however, increasing risk of incident diabetes as a result of depression was present. For both RR, significant heterogeneity was present, with a pooled RR of 1.41 (95% CI: 1.13 – 1.76) (**Figure 4.3.3.1**). For six studies that presented their findings in the form of hazard ratios, there were four studies in which the association was not statistically significant but increasing risk was evident. However, there was no evidence of heterogeneity and the pooled hazard ratio was 1.24 (95% CI: 1.05 – 1.47).

Studies with <10 years follow-up time had a significantly higher relative risk (RR: 2.05) than studies with ≥10 years (RR: 1.34) of follow-up time. Studies conducted in the US were almost similar to studies conducted outside the US (RR: 1.32). However, studies where the outcome was adjusted for ≤ 5 confounders showed almost double the risk compared to studies where more than five confounders were adjusted in analysis. The funnel plot to detect publication bias revealed gross asymmetry, as most of the studies reported higher relative risks on one side of the line representing the most precise relative risk. The Egger's test for publication bias also suggested asymmetry (intercept 0.449; p = 0.025). Using the Trim and Fill method to impute missing studies, three dummy studies were added and the revised QE estimate was 1.26 (95% CI: 1.02 – 1.57).

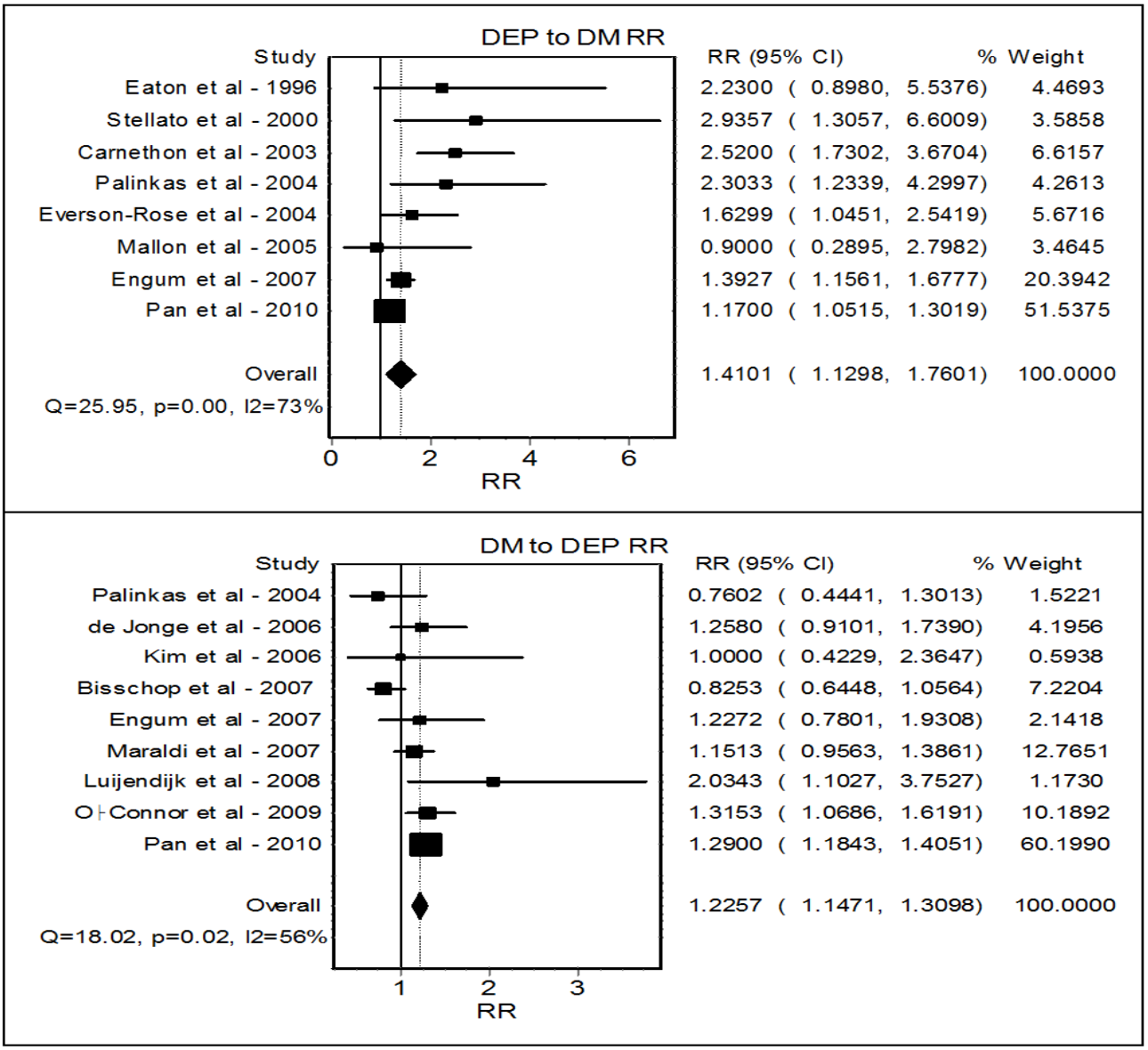

Figure 4.3.3.1: Quality-effects forest plot showing the risk of diabetes (top) and risk of depression for individual studies using self-report questionnaires, diagnostic criteria, and all studies combined; studies using reconstructed RR. Bars and diamonds indicate 95% CIs. DM = Diabetes Mellitus; DEP = Depression

4.3.3.2. Depression as a *consequence* of diabetes mellitus

Fourteen studies examined depression as a consequence of diabetes. Nine of them reported their findings using binary point estimates and provided sufficient data to formulate four-fold cells were used to reconstruct CIP, RR and RD. There were six studies in which the association was not statistically significant but increasing risk of incident depression as a result of diabetes was present in most cases. The pooled RR was 1.23 (95% CI: 1.15 – 1.31) (**Figure 4.3.3.1**). Five studies reported time-to-event (survival) estimates, and generated a pooled HR of 1.22 (95% CI: 1.05 – 1.42).

Studies with ≤5 years following time (RR: 1.40), non-US studies (RR: 1.36) and studies that used standard criteria (RR: 1.24) produced significantly higher relative risk than studies with >5 years of follow-up time (RR: 1.18), US studies (RR: 1.17) and studies that used self-report scales (RR: 1.20). Only non-US studies suggested diabetes as a significant predictor of depression. However, studies where more than 5 confounders were adjusted in analysis were almost similar to studies where the outcome was adjusted for less than or equal to 5 confounders. The funnel plot was reasonably symmetrical and Egger's regression concurred (intercept = 0.655, p= 0.107).

4.3.4. Meta-analysis 4: Anxiety as a *risk factor* for diabetes

The aim of this final review was to examine the relationship between anxiety and incident diabetes by conducting a meta-analysis of longitudinal studies using bias-adjustment as described by Doi (Doi et al., 2010). It has also been reported that the RR for a positive outcome (diabetes) may differ substantially from the RR for its negative complement (no diabetes) (Furuya-Kanamori & Doi, 2014) and thus the outcome with higher baseline risk is the correct outcome to report.

The risk of diabetes in exposed/unexposed groups in this study represents the smaller baseline risk and therefore its complement (no-diabetes) was reported as well. The reasoning behind this is that small baseline risks are associated with exaggerated RRs as a mathematical anomaly with ratios made from small numbers. In addition, RRs are reported rather than the ORs because this magnification occurs at both ends of the risk spectrum for the OR while it only arises at the lower end of the risk spectrum for the RR (Furuya-Kanamori & Doi, 2014). The risk difference (RD), and the number needed to be exposed for one additional person to be harmed (NNEH) at two years follow-up, were also computed from studies that followed subjects for 2 years or more.

Only four longitudinal studies were available for this review; these provided four longitudinal datasets assessing anxiety and incident diabetes. All four studies reported their findings in the form of odds ratios, and only two studies reported statistically significant associations.

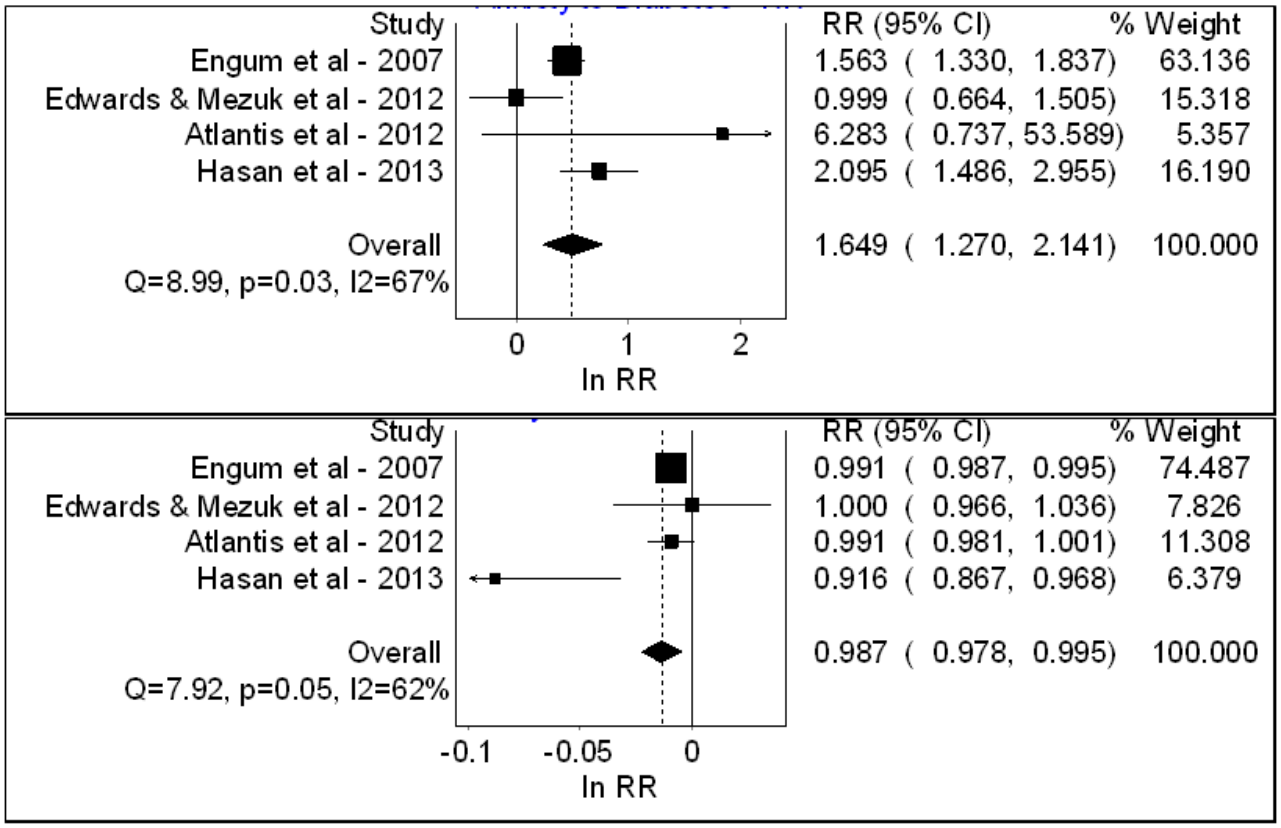

Figure 4.3.4.1: Quality-effects forest plot showing the risk of diabetes for individual studies using self-report questionnaires, diagnostic criteria, and all studies combined; studies using reconstructed RR, top (anxiety to diabetes) and below (anxiety to no diabetes). Bars and diamonds indicate 95% CIs.

The pooled QE estimate for diabetes after exposure to anxiety was a RR of 1.65. The RR for the negative complement, no-diabetes, was 0.987. Both analyses resulted in statistically significant results; however, the magnitude of the effect seems exaggerated when the risk of diabetes was directly computed (RR 1.65, 95% CI: 1.15 – 2.36) *versus* its negative complement (no-diabetes) (RR 0.987, 95% CI 0.978 – 0.995) (**Figure 4.3.4.1**). The pooled RD at 2 years was 0.031 (95% CI: - 0.007 – 0.054) (**Figure 4.3.4.2**). The NNEH was 33 (95% CI 19 to 143) at 2 years post exposure. The Egger's test for publication bias did not suggest asymmetry (intercept 0.379; p = 0.280). Using the Trim and Fill method to impute missing studies, one imputed study was added and this revised the effect size down to 1.52 (95% CI: 1.07 – 2.14).

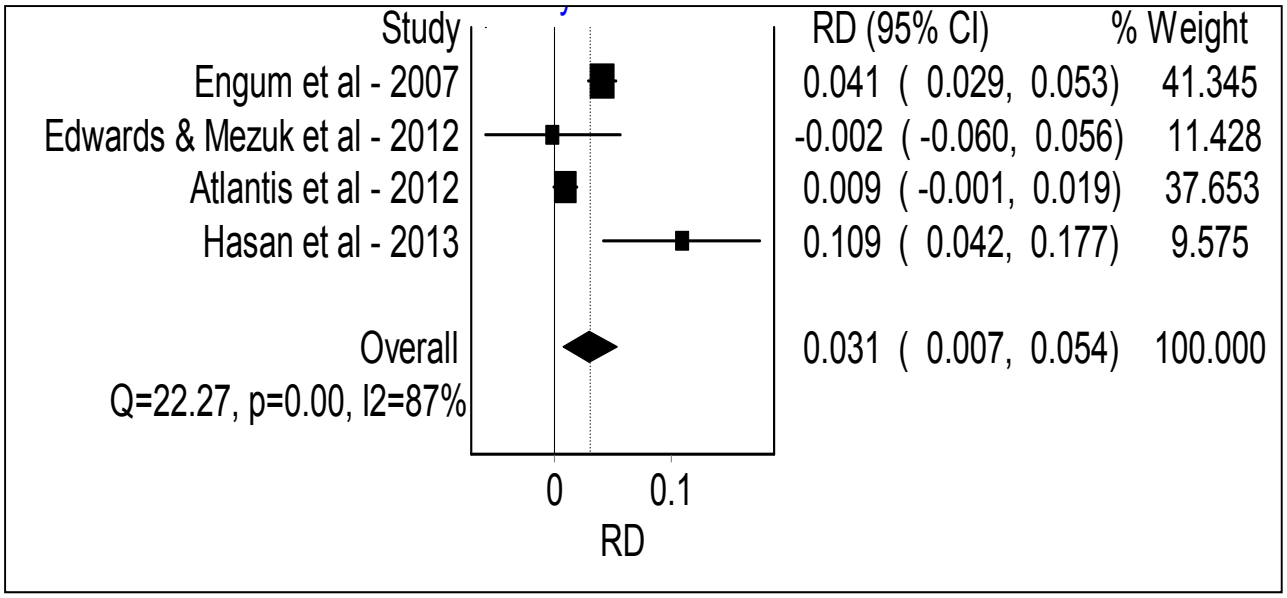

Figure 4.3.4.2: Quality-effects forest plot showing the risk of diabetes for individual studies using self-report questionnaires, diagnostic criteria, and all studies combined with outcome at 2 yrs; studies using RD. Bars and diamonds indicate 95% CIs.

4.4. Discussion of the findings of the meta-analyses

The first meta-analysis conducted documented higher cumulative incidence of diabetes in depressed than in non-depressed subjects. Of 15 studies included in the first review, eight studies were from Northern America, five from Europe and two from East Asia. A study conducted in Taiwan in East Asia (Chen et al., 2013) documented the highest CIPs whereas a study from Norway in Europe (Engum, 2007) recorded the lowest CIPs for diabetes in both the depressed and non-depressed groups. The first meta-analysis found a significant association between depression and incident diabetes and of the 16 studies assessing this association, 10 suggested increased risk. In our quantitative analysis using the random-effects model, there was a 1.67 fold increase in risk or 1.45 fold increase in hazard for diabetes in adults with depressive symptoms. Similar results were reported in previous meta-analyses, although binary point estimates had not been separated from HRs for estimating pooled effect sizes (Knol et al., 2006; Mezuk et al., 2008).

In the second meta-analysis, patients with diabetes showed greater cumulative incidence of depression compared to non-diabetes patients. Of the 16 studies of diabetes predicting incident depression, only eight studies suggested increased risk. In the quantitative analysis using random-effects model, a 1.27-fold increase in risk for depression in adults with diabetes was demonstrated. These relative estimates are similar to previously reported figures that were calculated without segregating binary point and time-to-event estimates by Mezuk et al. (1.15-fold) and Nouwan et al. (1.24-fold) (Mezuk et al. 2008; Nouwen et al. 2010). However, Routelle and Mannucci presented their findings as

adjusted hazard ratios (Routelle & Mannucci, 2012) and found a higher incidence of depression in diabetes subjects, with adjusted risk of 1.25-fold.

Given that the first and second meta-analyses did not consider sources of potential bias, it was prudent to re-visit the analyses using strict bias assessments and bias adjusted models. In the third meta-analysis, therefore, the effect sizes were re-estimated for the bidirectional association between depression and diabetes using the quality-effects model. This re-analysis revealed that the associations were weakened and the confidence interval, too, was shifted in the direction of the null. Nevertheless, results remained statistically significant. Therefore this suggests that the depression – diabetes association may be explained partly through sources of bias. Indeed, the residual effect seen may be due to residual confounding.

In the fourth and final meta-analysis examining anxiety as a risk for diabetes, a significant relationship between anxiety and incident diabetes was found in quantitative analysis, with a 65% increase in the risk of diabetes in adults with anxiety. This is higher than the 25% increase in odds reported previously by Smith et al. for the converse outcome of anxiety in diabetes (Smith et al. 2013). However, analysis of the negative complement outcome (no-diabetes) revealed a low relative risk of diabetes mellitus with anxiety when compared to reports that use the outcome of incident diabetes. Specifically, the RR estimate for 'no-onset of diabetes' was 0.987. This suggests only a 1.3% increase in the risk of new diabetes onset if patients who are unexposed to anxiety were to be exposed; this differs substantially from the magnitude of effect when risk of diabetes was the outcome.

It therefore seems that by selecting the RR as the effect size as well as the outcome with the higher baseline risk (in this case no-diabetes), artificial magnification of the effect size was avoided. In absolute terms however, the differences between the two groups (exposed and unexposed to anxiety) were not affected by the outcome chosen (diabetes or no-diabetes) and were statistically significant. The risk difference was 3% at two years follow-up and thus one more patient is harmed by the onset of diabetes for every 33 patients exposed to anxiety over a two year period when compared with the unexposed group. Again, we cannot be certain that this association is causal though care was taken to address sources of bias.

One major limitation that may affect the findings of these meta-analyses is that all longitudinal studies were from developed countries; not a single longitudinal study from

developing regions was available at the time of this PhD study. Additional limitations of the meta-analyses are discussed in detail in each of the attached article at the end of the thesis (*Appendices 4A to 4D*)

RESULTS

PART 2

MATER-UNIVERSITY OF QUEENSLAND STUDY OF PREGNANCY

CHAPTER 5

The validity of Personal Disturbance Scale (DSSI/sAD) in people with diabetes

The third objective of this thesis was to validate the personal disturbance scale (Delusions-Symptoms-States-Inventory/States of Anxiety and Depression) among women with diabetes using the MUSP dataset. This was necessary because DSSI/sAD used in this PhD study had not yet been validated among people with diabetes.

The validation process described in this chapter has been published. The formal citation for the published work:

1. **Hasan, S.S.,** Clavarino, A.M., Mamun, A.A., Dingle, K., Kairuz, T. (2015). The validity of personality disturbance scale (DSSI/sAD) in people with diabetes mellitus, using longitudinal data. *Pers Individ Dif*, 72, 182-8.

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The validity of personal disturbance scale (DSSI/sAD) in people with diabetes mellitus, using longitudinal data

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ABSTRACT

Despite being used since 1976, Delusions-Symptoms-States-Inventory/states of Anxiety and Depression (DSSI/sAD) has not yet been validated for use among people with diabetes. The aim of this study was to examine the validity of the personal disturbance scale (DSSI/sAD) among women with diabetes using Mater-University of Queensland Study of Pregnancy (MUSP) cohort data. The DSSI subscales were compared against DSM-IV disorders, the Mental Component Score of the Short Form 36 (SF-36 MCS), and Center for Epidemiologic Studies Depression Scale (CES-D). Factor analyses, odds ratios, receiver operating characteristic (ROC) analyses and diagnostic efficiency tests were used to report findings. Exploratory factor analysis and fit indices confirmed the hypothesized two-factor model of DSSI/sAD. We found significant variations in the DSSI/sAD domain scores that could be explained by CES-D (DSSI-Anxiety: 55%, DSSI-Depression: 46%) and SF-36 MCS (DSSI-Anxiety: 66%, DSSI-Depression: 56%). The DSSI subscales predicted DSM-IV diagnosed depression and anxiety disorders. The ROC analyses show that although the DSSI symptoms and DSM-IV disorders were measured concurrently the estimates of concordance remained only moderate. The findings demonstrate that the DSSI/sAD items have similar relationships to one another in both the diabetes and non-diabetes data sets which therefore suggest that they have similar interpretations.

1. Introduction

Anxiety and depression are two common, co-morbid, modifiable conditions associated with diabetes (Anderson, Freedland, Clouse, & Lustman, 2001; Grigsby, Anderson, Freedland, Clouse, & Lustman, 2002). Diabetes has well documented, detrimental effects on health, and studies have shown significant negative associations between Health-related Quality of Life (HRQoL) and its prognosis (Landman, van Hateren, Kleefstra, Groenier, Gans, & Bilo, 2010 ; Rubin & Peyrot, 1999). Depression and anxiety in people with diabetes are linked to at least two unfavorable outcomes: poor metabolic control (Anderson et al., 2002; Lustman, Anderson, Freedland, de Groot, & Carney, 2000) and decreased HRQoL (Ali, Stone, Skinner, Roberston, Davies, & Khunti, 2010; Kohen, Burgess, Catalán, & Lant, 1998). The strength of the association between these symptoms and HRQoL is stronger for females, people with low educational attainment, disrupted marital status, and low levels of social support (Khuwaja, Lalani, Dhanani, Azam, Rafique, & White, 2010). Anxiety and depression are more common among women suffering from diabetes, the target population of our study (Anderson et al., 2001; Grigsby et al., 2002).

According to a recent review of screening tools that are used for measuring depression and anxiety symptoms in people with type 1 and 2 diabetes, the Delusions-Symptoms-States-Inventory/States of Anxiety and Depression (DSSI/sAD), a tool developed in 1976, was not included as it has not been validated for use among people with diabetes (Bedford, Foulds, & Sheffield, 1976; Roy, Lloyd, Pouwer, Holt, & Sartorius, 2012). Although not developed or validated for use in the diabetes population, the DSSI/sAD has been extensively used to examine symptoms of anxiety and depression (Bedford, Watson, Henry, Crawford, & Deary, 2011; Mamun, Clavarino, Najman, Williams, O'Callaghan, & Bor, 2009; Najman, Andersen, Bor, O'Callaghan, & Williams, 2000; Saiepour, Najman, Clavarino, Baker, Ware, & Williams, 2013). Similar to the Hospital Anxiety and Depression Scale (HADS), the DSSI/sAD assesses both depression

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0191-8869/

and anxiety (Bedford & Foulds, 1978; Zigmond & Snaith, 1983). Unlike HADS, some items included in DSSI/sAD could be confounded with the symptoms of diabetes or poorly controlled diabetes (International diabetes federation (IDF): clinical guidelines task force, 2005), such as sleeplessness (Meisinger, Heier, & Loewel, 2005).

This is the first study to validate the DSSI/sAD in Australia, to determine whether the DSSI/sAD could be used to identify depression and anxiety symptoms in women with diabetes using a large prospective cohort (Mater-University of Queensland Study of Pregnancy). To date, no study has directly compared the correspondence of the DSSI anxiety and depression subscales with any DSM-IV depressive and anxiety diagnoses. As the Center for Epidemiologic Studies Depression Scale (CESD) and 36-item short form scale (SF-36) are the most commonly used scales in people with diabetes (Roy et al., 2012) we assessed the validity of the DSSI/sAD subscales, and their association with CES-D and SF-36.

2. Materials and methods

2.1. Participants

To validate the DSSI/sAD instrument, we examined a sample of women who were part of the Mater-University of Queensland Study of Pregnancy (MUSP), a multidisciplinary study that represents Australia's largest longitudinal study among women with data collected over 30 years since 1981. Pregnant women attending their first antenatal clinic visit (FCV = at approximately 18 weeks' gestation) at a major tertiary hospital (Mater Misericordiae Hospital) in South Brisbane were invited to participate in the study, data were collected over three years between January 1981 and December 1983 (Najman, Bor, O'Callaghan, William, Aird, & Shuttlewood, 2005). Originally 7861 women were enrolled (8556 pregnancies) of whom 6753 constitute the MUSP mothers' cohort. To be enrolled in the cohort women had to have delivered at least one live baby who neither died nor was adopted before leaving hospital, and had to have complete data from an initial first clinic visit (FCV) and a birth interview. Information regarding diabetes mellitus was collected with self-reported items. Women were asked "Have you EVER been told by a doctor that you have diabetes mellitus (high blood sugars)?" (Callaway, Lawlor, O'Callaghan, Williams, Najman, & McIntyre, 2007).

2.2. DSSI/sAD instrument

Depression and anxiety symptoms of women in the original MUSP study were assessed at seven time points over 27 years, using the 14-item DSSI/sAD instrument (Bedford & Foulds, 1978). The DSSI/sAD has been validated in previous studies using factor analysis (Bedford, Henry, & Crawford, 2005; Henry, Crawford, Bedford, Crombie, & Taylor, 2002). Recent studies using Mokken scale analysis suggested a uni-dimensional scale using seven of the 14 items (Bedford et al., 2011) and a stable structure over time (Saiepour et al., 2013). In the present study, the seven items were summed, each with 5-point response options (all the time, most of the time, some of the time, rarely, or never); the higher the score, the more depressive or anxious the person. Participants were classified as anxious or depressed when they scored 4 or more, and as non-anxious or non-depressed when they scored less than 4 out of a maximum score of 7.

2.3. Validation procedure

For our study, we utilized a four-part methodology to cover both views of validity (traditional and contemporary) (Zumbo, 2005). This methodology consisted of:

- (a) Exploratory Factor Analysis (EFA), and
- (b) Partial Confirmatory Factor Analysis (PCFA); both analyses were conducted on MUSP 21-year dataset using IBM SPSS version 22 (Gignac, 2009).
- (c) Concurrent (concordance with CES-D and SF-36 MCS) validity, and
- (d) Concordance with DSM-IV disorders using receiver operating characteristic (ROC) analyses and diagnostic efficiency tests; the latter were conducted on MUSP 27-year dataset with STATA IC version 12.

2.3.1. Exploratory and Confirmatory Factor Analyses

Exploratory factor analysis (EFA) is a widely utilized and broadly applied statistical technique in the social sciences (Costello & Osborne, 2005). EFA is a variable reduction technique which identifies the number of latent constructs and the underlying factor structure of a set of variables, that cannot be measured directly (Child, 1990).

The analysis may be referred to as a partial confirmatory factor analysis (PCFA) when the number of factors is expected to be known but the specific pattern of salient and nonsalient loadings may not be (Bollen, 1989). A PCFA may be considered to lie between conventional exploratory factor analysis (EFA) and confirmatory factor analysis (CFA) on the spectrum of evaluating the plausibility of a model (Gignac, 2009). We performed the factor analysis in two steps. In the first step we performed EFA of maximum likelihood estimation (MLE) unrestricted factor analysis, followed by a second step of restricted/PCFA analysis as estimated via MLE.

2.3.2. Concordance with SF-36 and CES-D, using MUSP 21-year dataset

We examined the degree to which symptoms measured by SF-36 and CES-D were associated with symptoms on the DSSI/sAD domains on MUSP 21-year dataset using the SF-36, a generic quality of life instrument, to examine both physical and mental health (Ware, Snow, Kosinki, & Gandek, 1993). A mental health sub-scale of SF-36 has been utilized in a number of studies of diabetes and depression (Roy et al., 2012). Note that unlike the DSSI/sAD domains, where high scores indicate a high number of anxiety or depressive symptoms, higher SF-36 component scores represent better quality of life. All questions were scored on a scale from 0 to 100, with 100 representing the highest level of functioning possible (Ware et al., 1993).

The CES-D was selected because it is the second most widely used instrument to measure depression symptoms among people with diabetes, after the Beck Depression Inventory (BDI) (Roy et al., 2012). In patients with T2DM, the CES-D is used more commonly than BDI (Roy et al., 2012). Overall scores range from 0 (no symptoms) to 60 (Radloff, 1977). Higher scores on the CES-D indicate a greater number of depression symptoms. Similarly, higher scores on the DSSI/sAD indicate a higher number of symptoms.

2.3.3. Concordance with DSM-IV disorders, using MUSP 27-year dataset

Although the DSSI/sAD has been in use for more than two decades, to date no study has directly compared the association of the DSSI anxiety and depression subscales with DSM-IV depressive and anxiety diagnoses. For this comparison, we used DSSI depression and anxiety symptoms measured at MUSP 27-year follow-up study. At the 27-year follow-up, psychiatric disorders were extracted from a validated, computerized structured interview of psychiatric symptoms, the World Health Organization-World Mental Health-Composite International Diagnostic Interview-CAPI Modularization Program (WHO WMH-CIDI CAPI: Version: 21.1.3) (Andrews & Peters, 1998; World Health Organization (WHO), 2004).

We used CIDI summary outcomes (any depressive or anxiety disorder) which were calculated as a positive diagnosis across a range of DSM IV diagnoses. The term 'any depressive or anxiety disorder' indicates the presence of at least one disorder. We estimated the risk of having a DSM-IV lifetime, and 12-month disorder for each DSSI subscale.

2.4. Statistical analysis

The data were analyzed using the Statistical Package for Social Sciences (SPSS)® version 22 and STATA IC® version 12, with a significance level of $\leqslant 0.05$. Results are presented for women with and without diabetes. Descriptive statistics were used to calculate percentage frequencies, means and standard deviations. Since the DSSI/sAD had not been previously validated in a sample of women with diabetes, we conducted an Exploratory Factor Analysis (EFA) (Bentler & Yuan, 1996; Costello & Osborne, 2005) to examine the underlying components or domains of DSSI/sAD. In order to achieve a favorable ratio (>10:1) of respondents over instruments items, a minimum of 200 participants was required to conduct factor analysis (Bentler & Yuan, 1996). The corrected item-total score correlations were also examined. Reliability of DSSI/sAD items and domains were assessed using Cronbach's alpha and intra-class correlation coefficients.

DSSI/sAD constructs were identified and confirmed using a SEM approach to PCFA (Gignac, 2009; Keller, Ware, Bentler, Aaronson, Alonso, Apolone, 1998). We performed the partial CFA model estimation using the maximum likelihood estimation (MLE) (Gignac, 2009; Gignac, Bates, & Jang, 2007). MLE extraction method was preferred because it allows for the computation of a wide range of indices of the goodness of fit of the model and testing of statistical significance of factor loadings (Fabrigar, Wegener, MacCallum, and Strahan, 1999.

Regarding various formal statistical fit indices, this study adapted both absolute as well as incremental fit indices. Absolute fit indices were derived from the fit of the observed and implied covariance matrices (Hu & Bentler, 1995). Concerning various absolute fit indices, our study evaluated model fit by using the model chi-square test, RMSEA (the root mean square error of approximation), and the SRMR (the standardized root mean square residual). The goodness of fit of the model to the MUSP 21-year data was evaluated for both diabetes and non-diabetes groups using chi-square. Since the sample sizes for both diabetes and non-diabetes groups were large, chi-square values were expected to be insignificant (indicating lack of fit) (Yu & Yu, 2007). Model fit was therefore defined as Normed Fit Index (NFI), Comparative Fit Index (CFI) and Tucker–Lewis Index (TLI) greater than 0.90 (Hu & Bentler, 1995). Incremental (comparative) fit indices measure goodness-of-fit that compare the current model to a specified "null" (independence) model to determine the degree of improvement over the null model (Hu & Bentler, 1995).

The current concordance of the DSSI subscales was assessed against lifetime and 12-month DSM-IV depressive and anxiety disorders. This was assessed by ROC analyses, reported using area under the curve (AUC) and 95% Confidence Interval (95% CI). We have calculated AUC to obtain a global summary statistic of diagnostic accuracy and to capture the trade-off between sensitivity and specificity over a continuous range. The AUC ranges from 0.5 (random chance or no predictive ability) to 1 (perfect discrimination or accuracy) (Doi, 2013). The sensitivity, specificity, and positive predictive value (PPV) for each subscale and major depression or anxiety were also calculated. Univariate logistic regressions with odds ratios (OR) and 95% CIs were used to estimate the risk of having a DSM-IV lifetime, and 12-month disorder for each DSSI subscale.

To validate the DSSI/sAD depression and anxiety domains against the SF-36 MCS and CES-D scores, linear regression was used, while logistic regression analysis determined the degree to which the presence or absence of diabetes was associated with depression and anxiety symptoms on the DSSI/sAD domains. Age, education, body mass index (BMI), and marital status were also included as covariates to control for their potential effects on both mental health and diabetes (Hasan, Clavarino, Mamun, Doi, & Kairuz, 2013). These variables were included as covariates in all linear and logistic regression analyses used in this study. Finally to examine the correlation between the instruments (DSSI, CES-D, and SF-36 MCS), Pearson correlation test was applied.

3. Results

About 8% of women who participated at the 21-year and 27-year follow up studies reported "ever" having been diagnosed with diabetes. The mean ages of women with and without diabetes were similar. As expected, women with diabetes had higher mean BMI compared to women without diabetes (30.82 versus 27.37 kg/m^2, $p < 0.05$) (Table 1). The majority of women were married or living with a partner and had completed (at least) secondary high schooling.

3.1. Exploratory Factor Analysis

The Kaiser–Meyer–Olkin (KMO) test of sampling adequacy was applied prior to factor extraction, which resulted in an overall index of 0.95, suggesting that the sample was adequate for factor analysis. The EFA revealed a bi-factorial model explaining 53.4% of the variation, where 9 items loaded onto the first factor and 5 items onto the second factor. The second factor explained only 5.2% of the variation. The items loaded highly on their factors (all factor loadings exceed 0.30) indicating good convergent validity, with the presence of cross-loadings of items and 50% of shared variance between the two factors indicating poor discriminant validity of DSSI/sAD. Similar results were obtained for both data sets (diabetes and non-diabetes), as shown in Table 2. There was good consistency between items, the Cronbach's alpha for the full scale (measured at 21-year) was 0.93 respectively. The alphas of DSSI/sAD depression and anxiety domains were almost comparable for women with and without diabetes, and both were within an acceptable range.

3.2. Confirmatory Factor Analysis

As indicated in Table 3, the model chi-square values indicate poor fit to the data (diabetes = 18.518; non diabetes = 1163.172). Owing to the large sample size of the present study (diabetes = 315; non diabetes = 2845), other indices for evaluating model fit are discussed.

An examination of the fit indices for our MUSP data (21 year follow-up) with DSSI/sAD, such as RMSEA which is a measure of model fit, showed that the two latent variables model was considered adequate (RMSEA = 0.077). Moreover, the SRMR values of the models range between 0.033 and 0.035 for diabetes and non-diabetes groups (cut-off < 0.10). In summary, regarding the absolute fit indices, the data fit the model well.

Concerning the incremental fit indices, the NFI (the normed fit index) defines the null model as a model in which all of the correlations or covariances are zero; the benchmark, however, is > 0.90. In our study, the NFI equals 0.93 (for both diabetes and non-diabetes groups), the CFI (comparative fit index) equals 0.95 (for diabetes and non-diabetes groups), and the TLI (Tucker–Lewis Index) equals 0.93 (for both diabetes and non-diabetes groups); all exceed the benchmark (> 0.90).

Table 1
Descriptive statistics of women with and without diabetes.

Items	Diabetes $n = 315$	No diabetes $n = 2845$	p-value
Age, mean (range)	47.26 (36.54–63.82)	46.48 ± 5.00	0.006
BMI, mean (range)	30.87 (18.30–66.10)	27.37 ± 5.96	0.001
Overall Mean DSSI score, mean ± SD	19.27 ± 6.84	18.71 ± 8.14	0.001
CESD score, mean ± SD	11.19 ± 10.69	9.02 ± 9.11	0.001
SF-36 MCS, mean ± SD	48.10 ± 10.86	49.76 ± 9.81	0.005

Independent t-test and Chi-square test were applied to obtain p-values.
21-Year follow-up dataset was used.

Table 2
Summary of exploratory factor analysis and corrected item total score correlations of the DSSI/sAD administered to diabetes and non-diabetes patients.

Items	Diabetes $n = 315$		No diabetes $n = 2845$	
	Anxiety	Depression	Anxiety	Depression
1. I have breathless or had a pounding heart (**Q3**)	0.80	–	0.59	–
2. I have been so worked up that I couldn't sit still (**Q4**)	0.78	–	0.72	–
3. For no good reason I have had feelings of panic (**Q7**)	0.71	–	0.50	–
4. I have worried about everything (**Q1**)	0.69	–	0.62	–
5. I have had a pain or tense feeling in my neck or head (**Q9**)	0.65	–	0.39	–
6. I have been so anxious that I couldn't make up my mind about the simplest thing (**Q13**)	0.64	–	0.53	–
7. I have been so miserable that I have had difficulty sleeping (**Q2**)	0.62	–	0.74	–
8. I have been depressed without knowing why (**Q5**)	0.61	–	0.48	–
9. Worrying has kept me awake at night (**Q11**)	0.52	–	0.72	–
10. I have been so depressed that I have thought of doing away with myself (**Q14**)	–	0.88	–	0.93
11. The future seems hopeless (**Q10**)	–	0.86	–	0.69
12. I have gone to bed not caring if I ever woke up (**Q6**)	–	0.82	–	0.88
13. I have lost interest in just about everything (**Q12**)	–	0.70	–	0.57
14. I have been so low in spirit that I have sat up for ages doing absolutely nothing (**Q8**)	0.41	0.46	0.40	0.42
Cronbach's alpha	0.91	0.90	0.86	0.88
Percent of variance (%)	53.41	5.16	44.55	5.14

*Items were listed in a descending order of magnitude of factor coefficients by factor for diabetes sample. The sequence of the items in the DSSI measure was put in the form of numbers in parentheses.
21-Year follow-up dataset was used.

Table 3
Fit index summary of partial confirmatory factor analysis model, by diabetes and no diabetes groups.

Fit index	Diabetes $N = 315$	No diabetes $N = 2845$	Benchmark
Absolute fit indexes			
Chi-square	180.52	1163.17	
Degrees of freedom	64	64	
p-value of Chi-square test	0.000	0.000	< 0.05
RMSEA	0.07	0.07	< 0.08
SRMR	0.03	0.03	< 0.100
Incremental fit indexes			
NFI	0.93	0.94	> 0.90
CFI	0.95	0.94	> 0.90
TLI	0.93	0.92	> 0.90

RMSEA = root Mean Square Error of Approximation; SRMR = Standardized Root Mean Residual; NFI = Normed Fit Index; CFI = Comparative Fit Index; TLI = Tucker–Lewis Index.
21-Year follow-up dataset was used.
Model solution via maximum likelihood estimation (MLE).

3.3. Concordance with SF-36 and CES-D

The correlation matrix also showed that there were strong correlations between the scale items. The correlation between the anxiety and depression subscales was 0.819 ($p = 0.001$), while between the subscales and the full DSSI/sAD scale it was 0.96 ($p < 0.001$) and 0.95 ($p < 0.001$) respectively. All the items correlated significantly with the domain specific and full DSSI/sAD scale, CES-D and SF-36 MCS ($p < 0.001$).

Table 4 displays the results of the linear regression analysis of the validation instruments, including covariates, on DSSI/sAD depression and anxiety domains. Our results indicated that better QoL on the SF-36 MCS sub-scale was significantly related to lower mean scores on DSSI-Anxiety and DSSI-Depression subscales. When the SF-36 MCS increased by one unit, the DSSI/sAD anxiety and domain score decreased by 0.443 units ($p = 0.001$) among participants with diabetes, while it decreased by 0.396 ($p = 0.001$) units in participants without diabetes. In both groups performance on the SF-36 MCS accounted for similar percentages of the variance in the DSSI/sAD anxiety domain scores (46% versus 40%).

Our results also showed that higher mean scores on DSSI-Anxiety and DSSI-Depression were significantly related to a higher mean

Table 4
Results of linear regression analyses with the DSSI/sAD domains as the dependent variables, CESD and SF-36 MCS scores as independent variables, and covariates.

Outcome	Factors	Diabetes (n = 315)				No diabetes (n = 2845)			
		Parameter coefficients	p-value	95% CI	Variance R^2	Parameter coefficients	p-value	95% CI	Variance R^2
DSSI – Anxiety	CESD	0.52	0.001	0.46, 0.57	0.554	0.47	0.001	0.45, 0.49	0.484
	Age [a]	−0.11	0.040	−0.21,−0.01		−0.03	0.037	−0.07,−0.01	
	BMI [b]	0.10	0.010	0.03, 0.18		−0.01	0.834	−0.03, 0.02	
	Education [c]	−0.38	0.593	−1.79, 1.03		−0.701	0.003	−1.16,−0.24	
	Marital status [d]	0.23	0.733	−1.07, 1.53		0.08	0.695	−0.31, 0.46	
	SF-36 MCS	−0.44	0.001	−0.50,−0.38	0.459	−0.40	0.001	−0.41,−0.38	0.403
	Age [a]	−0.07	0.239	−0.19, 0.05		−0.04	0.018	−0.08,−0.01	
	BMI [b]	0.18	0.001	0.09, 0.27		−0.03	0.035	0.01, 0.06	
	Education [c]	−0.71	0.387	−2.31, 0.90		−1.31	0.001	−1.82,−0.81	
	Marital status [d]	0.44	0.573	−1.08, 1.95		−0.34	0.107	−0.75, 0.07	
DSSI - Depression	CESD	0.54	0.001	0.49, 0.58	0.658	0.52	0.001	0.50, 0.53	0.586
	Age [a]	−0.02	0.701	−0.10, 0.07		−0.01	0.570	−0.04, 0.02	
	BMI [b]	0.05	0.175	−0.02, 0.11		0.01	0.534	−0.02, 0.03	
	Education [c]	−0.22	0.712	−0.97, 1.42		−0.27	0.171	−0.67, 0.12	
	Marital status [d]	−0.95	0.088	−2.05, 0.14		−0.39	0.020	−0.71,−0.06	
	SF-36 MCS	−0.48	0.001	−0.53,−0.42	0.558	−0.41	0.001	−0.43,−0.40	0.482
	Age [a]	0.03	0.591	−0.08, 0.13		−0.02	0.153	−0.06, 0.01	
	BMI [b]	0.12	0.003	0.04, 0.20		0.05	0.001	0.02, 0.07	
	Education [c]	−0.20	0.779	−1.601, 1.20		−1.03	0.001	−1.48,−0.57	
	Marital status [d]	−0.55	0.415	−1.87, 0.78		−0.96	0.001	−1.33,−0.59	
Overall DSSI	CESD	0.53	0.001	0.48, 0.58	0.659	0.50	0.001	0.48, 0.51	0.576
	SF-36 MCS	−0.46	0.001	−0.51, 0.41	0.555	−0.40	0.001	−0.42,−0.39	

CI = Confidence interval; MCS = Mental Component Score; CESD = Center for Epidemiologic Studies Depression Scale.
21-Year follow-up dataset was used.
[a] Age measured as continuous variables in years.
[b] BMI in kg/m^2.
[c] Education was measured as 1 = Incomplete High schooling; 2 = Completed High schooling or higher.
[d] Married/living together = 1; not presently married, i.e., divorced, single, widowed, separated = 0.

score on the CES-D scale. When the CES-D score increased by 1 unit, the score for the DSSI/sAD depression domain decreased by 0.535 (p = 0.001) in a sample of participants with diabetes, and it decreased by similar amount (0.516 units) in participants without diabetes. The association between CES-D and DSSI/sAD domains remained significant after adjusting for covariates. As reported in Table 4, similar results were obtained when the full DSSI/sAD scale was validated against the CES-D and SF-36 MCS scales.

3.4. Concordance with DSM-IV disorders

The DSSI subscales were good predictors of an absence of DSM-IV mood disorders, evidenced by the high negative predictive value (NPV) and specificity values (Table 5). The scale identified more than half of the participants with current anxiety disorders (sensitivity 52.8%). Women with diabetes had high odds of major depressive disorder (ORs ranged from 4.93 to 13.50) or anxiety disorder (ORs ranged from 4.65 to 8.10) compared with those without DSSI symptoms. The ROC analyses show that although the DSSI symptoms and DSM-IV disorders (both measured at 27-year after the initial interview) were measured concurrently the estimates of concordance remained only low to moderate (AUC ranged from 0.63–0.89). Our ROC analyses show that 12-month DSM disorders had moderate estimates (Depression = 0.78, Anxiety = 0.77) compared to lifetime disorders (Depression = 0.64, Anxiety = 0.63). Differences between DSM-based depressive and anxiety scales were significant. Confidence intervals of the DSSI subscales and DSM-IV depressive and anxiety disorders overlapped, indicating a lack of systematic differentiation between the diagnoses.

4. Discussion

The findings support the construct validity and confirmed the psychometric properties of DSSI/sAD for use among women with diabetes. The results provide evidence supporting the reliability of the DSSI/sAD for use among similar subjects. The full DSSI/sAD scale had high internal consistency (0.932), suggesting that the 14 items included in the instrument are reliable. The Cronbach's alphas were more than 0.80 for both groups with and without diabetes. The good consistency and reliability found here are similar to the findings of previous studies (Bedford, Foulds, and Sheffield, 1976; Bedford & Foulds, 1978).

An interesting finding of the present study is the confirmation of bi-factorial model of the DSSI/sAD; this is similar to reports for HADS (Bjelland, Dahl, Haug, & Neckelmann, 2002; Herrmann, 1997). With few exceptions, the coefficients were 0.40 or higher for each item with its hypothesized factor (demonstrating good convergent validity), but some items were cross-loaded and were highly correlated (demonstrating poor discriminant validity). Concerning the various fit indices of the current model, the data closely fit the hypothetical model. As expected, chi-square was significant, indicating lack of fit. However, the chi-square alone is not an appropriate indicator of fit in large data sets (Keller et al., 1998).The other absolute and incremental fit indices such as RMSEA and CFI suggested that this hypothesized two-factor CFA model of DSSI/sAD provided an excellent description of the pattern of relationships in both data sets, diabetes and non-diabetes. For example, the CFI values indicated that the model explained about 95% of the variation and covariation among observations in both diabetes and non-diabetes data sets. In the case of RMSEA, which is an absolute measure of model fit, showed that the two latent variables model was considered adequate (RMSEA = 0.077). This is comparable to what has been reported for CES-D (RMSEA = 0.069) (Zumbo, 2005). The data fit the model well regarding the fit indices for both data sets (diabetes and non-diabetes).

We examined the extent to which the DSSI subscales are associated with DSM-IV diagnoses of major depression and anxiety. The DSSI was highly specific with low sensitivity, compared to

Table 5
Sensitivity, specificity and concordance of DSM-IV depressive and anxiety disorders by DSSI subscales (women with diabetes only).

DSM-IV Affective disorders [a]	DSSI-Depression (measured at 27-year FU)								
	Cases	DSM-IV cases	Congruent (DSM-IV & DSSI)[b]	Se [c](%)	Sp [d](%)	PPV [e](%)	NPV [f](%)	OR (95% CI)	AUC (95% CI)
Lifetime disorder	32	74	18	64.30	73.30	25.01	93.70	4.93 (2.14–11.35)	0.64 (0.59–0.73)
12 month disorder	28	21	8	28.60	93.60	38.10	90.40	5.82 (2.15–15.71)	0.78 (0.67–0.88)
DSM-IV Anxiety disorders [g]	DSSI-Anxiety (measured at 27-year FU)								
Lifetime disorder	40	134	30	83.30	48.20	23.10	93.90	4.65 (1.85–11.68)	0.63 (0.56–0.71)
12 month disorder	36	76	26	72.20	75.60	35.60	93.60	8.10 (3.63–17.97)	0.77 (0.67–0.88)

Univariate analysis to obtain ORs; Se = sensitivity; Sp = specificity. 27-Year follow-up dataset was used.
[a] Major Depressive Disorder and/or dysthymia disorders.
[b] Empirical or DSM-oriented scales.
[c] The proportion of people with DSM-IV recent depression or anxiety who were cases on the relevant DSSI scale.
[d] The proportion of people with a negative DSM-IV recent depression or anxiety who had a negative screening test.
[e] Positive predictive value the proportion of cases on the DSSI scale that subsequently met the DSM-IV criteria for recent depression or anxiety.
[f] Negative predictive value the proportion of cases that were negative on the DSSI scale and subsequently did not met the DSM-IV criteria for recent depression or anxiety.
[g] Generalised Anxiety Disorder, PTSD, panic and/or phobic disorders.

the DSM IV. The number of participants in this study with diabetes, who had co-morbid depression, was too small (< 10%). However, the number of participants who screened negative using the DSSI (i.e. they had diabetes without depression) permits us to conclude that these patients would also screen negative using the DSM IV. Our ROC analyses show that 12-month DSM disorders had moderate estimates compared to lifetime disorders. This may be a result of a close time frame as the DSSI reports symptoms experienced in recent weeks.

The validity of the DSSI/sAD domains was also demonstrated through strong relationships with the equivalent SF-36 MCS scale. Our results indicated that better SF-36 MCS scores were significantly related to lower anxiety and depression symptoms of the DSSI/sAD. Correlation analysis showed a significant negative correlation between DSSI/sAD domains and the SF-36 MCS scale; thus, as anxiety or depression symptoms decreased, as measured by DSSI/sAD scale, the SF-36 MCS scores increased, indicating good mental health, endorsing the validity of our assessment. The assessment of depression and anxiety symptoms in people with diabetes is important as both conditions have been linked to the onset of diabetes and *vice versa* (Grigsby et al., 2002; Hasan et al., 2013). All three instruments (DSSI/sAD, CES-D, and SF-36 MCS) predicted the likelihood of diabetes, with differences in the sizes of the effect estimates.

