EEPRU

Economic Evaluation of Health and Social Care Interventions Policy Research Unit

RESEARCH REPORT

Whole pathway modelling of depression in patients with diabetes (Theme 2: Mental Health)
Part 1: Executive summary, introduction, clinical reviews and conceptual modelling

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RR0042

June 2014

The University Of Sheffield.

UNIVERSITY of York

The Policy Research Unit in Economic Evaluation of Health and Care interventions is funded by the Department of Health Policy Research Programme. It is a collaboration between researchers from then University of Sheffield and the University of York.

The Department of Health's Policy Research Unit in Economic Evaluation of Health and Care Interventions is a 5 year programme of work that started in January 2011. The unit is led by Professor John Brazier (Director, University of Sheffield) and Professor Mark Sculpher (Deputy Director, University of York) with the aim of assisting policy makers in the Department of Health to improve the allocation of resources in health and social care.

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Acknowledgement and disclaimer

We would like to thank our clinical advisors who gave up their time to provide invaluable expertise and knowledge at key stages of the project.

- Jackie Elliott (senior clinical lecturer in diabetes, University of Sheffield)
- David Gable (consultant diabetologist, Imperial College Healthcare NHS Trust)
- Deborah Gamsu (clinical psychologist in diabetes care, Sheffield Health and Social Care Foundation Trust)
- Richard Holt (Professor in Diabetes and Endocrinology, University of Southampton)
- Kamlesh Khunti (Professor of Primary Care Diabetes and Vascular Medicine, University of Leicester)
- Caroline Mitchell (senior clinical lecturer, University of Sheffield)
- Malcolm Peet (consultant psychiatrist, honorary professor, ScHARR Mental Health Group)
- Tom Ricketts (nurse consultant in psychotherapy & research, Sheffield Health and Social Care Foundation Trust)
- Geraldine Strathdee (consultant psychiatrist and associate medical director, Oxleas Foundation Trust and Mental Health NHS)
- Nic Wilkinson (clinical psychologist, Sheffield Health and Social Care Foundation Trust)
- Emily Wood (mental health nurse, ScHARR Mental Health Group)

We would like to thank the service users who gave-up their time to talk to us about their experiences of having diabetes with comorbid depression.

We would like to thank Naomi Holman, Hazel Squires, Penny Watson, Mike Gillett, Alan Brennan, Simon Walker, Moira Leahy and Simon Bennett for their contributions to this work.

The Policy Research Unit in Economic Evaluation of Health and Care interventions is funded by the Department of Health Policy Research Programme. It is a collaboration between researchers from the University of Sheffield and the University of York. The Department of Health's Policy Research Unit in Economic Evaluation of Health and Care Interventions is a 5 year programme of work that started in January 2011. The unit is led by Professor John Brazier (Director, University of Sheffield) and Professor Mark Sculpher (Deputy Director, University of York) with the aim of assisting policy makers in the Department of Health to improve the allocation of resources in health and social care. This is an independent report commissioned and funded by the Policy Research Programme in the Department of Health. The views expressed are not necessarily those of the Department.

This is the first part in the EEPRU report 'Whole pathway modelling of depression in patients with diabetes'. The second part contains details on the independent economic evaluation, along with the results, discussion and conclusion. The executive summary is found in both parts. All appendices are available in a separate file. All files may be found on the EEPRU website (http://www.eepru.org.uk/).

Abbreviations

ACCORD	Action to Control Cardiovascular Risk in Diabetes
BDI	Becks Depression Inventory
BNF	British National Formulary
CAD	Coronary artery disease
CBT	Cognitive behavioural therapy
CES-D	Center of Epidemiological Studies - Depression
CG	Clinical guideline
CHD	Coronary heart disease
CHF	Congestive heart failure
CI	Confidence interval
CIDI	Composite International Diagnostic Interview
CMHT	Community Mental Health Teams
DES	Discrete event simulation
DESM	Discrete event simulation model
DESMOND	Diabetes Education and Self-Management for Ongoing and Newly Diagnosed
DM/D	Diabetes and depression
DoH	Department of Health
DSM	Diagnostic and Statistical Manual of Mental Disorders
EEPRU	Economic Evaluation Policy Research Unit
GP	General practitioner
HADS	Hospital Anxiety and Depression Scale
HR	Hazard ratio
HRQoL	Health-related quality of life
IAPT	Improving Access to Psychological Therapies
ICD	International Classification of Diseases
ICER	Incremental cost-effectiveness ratio
IHD	Ischaemic heart disease
LTC	Long-term condition
LY	Life year
MD	Mean difference
MI	Myocardial infarction
NDA	National Diabetes Audit

NHS	National Health Service
NICE	National Institute for Health and Care Excellence
OM	Outcomes model
OR	Odds ratio
PAID	Problem Areas In Diabetes
PHQ	Patient Health Questionnaire
PSA	Probabilistic sensitivity analysis
PSSRU	Personal Social Services Research Unit
PTM	Post-trial monitoring
QALY	Quality-adjusted life year
QOF	Quality and Outcomes Framework
QoL	Quality of life
RCT	Randomised controlled trial
RR	Relative risk (also known as risk ratio)
SPS	Specialist Psychotherapy Services
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TAU	Treatment as usual
UK	United Kingdom
UKPDS	United Kingdom Prospective Diabetes Study
USA	United States of America

Executive Summary

Background

Diabetes is associated with premature death, along with a number of serious complications such as amputation, blindness and heart disease. The presence of diabetes with comorbid depression increases both the risk of mortality and the prevalence of complications, as well as resulting in increased healthcare use and costs.

Historically care pathways for diabetes and for depression have been isolated from each other, resulting in a siloing of care. There is now interest in exploring methods by which the care pathways may be integrated, and the impact that this has on both patient outcomes and costs to the healthcare system.

Objectives

This project aimed to assess the health economic outcomes associated with having both diabetes and depression, and explore potential changes to the care pathways for these diseases that could be implemented to improve the health economic outcomes.

Data Sources

Data were drawn from a range of sources including published literature identified through a series of searches. A scoping review in MEDLINE identified pooled data, followed by subsequent searches in MEDLINE, PsychInfo and Cochrane electronic databases for individual studies where no pooled data was available. Searches were conducted from July to November 2013. These searches were supplemented by papers identified through consultation with experts and by papers known to the authors.

Methods

The objective of the literature review was to understand the relationship between diabetes and depression to inform the model development and to identify evidence that may be used to populate the economic model. The search aimed to identify information for multiple parameters. The review of the literature consisted of 3 steps. Firstly, a scoping review of reviews was conducted to inform the model conceptualisation. This aimed to identify all types of reviews (narrative, systematic and meta-analytic) relating to depression in diabetes. Secondly, after the model had been developed, targeted searches were conducted to identify studies for parameters where suitable data had not

been identified in the reviews. Finally, a systematic search was conducted to provide a more comprehensive understanding of a "key" model parameter, namely the relationship between diabetes-related complications and depression.

A mathematical model of the depression care pathways experienced by people with diagnosed type-2 diabetes (T2DM) in England was created based on the conceptual model developed with the aid of an advisory group supplemented by a review of the published literature and a meeting with current service users. This model took the form of a discrete-event simulation, and was developed to assess the relative cost-effectiveness of proposed service changes from an NHS perspective, wider social benefits were also explored. The population considered for this project was adults with T2DM currently managed within primary care in England. Patients could have existing depression, develop depression, or remain depression free.

The health economic outcomes considered were morbidity, quality of life, mortality, and costs incurred by the healthcare system. The potential service changes (interventions) considered included: improvements in opportunistic screening for depression; collaborative care; both improvements in opportunistic screening for depression and collaborative care. The comparator was current standard care. An expert group of advisors assisted in the identification of relevant service changes and identification of relevant evidence.

Results

Sixty reviews of depression in diabetes were identified in the scoping search. Insufficient data was identified in the reviews to populate all of the model parameters. Targeted searches were therefore conducted to identify data from individual studies for: the prevalence of depression amongst T2DM in England; the natural history of depression in diabetes, including incidence, recurrence, relapse and persistence; and the effectiveness of screening for depression in diabetes. A review was also conducted to identify evidence on the link between the development of diabetes-related complications and depression, and the converse.

The model estimated that the proposed policies have the potential to reduce both the time spent with depression, and the number of diabetes-related complications experienced. All three policies were associated with an improvement in quality of life and an increase in depression-free years compared with current practice, but with an increase in health care costs. Overall Policy 3, which examined the effect of introducing both collaborative care and increasing opportunistic screening

together, was estimated to produce the greatest benefits in terms of both events avoided and depression free years. However, the incremental cost-effectiveness ratio (£37,421) comparing Policy 3 to current practice is above the cost per QALY currently considered cost-effective. In addition, when comparing across the policies, Policy 2 (improvement in opportunistic screening) is dominated by Policy 1 (collaborative care), and comparing Policy 3 with Policy 1, this policy would again not be considered cost-effective (with an ICER of £68,017) when assuming a willingness to pay threshold of either £20,000 or £30,000 per QALY. However, these estimates do not take into account the uncertainty surrounding both parameters and structural assumptions. All three policies produced some benefits when looking at a wider societal perspective and were associated with a reduction in both the number of days off sick due to ill health and the need for informal care.

Additional research is required to decrease the uncertainty in the results presented, such as in the bi-directional relationship between diabetes and depression, and the natural history of depression in patients with diabetes.

While this study examined the effects of policies in patients with diabetes, the proposed changes to the pathway are potentially generalizable to patients with other long term physical conditions predominantly treated within primary care.