4.1. Limitations

The results cannot be generalized to other women and they may differ for men. The data were collected from antenatal clinics, and women who frequently attended these outpatient clinics were more likely to be sampled than those who attended less frequently, and therefore were presumed to have fewer symptoms of anxiety and/or depression, which may have introduced selection bias. There may have been participant recall bias which would be a systematic error which may have affected accuracy of self-reported information and there was no objective confirmation of self-reported diabetes mellitus. It is likely that some women in this cohort had undiagnosed diabetes mellitus; this may be differential because women who have been diagnosed with depression or anxiety may go on to receive more health screening. Regarding sample size, it has been suggested that meaningful qualitative conclusions can be drawn from ROC/AUC experiments performed with a total of about 100 observations where a minimum of 50 cases may be required in each of the two groups (Doi, 2013). However in some groups we did not have a minimum of 50 observations. Despite the limitations, our investigation of the validity of the depression and anxiety domains of the DSSI/sAD found them to be valid measures to examine depression and anxiety symptoms in women with diabetes.

5. Conclusions

This is the first study to examine the validity of the DSSI/sAD symptoms with DSM-IV depressive and anxiety disorders in women with diabetes. These results also demonstrate that the DSSI/sAD items have similar relationships to one another in both diabetes and non-diabetes groups and therefore suggests that they have similar interpretations. Based on the partial CFA results, this study concluded that the items listed in the scale could generate the hypothesized two-factor CFA model of DSSI/sAD. As expected, the scale had poor discriminant validity and good convergent validity. The scale appears to be reliable based on good internal consistency and significant correlations with other validated instruments. The analyses presented here may be considered as a step towards better understanding of the factor structure of the DSSI/sAD.

Conflict of interest

The authors declare that they have no conflict of interest. The author(s) received no financial support for the research, authorship, and/or publication of this article.

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CHAPTER 6

Psychological health and the risk of diabetes mellitus in Australian women: A 21-year prospective study

The fourth objective of this thesis was to investigate whether change in depression symptoms was independently associated with a risk of diabetes mellitus; this was, measured at 21-years post index pregnancy in Australian women. This was necessary because changes in depression symptoms and the risk of diabetes have not been studied formally, particularly when symptoms can be recurrent or limited to one episode.

The analyses described in this chapter have been published. The research investigated depression symptoms as a risk factor for diabetes and the findings suggest that there is an elevated risk associated with persistent symptoms only. The formal citation for the published work:

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Psychological Health and the Risk of Diabetes Mellitus in Australian Women: A 21-Year Prospective Study

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Abstract

Background: Symptoms of depression can be recurrent or limited to one episode. This study discusses the prospective association between psychological health, measured as change in depression symptoms, and the risk of diabetes mellitus in Australian women.
Methods: Data obtained from the Mater-University of Queensland Study of Pregnancy. Depression was measured using the Delusions-Symptoms: States Inventory. To examine possible transitions over time, depression was grouped into four categories and assessed at different phases over the 21-year period. Multiple logistic regression models and sensitivity analysis to assess the robustness of our analytical strategy were performed.
Results: Three hundred and one women reported diabetes 21 years after the index pregnancy. Almost one-third of the women who reported depression symptoms continued to report these at a subsequent follow-up (FU) phase. About 1 in 20 women who had not reported depression symptoms at the 5-year FU did so at the subsequent 14-year FU. In prospective analyses, we did not find a significant association between diabetes and negative change (not depressed to depressed, at subsequent phase); however, for women with positive history of symptoms of depression and women with persistent symptoms, there was a 1.97-fold (95% confidence interval [CI]: 1.14–3.40) to 2.23-fold (95% CI: 1.09–4.57) greater risk of diabetes.
Conclusions: Our study suggests that an increased risk of diabetes is significantly associated with persistent depression symptoms. It highlights the importance of recognizing depression symptoms in terms of women's psychological wellbeing and thus provides a basis for targeting those most at risk.

Introduction

Diabetes mellitus may be described as a chronic progressive disorder, and is often coupled with multiple morbidities that include physical as well as psychological disorders.[1] Obesity and lack of physical exercise are well-known, modifiable risk factors of diabetes,[2] while depression is a common, comorbid, and modifiable condition[3,4] and is the most widely studied psychological condition associated with diabetes.[5–7] The prevalence of depression in people with diabetes is considerably higher than the normal population and ranges between 10% and 30%.[5,8,9] People with diabetes are at higher risk of developing depression,[3,5] and vice versa.[6,7] Symptoms of depression are recurrent, chronic, or limited to one episode; therefore depression often remains unrecognized and thus, untreated.[10]

Diabetes is a leading cause of mortality worldwide and resulted in 1.0 million (1.9%) deaths in 2000, which increased to 1.4 million (2.6%) deaths in 2011.[11] Depressive disorder is a major contributor to the burden of disease.[12] In Australia, both diabetes and depression contribute significantly to the burden of disease, with depression the leading contributor among women.[13] Stressful events are a well-documented cause of depression and women usually experience more potentially stressful life events (for example, pregnancy),[14] particularly prior to the onset of diabetes. Women with diabetes and comorbid depression reported experiencing greater disease burden and restrictions in their social interactions as well as more physical complaints,[15] poor diabetes self-care, and poor glycemic control.[16] However Rotella et al. suggested that clinical features have a much greater impact on attainment of therapeutic goals than psychopathology.[17]

Several longitudinal studies from developed countries suggest that the association between depression and diabetes is reciprocal or bidirectional.[3,18,19] The bidirectional association

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between diabetes and depression was first documented by Golden et al., who described the relationship as ''modest'' and ''partially explained by lifestyles,''[19] and Eaton and colleagues were the first to report the results of an epidemiological study that confirmed the relationship between depression and diabetes in 1996.[20] Multiple meta-analyses have suggested an association between depression and diabetes as bidirectional.[6,7,21,22] However, among psychiatric disorders or symptoms, not only depression or anxiety are independently associated with diabetes onset, impulse control disorders such as eating disorders are also important.[23]

A consistent association between diabetes and psychiatric disorders is commonly found in the literature;[3,6,7] however, change in depression symptoms (positive, negative, persistent symptoms) and the risk of developing diabetes have not been studied formally, particularly when symptoms of depression can be recurrent or limited to one episode. Therefore. this study examines the relationship between psychological health, measured as change in depression symptoms and the risk of diabetes for a large cohort of women who were followed up at intervals over a 21-year period postpartum, and takes into account a range of potential confounding factors. We performed sensitivity analysis to assess the robustness of our analytical strategy. Finally, we also examined the cross-sectional association between depression and diabetes.

Materials and Methods

Participants

We examined the association between depression symptoms and subsequent reporting of diabetes mellitus 21 years postpartum in a sample of women who were part of an Australian pregnancy and birth cohort. The Mater-University of Queensland Study of Pregnancy (MUSP) is a multidisciplinary study that represents Australia's largest longitudinal study spanning a large part of a woman's reproductive life from pre-birth for 21 years postpartum. The longitudinal study began in 1978–1979 with a number of pilot studies, and full data collection commenced in January, 1981. Women recruited into the study gave birth at the Mater Misericordiae Mothers' Hospital, which is one of two major obstetric units in Brisbane, Australia.[24,25] The original study was approved by the Human Subjects Research Ethics Committee of the University of Queensland and was conducted according to the Declaration of Helsinki.

Data were collected prospectively across the reproductive life course of a large group of women. Originally 7861 women were enrolled (8556 pregnancies), and of these women, 6753 constitute the ''MUSP mothers'' cohort. Women enrolled in the cohort had to deliver at least one live baby who neither died nor was adopted before leaving the hospital and have (initial) data from the first clinic visit (FCV), at approximately 18 weeks' gestation, and shortly after the birth. These women were reinterviewed 3 to 5 days after delivery, and data from their medical records were also collected. Additional interviews and follow-ups were conducted when the children were 6 months, 5 years, 14 years, and 21 years of age. At the start of the MUSP study, women who were cared for at this hospital were not screened routinely for gestational diabetes mellitus. Women who had been diagnosed with diabetes mellitus before the index pregnancy or who developed gestational diabetes mellitus, or type 1 diabetes mellitus, that was diagnosed during the index pregnancy ($n=46$), were excluded from analysis. After excluding women who did not provide any information regarding the presence of diabetes mellitus at the 21-year follow-up, 3663 women provided information regarding their own physical health and diabetes mellitus.

Measurement of diabetes mellitus

The outcome in our analyses was information regarding self-reported diabetes mellitus in the 21 years after the index pregnancy; data were collected using a self-administered questionnaire. Women were asked, ''Have you EVER been told by a doctor that you have diabetes mellitus (high blood sugar)?'' Women with preexisting or gestational diabetes mellitus at the time of the index pregnancy were excluded from this study, and a positive response to this question indicated that the woman had incident diabetes mellitus some time during the 21 years after the index pregnancy.[26]

Measurement of depression symptoms

The exposure was depression symptoms measured at 5 years and 14 years after delivery; symptoms were assessed using the seven-item depression subscale from the Delusion Symptoms States Inventory: State of Anxiety and Depression (DSSI/sAD).[27] This measure was developed to detect the signs and symptoms of psychopathology that limit a person's capacity to function and maintain relationships. The measure has high internal validity,[27,28] correlates well, and shares items with other measures of depression and anxiety, such as the Edinburgh Postnatal Depression Scale and the Hospital Anxiety and Depression Scale.[29] In MUSP, the Cronbach's alphas for the scale (DSSI/sAD) ranged from 0.79 to 0.88, measured at 14-year follow-up.[30] In the present study, the seven items, each with 5-point response options (never, rarely, some of the time, most of the time, or all the time), were summed [score range: 10 (all the time) to 50 (never)]; the lower the score, the more depressed the person. Women who reported four or more symptoms were considered to be depressed.[27]

Defining changes in depression symptoms: psychological health

We examined psychological health by estimating the observed proportion of women who reported a change in depression symptoms between subsequent phases of the study. In the present study, diabetes was the dependent variable at 21 years, and changes in depression symptoms (i.e., transitions) from the previous two phases (at 5- and 14-year follow-ups), was the main predictor. Potential confounding factors for each of the transition models (changes in depression symptoms) were included from the most recent or relevant previous phase. MUSP is a prospective study with unequal time intervals between data collection phases, and most of the variables are time dependent; therefore, the number of women making transitions (that is, experiencing changes in depression symptoms) for exposure at each of the unequal time intervals was estimated in the following manner:[30] possible transitions that could occur during the period from the 5-year follow-up (FU) (origin state) to the 14-year FU (destination state) were classified into four categories, based on 1 standard deviation above the mean cutoff. The

categories are (1) no depression, (2) women reporting depression at 5-year but not at 14-year FU (positive history of depression), (3) women reporting depression at 14-year FU but not at 5-year FU (negative change), and (4) women with persistent depression symptoms.

Given the length of time between the follow-ups, it is likely that some women may have experienced more than one episode of depression during that time. Two phases—post-delivery (3–5 days after delivery) and 6-month follow-up—were not included, as pregnancy or intervals after delivery may be sensitive periods with regard to depression symptoms and could confound the associations under investigation.

Sensitivity analysis

There were two phases that were not included in the main analysis: post-delivery (3–5 days after delivery) and 6-month follow-up. However, we used these phases to assess the robustness of our analytical strategy: the sensitivity analysis was performed using the same possible transitions during 3–5 days FU (origin state) to the 6-month FU (destination state). They were classified into the same four categories used in the main analysis.

Adjustment for potential confounding

The potential confounders and risk factors were identified on the basis of their association with outcomes and on the basis of *a priori* knowledge.[6,7] We determined six variables necessary to control for confounding: age, marital status to 5-year FU, family annual incomes to 5-year FU, education, use of psychotropic drugs and body mass index (BMI). Age at first clinic visit, both as a categorical and continuous variable, was included. At each phase during the study, the woman was asked her current marital status; that is, whether she was married, living together, separated/ divorced, or single. A change in marital status to 5 years post-delivery was included, and this measure was categorized into nil partner change, one change, or two plus changes. In the data collection stages of the study, namely at 5, 14, and 21 years, women were asked to select, from a 7-point scale, the (Australian) dollar range that best represented their total family annual income. In the current study, changes in family annual income to 5 years FU were categorized into consistent poverty, mid income, and high income. Maternal education at the first antenatal visit was recorded as one of three categories: did not complete secondary schooling, completed secondary schooling, and completed further or higher education. The information about psychotropic drugs was categorized as yes and no.

Participants' height and weight at first antenatal visit and an estimate of prepregnancy weight were obtained at the start of the study, from either obstetric records or questionnaires. Participants' estimates of prepregnancy weight and measured weight on the first antenatal visit correlated highly (Pearson's correlation coefficient, 0.95).[22] In the present study, BMI was categorized into normal, 10% low, and 10% high.

Statistical analysis

The data were analyzed using the Statistical Package for Social Sciences (SPSS)® version 20 and Stata IC® version 12 (StataCorp LP), with a significance level of ≤ 0.05. Descriptive statistics were used to calculate percentages, frequencies, means, and standard deviations. The Student *t*-test and chi-squared tests were used to compare the characteristics of those women who did and did not provide information about diabetes at 21-year evaluation, or who were lost to follow-up and therefore excluded from the analysis. Multiple logistic regression models were then used to further assess the association between the characteristics, depression symptoms, and diabetes, measured at FCV (at the start of the study), with those lost to follow-up or with incomplete data.

Logistic regression was used to assess the relationship between depression symptoms and self-reported diabetes mellitus. Multiple logistic regression was then used to further assess the relationship between depression symptoms and subsequent self-report of diabetes mellitus, after adjustment for other potential confounding variables. The same method was used for longitudinal and cross-sectional data.

We present a series of models that were adjusted for the potential confounders so that readers can see the effect of factors that we considered might confound this association. Multiple imputations were carried out to adjust for missing data.[31] Combining the results of the analyses of the complete datasets using Rubin's rules was performed in Stata IC version 12.0. The relationship between ''missingness'' (yes versus no) and the predictor variables was assessed using logistic regression.

Investigation of missing data

The distribution of missingness of study covariates by outcome (diabetes at 21-year follow-up is shown in Table 1. Of the 6753 women who were eligible for this study, 3663 women (54.2%) completed the 21-year follow-up and provided information regarding the diagnosis of diabetes mellitus (excluding type 1 and gestational diabetes). The same subset (3663) was used to impute for the missing values on study covariates. The proportion of missing data ranged from 0% to 20% for all variables. For the main predictor, ''changes in depression symptoms,'' 22% of data were missing, and therefore, data were imputed for all covariates except age, where the amount of missing data was zero. It is generally recommended to impute more than the percentage of missing data,[32] and therefore we imputed missing data based on the percentage of missing data on covariates. An imputation model was devised using the recommendations of Van Buuren et al.[33] The model included all the predictor variables excluding the outcome i.e. presence or absence of diabetes (yes/no). The data on covariates were assumed to be ''missing at random,'' which means that the probability of the data being missing may depend on observed values.[34]

For each of the completed datasets, a logistic regression was performed (inclusion of all predictor variables without outcome), from which the estimate of interest and its estimated variance were obtained. The results from the logistic regression modelling of the different datasets were combined using the rules proposed by Rubin to produce a multiple imputation estimate.[35] The estimate obtained for multiple imputations is simply the average of the different estimates.

Results

A total of 301 (8.2%) of the participating women reported diabetes at 21-year FU. The proportion of women with four or

Table 1. Comparison Between Lost to Follow-Up and Information Collected for Diabetes at 21-Year Follow-Up by Sociodemographic and Clinical Factors

Factors	*Number*	*Women who provided diabetes data at 21-year FU (n = 3686)*	*Women who were missing at 21-year FU (n = 3067)*	*Adjusted OR (95% CI)*[a]	*Chi-squared p-value*
Mothers' age at entry to study (years)	-	25.49 ± 5.02	24.43 ± 5.27	-	-
Changes in depression symptoms					
Persistently not depressed	3554	2710 (67.1)	844 (20.9)	1.00	> 0.05
No depression to depression	233	165 (4.1)	68 (1.7)	0.81 (0.57–1.14)	
Depression to no depression	161	119 (2.9)	42 (1.1)	1.08 (0.69–1.69)	
Persistent depression symptoms	85	59 (1.5)	26 (0.6)	0.66 (0.38–1.14)	
Age groups					
13–19	1146	482 (13.1)	664 (21.6)	1.00	
20–34	5307	3036 (82.4)	2271 (74.1)	1.17 (0.90–1.52)	
≥ 35	300	168 (4.6)	132 (4.3)	1.05 (0.66–1.68)	> 0.05
Changes in marital status to 5-year FU					
Nil partner change	3859	2695 (73.1)	1164 (37.9)	1.00	
One change	480	292 (7.9)	188 (6.1)	0.98 (0.72–1.33)	
Two plus	389	240 (6.5)	149 (4.9)	1.06 (0.76–1.47)	> 0.05
Changes in family annual income					
Consistent poverty	225	131 (3.6)	94 (3.1)	1.00	
Mid income	3424	2385 (64.7)	1039 (33.9)	1.30 (0.87–1.93)	
High income	476	369 (10.0)	107 (3.5)	1.60 (1.01–2.57)	0.001
Education level					
Incomplete secondary education	1215	572 (15.5)	643 (21.0)	1.00	
Complete secondary education	4294	2354 (63.9)	1940 (63.2)	1.23 (0.98–1.54)	
Post-secondary education	1190	734 (19.9)	456 (14.9)	1.69 (1.27–2.26)*	0.001
Body mass index					
Normal	5004	2843 (77.1)	2161 (70.5)	1.00	
Low 10%	629	303 (8.2)	326 (10.6)	1.08 (0.81–1.44)	
High 10%	599	322 (8.7)	277 (9.0)	0.96 (0.66–1.40)	> 0.05

[a]Adjusted for all other variables in table.
[b]Predictive variable equals ''diabetes at 21-year FU'' not missing (coded as ''0'') vs missing (coded as ''1'').
CI, confidence interval; FU, follow-up; OR, odds ratio.

more symptoms was 13.69% at post-delivery (3–5 days after delivery) and 13.35% at the 14-year FU. In our descriptive analysis, of the women with persistent depression symptoms, almost 17% reported diabetes compared with about 8% of women persistently not depressed. About 13% and 8% of women with positive and negative change, respectively, reported diabetes at 21-year follow-up (Fig. 1).

The proportion of women reporting transitions or changes (depression symptoms) between consecutive phases (5-year and 14-year FU) is presented in Table 2. About one-third (33.2%) of the women who reported depression symptoms (at 5-year FU) continued to report these at the subsequent 14-year FU phase. About 1 in 20 women (5.7%) who had not reported depression symptoms at the 5-year FU did so at the subsequent 14-year FU. However, transitions can only inform us of the proportion of women changing from one state to another, whereas multivariate analysis can provide further insight into the independent developmental processes associated with these transitions.[30] Results from multivariate analyses for women with imputed data on all variables are presented in Table 3, using four models. The first of these models, all of which used longitudinal data, presents unadjusted estimates, while age was included in Model 2. In Model 3, sociodemographic characteristics were included in the analysis, and finally, in the fourth model (4) the estimates were further adjusted for use of psychotrophic drugs and BMI. In the unadjusted Model 1, women with persistent symptoms (depression symptoms at both 5-year and 14-year FUs) had a 2.45-fold greater risk of diabetes (95% confidence interval [95% CI]: 1.23–4.92). The effect size of negative change (from no

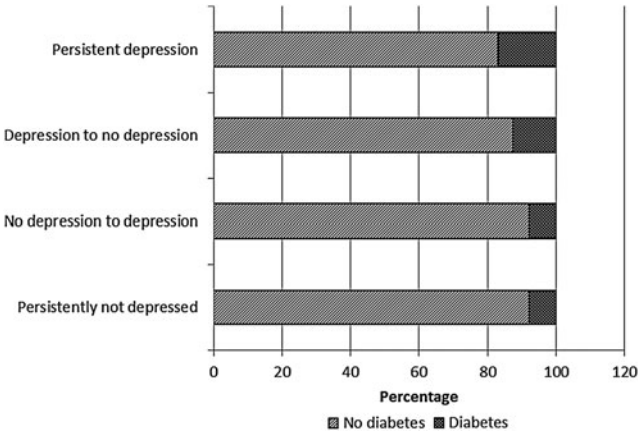

FIG. 1. Proportions of women reporting diabetes, by change in depression symptoms.

Table 2. Proportion (Percent) of Women Who Experienced Change in Depression Symptoms Between Phases

Symptom reported at each phase	*Symptom at subsequent phase (%)*		
Post-delivery	**6-month FU**		
	No depression	Depression	*n*
No depression	97.0	3.0	3415
Depression	83.1	16.9	118
6-month FU	**5-year FU**		
	No depression	Depression	*n*
No depression	94.8	5.2	3064
Depression	78.9	21.1	109
5-year FU	**14-year FU**		
	No depression	Depression	*n*
No depression	94.3	5.7	2875
Depression	66.8	33.2	178
14-year FU	**21-year FU**		
	No depression	Depression	*n*
No depression	91.4	8.6	3090
Depression	62.8	37.2	250

depression to depression) is comparable to a positive change (from depression to no depression); however, only positive change was significantly associated with diabetes (odds ratio [OR] 1.91; 95% CI: 1.12–3.25).

In Model 2, experiencing depression symptoms at both the 5-year FU and 14-year FU was significantly associated with diabetes at the 21-year FU (2.49;95% CI: 1.24–4.98), as well as positive change (1.95; 95% CI: 1.15–3.32) (Table 3). Models 3 and 4 were included to further adjust for the possible effects of sociodemographics, psychotropic drugs, and BMI, and the associations identified remained consistent and robust for persistent depression. In the fully adjusted model (Model 4), women with positive change had a 1.97-fold risk (95% CI: 1.14–3.40), while those with persistent symptoms had a 2.23-fold risk (95% CI: 1.09–4.57) of subsequent diabetes at the 21-year FU.

In cross-sectional analysis, the unadjusted and age-adjusted models produced significant associations between depression symptoms and diabetes (both measured at 21-year follow-up study) (Table 4). In the multivariate model, the association became insignificant. It is interesting to note that after multiple imputations, we observed that effect sizes were reduced, but there was increased precision suggested by narrow confidence intervals.

Sensitivity analysis

In order to examine the robustness of our findings and to ensure that our findings are not spurious, we conducted a sensitivity analysis using the same analytical strategy but with depression symptoms measured at different time points. Similar to the findings of our main analysis, women with persistent depression symptoms (6.33; 95% CI: 2.50–16.00) and women with positive change (1.82; 95% CI: 1.01–3.31) were significantly associated with diabetes.

Discussion

This study examines the prospective association between psychological health, measured as change in depression symptoms, and the reporting of diabetes mellitus in Australian women and found that almost one-third who reported depression symptoms at 5-year FU continued to report these at the subsequent 14-year FU phase. About 1 in 20 women who had not reported depression symptoms at 5-year FU did so at

Table 3. Unadjusted and Adjusted Odds Ratios (95% CI) of Reporting Diabetes at 21-Year Follow-Up, by Changes in Depression Symptoms (Longitudinal Analysis)

Items	*No diabetes (referent)*	*Diabetes mellitus*
Persistently not depressed *(referent)*	1.00	1.00
Model 1 (unadjusted)		*n* = 3663
No depression changes to depression	1.00	1.13 (0.84–1.51)
Depression changes to no depression	1.00	1.91 (1.12–3.25)*
Persistent depression symptoms	1.00	2.45 (1.23–4.92)*
Model 2[a] (age adjusted)		*n* = 3663
No depression changes to depression	1.00	1.13 (0.85–1.51)
Depression changes to no depression	1.00	1.95 (1.15–3.32)*
Persistent depression symptoms	1.00	2.49 (1.24–4.98)*
Model 3[b] (adjusted)		*n* = 3663
No depression changes to depression	1.00	1.11 (0.83–1.48)
Depression changes to no depression	1.00	1.91 (1.11–3.29)*
Persistent depression symptoms	1.00	2.41 (1.20–4.85)*
Model 4[c] (adjusted)		*n* = 3663
No depression changes to depression	1.00	1.12 (0.83–1.50)
Depression changes to no depression	1.00	1.97 (1.14–3.40)*
Persistent depression symptoms	1.00	2.23 (1.09–4.57)*

ORs obtained using imputed data.
[a]Adjusted for age.
[b]Adjusted for Model 2 plus marital status to 5-year FU, changes to family annual incomes to 5-year FU, and maternal education.
[c]Further adjusted for psychotropic drugs and body mass index.
*Statistically significant.

Table 4. Unadjusted and Adjusted Odds Ratios (95% CI) of Reporting Diabetes and Depression Symptoms at 21-Year Follow-Up (Cross-Sectional Analysis)

Items	*No diabetes (referent)*	*Diabetes mellitus*
Not depressed (referent)	1.00	1.00
Model 1 (unadjusted)		$n = 3663$
Depression symptoms	1.00	1.44 (1.03–2.02)*
Model 2[a] (age-adjusted)		$n = 3663$
Depression symptoms	1.00	1.48 (1.05–2.07)*
Model 3[b] (adjusted)		$n = 3663$
Depression symptoms	1.00	1.34 (0.94–1.89)
Model 4[c] (adjusted)		$n = 3663$
Depression symptoms	1.00	1.28 (0.90–1.82)

ORs obtained using imputed data.
[a]Adjusted for age.
[b]Adjusted for 2 plus marital status at 21-year FU, family income at 21-yr, maternal education.
[c]Further adjusted for body mass index at 21-year FU.
*Statistically significant.

the subsequent 14-year FU. Perhaps surprisingly, this study also found that a positive change in depression symptoms (depression to no depression) was significantly associated with diabetes at 21-year FU. Women who had persistent symptoms of depression at both 5-year FU and 14-year FU were significantly associated with diabetes at 21-year FU. A greater risk of diabetes in people with depression symptoms has been reported previously.[3,6,7] However, it is important to note that we did not observe a significant association between depression symptoms and diabetes in our cross-sectional analysis.

Our results indicated that psychological health, as measured by change in depression symptoms, was significantly associated with the reporting of diabetes, exerting effects independent of previously established risk factors for diabetes such as age, socioeconomic status, education, or obesity. These factors did not mediate the association between depression and diabetes; a negative change in their depression symptoms (no depression to depression symptoms) was not significantly associated with the adverse outcome (diabetes).

Conversely, women who experienced a positive change—that is, from having depression symptoms to having no symptoms—had a substantial impact on diabetes. This particular finding suggests that not only current but also previous episodes of depression are important determinant of diabetes onset. This finding is consistent with the previous study by Brown et al.[36] They examined an association between history of depression and incident diabetes and found individuals with newly diagnosed diabetes were 30% more likely to have had a previous history of depression compared with people without diabetes.[36] We replicated the same results in our sensitivity analysis, endorsing the accuracy of our main analysis.

The possible risk mechanisms linking depression with an increased risk for diabetes are described elsewhere.[6,7] Based on small relative and absolute effect sizes, Hasan et al. suggested that the causal direction (not association) between these two conditions may share common causes or risk factors.[6] Prior to this, Mezuk suggested exploring the common cause or risk factor.[37] One of the possible explanations for the increased risk of diabetes when symptoms of depression are present is chronic or recurrent stress. This would result in intermittent or sustained increased levels of cortisol and adrenaline in biologically vulnerable individuals.[38] Campayo et al. suggested that a metabolic syndrome in depressed patients may be the mediating mechanism with chronic stress as a potential mediator.[39] This hypothesis is further strengthened by the fact that antidepressant use is not associated with a lower risk of developing diabetes;[40] treating depression without addressing underlying stress does not remove or influence the risk of developing medical conditions subsequent to depression.[37] Moreover, controversy exists about the use of antidepressants and diabetes, with some antidepressants linked to worsening glucose control, others linked to improved control, and yet more showing mixed results.[41]

Stress can mediate between symptoms of depression and diabetes by over-activating the hypothalamus-pituitary-adrenal (HPA) axis; this results in elevated cortisol levels that can inhibit insulin function in a variety of ways.[42,43] The HPA dysregulation is assumed to contribute to appetite dysregulation,[44,45] or increased appetite,[46] and subsequent weight gain in stressed individuals, and it also stimulates a craving for high glycemic and high lipid foods.[45–49] Over a long period of time, this could predispose people to developing conditions such as diabetes mellitus.

Limitations of the study

There are some methodology-related limitations that may affect the generalizability of our findings. The sample was restricted to women who had at least one child, and therefore, the results cannot be generalized to other women, and it is possible that the associations identified may differ for men. Two-thirds of the original cohort provided information on depression throughout the study period, but in the regression analysis, complete data on all relevant variables was only available for just over half of these respondents. Information was derived from either medical records or self-reported, possibly leading to information bias and misclassification of depression symptoms, mental health status, and/or clinical conditions. One of the concerns with self-report measures is that it does not provide the exact timing of the onset of a medical condition.[5] It seems unlikely, however, that self-report is a major bias, as previous research has reported relatively good agreement between self-report and interviews regarding chronic somatic diseases such as diabetes.[50,51] The results suggest that with multiple follow-ups extending over a 21-year period, the relationship between depression and diabetes is strong; that is, persistent depression may lead to diabetes. Since depressive symptoms and major depression has been linked to the development of diabetes,[19,20] the possibility of comorbid anxiety and depression symptoms increasing the risk of developing diabetes should not be ruled out.

In our study a positive response for the outcome at the 21-year follow-up represents ''incident diabetes mellitus;'' however, it is possible that women developed diabetes during an earlier period (for example, between the 5-year and 14-year follow-ups); similarly, a woman could have developed gestational diabetes during a subsequent pregnancy and be included in the group of women who reported diabetes in the 21 years after the index pregnancy. These factors could lead to a higher prevalence and misclassification of the outcome as

well as potential bias. Therefore, we used the term association instead of prediction to reduce bias and also to signify a statistical relationship rather than causality.

Conclusions

Our study suggests that persistent symptoms of depression and women with a positive history of depression are associated with an elevated risk of diabetes. Despite some limitations, this study provides insight into the long-term association between changes in depression symptoms and diabetes across the reproductive life of women and provides an interesting finding that warrants further study. It also highlights that women who are depressed in their early ages (20s–30s) possibly have an increased risk of diabetes later in life, whether or not the depression persists. These women would be worth targeting for nutrition and other lifestyle modifications, as well as education about symptoms of diabetes.

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CHAPTER 7

Anxiety symptoms and the risk of diabetes mellitus in Australian women: evidence from 21-year follow-up

The fifth objective of this thesis was to investigate whether anxiety symptoms were independently associated with the risk of diabetes mellitus which was measured at 21-year post index pregnancy in Australian women. This study was undertaken because changes in anxiety symptoms and the risk of diabetes have not been studied formally, particularly when symptoms can be recurrent or limited to one episode.

The research described in this chapter investigated anxiety as risk factor for diabetes. Persistent anxiety symptoms, similar to depression, are significant risk factors for the onset of diabetes. The formal citation for the revised and resubmitted work:

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Anxiety symptoms and the risk of diabetes mellitus in Australian women: evidence from 21-year follow-up

Abstract

Objectives: This study aimed to explore the association between transitions in anxiety symptoms and the risk of diabetes in women, using longitudinal data.

Study design: This longitudinal study measured diabetes, and transitions in anxiety symptoms, using validated instrument.

Methods: Data obtained by the Mater-University of Queensland Study of Pregnancy were analysed. Anxiety was measured using the Delusion Symptoms States Inventory (DSSI). To examine possible transitions over different time periods, anxiety was grouped into four categories and assessed at different phases over a 21-year period.

Results: Three hundred and one women reported diabetes at 21-year after the index pregnancy. Almost half of the women who reported anxiety symptoms continued to report these at a subsequent Follow-up (FU) phase. About 1 in 10 women who had not reported anxiety symptoms at 5-year FU did so at the subsequent 14-year FU. In prospective analyses, we did not find significant association of diabetes with negative transition (no anxiety to anxiety at subsequent phase) or with positive history of anxiety symptom, but increasing risk was evident. Women with persistent symptoms had a 1.85-fold greater risk of diabetes (95% CI: 1.18 – 2.90). The cross-sectional analysis did not produce significant results.

Conclusions: Despite some limitations, this study provides insight into the long-term association between events of anxiety and the risk of diabetes across the reproductive life of women. However, the evidence is not strong enough to support a direct effect of anxiety in causing diabetes.

Keywords: prospective, anxiety, diabetes, Australia, women

Introduction

Diabetes mellitus (DM) may be described as a "complex chronic disease," and is defined as a disease involving multiple morbidities including physical as well as mental health conditions.[1,2] Anxiety is a common, co-morbid, modifiable condition associated with people of DM.[3-6] The prevalence of anxiety in people with DM is considerably higher than in general population.[4,7] Because of the difficulties associated with recognizing and properly diagnosing anxiety, epidemiological prevalence rates may underestimate the true number of people experiencing anxiety.[8]

A systematic review by Grigsby et al. reported that elevated symptoms of anxiety were present in 40% of patients with DM.[4] Anxiety symptoms appear to be higher among patients with type 2 diabetes mellitus (T2DM) and women compared with those with type 1 diabetes mellitus (T1DM) and men.[4,9] A recent meta-analysis (2013) found that DM is associated with an increased likelihood of having anxiety disorders and elevated anxiety symptoms. However, from the cross-sectional data used in the review, one cannot deduce the strength and/ or direction of association between DM and anxiety.[10] There are numerous other risks factors reported in previous studies which are associated with new-onset diabetes. As expected, body mass index (BMI), lifestyle factors (particularly physical inactivity), and family history of diabetes (two or more close relatives) significantly associated with new-onset diabetes, where some studies indicating that BMI and physical activity could be the major mediating factors.[11-12]

A limited number of longitudinal studies from developed countries have examined the association between anxiety and the risk of DM, but reported inconsistent results.[3,13,14] It is evident from the literature that there has been less focus on anxiety compared to depression in patients with DM,[10] although Engum (2007) attempted to examine the direction of causality and association, and concluded that anxiety was a significant independent risk factor for the onset of T2DM.[3] This prospective study examines the relationship between anxiety symptoms and the risk of DM for a large cohort of women who were followed up at intervals over a 21-year period, and takes into account a range of potential confounding factors. We performed sensitivity analysis to assess the robustness of our analytical strategy. Finally we also examined the cross-sectional association between anxiety

and DM, both measured at 21-year follow-up.

Methods

Participants

We examined the association between transitions in anxiety symptoms and subsequent reporting of DM at 21 years follow-up in a sample of women who were part of an Australian pregnancy and birth cohort. The Mater-University of Queensland Study of Pregnancy (MUSP) is a multidisciplinary study that represents Australia's largest longitudinal study of women's reproductive life-course from pre-birth for 21 years postpartum. The longitudinal study began in 1978-79 with a number of pilot studies and full data collection commenced in January, 1981. The recruited women gave birth at the Mater Misericordiae Mothers' Hospital which is one of two major obstetric units in Brisbane, Australia.[15,16]

The study prospectively collected data across the reproductive life course of a large group of 6753 women. To be enrolled in cohort women had to deliver at least one live baby who neither died nor was adopted before leaving hospital and have complete data from initial (first clinic visit (FCV) at approximately 18 weeks' gestation) and birth interview. These women were re-interviewed 3 to 5 days after delivery and data from their medical records were collected. Additional interviews were conducted when the children were 6 months, 5 years, 14 years, and 21 years of age.

The outcome in our analyses was information regarding self-reported DM in the 21 years after the index pregnancy; data were collected using a self-administered questionnaire. Women were asked "Have you EVER been told by a doctor that you have DM (high blood sugars)?" Because women with DM at the time of the index pregnancy (pre-existing or gestational) were excluded from this study, a positive response to this question indicated that the woman had incident DM some time during the 21 years after the index pregnancy.[17] Women with DM before the index pregnancy and gestational DM or T1DM, that was diagnosed during the index pregnancy (*n* = 46), were excluded from analysis.

Measurement of exposure – anxiety symptoms

The exposure was transitions in anxiety symptoms measured at 5-years and 14-years after delivery; symptoms were assessed using the seven-item anxiety subscale from the Delusion Symptoms States Inventory: State of Anxiety and

Depression (DSSI/sAD).[18] This measure had been developed to detect signs and symptoms of psychopathology that limit a person's capacity to function and maintain relationships.[18] The measure has been validated recently for use among people with and without DM.[19] The instrument correlates well, and shares items with other measures of depression and anxiety, such as the Edinburgh Postnatal Depression Scale (EPDS), and the Hospital Anxiety and Depression Scale.[20] In the present study, the seven items, each with 5-point response options (never, rarely, some of the time, most of the time, or all the time), were summed (score range: 10 (all the time) – 50 (never)); the lower the score, the more anxious the person. Anxiety symptoms were also categorized into number of symptoms (≥ 4 symptoms) and quartile based groups.[18]

Defining transitions in anxiety symptoms

We estimated the observed proportion of women who reported a transition in anxiety symptoms between subsequent phases of the study. In the present study, DM was the dependent variable at 21-years, and transitions in anxiety symptoms (i.e. transitions) from the previous two phases (at 5 and 14-year follow-ups), was the main predictor. Potential confounding factors for each of the transition models (transitions in anxiety symptoms) were included from the most recent or relevant previous phase. Since MUSP is a prospective study with unequal time intervals between data collection phases and most of the variables are time dependent,[21] the number of women making transitions (that is, experiencing transitions in anxiety symptoms) for exposure at each of the unequal time intervals was estimated in the following manner:[21] possible transitions that could occur during the period from the 5-year follow-up (FU) (origin state) to the 14-year FU (destination state) were classified into four categories, based on a cut-off of 4 or more symptoms: (1) no anxiety, (2) women reporting anxiety at 5-year but not at 14-year FU (positive transition or positive history of symptoms), (3) women reporting anxiety at 14-year FU but not at 5-year FU (negative transition or current symptoms), and (4) women with persistent anxiety symptoms. The continuous anxiety scale (10 – 50) was also categorised based on quartile ranges: (1) no anxiety symptoms, (2) mild anxiety symptoms, (3) moderate anxiety symptoms, and (4) severe anxiety symptoms.

Two phases, post-delivery (3-5 days after delivery) and 6-month follow-up were not included, as pregnancy or intervals after delivery may be sensitive periods with regards to anxiety symptoms, and could confound the associations under investigation. However these two phases were used to assess the robustness of our analytical strategy: the sensitivity analysis was performed using the same possible transitions during 3 to 5 days FU (origin state) to the 6-month FU (destination state). They were classified into the same four categories used in the main analysis.

Adjustment for potential confounding

Directed Acyclic Graphs (DAGs) have been used in epidemiological studies to represent causal relations among variables, and they have been used extensively to determine which variables are necessary to condition on for controlling for confounders.[22,23] In this study, we used a six-step process using an unbiased estimates approach to adjust for potential confounding.[24] Using the DAGs framework, we determined six variables necessary to condition on for controlling for confounders: maternal age, changes to marital status to 5-year FU, changes to family annual incomes to 5-year FU, maternal education, pre-pregnancy Body Mass Index (BMI), and depression symptoms. Maternal age at first clinic visit was included. At each phase, each woman was asked her current marital status, that is, whether she was married, living together, separated/ divorced, or single; a change in marital status to 5-years post-delivery was included. This measure was categorised into nil partner change, one change, or two plus changes. Follow-up stage of the study, namely 5, 14 and 21 year, women were asked to select, from a 7-point scale, the (Australian) dollar range that best represented their total annual family income. In the current study, changes in family annual income to 5-years FU were categorised into: consistent poverty, mid income, and high income. Maternal education at the first antenatal visit was recorded as one of three categories: did not complete secondary schooling, completed secondary schooling and completed further or higher education.

Participants' height and weight at first antenatal visit and an estimate of pre-pregnancy weight were obtained at the start of the study, either from obstetric records or questionnaires. In the present study, maternal body mass index (BMI) was derived from self-report of pre-pregnancy weight and height at the first visit and was categorized into normal, 10% low, and 10% high. Depression

symptoms at 5-year FU were measured by DSSI-Depression scale.

Statistical analysis

The data were analysed using the Statistical Package for Social Sciences (SPSS)® version 20 and STATA IC® version 12, with a significance level of ≤ 0.05. Descriptive statistics were used to calculate percentages, frequencies, means and standard deviations. The Student *t* test and chi-squared tests were used to compare the characteristics of those women who did and did not provide information about DM at 21-year evaluation, or who were lost to follow-up and, therefore, excluded from the analysis. Multiple logistic regression models were used to assess the relationship between anxiety symptoms and subsequent reporting of DM, after adjustment for potential confounding variables and for those who lost to follow-up. The cross-sectional association between anxiety symptoms and DM was also examined using 21-year follow-up data. We present a series of models that were adjusted for these potential confounders so that readers can see the effect of factors that we considered might confound this association.

Investigation of missing data

The distribution of study covariates for women who did and did not provide DM data at 21-year follow-up is shown in Table 1. Of the 6753 women who were eligible for this study, 3663 women (54.2%) completed the 21-year follow-up questionnaire and provided information regarding the diagnosis of DM. Multiple imputations were carried out to adjust for missing data.[25] The same subset (3663) was used to impute for the missing values on study covariates. An imputation model was devised using the recommendations of Van Buuren et al.[26] The model included all of the predictor variables excluding the outcome i.e. presence or absence of DM. The data on covariates were assumed to be 'missing at random'.[27]

We imputed the missing data based on the percentage of missing data on covariates.[28] The proportion of missing data ranged from 0% to 20% for all variables. For the main predictor, 'anxiety symptoms', 17% of data were missing. For the purpose of this paper, therefore, data were imputed for all covariates except age, where the amount of missing data was zero. For each of the completed datasets, a logistic regression was performed (inclusion of all predictor variables without outcome), from which

the estimate of interest and its estimated variance was obtained. The results from the logistic regression modelling of the different datasets were combined using the rules given by Rubin to produce a multiple imputation estimate.[29] This was performed in Stata IC version 12.0 (Stata Corporation, College Station, TX, USA). The estimate obtained for multiple imputations is simply the average of the different estimates. The relationship between 'missingness' (yes vs no) and the predictor variables was assessed using logistic regression. The results using both multiple imputations and complete case analysis are presented in this paper.

Our analyses show that those excluded because of missing data or loss to follow-up were more likely to be young when they gave birth (aged between 13 and 19 years), to have one change in marital status, to have been consistently poor, to have not completed secondary schooling, to have a low BMI, and to be depressed. Those who completed the questionnaire regarding self-reported diabetes mellitus at 21 years post delivery were slightly older, more likely to be young when they gave birth (aged between 13 and 19 years), more likely to have changes in marital status, more likely to belong to a high income household, better educated, and less likely to be overweight or obese compared to those who completed the questionnaire.

Results

A total of 301 (8.22%) of the participating women reported DM at 21-year FU. The proportion of women reporting transitions in mental health status (anxiety symptoms) between consecutive phases (5-year and 14-year FU) is presented in Table 2. Almost half of the women who reported anxiety symptoms continued to report these at the subsequent FU phase. About 1 in 10 women who had not reported anxiety symptoms at the 5-year FU did so at the subsequent 14-year FU.

About 15% of women with persistent anxiety symptoms reported DM at 21-year FU. However, transitions can only inform us of the proportion of women changing from one state to another, whereas multivariate analysis can provide further insight into the independent developmental processes associated with these transitions.[21] Results from multivariate analyses for women with complete case and imputed data on all variables are presented in Table 3, using four models. In the unadjusted Model 1, women with persistent symptoms (anxiety symptoms at both 5-year and 14-year follow-ups) had a 2.29-fold greater risk of

DM (95% CI: 1.54 – 3.40). After multiple imputations, the effect size (OR) was reduced by 0.16, but with increased precision i.e. narrow confidence interval (OR 2.13, 95% CI: 1.46 – 3.13). The OR of positive transition (women with positive history of symptoms of anxiety) is smaller compared to a negative transition (no anxiety to anxiety). However with imputed data, the effect size of positive history is comparable to a negative transition (difference = 0.01).

In Model 2[a], experiencing anxiety symptoms was significantly associated with DM at the 21-year FU, for either negative transition (1.61, 95% CI: 1.04 – 2.49) or persistent anxiety (2.18, 95% CI: 1.39 – 3.43). However, with imputed data, the negative transition became insignificant, while persistent anxiety remained a significant predictor of DM (Table 3). In the fully adjusted model (model 4[c]), women with negative transition had a 1.83-fold risk (95% CI: 1.17 – 2.87), while those with persistent symptoms had a 2.30-fold risk (95% CI: 1.38 – 3.84) of subsequent DM at the 21 year FU. Again with imputed data, persistent anxiety remained a significant predictor of DM with increased precision (1.85, 95% CI: 1.18 – 2.90).

In the case of quartile-based categories (derived from a continuous anxiety scale), only severe anxiety symptoms were a strong predictor of subsequent DM at 21-year FU (Table 4). The associations remained consistent and robust after adjustment for potential confounders. In the fully adjusted model, women experiencing severe anxiety symptoms had a 2.23-fold (95% CI: 1.45 – 3.42) greater risk of subsequent DM, while mild to moderate forms of anxiety did not increase the odds of subsequent DM in this study. We noticed wider confidence intervals and higher sample variability for complete case analysis compared to data generated by multiple imputations. Sensitivity analysis using the same analytical strategy but with depression symptoms measured at different time points resulted in similar findings where, women with persistent depression symptoms (2.27, 95% CI: 1.29 – 4.01) were significantly associated with the risk of DM.

In cross-sectional analysis, the unadjusted and age-adjusted models produced significant associations between anxiety symptoms and DM (both measured at 21-yr follow-up study). In the multivariate model, although the association became insignificant, an increasing trend is evident.

Discussion

This study examined the associations between transitions in anxiety symptoms and the risk of DM in a sample of women who provided information about DM at 21 year FU, and found that almost half of the women who reported anxiety symptoms 5 years after giving birth continued to report these at the subsequent 14-year FU phase. About 1 in 10 women who had not reported anxiety symptoms at 5-year FU did so at the subsequent 14-year FU. The odds of developing DM were higher among those who had persistent symptoms of anxiety at both 5-year FU and 14-year FU. This finding is in agreement with a previous study, where individuals reporting symptoms of anxiety at baseline had increased risk of onset of T2DM.[3]

A possible biological explanation for the increased risk of DM among women who have symptoms of anxiety may be associated with chronic or recurrent stress resulting in intermittent or sustained increased levels of cortisol and adrenaline in vulnerable individuals.[30] Numerous studies have suggested that anxiety are associated with an up-regulation or dysregulation of the Hypothalamo-Pituitary-Adrenal (HPA) axis resulting in elevated cortisol levels, which is also seen in depression, and that can inhibit insulin function in a variety of ways.[31-34] Obesity has been shown to be associated with anxiety disorders in various general population studies.[35] The HPA dysregulation is assumed to not only contribute to appetite dys-regulation,[36-37] or increase appetite,[38] and subsequent weight gain in stressed individuals, but stimulate a craving for high glycaemic and high lipid foods.[36,39-41] Kivimaki et al (2009) in a longitudinal study showed that people who developed anxiety or depression at one stage in their life were more likely to become obese than those in good mental health.[42]

Anxiety disorders are not only associated with DM but tend to be co-morbid with depression.[43] It is possible that the comorbidity between depression and anxiety is the most important factor. Since comorbid anxiety and depression is common; an estimated 85% of patients with depression have symptoms of anxiety,[44-46] the possibility of comorbid anxiety and depression symptoms increasing the risk of developing DM should not be ruled out. However, some studies suggest that anxiety and depression have different risk mechanisms, anxiety is characterised by hypocortisolaemia and up-regulation of glucocorticoid receptors; whereas, depression is generally characterised by

hypercortisolaemia and decreased numbers of glucocorticoid receptors.[47,48] In the present study, anxiety and depression as possible risk factors for DM could not be investigated separately.

There are a number of methodology-related limitations associated with this study that may affect the generalizability of our findings. In this study, information was derived from either medical records or self-reports and like other large population-based studies, information about exposure, outcome, and potential confounders was based on self-report and questionnaires, possibly leading to information bias and misclassification of mental health status. It seems unlikely; however, that this is a major bias, as previous research has reported relatively good agreement between self-report and in-person interviews with regard to chronic somatic diseases such as DM.[49-51] A positive response for the outcome at the 21-year follow-up represents "incident DM" but it is possible for a woman to develop DM in between the 5 and 14-year follow-ups. Similarly, it is also possible that women can develop gestational DM in a subsequent pregnancy and were included in the group of women who reported DM in the 21 years after the index pregnancy.

In conclusion, only persistent anxiety symptoms are associated with a modest increase in the risk of DM. However, the evidence is not strong enough to support a direct effect of anxiety in causing DM. Despite some limitations, this study highlights that women who are anxious in their early ages (20s-30s) possibly have an increased risk of DM later in life, whether or not the anxiety persists. The present study provides insight into the long-term association between events of anxiety and the risk of DM across the reproductive life of women and provides an interesting finding that warrants further study.

Competing interests

None declared.

Ethics approval and support

The core study was funded by the National Health and Medical Research Council (NHMRC) of Australia and was approved by the human research ethics committee of the University of Queensland.

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Table 1: Comparison between lost to follow-up and information collected for diabetes at 21-year follow-up by study variables

Factors	Number	Diabetes at 21-year		Adjusted Odds Ratio (OR: 95% CI)[b]
		Women who provided diabetes data at 21 yr (N=3663)	Women who were missing at 21 yr (N=3044)	
Mothers' age at entry (yrs)	6753	25.49 ± 5.02	24.43 ± 5.27	0.98 (0.96 – 1.00)
Transitions in anxiety				
Persistently not anxious	2994	2292 (76.5)	702 (23.5)	1.0
'No anxiety' to anxiety	421	303 (72.0)	118 (28.0)	1.36 (1.01 – 1.85)*
Anxiety to 'no anxiety'	333	246 (73.9)	87 (26.1)	1.02 (0.72 – 1.45)
Persistent anxiety symptoms	314	230 (73.2)	84 (26.7)	0.95 (0.66 – 1.37)
Changes marital status to 5-yr				
Nil partner change	3859	2695 (69.8)	1164 (30.2)	1.00
One change	480	292 (60.8)	188 (39.2)	1.09 (0.78 – 1.54)
Two plus	389	240 (61.7)	149 (38.3)	1.17 (0.83 – 1.66)
Changes in annual income				
Consistent poverty	225	131 (58.2)	94 (41.8)	1.00
Mid-income	3424	2385 (69.7)	1039 (30.3)	0.78 (0.51 – 1.20)
High-income	476	369 (77.5)	107 (22.5)	0.83 (0.50 – 1.38)
Maternal education				
Incomplete secondary education	1215	572 (47.1)	643 (52.9)	1.00
Complete secondary education	4294	2354 (54.8)	1940 (45.2)	0.92 (0.71 – 1.19)
Post secondary education	1190	734 (61.7)	456 (38.3)	1.06 (0.77 – 1.45)
Pre-pregnancy BMI				
Normal	5004	2843 (56.8)	2161 (43.2)	1.00
Low 10%	629	303 (48.2)	326 (51.8)	1.08 (0.79 – 1.48)
High 10%	599	322 (53.8)	277 (46.2)	0.96 (0.70 – 1.32)
Depression at 5-year				
No	4501	3092 (68.7)	1409 (31.3)	1.00
Yes	323	192 (59.4)	131 (40.6)	0.97 (0.65 – 1.44)

[a] =Adjusted for all other variables in table; BMI = Body Mass Index

[b] Predictive variable equals 'diabetes at 21-year' not missing (coded as '0') vs missing (coded as '1').