Using the evidence currently available, the results of this research suggest that policies targeted at identifying and treating depression early in patients with diabetes may lead to a reduction in diabetes related complications and depression, which in turn increase life expectancy and health related quality of life. Although there is an increase in overall health care costs, the results show that this is below the willingness to pay threshold currently considered acceptable in England.

1. Introduction and decision problem

1.1 Background

People who have a long-term condition (LTC) are more likely to have multiple conditions than a single condition [1]. However, historically care has been based around single-disease guidelines, leading to "siloing" of care [2]. There is growing evidence that the presence of comorbid physical and mental conditions has a substantial impact on both healthcare costs and patients' quality of life. For example, it has been estimated that compared to people with a single physical LTC, healthcare costs for people with concurrent physical and mental LTCs are increased by at least 45% [3]. Similarly, results from the World Health Organisation's World Health Survey showed that the presence of depression with a physical LTC had a greater impact on health-related quality of life (HRQoL) than the presence of any two physical LTCs [4].

Diabetes is a long-term condition associated with increased cardiovascular morbidity and premature death [5]. Having diabetes can also result in serious microvascular complications such as amputation, blindness and renal failure [6]. Self-management plays an important role in the treatment of diabetes, however patients with comorbid depression are known to have poorer self-management, leading to lower medication adherence, an increased prevalence of complications and poorer glycaemic control [7]. The effects of comorbid depression on outcomes for people with diabetes are marked; mortality is increased by over a third [8], healthcare costs are 4.5 times higher and use of both inpatient and outpatient services is doubled.[9]

Within England, the National Diabetes Audit (NDA) gives an all-age prevalence of 4.25% for diabetes [9]: NDA estimated that about 5% of all NHS expenditure is on diabetes. People with diabetes are two to three times more likely to have depression compared to the general population [3]. This association follows a socio-economic gradient; data from Scotland showed that within the most affluent decile 13% of people with diabetes had comorbid depression, with this figure rising to 21% in the most deprived decile [1]

Within the NHS, services of care are often centred around individual conditions, commonly resulting in fragmented care for patients with multimorbidity [10]. There is evidence that addressing comorbid depression amongst people with diabetes leads to improved outcomes and quality of life [3]. For example, one study showed that implementing a 12-month depression treatment program for people with diabetes led to reduced outpatient resource use [11].

NICE clinical guidance on the treatment of depression, both within the general population [12] and amongst individuals with a chronic physical health problem [13] recommend the use of a stepped-care service model. Stepped-care is based on two key principles [14]. The first principle is that the least burdensome treatment (to both the health care system and the individual) is received first. The second principle is that a self-correcting principle exists; if individuals do not respond to the initial treatment, they are stepped-up to the next least burdensome treatment. There are three different variations on stepped care.

- Pure stepped care: where all individuals start by receiving the least burdensome treatment (step 1).
- Stratified stepped care: where individuals are triaged (by a suitable healthcare professional) at their point of entry to an appropriate step.
- Hybrid stepped care: which includes an element of stratification, but not to the degree of stratified care. For example, acutely suicidal patients may move straight to high-intensity interventions, with all other patients receiving pure stepped care.

There are advantages and disadvantages with each type of stepped care [14]. NICE clinical guidance recommends the use of hybrid stepped care [12]. However, there is wide variation across England in how stepped care services for depression are organised [15].

1.2 Policy context

Within England there are two main initiatives relevant to the integration of diabetes and depression care. The first is an acknowledgement of the importance of physical and mental comorbidities by including an indicator within the Quality and Outcomes Framework (QOF) which asks if people with diabetes and/or chronic obstructive pulmonary disease have been screened for depression. However, as of the 2013/14 QOF this indicator has been removed due to a lack of evidence of its effectiveness [16]. The second is the explicit consideration of physical LTCs (including diabetes) within a number of 'pathfinder' Improving Access to Psychological Therapies (IAPT) services being piloted at selected sites across England. IAPT services were set-up in response to research that showed that, despite effective psychological therapies being available, waiting times for these were commonly in excess of 6 months [17]. It should be noted that these pathfinder IAPT services are in their infancy, and there is currently much uncertainty about how best to improve the care pathway for depression amongst people with T2DM.

1.3 Aims and objectives

The Economic Evaluation Policy Research Unit (EEPRU) was requested by the Department of Health to consider the health economic implications of long-term physical and mental conditions. The aim of this project was to develop a whole pathways model of current NHS services of care for people with diabetes and comorbid depression, to explore and evaluate current health economic outcomes (such as quality of life and healthcare costs) for individuals with both long-term physical and mental conditions, and then consider any possible changes that could be implemented to improve these outcomes. These changes will include improving the screening and identification of comorbid depression, as well as considering different ways of organising treatment care pathways to reduce any potential inefficiencies that may arise by having separate care pathways for each condition (for example, instead of 'siloing' of care, integrating care pathways). By modelling the entire pathway, the potential impact of an intervention at different points in the pathway can be assessed. This allows for a more realistic assessment of the potential impact of any service re-designs along the pathway. While there is scope to undertake a number of evaluations with differing combinations of conditions, the focus of the initial case study is the care pathway for depression amongst adults diagnosed with Type 2 diabetes (T2DM).

2. Review of the literature

The objective of the literature review was to understand the relationship between diabetes and depression to inform the model development and identify evidence that may be used to populate the economic model.

2.1 Reviews

The review of the literature consisted of 3 steps:

1) **Review 1 (Scoping review to inform the model conceptualisation):** Scoping searches were conducted to identify reviews relating to depression in diabetes. These searches were open, aimed at capturing any review of depression in diabetes in order to inform the development of the model. All types of reviews were sought at this stage (i.e. systematic reviews with or without meta-analysis, narrative reviews). Once reviews were identified, a judgement was made about their relevance to inform the model development.

   In addition to being used to inform the model conceptualisation, evidence for specific parameters was sought within the identified reviews once the conceptual model was constructed with input from the advisory group. Preference was given to systematic reviews reporting pooled data. However, non-systematic and narrative reviews were also scrutinised if it was thought that they may contain useful data to inform the model. Results of evidence used in the economic model are described in the modelling section (further details are provided in the relevant parts of section 4).

2) **Review 2 (Searches for individual studies for model parameters):** Targeted searches were conducted to identify individual studies for parameters where no pooled evidence was identified in existing systematic reviews. These parameters were identified by the modellers after development of the model. Reviews were not specifically excluded from these searches, in case any additional reviews not previously identified were found. Due to multiple parameters of interest, exhaustive searching was not possible. Targeted searches were conducted and stopped when citation searching failed to identify further studies of interest. Search terms were kept narrow to maximise precision, and searching was limited to one bibliographic database. No attempts at evidence synthesis were made, and therefore data for these parameters are from individual studies only.

3) **Review 3 (systematic search for individual studies to inform the link between diabetes and depression):** Systematic searches were conducted for individual studies to inform the link between diabetes and depression, i.e. the relationship between T2DM and diabetes-related complications. A more systematic approach was considered for this parameter as it was deemed 'key' to the economic model. The search terms were wider than the targeted searches for model parameters (Review 2), and included additional databases.

2.2 Review 1: Scoping review to inform the model conceptualisation

A scoping review was undertaken to inform the model conceptualisation. Existing reviews on diabetes and depression were sought to understand the evidence available and the link between depression and diabetes.

2.2.1 Identification of studies

Search strategy

The search aimed to identify reviews relating to T2DM and depression to inform the conceptual model development.

Sources Searched

One electronic bibliographic database was searched (Medline). In addition, the reference lists of relevant articles were checked.

Search Terms

A combination of free-text and thesaurus terms was used. A recent Cochrane review of interventions for depression in diabetes identified through initial scoping searches was used to develop keyword strategies) Baumeister et al 2012 [18]. 'Population' search terms (e.g. diabetes, non-insulin dependent, mood disorders, depression, dysthymia) were used to identify any references related to this population. Although searches were not restricted by diabetes type, papers relating to type 1 diabetes (T1DM) were excluded at the sifting stage. Searches were not restricted by outcome to prevent omission of relevant references. A copy of the search strategy used is included in Appendix 1. The searches were undertaken in July 2013.

Search Restrictions

Searches were restricted to human studies but were not restricted by language, date or publication type. Study design was restricted to reviews. The searches were broad and non-English papers were excluded at the sifting stage.

Inclusion and exclusion criteria

Population: Adults with T2DM and comorbid depression. T1DM was excluded unless a review contained papers relating to both T1DM and T2DM. Reviews concentrating on adolescents or children were excluded. Reviews that included other chronic long-term conditions were considered to be potentially relevant if the review also contained data specific to diabetes.

Outcomes: All outcomes measures were considered. No restrictions were applied.

Study type: Systematic reviews, meta-analyses, narrative reviews.

Data extraction strategy

Titles and abstracts of all retrieved papers were read by one reviewer, who excluded papers that did not meet the inclusion criteria. Full papers of the remaining potentially relevant papers were then retrieved. All full papers were read by one modeller who made decisions regarding potential relevance to inform the model conceptualisation and/or parameters. Summary characteristics for the reviews considered to be potentially relevant were extracted by the reviewer, and a summary of these review characteristics was synthesised and is presented in Appendix 2.

Quality assessment

Due to time and resource constraints, no formal quality assessments of individual reviews were conducted.