Table 2: Proportion (%) of women who experienced transition in anxiety symptoms between phases

Symptom reported at each phase	Symptom at subsequent phase (%)		
Post-delivery		6-month FU	
	No anxiety	*Anxiety*	n
No anxiety	92.3	7.7	5499
Anxiety	67.0	33.0	724
6-month FU		5-year FU	
	No anxiety	*Anxiety*	n
No anxiety	87.0	13.0	4219
Anxiety	52.9	47.1	440
5-year FU		14-year FU	
	No anxiety	*Anxiety*	n
No anxiety	87.6	12.4	3415
Anxiety	51.5	48.5	647
14-year FU		21-year FU	
	No anxiety	*Anxiety*	n
No anxiety	84.0	16.0	2782
Anxiety	46.8	53.2	600

FU = Follow-up

Table 3: Unadjusted and adjusted odds ratios (95% CI) of reporting diabetes at 21-year follow-up, by transitions in anxiety symptoms (longitudinal analysis)

Items	Diabetes at 21-year FU			
	No	Yes (complete case analysis)	No	Yes (imputed data)
Persistently not anxious *(Referent)*	1.00	1.00	1.00	1.00
Model 1 (unadjusted)		*n* = 3051		*n* = 3663
No anxiety to anxiety	1.00	1.34 (0.88 – 2.05)	1.00	1.14 (0.80 – 1.61)
Anxiety to no anxiety	1.00	1.22 (0.76 – 1.96)	1.00	1.15 (0.73 – 1.80)
Persistent anxiety symptoms	1.00	2.29 (1.54 – 3.40)*	1.00	2.13 (1.46 – 3.13)*
Model 2[a] (adjusted)		*n* = 2462		*n* = 3663
No anxiety to anxiety	1.00	1.61 (1.04 – 2.49)*	1.00	1.11 (0.76 – 1.58)
Anxiety to no anxiety	1.00	1.20 (0.70 – 2.04)	1.00	1.15 (0.73 – 1.81)
Persistent anxiety symptoms	1.00	2.18 (1.39 – 3.43)*	1.00	2.09 (1.41 – 3.08)*
Model 3[b] (adjusted)		*n* = 2431		*n* = 3663
No anxiety to anxiety	1.00	1.84 (1.18 – 2.88)*	1.00	1.18 (0.83 – 1.69)
Anxiety to no anxiety	1.00	1.32 (0.77 – 2.27)	1.00	1.17 (0.74 – 1.85)
Persistent anxiety symptoms	1.00	2.46 (1.54 – 3.92)*	1.00	2.15 (1.45 – 3.20)*
Model 4[c] (adjusted)		*n* = 2431		*n* = 3663
No anxiety to anxiety	1.00	1.83 (1.17 – 2.87)*	1.00	1.18 (0.83 – 1.68)
Anxiety to no anxiety	1.00	1.26 (0.71 – 2.23)	1.00	1.05 (0.65 – 1.71)
Persistent anxiety symptoms	1.00	2.31 (1.39 – 3.86)*	1.00	1.85 (1.18 – 2.90)*

[a] =adjusted for maternal age, marital status to 5-year FU, changes to family annual incomes to 5-year FU, maternal education.
[b] = adjusted for 2[a] plus pre-pregnancy body mass index.
[c] = further adjusted for depression symptoms 5-year FU.
* = $p<0.05$

Table 4: Unadjusted and adjusted odds ratios (95% CI) of reporting diabetes at 21-year follow-up, by quartile-based categories of anxiety symptoms

Items	Diabetes at 21-year			
	No *(Referent)*	Yes (complete case analysis)	No *(Referent)*	Yes (imputed data)
Quartile-based categories				
No anxiety symptoms (*Referent*)	1.00		1.00	1.00
Mild symptoms				
Model 1 (unadjusted)	1.00	0.73 (0.46 – 1.18)	1.00	0.92 (0.63 – 1.34)
Model 2[a] (adjusted)	1.00	0.69 (0.40 – 1.19)	1.00	0.92 (0.63 – 1.34)
Model 3[b] (adjusted)	1.00	0.75 (0.42 – 1.32)	1.00	0.90 (0.61 – 1.31)
Model 4[c] (adjusted)	1.00	0.74 (0.42 – 1.32)	1.00	0.90 (0.61 – 1.31)
Moderate symptoms				
Model 1 (unadjusted)	1.00	0.99 (0.69 – 1.42)	1.00	1.09 (0.78 – 1.53)
Model 2[a] (adjusted)	1.00	1.12 (0.75 – 1.66)	1.00	1.09 (0.77 – 1.53)
Model 3[b] (adjusted)	1.00	1.19 (0.79 – 1.81)	1.00	1.06 (0.75 – 1.50)
Model 4[c] (adjusted)	1.00	1.20 (0.79 – 1.81)	1.00	1.06 (0.75 – 1.49)
Severe symptoms				
Model 1 (unadjusted)	1.00	1.76 (1.24 – 2.50)*	1.00	1.82 (1.29 – 2.57)*
Model 2[a] (adjusted)	1.00	1.88 (1.27 – 2.80)*	1.00	1.81 (1.27 – 2.58)*
Model 3[b] (adjusted)	1.00	2.18 (1.44 – 3.31)*	1.00	1.83 (1.28 – 2.62)*
Model 4[c] (adjusted)	1.00	2.23 (1.45 – 3.42)*	1.00	1.70 (1.17 – 2.47)*

[a] =adjusted for maternal age, marital status to 5-year FU, changes to family annual incomes to 5-year FU, maternal education.
[b] = adjusted for 2[a] plus pre-pregnancy body mass index.
[c] = further adjusted for depression symptoms 5-year FU.
* = p<0.05; only imputed data was used.

CHAPTER 8

Diabetes mellitus and the risk of depressive and anxiety disorders in Australian women: a longitudinal study

The sixth objective of thesis was to investigate whether the presence of diabetes mellitus was independently associated with the risk of depressive and anxiety disorders; this was, measured at 27-year post index pregnancy in Australian women. Previous reports have several deficiencies, such as cross-sectional study design and most of the studies focused on symptoms measured by self-reported scales instead of DSM-based disorders.

The research described in this chapter investigated diabetes as risk factor for depressive and anxiety disorders. The formal citation for the accepted work:

1. **Hasan, S.S.,** Clavarino, A.M., Dingle, K., Mamun, A.A., Kairuz, T. (2015). Diabetes mellitus and the risk of depressive and anxiety disorders in Australian women: a longitudinal study. *J Womens Health*, *In Press*.

Diabetes mellitus and the risk of depressive and anxiety disorders in Australian women: a longitudinal study

Abstract

***Background*:** Longitudinal studies examining the risk of depressive and anxiety disorders associated with diabetes are limited. This study examined the association between diabetes and the risk of depressive and anxiety disorders in Australian women using longitudinal data.

Methods: Data were from a sample of women who were part of an Australian pregnancy and birth cohort study. Data comprised self-reported diabetes mellitus and the subsequent reporting of depressive and anxiety disorders. Mood disorders were assessed according to the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV obtained from participants using Composite International Diagnostic Interview (CIDI)-Auto (WHO WMH-CIDI CAPI: Version: 21.1.3). Multiple regression models with adjustment for important covariates were used.

Results: Women with diabetes had a higher *lifetime* prevalence of any depressive and/or anxiety disorder than women without diabetes. About 3 in 10 women with diabetes experienced a *lifetime* event of any depressive disorder, while 1 in 2 women with diabetes experienced a *lifetime* event of any anxiety disorder. In prospective analyses, diabetes was only significantly associated with a *30-day episode* of any anxiety disorder (1.53, 95% CI: 1.09–2.15). In the case of *lifetime* disorders, diabetes was significantly associated with any depressive disorder (OR 1.37, 95% CI: 1.03–1.84), major depressive disorder (OR 1.36, 95% CI: 1.01–1.85), and posttraumatic stress disorder (OR 1.42, 95% CI: 1.01–2.02).

Conclusions: The findings suggest that the presence of diabetes is a significant risk factor for women experiencing current anxiety disorders. However, in the case of depression, the association with diabetes only held for women who had experienced past episodes, there was no association with current depression. This suggests that the evidence is not strong enough to support a direct effect of diabetes as a cause of mood disorders.

Keywords: Prospective, diabetes, depressive, anxiety, disorder, women

Introduction

People with diabetes are at higher risk of developing depression and anxiety[1,2] and women are almost 50 percent more likely to experience a mood disorder than men over their lifetime.[3] Previous studies have demonstrated that a significant number of patients with diabetes have comorbid Major Depressive Disorder (MDD), Generalized Anxiety Disorder (GAD) or experience depressive and anxiety symptoms.[1,4] Globally, MDD is projected to be one of the three leading contributors to the burden of disease by 2030.[5] In industrialized countries, MDD occurs twice as frequently in women,[6] and the prevalence is significantly higher in women than in men with diabetes.[7]

Studies among people with Type 1 (T1DM) and Type 2 (T2DM) diabetes mellitus have shown a similar increase in the risk for developing depressive and anxiety disorders or symptoms;[1,8,9] In the majority of cases the initial onset of mood disorders seems to precede the diagnosis of T2DM while in T1DM, these disorders typically follow its diagnosis.[10,11] Although both types of diabetes have dissimilar etiologies and progression of the disease, depression was found to increase the severity of complications, with a similar effect on both T1DM and T2DM.[12]

Regarding anxiety disorders and diabetes, there is evidence of increased complications,[13] poor glycemic control,[14] weight gain,[15] and reduced quality of life;[16] however, there has been little focus on the possibility of diabetes as a risk factor for the onset of anxiety disorders. Unlike studies of depression, only a few longitudinal studies have examined the association between diabetes and the risk of anxiety symptoms or disorders.[10,17-21]

Most of the available studies have several methodology-related deficiencies, such as cross-sectional study design and use of self-reported scales instead of DSM-based diagnoses.[8,22] Despite the fact that literature suggests that anxiety is an important comorbid condition associated with diabetes, only one review published in 2013 examined the link between diabetes and the risk of developing anxiety.[8]

The current study bridges the gaps in the literature about depression, anxiety and diabetes. The aim is to examine the prospective association between diabetes and the risk of developing depressive and anxiety disorders, diagnosed using DSM-based criteria. The study focuses on women because both depression and anxiety are reported to be higher in women than men.[1,3,23]

Methods

Participants

We examined the association between diabetes mellitus, identified at 21-year follow-up, and the subsequent reporting of depressive and anxiety disorders, measured six years later at 27-year follow-up. The sample of women was part of an Australian pregnancy and birth cohort, the Mater-University of Queensland Study of Pregnancy (MUSP). This is a multidisciplinary study that represents Australia's largest longitudinal study of women's reproductive life-course from pre-birth for 27 years postpartum. The longitudinal study began in 1978-79 with a number of pilot studies and full data collection commenced in January, 1981. The recruited women gave birth at the Mater Misericordiae Mothers' Hospital which is one of two major obstetric units in Brisbane, Australia.[24,25]

The original study was approved by the Human Subjects Research Ethics Committees of the Mater Hospital and the University of Queensland. MUSP data were collected prospectively across the reproductive life course of a large group of women; originally 7861 women were enrolled in the study (8556 pregnancies), and 6753 of these women constitute the MUSP mothers' cohort. To be enrolled in the cohort study, women had to deliver at least one live baby who neither died nor was adopted before leaving hospital, and had to have complete data from an initial interview (first clinic visit (FCV) at approximately 18 weeks' gestation) and an interview conducted shortly after the birth. These women were re-interviewed 3 to 5 days after delivery and data from their medical records were collected. Additional interviews were conducted 6 months, 5 years, 14 years, 21 years, and 27 years after the index pregnancy. Table 1 presents the average age of the cohort at various stages, and the key outcome and exposure variables.

The exposure in our analyses was information regarding self-reported diabetes mellitus in the 21 years after the index pregnancy; data were collected using a self-administered questionnaire. Women were asked "Have you EVER been told by a doctor that you have diabetes mellitus (high blood sugars)?" Only 32 women had reported diabetes at the time of the index pregnancy, and a positive response to this question indicated that the woman had developed incident diabetes mellitus at some stage during the 21-year after the index pregnancy.[26]

A total of 3486 women provided information regarding diabetes mellitus at

21-year follow-up. These women were followed prospectively, and 283 responded positively to the question about diabetes, of whom 32 had previously been diagnosed with T1DM or gestational diabetes. The remaining 251 did not specify the type of diabetes, although their age at the time the diabetes was reported, suggested they would be predominantly participants with T2DM.

Measurement of depressive and anxiety disorders

At the 27-year follow-up, data on disorders were extracted from a computerized structured interview of depressive and anxiety symptoms using the Composite International Diagnostic Interview (CIDI). This instrument assesses current and *lifetime* prevalence of mental health disorders according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) diagnoses. The CIDI was administered via the World Health Organization-World Mental Health-Composite International Diagnostic Interview-CAPI Modularization Program (WHO WMH-CIDI CAPI: Version: 21.1.3).[27] Diagnostic concordance between the interviewer-administered CIDI and clinical checklists are satisfactory for depressive disorders, anxiety and phobic disorders.[28] The CIDI has been reported to have acceptable validity when compared with clinicians' diagnoses, with overall agreement similar to comparisons between the paper-and-pencil CIDI and clinician diagnoses.[28]

The CIDI summary outcomes (any depressive or anxiety disorder) were calculated as a positive diagnosis across a range of DSM IV diagnoses. The term 'any depressive or anxiety disorder' indicates the presence of at least one disorder. For specific disorders, we focused on MDD, GAD, panic disorder, specific phobias (e.g. social phobia), and post-traumatic stress disorder (PTSD). Other disorders were excluded because we did not have enough numbers in each category to produce reliable results. We included three categories to define onset of (any) depressive or anxiety disorders: *lifetime*, *12-month* and *30-day periods*. *Lifetime* disorders were included to estimate the prevalence of *lifetime* disorders in women with and without diabetes and to examine the association between *lifetime* disorders and diabetes irrespective of the onset of each condition.

Depressive and anxiety symptoms, measured using the Delusions-Symptoms-States-Inventory /states of Anxiety and Depression (DSSI/sAD) at

the 21-year follow-up, were used to identify cases of preexisting symptoms of anxiety and depression. Women who had symptoms of anxiety (*n* = 212), depression (*n* = 13), or comorbid depression and anxiety (*n* = 56) at the 21-year follow-up were excluded from analysis, and thus a total of 6472 women were included in the analysis.

Adjustment for covariates

The covariates were identified on the basis of their association with outcomes and on the basis of *a priori* knowledge.[8,22] The seven most frequently used covariates were selected, to adjust the associations in question;[8,22] these were: age, education level, marital status, income level, body mass index (BMI), alcohol consumption and smoking. The age of women at the 21-year follow-up was included as a continuous variable. Marital status, that is, whether she was married, living together, separated/ divorced, or single, was determined. Regarding income, women were asked to select, from a 7-point scale, the (Australian) dollar range that best represented their total annual family income. In the current study, family annual income at the 21-year follow-up was categorized into either low (<$10,440), or normal/ average income. Education was recorded as one of three categories: did not complete secondary schooling, completed secondary schooling and completed further or higher education. Smoking at the 21-year follow-up was categorized based on the number of cigarettes smoked per day: none, 1–19 cigarettes, and 20 or more cigarettes. Alcohol consumption at 21-year follow-up was categorized as abstainer, light drinker (less than half a drink per day), moderate drinker (half to less than one drink per day), or heavy drinker (average of 4 or more drinks per day).

During the interview at the 21-year follow-up, women were invited to attend a clinical assessment and to have height (*n* = 1907), and weight (*n* = 1907) measured. Height was measured using a portable stadiometer, which is accurate to 1 mm. Weight was determined with the average of 2 measurements, with the woman lightly clothed; the scale was accurate to 0.2 kg. Callaway et al. reported a high correlation between measured height and weight and self-reported height and weight at the 21-year follow-up (Pearson's correlation coefficient, 0.98) and did not find evidence of any systematic bias.[26]

Statistical analysis

The data were analyzed using the Statistical Package for Social Sciences

(SPSS) ® version 20 and STATA IC® version 12, with a significance level of ≤ 0.05. Descriptive statistics were used to present demographic data. The Student *t* test and chi-squared tests were used to compare the characteristics of those women who did and did not provide information about diabetes at the 21-year evaluation, or who were lost to follow-up and, therefore, excluded from the analysis. Multiple logistic regression analysis was then used to assess the association between characteristics, diabetes and mood (depressive and anxiety) disorders, with those lost to follow-up or with incomplete data.

Logistic regression was used to assess the relationship between diabetes and mood disorders (depression and anxiety). Multiple logistic regression models were then used after adjustment for other covariates. We present a series of models that were adjusted for these covariates so that readers can see the effect of factors that might change the strength of this association. Multiple imputations were carried out to adjust for missing data.[29] The results of the analyses of the complete datasets were combined using Rubin's rules, and were performed using Stata IC version 12.0 (Stata Corporation, College Station, TX, USA). The relationship between 'missingness' (yes/no) and the predictor variables, was assessed using logistic regression.

Investigation of missing data

First we investigated the distribution of missingness of study covariates by outcomes (depressive and anxiety disorders). Of the 6472 women who were eligible for this study, 2791 women (43.1%) completed the 27-year follow-up questionnaire and provided information regarding the classification of DSM-based depressive and anxiety disorders. The overall dataset (6472) was used to impute for the missing values on study covariates (excluding our outcomes). For the purpose of this paper, therefore, data were imputed for all covariates and the main predictor, excluding the outcomes i.e. depressive and anxiety disorders.

We imputed the missing data based on the percentage of missing data on covariates.[30] An imputation model was devised using the recommendations of Van Buuren et al.[31] The data on covariates were assumed to be 'missing at random' which means that the probability of the data being missing may depend on observed values.[32]

Data were imputed from the posterior predictive distribution of the missing data

given the observed data.[30] For each of the completed datasets, a logistic regression was performed (inclusion of all predictor variables without outcome), from which the estimate of interest and its estimated variance were obtained. The results from the logistic regression modelling of the different datasets were combined using the rules proposed by Rubin; to produce a multiple imputation estimate.[33] The estimate obtained for multiple imputations is simply the average of the different estimates.

Results

Prevalence of depressive disorders

Almost a quarter of the women who participated in the 27-year follow-up (24.4%; 681/2791) had a *lifetime* prevalence of any depressive disorder whereas the prevalence of *12-month* and *30-day* duration of any depressive disorder was much lower, at 8% (219) and 3% (87), respectively (Figure 1). A large proportion of women with diabetes (31%; 71/227) had a *lifetime* prevalence of any depressive disorder compared to 24% (611/2564) for women without diabetes, although the difference was not significant. Similarly, there was a higher proportion of women with diabetes who reported a period of duration of any depressive disorder of *12-month* (9.2% vs. 7.7%) and *30-day* (4.4% vs. 3.0%), compared to women without diabetes (Table 2).

Prevalence of anxiety disorders

Regarding any anxiety disorder, almost half of the women who participated at the 27-year follow-up (50.7%) had *lifetime* prevalence, whereas the proportion of *12-month* and *30-day* duration of any anxiety disorder was much lower, at 24% and 15% respectively (Figure 1). Just over half of the women with diabetes (54%) had a *lifetime* prevalence of any anxiety disorder compared to women without diabetes (50%). When comparing women with diabetes and those without, women with diabetes had a higher prevalence of *12-month* (27.9% vs. 23.8%) and *30-day* (20.8% vs. 14.1%) duration of any anxiety disorder (Table 2). Regarding specific disorders, most women with diabetes were found to have MDD, GAD, panic disorder, specific phobias and PTSD, as shown in Table 3.

Association between diabetes mellitus and lifetime disorders

In the unadjusted model, with complete case analysis, the proportion of women with diabetes at the 21-year follow-up was significantly associated with any *lifetime* depressive disorders (1.45, 95% CI: 1.08–1.95) (Table 4). After multiple imputations, the effect size (OR) was

reduced, but had increased precision i.e. narrow confidence interval (OR 1.37, 95% CI: 1.03–1.83). In the multivariate model, after controlling the effect on any *lifetime* depressive disorder for study covariates, diabetes remained significantly associated with a *lifetime* depressive disorder (OR 1.37, 95% CI: 1.03–1.84). In the case of MDD, diabetes was significantly associated only with *lifetime* MDD (OR 1.36, 95% CI: 1.01–1.85) (Table 5). In the case of specific anxiety disorders, diabetes was significantly associated only with *lifetime* PTSD (OR 1.42, 95% CI: 1.01–2.02) (Table 6).

Diabetes mellitus and the risk of current disorders

In case of depressive disorders, we did not find diabetes increasing the risk of *12-month* and *30-day* period of duration of any disorder in both, univariate and multivariate analyses. Similarly, in both univariate and multivariate analyses, we did not find that diabetes increased the risk of *12-month* period of duration of any anxiety disorder (Table 4).

However, in the adjusted model, with complete case analysis, women with diabetes had a 2.43-fold greater risk of any *30-day* period of duration of any anxiety disorder (95% CI: 1.59–2.25). After multiple imputations, the effect size (OR) was reduced, but with increased precision i.e. a narrow confidence interval (OR 1.54, 95% CI: 1.10–2.15). In the multivariate model, diabetes remained a significant predictor of *30-day* period of duration of any anxiety disorder (OR 1.53, 95% CI: 1.09–2.15).

Discussion

This study examined the association between diabetes and the risk of depressive and anxiety disorders in Australian women. Based on our analyses, a chronic condition (diabetes) at a baseline of 21 years post index pregnancy was significantly associated with current anxiety only during follow-up 6 years later, where 'current anxiety' was a *30-day* period of duration of any anxiety disorder. Regarding depressive disorders, diabetes was significantly associated only with *lifetime* depressive disorders as the association only held for past, not current, depression. This finding is more consistent with depression leading to diabetes, and not with diabetes increasing the risk of depression. However, diabetes may be affected by other factors (for example, weight gain or obesity) which may increase the risk of developing depression and anxiety.[34,35]

The findings should be used cautiously as establishing a causal sequence is not

straight forward in the case of depressive or anxiety disorders respectively. Generally mood disorders (anxiety and depression) begin at a young age, well before the onset of diabetes, particularly T2DM.[36] The second issue in establishing a causal sequence is that anxiety and depression are chronic or recurrent in nature,[1,23] so having a recent disorder tends to mean that the respondent has a history of such disorder.

Unlike most previous studies,[8,22] this study used standard DSM-based criteria of mood disorders to capture *lifetime*, *12-month* and *30-day* period of duration of depressive and anxiety disorders to examine their association with diabetes. In this study, we found that a higher proportion of women with diabetes had higher *lifetime*, *12-month* and *30-day* period of duration of any depressive and anxiety disorder compared to women without diabetes. Women with diabetes had a higher proportion of MDD, GAD, panic disorder, specific phobias and PTSD compared to women without diabetes.

Our finding that diabetes was significantly associated with *lifetime* depressive disorder and particularly *lifetime* MDD, are in concordance with previous studies.[1,10] This association with *lifetime* MDD may be due to the fact that in most instances the development of MDD precedes the diagnosis of diabetes by many years.[10] MDD, the most serious form of (unipolar) depressive disorders, is the most prevalent of the DSM mood disorders, among adults aged 18 years old and older,[37] with a *lifetime* prevalence of 16.6%.[38] It has been suggested that anxiety disorders are far more common in persons with MDD than *vice versa*, and pure MDD (MDD without a history of anxiety) is relatively rare.[39,40] The main anxiety disorders associated with chronic conditions are GAD and panic disorder.[41,42] However, unlike the case of MDD, we did not find significant associations between these disorders (GAD and panic) and diabetes.

Various explanations for an association between diabetes and mood disorders, particularly depression and anxiety, have been documented.[10,13,14,57] Most studies reported alterations in the activity of the Hypothalamus-Pituitary-Adrenal (HPA) axis, such as increases in cortisol production, as an underlying mechanism of increased mental disorders in people with diabetes.[8,10,22,43-45] Individuals experiencing diabetes-related complications and disability may experience depression and/ or anxiety as a consequence of the disability. [8,10,22,43,46]

Perceived disability and awareness of having a chronic illness may impose higher levels of psychological burden on people with diabetes, particularly in individuals with low levels of social support.[46]

A possible biological explanation for the increased risk of mood disorders (depression and anxiety) among people with diabetes could be obesity; it is strongly associated with diabetes,[47] and is also associated with depressive and anxiety disorders.[48,49] Roberts et al., using prospective data on older people, found evidence that obesity at baseline was associated with being depressed at follow-up 5 years later.[49] This finding is not limited to older people although females who have been obese since adolescence are also at greater risk of developing MDD and anxiety disorder compared to obese males.[50] In our sample, the only anxiety disorder significantly associated with diabetes was *lifetime* PTSD. Although there is strong evidence that PTSD increases the risk of diabetes.[51,52] The reverse is not clear despite the finding by Scott et al. that PTSD was more strongly associated with obesity compared with other anxiety subtypes or disorders.[53]

In our sample of women, these disorders may be due to alterations in hormone levels because they seemed to increase at times of changing hormone levels, such as menopause.[54] There is some evidence suggesting that managing or replacing female hormones during menopause may improve depression,[54,55] as well as glycemic control.[56] Management of depression and anxiety in patients with diabetes may be beneficial for various reasons. Appropriate recommendations may improve self-care behaviour and compliance with lifestyle modifications (dietary and physical) and adherence to prescribed medications.[57,58] This is important because mood disorders are associated with worse outcomes for patients with diabetes.[59,60] These disorders may have high recurrence rate and remain for longer duration if not properly managed.[10,61]

Limitations of the study

The strengths of this study include a large, population-based, mothers' cohort and the use of standard DSM-based classification of depressive and anxiety disorders. There are some methodology-related limitations that may affect the generalizability of our findings, such as the restriction to women who had at least one child. Therefore the results cannot be generalized to other women, and it is

possible that the associations identified may differ for men. We had limited data on some specific depressive and anxiety disorders limiting our ability to explore their association with diabetes. Another limitation is the use of self-reported diabetes. It is possible that women may have incorrectly reported the presence or absence of diabetes. However, self-report diabetes is considered to be a reliable measure of the presence of diabetes,[62] although not as accurate as direct glucose measurement. In the United States and Taiwan, a self-report of diabetes yielded high agreement when compared with medical records data and physical examination and HbA1c.[63,64] Finally, for the analysis of different types of diabetes and risk of mood disorders, we had limited information about the specific type of diabetes. However, distinguishing between T1DM and T2DM in large epidemiological studies may not be possible since the exact timing of diabetes onset and diagnosis may not be fully reliable.[65]

Implications

Although the strength of diabetes as a cause or risk factor for developing depressive or anxiety disorders is not strong, the present prospective study suggests that diabetes may represent one of the causes; other major causes such as diabetic complications for diabetes predicting mood disorders may be required to create a sufficient cause. The findings of the present study suggest that healthcare professionals, as well as people at risk, should be aware that there is an evidence of diabetes as a component cause (albeit weak) of mood disorders.

The findings of this study offer important implications for treatment and suggest that health care professionals managing people with diabetes should consider the possible link between diabetes and mood disorders. The treatment of one condition to limit the onset of another is critical in reducing the burden of disease.

Conclusions

Despite some limitations, this study suggests that the presence of diabetes significantly increases the risk of current anxiety disorders only. In case of *lifetime* disorders, diabetes was significantly associated with MDD and PTSD. This study provides evidence of mood disorders experienced by women with diabetes which warrants further study. Evidence is not strong enough to support a direct effect of diabetes in causing depressive and anxiety disorders; however, the study highlights the

importance of recognizing and managing depressive and anxiety disorders in terms of women's psychological wellbeing and, thus, provides a basis for targeting those most at risk.

Author Disclosure Statement

No competing financial interests exist.

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Table 1: Content of measurements

Stage	Average age in years	Selected variables measured
First clinic visit (1981-83)	25.01	Socio-demographics (e.g. marital status), lifestyle factors (e.g. smoking), mental health (e.g. DSSI-depression, DSSI-anxiety), physical health (e.g. weight), clinical factors (e.g. pre-existing diabetes, hypertension)
3-5 days after birth (1981-84)	25.42	Socio-demographics (e.g. employment during pregnancy), lifestyle factors (e.g. smoking), mental health (e.g. DSSI-depression, DSSI-anxiety), physical health (e.g. problems during labor, obstetrical data)
6 months follow-up (1981-1984)	26.10	Socio-demographics (e.g. changes in marital status), lifestyle factors (e.g. breastfeeding duration), mental health (e.g. post-natal DSSI-depression, DSSI-anxiety), physical health (e.g. child development)
5 years follow-up (1986-88)	31.32	Socio-demographics (e.g. children in household), lifestyle factors (e.g. patterns of child care), mental health (e.g. DSSI-depression, DSSI-anxiety, life events, CBCI), physical health (e.g. health problem inventory)
14 years follow-up (1995-97)	39.72	Socio-demographics (e.g. family income), lifestyle factors (e.g. food frequency, physical activity), mental health (e.g. DSSI-depression, DSSI-anxiety, CBCI, violence in marital status), physical health (e.g. health problem inventory)
21 years follow-up (2001-04)	46.56	Socio-demographics (e.g. number of children), lifestyle factors (e.g. food frequency, physical activity), mental health (e.g. DSSI-depression, DSSI-anxiety, medical service use, CES-D), physical health (e.g. weight, waist and hip circumference) clinical factors (e.g. diabetes, BP, respiratory function).
27 years follow-up (2008-2011)	53.26	Socio-demographics (e.g. marital status), lifestyle factors (e.g. smoking), mental health (e.g. DSSI-depression, DSSI-anxiety, CIDI), physical health (e.g. weight, waist and hip circumference) clinical factors (e.g. diabetes, BP).

Table 2: Proportion of any depressive and anxiety disorder, by main predictor, diabetes mellitus (*n* = 2791)

DSM disorders	No Diabetes n (%)	Diabetes n (%)	Total n	p-value
Any Depressive disorder				
No lifetime depressive disorder	1953 (69.97)	156 (5.59)	2109	0.012
Lifetime depressive disorder(s)	611 (21.89)	71 (2.54)	682	
No 12-month depressive disorder	2366 (84.77)	206 (7.38)	2572	0.412
12-month depressive disorder(s)	198 (7.10)	21 (0.75)	219	
No 30-day depressive disorder	2487 (89.11)	217 (7.77)	2704	0.244
30-day depressive disorder(s)	77 (2.76)	10 (0.36)	87	
Any Anxiety disorders				
No lifetime anxiety disorder	1269 (45.56)	103 (3.70)	1372	0.247
Lifetime anxiety disorders	1290 (46.32)	123 (4.42)	1413	
No 12-month anxiety disorder	1951 (70.10)	163 (5.85)	2114	0.165
12-month anxiety disorder(s)	608 (21.83)	63 (2.26)	671	
No 30-day anxiety disorder	2199 (78.96)	179 (6.43)	2378	0.006
30-day anxiety disorder(s)	360 (12.93)	47 (1.69)	407	

Note: For descriptive statistics original data without imputation was used

Table 3: Proportion of specific depressive and anxiety disorders, by main predictor, diabetes (n = 2791)

Disorders	No Diabetes n (%)	Diabetes n (%)	Total n	p-value
Major depression disorder				
No lifetime MDD	546 (19.6)	65 (2.3)	611	0.010
Lifetime MDD	2018 (72.3)	162 (5.8)	2180	
No 12-month MDD	177 (6.3)	19 (0.7)	196	0.407
12-month MDD	2387 (85.5)	208 (7.5)	2595	
No 30-day MDD	67 (2.4)	9 (0.3)	76	0.230
30-day MDD	2497 (89.5)	218 (7.8)	2715	
Generalized anxiety disorder				
No lifetime GAD	224 (8.0)	25 (0.9)	249	0.241
Lifetime GAD	2339 (83.9)	201 (7.2)	2540	
No 12-month GAD	81 (2.9)	9 (0.3)	90	0.503
12-month GAD	2482 (88.9)	217 (7.8)	2699	
No 30-day GAD	36 (1.3)	5 (0.2)	41	0.333
30-day GAD	2527 (90.5)	221 (7.9)	2748	
Panic disorder				
No lifetime panic disorder	863 (30.9)	84 (3.0)	947	0.307
Lifetime panic disorder	1701 (60.9)	143 (5.1)	1844	
No 12-month panic disorder	239 (8.6)	22 (0.8)	261	0.854
12-month panic disorder	2325 (83.3)	205 (7.3)	2530	
No 30-day panic disorder	65 (2.3)	6 (0.2)	71	0.921
30-day panic disorder	2499 (89.5)	221 (7.9)	2720	
Specific phobias				
No lifetime specific phobias	350 (12.5)	41 (1.5)	391	0.066
Lifetime specific phobias	2214 (79.3)	186 (6.7)	2400	
No 12-month specific phobias	255 (9.1)	30 (1.1)	285	0.119
12-month specific phobias	2309 (82.7)	197 (7.1)	2506	
No 30-day specific phobias	176 (6.3)	24 (0.9)	200	0.038
30-day specific phobias	2388 (85.6)	203 (7.3)	2591	
Posttraumatic stress disorder				
No lifetime PTSD	351 (12.6)	44 (1.6)	395	0.017
Lifetime PTSD	2209 (79.1)	182 (6.5)	2391	
No 12-month PTSD	148 (5.3)	14 (0.5)	162	0.799
12-month PTSD	2412 (86.4)	212 (7.6)	2624	
No 30-day PTSD	82 (2.9)	8 (0.3)	90	0.784
30-day PTSD	2478 (88.8)	218 (7.8)	2696	

Note: For descriptive statistics original data without imputation was used. MDD= major depressive disorder; GAD = generalized anxiety disorder; PTSD = posttraumatic stress disorder

Table 4: Unadjusted and adjusted odds ratios (95% CI) of reporting any DSM mood disorder by main predictor, diabetes

Disorders	Complete case analysis			Imputed data		
	No *(Referent)*	Diabetes Unadjusted OR (95% CI)	Diabetes Adjusted OR (95% CI)	No *(Referent)*	Diabetes Unadjusted OR (95% CI)	Diabetes Adjusted OR (95% CI)
Any Depressive disorder						
No lifetime depressive disorder	1.00	1.00	1.00	1.00	1.00	1.00
Lifetime depressive disorder(s)	1.00	1.45 (1.08 – 1.95)*	1.34 (0.89 – 2.01)	1.00	1.37 (1.03 – 1.83)*	1.37 (1.03 – 1.84)*
No 12-month depressive disorder	1.00	1.00	1.00	1.00	1.00	1.00
12-month depressive disorder(s)	1.00	1.22 (0.76 – 1.95)	1.00 (0.50 – 1.98)	1.00	1.17 (0.72 – 1.88)	1.16 (0.72 – 1.89)
No 30-day depressive disorder	1.00	1.00	1.00	1.00	1.00	1.00
30-day depressive disorder(s)	1.00	1.49 (0.76 – 2.92)	1.02 (0.35 – 2.97)	1.00	1.42 (0.72 – 2.79)	1.45 (0.73 – 2.88)
Any Anxiety disorder						
No lifetime anxiety disorder	1.00	1.00	1.00	1.00	1.00	1.00
Lifetime anxiety disorder(s)	1.00	1.17 (0.89 – 1.54)	1.29 (0.88 – 1.87)	1.00	1.15 (0.88 – 1.51)	1.15 (0.87 – 1.52)
No 12-month anxiety disorder	1.00	1.00	1.00	1.00	1.00	1.00
12-month anxiety disorder(s)	1.00	1.24 (0.92 – 1.68)	1.62 (1.09 – 2.40)*	1.00	1.22 (0.91 – 1.65)	1.22 (0.90 – 1.64)
No 30-day anxiety disorder	1.00	1.00	1.00	1.00	1.00	1.00
30-day anxiety disorder(s)	1.00	1.60 (1.14 – 2.25)*	2.43 (1.59 – 3.73)*	1.00	1.54 (1.10 – 2.15)*	1.53 (1.09 – 2.15)*

OR = odds ratio; models adjusted for age, education, income, marital status, body mass index, alcohol consumption, smoking

Table 5: Unadjusted and adjusted odds ratios (95% CI) of reporting MDD, by main predictor, diabetes

Disorders	No *(Referent)*	Diabetes Unadjusted OR (95% CI)	Diabetes Adjusted OR (95% CI)
No lifetime MDD	1.00	1.00	1.00
Lifetime MDD	1.00	1.37 (1.01– 1.85)*	1.36 (1.01 – 1.85)*
No 12-month MDD	1.00	1.00	1.00
12-month MDD	1.00	1.14 (0.70 – 1.87)	1.13 (0.69 – 1.86)
No 30-day MDD	1.00	1.00	1.00
30-day MDD	1.00	1.44 (0.67 – 3.13)	1.46 (0.67 – 3.20)

Note: ORs were obtained using imputed data; MDD = Major depressive disorders; models adjusted for age, education, income, marital status, body mass index, alcohol consumption, smoking

Table 6: Unadjusted and adjusted odds ratios (95% CI) of reporting anxiety disorders by main predictor, diabetes

Disorders	No *(Referent)*	Diabetes Unadjusted OR (95% CI)	Diabetes Adjusted OR (95% CI)
Generalized anxiety disorder			
No lifetime GAD	1.00	1.00	1.00
Lifetime GAD	1.00	1.22 (0.78 – 1.88)	1.19 (0.76 – 1.85)
No 12-month GAD	1.00	1.00	1.00
12-month GAD	1.00	1.17 (0.55 – 2.50)	1.10 (0.51 – 2.36)
No 30-day GAD	1.00	1.00	1.00
30-day GAD	1.00	1.46 (0.53 – 4.03)	1.38 (0.50 – 3.84)
Panic disorder			
No lifetime panic disorder	1.00	1.00	1.00
Lifetime panic disorder	1.00	1.13 (0.85 – 1.51)	1.15 (0.86 – 1.53)
No 12-month panic disorder	1.00	1.00	1.00
12-month panic disorder	1.00	1.02 (0.63 – 1.64)	1.03 (0.64 – 1.65)
No 30-day panic disorder	1.00	1.00	1.00
30-day panic disorder	1.00	1.06 (0.46 – 2.43)	1.04 (0.45 – 2.39)
Specific phobias			
No lifetime specific phobias	1.00	1.00	1.00
Lifetime specific phobias	1.00	1.32 (0.92 – 1.91)	1.31 (0.91 – 1.89)
No 12-month specific phobias	1.00	1.00	1.00
12-month specific phobias	1.00	1.33 (0.87 – 2.02)	1.32 (0.87 – 2.02)
No 30-day specific phobias	1.00	1.00	1.00
30-day specific phobias	1.00	1.53 (0.96 – 2.43)	1.51 (0.95 – 2.42)
Posttraumatic stress disorder			
No lifetime PTSD	1.00	1.00	1.00
Lifetime PTSD	1.00	1.42 (1.01 – 2.00)*	1.42 (1.01 – 2.02)*
No 12-month PTSD	1.00	1.00	1.00
12-month PTSD	1.00	1.01 (0.56 – 1.80)	1.01 (0.56 – 1.80)
No 30-days PTSD	1.00	1.00	1.00
30-days PTSD	1.00	1.06 (0.50 – 2.22)	1.04 (0.49 – 2.20)

Note: ORs were obtained using imputed data; MDD = Major depressive disorders; models adjusted for age, education, income, marital status, body mass index, alcohol consumption, smoking

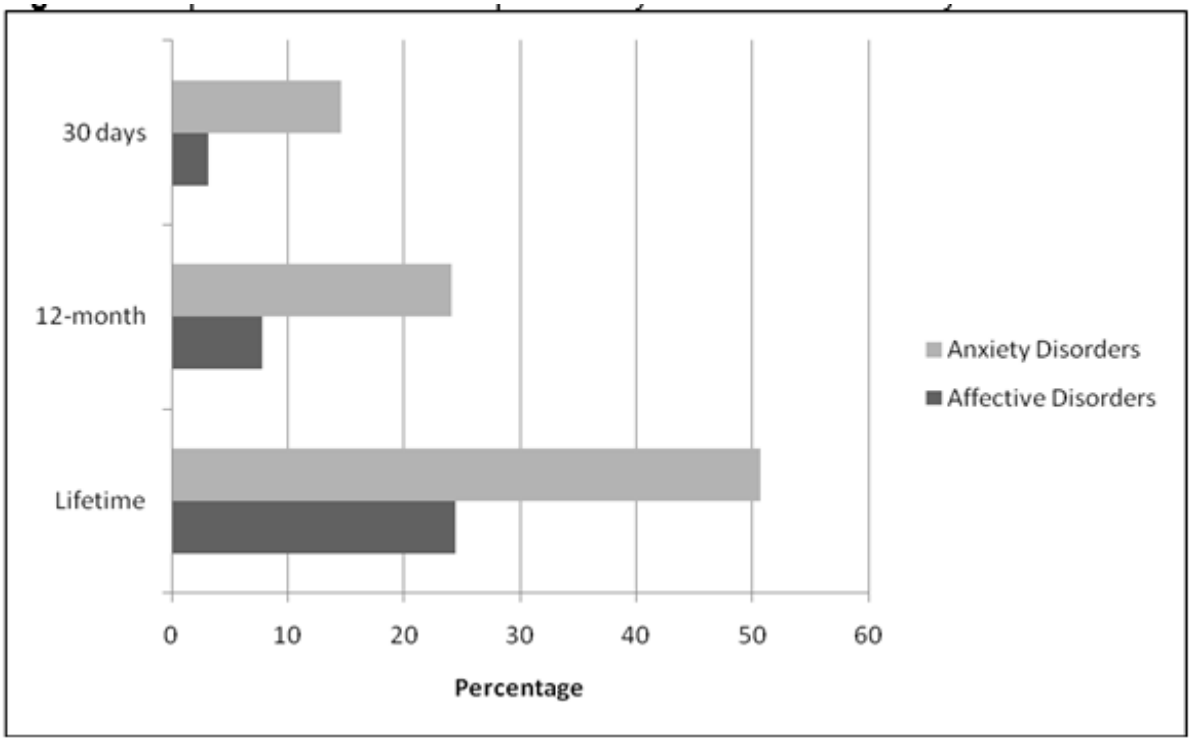

Figure 1: Proportions of women reported any depressive and anxiety disorders

RESULTS

PART 2

THE MALAYSIAN CASE-CONTROL STUDY

CHAPTER 9

Psychological health and menopause-specific quality of life of Malaysian women with type 2 diabetes

The seventh objective of this thesis was to investigate whether symptoms of depression and anxiety were associated with diabetes mellitus in Malaysian women. This study was undertaken to investigate this potential association because limited data was available about psychological problems in people with diabetes. The work described in this chapter has been revised for publication in the following form:

1. **Hasan, S.S.,** Thiruchelvam, K., Ahmed, S.I., Clavarino, A.M., Mamun, A.A., Kairuz, T. Psychological health and menopause-specific quality of life of Malaysian women with type 2 diabetes. *Asian J Psychiatr* [Revised & Resubmitted].

Psychological health and menopause-specific quality of life of Malaysian women with type 2 diabetes

Abstract

Anxiety and depression are more common among females and those experiencing diabetes and menopause. Menopausal symptoms experienced by women can vary tremendously from population to population; therefore, there is a need to investigate these symptoms and associated risk factors in different communities. This study investigated the differences in psychological health and menopause-specific quality of life (MENQOL) between women with and without diabetes type 2 (T2DM) in Malaysia. Women with T2DM (*n*=320) were matched by age range to controls without T2DM (*n*=320). Data were collected from March 2012 to January 2013. Two instruments were used to identify depression and anxiety symptoms: Center for Epidemiological Studies Depression Scale-10 and the Delusions Symptoms States Inventory. Women with diabetes had higher depressive (11.8% versus 8.4%) and anxiety (8.4% versus 6.6%) symptoms compared to women without diabetes. In both groups, the most common menopausal symptom was aches (muscles and joints). Women without diabetes had significantly higher scores for the sexual domain compared to women with diabetes (4.20 versus 3.21, $p = 0.001$). The odds that a postmenopausal woman with diabetes was depressed or anxious on the DSSI scale increased significantly when the MENQOL score on the physical, vasomotor, and psychosocial domains increased by one unit. Both diabetes and psychological problems have negative impact on MENQOL. Our findings support the view of screening postmenopausal women with diabetes for depressive and anxiety, to improve overall quality of life.

Keywords: Diabetes, type 2, depression, anxiety, women

1. Introduction

The world prevalence of diabetes is increasing rapidly; diabetes affected 382 million people worldwide in 2013 and the number is projected to rise to 592 million by 2035 (IDF, 2013). The prevalence is expected to shift to the South East Asia Region by 2025, with an estimated prevalence of 13.5% and affecting 145 million people (IDF, 2013; IDF, 2003). In Malaysia, a middle-income, developing country located in the South East Asia Region, the prevalence of diabetes has doubled over the past decade (Hasan et al., 2013; Zanariah et al., 2010). The National Health and Morbidity Survey I (NHMS-I) conducted in 1986, reported a 6.3% prevalence of diabetes among adults aged ≥35 years; however, the prevalence rose to 8.3% in 1996 and 15.2% in 2011 (Institute for Public Health, 2011; Zanariah et al., 2010). WHO estimates a total of 2.48 million people with diabetes in Malaysia by 2030 (Zanariah et al., 2010). In other developing countries such as China, Brazil and Egypt, diabetes is more prevalent among women, regardless of age (Hu et al., 2001; Wild et al., 2004). The prevalence of diabetes worldwide is similar among men and women although it is more prevalent in women after the age of 65 years (Wild et al., 2004).

Diabetes mellitus is one of the chronic, inherited or acquired diseases where patients experience a number of co-morbidities including physical and psychological problems ([a]Hasan et al., 2013). Depression and anxiety are two common, co-morbid, modifiable psychological conditions associated with diabetes ([b]Hasan et al., 2013; Smith et al., 2013), and recent meta-analyses have found significant and positive associations for diabetes with both depression ([b]Hasan et al., 2013), and anxiety (Smith et al., 2013) although, Brown et al. found no association (Brown et al., 2006). Co-morbid conditions of diabetes with depression and/or anxiety intensify the burden of diabetes symptoms (Katon, 1982; Konen et al., 1996), increase complications (Kaholokula et al., 2003), increase glycaemic levels (Gary et al., 2000), increase non adherence to medications (Lin et al., 2004), and reduce quality of life (Lloyd et al., 2000). Despite the high prevalence of diabetes in the general population in Malaysia (Institute for Public Health, 2011; Zanariah et al., 2010), only a few cohort or case-control studies are available on this topic. These studies support the hypotheses that people with diabetes are more likely to have depression or anxiety symptoms than

people who do not have diabetes (Kaur et al., 2013; Subramaniam et al., 2009). Some authors have also suggested that depression and anxiety symptoms are significantly higher in postmenopausal women compared to premenopausal women (Saqsoz et al., 2001).

Type 2 diabetes mellitus is one of the most common chronic diseases in women after menopause (Monterrosa-Castro et al., 2013). However, whether menopausal status independently influences or increases diabetes risk remains controversial (Kim, 2012; Monterrosa-Castro et al., 2013; Szmuilowicz et al., 2009). There is a higher prevalence of diabetes among women with a history of menstrual irregularity (Roumain et al., 1998), particularly in those with long and highly irregular menstrual cycles (Solomon et al., 2001). The increase in abdominal fat caused by depletion of ovarian function (Meyer et al., 2011), may cause disturbances in insulin sensitivity and glucose metabolism in postmenopausal women (Szmuilowicz et al., 2009). The changes in hormonal levels during the menopausal transition and after menopause can trigger fluctuations in blood glucose levels (Otsuki et al., 2007). The changes in hormonal levels may also result in weight gain (Simkin-Silverman et al., 2000), sleep (Australian Menopause Society, 2013), and sexual problems (Dennerstein et al., 2003).

Women can experience a number of menopausal symptoms as part of a normal physiological process that often occurs in women at an average age of 50 years (Burger et al., 2002). These symptoms are often attributable to reduced hormone levels and include vasomotor, psychological, musculoskeletal or physical and urogenital or sexual symptoms (Ogbera et al., 2011). These symptoms can affect the quality of life as measured by Menopause Specific Quality of Life (MENQOL) in postmenopausal women (Williams et al., 2009). Women with diabetes generally appeared to have worse quality of life and mental well-being compared to men with diabetes; explicitly, more diabetes-related worries and less ability to cope (Unden et al., 2008). This suggests that diabetes combined with menopausal symptoms may significantly reduce quality of life.

Anxiety and depression are more common among females and those experiencing diabetes and menopause; hence women are the target population in our study (Collins et al., 2009; Grigsby et al., 2002; Khuwaja & Kadir, 2010).

Menopausal symptoms experienced by women can vary tremendously from individual to individual, and population to population (Gold et al., 2000; World Health Organization, 1990; World Health Organization, 1996); therefore, there is a need to investigate these symptoms and associated risk factors in different communities. The primary objective of this study was to determine the pattern of menopausal symptomatology in Malaysian women with and without type 2 diabetes. The specific aims of this study include the following: to determine the association between symptoms of depression and anxiety and type 2 diabetes, and MENQOL domains and type 2 diabetes using case-control data; and to compare the symptomatology of menopause in postmenopausal women with and without type 2 diabetes.

2. Methods

2.1. Study design and population

This study involved women with diabetes matched to women without type 2 diabetes in the same age range. A frequency matching technique was used to match participants on cell instead of individual basis. The frequency matching was conducted using two conditions: presence or absence of diabetes and aged 35 years or more. The frequency matching was completed in two steps. In the first step, only women aged 35 and older who attended outpatient clinics for the management of T2DM and who had a known diagnosis of T2DM were selected (cases). In the second step, cases were matched with controls; these were women were aged 35 years and older, with no known diagnosis of T2DM. The control participants were healthy friends or unrelated family members (no blood relation) of women with type 2 diabetes.

Three Medication Therapy Adherence Clinics (MTACs), two hospital-based (Hospital Putrajaya and Hospital Tuanku Jaa'far Seremban) and one Health Clinic (Health Clinic, Seremban) in West Malaysia were selected as primary sampling sites. Non probability-based design was used to select the sampling sites. Recruitment was initially started in Hospital Putrajaya where the majority of the patients were of Malay origin. Therefore, to select a sample that included all three ethnic groups, sampling was extended to the Seremban region to include patients of Chinese and Indian ethnicity. Data were collected from March 2012 to January 2013.

Every second woman with diabetes on the respective patients' lists at the clinic sites was systematically invited to participate; verbal or written consent was

obtained from participants who met the inclusion criteria. Out of 415 women with diabetes invited to participate in the study, 320 (77%) accepted and participated. Out of 390 women without diabetes who were invited to participate, 320 (82%) accepted and participated. Face-to-face interviews were conducted at the outpatient clinics, using study questionnaires.

2.2. Assessment of Type 2 diabetes

Data on type 2 diabetes were collected through a self-administered questionnaire, where women were asked "Have you EVER been told by a doctor that you have diabetes (high blood sugars)?" with response options "yes" or "no." Participants were categorized as having type 2 diabetes if they had been told by a physician they had diabetes. Information was further confirmed by accessing patients' medical records. The presence of type 2 diabetes is identified in the hospital according to two criteria: A fasting plasma glucose (FPG) greater than or equal to 7.0 mmol/l, and random plasma glucose (RPG) greater than or equal to 11.1 mmol/l. Participants were not recruited if data on their blood glucose levels were missing, and women diagnosed with type 1 diabetes were excluded. The 320 women with diabetes were categorized based on the duration of type 2 diabetes: 0–5 years, 6–10 years, and >10 years.

2.3. Measurement of depression and anxiety symptoms

The information about the presence of depression and anxiety symptoms was measured by Delusion Symptoms States Inventory: State of Anxiety and Depression (DSSI/sAD). The DSSI is a 14-item measure developed for use with community samples and was validated against clinical samples with diagnosed mental illness (Bedford & Folds, 1977; Foulds & Bedford; Morey, 1985). The DSSI correlates well, and shares items with, other established symptoms scales such as the Edinburgh Postnatal Depression Scale (EPDS) and the Hospital Anxiety/Depression Scale (HADS) (Bedford & Deary, 1999; Najman et al., 2000). The DSSI/sAD was validated in people with diabetes (Hasan et al., 2015). The DSSI contains 14 symptoms; 7 for depression and 7 for anxiety. Participants in this study were classified as anxious or depressed when they scored 4 or more.

2.4. Menopausal status

Menopausal status was identified as pre-menopausal (no irregular periods in the previous 12 months, peri-menopausal (irregular periods less than 12 months), or

post-menopausal (cessation of menses for 12 months or longer; included both natural as well as surgical). There were very few women with peri-menopausal status; therefore we did not include them in the analysis and focused on pre and post-menopausal women only.

2.5. Measurement of menopause specific quality of life (MENQOL)

Since MENQOL is validated only in the postmenopausal population, MENQOL assessment was restricted to postmenopausal women only. The MENQOL is a validated instrument used to measure quality of life and is able to capture not only the existence of frequent menopausal symptoms, but also the extent to which the symptom(s) is/are bothersome (Hilditch et al., 1996; Van Dole et al., 2012). MENQOL was developed using data from postmenopausal women, aged between 47 to 62 years who had not been on hormone replacement therapy Hilditch et al., 1996; Van Dole et al., 2012). We used 29 questions in this study (3 questions on vasomotor aspects, 7 questions on psychosocial aspects, 16 questions on physical aspects and 3 questions on sexual aspects).

According to the scoring system of the original version of MENQOL, each question should be scored by 8 points using a Likert scale from 2 to 8, or 'not at all bothered' to 'extremely bothered'. Thus, higher scores represent poorer quality of life. For analyses, we scored the items ranging from 1 to 8 in the following manner: (1) The participant responded 'NO', she did not experience the problem; (2) the participant experienced the problem and rated it as '0' on the bothered scale; (3) The participant experienced the problem and rated it as '1' on the bothered scale; (4) rated as '2'; (5) rated as '3'; (6) rated as '4'; (7) rated as '5'; (8) rated as '6'. Each domain score ranges from 1 to 8 Hilditch et al., 1996; Van Dole et al., 2012). The total scores for vasomotor aspects ranged from 3 to 24; psychosocial aspects from 7 to 56; physical aspects from 16 to 128; and sexual aspects from 3 to 24. The total MENQOL score for each participant ranged from 29 (the lowest level) to 232 (the highest level) points. The MENQOL instrument has been validated for measuring quality of life in postmenopausal women with diabetes ([c]Hasan et al., 2013).

This study was approved by the Ethics Committee at the School of Pharmacy, The University of Queensland (Reg. No. 2011/14) and by the International Medical University Research and Ethics

Committee (Project ID No: B01/09-Res (04) 2012). The study was registered with the National Medical Research Registry (NMRR), Ministry of Health, Malaysia.

2.6. Statistical analysis

The data were analyzed using the Statistical Package for Social Sciences (SPSS)® version 20 and STATA IC® version 12, with a significance level of ≤ 0.05. Descriptive statistics were used to calculate percentages frequencies, means and standard deviations. The relationships between variables for categorical data were performed using the X^2 (Chi-Sq). Fisher's Exact test was applied in cases where the sample size was small and on occasions where we had less than 5 readings per cell for Chi-Square. Comparisons between groups with normal distribution were performed using the Student's t-test. To verify the existence of a correlation between the mean scores or other values of instruments, Pearson's correlation test was used. Logistic regression was used to investigate the relationship between: psychological conditions (depression and anxiety symptoms) and diabetes, and menopausal symptoms and diabetes. The potential confounders and risk factors were identified on the basis of their association with outcomes and on the basis of *a priori* knowledge ([b]Hasan et al., 2013; Kaur et al., 2013; Smith et al., 2013). Multiple logistic regressions were then used to assess the relationship, after adjustment for other potential confounding variables. We present a series of models that were adjusted for these potential confounders so that readers can see the effect of factors that we consider might confound this association. The overall extent to which a given model fits the data was measured by a Goodness-of-Fit test. Maximum Likelihood method was applied because it minimises bias and maximises precision of estimates. We did not include any interaction terms in the model.

The final multivariate model included seven covariates, selected using *priori* knowledge. Height (m) and weight (kg) measurements were obtained from participants' medical records and used to calculate body mass index (BMI) (kg/m^2). BMI 30 or greater was used as the cut-off point to categorize participants as obese and non-obese. The information on comorbidities or medical conditions other than type 2 diabetes was collected from medical records. Socio-demographic information were collected from patients and included age, ethnicity (Malay, Chinese, Indians and others), education (no formal education, primary education, secondary education and graduation or

post-graduation), monthly income in Ringgit Malaysia (1 RM = 3.2 $ US). In this study, the woman was asked about her current marital status, that is, whether she was single, married, divorced, or widowed.

3. Results

A total of 640 women (320 people with diabetes and 320 people without diabetes) were interviewed, and the socio-demographic characteristics of those with diabetes and those without diabetes are summarised in Table 1. The median age at diagnosis of diabetes was 50 years (Range: 27 – 70); patients with diabetes were slightly older than those without diabetes, with a mean difference in age of 9.3 ± 1.05. In the diabetes group, most of the participants were of Indian origin (37%), no income (54%), and had at least one comorbid condition. The diabetes group had lower education and income levels than the group without diabetes ($p<0.05$). None of the participants smoked and only a few (<5) were consuming alcohol at the time of study.

Of the total number of participants, 378 women (with diabetes = 258, control = 120) had attained menopausal status, while 262 women (with diabetes = 62, control = 200) had not attained menopausal status. Both women with and without diabetes experienced their first period around the same age (mean age: 13.25 versus 13.10, p = 0.680). Similarly they attained menopause around the same age (mean age: 49.35 versus 48.87, p = 0.426). Women with diabetes had a higher number of pregnancies (mean: 4.15 versus 3.64, p = 0.001), percentage of gestational diabetes and hypertension (13.4% versus 8.1%, p = 0.03) and miscarriages (22% versus 15%), compared to women without diabetes.

3.1. Anxiety, depression and type 2 diabetes

Women with diabetes had slightly higher depressive (11.8% versus 8.4%) and anxiety symptoms (8.4% versus 6.6%) compared to women without diabetes. Postmenopausal women in the diabetes group and premenopausal women in the control group had slightly higher proportions of depressive and anxiety symptoms compared to their counterparts.

In the diabetes group, most of the depressed and anxious participants were aged 45 – 54 years (27.0% and 27.5% respectively), married (49% and 50%), had completed secondary education (35% and 30%), and received a monthly

income of 7000 Ringgit Malaysia or more (24% and 23%). Anxiety was more commonly reported by Chinese women (30%), while depression was more frequently found among Indians (19%). In the non-diabetes group, most of the depressed and anxious participants were older, of Indian origin, had attained only primary education, and belonged to the lower socio-economic group. Women with 0 to 5 years' duration of diabetes had the highest percentages of depression and anxiety symptoms compared to those with 6 or more years of diabetes.

In the multivariate logistic regression model, the association between depressive symptoms and diabetes was not statistically significant, both in postmenopausal (OR 0.39, 95% CI: 0.13 – 1.17) as well as in premenopausal women (OR 0.27, 95% CI: 0.10 – 1.33), as shown in Table 2. Similarly, in the case of anxiety, we did not find significant association between anxiety symptoms and diabetes, both in postmenopausal (OR 0.46, 95% CI: 0.12 – 1.71) and premenopausal women (OR 0.91, 95% CI: 0.10 – 8.62).

3.2. MENQOL domains and type 2 diabetes

Since MENQOL is only validated in the postmenopausal population, MENQOL assessment was restricted to postmenopausal women only (case = 258, control = 120). A comparison of the pattern of occurrence of menopausal symptoms in postmenopausal women with and without the diabetes is presented in Table 3. In both groups, the most common menopausal symptom was aches of muscles and joints (> 70%) while symptoms originating from sexual aspects were the least self-reported. In terms of pattern of occurrence of specific menopausal symptoms in postmenopausal women, women with diabetes reported significantly higher percentages compared to women without diabetes for the following symptoms: nights sweats (32.9% versus 21.7%, p = 0.025), decrease in physical strength (72.1% versus 56.7%, p = 0.003), decrease in stamina (73.3% versus 53.3%, p = 0.001), lack of energy (73.6% versus 54.2%, p = 0.001), and frequent urination (51.9% versus 27.5%, p = 0.001).

Women with diabetes had insignificantly higher scores for vasomotor (6.17 versus 5.75, *p* = 0.357) and physical (37.01 versus 36.75, *p* = 0.884) domains compared to women without diabetes. However in terms of total MENQOL score, women without diabetes had an insignificantly higher score (59.85 versus

58.36, p = 0.566). Interestingly women without diabetes also had significantly higher score for the sexual domain compared to women with diabetes (4.20 versus 3.21, p = 0.001).

The odds that a postmenopausal woman did not have diabetes, significantly increased when the MENQOL score on the sexual domain decreased by one unit (OR 0.69, 95% CI: 0.57–0.84). The results for other domains were statistically insignificant. Table 4 shows the results of the logistic regression analysis examining the relationship between the presence or absence of diabetes and each of the four MENQOL domains.

3.3. Depression, anxiety and MENQOL domains

The odds that a postmenopausal woman with diabetes was depressed on the DSSI scale increased 1.13 times when the MENQOL score on the vasomotor domain increased by one unit (95% CI: 1.04–1.22), the odds ratio increased 1.14 times when the MENQOL score on the psychosocial domain increased by one unit (95% CI: 1.07–1.21), and the odds ratio increased 1.08 times when the MENQOL score on the physical domain increased by one unit (95% CI: 1.04–1.11). Similar results were obtained for anxiety symptoms and MENQOL domains. Similarly, the odds that a postmenopausal woman without diabetes was depressed or anxious on the DSSI scale increased significantly when the MENQOL score on the physical, vasomotor, and psychosocial domains increased by one unit. Table 5 shows the results of the logistic regression analysis examining the relationship between symptoms of depressive and anxiety and each of the four MENQOL domains.

4. Discussion

This study investigated the psychological health and menopause-specific quality of life among pre and postmenopausal women with and without diabetes in Malaysia. In this study, most of the patients with diabetes were of Indian origin (36.6%), followed by Chinese (30.9%) and Malay (30.6%); these demographics are similar to those of NHMS III (Zanariah et al., 2010). Women with diabetes were slightly older than women who did not have diabetes, suggesting that the age range differs between the two groups. The sharpest increase in the prevalence of diabetes occurred after the age of 55 years. Women in the 55 to 64 year age group had the highest proportion of diabetes. In our study, about 40% of those with type 2 diabetes had experienced menopause

compared to only 18% of those without diabetes, suggesting that an earlier onset of diabetes results in an earlier age of menopause. This is consistent with reports that revealed an early menopausal age for women with diabetes compared to women without diabetes (Malacara et al., 1997; Monterrosa-Castro et al., 2013).

As described earlier, women experience a variety of symptoms during or after menopause (Ogbera et al., 2011). Consistent with previous reports (Australian Menopause Society, 2013; Ogbera et al., 2011), the most common complaint reported by participants in both groups was aches in muscles and joints. Our findings are also similar to those of Ogbera et al., who found that half the women in both groups reported poor memory (Ogbera et al., 2011). In terms of MENQOL domains, symptoms originating from the sexual aspects were the least self-reported and the least reported symptom was that of facial hair, which occurred in 2.4% of the participants. This is in agreement with a study among menopausal Arabic women in Sydney (Lu et al., 2007), where the presence of facial hair was the least reported menopausal symptom.

Of the physical, psychosocial and sexual symptoms, our findings show that night sweats, decreased physical strength, decreased stamina, lack of energy, and frequent urination were the predominant menopausal symptoms reported by our participants with diabetes. The MENQOL instrument used for screening menopausal symptoms contained some symptoms that could be confounded with symptoms of diabetes or poor controlled diabetes (Hilditch et al., 1996; Van Dole et al., 2012). However, we demonstrated the validity of MENQOL domains in a sample of women with diabetes in a previous study and concluded that MENQOL can be administered to a population with diabetes ([c]Hasan et al., 2013).

Although women with diabetes reported higher percentages of depression (11.8% versus 8.4%) and anxiety symptoms (8.4% versus 6.6%) compared to women without diabetes, the differences were statistically insignificant. Similarly, anxiety (31.8% versus 33.3%) and depression symptoms (20.9% versus 20.8%) as measured by the psychosocial domain of MENQOL were also similar for both groups, suggesting that attainment of menopausal status did not increase or decrease the psychological burden in participating women. A recent study in

Malaysia (2013) found a relatively higher prevalence of depression and anxiety symptoms among people with diabetes (Kaur et al., 2013). This may be a result of differences in the screening instrument, the age groups (less than 35 and more than 75 years), and the inclusion of male participants. Consistent with the findings of previous studies, we found that depression was more prevalent among women of Indian ethnicity (19%), while anxiety was more prevalent among the Chinese ethnicity (30%) (Dunlop et al., 2003; Fisher et al., 2004). Ben-Haroush et al., hypothesized that minority groups, are more likely to experience socioeconomic constraints, poor education and perceived discrimination that may result in higher prevalence of psychological and chronic conditions (Ben-Haroush et al., 2004); this applies particularly to Indians in our study,.

Women with duration of 0 to 5 years of diabetes had the highest percentages of depression and anxiety symptoms compared to those with 6 or more years of diabetes. Our findings are in agreement with previous studies conducted in Malaysia (2013) and Bahrain (2008) (Almawi et al., 2008; Kaur et al., 2013). This may be attributed to inadequate or inefficient coping skills for managing diabetes shortly after diagnosis.

Co-morbid conditions of diabetes and anxiety disorders are linked to increased diabetes burden (Andrews et al., 1998), increased complications (Jonas et al., 1997), poor glycaemic control (Anderson et al., 2002), and reduced quality of life (Mendlowicz & Stein, 2001). However, there has been little focus on the association of diabetes with anxiety. A recent meta-analysis found significant and positive associations for diabetes with both anxiety disorders and elevated anxiety symptoms (Smith et al., 2013). However, a limited number of longitudinal studies from developed countries reported inconsistent results about the association between anxiety and diabetes (Smith et al., 2013). Anxiety is an episodic disorder and participants may have not had anxiety attacks during the time of the studies. We also noted significant positive correlation between anxiety and depression suggesting that as the depression symptoms increased, anxiety symptoms correspondingly increased. It is well established that depression and anxiety go hand in hand and they are usually diagnosed together (Center for Disease Control and Prevention, 2008).

Regarding depression as a cause of diabetes, previous studies reached different conclusions ([a]Hasan et al., 2013); Saydah et al. found no evidence to support an etiological relationship between depression and diabetes (Saydah et al., 2003), and a retrospective Scandinavian study published in 2004 also reported no overall relationship (van den Akker et al., 2004). However, a recent meta-analysis (2013) documented that symptoms of depression are associated with diabetes ([a]Hasan et al., 2013).

4.1. Limitations

There are a number of limitations associated with this study that may affect the generalizability of our findings. This study used self-report scales to assess menopausal, depressive and anxiety symptoms; although diagnosis of these conditions by a trained health care professional according to standard criteria would be preferable, this was not possible. Participant recall bias may be a systematic error due to lack of completeness of memory of past events or experiences, and may have affected the accuracy of self-reported information. Although we applied systematic sampling, participants who frequently attended the outpatient clinics were more likely to be sampled than those who attended less frequently; we presume that they had better overall health status due to their regular attendance. This may have introduced selection bias. Finally, the control group is slightly younger than the group of cases and there also seem to be differences in ethnicity and income level. These differences in cases and controls could well explain differences in depressive and anxiety symptoms.

5. Conclusions

Despite some limitations this study has both clinical and research implications. From the clinical perspective, the results indicate that symptoms of depression and anxiety are more prevalent among women with diabetes than women without diabetes. Both diabetes and psychological issues have negative impact on MENQOL. Except for some aspects, the menopausal symptomatology in Malaysian women with type 2 diabetes is comparable to symptomology among women without type 2 diabetes. The finding that symptoms of depression and anxiety are more prevalent among women with newly diagnosed diabetes warrants clinical attention because they are associated with an increased risk of developing major forms of depression and/or anxiety. In order to achieve desired therapeutic and non-therapeutic outcomes,

healthcare professionals should screen postmenopausal women with diabetes for depressive and anxiety symptoms.

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Table 1: Socio-demographic characteristics of women, by diabetes and menopausal status

Variables	No type 2 diabetes N = 320 N (%)			Type 2 Diabetes N = 320 N (%)		
	Pre-menopause	Post-menopause	Total N	Pre-menopause	Post-menopause	Total N
Age						
35 – 44	91 (90.0)	10 (10.0)	101	32 (91.4)	3 (8.6)	35
45 – 54	104 (67.0)	51 (33.0)	155	28 (39.4)	43 (60.6)	71
55 – 64	4 (9.1)	40 (90.9)	44	0 (0.0)	127 (100.0)	127
> 65	1 (5.0)	19 (95.0)	20	2 (2.3)	84 (97.7)	86
Marital Status						
Single – Not married	10 (90.9)	1 (9.1)	11	1 (100.0)	0 (0.0)	1
Married	174 (63.0)	102 (37.0)	276	61 (21.2)	226 (78.8)	287
Divorced	11 (73.3)	4 (26.7)	15	0 (0.0)	4 (100.0)	4
Widowed	5 (27.8)	13 (72.2)	18	0 (0.0)	28 (100.0)	28
Ethnicity						
Malay	49 (73.1)	18 (26.9)	67	23 (23.5)	75 (76.5)	98
Chinese	95 (59.4)	65 (40.6)	160	15 (15.1)	84 (84.9)	99
Indian	51 (61.5)	32 (38.5)	83	22 (18.8)	95 (81.2)	117
Others	5 (50.0)	5 (50.0)	10	2 (33.3)	4 (66.7)	6
Education level						
No educ.	1 (12.5)	7 (87.5)	8	1 (2.4)	40 (97.6)	41
Primary educ.	20 (55.6)	16 (44.4)	36	29 (18.2)	130 (81.8)	159
Secondary educ.	100 (59.5)	68 (40.5)	168	25 (25.0)	75 (75.0)	100
Bachelors or higher	79 (73.1)	29 (26.9)	108	7 (35.0)	13 (65.0)	20
Monthly income						
No income	30 (49.2)	31 (50.8)	61	15 (8.6)	159 (91.4)	174
< 3500	35 (66.0)	18 (34.0)	53	20 (23.8)	64 (76.2)	84
3500 – 6999	54 (62.8)	32 (37.2)	86	12 (36.4)	21 (63.6)	33
≥ 7000	81 (67.5)	39 (32.5)	120	15 (51.7)	14 (48.3)	29
Co morbidities						
No	170 (69.1)	76 (30.9)	246	0 (0.0)	0 (0.0)	0
Yes	30 (40.5)	44 (59.5)	74	62 (19.4)	258 (80.6)	320
Obesity						
Non obese	182 (61.1)	116 (38.9)	298	53 (17.9)	243 (82.1)	296
Obese	18 (81.8)	4 (18.2)	22	8 (34.8)	15 (65.2)	23

Table 2: Unadjusted and adjusted odds ratios (95% CI) of depression and anxiety symptoms according to diabetes and menopausal status

Variables	Postmenopausal women (N = 378)		Premenopausal women (N = 252)	
	No Diabetes (Referent)	Diabetes	No Diabetes (Referent)	Diabetes
Depression symptoms				
Unadjusted	1.0	0.42 (0.21 – 0.83)	1.0	0.71 (0.26 – 1.96)
Age Adjusted	1.0	0.55 (0.26 – 1.15)	1.0	0.71 (0.26 – 1.98)
Fully Adjusted	1.0	0.39 (0.13 – 1.17)	1.0	0.27 (0.10 – 1.33)
Anxiety symptoms				
Unadjusted	1.0	0.47 (0.21 – 1.04)	1.0	0.74 (0.24 – 2.29)
Age Adjusted	1.0	0.54 (0.23 – 1.25)	1.0	0.75 (0.24 – 2.32)
Fully Adjusted	1.0	0.46 (0.12 – 1.71)	1.0	0.91 (0.10 – 8.62)

Note: Full logistic model adjusted for age, ethnicity, marital status, education level, monthly income, comorbidities, and obesity.

Table 3: Comparison of the pattern of occurrence of menopausal symptoms in post-menopausal women with and without diabetes, given as n (%)

Domains	Total N = 378	No diabetes N = 120	Diabetes N = 258	p-value
Vasomotor				
1. Hot flushes or flashes	86	42 (35.0)	44 (17.1)	0.001
2. Night sweats	111	26 (21.7)	85 (32.9)	0.025
3. Sweating	165	54 (45.0)	111 (43.0)	0.718
Psychosocial				
4. Being dissatisfied with personal life	26	17 (14.2)	9 (3.5)	0.001
5. Feeling anxious or nervous	122	40 (33.3)	82 (31.8)	0.764
6. Experiencing poor memory	199	63 (52.5)	136 (52.7)	0.969
7. Accomplishing less than I used to	82	37 (30.8)	45 (17.4)	0.003
8. Feeling depressed, down or blue	79	25 (20.8)	54 (20.9)	0.983
9. Being impatient with other people	134	60 (50.0)	74 (28.7)	0.001
10. Feelings of wanting to be alone	70	26 (21.7)	44 (17.1)	0.283
Physical				
11. Flatulence (wind) of gas pains	149	49 (40.8)	100 (38.8)	0.701
12. Aches in muscles and joints	278	85 (70.8)	193 (74.8)	0.415
13. Feeling tired or worn out	254	81 (67.5)	173 (67.1)	0.932
14. Difficulty sleeping	164	50 (41.7)	114 (44.2)	0.645
15. Aches in back of head or neck	146	65 (54.2)	81 (31.4)	0.001
16. Decrease in physical strength	254	68 (56.7)	186 (72.1)	0.003
17. Decrease in stamina	253	64 (53.3)	189 (73.3)	0.001
18. Feeling a lack of energy	255	65 (54.2)	190 (73.6)	0.001
19. Drying skin	167	52 (43.3)	115 (44.6)	0.821
20. Weight gain	92	44 (36.7)	48 (18.6)	0.001
21. Increased facial hair	9	8 (6.7)	1 (0.4)	0.001
22. Changes in appearance, texture or tone skin	67	40 (33.3)	27 (10.5)	0.001
23. Feeling bloated	56	32 (26.7)	24 (9.3)	0.001
24. Low backache	148	43 (35.8)	105 (40.7)	0.367
25. Frequent urination	167	33 (27.5)	134 (51.9)	0.001
26. Involuntary urination when laughing or coughing	77	27 (22.5)	50 (19.4)	0.483
Sexual				
27. Changes in sexual desire	36	27 (22.5)	9 (3.5)	0.001
28. Vaginal dryness during intercourse	39	29 (24.2)	10 (3.9)	0.001
29. Avoiding intimacy	26	18 (15.0)	8 (3.1)	0.001

Note: p-value obtained by Chi-Sq test

Table 4: Results of logistic regression analyses with diabetes as the dependent variable and the MENQOL domains as the independent variables (*N* = 378)

Domains	No Diabetes N = 120 *(Referent)*	Diabetes N = 258	p-value
Vasomotor			
Mean (SD)	5.75 (0.33)	6.17 (0.27)	*p* = 0.357
Unadjusted	1.0	1.03 (0.97 – 1.08)	
Age Adjusted	1.0	1.06 (0.99 – 1.12)	
Fully Adjusted	1.0	1.07 (0.97 – 1.18)	
Psychosocial			
Mean (SD)	13.15 (0.66)	11.96 (0.37)	*p* = 0.096
Unadjusted	1.0	0.97 (0.94 – 1.01)	
Age Adjusted	1.0	0.98 (0.94 – 1.01)	
Fully Adjusted	1.0	0.95 (0.91 – 1.00)	
Physical			
Mean (SD)	36.75 (1.67)	37.01 (0.93)	*p* = 0.884
Unadjusted	1.0	1.00 (0.99 – 1.02)	
Age Adjusted	1.0	1.00 (0.99 – 1.02)	
Fully Adjusted	1.0	0.99 (0.97 – 1.01)	
Sexual			
Mean (SD)	4.20 (0.20)	3.21 (0.08)	*p* = 0.001
Unadjusted	1.0	0.68 (0.58 – 0.81)*	
Age Adjusted	1.0	0.68 (0.58 – 0.80)*	
Fully Adjusted	1.0	0.69 (0.57 – 0.84)*	
Total MENQOL score			
Mean (SD)	59.85 (2.48)	58.36 (1.38)	*p* = 0.566
Unadjusted	1.0	1.00 (0.99 – 1.01)	
Age Adjusted	1.0	0.99 (0.99 – 1.01)	
Fully Adjusted	1.0	0.99 (0.98 – 1.01)	

Note: Means were compared using t test. Full logistic model adjusted for age, ethnicity, marital status, comorbidities, and obesity.

Table 5: Results of logistic regression analyses with depression and anxiety symptoms as the dependent variables and the MENQOL domains as the independent variables, by diabetes (*N* = 378)

Dependent	Domains	Odds Ratio	p-value	95% CI
Women with diabetes (*n* = 258)				
Depression [a]	Vasomotor	1.13	0.004	1.04 – 1.22
	Psychosocial	1.14	0.001	1.07 – 1.21
	Physical	1.08	0.001	1.04 – 1.11
Anxiety [b]	Vasomotor	1.18	0.001	1.07 – 1.29
	Psychosocial	1.14	0.001	1.07 – 1.22
	Physical	1.09	0.001	1.05 – 1.13
Women without diabetes (*n* = 120)				
Depression [a]	Vasomotor	1.22	0.002	1.08 – 1.39
	Psychosocial	1.19	0.001	1.10 – 1.30
	Physical	1.06	0.001	1.03 – 1.10
	Vaginal/Sexual	0.98	0.884	0.78 – 1.24
Anxiety [b]	Vasomotor	1.23	0.006	1.06 – 1.42
	Psychosocial	1.21	0.001	1.10 – 1.34
	Physical	1.06	0.289	1.03 – 1.10
	Vaginal/Sexual	1.01	0.931	0.79 – 1.29

[a] = depression was measured with DSSI: depressed = 1; not depressed = 0; [b] = anxiety was measured with DSSI: anxious = 1; not anxious = 0; Logistic model adjusted for age and marital status

CHAPTER 10

Relation between mental health-related variables and glycemic control in Malaysian women with type 2 diabetes mellitus

The eighth and final objective of this thesis was to investigate whether depression and anxiety symptoms were associated with the poor glycemic control in Malaysian women. This study was undertaken as good quality data on this association was lacking in Malaysia, yet T2DM is a major public health problem in Malaysia.

The work described in this chapter investigated the association between symptoms of depression and anxiety and poor glycemic control and has been published in the following form:

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ORIGINAL ARTICLE

Relation between mental health-related variables and glycemic control in Malaysian women with type 2 diabetes mellitus (T2DM)

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Abstract The primary objective of this study was to examine the association between depression, anxiety symptoms, and glycemic control in Malaysian women with type 2 diabetes mellitus (T2DM). Another objective was to examine the association between glycemic control and mental status, measured by mental composite score (MCS). This study was conducted on 611 randomly sampled Malaysian women with T2DM who were treated as outpatients at medication therapy adherence clinics (MTAC). The Delusions-Symptoms-States Inventory: State of Anxiety and Depression (DSSI/SAD) and Center for Epidemiologic Studies Depression Scale 10 (CES-D 10) were used. Five most recent readings of hemoglobin A1c (HbA1c), fasting, and random glucose levels were recorded. Regression analysis was used to correlate glycemic control with depression, anxiety symptoms, and MCS, while considering potential confounders. For depression symptoms, an increase of one category was associated with a small average HbA1c increase of 0.10 % (95 % CI −0.38, 0.68), whereas for anxiety symptoms, there was a small decrease in average HbA1c of 0.44 % (95 % CI −1.17, 0.28); both were not significant. Very poorly controlled HbA1c was not significantly associated with symptoms of depression (OR 1.43, 95 % CI 0.45–4.55) or anxiety (OR 0.47, 95 % CI 0.15–1.49). MCS was found to have a strong inverse correlation with HbA1c. That is, women who reported poor MCS had a significantly higher, and therefore very poorly controlled, HbA1c (OR 1.70, 95 % CI 1.01–2.88). The presence of depression and anxiety symptoms was not significantly associated with glycemic control in women with T2DM, supporting the hypothesis that argues against the existence of a link between depression, anxiety, and glycemic control.

Keywords Mental health · Depression · Anxiety · Type 2 diabetes mellitus · Women · Malaysian

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Introduction

People with diabetes mellitus (DM) experience a number of complications during the course of the disease, including psychological problems. Depression and anxiety are the two most common comorbid conditions associated with DM [1]. Comorbid depression or anxiety together with DM may result in poor metabolic control, higher complication rates, poorer quality of life (QoL), increased management costs, disability, and mortality rates [2–4]. It has been estimated that depressive disorders are higher among women with or without diabetes than among men; globally, depressive disorders in women were the fourth leading cause of disease burden and the seventh leading cause in men [2–4]. Studies from developed countries reported higher prevalence of depression in women compared to men [3, 5]. Although not many studies have been

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conducted in developing countries, a higher prevalence of depression and anxiety symptoms among women has been reported [6, 7]. Women with DM also exhibit poorer diabetes self-care, glycemic control, and QoL than men with DM, which are further exacerbated by depression [8].

Glycemic control is one of the top priorities in the management of people with DM in order to reduce the macro- and micro-vascular complications [9]. Depression has been found to affect glycemic control as well as macro-vascular and micro-vascular complications [9–11], and there is substantial evidence that comorbid depression among individuals with DM is associated with poor DM outcomes such as poor glycemic control [9, 12].

Significant controversy exists over whether or not depression and anxiety in patients with DM is associated with poorer glycemic control, with some studies reporting moderate to strong associations [10, 13–15] between depression symptoms and hemoglobin A1c (HbA1c), while others have found no association [16–18]. Recent studies suggest that anxiety disorders may also be associated with less favorable glycemic control among adults with DM [19–21]. However, glycemic control as a risk factor was associated only with higher anxiety scores [22]. Prevalence of moderate to severe depression was found to be significantly associated with poor glycemic control in men but not in women [19, 23], and cross-sectional studies have found a significant positive correlation between depression symptoms and HbA1c in patients with type 1 diabetes but no significant correlation in patients with type 2 diabetes mellitus (T2DM) [24, 25]. The evidence gives rise to the hypothesis that depression and anxiety affect glycemic control in men and those with type 1 DM but not women and patients with T2DM. In order to test this hypothesis in a developing country, we conducted a study to examine the association between depression, anxiety symptoms, and glycemic control in Malaysian women with T2DM.

Methods

Study design and participants

Six hundred and eleven Malaysian women with a known diagnosis of T2DM for at least 1 year, who were treated as outpatients at medication therapy adherence clinics (MTAC) at PutraJaya Hospital in PutraJaya, and Tuanku Jaa'far Hospital and Seremban Health Clinic in Negeri Sembilan, were invited to participate in this study. Face-to-face interviews were conducted at the outpatient clinics, using self-administered questionnaires. The study was conducted according to the principles expressed in the Declaration of Helsinki and was approved by the School of Pharmacy Ethics Committee at The University of Queensland, Australia (Ref. No. 2011/14), and the International Medical University Research and Ethics Committee (Project ID No: B01/09-Res (04) 2012).

Women were categorized as having T2DM if they were attending MTAC for the management of T2DM. Every second woman with diabetes on the respective patients' list at the clinic sites was invited to participate; verbal or written consent was obtained from participants who met the inclusion criteria. The data were collected on women aged 35 and above. Information was confirmed by accessing patients' medical records. The presence of T2DM was identified according to two criteria: A fasting plasma glucose (FPG) greater than or equal to 7.0 mmol/l and random plasma glucose (RPG) greater than or equal to 11.1 mmol/l. Women diagnosed with T1DM were excluded.

Measurement of depression and anxiety symptoms

Center for Epidemiologic Studies Depression Scale 10 (CES-D 10), a brief self-report screening tool for depressive symptoms derived from the validated 20-item CES-D 20 [26], was used to assess depression symptoms. It has been shown to have reliability and validity comparable to the standard 20-item CES-D instrument and is considered a good instrument for screening depression in patients with T2DM [27]. The CES-D 10 uses a zero-to-three response scale, with total symptom severity scores ranging from 0 (no depression) to 30 (severe depression) [28]. Participants in this study were categorized as depressed if they scored 11 or more; this is a commonly used cutoff point for CES-D [26].

The anxiety symptoms were assessed using the Delusions-Symptoms-States Inventory: State of Anxiety and Depression (DSSI/SAD). It contains 14 symptoms, 7 for depression and 7 for anxiety. The DSSI was developed for use with community samples and has been validated against clinical samples with diagnosed mental illness [29–31], and was also found to correlate well, and shares items with, other established symptoms scales such as the Edinburgh Postnatal Depression Scale (EPDS) and the Hospital Anxiety/Depression Scale (HADS) [32]. Participants in this study were classified as anxious when they reported four or more symptoms.

DSSI/SAD is an instrument used to evaluate anxiety and depression symptoms but has not yet been validated for use among people with diabetes [29]. Therefore, we validated the DSSI instrument. Internal consistency was 0.86 for the anxiety and 0.90 for depression subscales, and 0.93 for the full scale of DSSI/SAD. Principal component analysis revealed a bi-factorial model. Correlation analysis showed a significant negative correlation between DSSI-Anxiety and the mental composite score (MCS) scale of Short Form 12 of the Medical Outcomes Study (SF-12; $r=-0.404$, $p=0.001$); thus, as anxiety symptoms decreased (DSSI), the MCS increased, indicating lower mental health-related limitations. We found significant variations in the DSSI/SAD domain scores that could be

explained by CES-D (DSSI-Anxiety 55 %, DSSI-Depression 46 %) and SF-36 MCS (DSSI-Anxiety 66 %, DSSI-Depression 56 %) suggesting that the DSSI/SAD can be used for measuring depression and anxiety symptoms in people with diabetes.

Mental health status by mental composite score (MCS)

We also measured overall mental health functioning using MCS of the SF-12. SF-12 is a multipurpose survey instrument comprising 12 questions, developed as a legitimate alternative to the SF-36. The two summary scales, MCS and the Physical Component Summary (PCS), provide an insight into mental and physical health as well as disability level [33]. MCS examining the impact of health on mental health function was calculated using the method described by Ware et al. [34]. The MCS ranged from 0 to 100; "0" implies poor mental health and "100" implies good mental health. The median split method was used to categorize participants where scores less than the median indicate poor MCS.

Assessment of glycemic control

Five most recent blood glucose readings were collected from patients' medical records. Mean and median values were calculated and used for all comparisons. The monitoring of hemoglobin A1c (HbA1c) is considered the gold standard for glycemic control. The general HbA1c target in people with T2DM is ≤7 %, and adjustment to diabetes treatment should be considered when HbA1c is above this level [35], although other guidelines suggest 6.5 % or less as the treatment goal, which is closer to the normal healthy value [36]. The HbA1c, fasting blood glucose (FBG), and random blood glucose (RBG) values were used as both continuous and categorical outcomes. We used >7 % HbA1c value as the cutoff point to define poor glycemic control. The HbA1c was also categorized based on quartile values: good controlled, moderately controlled, poorly controlled, and very poorly controlled HbA1c.

For fasting and random blood glucose, we used the National Health and Medical Research Council (NHMRC) classification for people with T2DM, namely normal, moderate, and high levels [37]. A fasting value between 4 and 6 mmol/l was normal, between 6.1 and 6.9 mmol/l was moderate, and anything above 7 mmol/l was high [37]. For non-fasting or random blood glucose, a normal value was between 4 and 7.7 mmol/l, between 7.8 and 10.9 mmol/l was moderate, and anything above 11 mmol/l was high [37].

Assessment of covariates

Potential confounders and risk factors were identified on the basis of their association with outcomes and a priori knowledge [11, 23, 38]. *Socio-demographic* information included age, ethnicity, education, occupation, monthly income, alcohol consumption, and cigarette smoking (non-smokers, past smokers, and current smokers). These were collected from participants. *Clinical and physical parameters* such as comorbidities or medical conditions other than T2DM and height (m) and weight (kg) measurements were obtained from participants' medical records. Body mass index (BMI, kg/m^2) was then calculated to categorize participants based on the WHO criteria [39]. For *physical health*, the Short Form 12 of the Medical Outcomes Study (SF-12) was used, with lower scores indicating poor physical health. The PCS scores were calculated using the scores of the questions, ranging from 0 to 100, with lower scores indicating greater physical limitation [33]. The median split method was used to categorize participants where scores less than median indicate poor PCS. The self-reported information on level of physical activity (not at all, one to two times a week, three or more times a week), and sleep problems (Nil, acute and chronic), were collected from participants.

Statistical analysis

The data were analyzed using the Statistical Package for the Social Sciences (SPSS)® version 20 and Stata IC® version 12, with a significance level of ≤0.05. Descriptive statistics were used to calculate percentages, frequencies, means, and standard deviations. The relationship between variables for categorical data was performed using the χ^2 (Chi-Sq). Fisher exact test was applied in cases where sample size was small. Similarly, on occasions where we had less than five readings per cell for Chi-Sq, likelihood ratio test was applied. Comparisons between groups with normal distribution were performed using the Student's t test. Pearson's correlation test was used to verify the existence of a correlation between instruments' mean scores or other values.

Therefore, a series of multiple linear, logistic, and multinomial regression models (see footnotes of Tables 3, 4, 5, and 6) was used to determine the association of mean blood glucose levels with depression and anxiety symptoms assessed as continuous and categorical outcomes. The effects were adjusted for demographic, lifestyle, and clinical factors [11, 23, 38]. For logistic regression, we used the median split method to categorize the variables into binary groups. These binary groups include number of pregnancies, age at last pregnancy, and PCS. For potential confounding, the unadjusted associations of depression and anxiety symptoms with glycemic control were compared with the adjusted associations, with confounding confirmed when the unadjusted effect size and adjusted effect size estimates differed.

Results

Socio-demographic characteristics and glycemic control

The median ages of the 611 participating women at the time of this study and at diabetes diagnosis were 58 and 48 years, respectively. The majority were aged between 45 and 64 years (67 %), were married (82 %), were of Malay ethnicity (38 %), had completed only primary education (76.3 %), and were earning less than 3500 Ringgit Malaysia monthly (1 RM=3.1 US$). Regarding HbA1c levels, there were higher levels among younger women aged 35 to 44 (8.14±1.47) and 45 to 54 years (8.37±1.98) than older women (7.43±1.51). Women of Indian ethnicity had higher levels of HbA1c (8.73±1.98) compared to other ethnic groups. The median values of HbA1c, FBG, and RBG were 7.77 % (N=611), 7.65 mmol/l (N=352), and 9.80 mmol/l (N=314), respectively.

Anxiety and depression symptoms and glycemic control

Depression (8.7 %) and anxiety (9.0 %) symptoms were not commonly reported by participants in this study. Women with anxiety had slightly higher FBG (8.54 versus 8.34) and RBG (11.10 versus 9.87) levels compared to women without anxiety symptoms. Unlike women with anxiety, women with depression symptoms had slightly higher HbA1c (8.24 versus 8.10) compared to women with no depression (Table 1). Correlation analysis shows a weak correlation between HbA1c and *anxiety* (inverse) and HbA1c and *depression* (positive) symptoms.

The univariate analysis shows that for an increase of one category of depression symptoms, there were small increases in HbA1c (0.15 %, 95 % CI −0.38–0.68), FBG (0.33 mmol/l, 95 % CI −0.77–1.42), and RBG (1.02 mmol/l, 95 % CI −0.20–2.25). The effect estimates were reduced after adjustments for the effect of confounders (Table 2). In case of anxiety symptoms, HbA1c decreased by a small amount.

Very poorly controlled HbA1c was not significantly associated with increased odds of depression (OR 1.43, 95 % CI 0.45–4.55) and anxiety (OR 0.47, 95 % CI 0.15–1.49) symptoms; similarly, neither were moderately and poorly controlled HbA1c (Table 3). The high FBG range was not significantly associated with increased odds of anxiety (3.38, 95 % CI 0.67–17.11) and depression (1.47, 95 % CI 0.41–5.26) symptoms (Table 4). Similarly, the expected risk remaining in the high RBG range was higher for women with anxiety and depression symptoms, but this was not significant (Table 5).

Mental health function and glycemic control

Almost half of the participating women were found to have poor mental health functional status, as measured by MCS. On average, women with poor MCS had higher HbA1c, FBG, and RBG compared to women with good MCS (Table 1). Correlation analysis shows a strong inverse correlation between HbA1c and MCS.

A 1-unit score increase in the MCS was associated with 0.47 % (0.17, 0.77), 0.70 mmol/l (0.10, −1.31), and 0.11 mmol/l (−0.58, 0.79) HbA1c, FBG, and RBG levels, respectively. We found very little confounding of MCS, since there was little difference between the univariate analysis coefficients and the adjusted coefficients (Table 2). Poor MCS were significantly associated with very poorly controlled HbA1c (OR 1.93, 95 % CI 1.22–3.03) and remained significant after adjustments for confounders (OR 1.70, 95 % CI 1.01–2.88); however, neither moderately nor poorly controlled HbA1c was observed compared to women with normal level (Table 3).

Discussion

This was the first study to investigate the association between depression, anxiety symptoms, and glycemic control among Malaysian women with T2DM. We did not find strong associations between depression and glycemic control or between anxiety and glycemic control. However, women with comorbid depression and anxiety symptoms had higher mean blood glucose values compared to those without depression and/or anxiety symptoms. In our study, fewer than 10 % of women with T2DM exhibited depression and anxiety symptoms. In contrast, almost half of the women reported poor mental functional status, as measured by MCS, indicating the opposite trend. Almost two thirds of the women (65.6 %) had HbA1c values greater than 7 % and more than a quarter of them were above 9 % indicating poor glycemic control. This reflects the trend reported by the American Diabetes Association (ADA) which suggest that only one of every two patients with diabetes has glycosylated HbA1c levels <8.0 %, and very few patients sustain HbA1c levels <7.0 % [40].

Depression and anxiety were more common among people with poor glycemic control; however, the underlying mechanisms are not well elucidated, with some studies reporting that people with poor glycemic control are more likely to become depressed or anxious [4, 10, 13–15, 19–21], while we found that only people with very poorly controlled glucose levels, as measured by MCS, were associated with poor mental health status. Our study found differences between people with poor glycemic control and normal glycemic level in overall mental health functioning but not specifically in mental health or vitality domains of MCS. The exact explanation for the association we observed is unclear: glycemic control may affect emotional and social function, persons with better emotional function may be more likely to be prevented from negative

Table 1 Mental health status of women with T2DM, by means and standard errors of HbA1c, fasting, and random blood glucose levels

Variables	HbA1c (*N*=611)				Fasting BG (*N*=352)				Random BG (*N*=314)			
	N	Mean	SE	95 % CI	*N*	Mean	SE	95 % CI	*N*	Mean	SE	95 % CI
Depression												
No depression	558	8.10	0.08	7.94–8.25	321	8.32	0.16	8.00–8.65	288	9.88	0.18	9.53–10.23
Depression symptoms	53	8.24	0.27	7.70–8.78	31	8.65	0.61	7.40–9.90	26	10.91	0.67	9.53–12.28
Anxiety												
No anxiety	558	8.11	0.08	7.95–8.27	321	8.34	0.16	8.01–8.66	289	9.87	0.18	9.53–10.22
Anxiety symptoms	53	8.06	0.25	7.56–8.57	31	8.54	0.60	7.31–9.76	25	11.10	0.71	9.60–12.54
Mental health—MCS												
Good MCS	323	7.88	0.10	7.69–8.07	173	8.00	0.20	7.60–8.40	177	9.92	0.22	9.49–10.35
Poor MCS	288	8.35	0.12	8.12–8.59	179	8.70	0.24	8.22–9.17	137	10.04	0.28	9.47–10.59

BG blood glucose, *SE* standard error, *MCS* mental composite score

and positive effects of poor glycemic control, or glycemic control may be linked with other confounding variables that affect mental health function.

Our study shows that for an increase of one category of symptoms of depression, HbA1c increased, on average, by only a small amount of 0.10 %. A similar increment was reported in a longitudinal study of people with T2DM who showed, over a 4-year period, HbA1c values which were, on average, 0.13 % higher in people who had depression [12]. Previous studies have come to different conclusions about the association of depression symptoms and glycemic control; some reported a significant relationship between poorer glycemic control and depressive symptoms [14, 41] while others found an insignificant or weak association between glycemic control and depressive symptoms [18, 38, 42]. However, a meta-analysis reported a significant association [9], and randomized clinical trials of therapies for depression demonstrated improvement in depressive symptoms corresponding with improvements in glycemic control [43, 44], and vice versa [14].