2.2.2. Results of the scoping review (Review 1)

Quantity and theme of research available

For this review a total of 60 reviews were identified. A full summary of characteristics of these reviews is presented in Appendices 2 and 3. Where possible, numbers of included studies in each review are given, however for narrative reviews it is not possible to provide this information. No preference was given at this stage to systematic reviews and meta-analyses over narrative reviews, although review type was noted. In total, 21 reviews reported systematic searches and meta-analyses/pooled data (Ali et al 2006 [19], Anderson et al 2001 [20], Barnard 2006 [21], Cosgrove et al 2008 [22], de Groot et al 2001 [23], Knol et al 2006 [24], Mezuket al 2008 [25], Rotella and Manucci 2013, Albers et al 2011 [26], Lustman et al 2005 [27], Nouwen et al 2011 [28], Nouwen et al 2010 [29], Van der Feltz-Cornelius et al 2010, Baumeister et al 2012 [18], Wang et al 2008 [30], Ye et al 2011 [31], Smith et al 2007 [32], Serretti et al 2010 [33], Meader et al 2011 [34], Lysy et al 2008 [35], Gonzales 2008); 17 reviews reported systematic searches but no pooled data/meta-analyses (Ali et al 2010, Gavard et al 1993 [36], Katon et al 2007 [37], Korczak et al 2011 [38], Astle et al 2007 [39], Bowser et al 2010 [40], Khozu et al 2011, McIntyre et al 2011 [41], Renn et al 2011 [42], Cimpean et al 2011 [43], Gill et al 2000 [44], Markowitz et al 2011 [45], Snoek et al 2002 [46], Steed et al 2003 [47], Goodnick et al 1995 [48], Wandell et al 2005 [49], Schram et al 2009 [50]); 19 reviews were

narrative reviews (i.e. did not report systematic search methods or meta-analyses) (Dziemidok et al 2011 [51], Popkin et al 2001 [52], Sobel et al 2005 [53], Beardsley et al 1993 [54], Egede and Ellis 2010 [55], Lustman et al 2005 [27], McIntyre et al 2007 [56], Musselman et al 2003 [57], Ramasubbu et al 2002 [58], Jacobson et al 2002 [59], Jakovlievic et al 2007, McIntyre et al 2006 [60], Iwata et al 2009 [61], McIntyre et al 2005 [62], Piette et al 2004 [63], Rustad et al 2011 [64], Agius et al 2010 [65], Sajatovic et al 2010 [66], Egede and Ellis 2006 [67]); and 3 reviews were of unknown methods due to the papers being unavailable (Joss et al 1999 [68], Breitscheidel et al 2010 [69], Lehnert et al 2011 [70]).

Reviews spanned a range of years of publication, with the earliest published in 1993 (Gavard et al 1993 [36]), and the most recent published in 2012 (Rotella and Manucci 2013, Baumeister et al 2012 [18]). Most reviews focused on T2DM, however 2 (Barnard et al 2006 [21], Korczak et al 2011 [38]) focused solely on T1DM, whilst a further 10 focused on both T2DM and T1DM (Anderson et al 2001 [20], de Groot et al 2001 [23], Rotella and Manucci 2013, Lustman et al 2000 [71], Renn et al 2011 [42], Steed et al 2003 [47], Van der Feltz-Cornelius et al 2010, Baumeister et al 2012 [18], Wandell et al 2005 [49], Gonzales et al 2008). In addition, 8 reviews included studies relating not only to diabetes, but also to other long term or chronic conditions (Katon et al 2007 [37], Sobel et al 2005 [53], McIntyre et al 2011 [41], Cimpean et al 2011 [43], Gill et al 2000 [44], Smith et al 2007 [72], Sajatovic et al 2010 [66], Meader et al 2011 [34]).

A thematic analysis of the reviews identified 10 themes. The following section outlines these and the number of reviews focused on each. Whilst some reviews may have discussed more than one theme, the themes under which they have been categorised below reflect the main focus of the review.

Interventions (n=11 reviews)

Reviews of studies exploring the nature and effectiveness of interventions for the treatment of depression in people with diabetes. Interventions were both psychological and pharmacological.

Epidemiology/Comorbidity (n=36 reviews)

Reviews of studies exploring either the epidemiology (incidence/prevalence) or the relationship between depression and diabetes. These reviews may discuss the odds and prevalence of depression in people with diabetes (onset and progression) or proposed risk factors for and biological links between depression and diabetes.

Quality of Life (n=2 reviews)

Reviews of studies evaluating the effect of depressive symptoms on quality of life in people with diabetes.

Shared care (n=2 reviews)[1]

Reviews of studies evaluating the effectiveness of shared care in the treatment of depression in people with diabetes.

Antidepressants and weight (n=1 review)

Reviews of studies exploring weight change associated with antidepressant treatment.

Prevention (n=1 review)

Reviews of studies exploring methods of prevention of depression in people with diabetes.

Screening (n=1 review)

Reviews of studies that assess the effectiveness of screening instruments or programmes used to identify depression in people with diabetes.

Physical activity (n=1 review)

Reviews of studies exploring the association between physical exercise and depressed mood in people with diabetes.

Adherence (n=1 review)

Reviews of studies exploring the relationship between depression and treatment adherence in people with diabetes.

Cost (n=3 reviews)

Reviews of studies examining the costs associated with depression in people with diabetes.

Complications (n=1 review)

Reviews of studies exploring the association between depression and diabetes-related complications.

[1] *See also Van der Feltz-Cornelius 2010 for collaborative care under interventions*

After these potential included reviews were examined, 36 reviews were excluded from consideration. A table of excluded reviews is presented in Appendix 2. A common reason for exclusion is given as 'insufficient data' which is defined as narrative reviews where a comprehensive list of data for each of the included studies was not presented. A second common reason for exclusion was for the review not being 'specific to diabetes'. This is defined as where the review contained data relating to other chronic conditions, but where there was insufficient diabetes data within the review for it to be potentially useful (or where diabetes data were not presented separately).

Reasons for exclusion from *epidemiology/comorbidities*: included insufficient data (n=8): Dziemidok et al 2011 [51], Popkin et al 2001 [52], Sobel et al 2005 [53], Beardsley et al 1993 [54], McIntyre et al 2007 [56], Musselmanet al 2003 [57], Jacobsonet al [59] 2002, Iwata 2009 [61] ; only T1DM data available (n=2) : Barnard et al 2006 [21], Korczak et al 2011 [38]; population not relevant e.g. only bipolar depression/schizophrenia (n=2): Jakovljevic et al 2007 [73], McIntyre et al 2005 [62]; theme not relevant to the model e.g. pathophysiological alterations related to glucose intolerance and diabetes in depressed patients, physical not diabetes-related symptoms (n= 5): Katon et al 2007 [37], Khoza et al 2011 [74], Nouwen et al 2011 [28], Ramasubbu et al 2002 [58], McIntyre et al 2006 [60]; review superseded by more recent review (n=2): Gavard et al 1993 [36], Goodnick et al 1995 [48]; not specific to diabetes (n=2): McIntyre et al 2011 [41], Rustad et al 2011 [64]; review relates to development of diabetes in already depressed patients (n=2): Cosgrove et al 2008 [22], Knol et al 2006 [24].

Reasons for exclusion from *interventions*: review superseded by more recent review (n=3): Snoek and Skinner 2002 [46], Steed et al 2003 [47], Wang et al 2008 [30]; insufficient data available (n=1): (Cimpean and Drake 2011 [43]; not specific to diabetes (n=1): Gill and Hatcher 2000 [75]; paper unavailable (n=1): Joss 1999 [68].

Reasons for exclusion from *shared care*: insufficient data available (n=1): Agius et al 2010 [65]; not specific to diabetes (n=1): Smith et al 2007 [32].

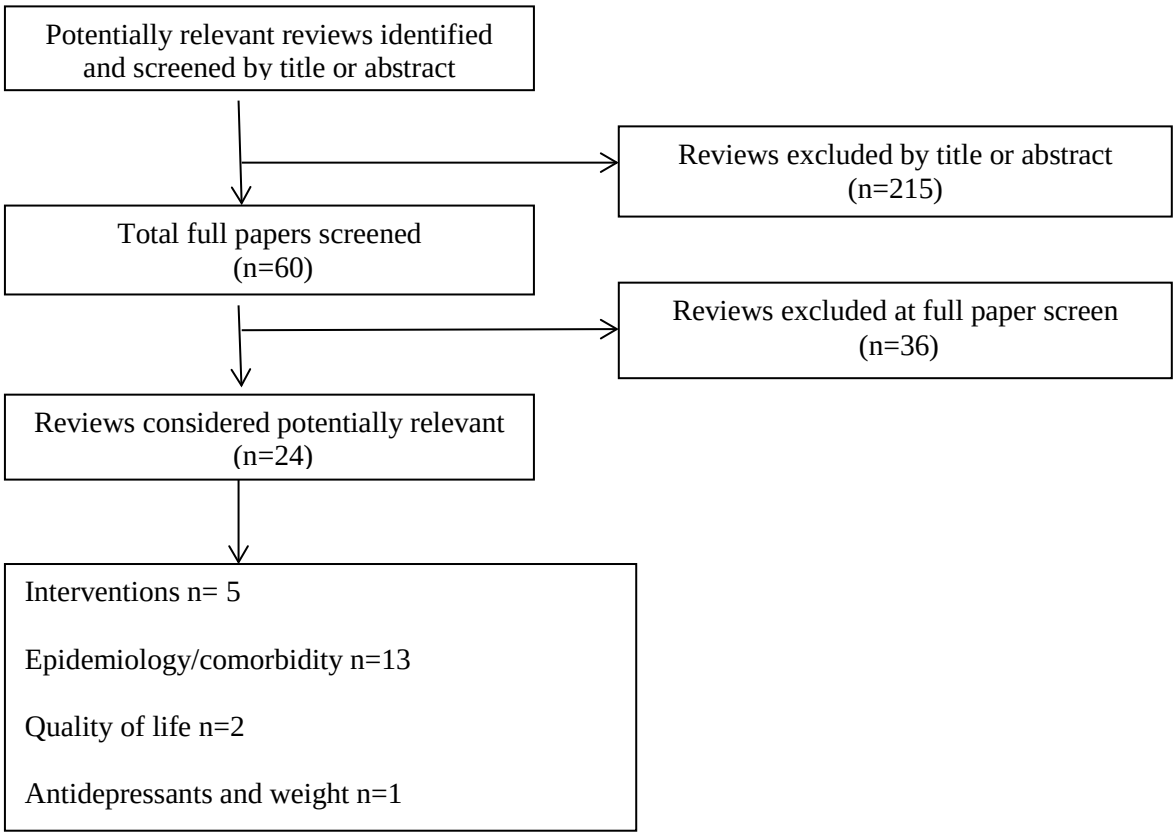
Reasons for exclusion from *prevention*: insufficient data available (n=1): Sajatovic et al [66] 2010.

Reasons for exclusion from *physical activity*: no data reported specifically for the effect of physical activity on depression (n=1): Lysy et al 2008 [35].

Reasons for exclusion from cost: paper not available (n=2): Breitscheidel et al 2010 [69], Lehnert et al 2011 [70]; insufficient data (n=1): Egede 2006 [67].

Overall, 24 reviews were examined in more detail to inform the model conceptualisation and to populate the economic model. These include*: Interventions* (n=5): Baumeister et al 2012 [18]; Markowitz et al 2011 [45]; Piette et al 2004 [63]; Van der Feltz-Cornelius et al 2010 [76]; Ye 2011 [77]. *Epidemiology and/or comorbidity* (n=13): Ali et al 2006 [19]; Ali et al 2010 [78]; Anderson et al 2001 [20]; Bowser et al 2010 [40]; Lustman et al 2000 [71]; Lustman and Clouse 2005 [27]; Nouwen et al 2010 [29]; Renn et al 2011 [42]; Albers et al 2011 [26]; Astle 2007 [39]; Rotella and Manucci 2013; Egede and Ellis 2010 [55]; Mezuk et al 2008 [25]. *Quality of Life* (n=2): Wandell 2005 [49]; Schram et al 2009 [50]. *Antidepressants and weight* (n=1): Serretti and Mandelli 2010 [33]. *Screening* (n=1): Meader et al 2011 [34]. *Adherence* (n=1): Gonzales et al 2008. *Complications* (n=1): de Groot et al 2001 [23]. Tables of summary characteristics for these reviews are presented in Appendix 2. Figure 1 shows the PRISMA flowchart for the included reviews. Section 4 describes these reviews in more detail.

Figure 1: PRISMA flowchart for included reviews



2.2.3 Summary of reviews considered as potentially relevant to the model

2.2.3.1 Review of Interventions

Five reviews were considered to contain potentially relevant data on interventions:

Piette et al 2004 [63]performed a narrative review of depression management for patients with diabetes (type not specified) with comorbid depression. Methods of searching were unclear, and therefore it is not possible to comprehensively report any inclusion or exclusion criteria that may have been applied. In addition, a full report of the characteristics of included studies was not provided, therefore it is not possible to report numbers of trials or participants. However, the review was considered as potentially relevant due to its focus on the management of depression in diabetes, and how this affects: health-related quality of life; physician activity levels; adherence to self-care regimens; and patient's ability to communicate effectively with clinicians. The review summarised the research findings into both epidemiology and interventions, with included pharmacotherapy; psychotherapy; stepped care; physical activity; and depression management. The review provides a useful conceptual framework for the relationship between diabetes and depression, including an overview of the evidence for these pathways, including how: depression directly affects the quality of life and functioning in patients with diabetes and depression (DM/D); how depression affects the level of physical activity in DM/D; how depression affects self-care behaviours in DM/D; and how depression affects communication with healthcare providers in DM/D. The authors review findings from recent research on therapeutic and health services implications of DM/D. The authors highlight issues within the health services pertinent to the management of depression for patients with diabetes. These include the importance of patient identification and the importance of a 'quality of care review'; proactive and systematic monitoring between outpatient encounters; coordination across providers; increased availability of cognitive behavioural therapy and similar approaches; and physical activity to address patients' glucose dysregulation and depressive symptoms. Whilst the review is useful as an overview of issues, no data are available for use within the model, as only a narrative synthesis is offered.

Ye 2011 [77]report a systematic review and meta-analysis of the metabolic effects of fluoxetine in adults with T2DM. Only randomised, placebo-controlled clinical trials were considered for inclusion. Outcomes of interest were body weight loss, fasting plasma glucose, HbA1c, triglyceride and total cholesterol decrement. Weighted mean difference and 95% confidence intervals were reported. Several databases were searched, from inception to 2011. 5 studies were included in the meta-analysis, all of which were double-blind parallel RCTs. The meta-analysis showed that fluoxetine

therapy led to a 4.27kg weight loss (95%CI 2.58-5.97, p<0.00001); 1.41 mmol/L of fasting plasma glucose decrement (95%CI 0.19-2.64, p=0.02) and 0.54 mmol/L of triglyceride reduction (95%CI 0.35-0.73, p<0.00001) compared with placebo. Fluoxetine therapy showed a non-statistically significant 0.78% reduction in HbA1c decrement (95%CI -0.23-1.78). Whilst this review was well-conducted and is recent, its focus on only one pharmacological intervention was considered too narrow to use in the model.

Markowitz et al 2011 [45] reviewed studies evaluating treatments for depression in both T1DM and T2DM. They included adults, children and adolescents. Study designs included either pre-post or controlled trials. Interventions included psychosocial and/or pharmacological, or collaborative care intended to treat depressive symptoms. Studies were excluded if the intervention only consisted of diabetes education or adherence training, or if depression or depression severity was not a main outcome measure. Glycaemic control was also used as an outcome measure, identified through HbA1c levels. The searches covered the years 1995 to 2008 inclusive. The review identified 17 trials, 6 of which were psychosocial interventions, 8 of which were pharmacological interventions, and 3 were of collaborative care. Included studies reported 1,966 participants enrolled in total. The authors report that the evidence for the efficacy of these interventions was mixed. They conclude that the evidence for the effectiveness of psychosocial interventions, particularly cognitive base therapy (CBT), in improving depression is positive. The studies of pharmacological interventions suggested that selective serotonin reuptake inhibitors (SSRIs) are effective in reducing depressive symptoms and preventing relapse, and may also help to reduce HbA1c levels. Tricyclic antidepressants were shown to reduce depressive symptoms but not HbA1c levels, although this conclusion is based on only one study. Finally, collaborative care was concluded to be cost-effective and to improve depression in people with diabetes. However these conclusions are based solely on a narrative synthesis of the evidence, as no attempts at any pooled analyses were made. Whilst the review reported systematic searches, two other recent reviews (Baumeister 2010 [18], Van der Feltz-Cornelius 2010 [76]) of studies of these interventions with similar outcomes of interest reported pooled analyses and therefore only these were considered in more detail. These are summarised below.

Van der Feltz-Cornelius et al 2010 [76] conducted a systematic review and meta-analysis investigating the effectiveness of antidepressant therapies in diabetes. Randomised controlled trials of studies of psychotherapeutic, pharmacological, or health services interventions such as collaborative care interventions were sought. Adult patients with either T1DM or T2DM and a

comorbid depressive disorder such as major depressive disorder (MDD), minor depressive disorder, dysthymic disorder or significant depressive symptoms were included. Depression had to be assessed by a validated questionnaire or diagnostic interview. Outcomes of interest were depressive symptom severity (assessed by validated questionnaires or methods) and glycaemic control (assessed either by HbA1c or fasting blood glucose/fasting plasma glucose (FBG/FPG)). Pooled effect sizes for depressive symptom severity and blood glucose levels were calculated. A combined assessment of illness burden was also calculated, reflecting the impact of the intervention on the general clinical condition of the patients. 15 studies were identified, only 14 of which were included in the meta-analyses due to the comparator of 1 study being another active treatment rather than Care As Usual or placebo. A total of 1724 participants were included in the trials. Five studies investigated a psychotherapeutic intervention, 3 of which combined psychological treatment with diabetes self-management interventions; 7 studies evaluated a pharmacotherapy intervention; and 3 studies evaluated a collaborative care intervention. Results of the overall meta-analysis for T1DM and T2DM of the combined effect of all intervention studies on depressive symptom severity as well as glycaemic control taken together showed a moderate effect in favour of the intervention, with a pooled effect of -0.370; 95% CI -0.470 to -0.271. Subgroup analyses were conducted for changes in severity of depression and glycaemic control as the outcome measures. For severity of depression, interventions had a positive effect on depressive symptom severity -0.512; 95%CI -0.633 to -0.390. For glycaemic control, interventions had a positive but smaller effect: -0.274; 95% CI -0.402 to -0.147. Finally, subgroup analyses were conducted by intervention on combined outcomes (severity of depressive symptoms and glycaemic control). The pooled estimate of collaborative care on combined outcomes was -0.292 (95% CI -0.429 to -0.155); of pharmacological treatment was -0.467 (95% CI -0.665 to -0.270); and of psychotherapy was -0.581 (95% CI -0.770 to -0.391). Strengths of the review were the inclusion of several foreign language studies that had not been previously included in other meta-analyses. Heterogeneity between the studies remained low, despite the inclusion of these studies. Limitations include the use of weighted means for combined measures in order to give an effect size for general clinical impact as an outcome, which the authors acknowledge may be influenced by the possible interdependence of multiple outcomes. This was a well-conducted systematic review and meta-analysis, covering a range of interventions and outcomes, and these data were therefore considered for inclusion in the model.