Table 2 The associations between symptoms of depression and HbA1c, anxiety and HbA1c (%), and FBG and RBG (mmol/l)

Variables	Depression symptoms		Anxiety symptoms		Mental health—MCS	
	No (referent)	Yes	No (referent)	Yes	Good MCS (referent)	Poor MCS
HbA1c in %—(*N*=611)						
Unadjusted estimate (95 % CI)	8.10 (7.93, 8.25)	0.15 (−0.38, 0.68)	8.11 (7.95, −8.27)	−0.05 (−0.58, 0.49)	7.88 (7.68, 8.10)	0.47 (0.17, 0.77)[a]
Adjusted estimate (95 % CI)	8.81 (7.67, 9.94)	0.10 (−0.63, 0.81)	8.81 (7.67,9.94)	−0.44 (−1.17, 0.28)	8.39 (7.26, 9.52)	0.46 (0.12, −0.80)
Fasting BG in mmol/l—(*N*=352)						
Unadjusted estimate (95 % CI)	8.32 (8.00, 8.65)	0.33 (−0.77, 1.42)	8.34 (8.01, 8.66)	0.20 (−0.90, 1.30)	8.00 (7.56, 8.44)	0.70 (0.10, −1.31)
Adjusted estimate (95 % CI)	11.82 (9.39, 14.25)	−0.10 (−1.53, 1.33)	11.82 (9.39, 14.25)	−0.03 (−1.49, 1.44)	11.37 (8.90, 13.86)	0.44 (−0.33, 1.21)
Random BG in mmol/l—(*N*=314)						
Unadjusted estimate (95 % CI)	9.88 (9.53, 10.24)	1.02 (−0.20, 2.25)	9.87 (9.52, 10.23)	1.19 (−0.05, 2.44)	9.92 (9.47, 10.38)	0.11 (−0.58, 0.79)
Adjusted estimate (95 % CI)	10.75 (8.13, 13.37)	0.41 (−1.55, 2.36)	10.75 (8.13, 13.37)	0.13 (−1.86, 2.12)	10.75 (8.19, 13.32)	−0.02 (−0.81, 0.77)

Approach used was linear regression. Depression and anxiety symptoms adjusted for depression or anxiety, age, comorbidities, physical activity, BMI, physical health, and sleep problems

BG blood glucose, *MCS* mental composite score

[a] Statistically significant

Table 3 Odds ratio (95 % CI) of poor glycemic control (HbA1c >7 %) according to depression and anxiety symptoms (N=611)

Items	Depression symptoms		Anxiety symptoms		Mental health—MCS	
	No (referent)	Yes	No (referent)	Yes	Good MCS (referent)	Poor MCS
HbA1c—binary outcome						
Normal level, *N* (%) (referent)	195 (31.9)	16 (2.6)	193 (31.6)	18 (2.9)	126 (20.6)	85 (13.9)
Poor level, *N* (%)	363 (59.4)	37 (6.1)	365 (59.7)	35 (5.7)	197 (32.2)	203 (33.2)
Unadjusted odds	1.0	0.81 (0.44–1.48)	1.0	0.97 (0.54–1.76)	1.0	0.65 (0.47–0.92)[a]
Adjusted odds	1.0	0.82 (0.35–1.95)	1.0	1.36 (0.58–3.21)	1.0	0.71 (0.46–1.05)
HbA1c—quartile-based categories						
Good controlled, *N* (%) (referent)	142 (23.3)	13 (2.1)	140 (23.0)	15 (2.5)	94 (15.4)	61 (10.0)
Moderately controlled, N (%)	141 (23.2)	10 (1.6)	138 (22.7)	13 (2.1)	81 (13.3)	70 (11.5)
Unadjusted odds	1.0	0.77 (0.33–1.82)	1.0	0.90 (0.40–1.92)	1.0	1.33 (0.85–2.10)
Adjusted odds	1.0	0.90 (0.28–2.91)	1.0	0.95 (0.32–2.82)	1.0	1.29 (0.77–2.16)
Poorly controlled, *N* (%)	135 (22.2)	15 (2.5)	137 (22.5)	13 (2.1)	80 (13.1)	70 (11.5)
Unadjusted odds	1.0	1.21 (0.57–2.64)	1.0	0.89 (0.41–1.93)	1.0	1.35 (0.86–2.12)
Adjusted odds	1.0	1.59 (0.52–4.87)	1.0	0.58 (0.20–1.79)	1.0	1.24 (0.74–2.10)
Very poorly controlled, *N* (%)	139 (22.8)	14 (2.3)	141 (23.2)	12 (2.0)	68 (11.2)	85 (14.0)
Unadjusted odds	1.0	1.10 (0.50–2.42)	1.0	0.79 (0.36–1.76)	1.0	1.93 (1.22–3.03)[a]
Adjusted odds	1.0	1.43 (0.45–4.55)	1.0	0.47 (0.15–1.49)	1.0	1.70 (1.01–2.88)[a]

Odds ratio adjusted for depression or anxiety, age, comorbidities, physical activity, BMI, and physical health. Classification method used was logistic and multinomial regression

[a] Statistically significant

Although our data found no significant association between anxiety and HbA1c, HbA1c values were, on average, 0.44 % lower in those with anxiety symptoms. In contrast to previous studies which suggest that anxiety disorders are associated with less favorable glycemic control among adults with DM [19–21], our data did not show such a relationship. Interestingly, insignificant correlations of HbA1c with depression and anxiety symptoms also indicated a weak link between the two. Contrary to this, a strong inverse correlation between HbA1c and MCS was found, suggesting that women who score high on MCS scale appear to have lower HbA1c level than women who score low on MCS. A 1-unit score increase in the MCS was associated with 0.47 % (−0.17, −0.77), 0.70 mmol/l (0.10, −1.31), and 0.11 mmol/l (−0.58, 0.79) for HbA1c, FBG, and RBG levels, respectively. The adjusted effect of MCS on HbA1c was almost unchanged (reduced by only 1 %), suggesting no—or very little—confounding. Despite strong inverse correlations of MCS with DSSI and CES-D 10, only MCS reflected significant changes in glycemic control in this study. MCS might have captured the distress associated with diabetes and is reflected in the correlation between MCS and glycemic control.

Table 4 Odds ratio (95 % CI) of fasting glucose level according to depression and anxiety symptoms (n=352)

Items	Depression symptoms		Anxiety symptoms		Mental health—MCS	
	No (referent)	Yes	No (referent)	Yes	Good MCS (referent)	Poor MCS
FBG—categories						
Normal level, *N* (%) (referent)	75 (21.3)	5 (1.3)	75 (21.3)	5 (1.3)	43 (12.2)	37 (10.5)
Moderate level, *N* (%)	52 (14.8)	6 (1.7)	49 (13.9)	9 (2.6)	33 (9.4)	25 (7.1)
Unadjusted odds	1.0	1.73 (0.50–5.97)	1.0	2.75 (0.87–8.71)	1.0	0.88 (0.44–1.74)
Adjusted odds	1.0	0.88 (0.17–4.58)	1.0	3.38 (0.67–17.11)	1.0	0.81 (0.33–1.74)
High level, *N* (%)	194 (55.1)	18 (5.1)	197 (56.0)	13 (3.7)	97 (27.6)	117 (33.2)
Unadjusted odds	1.0	1.55 (0.56–4.27)	1.0	1.29 (0.46–3.63)	1.0	1.40 (0.84–2.35)
Adjusted odds	1.0	1.47 (0.41–5.26)	1.0	0.92 (0.23–3.61)	1.0	1.18 (0.60–2.34)

Fasting glucose adjusted for depression or anxiety, age, comorbidities, physical activity, BMI, physical health, and sleep problems. Classification method used was logistic and multinomial regression

Table 5 Odds ratio (95 % CI) of random glucose level according to depression and anxiety symptoms (n=314)

Items	Depression symptoms		Anxiety symptoms		Mental health—MCS	
	No (referent)	Yes	No (referent)	Yes	Good MCS (referent)	Poor MCS
RBG—categories						
Normal level, *N* (%) (referent)	83 (26.4)	5 (1.4)	82 (26.1)	6 (1.9)	51 (16.2)	37 (11.8)
Moderate level, *N* (%)	105 (33.4)	8 (2.6)	107 (34.1)	6 (1.9)	62 (19.7)	51 (16.2)
Unadjusted odds	1.0	1.26 (0.40–4.01)	1.0	0.77 (0.24–2.46)	1.0	1.18 (0.67–2.06)
Adjusted odds	1.0	2.26 (0.33–15.69)	1.0	0.25 (0.04–1.74)	1.0	1.27 (0.63–2.57)
High level, *N* (%)	100 (31.8)	12 (3.8)	100 (31.8)	13 (4.1)	64 (20.4)	49 (15.6)
Unadjusted odds	1.0	2.16 (0.74–6.30)	1.0	1.78 (0.65–4.88)	1.0	1.06 (0.60–1.85)
Adjusted odds	1.0	2.08 (0.33–13.16)	1.0	0.46 (0.10–2.68)	1.0	0.94 (0.47–1.89)

Blood glucose adjusted for depression or anxiety, age, comorbidities, physical activity, BMI, physical health, and sleep problems. Classification method used was logistic and multinomial regression

Limitations

Our assessment of depression and anxiety symptoms was based on self-report of symptoms using validated instruments and not on the Diagnosis and Statistical Manual (DSM) criteria based clinical diagnostic interview. A clinical confirmation of depression or anxiety could not be done because the DSM for diagnosis of mental disorders states that the standard diagnostic criteria are applied "in the presence of a psychiatrist or trained healthcare professional." Therefore, two instruments were used to examine depression or anxiety symptoms as no clinical confirmation was available. Although we applied systematic sampling, participants who frequently attended the outpatient clinics were more likely to be sampled than those who attended less frequently, and therefore were presumed to have better glycemic control. This might have introduced selection bias.

Conclusions

This study did not find significant associations between depression and glycemic control and anxiety and glycemic control in Malaysian women with T2DM. Despite strong inverse correlations of MCS with DSSI-Anxiety and CES-D 10, only MCS tended to be associated with significant changes in glycemic control in this study. This evidence supports the hypothesis that argues against the existence of a link between depression and glycemic control and anxiety and glycemic control. However, as primary care physicians may fail to recognize a substantial number of patients with depression and/or anxiety symptoms and as the prevalence of diabetes continues to increase, in Malaysia, it is important for health care professionals managing patients with DM to be aware of the association between depression, anxiety symptoms, and glycemic control to prevent further complications.

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CHAPTER 11
General Discussion

11.1. Introduction

A range of analyses and reviews were rigorously undertaken during this PhD study in order to explore the relationships between depression and diabetes, and anxiety and diabetes, in both a developed and a developing country. The analyses and reviews conducted produced a large number of research papers (12) of which six have been published, two accepted for publication, and four have been revised according to reviewers' comments and editorial specifications and resubmitted to journals. The published papers and manuscripts are included in the results sections and in Appendices 1A and 4A to 4D and will be referred to where relevant. An attempt was also made to identify any bidirectional relationships using longitudinal data. These associations are likely to involve complex interactions including those associated with socio-demographic and clinical factors (Mezuk et al., 2008; Smith et al., 2013; Venables et al., 2009). Detailed discussion on the possible mechanisms underpinning these associations was included in previous chapters particularly in Chapter 1. A considerable literature is available that examined the association between depression and diabetes; however, very few prospective studies have examined the strength and magnitude of the association between anxiety and diabetes, controlling for potential confounders. Conclusions presented in previous studies that have examined the associations between depression and diabetes, and anxiety and diabetes, were based on cross-sectional data (Smith et al., 2013) and specific geographic locations (US and European Region). These two issues are important limitations because it is not ideal to answer questions about the causal or temporal sequence of associations and to extrapolate findings to populations living in other regions of the world.

To examine the nature of the association between psychological disorders and diabetes, a rigorous methodology was adopted to confirm the association using more than one study design. The findings presented in this thesis are based on original data as well as data derived from previous studies which have produced meta-analyses and a systematic review. Initially, a systematic review was completed using prevalence data obtained from previous studies to estimate the burden of comorbid depression and anxiety in people with diabetes. Following this, four meta-analyses were conducted, and pooled estimates were

generated using longitudinal data from previous studies. Finally, original datasets from a developed country (Australia - MUSP – longitudinal data) and a developing country (Malaysia – cross-sectional data) were analyzed individually to examine the associations from two perspectives.

A series of investigations using data from MUSP, a 27-year follow-up study, examined the associations between depression and diabetes, and anxiety and diabetes. It is worth mentioning here that MUSP was not primarily designed to investigate these associations, but the collection of data over 27 years provided a platform to examine the associations between risk factors, to which the participating women were exposed early in life and the consequences or adverse outcomes in later life. The MUSP study, including the design, execution, data collection and entry was conducted by a team of senior investigators and their colleagues between 1981 and 2011. However, the development of the current concept, construction of derived variables used in this thesis, and the methodological procedures and analyses it presents were the work of the candidate himself under the guidance of supervisors. In addition to the MUSP analyses, the candidate developed the concept, construction of variables, and the methodological procedures and statistical analyses for a case-control study in Malaysia.

This chapter summarizes the findings of systematically reviewed literature and research articles completed as part of this thesis and presents conclusions based on the research findings. It concludes with a discussion of their implications for policy and decision making. In the following section, findings from a systematic review, meta-analyses and original research papers are presented and discussed. A detailed description of each set of findings, including possible explanations of the associations and relevant limitations, can be found in the individual manuscripts in the results section.

11.2. Summary of findings related to the main research questions

In a stepwise approach, the independent associations between depression and diabetes and anxiety and diabetes, in both a developed and a developing country, were examined. The research objectives are outlined in Chapter 1 (*section 1.6.1*) and discussed in the following sections.

11.3. Association between depression and diabetes

11.3.1. Global distribution of comorbid depression in people with diabetes

The first objective of this thesis was to estimate the global distribution of comorbid depression in people with type 1 (T1DM) and type 2 (T2DM) diabetes mellitus, via risk-adjustment. A review of 71 studies found a higher burden of comorbid depression in people living in developing regions (26.32%), in people with T1DM (17.90%), in women (15.41%) and when assessed by self-report scales (22.66%). No statistically significant differences were seen due to gross heterogeneity across countries.

11.3.2. Summary of findings from meta-analyses (depression and diabetes)

Three meta-analyses were conducted by the candidate and have been published (*objective 2*), they examined the association between depression and diabetes. The first meta-analysis examining depression as risk factor for diabetes revealed greater cumulative incidence of diabetes in depressed than in non-depressed groups. Both the relative risk (67%) and hazard ratio (45%) showed a significant association between depressive symptoms and the risk of incident diabetes. The second meta-analysis investigated diabetes as risk factor for depression, and found higher cumulative incidence of depression in people with diabetes than in people without diabetes. Similar to the first meta-analysis, both the relative risk (27%) and hazard ratio (23%) revealed significant associations between diabetes and the risk of incident depression. The evidence obtained from these meta-analyses endorses the findings of previous studies, and suggest a bidirectional association between depression and diabetes (Mezuk et al., 2008; Routella & Mannucci, 2012; Routella & Mannucci, 2013). In the third meta-analysis, the effect sizes were re-estimated for the bidirectional association between depression and diabetes using the quality-effects model. This re-analysis revealed that the associations were weakened and the confidence interval, too, was shifted in the direction of the null. Nevertheless, results remained statistically significant.

11.3.3. Summary of findings from MUSP (depression and diabetes)

One of the objectives of this thesis was to validate the personal disturbance scale, the Delusions-Symptoms-States-Inventory/States of Anxiety and Depression (DSSI/sAD), among women with diabetes using the MUSP dataset. The findings of factor analyses and concordant validity analysis, conducted during this PhD study, support the validity and confirmed the psychometric properties of DSSI/sAD for use among women with diabetes.

The results also demonstrate that the DSSI/sAD items have similar relationships to one another in both diabetic and non-diabetic groups and therefore suggest that they provide similar interpretations.

The next objective was to investigate whether depressive symptoms were independently associated with diabetes mellitus; this was measured at 21-years post index pregnancy in Australian women and longitudinal data collected as a part of the MUSP study was used to examine this association. In the 21-year follow-up study, after excluding diabetes cases reported at the start of the MUSP study, 301 women reported diabetes. In prospective analyses of this subset, women with a positive history of symptoms of depression and women with *persistent* symptoms, had a 1.97-fold (95% CI: 1.14 – 3.40) to 2.23-fold (95% CI: 1.09 – 4.57) greater risk of diabetes. These original research results based on the MUSP dataset endorse the findings of the meta-analyses undertaken as a part of this thesis.

Lastly, the present study investigated whether the presence of diabetes mellitus was independently associated with depressive disorders: this was measured at 27-year post index pregnancy in Australian women. In the 27-year follow-up study, women with diabetes had a greater lifetime prevalence of *any* depressive disorder compared with women without diabetes. Women with diabetes also had higher prevalence of major depressive disorder (MDD) compared with women without diabetes. In prospective analyses, diabetes increased the risk of *any* lifetime depressive disorder (OR 1.37, 95% CI: 1.03–1.84) and lifetime MDD (OR 1.36, 95% CI: 1.01–1.85).

11.3.4. Summary of findings from Malaysian Study (depression and diabetes)

This thesis also examined the association between symptoms of depression and anxiety and T2DM, in a developing country. Using cross-sectional data obtained in Malaysia, women with diabetes (11.8%) had higher depressive symptoms compared with women without diabetes (8.4%). In multivariate regression analysis, the presence of T2DM did not increase the odds of depression (OR 0.75, 95% CI: 0.38-1.46). Similarly, the duration of T2DM did not increase the odds of depression symptoms significantly.

Cross-sectional analyses suggest that T2DM is not a significant risk factor for depression; similarly, neither is depression a significant risk factor for T2DM. Interestingly, the cross-

sectional analysis using the MUSP 21-year dataset produced similar results; that is, no significant cross-sectional association between depression symptoms and diabetes.

11.4. Association between anxiety and diabetes

11.4.1. Global distribution of comorbid anxiety in people with diabetes

The global distribution of comorbid anxiety in people with T1DM and T2DM diabetes mellitus was estimated, via risk-adjustment. A review of 35 studies found a higher burden of comorbid of anxiety in developed regions in people with T2DM (20.15%) and when assessed by self-report scales (20.75%). Regarding specific anxiety disorders, the burden of GAD was higher in developing regions compared to developed regions (12.10 vs. 5.41%). No statistically significant differences were seen due to gross heterogeneity across countries.

11.4.2. Summary of findings from meta-analysis (anxiety and diabetes)

A previous meta-analysis found that people with diabetes are at greater risk of developing anxiety symptoms or disorders (Smith et al., 2013). However, no meta-analysis has investigated the development of diabetes in relation to the presence of anxiety symptoms. Therefore the risk of diabetes associated with anxiety was examined, using a rigorous methodology of bias-adjusted models for conducting a meta-analysis of longitudinal studies. A pooled estimate for incident diabetes with subjects who exhibited anxiety (exposure) of 1.65 was found, suggesting a 65% increase in the risk of diabetes; however, the relative risk for the negative complement (no-diabetes), was 0.987, suggesting there would be a 1.3% increase in diabetes had the unexposed group been exposed to anxiety. The pooled risk difference was 0.031 (95% CI: - 0.007 to 0.054) and the number needed to be exposed for one additional person to be harmed (NNEH) was 33 (95% CI 19 to 143) at 2 years post exposure. Based on these findings it is suggested that anxiety could lead to an increased risk of developing diabetes.

11.4.3. Summary of findings from MUSP (anxiety and diabetes)

Similar to the analyses conducted for depression, I also investigated whether anxiety symptoms were independently associated with diabetes mellitus: this was measured at the 21-year follow-up in Australian women. In prospective analyses, no significant association of diabetes with negative change (not anxious to anxious at subsequent phase) or with positive change in symptoms of anxiety (anxious to not anxious at subsequent phase) was

found; however, increasing risk was evident. Women with *persistent* symptoms of anxiety had a 1.85-fold greater risk of developing diabetes (95% CI: 1.18 – 2.90). The finding suggests that only *persistent* anxiety symptoms are associated with a modest increase in the risk of diabetes at the 21 years follow-up.

Women with diabetes had a higher lifetime prevalence of *any* anxiety disorder compared with women without diabetes that is about one in two women with diabetes. In a multivariate model, diabetes was significantly associated with a 30-day episode of *any* anxiety disorder (95% CI: 1.14–2.25) and lifetime posttraumatic stress disorder (OR 1.42, 95% CI: 1.01–2.02). The present study therefore, endorses the findings of a previous meta-analysis suggesting that people with diabetes are at greater risk of developing anxiety symptoms or disorders (Smith et al., 2013).

11.4.4. Summary of findings from Malaysian Study (anxiety and diabetes)

Women with diabetes reported higher anxiety (8.4%) symptoms compared with women without diabetes (6.6%); this was similar to the findings for depression. In cross-sectional analyses using data collected in Malaysia, the presence of T2DM did not increase the odds of anxiety (OR 0.72, 95% CI: 0.38-1.38) symptoms. Similarly the duration of T2DM did not increase the odds of anxiety symptoms significantly.

This was similar to findings from the cross-sectional analysis using the MUSP 21-year dataset, where there was no significant association between anxiety symptoms and diabetes. On the DSSI scale, the odds that a postmenopausal Malaysian woman with diabetes was anxious increased significantly when the MENQOL score on the physical, vasomotor, and psychosocial domains increased by one unit.

11.5. Glycemic control and symptoms of depression and anxiety

The data collected from Malaysia included variables that provided an opportunity to determine whether symptoms of depression were associated with glycemic control in Malaysian women. It has been reported that poor glycemic control is linked to moderate to severe depressive symptoms (Anderson et al., 2002; Lustman et al., 2000), and glycemic control as a risk factor is associated with higher anxiety scores (Collins et al., 2009).

Two thirds of the women had HbA1c values greater than 7% and more than a quarter of them were above 9% indicating poor glycemic control; however there was no significant

association between symptoms of depression and anxiety and poor or very poor glycemic control in both unadjusted and adjusted cross-sectional analyses. These findings support the hypothesis that argues against the existence of a link between depression and glycemic control, and anxiety and glycemic control.

11.6. Strength and limitations of the thesis

The strength of the research findings reported in this thesis lies in analyses of datasets obtained from a developed (Australia) and a developing (Malaysia) country. In Australia the longitudinal dataset was obtained from a large, ongoing birth cohort study based on recruitment between 1981 and 1983, and 6753 mothers were included as the overall study sample. In Malaysia, a case-control study based on recruitment of 1240 women with and without T2DM between March 2012 and January 2013 provided a cross-sectional dataset.

There are several advantages of using longitudinal data. Longitudinal data obtained from a large study usually produces or generates precise and reliable estimates of effects. The MUSP longitudinal dataset provided an opportunity to study the associations between risk factors that women are exposed to in their early life or around pregnancy, and later-age outcomes. MUSP is one of the longest follow-up studies in Australia (27-year follow-up) and its sample size (6753) is sufficient for the investigation of common outcomes such as mental health problems and chronic diseases.

The main difference between MUSP and the study conducted in Malaysia is the study design; the latter was a case-control study. A similar set of variables to that used in MUSP was collected from the case-control study in Malaysia. This provided an opportunity to examine the strength and magnitude of the associations between depression and diabetes, and anxiety and diabetes. Unlike MUSP, where diabetes was self-reported, in the Malaysian case-control study, diabetes was confirmed by physician diagnosis and blood glucose measurements. The Malaysian study also provided additional data on blood glucose levels.

The limitations associated with MUSP and the Malaysian studies have been discussed in detail in each of the papers, submitted or published (*Results section*). It is important to understand the limitations and to bear these in mind when interpreting the findings. A common limitation of population-based cohort studies is the dropt-out or attrition from the original sample, and this is demonstrated in **Figure 11.1** using data from the MUSP study.

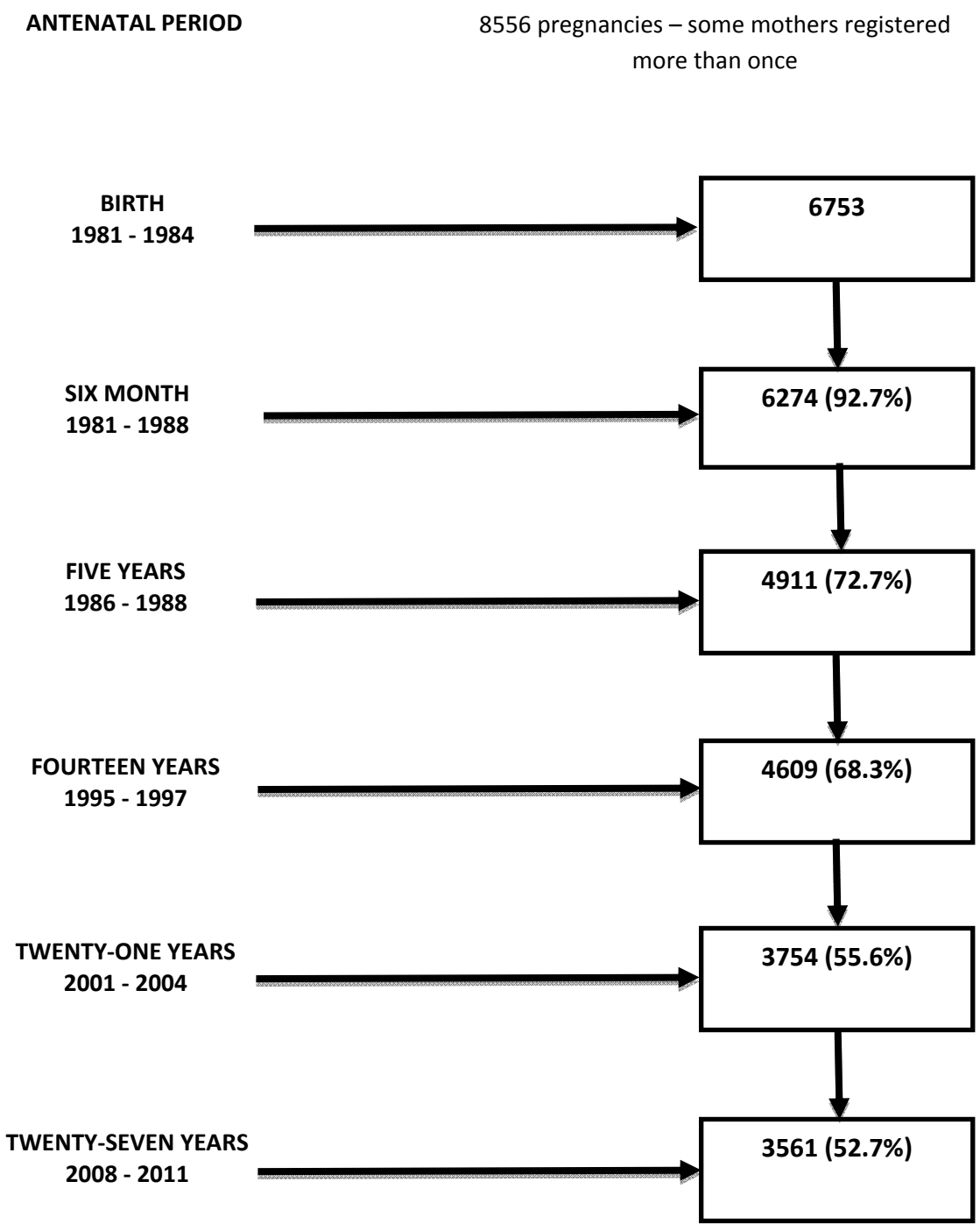

Figure 11.1: Proportion of women who were retained in the study at each phase

The original mothers' cohort comprised 6753 women at the start of the study. However, at 21-year follow-up, only 55.6 percent of women completed the follow-up. Similarly, at 27-year follow-up, only 49 percent were administered the CIDI-Auto to assess depressive and anxiety disorders. Missing data due to drop-out or item non-response may cause bias in the analyses and loss of statistical power (Little & Rubin, 1987). Therefore, to improve the

precision of estimates and the statistical power, a multiple imputations technique was employed to adjust for missing data. This technique was discussed in detail in Chapter 1 (*section 2.1.8*) and in each of the MUSP papers (incorporated in *Chapters 6 to 8*) with the exception of the paper on the validation of the DSSI/sAD (*Chapter 5*). Although the multiple imputations technique has been used to adjust for missing data, it is important that the reader exercises caution when generalizing the findings to the broader population of women with mental health issues or with diabetes.

Important limitations of MUSP data are self-reported diabetes and the use of self-report scales to identify depression and anxiety symptoms. It is possible that women may have incorrectly reported the presence or absence of diabetes. However, self-report diabetes is considered to be a reliable measure of the presence of diabetes (Kriegsman et al., 1996), although not as accurate as direct glucose measurement. An evaluation of self-report of chronic conditions in the US National Health Interview Survey found that self-report of diabetes showed very high agreement with medical records data (NCHS, 1994). Data from Taiwan also showed that self-report of diabetes yielded high agreement when compared with physical examination and HbA1c (Goldman et al., 2003).

In the present study, information about depressive and anxiety symptoms, among the MUSP cohort, measured at the 5, 14 and 21 year MUSP follow-ups, was derived from a self-report scale (DSSI/sAD) possibly leading to information bias and misclassification of mental health status, including symptoms of depression and anxiety. However, to improve the quality of reporting and findings of this thesis, the DSSI/sAD scale in women with and without diabetes was validated, prior to its use for the main analyses.

Unlike MUSP, data obtained from Malaysia was cross-sectional in nature and therefore did not provide an opportunity to study long-term associations between risk factors and outcomes. Despite this limitation, the Malaysian study did provide information about the strength and magnitude of the associations of interest. The findings based on cross-sectional Malaysian data and cross-sectional analyses of MUSP are similar, endorsing the validity of our findings.

For adjustment for confounders, both direct acyclic graphs and priori knowledge were used, and were discussed in detail where relevant (*Chapters 5 to 10*). In both, the MUSP and the Malaysian study, it was possible to adjust the statistical models for a wide range of

possible confounders; however, in this study I did not examine the effects of drugs used by participants for chronic conditions.

MUSP is a prospective study with unequal time intervals between data collection phases. For example, the MUSP study did not collect data for long periods between 5 to 14 years and 14 to 21 years post birth of the index child, thereby ignoring the influence of other factors which may have been present during these intervals, and their influence on the associations between depression and diabetes, and anxiety and diabetes. Finally, there is a possibility that some covariates that were not measured or included in this study, may explain the associations between depression and diabetes, and anxiety and diabetes.

11.7. Are these associations causal?

The main objectives of this thesis were to investigate the independent association between depression and diabetes, and anxiety and diabetes and not to examine causal or temporal sequences. However it was felt important to discuss causal pathways and identify links between depression and diabetes, and anxiety and diabetes.

Bradford Hill's criteria provide a framework to investigate the causal pathway or sequence of the observed associations under investigation (Hill, 1965), and have typically been used in epidemiological studies to examine associations between an exposure variable and an outcome (Lucas & McMichael, 2005). Lucas and McMichael suggested that causation is an interpretation, not an entity; it is merely an inference based on an observed conjunction of exposure and health status in time and space (Lucas & McMichael, 2005).

Generally in uncontrolled studies and to a certain extent in longitudinal studies, the measurement of exposure and outcome is of less quality than in controlled clinical trials (Lucas & McMichael, 2005). The focus of this thesis was on the bidirectional associations between depression and diabetes. Although some evidence of bidirectional associations between these variables have been reported in previous studies, as well as the present study, establishing the causal sequence has not been straight forward. This is because mood disorders such as anxiety and depression usually begin at a young age, well before the onset of diabetes, particularly T2DM (Kessler et al., 2005), suggesting that depression and anxiety are stronger risk factors for diabetes onset than *vice versa*. Another issue is that anxiety and depression are chronic or recurrent in nature (Anderson et al, 2001; Grigsby et al., 2002), and having a recent disorder tends to mean that the respondent has

a history of that disorder. Lastly, like most other diseases, the development of diabetes involves a multifactorial pathogenesis (Lucas & McMichael, 2005), and it is not simply a consequence of depression and anxiety. **Table 11.1** discusses the application of the nine criteria to the findings of this current study together with evidence from other published sources.

Table 11.1: Evidence for a causal association between depression and diabetes, anxiety and diabetes using Bradford Hill's criteria

Criteria for causation	**Application to the findings of the present study**
Strength of Association	An effect size of less than two indicates a weak association, while greater than three is a strong association (Holt & Peveler, 2006). Most studies estimate that the risk of diabetes (attributable to depression or anxiety) has a stronger strength of association than the risk of depression or anxiety attributable to diabetes. The strength of association in both directions, however, is not strong, as the effect sizes were less than two in the majority of studies (including present study). Under this criterion therefore there is weak evidence for causality. (Smith et al., 2013; Mezuk et al., 2008).
Consistency	The studies reporting associations in either direction did not report these to be consistently present and a large number of studies reported no association for the diabetes outcome or the depression/anxiety outcome (Mezuk et al., 2008; Rotella et al., 2012, Rotella & Mannucci, 2013).
Specificity	This criterion does not seem to be true for diabetes or exposure to depression and anxiety; multiple risk factors may produce or increase the risk of diabetes, or a single exposure (depression or diabetes) may produce a number of outcomes (diabetes and cardiovascular problems).
Temporal Relationship	Establishing a finding of new-onset cases or some new-onset feature of the outcome, can add to the evidence of causal or temporal sequence (van Reekum et al., 2001). It could be argued that if the association exists between diabetes and depression or anxiety, then patients with T2DM may be at higher risk of depression or anxiety, because mood disorders begin at a young age, well before the onset of T2DM (Kessler et al., 2005).
Biological Gradient	Almost all previous prospective studies, as well as the present study, restricted analyses to moderate to severe depression and anxiety and excluded mild cases of exposures, the impact of a biological gradient therefore is difficult to establish (Mezuk et al., 2008; Rotella et al., 2012, Rotella & Mannucci, 2013).
Biological Plausibility	The association between depression or anxiety and obesity or weight gain resulting in diabetes is well recognized and this is one potential mechanism by which depression or anxiety may increase the risk of diabetes (Bjorntorp, 2001; Bjorntorp et al., 1999; Maes et al., 1991; Gariepy et a., 2010; Chiodini et al., 2007; Ehlert et al., 2001; Merswolken et al., 2012; Steudte et al., 2011; Young et al., 2004; Torres & Nowson, 2007). There is limited evidence as to whether diabetes *causes* depression or anxiety disorders. Generally it is perceived that individuals experiencing diabetes-related complications and disability experience depression as a consequence of their disability (Nouwen et al., 2010; Talbot et al., 1999).
Coherence of Evidence	The present study found that there is a greater likelihood that depression causes diabetes than diabetes causes depression based on the magnitude of the effect sizes. The findings of the previous studies are inconsistent, where

	some studies reported no significant association between depression and diabetes (Mezuk et al., 2008; Routella & Mannucci, 2012; Routella & Mannucci, 2013). In the case of anxiety, only one of three longitudinal studies suggested increased risk of diabetes as a consequence of anxiety (Engum, 2007; Edwards & Mezuk et al, 2012; Atlantis et al., 2012). Similarly only three of seven studies, included in a meta-analysis, suggested increased risk anxiety disorders as a consequence of diabetes (Smith et al. 2012).
Experimental Evidence	All of the available evidence comes from prospective and cross-sectional studies. No direct experimental evidence is available to support a causal inference.
Analogous Evidence	For depression or anxiety causing diabetes, an analogy showing consistencies with other similar situations could be that other lifestyle factors (Venables & Jeukendrup, 2009), medical conditions such as polycystic ovary syndrome (Barber & Franks, 2012) or drugs, such as antipsychotics (Holt & Peveler, 2006), that cause weight gain or obesity are associated with increased rates of diabetes. Anxiety and depression are two psychological disorders that are associated with larger weight change and are frequently reported by both obese men and women (Brumpton et al., 2013; Bjerkeset et al., 2008; Roberts et al., 2003; Herva et al., 2006).The present study found that more than two thirds of women in our sample with diabetes were obese (almost 83% had BMI > 30 kg/m^2) increasing the risk of depression and anxiety symptoms. This sequence is endorsed by the recent reviews which support a prospective association of obesity-to-depression (Faith et al., 2011; Luppino et al., 2010).

11.8. Necessary or component causes

Since the evidence is not strong that diabetes and anxiety/ depression are necessary causes without which the respective outcome will not occur, there remains a question about whether they are component causes. Previous investigations have shown that lifestyle factors (Venables et al., 2009; Jacka et al., 2010a; Jacka et al., 2011a; Jacka et al., 2010b) represent potential component causes of both mood disorders as well as diabetes. In the present work we undertook several multivariate analyses to examine the association for each factor when the other variables were controlled. In addition, we took into account a wide range of factors that might confound the relationships. However, we must conclude that if diabetes or mood disorders are component causes, their strength as a cause is necessarily weak. This strength of course depends on the prevalence of other causal factors for both of these disorders. In the present study we also estimated the absolute estimates in addition to relative estimates in our meta-analyses. The small relative and absolute effect sizes found in our meta-analyses suggest that again the strength of these factors as component causes is low and may be acting far apart in time.

The finding of the present study that more than two thirds of women with diabetes were obese suggests that obesity or weight gain may be the necessary cause required in addition to component causes to create a sufficient cause for the outcome. As discussed above, presence of obesity in the population may augment the impact of mood disorders on diabetes and *vice versa*.

11.9. Implications

The data used in this thesis showed that about 8% of women reported diabetes at the 21-year follow-up of the MUSP study. The associations between depression and diabetes, anxiety and diabetes found in this study were not strong in terms of effect sizes. Despite the limitations discussed, if we accept that these are component causes of diabetes, then blocking their development prevents the completion of a sufficient cause that can contribute to both the prevention and treatment of diabetes by this pathway.

11.9.1. Implications for prevention

Preventive interventions in the area of diabetes and mood disorders are generally well established particularly in the case of diabetes (Cabassa et al., 2010). For instance lifestyle modifications (that is, physical activity and dietary changes) have been commonly used to decrease the risk of diabetes or improve the condition of people with diabetes

(Cabassa et al., 2010; Tuomilehto et al., 2011; Rubin et al., 2014). However, since these are component causes, it is important to pay attention to the broad constellation of factors that are implicated simultaneously. This approach was demonstrated by a previous study, where none of the high-risk individuals with impaired glucose tolerance (IGT) developed diabetes during the initial trial period if they reached at least four out of five predefined lifestyle targets (Tuomilehto et al., 2001). This is strong evidence that blocking the action of a component cause inhibits the completion of the sufficient cause, thereby preventing the disease by that pathway. There are many published studies providing support for this concept (Tuomilehto et al., 2011; DPPRG, 2009). T2DM can be delayed or prevented among people who have IGT with lifestyle interventions or medication (Tuomilehto et al., 2011). A randomized clinical trial also indicated that an intensive lifestyle intervention decreased the diabetes incidence in high-risk adults by 58% (DPPRG, 2009).

Similar to diabetes, depression and anxiety, two modifiable mental health conditions, can be prevented or treated successfully with lifestyle intervention, (Rubin et al., 2014; Ruusunen et al., 2012) since diabetes does not seem to be a necessary cause, but rather a component cause. Lifestyle interventions, for example exercise, prevent the completion of a sufficient cause and thus can prevent the disorder (Cabassa et al., 2010). It therefore seems that lifestyle risk factors are component causes for both diabetes and mood disorders and thus intervention can prevent the development of both diabetes as well as clinically significant symptoms of depression and preserve physical HRQoL in overweight/obese patients with type 2 diabetes (Rubin et al., 2014). This intervention appears to be successful even in non-diabetic populations. Additionally, a Finnish study of 522 middle-aged participants, who were overweight or obese, reported that among the lifestyle changes, particularly, successful reduction of body weight was associated with the greatest reduction of depressive symptoms (Ruusunen et al., 2012).

Observational studies have provided evidence for other component causes, for example improved diet quality has been found to decrease the symptoms of depression (Jacka et al., 2010a; Jacka et al., 2011a; Jacka et al., 2010b; Jacka et al., 2011b). Jacka and colleagues conducted several studies to examine the association between diet quality and depression (Jacka et al., 2010a; Jacka et al., 2011a; Jacka et al., 2010b; Jacka et al., 2011b). In their population based study of 1046 Australian women aged 20–94 years, they found that a ‘healthy’ dietary pattern was associated with a reduced likelihood of clinically

diagnosed depressive disorders, and a dietary pattern comprising processed and 'unhealthy' foods was associated with an increased likelihood of psychological symptoms and depression ([a]Jacka et al., 2010). They replicated the findings in the Hordaland Health Study of 5731 adults in Norway where participants with better quality diets were less likely to be depressed or anxious (Jacka et al., 2011a). A population based study has also demonstrated both a cross sectional and longitudinal relationship between diet quality and mental health in approximately 3000 Australian adolescents (Jacka et al., 2011b).

Although the strength of diabetes and mood disorders as a cause is not strong, the present prospective study suggests that they may represent component causes and that other major causes such as obesity for depression or anxiety predicting diabetes and diabetic complications for diabetes predicting mood disorders may be required to create a sufficient cause. The present study suggests that women who were overweight or obese are at greater risk of developing diabetes as well as reported higher proportions of mood disorders, suggesting that obesity may be a stronger component cause that either diabetes or the mood disorders. Nevertheless, in regard to prevention of diabetes, the findings of the present study suggest that healthcare professionals as well as people at risk should be aware that the evidence is in favor of mood disorders as a component cause (albeit weak) of diabetes.

11.9.2. Implications for treatment

The present work provides significant implications for treatment since we find that symptoms of depression and anxiety are component causes of diabetes. These findings suggest that health care professionals managing people with diabetes or mood disorders should consider the possible link between diabetes and mood disorders. This is important because medications play a vital role in the treatment of medical illnesses. The role of medications is particularly important in cases of chronic illnesses such as diabetes, chronic depression or anxiety.

Both depression and anxiety have been linked to poor glycemic control in previous studies (Anderson et al., 2002; Lloyd et al., 2000; Lustman et al., 2000; Niemcryk et al., 1990). However the present study did not find significant association between glycemic control and symptoms of depression and anxiety. There is a substantial evidence that treatment of mental health conditions is associated with improved glycemic control (Rubin and Peyrot, 2001; Lustman et al., 2000; Richardson et al., 2008). In non-diabetic populations,

untreated depression and anxiety events may predispose the population to increased risk of developing diabetes (Mezuk et al., 2011; Smith et al., 2013). However, in terms of prevention, it has been reported that the use of antidepressants to treat depression does not lower the risk of developing diabetes (Pan et al., 2010).

It is assumed and often found, that high income, developed countries have adequate resources to make drug treatments available for all patients. However, low or middle income, developing countries usually have inadequate resources as well as financial instability, and it is near to impossible to provide optimal treatment for the majority of patients. The affordability or availability of medications, including medications to treat diabetes, is a public health issue in developing countries, such as Malaysia (Babar et al., 2007). The treatment gap between a developed and a developing country is endorsed by the present study which found that the use of drugs to treat diabetes in Malaysia, a developing country does not correlate with the use of drugs to treat diabetes in Australia (*full paper can be found in Appendix 1A*). The present study found insulin use in Australia was substantially higher than in Malaysia and although there was a small decrease, insulin use in Australia increased steadily during the study period. This finding is of concern, as many patients in Malaysia may be undiagnosed or inappropriately treated.

While the present study suggests that overall burden of any anxiety disorder in people with diabetes was within the range reported for the general population, this is consistent with the mood disorders acting as component causes and may interact with other factors (for e.g. obesity) to increase the risk of developing diabetes by inhibiting insulin function in a variety of ways (Chiodini et al., 2007; Ehlert et al., 2001; Merswolken et al., 2012; Steudte et al., 2011; Young et al., 2004). Therefore the treatment of one to reduce onset of the other is critical in reducing the burden of disease.

General Conclusions

This PhD study provides insight into the long term association between diabetes and mood disorders. Over the past decade, diabetes has reached epidemic proportions, particularly in developing countries (Shaw et al., 2010) and differences in the drug treatment of diabetes in a developed and a developing country were identified, contributing to the relatively scarce literature from developing countries.

Based on standardized estimates, one in five people with diabetes will have depression and/ or anxiety. Modest evidence of an association or increased risk of mood disorders as a consequence of diabetes was detected in this study. While there are a number of component causes associated with the outcomes, the most interesting finding is arguably the fact that both represent potential component causes of the other. The study also recommends some caution about the strength of these component causes.

The value of this study is that it provides a platform for the development of preventive programs; targeting people with diabetes is based as much on reducing the burden of component causes, as it is on the treatment and associated medication adherence among people with the disorder itself.

The findings of this work raise some fundamental questions about whether decision makers have an adequate understanding of the interaction of the depression and anxiety issues with diabetes. Although the present study provides insight into these issues, knowledge about the long-term health consequences of these comorbid conditions has been limited or incomplete.

The findings also raise some caution about the possible strength of these component causes. Firstly, although the association is not strong in epidemiological terms, and these are not necessary causes, then should people with diabetes be screened for depression and anxiety on a regular basis? Secondly is it helpful, to the broader population with diabetes or to the individual with diabetes, to treat the symptoms of depression and anxiety to reduce the risk of future diabetes? Would such approach produce a reduction not only in diabetes prevalence but the adherence problems associated with diabetes?

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APPENDIX 1A

AMJ Australasian Medical Journal

[AMJ office use only]

A comparative drug utilisation study of the treatment of diabetes in Malaysia and Australia

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RESEARCH

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ABSTRACT

Background
Once a disease of developed countries, Type 2 Diabetes Mellitus (T2DM) has become widespread around the globe. In people with T2DM, achievement of therapeutic outcomes demands the rational and quality use of medicine.

Aims
The primary aim of this descriptive study was to examine the prevalence of diabetes and prescribing patterns of antidiabetic medications in Australia and Malaysia.

Methods
The most recent, publicly available, statistical reports (2004-2008) on the use of medicines published in Australia and in Malaysia were evaluated. Defined daily doses (DDDs/1000 population/day) were derived from the reports and used to rank and compare individual drug use.

Results
There was an increasing trend in the prevalence of diabetes in Australia although there is a greater predicted increase in prevalence for Malaysia. While drugs used for the treatment of diabetes were not the most highly utilised drugs in Australia, their use increased during the study period, from 42.64 to 48.61 DDD/1000/day. Antidiabetic drugs were the most frequently dispensed class of drugs in Malaysia. Although the total consumption of antidiabetic drugs in Malaysia decreased between 2006 and 2007 (from 40.30 to 39.72); this was followed by a marked increase to 46.69 in 2008. There was a marked reduction in the dispensing of insulin in Malaysia from 2004 to 2007 (7.77 to 3.23).

Conclusion
The utilisation of drugs to treat diabetes does not reflect the patterns of utilisation found in Australia. Effective drug utilisation reviews are required to ensure impartial access in middle and low-income countries.

Word count: 2900
Figures and Tables: 5

Key Words
Utilisation, drugs, diabetes, Malaysia, Australia, insulin, metformin

What this study adds:

1. What is known about this subject?
There is a changing trend in the prevalence of diabetes worldwide with emerging focus on treatment of diabetes and associated complications. Dispensing trends reflect the use of drugs and therefore the treatment of medical conditions.

2. What new information is offered in this study?
The paper highlights the differences in utilisation of drugs to treat diabetes, between Australia and Malaysia and their concordance with national and international treatment guidelines.

3. What are the implications for research, policy, or practice?
There is a need to include effective drug utilisation reviews in diabetes management protocol in developing countries, and to facilitate the development of educational

interventions, review of treatment guidelines, and education of prescribers and patients.

Background

Diabetes mellitus is a chronic, progressive disorder that affects millions of people worldwide.[1] Once a disease of developed countries, Type 2 Diabetes Mellitus (T2DM) has spread to every country in the world.[2] The global estimates published in 2010 by Shaw et al. reported the world prevalence as 6.4%, affecting 285 million adults (aged 20–79 years); it is predicted to rise to 7.7% and 439 million, by 2030.[3] The predicted increase in patients with diabetes is nearly twice the annual growth of the total world adult population.[3]

Both the incidence and prevalence of diabetes are escalating particularly in developing and newly industrialized nations, and also among disadvantaged people in developed countries; these populations are said to be at highest risk of having diabetes.[3] By 2030, the increase in the number of adults with diabetes over the preceding decade is estimated to be 20% in developed and 69% in developing countries respectively.[3] Malaysia, situated in Southeast Asia, is one of the most prominent developing, middle-income countries;[4] it was also among the top 10 countries for diabetes prevalence in 2010 and is predicted to remain so until 2030.[3] Diabetes prevalence among the adult population in Malaysia (>18 years) has increased significantly over the years, from 11.6% (2006),[5,6] to 22.9% (2013).[7]

Diabetes is the fastest growing chronic disease in Australia and the AusDiab Follow-up Study (2010) estimated the total number of Australians with diabetes *and pre-diabetes* at 3.2 million,[8] or 14.3% of the population at the time. This is a marked increase since 1995, when self-report census data indicated that 2.4% of Australians (430,700 people) had been diagnosed with diabetes at some time during their lives; the figure increased to 3.6% in 2004-05,[9] and to 3.8% (an estimated 818,200 persons) in 2007-08.[10] In 2011-12, 4.0% of the Australian population (875,400 people) reported having some type of diabetes; however the prevalence of diabetes remained stable between 2007-08 and 2011-12 (both 4.0%).[11] Diabetes is expected to become the leading contributor to disease burden in Australia by 2023.[12]

Dispensing trends reflect the use of drugs and therefore the treatment of medical conditions.[13] The primary aim of this descriptive study was to examine the prevalence of diabetes and prescribing patterns of antidiabetic medications in Australia and Malaysia, to evaluate prescribing trends and their concordance with national and international treatment guidelines. This comparison was made between a developed country with adequate health resources and an increasing prevalence of diabetes (Australia), and a middle-income developing country with a high prevalence of diabetes (Malaysia). The underpinning research questions were "How does the utilisation of drugs to treat diabetes, differ between Australia and Malaysia?" The findings may serve as means of improving the quality use of medicine, enhancing therapeutic outcomes, and indicating over- or under-consumption of medicines.

Method

Assessing the prevalence of Diabetes in Australia and Malaysia

The prevalence of diabetes in this paper is presented using estimates reported by Shaw et al.,[3] where the authors derived prevalence estimates for Australia from the Australian Diabetes, Obesity and Lifestyle Study,[14] and the National Diabetes Service Scheme, Diabetes Australia.[15]

The prevalence of diabetes in Malaysia is based on figures published in National Health and Morbidity Survey (NHMS) reports.[5,7] NHMS is a nationwide survey of self-reported data that includes medicine use, dietary habits, various disease states, and demographics, which was first published in 1986 and is now published every ten years.[5,7] Although we focused on both types (type 1 and 2) of diabetes in this study, about 90% of all cases of diabetes in both countries are T2DM.[3]

Assessing Diabetes related Medicines Use

Publicly available Australian and Malaysian reports containing statistics on medicine use for each year from 2004 to 2008 (inclusive) were used, and the focus for this paper were antidiabetic drugs.[16,17] The published reports from both countries adopted the same unit (DDD/1000 population/day) to describe medicine usage which facilitated comparison between the two countries. Dispensing databases are compiled from claims data and essentially such data are designed for administrative purposes; however, the large size of such databases makes them suitable for drug utilisation studies despite their lack of clinical information. To facilitate international comparison, drugs are classified according to the World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) classification system, and Defined Daily Doses (DDDs) can be used to rank and compare individual drugs.[18] The DDD is the international unit of drug use

established by the Nordic Council on Medicines and the WHO and is assumed to be an average dose of the drug per day for adults for its main indication.[19,20]

Medicines Use Data, Australia

The Australian Statistics on Medicines (ASM) is an annual government publication produced by the Drug Utilisation Sub-Committee (DUSC) of the Pharmaceutical Benefits Advisory Committee, and was first published in 1997. The "...comprehensive and valid statistics on the Australian use of medicines..." is published in the public domain "...for use by interested parties...".[17] The reports contain analyses of retrospective data of subsided medicines prescribed by registered General Practitioners (GP) in community practice in Australia. For example, the report published in 2013 contained data from 2010. These reports provide information about medicines which are subsidised by the Australian Government for its citizens under the Pharmaceutical Benefits Scheme (PBS) or the Repatriation Pharmaceutical Benefits Scheme (RPBS); the latter is specifically for war veterans and their dependents.[17] Dispensing data are collected electronically from two sources, namely Medicare Australia records through the PBS/RPBS and the DUSC survey of community pharmacies;[17] both sources are compiled from databases based on electronic claims data.

Medicines Use Data, Malaysia

The Ministry of Health in Malaysia publishes statistics on medicines using retrospective data derived from the Ministry of Health (public institutions), as well as from private hospitals, university and armed forces, (private) GP prescribing and (private) pharmacy dispensing.[16] The medicines provided through public hospitals or clinics are dispensed free of charge to Malaysian citizens and reports are therefore restricted to 'prescription' medicines,[16] while prescription medicines dispensed in community pharmacies are paid for in full by the patient. The first Malaysian statistics on medicine (MSM) report was published in 2013 contains data from 2008.[16] The major antidiabetic drug classes included for comparison were insulin and analogues, biguanides, sulfonylureas, alpha glucosidase, thiazolidinediones, Dipeptidyl peptidase 4 inhibitors. Descriptive analyses presented in the tables and figures in the current paper were carried out using Microsoft Excel 2010. Descriptive statistics were used to analyze frequency, percentage and mean.