A recent Cochrane review by Baumeister et al 2012 [18] studied the effectiveness of psychological and pharmacological interventions used to treat depression in adults with either T1DM or T2DM. Depressive disorder was assessed by standardised interviews, self-reports, medical records or

physicians' diagnosis. Controls for psychological interventions had to be 'no intervention' or 'usual care', for pharmacological interventions, controls had to be placebo. Primary outcomes were reduction in depressive symptoms or remission of clinically significant depression, and glycaemic control. 19 trials were identified, with 1592 participants. Of these, 8 trials were of psychological interventions and 8 trials were of pharmacological interventions. Mean differences (MD) with 95% CIs were computed for glycaemic control (HbA1c). Standardised mean differences with 95% CI were computed for depressive symptoms. For remission of clinically significant depression, Odds Ratios (OR) with 95% CIs were computed. Depression scores were reported for short-term (end of treatment), medium-term (1-6 months after treatment), and long-term (greater than 6 months after treatment). Depression remission was reported for short-term, and medium-term. Glycaemic control was reported for short-term, medium-term and long-term. Secondary outcomes included health-related quality of life (short-term, medium-term and long-term). For psychological interventions on depressive symptoms, meta-analyses showed significant heterogeneity for short-term (I_2 = 86%) and were therefore not pooled. For medium-term, intervention was favoured with a combined effect size of 0.42; 95% CI -0.70 to -0.14; p=0.003, although there was substantial heterogeneity. Only one study measured long-term depressive symptoms and therefore there was no meta-analysis. For short-term and medium-term remission, meta-analysis indicated a beneficial effect of psychological interventions (short-term OR 2.88; 95% CI 1.58 to 5.25; p=0.0006), (medium-term OR 2.49; 95%CI 1.44 to 4.32; p=0.001. Evidence regarding glycaemic control was heterogeneous and inconclusive. Meta-analysis also indicated a beneficial effect for pharmacological interventions (Standardised Mean Difference (SMD) -0.61; 95% CI -0.94 to 0.27; p = 0.0004). For depression remission, a beneficial effect for pharmacological interventions was indicated (OR 2.50, 95% CI 1.21 to 5.15; p=0.01). For glycaemic control, a beneficial effect of SSRIs was indicated (MD for HbA1c -0.4% (95% CI -0.6 to -0.1; p=0.002). For pharmacological interventions, heterogeneity was low. Strengths of the review included the inclusion of foreign language papers (as Van der Feltz-Cornelius), although the authors acknowledge that the translation may have resulted in risk of bias. The authors also note higher effect sizes for these studies. Due to the systematic, high-quality methodology and the range of interventions included, the pooled data in this review were considered for inclusion in the model, alongside the Van der Feltz-Cornelius review.

Although overall, results from both reviews were similar, differences in statistical methodology were identified. Table 1 shows studies in common from the 2 reviews.

Table 1: Studies common to both Baumeister et al 2012 [18] and Van der Feltz-Cornelius et al 2010 [76]

Study	Intervention	Baumeister [18]	Van der Feltz-Cornelius [76]
Barragan-Rodriguez 2008 [79]	Pharmacological	YES	NO
DELTA 2006[80]	Psychological	YES	NO
Echeverry 2009 [81]	Pharmacological	YES	YES
Gulseren 2005 [82]	Pharmacological	YES	YES
Huang 2002 [83]	Psychological	YES	YES
Khazaie 2011 [84]	Pharmacological	YES	NO
Komorousova 2010 [85]	Pharmacological	YES	NO
Li 2003 [86]	Psychological	YES	YES
Lu 2005 [87]	Psychological	YES	YES
Lustman 1997 [88]	Pharmacological	YES	YES
Lustman 1998 [89]	Psychological	YES	YES
Lustman 2000 [90]	Pharmacological	YES	YES
Paile-Hyvarinen 2003 [91]	Pharmacological	YES	YES
Paile-Hyvarinen 2007 [92]	Pharmacological	YES	YES
Piette 2011 [93]	Psychological	YES	NO
Qu 2005 [94]	Psychological	YES	NO
Simson 2008 [95]	Psychological	YES	YES
Van Bastelaar 2011 [96]	Psychological	YES	NO
Xue 2004 [97]	Pharmacological	YES	YES
Katon 2004 [98]	Collaborative care	NO	YES
Williams 2004 [99]	Collaborative care	NO	YES
Ell 2009 [100]	Collaborative care	NO	YES

Van der Feltz-Cornelius et al included 3 studies on collaborative care not included in the Baumeister et al review. However, due to the dates of the reviews, the Baumeister et al review includes more recent studies not included in Van der Feltz-Cornelius et al. Methods of outcome assessment varied between reviews. Table 2 shows the differences in reported outcomes between the 2 reviews. The Van der Feltz-Cornelius et al review did not include depression remission. In terms of depression severity, Van der Feltz-Cornelius et al did not differentiate between short, medium and long-term, unlike Baumeister et al. Van der Feltz-Cornelius et al combined outcomes for their meta-analysis of interventions, and combined interventions for their meta-analysis of individual outcomes.

Table 2 Main outcomes investigated

Outcome	Baumeister [18]	Van der Feltz-Cornelius [76]
Depression remission (short-term)	OR 2.88 (95% CI 1.58 to 5.25) favours psychological care over TAU[a] OR 2.50 (95% CI 1.21 to 5.15) favours pharmacological intervention over placebo	Not investigated
Depression remission (medium-term)	OR 2.49 (95% CI 1.44-4.32) favours psychological care over TAU Not investigated for pharmacological intervention trials	Not investigated
Depression severity	SMD -0.61 (95% CI -0.94 to -.027) favours pharmacological intervention over placebo for short-term severity	Cohens *d* -0.512 (95% CI -0.633 to -0.390) positive effect for combined interventions.
Health related quality of life	No significant effect for psychological intervention over Usual Care No pooled analysis for pharmacological intervention (1 study).	Not investigated
Medication adherence/adverse effects	Not pooled	Not investigated
Glycaemic control	Heterogeneous and inconclusive for psychological care MD for short-term glycosylated haemoglobin A1c (HbA1c) -0.4% (95% CI -.06 to -.01) improvement for pharmacological intervention. Not investigated for medium or long term	Cohens *d* -0.274 (95% CI -0.402 to -0.147) positive effect for combined interventions on glycaemic control
Healthcare costs	Not pooled for psychological Not investigated for pharmacological	Not investigated
Combined outcomes	Not investigated	Cohens d -0.292 (95% CI -0.429 to -0.155) effect of collaborative care on pooled outcomes Cohens d -0.467 (95% CI -0.665 to -0.270) effect of pharmacological treatment on pooled outcomes Cohens d -0.581 (95% CI -0.770 to -0.391) effect of

		psychotherapy on pooled outcomes

[a] TAU=Treatment as usual

2.2.3.2 Reviews of epidemiology and/or comorbidity

Thirteen reviews of epidemiology and/or comorbidity were considered for inclusion in the model. Five of these reviews contained pooled data and these five are summarised below.

Rotella and Mannucci 2013 [101]reviewed evidence assessing the incidence of clinical depression or depressive symptoms between people with diabetes compared with people without diabetes. Studies had to be longitudinal observational studies (with either cohort or case-control design); to include an assessment of incidence of clinical depression/depressive symptoms; and to compare the risk of clinical depression/depressive symptoms in subjects with or without diabetes. 16 studies were included in the meta-analysis, with 497,223 participants. Mean follow-up was 5.8 years. Unadjusted and adjusted risk ratios of incident clinical depression/depressive symptoms in subjects with diabetes versus individuals without diabetes are reported. Subgroup analyses of hazard ratios were conducted for body mass index (BMI), medical comorbidity, general psychopathology, concurrent treatments, alcohol, and physical activity. 42,633 incidences of depression were identified. The observed yearly incidence of depression was 1.6% in patients with diabetes, and 1.4% in patients without diabetes, with unadjusted risk 1.29 (95% CI 1.18 to 1.40), and adjusted risk 1.25 (95% CI 1.10 to 1.44). Heterogeneity was high (I_2=71.2). None of the studies included in this review were for UK data, with countries including the US, Netherlands, Spain, Canada, Finland, South Korea and Norway.

Mezuk et al 2008 [25] examined the bi-directional relationship between depression and T2DM. For inclusion, studies had to have a prospective design; include cases of probable T2DM; provide enough data to generate a relative risk estimate; exclude prevalent cases of either depression (for diabetes predicting depression), or diabetes (for depression predicting diabetes onset). Pooled relative risk was calculated from each study. Two separate analyses were conducted: depression predicting T2DM, and T2DM predicting depression. 18 studies were included in the meta-analyses. 13 studies examined depression predicting incidence of depression, with 6,916 cases of diabetes, generating a pooled relative risk of 1.60 (95% CI 1.37 to 1.88). 7 studies examined the association between diabetes and risk of depression, with 6,414 incidences, generating a pooled relative risk of 1.15 (95% CI 1.02 to 1.30). The review included studies from multiple countries (USA, Sweden, Netherlands, Japan), with one UK study included (Kumari et al 2004[102], which studied a range of social and other risk factors for the development of T2DM in an occupational sample. Depression was included as one of the risk factors.)

Anderson et al 2001 [20] estimated the odds and prevalence of clinically relevant depression in adults with T1DM or T2DM. The review sought all available studies that identified clinically relevant depression, including major depressive disorder as well as minor and subsyndromal depression. Depression was assessed by diagnostic interview or self-report symptom scales (e.g. Beck Depression Inventory). Odds ratios were calculated for controlled studies (i.e. had a group without diabetes). Depression prevalence was calculated as an aggregate mean, weighted by the number of subjects in the study or grouping of interest. 42 studies were included in the meta-analysis, with a combined sample size of 21,351 participants. 20 were controlled studies, 22 were uncontrolled. 3 controlled studies were exclusively in T1DM, and 8 were exclusively in T2DM, whilst a further 9 were a mix of T1DM and T2DM. 6 uncontrolled studies were exclusively in people with T1DM, 5 were exclusively in T2DM, and 11 were both in T1DM and T2DM. Odds of depression were increased by both T1DM (OR 2.9, 95% CI 1.6 to 5.5, p=0.0003), and T2DM (OR 2.9, 95% CI 2.3 to 3.7) compared to controls without diabetes. Unadjusted prevalence rates for depression in T2DM were estimated at 16.5% for controlled studies, 33.8% for uncontrolled studies, and 27.0% for both controlled and uncontrolled studies. The review includes studies from multiple countries and no distinctions were made between data from different countries/continents. Some of the included studies contained small numbers of participants.

Ali et al 2006 [19] review the evidence for the prevalence and odds ratio of clinically relevant depression in adults with T2DM. A systematic review and meta-analysis was conducted. Clinically relevant depression was identified through self-report or diagnostic interview, and was defined by Anderson's 2001 [20] definition which includes major, minor and subsyndromal depression. Due to perceived limitations of the small sample sizes in the Anderson review, this review included only studies involving more than 50 participants. Only controlled studies were included (i.e. by a group without diabetes). Non-weighted prevalence rates were calculated. 12 studies were included in the review. This is 3 more than the earlier Anderson review, although the 2 reviews only have 5 studies in common, due to the stricter inclusion criteria. Ali did not include studies where control participants were spouses, first-degree relatives or patients with other chronic conditions. Therefore this review includes an additional 7 studies to the Anderson review. For odds ratios of depression in T2DM, 10 studies were analysed to examine the cross-sectional relationship between depression in people with diabetes compared to people without diabetes. This analysis included 18,445 participants with diabetes, and 32,866 without and showed an increased risk of depression in people with diabetes than without OR = 1.77 (95% CI 1.5 to 2.0). Moderate heterogeneity was found (I_2 59%). To test the cause of this heterogeneity, an outlier was removed from the analyses. The

subsequent analysis resulted in an OR of 1.59 (95% CI 1.5 to 1.7), and reduced the heterogeneity to I_2 3%. This OR is lower than the risk identified in the Anderson review. As with the previous systematic reviews, studies were multi-national. No UK studies were identified.

Nouwen et al 2010 [29] conducted a more recent review, searching for studies up to 2009. All included studies were longitudinal, examining the relationship between T2DM and onset of depression. Studies had to specifically exclude patients with prevalent depression at the beginning of the study. Depression was identified either through diagnostic interview or self-report questionnaire, or diagnosis by a physician. Overall incidence per year was extracted as crude incidence of depression divided by follow-up duration, for the whole study population. 10 studies were included in the meta-analysis, with 48,808 people with T2DM. The pooled OR for incidence of depression was 1.24 (95% CI 1.09 to 1.40). Significant heterogeneity was indicated (Q=30.84 df=10; p=0.001). Subgroups analyses were conducted for method of diagnosis of depression. For studies using self-report questionnaires to define depression (n=6), pooled OR was 1.19 (95% CI 1.03 to 1.39), with non-significant heterogeneity (Q=8.03 df=5; p=0.16). For studies using diagnostic criteria to define depression (n=5), a higher risk of depression was identified OR 1.29 (95% CI 1.05 to 1.59). This time heterogeneity was significant (Q=22.42 df=4; p<0.001). Studies were multinational. A further 8 reviews were identified, which, on scrutiny of the full papers, were not considered to be relevant to the economic model requirements. These are summarised and presented in Appendix 3.

2.2.3.2 Reviews of quality of life

Two reviews focusing on quality of life in people with depression in diabetes were identified.

Wandell 2005 [49] reviewed studies of the measurement of health-related quality of life in patients with diabetes in primary care settings in Nordic countries. Whilst the review was not specific to depression in diabetes, predictive factors for impaired HRQoL were sought. T1DM and T2DM were included. Studies were limited to generic questionnaires used to measure HRQoL. Nineteen studies were identified and included in the review; these were from Finland and Norway. The review presented a narrative synthesis of the evidence. Having a psychiatric disorder with diabetes, especially depression, was predictive of reduced HRQoL. In general, HRQoL was identified through use of a range of instruments, including the Swedish Health-Related Quality of Life Survey (SWED-QUAL), reflective of the study settings being Nordic countries, the Medical Outcomes Study Short Form Health Surveys (SF-20, SF-36), and Glaucoma Quality of Life (GQL). None of the studies reported results using the EQ-5D, which is the preferred instrument for the current project.

Schram et al 2009 [50] reviewed the impact of depressive symptoms on quality of life in individuals with diabetes. Studies had to compare quality of life in individuals with diabetes with or without depression or depressive symptoms. Searches identified studies up to 2007. Generic, domain specific and disease specific measure of quality of life were included. Depression was identified through diagnostic interview or self-report questionnaire. 20 studies were included in the review. 18 were cross-sectional, and 2 were longitudinal. Both T1DM and T2DM were included. A range of measures for quality of life were utilised Activities of Daily Life (ADL), Instrumental activities of Daily Life (IADL), SF-36, SF-28, SF-12, World Health Organisation Quality of Life Assessment Brief version (WHO QOL-BREF), Diabetes Quality of Life Measure (DQOL). No meta-analysis was conducted, but data were presented for individual studies. All studies reported a negative association between depressive symptoms and quality of life in people with diabetes. This review was broader than the Wandell review, as it did not limit by country, and included studies from the US, Australia, Finland, Hawaii, Turkey and Germany. Three UK studies were identified, Paschalides 2004[103], a cross-sectional study of 792 individuals with T2DM. This study used the Center for Epidemiological Studies (Depression) (CES-D) instrument to identify depression, and the SF-12 to measure quality of life. Pouwer 2005[104] used a cross-sectional design to study 539 individuals with T1DM or T2DM in the UK, the Netherlands and Croatia, identifying depression with the CES-D, and measuring quality of life with PAID. Finally, Kohen 1998[105] conducted a cross-sectional study of 100 individuals with T1DM or T2DM using Hospital Anxiety and Depression Scale (HADS) to identify depression, and the SF-28 to measure quality of life.

One review examined the relationship between antidepressant medication and body weight (Serretti and Mandelli 2010).

2.2.3.3 Review of screening

One review was identified which was relevant to the theme of screening.

Meader et al 2011 [34] sought to define the most effective tool for use in consultations to detect depression in people with chronic conditions. A systematic review and meta-analysis of diagnostic accuracy was conducted to assess the sensitivity and specificity of widely used instruments used for this purpose. The reference standard was diagnosis by Diagnostic and Statistical Manual of Mental Disorders (DSM) or International Classification of Diseases (ICD). Pooled estimates of sensitivity, specificity and likelihood ratios were calculated. Table 3 shows the pooled sensitivity and specificity of all instruments identified in the review.

Table 3: Pooled sensitivity and specificity of instruments for screening of depression in chronic illness from Meader et al. 2011 [34]

Instrument	Sensitivity (95% CI)	Specificity (95% CI)
PHQ-9	0.84 (0.69 to 0.92)	0.88 (0.83 to 0.91)
Two stem questions	0.98 (0.85 to 0.99)	0.86 (0.70 to 0.94)
BDI	0.83 (0.79 to 0.87)	0.79 (0.74 to 0.84)
BDI (non somatic items)	0.83 (0.68 to 0.92)	0.79 (0.70 to 0.85)
Center of Epidemiological Studies - Depression	0.77 (0.71 to 0.85)	0.85 (0.80 to 0.90)
Geriatric Depression Scale-30	0.79 (0.73 to 0.84)	0.73 (0.67 to 0.79)
Geriatric Depression Scale-15	0.84 (0.78 to 0.88)	0.77 (0.73 to 0.81)
One item	0.73 (0.60 to 0.83)	0.77 (0.62 to 0.88)
General Health Questionnaire-12	0.81 (0.70 to 0.89)	0.64 (0.52 to 0.75)
General Health Questionnaire-28	0.90 (0.79 to 0.96)	0.80 (0.62 to 0.90)
HADS - depression	0.75 (0.67 to 0.81)	0.81 (0.74 to 0.86)
Hamilton Depression Rating Scale	0.81 (0.75 to 0.86)	0.85 (0.76 to 0.91)
Zung Self Rating Depression Scale	0.78 (0.56 to 0.91)	0.92 (0.68 to 0.98)

PHQ-9: 9-item Patient Health Questionnaire; BDI: Beck Depression Inventory; HADS: Hospital Anxiety and Depression Scale.

An important factor when considering diabetes with comorbid depression is the prevalence of undiagnosed comorbid depression. Although the Meader et al review includes any chronic conditions and is not specific to diabetes, the sensitivity and specificity of screening tools is an important indicator of how much depression is identified [34]. Hence this study was deemed to be of potential use for the economic model.