Results

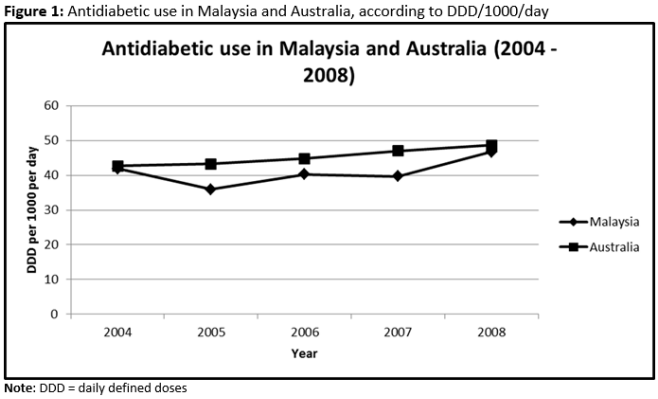
Diabetes prevalence

The population characteristics of Malaysia (a developing country) and Australia (a developed country) for the period of this study were similar.[21,22] There was an increasing trend in the percentage prevalence of diabetes in both countries; however, it was 1.5 times higher in Malaysia (10.9) than Australia (7.2).[3]

Drugs used to treat diabetes

Although the increase in the use of drugs used to treat diabetes in Australia was steady, in Malaysia it declined pointedly in 2005 (35.90 DDDs/1000/day), with a smaller reduction in 2007 (from 40.39 in 2006 to 39.72 DDDs/1000/day in 2007), which was followed by a marked increase in 2008 to 46.69 DDDs/1000/day (Figure 1).

Figure 1: Antidiabetic use in Malaysia and Australia, according to DDD/1000/day



Note: DDD = daily defined doses

In Australia the overall use of antidiabetic drugs increased between 2004 (42.64 DDDs/1000/day) and 2008 (48.61 DDDs/1000/day), although the most frequently dispensed therapeutic drug class during the study period (2004-2008) included drugs to treat hyperlipidaemia and cardiovascular diseases.[17] The two most frequently dispensed sub-groups to treat diabetes in Australia were sulfonylureas and biguanides (2004-2008; Table 1) although there was a decrease in the use of sulfonylureas over the study period (14.35 in 2004, to 11.55 DDDs/1000/day in 2008). The biguanide (metformin) was the most frequently used oral antidiabetic drug in Australia from 2004 to 2008 and while the use of the sulfonylurea (glibenclamide) was relatively low, the use of glibenclamide as well as gliclazide declined between 2004 and 2008.

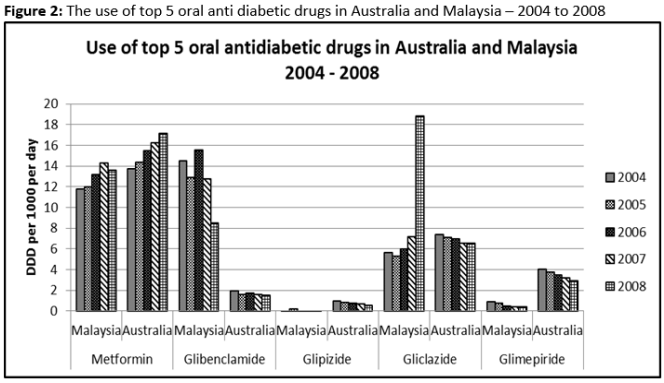
Table 1: Comparison of antidiabetic medication utilization in Australia and Malaysia – 2004 to 2008

Therapeutics groups	2004		2005		2006		2007		2008	
	Malaysia	Australia	Malaysia	Australia	Malaysia	Australia	Malaysia	Australia	Malaysia	Australia
Total antidiabetics use	41.93	42.64	35.90	43.25	40.30	44.80	39.72	46.99	46.69	48.61
Insulin and analogues	7.77	13.49	3.81	13.93	3.29	14.57	3.23	15.70	3.71	16.66
Biguanides (Meformin)	11.74	13.72	11.98	14.34	13.15	15.46	14.28	16.24	13.55	17.16
Sulfonylureas	21.15	14.35	19.16	13.31	22.08	12.84	20.45	11.98	27.75	11.55
Alpha glucosidase inhibitors (Acarbose)	0.38	0.25	0.49	0.22	0.45	0.18	0.83	0.17	0.71	0.16
Thiazolidinediones	0.57	0.81	0.21	1.46	0.20	2.31	0.44	2.87	0.21	2.81
Dipeptidyl peptidase 4 inhibitors (Sitagliptin)	-	-	-	-	-	-	0.02	-	0.09	0.14
Others, excl. insulin	0.27	0.006	0.15	0.003	0.07	0.005	0.08	0.01	0.04	0.005

Note: Comparisons are based on DDD/1000/day (daily defined doses)

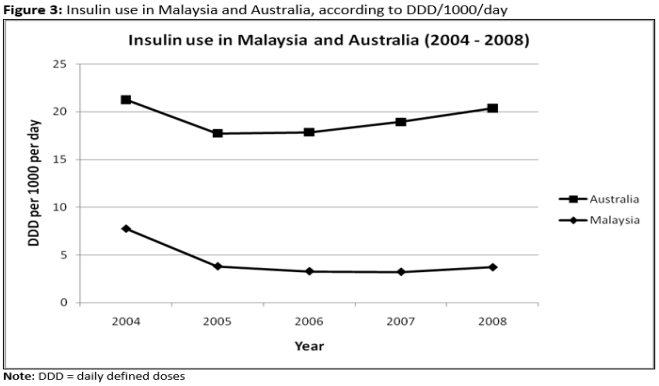
In contrast, the most frequently dispensed drugs in Malaysia were sulfonylureas, used for the treatment of diabetes. Nationally, the drug glibenclamide was ranked first among the top 40 drugs between 2004 (14.49 DDDs/1000/day) and 2006 (15.53 DDDs/1000/day). Glibenclamide was replaced in subsequent years by metformin (14.28 DDDs/1000/day in 2007) and gliclazide (18.80 DDDs/1000/day in 2008) (Figure 2).

Figure 2: The use of top 5 oral anti diabetic drugs in Australia and Malaysia – 2004 to 2008



The use of the alpha glucosidase inhibitor acarbose increased more than two-fold In Malaysia between 2004 and 2007 (from 0.38 to 0.83 DDDs/1000/day) followed by a decrease to 0.71 DDDs/1000/day (2008). The thiazolidinediones (rosiglitazone and pioglitazone) were used less frequently in Malaysia in 2008 (0.21) compared to Australia (2.81 DDDs/1000/day respectively; Table 1), although the use of rosiglitazone in Malaysia almost doubled from 2006 to 2007 (0.20 to 0.43 DDDs/1000/day; Figure 2).

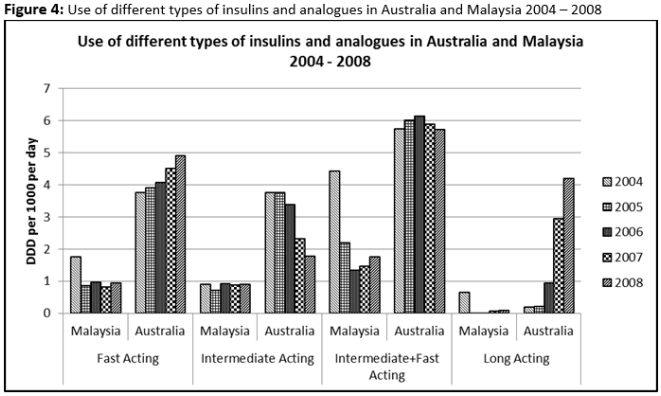
Figure 3: Insulin use in Malaysia and Australia, according to DDD/1000/day



Note: DDD = daily defined doses

Insulin use in Australia was substantially higher than in Malaysia; despite a small decrease in insulin use in Australia between 2004 and 2008, the overall increase from 13.49 to 16.66 during the study period (Table 1) was not reflected in Malaysia (Figure 3). Insulin dispensing decreased by 50% in Malaysia from 2004 to 2007 (7.78 to 3.23 DDDs/1000/day), followed by a small increase to 3.71 DDDs/1000/day in 2008 (Figure 4). The most widely used insulin in both countries was premixed insulin and analogues (intermediate + fast-acting).

Figure 4: Use of different types of insulins and analogues in Australia and Malaysia 2004 – 2008



Discussion

There were similar trends of increasing diabetes prevalence between the two countries but marked differences in the utilisation of antidiabetic drugs.[3,16,17] The total consumption of drugs used to treat diabetes in Malaysia decreased between 2004 and 2007 and was followed by a marked increase in 2008, while in Australia their use steadily increased during the same period (2004-2008).

Based on global estimates, the prevalence of diabetes in Malaysia is significantly higher than Australia, a difference that is predicted to continue to widen by 2030.[3] The increasing prevalence among adults aged ≥ 18 years in Malaysia has been reported elsewhere;[5,7,23] we observed that the prevalence was steeper in Malaysia than Australia. The situation in Malaysia is alarming and as the prevalence of diabetes is expected to increase, the number of patients with diabetes - diagnosed and undiagnosed, treated and untreated - is expected to rise proportionately. Previous studies in Malaysia using NHMS III data reported that diabetes was most prevalent among Malaysians of Indian origin (37.9%) and among people aged between 45-75 years of age (> 20%);[5,7] however, it was comparable between genders and geographical locations.[7] The incidence of diabetes in Australia was also reported to increase at around 45 years of age and by 2008, was highest among patients aged 75 years and over.[10] However, a few years later (2011-12), the age group with the highest incidence of diabetes had decreased to 65-74 years.[17] Regarding gender,

just over half (52%) of all diabetic cases (T1DM and T2DM) in Australia occurred among women in 1995,[9] while a years later (2011-12), more men in Australia reported having diabetes (4.3%) than women (3.6%).[17]

Despite the high prevalence of diabetes among people living in Malaysia, the utilisation of drugs to treat diabetes was not as high as expected. It has also been reported that less than a quarter of patients achieve their target HbA1c level (< 7%),[24] which suggests that there may be a large number of people with untreated diabetes in Malaysia or diabetics who do not take appropriate medication.[5] Perhaps surprisingly, while the 10 most frequently dispensed drugs in Malaysia included those to treat diabetes,[16] in Australia the most frequently dispensed drugs were drugs to treat cardiovascular conditions.[17] Despite the fact that there were no antidiabetic drugs included among the 10 most frequently dispensed drugs in Australia, it is interesting that their use was higher than in Malaysia, at 4.35 DDD/1000/day, on average.

The two most frequently dispensed drug classes in Malaysia were biguanides and sulfonylureas. In Australia, the most frequently used antidiabetic drugs were biguanides and insulins. The increased use of metformin in Malaysia indicates (improved) adherence to prescribing guidelines, which recommend metformin as first line oral medication, particularly in obese individuals.[25,26] The introduction of the fixed-dose combination of metformin and sulfonylurea may be associated with improved patient compliance and hence, utilisation.[16,26] In Australia, metformin use followed a similar increasing trend during the study period. Thiazolidinedione usage in Malaysia decreased during 2005 and 2006 but then increased in 2007, when pioglitazone was introduced,[16] and the use of rosiglitazone almost doubled in 2007 in Malaysia while its use remained constant in Australia.[17] With the current controversy surrounding the use of rosiglitazone,[27] we expect the decreasing trend in Malaysia and Australia to continue.

Surprisingly, the use of insulin in Malaysia decreased by 50% during the study period, from 7.78 (2004) to 3.71 DDD/1000/day (2008), although there was an encouraging increase of 0.48 DDD/1000/day between 2007 and 2008; by comparison, despite a decrease from 2004 to 2005, insulin use in Australia increased overall and was substantially higher than in Malaysia.

Due to the progressive failure of insulin secretion, therapy has to be increased over time.[28,29] Patients with T2DM who do not achieve optimal glycaemic control with oral antidiabetic drugs (HbA1c < 7.0%) may require insulin therapy, and should start insulin therapy as soon as possible if HbA1c > 9.0% and blood glucose levels >15mmol/L.[30,31] The early use of insulin in the treatment of T2DM is not without controversy both in terms of micro-vascular and macro-vascular complications.[32] However, studies included in the NICE Guidelines suggest that combination treatment with insulin and metformin, or insulin and a sulfonylurea, show significantly lower HbA1ac levels compared to insulin monotherapy.[29] Results from clinical trials have led to international management guidelines emphasising the importance of blood glucose control to reduce vascular complications in people with diabetes.[33-35]

A number of potential barriers to and lower acceptance of insulin use among Malaysian patients have been identified. These include lack of knowledge (e.g. fear of injections, glucose monitoring, patient ignorance, lack of awareness about the importance of diabetes treatment),[5,16,36] negative side effects (e.g. insulin-related hypoglycaemia),[16,36] patients' preference (e.g. oral medication, alternative medicines),[16,37,38] and cost of treatment.[36] The affordability or availability of drugs may also be a factor as it has been reported that essential drugs are expensive in Malaysia and are not available in all areas such as the far-eastern region where the logistics of transporting medicines is challenging.[39]

Due to the increasing burden of chronic diseases in Malaysia, the Malaysian government has increased the spending on health related issues; however, under-treatment, under-diagnosis, non-adherence and the use of traditional medicines may lead to sub-optimal use of antidiabetic agents. We suggest that a crucial step may have been overlooked; robust screening strategies should be conducted in urban and rural areas, to identify patients at risk of, and suffering from, undiagnosed diabetes. In order to control, delay or prevent complications associated with diabetes effective prescribing through targeted training and professional development of health care professionals, and patient education on appropriate treatment, must be promoted by the authorities who are responsible for coordinating services, resources and facilities.

This study had several limitations that may affect generalisation. The variability in antidiabetic medicine use in Malaysia suggests that there may be some problem with sampling procedures, response rates and hence the quality of the data during the period 2004-8. Although reports from both countries presented the data in the same unit (DDD/1000 population/day), the data sources are very

different; Malaysian data are not as comprehensive as Australian data although this improved over the study period. For example, in Malaysia there were only 32 participating private pharmacies in 2004 which increased to 814 in 2008.[16] It is also possible that only essential and accessible sources were included in the collection of data. It is known that Australian reports may underestimate the use of under-copayment medicines (i.e. non-subsidised medicines which are therefore not included in the claims databases) by up to 20%.[17] Finally, this drug utilisation study is based on reports of dispensing data and the drugs may not necessarily have been consumed.[16,17]

Conclusion

Despite these limitations this comparative study does highlight differing prescribing trends. Although there is an increasing trend in the prevalence of people with diabetes in Malaysia and Australia, the utilisation of drugs to treat diabetes in Malaysia does not reflect the patterns of antidiabetic drug utilisation in Australia. Many patients in Malaysia may be undiagnosed or inappropriately treated. Insulin is considered to be the most appropriate form of treatment for certain types or stages of diabetes and more research into the low use of insulin in Malaysia is required. It will be necessary to lay a firm foundation for the development of educational interventions, review of treatment guidelines, and education of prescribers and patients to increase the acceptance of insulin therapy. Moreover, effective drug utilisation review to promote rational medicine use should be included in the diabetes management protocol in Malaysia.

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PEER REVIEW

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CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

APPENDIX 4A

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Original Article

Incidence and risk of diabetes mellitus associated with depressive symptoms in adults: Evidence from longitudinal studies

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ABSTRACT

Aims: We estimated the incidence and risk of diabetes associated with depressive symptoms using data from longitudinal studies.
Materials and methods: Databases were systematically searched for relevant studies. Incidence of diabetes is presented as cumulative incident proportion (CIP). Pooled effect sizes were calculated using random-effects model. The data were reconstructed to compute relative risk (RR).
Results: The 16 studies selected for review generated 16 datasets of which 8 studies reporting binary estimates (RR) and 8 studies reporting time-to-event estimates (hazard ratio (HR)). Both RR and HR were significant at 1.67 (95% CI: 1.30–2.15) and 1.45 (95% CI: 1.12–1.87) for incident diabetes associated with depressive symptoms.
Conclusion: Our observations revealed greater cumulative incidence of diabetes in depressed than in non depressed groups. Depression should be included among risk factors that required regular screening for diabetes.

1. Introduction

Depression is responsible for a large proportion of burden associated with non-fatal health outcomes [1,2]. It is also one of the most common co-morbid conditions associated with diabetes mellitus (DM) [3,4]. People with DM are almost twice as likely to suffer from depression as the general population [4–7]. Sadly, this depression often remains unrecognized and thus untreated [8], leading to a higher prevalence of depression among people with DM [5,8]. Diabetes is also thought to be a consequence of depression and Thomas Willis, a famous physician from Great Britain, was the first to report that diabetes was caused by "sadness or long sorrow and other depressions" [9]. This relationship was then demonstrated in a number of epidemiological studies and the majority agreed with Willis' hypothesis [10–14]. However, other studies have suggested that the relationship between diabetes and depression was modest [15–17], and existed only with cases of severe depression [11,18–23].

Depression as a risk factor for the development of DM has no strong physiological basis but this relationship may be a consequence of decline in health-maintenance behaviors among depressed persons [15,24], or biochemical changes associated with depression [25,26], with some studies suggesting that depression is an independent risk factor for the development of DM [27,28]. The aim of this review was to examine the relationship between depression and incident diabetes by conducting a meta-analysis of longitudinal studies using relative risk, and extensive review and synthesis of the data. Previous meta-analyses have demonstrated an increased risk of diabetes [25,29,30], they are far from conclusive because of several deficiencies. For example, incidence measures were not computed because most of the longitudinal studies neither presented data in a four-fold table form nor supplied adequate information to calculate cumulative incident proportion (CIP) (i.e. raw numbers of incident diabetes by risk category). For studies which did not provide data in a four-fold table form, we imputed (from four-fold table reconstruction) the CIP. The CIP was also used to estimate cumulative incidence. Finally to estimate pooled effect sizes studies have not separated binary point and time-to-event estimates, which we consider may

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be inappropriate [25,29]. We converted all odds ratios (ORs) to relative risks (RRs) so that risks are uniform.

2. Methods

2.1. Data sources

The following electronic databases were searched: MEDLINE (1950–July 2013); EMBASE (1980–July 2013); CINAHL (1982–July 2013); PsycINFO (1880–July 2013). After identifying possible papers, titles and abstracts were screened to select studies, relevant to the aim of this review. The full texts of the selected studies were then examined to determine whether the studies met our inclusion criteria. To locate additional relevant papers, the list of references in identified studies was also examined. When multiple publications from the same study population were available, we only included the most recent publication.

2.2. Eligibility criteria

The eligibility criteria were based on study type and population attributes. Regarding study type, the following were included: studies that investigated the association, comorbidity and/or coexisting prevalence of diabetes and depression, and/or depressive symptoms, in adults with diabetes mellitus. In this meta-analysis we included all studies that longitudinally examined the relationship between depression and onset of diabetes. Studies that focused on efficacy of treatment, or comorbidities, or which included other psychiatric conditions were excluded, as were studies that only examined gestational diabetes mellitus.

2.3. Data abstraction

Data extracted from the studies included the name of first author; publication year; study design; follow-up time in years; number of subjects in the analysis; gender and age of subjects; method of depression assessment; method of diabetes assessment; binary point estimates and time-to-event (survival) analysis estimates with 95% CI (adjusted for the largest number of confounders); number of confounders that were adjusted for in the analyses (see Tables 2 and 3 for details of confounders considered); method of exclusion of depressive and patients with diabetes at baseline; and new-onset cases. The method of assessment of diabetes was either based on self-report or clinically diagnosed based on blood glucose levels or based on the diagnosis of diabetes from administrative data (drug consumption/hospitalization). Depression was based on a diagnosis by psychiatrist (using Diagnosis and Statistical Manual (DSM) criteria); the assessment of depressive symptoms was by a self-administered questionnaire.

2.4. Data analyses

Four-fold cells (2×2 tables; exposure yes/no vs. outcome yes/no) were imputed for all binary point estimates using the reconstruction method proposed by Pietrantonj [31]. Studies using time-to-event estimates (hazard ratios) were presented separately, as 2×2 table reconstruction was not possible for studies using time-to-event estimates. The four-fold cells were used to compute relative risk (RR), and cumulative incident proportion (CIP). For studies that presented graded relationships such as low, medium, or high depressive symptoms, only the estimate for the highest category was selected. We evaluated heterogeneity using the Cochran's Q (Q test) and a related metric, the I^2. A p-value of 0.10 was used as the cut-off point for heterogeneity; therefore a related metric I^2 was also reported ($I^2 = (Q - df)/Q \times 100\%$). Pooled results were calculated via the random effects (RE) model.

To assess the robustness of this meta-analysis, sensitivity analyses were performed by modifying our selection criteria and then examining the effect of the variously modified selection criteria on the pooled results. A funnel plot was used to examine the existence of publication bias through visual inspection for asymmetry and was considered asymmetrical if the intercept of Egger's regression line deviated from zero with $p < 0.10$. When the funnel plot was found to be asymmetric, additional analyses for publication bias were performed using the Duval and Tweedie non-parametric "Trim and Fill" method of accounting for missing studies in meta-analysis [32]. All imputations were done assuming random error only. All analyses were conducted using Microsoft Excel and MetaXL software version 1.3 [33].

3. Results

Our search yielded 850 unique abstracts from MEDLINE, 180 unique abstracts from EMBASE/CINAHL, and 230 from PsycINFO. After removal of duplication and applying the eligibility criteria, 96 relevant papers were examined for further consideration. Of these, 80 studies were excluded for reasons such as failing to remove prevalent cases of diabetes at baseline and insufficient data to generate pooled effect sizes. Studies that examined the association of antidepressant use and DM were also excluded [34–36]. A total of 16 articles were then included in our review; these provided 16 datasets.

Three studies used the same sample [13,23,37]; however, two of these were retained: the most recent publication by Pan et al. [13], and Saydah et al. [23] who used a different risk estimates (hazards ratio), in the 2003 publication, and thus were in different analyses. However for estimating CIP, these studies were not

Table 1
Incidence proportions of diabetes in people exposed/not exposed to depressive symptoms.

Authors [Ref]	Country Year	Follow-up years	CIP	Cumulative incidence (%)
1. Eaton et al. [11]	USA 1996	13.0	E: 6/76 UE: 80/1604	7.89 4.99
2. Kawakami et al. [21]	Japan 1999	8.0	E:9/278 UE:34/2102	3.24 1.62
3. Stellato et al. [14]	USA 2000	9.0	E: 7/90 UE: 23/910	7.78 2.53
4. Carnethon et al. [18]	USA 2003	15.6	E: 32/534 UE: 128/5496	5.99 2.33
5. Palinkas et al. [22]	USA 2004	8.0	E: 10/70 UE: 51/840	14.29 6.07
6. Everson-Rose et al. [12]	USA 2004	3.0	E: 28/578 UE: 58/1998	4.84 2.90
7. V den Akker et al. [17]	Netherlands 2004	15.0	E: 89/1334 UE: 3156/66670	6.67 4.73
8. Mallon et al. [16]	Sweden 2005	12.0	E: 3/128 UE: 29/1010	2.34 2.87
9. Carnethon et al. [19]	USA 2007	8.0	E: 39/936 UE: 108/3745	4.17 2.88
10. Engum et al. [20]	Norway 2007	10.0	E: 152/8159 UE: 382/28598	1.86 1.34
11. Golden et al. [15]	USA 2008	3.2	E:60/911 UE: 215/4290	6.59 5.01
12. Campayo et al. [10]	Spain 2010	5.0	E: 25/214 UE: 138/1949	11.68 7.08
13. Demakakos et al. [47]	UK 2010	5.0	E: 51/823 UE: 158/5288	6.20 2.99
14. Pan et al. [13]	USA 2010	10.0	E: 524/7051 UE: 2320/50829	7.43 4.56
15. Chen et al. [46]	Taiwan 2013	7.0	E: 1156/5847 UE: 762/5847	19.77 13.03

E = exposed group, UE = unexposed group; CIP = cumulative incident proportion.

Table 2
Summary of findings of longitudinal studies assessing relationship between depression and incident diabetes using binary point estimates.

Authors (country – year)	Follow-up years	% female	Age (yrs)	Assessment of depression	Assessment of diabetes	Original effect size	Reconstructed RR	Adjustment for confounders
1. Stellato et al. (USA – 2000)	9.0	0.0	40–70	CES-D	Self-report	OR: 3.09 (1.34–7.12)	2.94 (1.31–6.60)	Testosterone, SHBG, hypertension, CVS, BMI
2. Everson-Rose et al. (USA – 2004)	3.0	100	≥42	CES-D	Self-report + FPG	OR: 1.66 (1.05–2.61)	1.63 (1.05–2.54)	Age, site, race, education, medication use
3. Palinkas et al. (USA – 2004)	8.0	57.0	≥50	BDI	OGTT/FPG	OR: 2.50 (1.29–4.87)	2.30 (1.23–4.30)	Age, sex, physical activity, BMI
4. Engum et al. (Norway – 2007)[a]	10.0	55.0	≥30	ADI	Self-report + FPG	OR: 1.40 (1.16–1.69)	1.39 (1.16–1.68)	Age, gender, socioeconomic status, lifestyle, metabolic and clinical factors
5. Eaton et al. (USA – 1996)	13.0	63.0	>18	DIS	Self-report	RR: 2.23 (0.90–5.55)	2.23 (0.90–5.54)	Age, sex, race, BMI
6. Carnethon et al. (USA – 2003)	15.6	59.0	≥25	GWBS	Self-report + MRD	RR: 2.52 (1.73–3.67)	2.52 (1.73–3.67)	Age, race, sex
7. Mallon et al. (Sweden – 2005)[a]	12.0	53.0	≥45	Self-report	Self-report	RR: 0.90 (0.30–2.90)	0.90 (0.29–2.80)	Age, not married, living alone, hypertension, obesity, smoking, alcohol, snoring and sleep duration
8. Pan et al. (USA – 2010)	10.0	100	50–75	MHI-5	Self-report + MR	RR: 1.17 (1.05–1.30)	1.17 (1.05–1.30)	Age, marital status, family history, physical activity, BMI, antidepressant use

[a] Most adjusted model was not used in previous review.

included, so there was no over-inflation of the sample. There were two studies published by Golden et al., in 2004 [38], and 2008 [15], where they used the same sample, and only the most recent was retained. Among studies assessing depression predicting diabetes, four-fold cells were reconstructed and used to compute CIP from ORs (4 studies) or RR (4 studies). The data presented by Kumari et al. [39] was insufficient to compute a four-fold cell and the study was excluded. The reconstructed CIP was then used to compute RR and RD for meta-analysis while original effect sizes (HRs) were presented separately.

Table 1 presents the country-specific cumulative incident proportions and incidences of diabetes onset for depression (exposed) and non depression (unexposed) groups.

3.1. Depressive symptoms as a risk factor for diabetes

The summary of cohort studies assessing depression as a risk factor for diabetes (in binary estimates) included in the review is presented in Table 2. Nine studies reported their findings in the form of binary point estimates. However, only eight studies that presented complete data to formulate four-fold cell were used to calculate CIP and RR. Of these eight studies, six studies reported statistically significant associations; where, increasing risk of incident diabetes as a result of depression was present. A significant heterogeneity was present, with a pooled RR of 1.67 (95% CI: 1.30–2.15) (Fig. 1) for studies examining depression as a risk factor of diabetes.

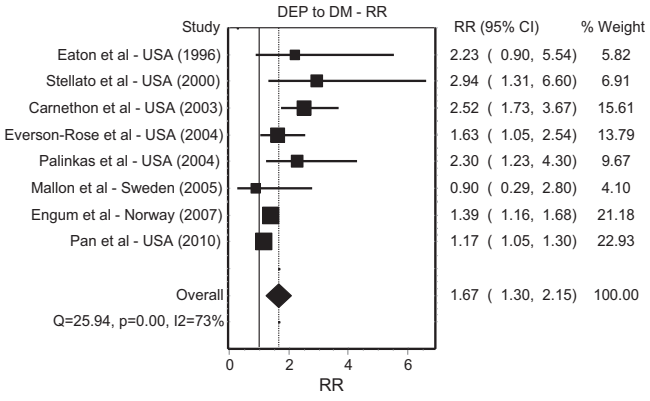

Fig. 1. Random-effects forest plot showing the risk of diabetes for individual studies using self-report questionnaires, diagnostic criteria, and all studies combined; studies using reconstructed relative ratios. Bars and diamonds indicate 95% CIs. DEP = depression; DM = diabetes mellitus; RR = relative risk.

For eight studies that presented their findings in the form of hazard ratios, there were four studies in which the association was statistically significant where increasing risk was evident (Table 3). The pooled hazard ratio was 1.45 (95% CI: 1.12–1.87) and there was an evidence of heterogeneity (Fig. 2).

3.2. Sensitivity analysis and publication bias

Studies with <10 years follow-up (RR: 1.98), those adjusted for ≤5 confounders (RR: 2.20), and conducted in the United States (US) (RR: 1.92) showed significantly higher risk of incident diabetes than studies with ≥10 years of follow-up (RR: 1.52), adjusted for >5 confounders (RR: 1.24) and conducted outside the US (RR: 1.37). The funnel plot revealed gross asymmetry, as most of the studies reported higher relative risks on one side of the line representing the most precise relative risk (Fig. 3). The Egger's test for publication bias also suggested asymmetry (intercept 0.449; $p = 0.025$). Using the Trim and Fill method to impute missing studies, three dummy studies were added and the revised estimate was 1.26 (95% CI: 1.02–1.57).

4. Discussion

The current study is the first to report cumulative incidences of diabetes in depressed and non depressed groups, using data from longitudinal studies. A greater risk of diabetes in people with depressive symptoms has been reported previously [25,29,30]. In line with these studies, our observations revealed greater CIPs of diabetes in depressed than in non depressed groups. Of 15 studies included in our review, 8 studies were from Northern America, 5 from Europe and 2 from East Asia. We note that a study conducted in Taiwan [46] documented highest whereas a study from Norway

Table 3
Summary of findings of longitudinal studies assessing relationship between depression and incident diabetes using time-to-event estimates (HR: hazards ratio).

Authors (country – year)	Follow-up years	% female	Age (yrs)	Assessment of depression	Assessment of diabetes	Hazards ratio	Adjustment for confounders
1. Kawakami et al. (Japan – 1999)[a]	8.0	0.0	≥18	ZSDS	OGTT + FPG	2.31 (1.03–5.20)	Age, education, occupation, work shift, obesity, physical activity, smoking, alcohol, chronic conditions, family history
2. Saydah et al. (USA – 2003)	9.0	74.0	32–86	CES-D	Self-report	1.11 (0.79–1.56)	Age, sex, race, BMI, physical activity, education
3. V den Akker et al. (Netherlands – 2004)	15.0	58.0	≥20	ICPC-P76	ICPC-T90	1.04 (0.84–1.28)	Age, sex, BMI, socioeconomic, interaction with depression
4. Carnethon et al. (USA – 2007)[a]	8.0	59.2	≥65	CES-D	Medication + FPG	1.41 (0.91–2.19)	Age, race, sex, education, marital status, physical activity, smoking, alcohol intake, BMI, C-reactive protein level
5. Golden et al. (USA – 2008)[a]	3.2	60.1	45–84	CES-D + antidepressant use	FPG	1.21 (0.87–1.67)	Age, sex, ethnicity, examination site, BMI, Lipids, BP, IL-6, C-reactive protein, SES, daily caloric intake, smoking status, alcohol, and physical activity
6. Campayo et al. (Spain – 2010)	5.0	55.0	≥55	GMSS + AGECAT	Self-report	1.65 (1.02–2.66)	Age, sex, family history of DM, hypertension, functional disability, smoking, alcohol, antidepressant/antipsychotics/ statin use
7. Demakakos et al. (UK – 2010)	5.0	55.7	≥50	Medication	CES-D	1.62 (1.15–2.29)	Age, sex, marital status, clinical factors, education, income, BMI
8. Chen et al. (Taiwan – 2013)	7.0	46.4	≥20	Medical records	ICD-9-CM	2.02 (1.80–2.27)	Age, sex, complications, clinical factors, geographical area

[a] Most adjusted model was not used in previous review.

[20] recorded lowest CIPs for diabetes in both the depressed and non depressed groups.

The study found a significant association between depression and incident diabetes and of the 16 studies assessing this association, 10 suggested increased risk. In our quantitative analysis using the random-effects model, we found a 1.67-fold increase in risk or 1.45-fold increase in hazard for diabetes in adults with depressive symptoms. Similar results were reported in previous meta-analyses, although they had not separated binary point estimates from HRs for estimating pooled effect sizes [25,29]. Potential mechanisms involving psychological, socioeconomic and biological factors are described elsewhere [27,40,41].

Our funnel plot suggested possible publication bias. However, the variation across different means of assessment was insignificant when studies using standard diagnostic criteria were separated from studies using self-report scales; this suggests that the finding was unlikely to be an artificial result of measurement error. The funnel plot suggested possible publication bias (Fig. 3). Funnel plot asymmetry may be due to publication bias, but it may also result from clinical heterogeneity between studies or methodological heterogeneity between studies [40]. Two assessment methods are often used to identify depressive symptoms and DM, self-report and diagnostic criteria. Most studies used non-standardized self-report measures of diabetes. The variation across different means of diabetes assessment was insignificant when studies using standard diagnostic criteria were separated from studies using self-report scales; this suggests that the finding was unlikely to be an artificial result of measurement error. Knol et al. conducted a meta-analysis in which they separated the studies where DM was assessed by blood

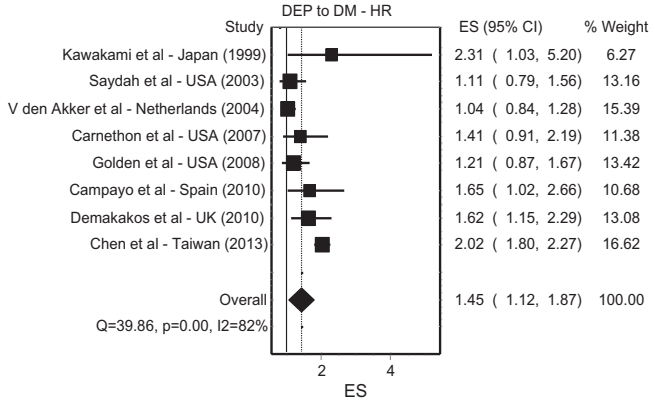

Fig. 2. Random-effects forest plot showing the risk of diabetes for individual studies using self-report questionnaires, diagnostic criteria, and all studies combined; studies using HRs. Bars and diamonds indicate 95% CIs. ES = HR (hazard ratios); DEP = depression; DM = diabetes mellitus.

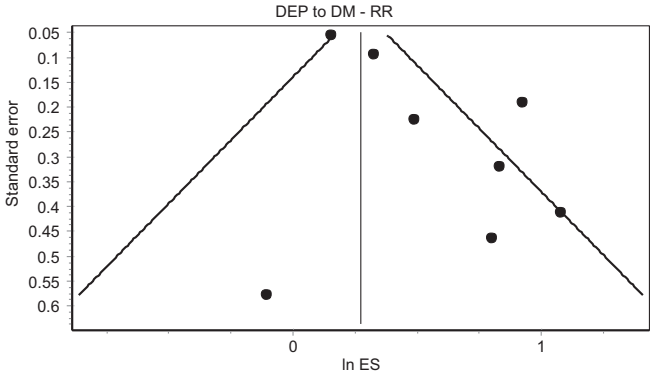

Fig. 3. Funnel plot with 95% confidence interval relative risk of studies examining risk of diabetes included in the meta-analysis using reconstructed relative ratios (RR) ($n = 8$). ES = RR (relative risk); DEP = depression; DM = diabetes mellitus.

glucose measures from physician diagnosis or patient self-report, and their study demonstrated a similar pooled relative risk of depression [25]. Confounding therefore may have resulted in the asymmetry seen in our study but has been adjusted for in the pooled analysis and so has been accounted for. Finally, publication bias may exist as the published studies may not be representative of all studies that have been done since positive results tend to be submitted and published more often than negative results [42] and we have tried to address what its impact might have been via our trim and fill analysis.

4.1. Limitations

Limitations of the current review include language bias (only English-language databases and journals were searched), and publication bias, as significant studies were more likely to be published and easily indentified. The majority of the longitudinal studies were published from the USA, Europe and other developed countries where people of color and Caucasians experienced similar rates of depression and diabetes risk [43]; studies in developing countries may present different findings. Moreover, issues with longitudinal research designs and confounding bias cannot be entirely ruled out [44,45]. Both depression and diabetes are multifactorial diseases and is therefore quite obvious that the impact of a single risk factor can be modest. In other words, the impact of a single risk factor, corrected for other confounding variables, on a multifactorial disease, is usually small, but this is not necessarily linked to a low impact from a clinical point of view.

5. Conclusions

This study provides evidence using longitudinal data that cumulative incidence of diabetes is higher in depressed than in non depressed subjects. We also found a significant association between depression and incident diabetes in terms of relative measures. Depression should be included among risk factors that required regular screening for diabetes.

Conflict of interest

No conflict of interest.

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APPENDIX 4B

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BRIEF REPORT

Incidence and Risk of Depression Associated with Diabetes in Adults: Evidence from Longitudinal Studies

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Abstract This meta-analysis examined depression as a consequence of diabetes by conducting a meta-analysis, using data from longitudinal studies. Databases were systematically searched for relevant studies. Incidence of depression is presented as cumulative incident proportion (CIP). Pooled effect sizes were calculated using random-effects model. The data were reconstructed to compute relative risk (RR) and CIP. The 16 studies selected for review generated 16 datasets of which 11 studies reporting binary estimates (RR) and 5 studies reporting time-to-event estimates [hazard ratio (HR)]. Both RR and HR were significant at 1.27 (95 % CI 1.17–1.38) and 1.23 (95 % CI 1.08–1.40) for incident depression associated with diabetes mellitus. Our observations also revealed greater cumulative incidence of depression in diabetes than in non diabetes groups. Our study shows that diabetes is a significant risk factor for the onset of depression.

Keywords Depression · Diabetes mellitus · Longitudinal · Meta-analysis

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Introduction

The prevalence of diabetes mellitus is increasing worldwide. The International Diabetes Federation (IDF) reported that almost 382 million people suffered from diabetes in 2013, and the number is expected to rise to 592 million by the year 2035 (IDF 2013). People with diabetes experience a number of complications in the course of the disease, including mental health-related illnesses such as depression. Depression is one of the most common co-morbid conditions associated with diabetes (Kessler et al. 1995; WHO 2000), and people with diabetes are almost twice as likely to suffer from depression as the general population (Anderson et al. 2001). However this often remains unrecognized and thus untreated, leading to a higher prevalence of depression among people with diabetes (Bouwman et al. 2010; Silva et al. 2012). People with diabetes are more likely to suffer from depression and to rate their health as worse when compared with non-diabetic people (Zhang et al. 2005). Depression and diabetes are two serious medical conditions and health concerns that afflict million of people worldwide.

Diabetes is a significant risk factor for depression and doubles the likelihood of co-morbid depression (Anderson et al. 2001). The psychosocial burden of a chronic disease such as diabetes may carry with it a risk for developing depressive symptoms (Knol et al. 2007). Individuals experiencing diabetes-related complications and disability may experience depression as a consequence of their disability (Palinkas et al. 1991; Talbot et al. 1999; de Jonge et al. 2006). Perceived disability and awareness of having a chronic illness may impose higher levels of psychological burden on people with diabetes, particularly in individuals with low levels of social support (Talbot and Nouwen 2000). Depression as a consequence of diabetes could be

explained by the burden of chronic disease or by biochemical changes that occur as a result of diabetes (Knol et al. 2007; Kinder et al. 2002). Depression may also be regarded as a co-morbid condition that results from the daily burden of having diabetes and/or its complications (Kinder et al. 2002; Golden et al. 2008; Katon et al. 2004; Barbour and Blumenthal 2005). There is only a modest association between diabetes and the incidence of depression. It may be that competing risks for late-life depression such as macro-vascular disease, functional or cognitive decline, mask this relationship. Moreover, depression is also difficult to diagnose in older adults (Gallo et al. 1994).

The aim of this review was to examine the relationship between diabetes and incident depression by conducting a meta-analysis of longitudinal studies using relative risk (RR), in addition to cumulative incidence, and extensive review and synthesis of the data. Previous meta-analyses have demonstrated an increased risk of depression (Knol et al. 2007; Mezuk et al. 2008; Nouwen et al. 2010; Rotella and Mannucci 2012; Hasan et al. 2013); they are far from conclusive because of several deficiencies. For example incidence measures were not computed because most of the longitudinal studies available have neither presented data in a fourfold (2 × 2) table form nor supplied adequate information to calculate a cumulative incident proportion (CIP). Moreover to estimate pooled effect sizes studies have not separated binary point and time-to-event estimates, which we consider may be inappropriate (Mezuk et al. 2008; Nouwen et al. 2010). For consistency, we have converted odds ratios (ORs) to RRs and presented hazard ratio (HR) separately.

Methods

The following electronic databases were searched: MEDLINE (up to December, 2013); EMBASE (up to December, 2013); CINAHL (up to December 2013); PsycINFO (up to December 2013). In the final stage Google Scholar was also carefully scanned to find any missed or additional studies. The following main keywords: depression disorders and/or symptoms, mental disorders, major depressive disorder, depressive reactions and/or symptomatology, diabetes mellitus, diabetes mellitus, type 2, longitudinal, cohort studies. Studies using longitudinal design and probable type 2 diabetes containing sufficient data to generate a risk estimate were included. Studies that only examined gestational diabetes mellitus and type 1 diabetes were excluded, but those with mixed samples of type 2 diabetes and type 1 diabetes, were included. There were some studies that did not specify the type of diabetes, but were included because the age of the recruited populations suggested they would be predominantly subjects with type 2 diabetes. We excluded studies that contained cases of existing depression.

After identifying possible studies, titles and abstracts were screened to remove studies that were not relevant to the aim of this review. The full texts of the remaining studies were then examined to determine whether the studies met our inclusion criteria. The references cited in identified, relevant, original research and review articles were then scanned for any additional articles that would possibly be relevant to our review; moreover, the reference lists of previous reviews and their included studies were also examined. When multiple publications from the same study population were available, we only included the most recent publication.

The eligibility criteria were based on study type and population attributes. Regarding study type, studies that investigated the association, comorbidity and/or coexisting, prevalence of diabetes and depression and/or depressive symptoms or reaction were included. For population attributes, studies that assessed depression and/or depressive reaction or symptomatology in adults with diabetes were included. In this meta-analysis we included all studies that longitudinally examined the relationship between diabetes and onset of depression. Studies that focused on efficacy of treatment, or comorbidities, or which included other medical and psychiatric conditions were excluded, as well as any studies that were not longitudinal in design.

Data extracted from the studies included the name of first author; publication year; study design; follow-up time in years; number of subjects in the analysis; gender and age of subjects; method of depression assessment; method of diabetes assessment; binary point estimates and time-to-event (survival) analysis with 95 % CI (adjusted for the largest number of confounders); number of confounders; method of exclusion of depressive and diabetes patients at baseline; and new-onset cases. The method of assessment of diabetes was either based on self-report or clinically diagnosed based on blood glucose levels or based on the diagnosis of diabetes on administrative data (drug consumption/hospitalization). Depression was based on a diagnosis by psychiatrist [using Diagnosis and Statistical Manual (DSM) criteria]; the assessment of depressive symptoms was by a self-administered questionnaire.

Statistical Analysis

Four-fold cells (2 × 2 tables) were imputed for all binary point estimates using the reconstruction method proposed by Pietrantonj (2006). Studies using time-to-event estimates (HRs) were presented separately, as 2 × 2 table reconstruction was not possible for studies using time-to-event estimates. The four-fold cells were used to compute RR, and cumulative incidence proportion (CIP). For studies

that presented graded relationships such as low, medium, or high depressive symptoms, only the estimate for the highest category was selected. We evaluated heterogeneity using the Cochran's Q heterogeneity test (Q test) and a related metric, the I^2. A p value of 0.10 was used as the cut-off point for heterogeneity. However, when the number of studies is small, Cochran's Q test has low power; therefore a related metric I^2 was also reported as it quantifies the percentage of variability due to heterogeneity rather than chance, as variability due to chance depends on study size ($I^2 = (Q - df)/Q \times 100\ \%$). Pooled results were calculated via random effects (RE) model (Mezuk et al. 2008; Rotella and Mannucci 2012).

To ensure the robustness of our meta-analysis, we performed sensitivity analyses by modifying our selection criteria and then examining the effect of the modified selection criteria on the pooled results. We thus examined selection by self-report versus clinical assessment of depression and diabetes, by regional differences [United Studies (US) versus non-US], by number of confounders that were adjusted for in the analyses and length of follow-up period. The follow-up period was classified into $\leq$5 years and >5 years for diabetes predicting depression. We considered the funnel plot to be asymmetrical if the intercept of Egger's regression line deviated from zero with $p < 0.10$. Additional analyses for publication bias were performed when the funnel plot was asymmetric using the Duval and Tweedie (2000) non-parametric "Trim and Fill" method of accounting for missing studies in meta-analysis. All analyses were conducted using Microsoft Excel and MetaXL software version 1.3 (MetaXL 2012).

Results

Our search yielded 846 unique abstracts from MEDLINE, 280 unique abstracts from EMBASE/CINAHL, 260 from PsycINFO and 50 from Google Scholar. After removal of duplication and applying the eligibility criteria, 68 relevant papers were examined for further consideration. Of these, 52 studies were excluded for the following reasons: failing to remove prevalent cases of depression at baseline; case–control study design; insufficient data to generate pooled effect sizes; and presence of specific depression risk factors. Although it is assumed that antidepressant use may mask the longitudinal relationship between depression and diabetes, studies that examined the association of antidepressant use and diabetes were also included (Egberts et al. 1997; Kivimaki et al. 2010; Knol et al. 2009; Luijendijk et al. 2008). Of these, two studies (Egberts et al. 1997; Luijendijk et al. 2008) used the same data, and only the most recent study by Luijendijk et al. was retained.

Two studies used the same sample (Arroyo et al. 2004; Pan et al. 2010); and only the most recent publication by Pan et al. (2010) was retained. Similarly, there were two studies published by Golden et al. (2004, 2008), where they used the same sample, and only the most recent was retained, which examined diabetes predicting depression. A total of 16 articles were then included in our review; eleven assessing diabetes and incident depression using binary point and five studies using time-to-event estimates.

Among the studies ($n = 11$) assessing diabetes predicting depression, four-fold cells were reconstructed and used to compute CIP from ORs (10 studies) or RR (1 study). The reconstructed CIP was then used to compute RR and CIP for meta-analysis while original effect sizes (HRs) were used for studies that reported time-to-event estimates and presented separately. Table 1 presents the country-specific CIPs and incidences of depression onset for diabetes (exposed) and non diabetes (unexposed) groups.

Depression as a Consequence of Diabetes

A total of 16 longitudinal studies assessing depression as a consequence of diabetes were included in this review; these provided 16 datasets. Eleven studies that reported their findings using binary point estimates and provided sufficient data to formulate four-fold cell were used to reconstruct RR and CIP. In six studies the association was not statistically significant but increasing risk of incident depression as a result of diabetes was present in most cases. For RR, significant heterogeneity was present, with a pooled RR of 1.27 (95 % CI 1.17–1.38). Only five studies reported time-to-event (survival) estimates but there was significant heterogeneity. The five studies generated a pooled HR of 1.23 (95 % CI 1.08–1.40).

Sensitivity Analysis and Publication Bias

In our sensitivity analysis, non-US studies (RR 1.33, 95 % CI 1.09–1.64) and studies that adjusted for less than 5 confounders (RR 1.22, 95 % CI 1.05–1.43) produced a significantly higher RR than studies conducted in the US (RR 1.24, 95 % CI 1.13–1.37) and studies that adjusted for 5 or more confounders (RR 1.22, 95 % CI 1.05–1.43). Moreover, studies with $\leq$5 years of follow-up produced a significantly higher relative risk (RR 1.54, 95 % CI 1.16–2.04) than studies with more than 5 years of follow-up (RR 1.25, 95 % CI 1.17–1.33). The funnel plot was reasonably asymmetrical and Egger's test for publication bias also suggested asymmetry (intercept = 0.243, $p = 0.001$) for studies using binary point estimates. However 'Trim and Fill' method used to impute missing studies did not result in additional dummy studies.