One review identified focused on the effect of depression on diabetes treatment non-adherence. Gonzalez et al 2008 [106] conducted a systematic review and meta-analysis to examine the relationship between depression and non-adherence in patients with T1DM and T2DM. Effect size r was calculated for meta-analysis. Treatment adherence was the primary outcome measure. This was defined as adherence to medication, dietary recommendations, exercise, glucose monitoring, foot self-care, scheduled medical appointments, or overall adherence composite measures. 47 studies were included, with 17,319 participants. Results of the meta-analysis indicated a significant association between depression and poorer self-care ($p<0.0001$), and a weighted effect size ($r=0.21$, 95% CI 0.17 to 0.25). Individual analyses were conducted by type of self-care. Foot care was the only self-care type that was non-significant. Of the others, the largest effect size was for missed medical appointments ($k=4$, $r=0.31$, 95% CI 0.29 to 0.34). Based on the results of the conceptual modelling it was decided that the association between depression and diabetes non-adherence would not be

explicitly included within the economic model (see Section 5.8). Instead, the association between depression and diabetes non-adherence was implicitly included within the economic model via the impact of depression on the development of diabetes-related complications.

Another review considered as potentially relevant to the model was a systematic review and meta-analysis on the association of depression and diabetes-related complications. De Groot et al 2001 [23] examined the strength and consistency of the relationship between depression and diabetes. Adults with either T1DM or T2DM were included. Searches captured papers between 1975 and 1999. Only studies with more than 25 participants were included. The relationship between depression and at least one diabetes-related complication of interest had to be studied. These were: diabetes retinopathy, diabetes neuropathy, diabetes nephropathy, end-stage renal disease (ESRD), macrovascular complications such as coronary artery disease, and sexual dysfunction. The relationship between diabetes-related complications and current depression was the focus of the meta-analysis. 27 studies with 5,347 participants were included in the review. 20 studies used self-report methods to identify depression, with the remaining 7 studies using diagnostic interviews. 10 studies were of T1DM only, 5 studies were of T2DM only, and the remaining studies were a mix of both T1DM and T2DM. For all diabetes types and combined complications, a significant association between depression and complications was found r =0.25 (95% CI 0.22 to 0.28). Depression was also significantly association with a range of individual complications: nephropathy weighted r =0.25 (95% CI 0.19 to 0.30); neuropathy weighted r 0.28 (95% CI 0.22 to 0.34); sexual dysfunction weighted r=0.32 (95% CI 0.22 to 0.42); macrovascular complications weighted r 0.20 (95% CI 0.16 to 0.24); and retinopathy weighted r=0.17 (95% CI 0.17). The association between depression and diabetes-related complications is key to the model. No other meta-analyses for complications were identified, however the searches in the de Groot review only cover the period up to 1999, and it is therefore likely that more recent individual studies have since been published.

The literature review of reviews identified a range of useful pooled data that may be used to populate the model. A full description of the decision-making process for the selection of data to be used in the model is provided in section 4. However, there was a lack of data in some areas. In particular, no pooled evidence for the UK prevalence of diabetes was identified. Little useful data was identified regarding the progression of depression in people with diabetes, in particular UK incidence, and recurrence and remission. Whilst the Meader et al [34] review provided a good quality meta-analysis of screening instruments for depression in chronic diseases, no data was provided that was specific to diabetes. Therefore, further targeted searches were subsequently

conducted in an attempt to identify data for these parameters. For complications, whilst the de Groot et al [23] review provided a good quality meta-analysis of both microvascular and macrovascular complications, only studies up to 1999 were included. Therefore, an additional systematic search was conducted for this key parameter, to identify more recent studies that may be considered more appropriate for the model.

2.3 Review 2: Supplementary targeted searches for model parameters

Whilst the scoping review identified reviews that provided pooled data considered relevant to the model, there was insufficient data required for several model parameters. Due to the number and diverse nature of these parameters, it was not possible to perform exhaustive and systematic reviews to identify papers that may contain these data. Therefore a series of targeted searches in Medline were performed to supplement the data identified in the reviews, and data identified through consultation with experts. Reference lists of these papers were studied to identify further papers that may also provide data to supplement the other methods.

2.3.1 Identification of studies

Search strategy

The targeted searches aimed to identify individual studies relating to model parameters where insufficient data were identified through the reviews search. In particular, these were UK prevalence data; progression of depression in T2DM, including incidence, recurrence, relapse and persistence; and screening. To maximise precision, search terms were kept narrow.

Sources Searched

Targeted searches were conducted in Medline. This was followed by secondary retrieval via citation searching of retrieved papers. These searches were supplemented by papers identified through consultation with clinical experts.

Search Terms

The following search terms were applied:

> *UK depression in diabetes prevalence*: depression *and* diabetes *and* prevalence *and* UK.
>
> *Depression progression*: depression *and* diabetes *and* progression; depression *and* diabetes *and* relapse; depression *and* diabetes *and* recurrence; depression *and* diabetes *and* recovery; depression *and* diabetes *and* incidence *and* UK.
>
> *Screening*: depression *and* diabetes *and* screening

Search Restrictions

No formal restrictions were applied to the searches and non-English papers were excluded at the sifting stage.

Inclusion and exclusion criteria

Population: Adults with T2DM and comorbid depression. T1DM was excluded as were studies involving just adolescents and children.

Outcomes: Model parameters for which no suitable data had been retrieved from the reviews search were targeted. These included data relating to UK prevalence of depression in T2DM; depression progression in adults with diabetes, including incidence, recovery, relapse, remission; and screening for depression in adults with T2DM.

Study type: RCTs, non-RCTs, observational studies.

Data extraction strategy

Titles and abstracts of all retrieved papers were read by one reviewer, who excluded papers that did not meet the inclusion criteria. Full papers of the remaining potentially relevant papers were then retrieved. All full papers were read by one modeller who made decisions regarding potential relevance to the model. Summary characteristics for the studies considered to be potentially relevant were extracted by the reviewer, and a summary of these study characteristics was synthesised. A more detailed description of each study is presented in section 2.3.4.

Quality assessment

Due to time and resource constraints, no formal quality assessments of individual studies were conducted.

2.3.2 Results of targeted searches

Targeted searches were conducted for: UK prevalence of depression in T2DM; depression progression in adults with diabetes, including incidence, recovery, relapse, remission; and screening for depression in adults with T2DM. These searches provided the following supplementary studies considered to be of potential use to the model:

Baseline:

Prevalence of depression in diabetes (UK): Citations retrieved: 19. Papers satisfying inclusion criteria: 3: Skinner et al 2010 [107]; Das-Munshi et al 2007 [7]; Ali et al 2009 [108].

Depression progression:

Progression: Citations retrieved: 167. Papers satisfying inclusion criteria: 3: Molife et al 2010; Rustad et al 2011 [64]; Bruce et al 2005 (but insufficient data for these papers to be useful. However, see citation searching below for further results.

Recovery: Citations retrieved: 93. Papers satisfying inclusion criteria: 0

Incidence (UK): Citations retrieved: 5. Papers satisfying inclusion criteria: 0

Relapse: Citations retrieved: 35. Papers satisfying inclusion criteria: 2: Ell 2012 [109]; Lustman 1997 [110]

Recurrence: Citations retrieved: 82. Papers satisfying inclusion criteria: 0

Screening:

Citations retrieved: 477. Papers satisfying inclusion criteria: 2: Fleer et al 2013 [111]; Pouwer et al 2011 [112].

Secondary retrieval via citation searching of retrieved papers yielded an additional 5 papers of potential relevance. These were: *Recurrence*: Lustman et al 2006 [113]; Bot et al 2010 [114] *Progression*: Peyrot et al 1999 [115]; Nefs et al 2012 [116]; Fisher et al 2008 [117]. Results of these searches are presented in table 4 below.

A table of summary characteristics of all studies identified through targeted searching and citation searching can be found in Appendix 4. A more detailed summary of these studies can be found below in section 2.3.4. Three studies describe UK data for prevalence of depression in diabetes. Ali et al 2009 [108] reported data from a cross-sectional study of T2DM and T1DM, with a total 6,230 patients, whilst Skinner et al 2010 [107] records prevalence of depression in 824 newly diagnosed T2DM patients from an RCT. Das-Munshi et al 2007 [7] report results from a cross-sectional survey, which identified 249 individuals with diabetes. Depression was diagnosed differently in each study. Ali et al 2009 [108] used medical records to identify patients in receipt of antidepressants or with case documentation of depression; Skinner et al [107] identified depression using the HADS); and Das-Munshi et al [7] assessed psychiatric morbidity using the Revised Clinical Interview Schedule.

Table 4: Results of targeted searches for specific parameters

Topic (specific search term)	Number of citations retrieved	Papers satisfying inclusion criteria	Papers identified through secondary retrieval
UK prevalence of depression in diabetes UK (UK prevalence)	19	N=3 Skinner et al 2010 [107] Das-Munshi et al 2007 [7] Ali et al 2009 [108]	
Depression progression in diabetes (progression)	167	N=3 (but only used for secondary retrieval) Molife et al 2010 [118] Rustad et al 2011 [64] Bruce et al 2005 [119]	
Depression progression in diabetes (UK incidence)	5	N=0	N=2 Nefs et al 2012 [116] Bot et al 2010 [114]
Depression progression in diabetes (relapse)	35	N=2 Ell et al 2012 [109] Lustman et al 1997 [110]	N=3 Lustman et al 2006 [113] Peyrot et al 1999 [115] Fisher 2008 [117]
Depression progression in diabetes (recurrence)	82	N=0	
Screening (screening)	477	N=2 Fleer 2013 [111] Pouwer 2011 [112]	

Seven studies were identified that reported data of potential relevance to the progression of depression in people with diabetes. Two studies reported data relevant to the incidence of depression in T2DM (Nefs et al 2012 [116], Bot et al 2010 [114]); Five studies report data relating to the recurrence, persistence or relapse of depression in T2DM (Lustman et al 1997 [110], Fisher et al 2008 [117], Lustman et al 2006 [113], Nefs et al 2012 [116], and Peyrot 1999 [115]); and one study reported data on symptom deterioration (Ell et al 2012 [109]). Duration of follow-up ranged from 6 months (Peyrot 1999 [115]) to 1 year (Lustman et al 2006 [113]); Eighteen months (Fisher et al 2008 [117]); Two years (Bot et al 2010 [114], Nefs et al 2012 [116], Ell et al 2012 [120]) to the longest follow-up of 5 years (Lustman et al 1997 [110]). Depression was assessed using a range of methods: The Centre for Economic Studies Depression Scale (Bot et al 2010 [114], Peyrot 1999 [115], Fisher et al 2008 [117]); Edinburgh Depression Scale (Nefs et al 2012 [116]); Depression Interview and Structured Hamilton Scale (DISH) (Lustman et al 2006 [113]); DSM-III-R (Lustman et al 1997 [110], Lustman et al 2006 [113]); Patient Health Questionnaire (PHQ-9) criteria for Major Depressive Disorder (Ell et al 2012 [121]).