Table 1 Summary of findings of longitudinal studies assessing relationship between diabetes and incident depression

Authors (year)	Follow-up years	% Female	Age (years)	Assessment of depression	Assessment of diabetes	Original effect size	Number of events	% Cumulative incidence	Imputed RR	Adjustment for confounders
Studies reported odds ratio (OR)										
1. Bisschop et al. (2004)	6.0	53.3	55–85	CES-D	Self-report	OR 0.65 (0.35–1.19)	E: 11/110 UE: 244/1,617	10.0 15.1	0.69 (0.39–1.23)	Physical limitation, age, sex, education level, and living with a partner
2. Palinkas et al. (2004)	8.0	57.0	≥50	BDI	OGTT	OR 0.73 (0.41–1.30)	E: 13/103 UE: 126/729	12.4 17.0	0.76 (0.44–1.30)	Age, sex, physical activity, and BMI
3. de Jonge et al. (2006)[a]	5.0	58.0	≥55	GMS-AGECAT	Self-report + MR	OR 1.28 (0.91–1.79)	E: 40/465 UE: 231/3,471	16.6 12.4	1.26 (0.91–1.74)	Age, sex, partner, education, hypertension, smoking, statin use and cognitive functioning
4. Kim et al. (2006)	2.0	55.0	≥65	GMS-AGECAT	Self-report + FBG	OR 1.0 (0.4–2.5)	E: 5/42 UE: 51/423	11.9 12.1	1.0 (0.42–2.36)	Unadjusted
5. Engum (2007)	10.0	55.0	≥30	HADS	Self-report + FPG	OR 1.24 (0.78–1.98)	E: 18/319 UE: 1,600/35,354	5.6 4.5	1.23 (0.78–1.93)	Age, sex, education, and marital status
6. Maraldi et al. (2007)[a]	5.9	48.0	70–79	CES-D + antidepressant	Self-report + MR	OR 1.19 (0.96–1.47)	E: 122/475 UE: 340/1,585	24.3 19.3	1.15 (0.96–1.39)	Age, sex, race, study site, baseline CES-D score, education level, lifestyle, and clinical variables
7. Luijendijk et al. (2008)	5.0	58.0	≥61	DSM-IV CES-D	MR	OR 2.07 (1.11–3.85)	E: 13/378 UE: 42/2,498	3.4 1.7	2.03 (1.10–3.75)	Age, sex, education, income, disability, cognitive function, BMI, and medication
8. Knol et al. (2009)	7.7	52.5	≥40	Antidepressants	Medication	OR 1.32 (1.28–1.35)	E: 7,631/41,962 UE: 18,065/136,376	18.2 13.3	1.27 (1.24–1.30)	Unadjusted
9. O'Connor et al. (2009)	6.0	48.1	≥40	ICD + MR	ICD + MR	OR 1.32 (1.07–1.63)	E: 207/13,937 UE: 153/13,627	1.5 1.1	1.32 (1.07–1.62)	Age at index date, sex, primary care visits in the at-risk period
10. Kivimaki et al. (2010)	4.0	58.1	25–64	Antidepressants	FPG	OR 2.00 (1.57–2.55)	E: 63/430 UE: 170/2,280	14.6 7.5	1.84 (1.40–2.42)	Unadjusted
Studies reported relative risk (RR)										
11. Pan et al. (2010)	10.0	100	50–75	SF-36/MHI-5	Self-report + MR	RR 1.29 (1.18–1.40)	E: 464/2,227 UE: 7,244/46,922	20.8 15.4	1.29 (1.18–1.41)	Age, marital status, family history, lifestyle factors, BMI, insulin therapy
Studies reported time-to-event estimates (HR: hazard ratio)										
12. Polsky et al. (2005)	6.0	52.0	51–61	CES-D	Self-report	HR 1.17 (0.98–1.41)	E: 31/571 UE: 1,311/7,816	5.4 5.7	–	Age, sex, race, marital status, education, wealth, income, self-rated health, disability, baseline CES-D, and chronic conditions
13. Brown et al. (2006)	12.0	53.0	≥20	ICD and Rx based	Medical records and ICD	HR 1.04 (0.94–1.15)	E: 919/31,635 UE: 1,615/57,141	2.9 2.8	–	Age, sex, number of MD visits, co-morbid arthritis, cancer, vascular disease, insulin use

Table 1 continued

Authors (year)	Follow-up years	% Female	Age (years)	Assessment of depression	Assessment of diabetes	Original effect size	Number of events	% Cumulative incidence	Imputed RR	Adjustment for confounders
14. Golden et al. (2008)[a]	3.1	45.5	45–84	CES-D + antidepressant	FPG	HR 1.52 (1.09–2.12)	E: 75/620 UE: 336/2,868	12.1 11.7	–	Demographics, BMI, metabolic and inflammatory factors, SES and lifestyle factors, medication, hypertension
15. Aarts et al. (2009)	8	51.9	≥40	ICPC-P76	ICPC-T90	HR 1.26 (1.12–1.42)	E: 122/6,140 UE: 295/18,416	2.0 1.6	–	Age, practice identification code and depression preceding DM
16. Chen et al. (2013)	7	48.5	≥20	MR	ICD-9-CM	HR 1.43 (1.16–1.77)	E: 713/16,957 UE: 543/16,957	4.2 3.2	–	Age, sex, occupation, income, hypertension, stroke, hyperlipidemia, CAD

CIP cumulative incidence proportion, *E* exposed group, *UE* unexposed group, *MR* medical records

[a] Most adjusted model was not used in previous review

For studies using time-to-event, the funnel plot revealed gross asymmetry, as most of the studies reported higher RRs on one side of the line representing the most precise RR. It is evident that negative studies are missing in the funnel plot or that smaller studies were reporting more extreme effects as a result of systematic biases. The Egger's test for publication bias also suggested asymmetry. The Trim and Fill method resulted in two dummy studies being added and the revised estimate was 1.14 (95 % CI 1.00–1.30).

Discussion

Patients with diabetes showed greater cumulative incidence of depression compared to non diabetes patients. Of the 16 studies of diabetes predicting incident depression, only eight studies suggested increased risk. In our quantitative analysis using random-effects model, we demonstrated a 1.27-fold increase in risk for depression in adults with diabetes. These relative estimates are similar to previously reported figures that were calculated without segregating binary point and time-to-event estimates by Mezuk et al. (1.15-fold) and Nouwan et al. (1.24-fold) (Mezuk et al. 2008; Nouwen et al. 2010). Routelle et al., however, presented their findings as unadjusted odds ratios and adjusted HRs (Rotella and Mannucci 2012). They found a higher incidence of depression in diabetes subjects, with unadjusted and adjusted risk of 1.29-fold and 1.25-fold, respectively. For five studies using time-to-event estimates, we generated a pooled HR of 1.23.

Interestingly studies with 5 or less years of follow-up produced a significantly higher RR compared to studies with more than 5 years of follow-up. Most studies used non-standardized self-report measures of depression suggesting that the methods for screening and diagnosis of depression may not be fully reliable. Similar variations were noted when studies were separated based on regions and numbers of confounders adjusted for. However, it is important to remember that published studies are not representative of all studies as positive results tend to be submitted and published more often than negative findings (Tsoi et al. 2009).

The association between diabetes and the onset of depression is often conceptualized as having various possible indirect mechanisms (Hasan et al. 2013). In our analysis, with separate pooled effect sizes (RR and HR), we did found evidence to support the hypothesis that diabetes is a "depressogenic" condition. This finding is alarming because increased risk of depression in people with diabetes might lead to increased fatal or non fatal suicidal ideation or behavior (Pompili et al. 2009). Generally, suicide is associated with psychiatric disorder where

presence of depression is one of the contributing risk factor (Goldston et al. 1997; Harris and Barraclough 1997).

There are several limitations that may affect its generalizability and acceptability, including language bias (only English-language databases and journals were searched), and publication bias (significant studies were more likely to be published and easily indentified). The majority of the longitudinal studies included were published from the US, Europe and other developed countries where people of color and Caucasians experienced similar rates of depression and diabetes risk (Wagner et al. 2007). Brayne et al. (2005) argued that longitudinal research designs, which examine direction of a relationship, could be murky, as some of the lifestyle factors and biological substrates, or other common antecedents of both conditions, may have been operating for years before diagnosis. Moreover, confounding bias cannot be entirely ruled out. For instance the analyses in most of the studies were not adjusted for smoking, which appears to strengthen the association between depression and diabetes, and alcohol abuse which can be very difficult to establish in large-scale studies (Albers et al. 2011). According to IDF, 80 % of people with diabetes live in low- and middle-income countries (IDF 2013). This may also cause significant limitation to our incidence estimation as all longitudinal studies included in our study were from developed and high income countries. Based on our sensitivity analysis, we assume that the association between these two conditions may also result from clinical heterogeneity between studies or methodological heterogeneity between studies.

Despite some limitations, our study did provide the evidence using longitudinal data that incidence of depression is higher in diabetes than in non diabetes subjects and there is a significant association between diabetes and incident depression.

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APPENDIX 4C

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Review

Population impact of depression either as a risk factor or consequence of type 2 diabetes in adults: A meta-analysis of longitudinal studies

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ABSTRACT

This meta-analysis examined the reciprocal relationship between depression and diabetes mellitus type 2 (T2DM) by conducting a bias adjusted meta-analysis of longitudinal studies using relative and absolute risk estimates. Specifically, the data were reconstructed to compute relative risk (RR), risk difference (RD), and the number needed to be exposed for one additional person to be harmed (NNEH) or benefited (NNEB). The 25 studies selected for review generated 29 datasets of which 15 examined endpoint A (depression as a risk factor for T2DM), and 14 examined endpoint B (T2DM as a risk factor for depression). For both endpoints, there was a small relative risk increase (for both the RR and hazard ratio (HR)) though with significant heterogeneity between studies. This however translated to a non-significant NNEH of 87 (NNEB 161 to ∞ to NNEH 35) and NNEH of 233 (NNEB 28 to ∞ to NNEH 23) for studies examining endpoint A and endpoint B respectively. This study suggests that the magnitude of the relative risk increase for depression as a risk factor or consequence of T2DM is small without significant impact on absolute risk indices. While these risks may be considered in terms of individual patient management, they are unlikely to have an impact on a population perspective.

Contents

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1. Introduction

People with diabetes mellitus type 2 (T2DM) experience a number of complications in the course of the disease, including mental health-related illnesses such as depression. The latter is one of the common co-morbid conditions associated with T2DM (Kessler et al., 1995; WHO, 2000), and is particularly prevalent among such patients (Anderson et al., 2001; Ali et al., 2006). The presence of T2DM doubles the risk for having a diagnosis of depression compared to those without this condition (Eaton et al., 1996), and such patients are also more likely to have deficits in cognitive function (Wandell and Aberg, 1998; Wandell, 1999). Furthermore, the latter are also almost twice as likely to suffer from depression as the general population (Anderson et al., 2001; Egede et al., 2002; Nichols et al., 2007; Bouwman et al., 2010). Once depression develops, it can represent a barrier to glycemic control (Silva et al., 2012) and, sadly, often remains unrecognized and thus untreated (Pouwer, 2009) thus perpetuating the presence of depression among people with T2DM (Bouwman et al., 2010; Pouwer, 2009).

Conversely, depression is quite common itself being responsible for a large proportion of the burden associated with non-fatal health outcomes (WHO, 2005; Murray and Lopez, 1997) and there is some suggestion that it could increase the risk of T2DM. Thomas Willis, a famous physician from Great Britain was the first to report that diabetes was caused by "sadness or long sorrow and other depressions" (Willis, 1971). This relationship was never convincingly demonstrated until Eaton et al. (1996) reported an association that agreed with Willis' hypothesis (Willis, 1971). However the general response from researchers was that given the "modest" relationship, it could be "partially explained by lifestyle" (Golden et al., 2008), or might only exist with severe depression (Eaton et al., 1996; Carnethon et al., 2003; Arroyo et al., 2004; Brown et al., 2005; Kawakami et al., 1999; Palinkas et al., 2004; Golden et al., 2004; Saydah et al., 2003).

It is clear therefore that the relationship between depression and T2DM, while not conclusive (Brown et al., 2006), could be bidirectional (Golden et al., 2008; Engum, 2007). Biologically both hypotheses have some support. For example, depression as a consequence of T2DM could be explained by the burden of chronic disease or biochemical changes that occur as a result of T2DM (Kinder et al., 2002; Knol et al., 2007). Depression however may also be a co-morbid condition that results from the daily burden of having T2DM and/or its complications. Conversely, depression as a risk factor for the development of T2DM could be the consequence of a decline in health-maintenance behaviors among depressed persons (Golden et al., 2008; Kinder et al., 2002; Katon et al., 2004; Barbour and Blumenthal, 2005), or biochemical changes associated with depression (Bjorntorp, 2001; Knol et al., 2006).

While previous meta-analyses exist on this topic which support somewhat the bidirectional hypotheses (Knol et al., 2006; Mezuk et al., 2008; Nouwen et al., 2010; Rotella and Mannucci, 2012), they are far from conclusive because of several deficiencies. For example, absolute risk measures were not computed because most of the longitudinal studies neither presented data in a four-fold table form nor supplied adequate information to calculate cumulative incidence proportions (i.e. raw numbers of incident diabetes or depression by risk category). They also mainly focused on relative measures (the binary point estimates relative risk; RR and odds ratio; OR) or the time-to-event estimate (hazard ratio; HR). Also, there was no examination of bias risks. The aim of this review was therefore to use more rigorous methodology to examine the reciprocal relationship between depression and DM by conducting a meta-analysis of longitudinal studies using bias adjusted models, and extensive review and synthesis of the data. The advantage this provides is to reduce the variance of the final estimator thus precluding results that could be unrealistically far from true estimates. In addition to bias adjustment we also separated binary point estimates (OR, RR) and time-to-event estimates (HR), which we think were inappropriately combined in previous reviews (Knol et al., 2006; Mezuk et al., 2008; Nouwen et al., 2010). We also converted all odds ratios (ORs) to relative risks (RRs) (see Section 2) so that risks are uniform. Finally, and most importantly, we also imputed (from four-fold table reconstruction) both the Cumulative Incident Proportion (CIP) and then the absolute effect measure (risk difference) which was then pooled and compared against the relative pooled estimates, thus allowing us to judge the impact of any excess risk on the real world.

2. Methods

2.1. Data sources

Search terms included combinations of the following: incident diabetes, diabetes mellitus, type 2 diabetes mellitus, direction, co-morbid, relationship, risk factor, depression, and/or depressive reaction and/or symptomatology, incident depression. Studies using longitudinal design and probable type 2 diabetes to generate a risk estimate were included, whereas we excluded existing cases of either depression (for diabetes predicting incident depression) or diabetes (for depression predicting incident diabetes). Various electronic databases were searched: MEDLINE (1950 to December, 2012); EMBASE (1980 to December, 2012); CINAHL (1982 to December 2012); PsycINFO (1880 to December 2012). In the final stage Google Scholar was also carefully scanned to find any missed or additional studies.

After possible studies were identified, titles and abstracts were screened to remove studies that were clearly irrelevant to the aim of this review. The full texts of the remaining studies were then examined to determine whether the studies met our inclusion criteria. The references cited in identified relevant original research and review articles were then scanned for any additional articles that would possibly be relevant to our review; moreover, the reference lists of previous reviews and included studies were also examined. Studies were excluded if the authors did not explicitly exclude subjects with prevalent diabetes at baseline and if there were insufficient data to estimate a relative risk, an odds ratio, risk ratio or hazard ratio. When multiple publications from the same study population were available, we only included the most recent publication.

2.2. Eligibility criteria

Only studies relevant to the scope of the review were included. The eligibility criteria were based on study type and population attributes. Regarding study type, studies that investigated the association, unidirectional or bidirectional, comorbidity and/or

coexisting, prevalence of diabetes and depression and/or depressive symptoms or reaction were included. For population attributes, studies that assessed depression and/or depressive reaction or symptomatology in adults with T2DM or in mixed samples of T2DM and type 1 diabetes mellitus (T1DM), were included. However, in the latter mixed studies, only data on type 2 diabetes were extracted. Studies that only examined gestational diabetes mellitus and type 1 diabetes were also excluded. Seven studies (Bisschop et al., 2004; Polsky et al., 2005; Kim et al., 2006; de Jonge et al., 2006; Maraldi et al., 2007; Luijendijk et al., 2008; Mallon et al., 2005) did not specify the type of diabetes, but were included because the ages of populations recruited suggested they would be predominantly subjects with T2DM. In this meta-analysis we only included studies that longitudinally examined the relationship between depression and onset of diabetes and vice versa. Studies that focused on efficacy of treatment, or which included other medical and psychiatric conditions were excluded, as well as editorials, commentaries, and any studies that were not longitudinal in design. Studies that examined the association of antidepressant use and DM were also excluded because we assume that antidepressant use may mask the longitudinal relationship between depression and DM.

2.3. Data abstraction and quality assessment

Data extracted from the studies included the name of first author; publication year; study design; follow-up time in years; number of subjects in the analysis; gender and age of subjects; method of depression assessment; method of diabetes assessment; binary point estimates and time-to-event (survival) estimates with 95% CI (the one adjusted for the largest number of confounders); number of confounders that were adjusted for in the analyses (see Tables 1–3 for details of confounders considered); method of exclusion of depressive and patients with diabetes at baseline; and new-onset cases. The method of assessment of diabetes was either based on self-report or clinically diagnosed based on blood glucose levels or based on the diagnosis of diabetes from administrative data (drug consumption/hospitalization). At the baseline this was corrected for undetected diabetes as well. Depression was determined based on a diagnosis of depression during a consultation with a psychiatrist (based on Diagnosis and Statistical Manual (DSM) criteria); the assessment of depressive symptoms was by a self-administered questionnaire.

The researchers carefully weighed the studies against a quality checklist to estimate a quality index that would serve to rank studies in terms of deficiencies. Quality was assessed using a study-specific modification of the quality criteria of observational studies published by Shamliyan et al. (2010). The final checklist contained 11 items that were scored equally and consisted of questions related to design specific protection against bias (prospective vs retrospective), protection against selection bias (e.g. refusals, attrition), protection against information bias (adequate follow-up, accuracy of measurements of diabetes and depression) and adequate consideration of confounders. We examined the possible effect of various methodological factors on the magnitude of the effect size by sub-grouping the studies into higher and lower risk. Associations of the latter sub-groups with methodology-related items were then quantified and used to weight quality-related items within our quality score.

2.4. Statistical analysis

Four-fold cells (2×2 tables; exposure yes/no vs outcome yes/no) were imputed for all binary point estimates using the reconstruction method proposed by Pietrantonj (2006). Studies using time-to-event estimates (hazard ratios) were presented separately, as 2×2 table reconstruction was not possible for studies using time-to-event estimates. The four-fold cells were used to compute relative risk (RR), risk difference (RD) and cumulative incidence proportion (CIP). From pooled RD, the number needed to be exposed for one additional person to be harmed (NNEH) was also computed (reciprocal of average RD). Two separate analyses were conducted: looking at depression as a risk factor for T2DM, and looking at T2DM as a risk factor for depression. For studies that presented graded relationships such as low, medium, or high depressive symptoms, only the estimate for the highest category was selected.

We evaluated heterogeneity using the Cochran's Q heterogeneity test (Q test) and a related metric, the I^2. A smaller p-value of Cochran's Q test means significant heterogeneity among different studies. In our review, a usual p-value of 0.10 was used as the cut-off point for heterogeneity. However, when the number of studies is small, Cochran's Q test has low power. Therefore a related metric I^2 was also reported as it quantifies the percentage of variability due to heterogeneity rather than chance as variability due to chance depends on study size ($I^2 = (Q - \mathrm{df})/Q \times 100\%$). Pooled results were calculated via both the quality effects (QE) (Doi et al., 2011, 2012; Doi, 2010; Doi and Thalib, 2008) and the random effects (RE) models (Mezuk et al., 2008).

2.5. Sensitivity analysis and publication bias

To assess the robustness of this meta-analysis, sensitivity analyses were performed by modifying our selection criteria and then examining the effect of the variously modified selection criteria on the pooled results. We thus examined selection by self-report vs clinical assessment of depression and diabetes, by regional differences (United States (US) vs non-US), by length of follow-up period, and by number of confounders adjusted for in the analyses. The follow-up period was classified into <10 years and ≥ 10 years for depression predicting diabetes, and ≤ 5 years and >5 years for diabetes predicting depression; different considerations for follow-up were used because the studies following diabetes had much less follow-up than studies following depression.

A funnel plot was used to examine the existence of publication bias through visual inspection for asymmetry. However, it is difficult to establish the symmetry of the funnel plots through visual examination alone and we therefore also considered the funnel plot to be asymmetrical if the intercept of Egger's regression line deviated from zero with $p < 0.10$.

Additional analyses for publication bias were performed when the funnel plot was asymmetric using the Duval and Tweedie non-parametric "Trim and Fill" method of accounting for missing studies in meta-analysis (Duval and Tweedie, 2000). This method provides an estimate of the number of missing studies (with imputed estimates). All imputations were done assuming random error only. The QE meta-analysis was then re-run with quality scores given to the imputed studies of their corresponding (same standard error) existing studies to arrive at a pooled estimate that corrects somewhat for publication bias. No protocol for this review had been previously submitted or published. All analyses were conducted using Microsoft Excel and MetaXL software version 1.3 (Meta XL, 2012) and Stata version 11 (Stata Corp, College Station, USA) was used for the Trim and Fill analysis.

3. Results

Our search (Fig. 1) yielded 2665 unique abstracts from MEDLINE, 1630 unique abstracts from EMBASE/CINAHL, 560 from PsycINFO and 550 from Google Scholar. After removal of duplication and applying the eligibility criteria, 100 relevant

Table 1
Summary of findings of longitudinal/cohort studies assessing relationship between depression and incident diabetes using binary point estimates.

Authors (country-yr)	Follow-up years	% Female	Age (yrs)	Assessment of depression	Assessment of diabetes	Original effect size	Reconstructed CIP	Reconstructed RR	Adjustment for confounders
Studies reported odds ratios									
1. Stellato et al. (USA – 2000)	9.0	0.0	≥40	CES-D	Self-report	OR: 3.09 (1.34–7.12)	E: 7/90 UE: 23/910	2.94 1.31–6.60	Testosterone, SHBG, hypertension, CVS, BMI
2. Everson-Rose et al. (USA – 2004)	3.0	100	≥42	CES-D	Self-report + FPG	OR: 1.66 (1.05–2.61)	E: 28/578 UE: 58/1998	1.63 1.05–2.54	Age, site, race, education, medication use
3. Kumari et al. (UK – 2004)[a]	10.5	44.0	≥35	GHQ with depression subscale based on factor analysis	Self-report + OGTT	OR: 1.14 (0.83–1.57)	New cases: 361 Total: 10138	Incomplete data	Age, length of follow-up, employment grade, ethnic group, ECG abnormalities, family history of diabetes, body mass index, height, systolic blood pressure, exercise, smoking, and life events
4. Palinkas et al. (USA – 2004)	8.0	57.0	≥50	BDI	OGTT/FPG	OR: 2.50 (1.29–4.87)	E: 10/70 UE: 51/840	2.30 1.23–4.30	Age, sex, physical activity, BMI
5. Engum et al.[a] (Norway – 2007)	10.0	55.0	≥30	ADI	Self-report + FPG	OR: 1.40 (1.16–1.69)	E: 152/8159 UE: 382/28598	1.39 1.16–1.68	Age, gender, socioeconomic status, lifestyle, metabolic and clinical factors
Studies reported relative risk									
6. Eaton et al. (USA – 1996)	13.0	63.0	>18	DIS	Self-report	RR: 2.23 (0.90–5.55)	E: 5/71 UE: 46/1558	2.23 (0.90–5.54)	Age, sex, race, BMI
7. Carnethon et al. (USA – 2003)	15.6	59.0	≥25	GWBS	Self-report + MRD	RR: 2.52 (1.73–3.67)	E: 32/534 UE: 128/5496	2.52 (1.73–3.67)	Age, race, sex
8. Mallon et al.[a] (Sweden – 2005)	12.0	53.0	≥45	Self-report	Self-report	RR: 0.90 (0.30–2.90)	E: 3/128 UE: 29/1010	0.90 (0.29–2.80)	Age, not married, living alone, hypertension, obesity, smoking, alcohol use, snoring, sleep duration
9. Pan et al. (USA – 2010)	10.0	100	50–75	MHI-5	Self-report + medical records	RR: 1.17 (1.05–1.30)	E: 371/6680 UE: 2288/48541	1.17 (1.05–1.30)	Age, marital status, family history, physical activity, BMI, antidepressant use

CIP = cumulative incidence proportion, E = exposed group, UE = unexposed group.
[a] Most adjusted model was not used in previous review; estimates for Kumari et al. derived from previous review by Mezuk et al. (Everson-Rose et al., 2004; Stellato et al., 2000).

Table 2
Summary of findings of longitudinal/cohort studies using time-to-event estimates (HR: hazards ratio).

Authors (country-yr)	Follow-up years	% Female	Age (yrs)	New cases	Assessment of depression	Assessment of diabetes	HR	Adjustment for confounders
Studies assessing relationship between depression and incident diabetes								
1. Kawakami et al. (Japan – 1999)[a]	8.0	0.0	≥18	43/2380	Zung-SDS	OGTT + FPG	2.31 (1.03–5.20)	Age, education, occupation, work shift, obesity, physical activity, smoking, alcohol, chronic medical conditions, family history
2. Saydah et al. (USA – 2003)	9.0	74.0	32–86	465/8870	CES-D	Self-report	1.11 (0.79–1.56)	Age, sex, race, BMI, physical activity, education
3. V den Akker et al. (Netherlands – 2004)	15.0	58.0	≥20	3245/68004	ICPC-P76	ICPC-T90	1.04 (0.84–1.28)	Age, sex, BMI, socioeconomic, interaction with depression
4. Carnethon et al. (USA – 2007)[a]	8.0	59.2	≥65	147/4681	CES-D	Medication + FPG	1.41 (0.91–2.19)	Age, race, sex, education, marital status, physical activity, smoking, alcohol intake, BMI, C-reactive protein level, baseline CES-D score
5. Golden et al. (USA – 2008)[a]	3.2	60.1	45–84	275/5201	CES-D + antidepressant use	FPG	1.21 (0.87–1.67)	Age, sex, race/ethnicity, examination site, BMI, lipids, BP, IL-6, C-reactive protein, SES factors, daily caloric intake, smoking status, alcohol use, and physical activity
6. Campayo et al. (Spain–2010)	5.0	55.0	≥55	163/3521	GMSS + AGECAT	Self-report	1.65 (1.02–2.66)	Age, sex, family history of DM, hypertension, functional disability, smoking, alcohol, antidepressant/ antipsychotics/statin use
Studies assessing relationship between diabetes and incident depression								
1. Polsky et al. (USA – 2005)	6.0	52.0	51–61	571/7909	CES-D	Self-report	1.17 (0.98–1.41)	Age, sex, race, marital status, education, wealth, income, self-rated health, disability, baseline CES-D, and chronic conditions
2. Brown et al. (Canada – 2006)	12.0	53.0	≥20	2534/88776	ICD and Rx based	Medical records and ICD	1.04 (0.94–1.15)	Age, sex, number of MD visits, co-morbid arthritis, cancer, vascular disease, insulin use
3. Golden et al. (USA – 2008)[a]	3.1	45.5	45–84	60/4847	CES-D + antidepressant	FPG	1.52 (1.09–2.12)	Demographics, BMI, metabolic & inflammatory factors, SES & lifestyle factors, medication, hypertension
4. Aarts et al. (Netherlands–2009)	8	51.9	≥40	122/6140	ICPC-P76	ICPC-T90	1.26 (1.12–1.42)	age, practice identification code and depression preceding DM
5. Hsu et al. (Taiwan–2012)	7	48.5	≥20	258/14048	Medical records	ICD-9-CM	1.46 (1.24–1.71)	Age, sex, occupation, income, hypertension, stroke, hyperlipidemia, CAD.

[a] Most adjusted model was not used in previous review (Aarts et al., 2009; Campayo et al., 2010; Carnethon et al., 2007; van den Akker et al., 2004; Hsu et al., 2012).

papers were examined for further consideration. Of these, 75 studies were excluded for the following reasons: failing to remove prevalent cases of depression or diabetes at baseline; study design; insufficient data to generate pooled effect sizes; and presence of specific diabetes or depression risk factors. Studies that examined the association of antidepressant use and DM were also excluded because we assume that antidepressant use may mask the longitudinal relationship between depression and DM (Egberts et al., 1997; Kivimaki et al., 2010; Knol et al., 2009). A total of 25 articles were then included in our review; these provided 15 datasets assessing depression and incident diabetes and 14 datasets examining diabetes and incident depression. There were four more data-sets than studies because four studies (Palinkas et al., 2004; Engum, 2007; Golden et al., 2008; Pan et al., 2010) examined both depression predicting diabetes and diabetes predicting depression and thus these each provided two data-sets for

Table 3
Summary of findings of longitudinal studies assessing relationship between diabetes and incident depression using binary point estimates.

Authors (country-yr)	Follow-up years	% Female	Age (yrs)	Assessment of depression	Assessment of diabetes	Original effect size	Reconstructed CIP	Reconstructed RR	Adjustment for confounders
Studies reported relative risk									
1. Palinkas et al. (USA – 2004)	8.0	57.0	≥50 years	BDI	OGTT	OR: 0.73 (0.41–1.30)	E: 13/103 UE: 126/729	0.76 0.44–1.30	Age, sex, physical activity, and BMI
2. de Jonge et al. (Spain – 2006)[a]	5.0	58.0	≥55	GMS-AGECAT	Self-report + medical records	OR: 1.28 (0.91–1.79)	E: 40/465 UE: 231/3471	1.26 0.91–1.74	Age, sex, partner, education, hypertension, smoking, statin use and cognitive functioning
3. Kim et al. (Korea – 2006)	2.0	55.0	≥65	GMS-AGECAT	Self-report + FBG	OR: 1.0 (0.4–2.5)	E: 5/42 UE: 51/423	1.0 0.42–2.36	Unadjusted
4. Bisschop et al. (USA – 2007)[a]	6.0	53.3	55–85	CES-D	Self-report	OR: 0.73 (0.53–0.99)	E: 43/78 UE: 796/1065	0.83 0.64–1.06	Physical limitation, age, sex, education level, and living with a partner
5. Engum et al. (Norway – 2007)	10.0	55.0	≥30	HADS	Self-report + FPG	OR: 1.24 (0.78–1.98)	E: 18/319 UE: 1600/35354	1.23 0.78–1.93	Age, sex, education, and marital status
6. Maraldi et al. (USA – 2007)[a]	5.9	48.0	70–79	CES-D + self reported antidepressant use	Self-report + medical records	OR: 1.19 (0.96–1.47)	E: 122/475 UE: 340/1585	1.15 0.96–1.39	Age, sex, race, study site, baseline CES-D score, education level, smoking, alcohol intake, physical activity, hypertension, cerebro-vascular disease, ankle-brachial index, obesity, cystatin-C levels, IL-6 levels, 6-m walking speed, and cognitive impairment
7. Luijendijk et al. (Netherlands – 2008)	5.0	58.0	≥61	DSM-IV CES-D	MR	OR: 2.07 (1.11–3.85)	E: 13/378 UE: 42/2498	2.03 1.10–3.75	Age, sex, education, income, disability, cognitive function, BMI, and medication
8. O'Connor et al. (USA – 2009)	6.0	48.1	≥40	ICD + medical records	ICD + medical records	OR: 1.32 (1.07–1.63)	E: 207/13937 UE: 153/13627	1.32 1.07–1.62	Age at index date, sex, primary care visits in the at-risk period
Studies reported relative risk									
9. Pan et al. (USA – 2010)	10.0	100	50–75	SF-36/MHI-5	Self-report + medical records	RR: 1.29 (1.18–1.40)	E: 464/2227 UE: 7244/46922	1.29 (1.18–1.41)	Age, marital status, family history, lifestyle factors, BMI, insulin therapy

CIP = cumulative incidence proportion, E = exposed group, UE = unexposed group.
[a] Most adjusted model was not used in previous review (O'Connor et al., 2009).

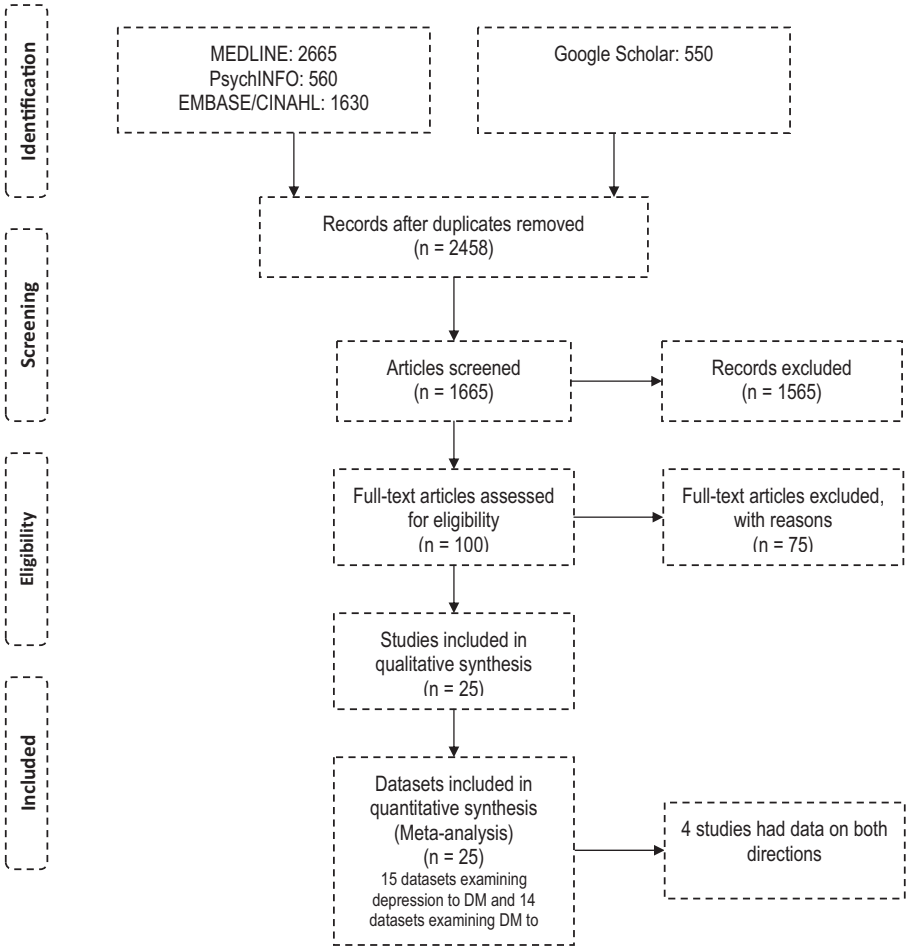

Fig. 1. Study flow diagram – process of including studies.

analysis. These data-sets are referred to subsequently under results in terms of their parent studies because data from the same study appear in different analyses.

Three studies used the same sample (Saydah et al., 2003; Arroyo et al., 2004; Pan et al., 2010); however, two of these were retained: the most recent publication by Pan et al. (2010) and Saydah et al. (2003). These two studies used different risk estimates, (RR vs HR), and thus were in different analyses (Pan et al. in the binary estimates analysis and Saydah et al. in the time-to-event analysis), so there was no over-inflation of the sample. There were two studies published by Golden et al. (2004, 2008), where they used the same sample, and only the most recent which examined both depression predicting diabetes and diabetes predicting depression was retained.

Among studies assessing depression predicting diabetes, four-fold cells were reconstructed and used to compute CIP from ORs (4 studies) or RR (4 studies). The data presented by Kumari et al. (2004) was insufficient to compute a four-fold cell and the study was excluded when the authors did not respond to our request for additional data. Similarly CIP was reconstructed from 9 studies examining diabetes predicting depression. The reconstructed CIP was then used to compute RR and RD for meta-analysis while original effect sizes (HRs) were used for studies that reported time-to-event estimates and presented separately.

3.1. Quantitative synthesis

3.1.1. Depression as a risk factor for diabetes mellitus

The summary of cohort studies assessing depression as a risk factor for diabetes included in the review is presented in Table 1. Nine studies reported their findings in the form of binary point estimates. However, only eight studies that presented complete data to formulate four-fold cell were used to reconstruct CIP, RR and RD. Of these eight studies, only two studies reported statistically insignificant associations; however, increasing risk of incident diabetes as a result of depression was present. For both RR and RD, significant heterogeneity was present, with a pooled RR of 1.41 (95% CI: 1.13–1.76) (Fig. 2) and RD of 0.0115 (95% CI: −0.0062 to 0.0292). The NNEH was 87 (NNEB 161 to ∞ to NNEH 35) for studies examining depression as a risk factor of diabetes (Fig. 2).

For six studies that presented their findings in the form of hazard ratios, there were four studies in which the association was not statistically significant but increasing risk was evident (Table 2). However, there was no evidence of heterogeneity (Fig. 3) and the pooled hazard ratio was 1.24 (95% CI: 1.05–1.47).

3.1.2. Diabetes as a risk factor for depression

Fourteen studies examined depression as a consequence of DM. The summary of longitudinal studies assessing depression as a consequence of diabetes that were included in this review is presented in Table 3. Nine studies that reported their findings using binary point estimates and provided sufficient data to formulate four-fold cell were used to reconstruct CIP, RR and RD. There were six studies in which the association was not statistically significant but increasing risk of incident depression as a result of diabetes was present in most cases. For both RR and RD, significant heterogeneity was present, with a pooled RR of 1.23 (95% CI: 1.15–1.31) (Fig. 2) and RD of 0.0043 (95% CI: −0.0358 to

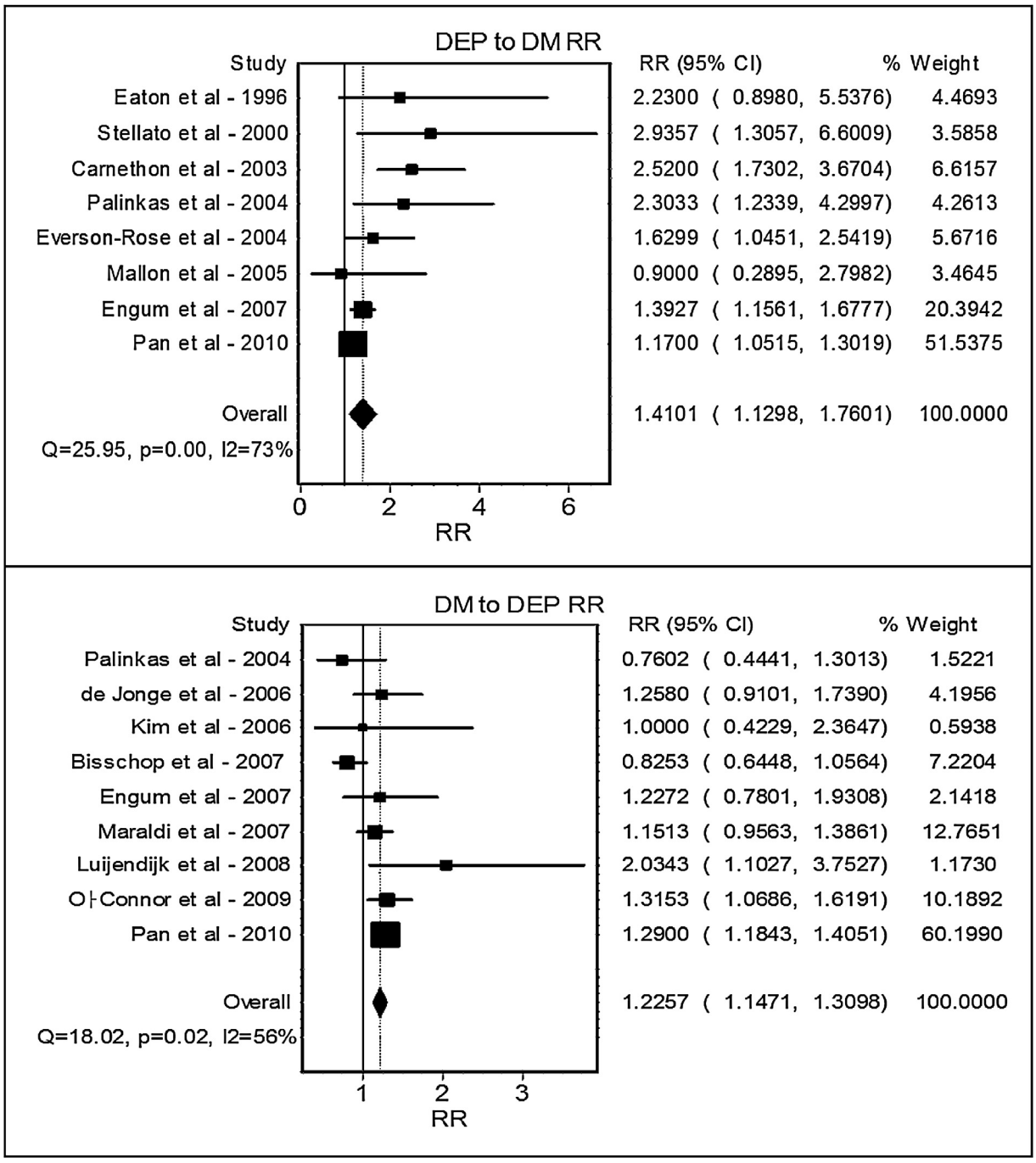

Fig. 2. Quality-effects forest plot showing the risk of diabetes (top) and risk of depression for individual studies using self-report questionnaires, diagnostic criteria, and all studies combined; studies using reconstructed RR. Bars and diamonds indicate 95% CIs. DM = diabetes mellitus; DEP = depression.

0.0444). The NNEH was 233 (NNEB 28 to ∞ to NNEH 23) for studies examining depression as a consequence of diabetes.

Five studies reported time-to-event (survival) estimates but there was significant heterogeneity (Table 2 and Fig. 3). The five studies generated a pooled HR of 1.22 (95% CI: 1.05–1.42).

3.2. Sensitivity analysis and publication bias

We conducted a number of sensitivity analyses using reconstructed RR to examine the robustness of our findings. Since both depression and diabetes can have extended prodromal periods (Mezuk et al., 2008), we also categorized studies based on follow-up time.

3.2.1. Depression as a risk factor for diabetes mellitus

Studies with <10 years follow-up time had a significantly higher relative risk (RR: 2.05) than studies with ≥10 years (RR: 1.34) of follow-up time. Studies conducted in the US were almost similar to studies conducted outside the US (RR: 1.32). However, studies where the outcome was adjusted for less than or equal to five confounders showed almost double the risk compared to studies where more than five confounders were adjusted in analysis. The funnel plot to detect publication bias revealed gross asymmetry, as most of the studies reported higher relative risks on one side of the line representing the most precise relative risk (Fig. 4). It is evident that negative studies are missing in the funnel plot or that smaller studies were reporting more extreme effects as

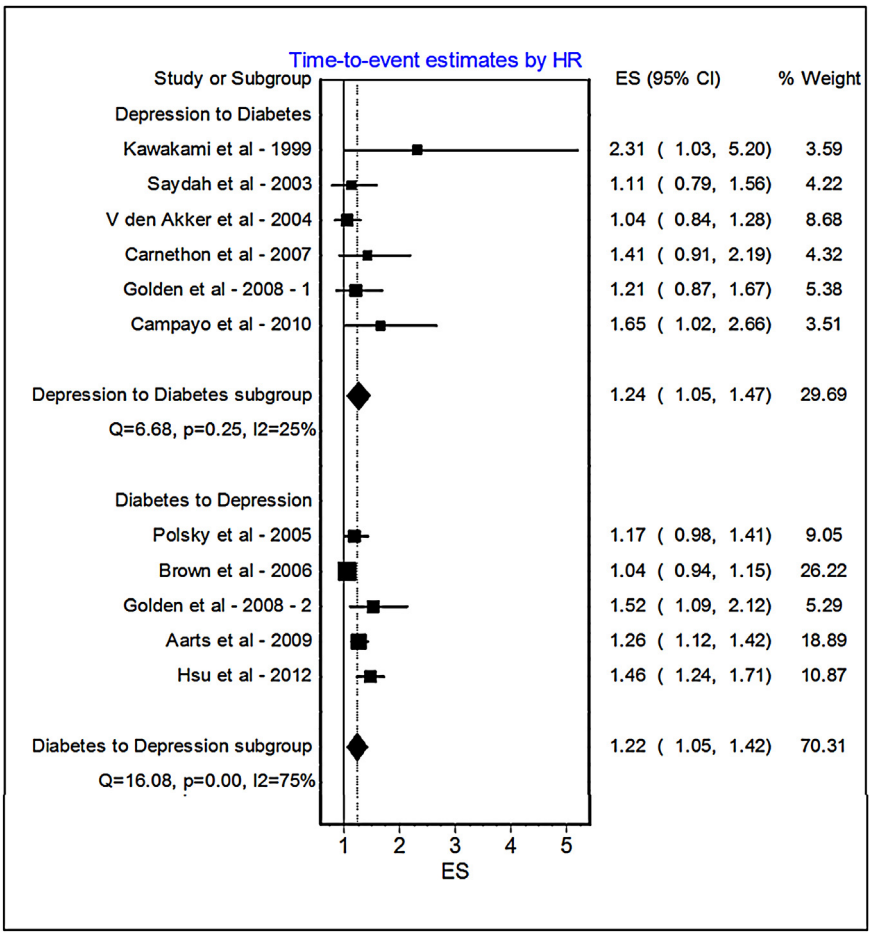

Fig. 3. Quality-effects forest plot showing the risk of diabetes and depression for individual studies using self-report questionnaires, diagnostic criteria, and all studies combined; studies using time-to-event estimates. Bars and diamonds indicate 95% CIs. ES: effect size. HR = hazards ratio.

a result of systematic biases. The latter is more likely given that the QE model 'down-weighted' the majority of these studies. The Egger's test for publication bias also suggested asymmetry (intercept 0.449; $p = 0.025$). Under the assumption of missing studies, the Trim and Fill method was used to impute missing studies, and this resulted in three dummy studies being added and the revised QE estimate (assuming the same quality and standard error as the corresponding study) was 1.26 (95% CI: 1.02–1.57). The revised RD was 0.0108 (95% CI: −0.0040 to 0.0255) with an adjusted NNEH of 93 (NNEB 250 to ∞ to NNEH 40).

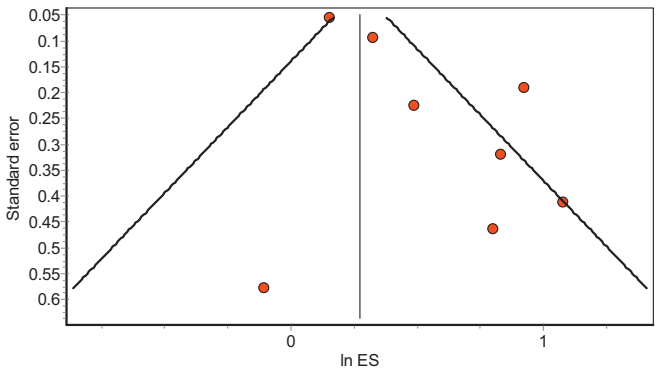

Fig. 4. Funnel plot with 95% confidence interval relative risk of studies examining risk of diabetes included in the meta-analysis using reconstructed RR ($n = 8$).

3.2.2. Diabetes mellitus as a risk factor for depression

Studies with ≤5 years following time (RR: 1.40), non-US studies (RR: 1.36) and studies that used standard criteria (RR: 1.24) produced significantly higher relative risk than studies with >5 years of follow-up time (RR: 1.18), US studies (RR: 1.17) and studies that used self-report scales (RR: 1.20). Only non-US studies suggested diabetes as a significant predictor of depression. However, studies where more than 5 confounders were adjusted in analysis were similar to studies where outcome was adjusted for less than or equal to 5 confounders. The funnel plot was reasonably symmetrical and Egger's regression concurred (intercept = 0.655, $p = 0.107$).

4. Discussion

4.1. Depression as a risk factor for diabetes mellitus

We found a modest relationship between depression and incident T2DM and of the 15 studies examining this relationship, eight suggested increased risk. In our quantitative analysis using the quality-effects model, we demonstrate a 1.41 fold increase in risk or 1.24 fold increase in hazard for T2DM in adults with depression. This concurs with the 1.37 fold risk increase reported previously (Knol et al., 2006).

Although our results on a relative scale concur with previous reports, the risk difference, which is a measure of absolute risk (not reported in previous reviews), shows a very small difference in risk of T2DM between depressed and non-depressed persons. Our

findings also suggest that if we increase the length of follow-up time, based on what we found in our sensitivity analysis, we may end up with an insignificant association, negligible risk difference, and large NNEH of 87. It may be pointed out that the NNEH describes the disease burden associated with exposure or risk factor(s) and is a useful measure especially if the exposure is modifiable (such as diabetes and depression) (Bender and Blettner, 2002). In order to understand the impact of the NNEH, we could take an example of Australia where the prevalence of depression in the adult population was 4% (859,942) in 2007–08 (ABS, 2007, 2008, 2009). It can therefore be estimated that 9885 (859942/NNEH) depressed persons may develop diabetes over approximately 10 years that would not have done so otherwise. These are very small numbers compared to the population prevalence suggesting that from a population perspective, the impact is small. This is especially so given the non-significance of the pooled average risk differences.

4.2. Diabetes mellitus as a risk factor for depression

We also found a modest relationship between DM and incident depression. Of 12 studies reporting DM predicting incident depression, only four studies suggested increased risk. In our analysis using the quality-effects model, there was a 1.2 fold increase in both the risk and the hazard of incident depression after diabetes onset. The reported prevalence of T2DM in Australia in the adult population was about 3.3% (709,452) in 2007–08 (ABS, 2007, 2008, 2009). Therefore, again, absolute risks were small and it can be estimated that an additional 3045 (709452/NNEH) people with diabetes will develop depression as a consequence of diabetes over approximately 5 years.

A previous meta-analysis (Mezuk et al., 2008) provided similar evidence for a bidirectional relationship but reported a weaker relationship for people with T2DM developing depression (increase of 15%) as opposed to depressed persons developing diabetes (increase of 60%). We found a similar trend but a follow-up meta-analysis of 11 studies conducted by Nouwen et al. (2010) found a lesser increase (24%) in the risk of T2DM.

4.3. Risk mechanisms

The evidence suggests that depression is "diabetogenic" but we must be wary of detection bias; people with depression are more likely to seek a physician's care, resulting in a greater likelihood of medical conditions, such as T2DM, being diagnosed (Nouwen et al., 2010). Depression is associated with increased activity of the HPA-axis and the sympathetic nervous system (Bjorntorp, 2001), resulting in increased cortisol release and increased release of the catecholamines (epinephrine and nor-epinephrine). Cortisol is a stress hormone, which stimulates glucose production, increases lipolysis and circulating free fatty acids, decreases insulin secretion from beta cells and decreases sensitivity to insulin (Bjorntorp, 2001; Ramasubbu, 2002). It is postulated that a chronically high cortisol level, which is a feature of about 50% of depressed patients, results in obesity, insulin resistance and T2DM (Bjorntorp, 2001; Bjorntorp et al., 1999).

Epinephrine generates responses in glucose and fat metabolism similar to those of cortisol (148), possibly resulting in insulin resistance and T2DM. The credibility of this hypothesis is further strengthened by findings on other medical problems that are accompanied by hypercortisolemia such as Cushing's syndrome, sleeping disorders, work stress and schizophrenia (Buckley and Schatzberg, 2005; Lundberg, 2005; Ryan et al., 2003), which appeared to be associated with an increased level of cortisol and an increased risk of T2DM and insulin resistance (Ryan et al., 2003; Kawakami et al., 1999). A dys-regulation of the immune system also plays a role in the association between depression and elevated risk of T2DM; both depression and T2DM are found to be associated with increased C-reactive protein, TNF-α and pro-inflammatory cytokines, including IL-6 (Dentino et al., 1999; Kiecolt-Glaser and Glaser, 2002; Maes et al., 1997; Pradhan et al., 2001; Schmidt et al., 1999).

The role of inflammatory mediators in the development of diabetes was supported by two population-based studies (Schmidt et al., 1999; Ford, 2002). It is suggested that inflammation may be associated with oxidative damage and the release of free radicals (Paolisso et al., 1993) that damage pancreatic β cells (Rabinovitch et al., 1992), thus limiting the release of insulin. The inflammatory process also may inhibit insulin uptake (Paolisso et al., 1993), a critical process in glucose regulation. Moreover, in cross-sectional studies, inflammatory markers including the cytokines interleukin-1β, and tumor necrosis factor-α (Appels et al., 2000) and C-reactive protein (Dotevall et al., 2001) were also found to be elevated in depressed persons. However, there is disagreement between this assumption and the previous assumption that cortisol inhibits inflammation and the immune response; whereas depression is correlated with both elevated cortisol and increased inflammatory markers. This contradiction could be explained with the help of a recent finding that melancholic depressed patients had increased HPA axis activity and no signs of inflammation, whereas non-melancholic depressed patients did show signs of inflammation and normal HPA axis activity (Kaestner et al., 2005).

Conversely, the association between T2DM and the onset of depression is weaker and often conceptualized as having various possible indirect mechanisms. For example, the psychosocial burden of a chronic disease such as T2DM may carry with it a risk for developing depressive symptoms (Knol et al., 2007); the authors implicate the psychosocial burden of chronic disease, rather than the disturbed glucose regulation specific to diabetes, as a risk factor for depression. Cognition related to diabetes, such as perceived disability and awareness of having a chronic illness, may impose higher levels of psychological burden on people with diabetes, particularly in individuals with low levels of social support (Talbot and Nouwen, 2000). It has also been hypothesized that an increased risk of depression in DM might be due to an increased awareness of depression among patients with DM, yielding more diagnoses of depression in this population (Nouwen et al., 2010). Finally, individuals experiencing diabetes-related complications and disability may experience depression as a consequence of their disability (de Jonge et al., 2006; Palinkas et al., 1991; Talbot et al., 1999). There is little evidence for biochemical changes associated with diabetes which then lead to depression although there is some suggestion that activation of the HPA axis could account for an increased risk of depression in individuals with diabetes compared to those without the condition (Knol et al., 2007; Kinder et al., 2002).

4.4. Problems in interpretation of the data

The funnel plot suggested possible publication bias (Fig. 4). From our analysis, we can see that a funnel plot is not a very reliable method of investigating publication bias, although it does give us some idea of whether our study results are scattered symmetrically around a central, more precise effect. Although depression was a stronger risk factor for diabetes, the funnel plot was asymmetrical and this may be due to publication bias, however, it may also result from clinical heterogeneity between studies or methodological heterogeneity between studies. We therefore ran a sensitivity analysis and noted that adjustment for fewer confounders was associated with larger risk estimates. The variation across different means of diabetes assessment was not really large although there was a trend for higher estimates of risk

with self reports. Knol et al. (2006) conducted a meta-analysis in which they separated the studies where DM was assessed by blood glucose measures from physician diagnosis or patient self-report, and their study too demonstrated a small impact on the relative risk of depression. Confounding therefore may have resulted in the asymmetry seen in our study but has been adjusted for in the pooled analysis and so has been accounted for. Finally, publication bias may exist as the published studies may not be representative of all studies that have been done since positive results tend to be submitted and published more often than negative results (Tsoi et al., 2009) and we have tried to address what its impact might have been via our trim and fill analysis.

4.5. Strengths and limitations

There are some strengths and limitations of this review. The strengths include comprehensive literature search and a more precise outcome definition and method of research synthesis. A meta-analysis based on the RE model is considered as conservative and results in wider CIs around the point estimate; it is commonly used when heterogeneity between studies exists (Fleiss and Gross, 1991). The problem with the RE model is that it introduces other errors (Knol et al., 2006). In particular, the methodology in the RE model is, in the authors' opinion, grossly flawed to the extent that, even in standard meta-analyses, there is a lack of interpretation of a RE summary (Alkhalaf et al., 2011). Peto referred to the use of RE model in meta-analysis as "wrong" because it answers a question that is "abstruse and uninteresting" (Peto, 1987). However, the considerations of Peto on RE may not be appropriate, because they are specifically referred to clinical trials, and not to observational studies. Moreover, use of the RE model requires strong assumptions that are unlikely to be valid in practice. Most notably, the RE analysis is based on "the peculiar premise that the trials done are representative of some hypothetical population of trials, and that the heterogeneity can be represented by a single variance" (Senn, 2007). We take the approach in this paper that when heterogeneity has been detected, there is a strong case for investigating its possible origin, and redistributing the weights based on such a determination. Weight redistribution based on the common between study variance will not be helpful in such cases since it is doubtful that any useful question can be formulated that a RE model analysis could answer. The advantage of the QE model is the adjustment for bias in observational studies and also the absence of the conceptual problems that abound with the RE model (Alkhalaf et al., 2011).

This review had several limitations that may affect its generalizability and acceptability. Limitations of the current review include language bias (only English-language databases and journals were searched), and publication bias (significant/positive studies were more likely to be published and easily indentified). The majority of the longitudinal studies were published from USA, Europe and other developed countries where non-Caucasians and Caucasians experience similar rates of depression and diabetes risk (Wagner et al., 2007). Brayne et al. (2005) has also argued that longitudinal research designs, examining direction of the relationship could be murky, as some of the lifestyle factors and biological substrates, or other common antecedents of both conditions, may have been operating years before diagnosis. Moreover, confounding bias cannot be entirely ruled out. For instance the analyses in most of the studies were not adjusted for smoking, which appears to strengthen the association or alcohol abuse which can be very difficult to establish in large-scale studies (Albers et al., 2011). Finally, the limitation of methods for detecting depression in large epidemiological studies should also be considered since the methods for screening and diagnosis of depression may not be fully reliable.

5. Conclusions

This study provides evidence that depression results in a small increase in relative risk for the development of T2DM and at the same time, T2DM also results in a small relative risk increase for depression. However, average (pooled) risk differences are insignificant suggesting that the relative risk increase is too small to have a significant impact on absolute risk at the population level for individuals with either depression or diabetes. Based on small relative and absolute effect sizes, we assume that the causal direction (not association) between these two conditions (both directions) may share common causes or risk factors. Further studies are needed to draw definitive conclusions.

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Authors' contribution

All authors contributed to this paper.

Conflict of interest

The authors declare that they have no conflict of interest.

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APPENDIX 4D

Is anxiety a risk factor for the onset of type 2 diabetes mellitus in adults? Application of biased-adjusted method

Abstract

Objective

This study investigated the association between anxiety and diabetes onset using data from four longitudinal studies.

Methods

The risk difference (RD), and the number needed to be exposed for one additional person to be harmed (NNEH) at two years follow-up, were computed. We compared relative risk (RR) for a positive outcome (diabetes) with the RR for its negative complement (no diabetes) for each study.

Results

The pooled estimate for incident diabetes with subjects who exhibited anxiety (exposure) was 1.65, suggesting a 65% increase in the risk of diabetes. The RR for the negative complement (no-diabetes), was 0.987, suggesting there would be a 1.3% increase in diabetes had the unexposed group been exposed to anxiety. The pooled RD was 0.031 (95% CI: - 0.007 to 0.054) and the NNEH was 33 (95% CI 19 to 143) at 2 years post exposure.

Conclusion

Despite some limitations this study showed that anxiety could lead to an increased risk of developing diabetes. The findings suggest that by selecting the RR as the effect size as well as the outcome with the higher baseline risk (in this case no-diabetes), we can avoid the artificial magnification of the effect size.

Keywords

Anxiety, diabetes, longitudinal, adults

Introduction

Anxiety is one of the most common problems experienced by individuals suffering from type 2 diabetes and the prevalence is considerably higher than that of the normal population [1], or even among patients with mental illness [2]. It is estimated that in the general population the prevalence of anxiety ranges between 12% and 21% [3- 6], while among patients with type 2 diabetes, 42% have symptoms of anxiety [7]. The results from available longitudinal studies examining the association between type 2 diabetes and anxiety are inconsistent [8-10]. There is evidence regarding anxiety disorders and increased type 2 diabetes burden [11], increased complications [12], poor glycemic control [13], and reduced quality of life [14]; however, there has been little focus on the possibility of anxiety as a risk factor for later onset of type 2 diabetes.

The findings of a meta-analysis by Smith et al., suggests that people with diabetes are more likely to have anxiety disorders or elevated anxiety symptoms compared to people who do not have diabetes [15]. However, there are no meta-analyses investigating the development of diabetes in relation to anxiety symptoms. This study investigated the association between anxiety and the risk of diabetes in two steps. In the first step, the diabetes outcome was assessed to obtain pooled estimates [16]. In the second step, we also compared the pooled relative risk (RR) for the negative complement (no diabetes) as suggested previously [17]. These approaches were used in the current study to more clearly determine the magnitude of any excess risk (e.g. anxiety) on diabetes incidence.

Methods

Two electronic databases were searched: MEDLINE/PubMed, and PsycINFO using the following main keywords: anxiety disorders and/or symptoms, mental disorders, generalized anxiety disorder, GAD, OCD, panic disorder and/or attack, phobias (e.g. agoraphobia, and social phobia), claustrophobia, post-traumatic stress disorder (PTSD), diabetes mellitus, diabetes insipidus, diabetes mellitus, type 2, longitudinal, cohort studies. Inclusion criteria were studies of a longitudinal design which had no type 2 diabetes among subjects at baseline, while studies that examined existing cases of diabetes were excluded. After possible studies were identified, titles and abstracts were screened to remove studies that were clearly irrelevant to this study. The full texts of the remaining studies, which included narrative reviews, were then

examined to determine whether the studies met our inclusion criteria. References cited in the reference list of each identified relevant original research or review article were scanned to identify any additional articles that would possibly be relevant to our review; these were then also subsequently scanned for reviews and studies which may have been relevant.

Eligibility criteria were based on study type and population attributes. Studies that only examined gestational diabetes mellitus and type 1 diabetes were excluded. For population attributes, studies that assessed anxiety and/or anxiety reaction or symptomatology in adults with type 2 diabetes or in mixed samples of type 2 diabetes and type 1 diabetes, were included. Two studies did not specify the type of diabetes [10,18], but were included because the age of the recruited populations suggested they would be predominantly subjects with type 2 diabetes. In this meta-analysis we only included studies that examined the relationship between anxiety and the onset of diabetes longitudinally. Studies that focused on other medical and psychiatric conditions were excluded. Editorials, commentaries, and any studies that were not longitudinal in design were also excluded.

Data extraction and quality assessment

Data extracted from the studies included the name of first author; publication year; study design; follow-up time in years; number of subjects in the analysis; gender and age of subjects; method of anxiety assessment; method of diabetes assessment; binary point estimates and time-to-event (survival) estimates with 95% CI (adjusted for the largest number of confounders); number of confounders that were adjusted for in the analyses (see Table 1 for details of confounders considered); method of exclusion of patients with diabetes at baseline; and new-onset cases. The method of assessment of diabetes was either based on self-report or clinically diagnosed based on blood glucose levels or based on the diagnosis of diabetes from administrative data (drug consumption or hospitalization). The condition of anxiety was based on a diagnosis by a psychiatrist (based on Diagnosis and Statistical Manual (DSM) criteria for anxiety); the assessment of anxiety symptoms was by a self-administered questionnaire.

Quality was assessed using a study-specific modification of the quality criteria of observational studies published by Shamliyan et al [19]. The researchers carefully weighted the studies against a

quality checklist to estimate a quality index that would serve to rank studies in terms of deficiencies. The final checklist contained 11 items that were scored equally and consisted of questions related to design specific protection against bias (prospective versus retrospective), protection against selection bias (e.g. refusals, attrition), protection against information bias (adequate follow-up, accuracy of measurements of diabetes and anxiety) and adequate consideration of confounders. For studies that presented graded relationships such as low, medium, or high anxiety symptoms, only the estimate for the highest category was selected.

Negative complement analysis

The relative risk (RR) is affected by both the magnitudes of the RD as well as the baseline risks and for any given RD is magnified when baseline risks are small. Thus the RR for a positive outcome (diabetes) may differ substantially from the RR for its negative complement (no diabetes) [17]. It has been suggested that the outcome with higher baseline risk is the correct outcome to report because such magnification only occurs at the lower spectrum of baseline risks. In this study the risk of diabetes in the exposed/unexposed groups represents the smaller baseline risk and thus we chose to compare its complement, "no-diabetes", with the diabetes outcome. In addition, RRs are subject to this anomaly at only the lower end of the risk spectrum but with ORs the anomaly occurs at both ends of the risk spectrum [17]. Hence our choice of converting effects back to RR's.

Statistical analysis

Four-fold cells (2 X 2 tables; exposure yes/no vs outcome yes/no) were imputed for all ORs using the reconstruction method proposed by Pietrantonj [20]. Studies using time-to-event estimates (hazard ratios) were presented separately, as 2 x 2 table reconstruction was not possible for studies using time-to-event estimates. The four-fold cells were used to compute relative risk (RR) and cumulative incidence proportion (CIP). Finally, and most importantly, we also examined whether RR for the positive outcome (diabetes) differs substantially from the RR for its negative complement, that is, no-diabetes and how this would impact on different baseline levels of risk.

The risk difference (RD) at two years follow-up was computed by estimating the events based on the yearly incidence rate of the complementary outcome in each study. For studies which had duration

more than two years, the yearly incidence rate (IR) was estimated as IR = - [ln(1 – CI_t/t] where CI_t is the cumulative incidence proportion of events at the end of the study and *t* is the duration of follow-up [21]. The two year cumulative incidence was then computed as $1 - e^{-IR(2)}$. From pooled RD, the number needed to be exposed for one additional person to be harmed (NNEH) at two years was also computed (reciprocal of pooled RD).

Pooled results were calculated via both the quality effects (QE) [22-24], and the conventional random effects model. We considered the funnel plot to be asymmetric if the intercept on Egger's regression deviated from zero with $p < 0.10$. Additional analyses for publication bias were performed when the funnel plot was asymmetric using the Duval and Tweedie non-parametric "Trim and Fill" method of accounting for missing studies in meta-analysis [25]. This method provides an estimate of the number of missing studies (with imputed estimates). All imputations were done assuming random error only. The QE meta-analysis was then re-run with quality scores given to the imputed studies of their corresponding (same standard error) existing studies to arrive at a pooled estimate that corrects somewhat for publication bias. This method used in sensitivity analysis is novel; no protocol has been published. All analyses were conducted using Microsoft Excel and MetaXL software version 1.4 [26] and Stata version 12 (Stata Corp, College Station, USA) was used for the Trim and Fill analysis.

Results

Diabetes outcome

Only four longitudinal studies were available; these provided four longitudinal datasets assessing anxiety and incident diabetes. The cumulative incidence of diabetes by exposure groups and summary of cohort studies are given in Table 1. All four studies reported their findings in the form of odds ratios, and only two studies reported statistically significant associations.

The pooled QE estimate for diabetes after exposure to anxiety was a RR of 1.65, suggesting a 65% increase in the risk of diabetes. The Egger's test for publication bias did not suggest asymmetry (intercept 0.379; p = 0.280).

Negative complement analysis

The RR for the negative complement, no-diabetes was 0.987, suggesting there would be a 1.3% decrease in non-diabetics had the unexposed group been exposed to anxiety. Both analyses

resulted in statistically significant results; however, the magnitude of the effect seems exaggerated when the risk of diabetes was directly computed (RR 1.65, 95% CI: 1.15 – 2.36) versus its negative complement (no-diabetes) (RR 0.987, 95% CI 0.978 – 0.995) (Figure 1).

Comparison to the RD at 2 years

We computed the RR that would result if our RD data at 2 years was to be used to compute it in conjunction with baseline risk. The results are given in Figure 2 and Table 2. Minor variations in the magnitude of the RD and baseline risks result in large variation in RR-Y but not in RR Not-Y. Thus the RR-Y does not seem generalizable to different baseline risks.

Discussion

We found a significant relationship between anxiety and incident diabetes in our quantitative analysis with a 65% increase in the risk of diabetes in adults with anxiety. This is higher than the 25% increase in odds reported previously by Smith et al. for the converse outcome of anxiety in diabetes [15]. However, the negative complement outcome (no-diabetes) reveals a low relative risk of diabetes mellitus with anxiety when compared to reports that use the outcome of incident diabetes. Specifically, the RR estimate for no-onset of diabetes was 0.987. This suggests only a 1.3% increase in the risk of new diabetes onset if patients who are unexposed to anxiety were to be exposed; this differs substantially from the magnitude of effect when risk of diabetes was the outcome.

The question is which RR represents the underlying risk correctly. We show that RR for diabetes is grossly affected by minor variations in RD and baseline risk (Figure 1 & Table 2). Thus to generalize from RR back to RD for varying levels of CER requires the RR with larger baseline risks. The RR with smaller baseline risk does not seem generalizable.

Numerous studies have suggested that anxiety is associated with an up-regulation or dysregulation of the Hypothalamo-Pituitary-Adrenal (HPA) axis resulting in elevated cortisol levels, which is also seen in depression, and that can inhibit insulin function in a variety of ways [27-29]. Obesity has been shown to be associated with anxiety disorders in various general population studies; it is possible for anxiety disorders to lead to weight gain [30]. Psychiatric conditions are often comorbid and some psychiatric problems have been found to lead to weight gain, including mood disorders [31,32], and personality disorders [32]. Anxiety disorders tend to co-morbid with

depression [33], and it is possible that the comorbidity between depression and anxiety is the most important factor.

Limitations

This review had several limitations that may affect its generalizability and acceptability. Limitations of the current review include language bias (only English-language databases and journals were searched), and publication bias (significant/ positive studies were more likely to be published and easily identified) and the limited number of longitudinal studies. Brayne et al. (2005) has argued that longitudinal research designs which examine the direction of a relationship could be "murky", as some of the lifestyle and biological factors, or other common antecedents of both conditions may have been present years before diagnosis [34]. The methods used to ascertain the presence of anxiety were not uniform and included studies that measured anxiety after diagnosis and studies that used self-report scales; both types were used to obtain pooled estimate. This may have important implications, as different types of anxiety disorders have been associated with diabetes, such as panic disorder and generalised anxiety disorder (GAD) which are common in people with diabetes [35]. Finally, distinguishing between type 1 and type 2 diabetes in large epidemiological studies, is not always possible since the exact timing of diabetes onset and diagnosis may not be fully reliable.

Conclusions

Despite these limitations, this study did support the assumption that anxiety could lead to an increased risk of developing diabetes. It is clear that reclassification of the event as the outcome with higher baseline risk (no-onset of diabetes) puts the RR into perspective and thus avoids the mathematical exaggeration of the RR that occurs with the use of lower baseline risks [17]. There is still a documented risk but it is small. Further research is warranted to confirm this finding so that patients at risk can be correctly identified and the development of diabetes can be prevented.

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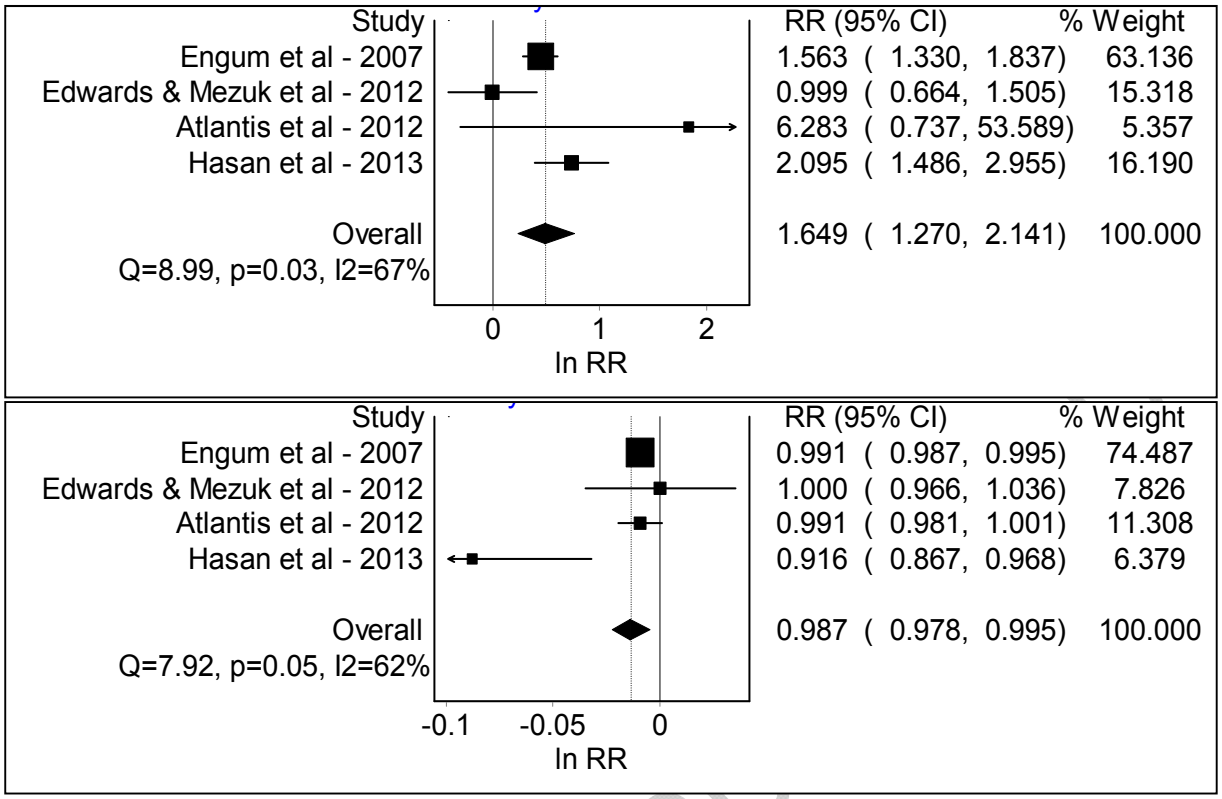

Figure 1: Quality-effects forest plot showing the risk of diabetes for individual studies using self-report questionnaires, diagnostic criteria, and all studies combined; studies using reconstructed RR, top (anxiety to diabetes) and below (anxiety to no diabetes). Bars and diamonds indicate 95% CIs.

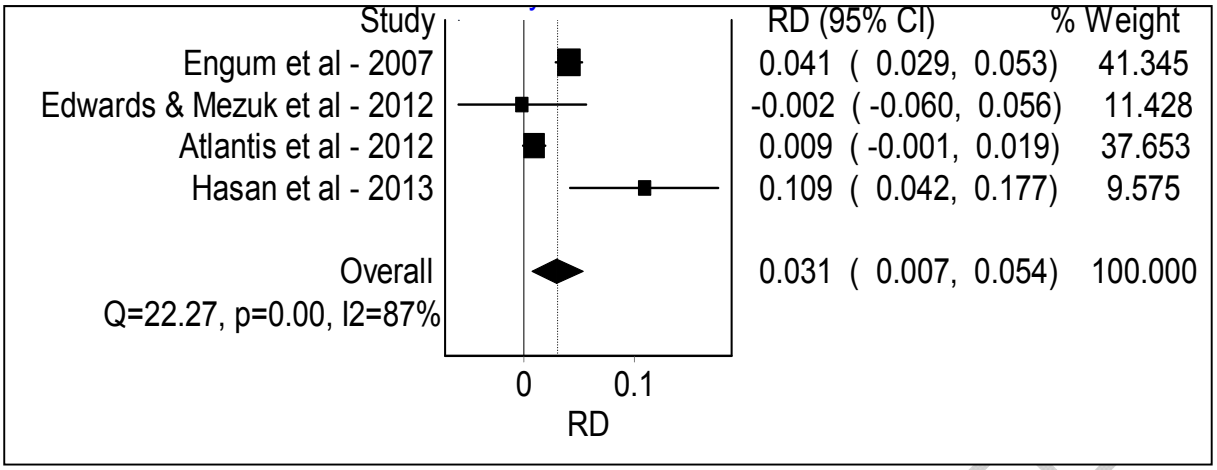

Figure 2: Quality-effects forest plot showing the risk of diabetes for individual studies using self-report questionnaires, diagnostic criteria, and all studies combined with outcome at 2 yrs; studies using RD. Bars and diamonds indicate 95% CIs.

Table 1: Summary of findings of longitudinal studies assessing relationship between anxiety and incident diabetes

Authors (country-yr)	Follow-up years	Age yrs	Depression assessment	Diabetes assessment	Adjustment for confounders	Original OR	Imputed RR	EER at 2 yrs %
1. Engum et al **(Norway - 2007)**	10.0	≥ 30	ADI	Self-report + FPG	Age, gender, SES, lifestyle factors, clinical factors	1.40 (1.16-1.63)	1.56 (1.33-1.84)	**E:** 0.51 **UE:** 0.32
2. Edwards & Mezuk **(USA - 2012)**	11.0	≥ 42	DIS	Self-report	Demographics, health behaviours, comorbidity	1.00 (0.53-1.89)	1.00 (0.66-1.50)	**E:**1.48 **UE:**1.49
3. Atlantis et al **(Netherlands – 2012)**	2.0	18--65	CIDI	Self-report + FPG	Age & lifestyle cumulative risk score	10.5 (1.4-78.7)	6.28 (0.74-53.59)	**E:** 1.10 **UE:** 0.18
4. Hasan et al **(Australia - 2014)**	7.0	> 18	DSSI	Self-report	Age, BMI, depression, education, marital status	2.30 (1.38-3.84)	2.10 (1.49-2.95)	**E:** 4.51 **UE:** 2.09

OR = odds ratio; RR = relative risk; EER = Exposed Events Rate

Table 2: Summary of negative component analysis and comparison to the risk difference at 2 years

Study	Baseline Risk at 2 yrs	RD at 2 yrs	RR Not Y[a]	RR Y[b]
Engum et al - 2007	0.00322	0.001833	0.998	1.6
Edwards & Mezuk et al - 2012	0.01485	-8.3E-06	1.000	1.0
Atlantis et al - 2012	0.00175	0.00922	0.991	6.3
Hasan et al - 2013	0.02088	0.024216	0.975	2.2

[a] RR (outcome not Y) = (RD/(CER-1))+1
[b] RR (outcome Y) = (RD/CER)+1
RR = Relative Risk
RD = Risk Difference

APPENDIX 5A

MR Number:

F				

Date questionnaire completed: _____ / _____ / _____

Year of diagnosis of diabetes mellitus: _____

STUDY OF MENTAL HEALTH AND RELATED FACTORS AMONG WOMEN WITH AND WITHOUT DIABETES

QUESTIONNAIRE

THE QUESTIONS ARE ABOUT YOURSELF AND THERE ARE NO RIGHT OR WRONG ANSWERS OR TRICK QUESTIONS. ALL ANSWERS ARE STRICTLY CONFIDENTIAL. ANSWERING EACH QUESTION IS VOLUNTARY.

If you feel the need to discuss any issues that might arise as a result of your participation in this study, please see the contact list provided in the participant information sheet if you require further clarification.

Thank you very much for agreeing to participate in this study.

Please turn the page to begin

Your Background

For the questions regarding your background, please answer or circle the item that describes you most appropriately.

1. **What is your age in years?** ____

2. **With which ONE of the following ethnic groups do you identify?**

a. Malay	1
b. Chinese	2
c. Indian	3
d. Iban	4
e. Bidayu	5
f. Melanau	6
g. Kadazan	7
f. Other (specify) _____	8

3. What is (or was) your main occupation? *(circle one that best suits you)*

a. Government employee	1
b. Non-government employee	2
c. Self employed	3
d. Non paid/volunteer	4
e. Student	5
f. Homemaker *(carrying out household tasks without being paid)*	6
g. Retired/pensioner	7
h. Unemployed *(able to work)*	8
i. Unemployed *(unable to work)*	9
j. Never had a paid job	10
k. Other (please specify) _____	11

4. How many hours do you normally work in all your PAID jobs each week?

a. No paid job	1
b. 1-15 hours	2
c. 16-24 hours	3
d. 25-34 hours	4

e. 35-40 hours	5
f. 41 hours or more	6

5. What is your current marital status? *(circle one that best describes you)*

a. Single (not married)	1
b. Living together	2
c. Married	3
d. Separated	4
f. Divorced	5
g. Widowed	6
h. Other (specify) _____	7

6. How many children do you have? ☐

7. What is the highest level of education you have completed? *(circle one that best describes you)*	
a. No formal education	0
b. Pre-school	1
c. Primary school	2
d. LCE/PMR/SRP *(awarded after completing 9 years of schooling)*	3
e. SPM/MCE/O'Level *(lower secondary)*	4
f. STPM/HSC/A-Level *(upper secondary)*	5
g. Diploma	6
h. Bachelor degree	7
i. Post Graduate degree	8

8. From the list below, please circle the number closest to your household average monthly and annual income.

Gross income is your income before tax and other deductions are taken out. This includes wages, pensions, government payments and income from other sources such as investments. If unsure, circle the number closest to the amount you think may be correct.

Monthly income	**Annual income**	
a. No income		1
b. Less than RM1650	Less than RM20,000	2
c. RM1650-RM2499	RM20,000-RM29,999	3

d. RM2500-RM3499	RM30,000-RM39,999	4
e. RM3500-RM4299	RM40,000-RM49,999	5
f. RM4300-RM4999	RM50,000-RM59,999	6
g. RM5000-RM5899	RM60,000-RM69,999	7
h. RM5900-RM6999	RM70,000-RM79,999	8
i. RM7000-RM7599	RM80,000-RM89,999	9
j. RM7500-RM8499	RM90,000-RM99,999	10
k. RM8500-RM10499	RM100,000-RM124,999	11
l. RM10500-RM12499	RM125,000-RM149,000	12
m. RM12500 or more	RM150,000 or more	13

9. In what type of area do you live?

Urban areas are built-up, non agricultural areas whereas rural areas are mainly agricultural lands

a. Urban *Name of area*: _____	1
b. Rural *Name of area*: _____	2

Your medical and pregnancy history

In this section we would like to ask about your health and social life.

1. The next few questions are about health problems you might have had at any time in your life. Have you ever been diagnosed with any of the following? *(circle one response for each item)*	**No**	**Yes**	**How old were you when first diagnosed? (enter you age in years)**	**Did you receive any treatment?**	
				No	**Yes**
a. Early onset diabetes (high blood sugar) Type-I	1	2		1	2
b. Late onset diabetes Type-II	1	2		1	2
c. Heart attack (myocardial infarction)	1	2		1	2
d. Hypertension (high blood pressure)	1	2		1	2
e. Heart failure	1	2		1	2
f. Cardiac arrhythmias (irregular heart beat)	1	2		1	2
g. Stroke	1	2		1	2
h. Lung disease (Asthma, COPD)	1	2		1	2
i. Kidney disease	1	2		1	2
j. Others (specify) _____	1	2		1	2

2. How many times have you? *Please identify the total number of pregnancies, your age at each pregnancy, and the outcome*	**Number of times** (if never, write 0)	**Age (s)** (write age you were at each pregnancy or the year)
a. Been pregnant		
b. Pregnancies from assisted reproduction (IVF)		
c. Had a miscarriage		
d. Had stillbirth		
e. Had a termination or abortion (s)		
f. Given birth to a live child		

3. Have you EVER had ANY of the following complications during pregnancy?	**No**	**Yes**
a. Gestational diabetes (high sugar during pregnancy)	1	2
b. High blood pressure	1	2
c. Pre-eclampsia (e.g. high blood pressure, protein in urine)	1	2
d. Depression (feeling sad or depressed)	1	2

3. Have you EVER had ANY of the following complications during pregnancy?	**No**	**Yes**
e. Anxiety (feeling anxious)	1	2
f. Sleep disturbances	1	2

4. The next few questions are about health problems your CHILDREN might have had at any time in life. Have your children ever had any of the following:	**No**	**Yes**	**How many children have this condition?**	**How many children are receiving treatment?**
a. Early onset diabetes (high blood sugar) - Type-I	1	2		
b. Late onset diabetes - Type-II	1	2		
c. Heart attack (myocardial infarction)	1	2		
d. Hypertension (high blood pressure)	1	2		
e. Heart failure	1	2		
f. Cardiac arrhythmias (irregular heart beat)	1	2		
g. Stroke	1	2		
h. Lung disease (e.g. Asthma, COPD)	1	2		
i. Kidney disease	1	2		
j. Others (specify) _____	1	2		

5. How often do you or your carer measure your blood glucose level?

a. My blood glucose is not measured regularly	1
b. Everyday	2
b. Once a week	3
c. Once a month	4
d. Every 6 months	5
e. Every 12 months	6

6. Have you received any advice on diabetes management from the following health care professional (s)? *(circle either 1 or 2 for each person)*	**NO**	**YES**
a. Consultant/specialist (endocrinologist)	1	2
b. General practitioner	1	2
c. Pharmacist	1	2
d. Nurse	1	2

6. Have you received any advice on diabetes management from the following health care professional (s)? *(circle either 1 or 2 for each person)*	**NO**	**YES**
e. Dietitian/Nutritionist	1	2
f. Dentist	1	2
g. Physiotherapist	1	2
h. Other (specify) _____	1	2

7. How useful did you find this information? *(circle one of the numbers from 0 to 5 for each healthcare professional)*	**Did not see this person**	**Not useful at all**				**Extremely useful**
a. Consultant/specialist (e.g. endocrinologist)	0	1	2	3	4	5
b. General practitioner	0	1	2	3	4	5
c. Pharmacist	0	1	2	3	4	5
d. Nurse	0	1	2	3	4	5
e. Dietitian/Nutritionist	0	1	2	3	4	5
f. Dentist	0	1	2	3	4	5
g. Physiotherapist	0	1	2	3	4	5
h. Other (specify) _____	0	1	2	3	4	5

Your lifestyle

The next questions are concerned with your average physical activity over the LAST 6 MONTHS.

1. On average, how many times a week do you exercise vigorously for a period of at least 20 minutes? *(Vigorously means exercise which makes you breathe harder or puff and pant, and includes activities such as swimming, athletics)*

a. Not at all	1
b. 1 to 2 times a week	2
c. 3 or more times a week	3

2. On average, how many times a week do you walk for recreation or exercise?

a. Not at all	1
b. 1 to 2 times a week	2
c. 3 or more times a week	3

3. Have you used any of these methods to lose weight or to control your weight in the LAST 12 MONTHS? *(circle either 1 or 2 for each of the statements)*	**NO**	**YES**
a. Commercial weight loss programs	1	2
b. Meal replacements or slimming products	1	2
c. Exercise	1	2
d. Cut down on the size of meals or between meal snacks	1	2
e. Cut down on fats of sugar	1	2
f. Low glycemic index (GI) diet	1	2
g. Diet book diets	1	2
h. Laxatives, diuretics or diet pills	1	2
i. Vegetarian diet	1	2
j. Fasting	1	2
k. Smoking	1	2
l. Surgery	1	2
m. Other (please specify) _____	1	2

4. How would you describe yourself now? (*Circle the number that best describes you)*

a. Very underweight	1
b. Moderately underweight	2
c. Average	3

d. Moderately overweight	4
e. Very overweight	5
f. Obese	6

5. Excluding pregnancy, how many times EVER in your adult life have you? *(circle one response for each question)*	**Never**	**1-2 times**	**3-4 times**	**5 or more times**
a. Lost 5 kg or more on purpose	1	2	3	4
b. Lost 5 kg or more for any other reason	1	2	3	4
c. Gained 5 kg or more which you had previously lost on purpose	1	2	3	4

6. Which of the following best describes your smoking status now? *(circle one that best describes you)*

a. I have never smoked	1	*If **1**, go to Q9*
b. I used to smoke	2	
c. I now smoke occasionally	3	
d. I now smoke regularly	4	

7. In the LAST WEEK how many cigarettes did you usually smoke PER DAY? *(circle one that best describes you)*

a. Did not smoke at all	1
b. 1-9 per day	2
c. 10-19 per day	3
d. 20-29 per day	4
e. 30-49 per day	5
f. 50 or more per day	6

8. **How many times have you tried to quit smoking?**

(Write '0' if never tried)

☐ Number of times

9. Have you ever consumed a drink that contains alcohol such as beer, wine, spirits, fermented cider, sake, samsu, tuak or others?

☐ Yes ☐ No *if **No**, go to Q1 in the next section.*

10. Over the last 12 months, on days when you were drinking, how many glasses of alcohol or equivalent did you usually drink? *(total number per day)*

a. 1 glass	1
b. 2 glasses	2
c. 3 glasses	3
d. 4 glasses	4
e. 5 or more glasses	5

11. How many times have you tried to quit drinking alcohol?

(Write '0' if never tried)

☐ Number of times

Your Reproductive Health

1. For each of the following statements, please circle Yes or No to indicate whether you have experienced the problem in the PAST MONTH. If YES, please rate how much the problem has bothered you using the scale from 1 (Not at all bothered) to 7 (Extremely bothered)

	No	**Yes**	**Not at all bothered**					**Extremely bothered**	
a. Hot flushes or flashes	No	Yes	1	2	3	4	5	6	7
b. Night sweats	No	Yes	1	2	3	4	5	6	7
c. Sweating	No	Yes	1	2	3	4	5	6	7
d. Being dissatisfied with my personal life	No	Yes	1	2	3	4	5	6	7
e. Feeling anxious or nervous	No	Yes	1	2	3	4	5	6	7
f. Experiencing poor memory	No	Yes	1	2	3	4	5	6	7
g. Accomplishing less than I used to	No	Yes	1	2	3	4	5	6	7
h. Feeling depressed, down or blue	No	Yes	1	2	3	4	5	6	7
i. Being impatient with other people	No	Yes	1	2	3	4	5	6	7
j. Feelings of wanting to be alone	No	Yes	1	2	3	4	5	6	7
k. Flatulence (wind) or gas pains	No	Yes	1	2	3	4	5	6	7
l. Aching in muscles and joints	No	Yes	1	2	3	4	5	6	7
m. Feeling tired or worn out	No	Yes	1	2	3	4	5	6	7
n. Difficulty sleeping	No	Yes	1	2	3	4	5	6	7
o. Aches in back of neck or head	No	Yes	1	2	3	4	5	6	7
p. Decrease in physical strength	No	Yes	1	2	3	4	5	6	7
q. Decrease in stamina	No	Yes	1	2	3	4	5	6	7
r. Feeling a lack of energy	No	Yes	1	2	3	4	5	6	7

	No	**Yes**	**Not at all bothered**					**Extremely bothered**	
s. Drying skin	No	Yes	1	2	3	4	5	6	7
t. Weight gain	No	Yes	1	2	3	4	5	6	7
u. Increased facial hair	No	Yes	1	2	3	4	5	6	7
v. Changes in appearance, texture or tone of your skin	No	Yes	1	2	3	4	5	6	7
w. Feeling bloated	No	Yes	1	2	3	4	5	6	7
x. Low backache	No	Yes	1	2	3	4	5	6	7
y. Frequent urination	No	Yes	1	2	3	4	5	6	7
z. Involuntary urination when laughing or coughing	No	Yes	1	2	3	4	5	6	7
aa. Change in your sexual desire	No	Yes	1	2	3	4	5	6	7
bb. Vaginal dryness during intercourse	No	Yes	1	2	3	4	5	6	7
cc. Avoiding intimacy	No	Yes	1	2	3	4	5	6	7

2. Have your periods stopped?

a. No	1
b. Yes	2

*If **Yes**, go to Q5*

3. If No, do you have irregular periods (heavy/light or shorter/longer periods)?

a. No	1
b. Yes	2
c. Don't know	3

*If **Yes** or **Don't know**, go to Q5*

4. If No, when did you have your last period?

a. In the last month	1
b. In the last 3 months	2
c. Between 3 and 11 months ago	3
d. 12 months ago or more	4

5. Are you currently taking:	**No**	**Yes**
a. Oral contraceptives (OC) e.g. "the pill"	1	2
b. Hormone replacement therapy (HRT)	1	2

Your Mental Health

The next questions are about your mental health.

1. Have you ever been diagnosed with the following conditions by a doctor?	**No**	**Yes**
a. Depression	1	2
b. Anxiety	1	2
c. Sleep problem	1	2

2. If YES, at what age were you first diagnosed with the following conditions?	**Age (years)**
a. Depression	
b. Anxiety	
c. Sleep problem	

3. Since diagnosis, how many episodes have you had, lasting 2 weeks or more?	**None**	**1 episode**	**2 episodes**	**3 or more**
a. Depression	1	2	3	4
b. Anxiety	1	2	3	4
c. Sleep problems	1	2	3	4

4. Below is a list of ways you might have felt or behaved. Please circle the response that is closest to how you have been feeling in the LAST TWO WEEKS.	**All the time**	**Most of the time**	**Some of the time**	**Rarely**	**Never**
a. I have worried about every little thing	1	2	3	4	5
b. I have been so miserable that I have had difficulty sleeping	1	2	3	4	5
c. I have been breathless or had a pounding heart	1	2	3	4	5
d. I have been so worked up that I couldn't sit still	1	2	3	4	5
e. I have been depressed without knowing why	1	2	3	4	5
f. I have gone to bed not caring if I ever woke up	1	2	3	4	5
g. For no good reason I have had feelings of panic	1	2	3	4	5
h. I have been so low in spirit that I have sat up for ages doing absolutely nothing	1	2	3	4	5
i. I have had a pain or tense feeling in my neck or head	1	2	3	4	5
j. The future seems hopeless	1	2	3	4	5
k. Worrying has kept me awake at night	1	2	3	4	5

4. Below is a list of ways you might have felt or behaved. Please circle the response that is closest to how you have been feeling in the LAST TWO WEEKS.	**All the time**	**Most of the time**	**Some of the time**	**Rarely**	**Never**
l. I have lost interest in just about everything	1	2	3	4	5
m. I have been so anxious that I couldn't make up my mind about the simplest thing	1	2	3	4	5
n. I have been so depressed that I have thought of doing away with myself	1	2	3	4	5

5. Below is a list of ways you might have felt or behaved. Please indicate how often you have felt these DURING THE PAST WEEK.	**Rarely or none of the time (less than 1 day)**	**Some or little of the time (1-2 days)**	**Occasionally or a moderate amount of time (3-4 days)**	**Most or all of the time (5-6 days)**
a. I was bothered by things that don't usually bother me	1	2	3	4
b. I had trouble keeping my mind on what I was doing	1	2	3	4
c. I felt depressed	1	2	3	4
d. I felt everything I did was an effort	1	2	3	4
e. I felt hopeful about the future	1	2	3	4
f. I felt fearful	1	2	3	4
g. My sleep was restless	1	2	3	4
h. I was happy	1	2	3	4
i. I felt lonely	1	2	3	4
j. I could not "get going"	1	2	3	4

Your Sleep

The next questions are about your quality of sleep.

1. During the PAST MONTH, when have you usually gone to bed at night?

USUAL BED TIME

AM	PM

2. During the PAST MONTH, how long (in minutes) has it usually taken you to fall asleep each night?

NUMBER OF MINUTES

3. During the PAST MONTH, when have you usually gotten up in the morning?

USUAL GETTING UP TIME

AM	PM

4. During the PAST MONTH, how many hours of actual sleep did you get at night?
(This may be different from the number of hours you spend in bed)

HOURS OF SLEEP PER NIGHT

For each of the following questions, check one best response. *Please answer all questions*

5. During the PAST MONTH, how often have you had trouble sleeping because you:	**Not during the past month**	**Less than once a week**	**Once or twice a week**	**Three or more times a week**
a. Cannot get to sleep within 30 minutes	1	2	3	4
b. Wake up in the middle of the night or early morning	1	2	3	4
c. Have to get up to use the bathroom	1	2	3	4
d. Cannot breathe comfortably	1	2	3	4
e. Cough or snore loudly	1	2	3	4
f. Feel too cold	1	2	3	4
g. Feel too hot	1	2	3	4
h. Had bad dreams	1	2	3	4
i. Have pain	1	2	3	4
j. Other reasons *please specify*	1	2	3	4

5. During the PAST MONTH, how often have you had trouble sleeping because you:	**Not during the past month**	**Less than once a week**	**Once or twice a week**	**Three or more times a week**
_____				

6. During the PAST MONTH, how would you rate your overall sleep quality?

a. Very good	1
b. Fairly good	2
c. Fairly bad	3
d. Very bad	4

7. During the PAST MONTH, how often have you taken medicine (prescribed or "over the counter") to help you sleep?

a. Not during the past month	1
b. Less than once a week	2
c. Once or twice a week	3
d. Three or more times a week	4

8. During the PAST MONTH, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?

a. Not during the past month	1
b. Less than once a week	2
c. Once a twice a week	3
d. Three or more times a week	4

9. During the PAST MONTH, how much of a problem has it been for you to keep up enough enthusiasm to get things done?

a. No problem at all	1
b. Only a very slight problem	2
c. Somewhat of a problem	3
d. A very big problem	4

Your Well Being

The next questions are about your quality of life over the LAST TWO WEEKS.

1. In general, would you say that your health is:

a. Excellent	1
b. Very good	2
c. Good	3
d. Fair	4
e. Poor	5

2. The following two questions are about activities you might do during a typical day. Does YOUR HEALTH NOW LIMIT YOU in these activities? If so, how much?	**Yes, limited a lot**	**Yes, limited a little**	**No, not limited at all**
a. MODERATE ACTIVITIES, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
b. Climbing SEVERAL flights of stairs	1	2	3

3. During the PAST 4 WEEKS have you had any of the following problems with your work or other regular activities AS A RESULT OF YOUR PHYSICAL HEALTH?	**Yes**	**No**
a. ACCOMPLISHED LESS than you would like	1	2
b. Were limited in the KIND of work or other activities	1	2

4. During the PAST 4 WEEKS, were you limited in the kind of work you do or other regular activities, AS A RESULT OF ANY EMOTIONAL PROBLEMS (such as feeling depressed or anxious)?	**Yes**	**No**
a. ACCOMPLISHED LESS than you would like	1	2
b. Didn't do work or other activities as CAREFULLY as usual	1	2

5. During the PAST 4 WEEKS, how much did PAIN interfere with your normal work (including both work outside the home and housework)?

a. Not at all	1
b. A little bit	2
c. Moderately	3
d. Quite a bit	4
e. Extremely	5

The next three questions are about how you feel and how things have been DURING THE PAST WEEKS. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the PAST WEEKS –

6. Think back over the LAST TWO WEEKS	**All of the time**	**Most of the time**	**A good bit of the time**	**Some of the time**	**A little of the time**	**None of the time**
a. Have you felt calm and peaceful?	1	2	3	4	5	6
b. Did you have a lot of energy?	1	2	3	4	5	6
c. Have you felt downhearted and blue?	1	2	3	4	5	6

7. During the PAST 4 WEEKS, how much of the time has your PHYSICAL HEALTH OR EMOTIONAL PROBLEMS interfered with your social activities (like visiting with friends, relatives, etc.)?

a. All of the time	1
b. Most of the time	2
c. A good bit of the time	3
d. Some of the time	4
e. A little of the time	5
f. None of the time	6

8. How true or false are each of the following statements for you?	**Definitely true**	**Mostly true**	**Don't know**	**Mostly false**	**Definitely false**
a. I seem to get sick a little easier than other people	1	2	3	4	5
b. I am as healthy as anybody I know	1	2	3	4	5

9. How satisfied are you with your life as a whole these days? Would you say you are:

a. Very satisfied	1
b. Satisfied	2
c. Dissatisfied	3
d. Very dissatisfied	4

10. How would you say you feel these days? Would you say you are:

a. Very happy	1
b. Fairly happy	2

c. Not too happy	3
d. Very unhappy	4

Hooray you are finished!!!!!

To be completed by researcher

PATIENT ASSESSMENT SHEET – DIABETIC PATIENTS

CODE NUMBER:

F				

1. Physical Measurements

a. Height _____ cm

b. Weight _____ kg

c. Waist circumference _____ cm

2. Last five readings of participant's blood pressure (BP)

Date of measurement (DD/MM/YY)	*Systolic BP*	*Diastolic BP*
1.		
2.		
3.		
4.		
5.		

3. Last five readings of participant's glucose level

Date of measurement (DD/MM/YY)	*Random glucose level*	*HbA1c*
1.		
2.		
3.		
4.		
5.		

4. Please provide the following details for each current prescribed antidiabetic medicine taken

Name of medications	No	Yes	Dose taken	
			How often per day	How much
Insulin	1	2		
Metformin	1	2		
Glibenclamide	1	2		
Glimepride	1	2		
Gliclazide	1	2		
Glipizide	1	2		
Acarbose	1	2		
Rosiglitazone	1	2		
Pioglitazone	1	2		
Repaglinide	1	2		
Others, _____	1	2		

5. Diabetes complications chart

Complications	No	Yes	Comments
Retinopathy	1	2	
Nephropathy	1	2	
Neuropathy	1	2	
Cardiovascular disease	1	2	
Hyperlipidemia	1	2	
Diabetic foot ulcer (amputation)	1	2	
Others, _____	1	2	

APPENDIX 6A: Estimation of sample size

Sample size was calculated using formula below:

$$SS = \frac{(Z)^2 * (p) * q}{(c)^2}$$

Where:

Z = Z value (e.g. 1.96 for 95% confidence level)

p = percentage prevalence, expressed as decimal

q = 1 – p

c = margin of error, expressed as decimal (2.5%, 0.025)

Prevalence estimation:

For sample size estimation, we need prevalence (p). Since data was collected in 2012, so prevalence of diabetes in 2012 was used.

Increase in expected prevalence of diabetes/year = 0.11

Estimated prevalence in 2012 = 0.11 X 2012 - 2010 = 0.22

= 0.22 + 11.6

= *11.82%*

Sample size estimation:

Based on the formula above, the estimated sample size was:

$$ss = \frac{(1.96 * 1.96)^2 \times (0.1182) \times (1-0.1182)}{(0.025 * 0.025)}$$

ss = 640

Note: 640 was the required sample size for cases, to match the frequency of cases, 640 controls were selected.

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3. Draugalis JR, Plaza CM (2009). Best practices for survey research reports revisited: Implications of target population, probability sampling, and response rate. Am J Pharm Educ 73(8), Article 142.