2.3.4. Summaries for included studies from targeted searches

2.3.4.1 Prevalence of depression in diabetes in the UK.

Three individual studies were retrieved that reported data of potential use for prevalence of depression in diabetes in the UK.

Das-Munshi et al 2007 [7] report findings of the UK National Psychiatric Morbidity Survey (reporting on results from the 2000 survey). The study aimed to estimate the prevalence of psychiatric morbidity in individuals with diabetes using data from a cross-sectional survey of a representative sample of the UK adult population. Psychiatric morbidity was identified through use of the Clinical Interview Schedule. Diabetes was identified through self-report or by reported use of insulin or hypoglycaemic medication. Odds ratios were calculated to summarise the association between diabetes and common mental disorders. Out of 8,580 participants, 249 individuals were identified as having diabetes. Out of 249 individuals with diabetes, 5 met the criteria for depression (1.6%). This is compared to a rate of 1.1% of individuals without diabetes (OR 1.5; 95% CI 0.6 to 4.0). Limitations include the small number of individuals with diabetes identified in the study. Also, although the paper is from 2007, the data is from the 2000 survey and this has now been superseded by a more recent survey.

Skinner et al 2010 [107] reports data on the prevalence of depression from the DESMOND trial (UK). The study provides post-hoc analysis of data from an RCT. Eight hundred and twenty four individuals who were newly diagnosed with T2DM (i.e. referred to the study within 6 weeks of diagnosis) were included in the study. Depression was identified using the HADS. Data was collected at baseline and then 4, 8 and 12 months. Out of 739 individuals who completed the baseline depression questionnaires, 12% were identified as depressed at baseline; 13% were identified as depressed at 4 months; 12% were identified as depressed at 8 months; and 14% were identified as depressed at 12 months. There was no significant increase in the rate of depressive symptoms compared with data from a normative population. This study is unique in that it provides data for newly diagnosed individuals with T2DM, however it may be that depressive symptoms develop over a longer period of time and this longer term prevalence data is not captured here.

Ali et al 2009 [108] reports a large scale cross-sectional study examining the prevalence of depression amongst a sample of South Asians and white Europeans in Leicester, UK. Computerised medical records were scrutinised for 6,230 patients with diabetes attending a clinic between 2003 and 2005. Depression was identified by documentation of depression, or by receipt of

antidepressant medication. The sample consisted of 1405/6230 with T1DM, and 4781/6230 with T2DM. Of those with T2DM, 2,212 had medical comorbidities (coronary heart disease, cerebrovascular disease, asthma, chronic obstructive pulmonary disease, heart failure, peripheral vascular disease, inflammatory bowel disease, irritable bowel syndrome, epilepsy, hypothyroidism, transient ischaemic attack, fibromyalgia or malignant neoplasm, as identified through electronic patient records), and 2,244 had diabetes-related complications (peripheral neuropathy, diabetes retinopathy, nephropathy, neuropathy, or microalbuminuria). 435/4781 (9.3%) met the criteria for depression. This compared with 8% for T1DM. Due to the design of the study, there was no normative population to compare this prevalence data with. Data is compared for South Asians and white Europeans. Prevalence estimates of depression in diabetes have been shown to vary widely. The authors note studies that have found higher prevalence rates in clinical compared to population settings (Anderson et al 2001). [20] They also suggest that due to the method of defining depression, the possibility of under-reporting may represent an underestimation of the prevalence of depression. Nevertheless, the study offers recent data on depression prevalence in a large sample of individuals with T2DM in the UK.

2.3.4.2 Progression of depression in diabetes

Seven individuals studies were retrieved that looked at the progression of depression in people with diabetes.

Lustman et al 1997 [110] reports data on the recurrence or persistence of depression in patients with diabetes in the US. This was a 5 years follow-up study of 25 patients with diabetes from a previous trial. Depression was identified using DSM-III criteria, broken down by severity. Recurrence or persistence occurred in 23/25 patients, with an average 4.8 depressive episodes over the 5 year period. As this is a follow-up of an intervention study, the paper reports data by groups according to whether or not participants had successfully responded to the antidepressant drug nortryptaline. The groups were therefore: nortryptaline responders/non responders; placebo responders/non responders. Whilst the study gives an insight into the progression of depression individuals with diabetes over time, it is unlikely to be useful for the model as the sample is small.

Ell et al 2012 [109] studied depressive symptom deterioration in a sample of Hispanic patients with diabetes (type not specified) in the US. A sub-cohort of 193 patients was recruited from a previous trial. All patients had been identified with major depression at baseline, had received a collaborative

care intervention or enhanced usual care, and no longer met the criteria for depression at 12 months post intervention. Major depressive disorder was defined by having at least one of the two cardinal depression symptoms more than half the days to nearly every day over the past two weeks, and scoring >10 on PHQ-9. Symptom deterioration was defined as meeting the criteria for major depression at 12 or 18 months among those who did not meet the criteria at 12 months. Rates of depressive symptom deterioration were 35.2% (intervention group) and 35.3% (care as usual group). The study had a relatively small sample size and a homogenous population of a low-income ethnic minority group.

Lustman et al 2006 [113] used an RCT design to study the effect of sertraline on the recurrence of depression in a sample of 152 patients with T2DM who had previously recovered from depression. Major depression was defined by the Depression Interview and Structured Hamilton Scale, and the BDI. Time to recurrence for the treatment group and placebo group was the primary outcome. Proportional hazard ratios were calculated. The sertraline group were less likely to have recurrent depression than the placebo group HR 0.51 (95% CI 0.31 to 0.85). The study provides some useful data on the effect of antidepressant medication on prevention of recurrence of depression in diabetes, however due to the RCT design and the relatively small sample size, the utility of this data for use in the model may be limited.

Bot et al 2010 [114] report a follow-up study originally designed to evaluate the effect of a stepped care intervention on depressive symptoms in patients with diabetes and sub-threshold depression. A sample of 114 patients with diabetes (T1DM and T2DM) was recruited. Individuals with major depression at baseline were excluded. 73 participants remained in the study at 2 year follow-up. The main outcome was incidence of major depression during the 2 year follow-up, with depression initially identified by diagnostic interview (MINI), and assessed by the CES-D at follow-up. Incidence of major depression at follow-up was 42%. Baseline depression severity related to the onset of major depression (OR 1.08; 95% CI 1.00 to 1.18, p=0.02). The type of intervention originally received was not related to incidence of major depression during 2 year follow-up (OR 1.25; 95% CI 0.49 to 3.18, p=0.64). As with previously described studies, the study findings are limited by small sample size. Results are also limited due to the fact that the data was based on a trial designed to evaluate a stepped care intervention, and the identification of incidences of depression was only a secondary aim.

Peyrot 1999 [115] conducted a study to determine the level and pattern of persistent depressive symptoms amongst adults with T1DM or T2DM. Two hundred and forty five adults who had completed a one week diabetes education program were recruited. These were either self-referred or referred by community physicians. Depression was identified by self-report questionnaire (CES-D), administered at 3 time points: the beginning and end of the trial period, and at six months follow-up. 93/245 participants were depressed at pre-intervention, 152/245 were not depressed. Post-intervention 44/93 of the depressed group were still depressed, and 49/93 were not depressed. 9/152 of those who were not previously depressed developed depression, and 143/152 who were not previously depressed, were still not depressed. At 6 month follow-up 32/44 of those depressed were still depressed, with 12/44 who were previously depressed no longer depressed. 31/49 who were not depressed were still not depressed. Data is further broken down by on-going depression groups. The study provides a useful indication of the progression of depression over time in individuals with diabetes, although it is now fairly dated, and, again is limited by a small sample size.

Fisher et al 2008 [117] report data from a longitudinal study of 506 patients with T2DM. A normative sample using data from the National Comorbidity Study Revised was used to compare results. The study reported the prevalence and correlates of mood disorders in adults with T2DM over time. Outcomes were MDD, as assessed by the CES-D; dysthymia, as assessed by the Composite International Diagnostic Interview (CIDI); and depressive affect and diabetes distress, as assessed by the Diabetes Distress Scale (DDS). Outcomes were recorded at three time points. Point prevalence for each condition was reported for time 1, prevalence at 18 months was reported, and finally persistence was defined as the percentage of patients with any of the conditions at: a single time point, any 2 time points, or all 3 time points. Rates of mood disorders were higher than the normative sample for those with mood disorders – 60% higher for MDD, and 7% for dysthymia.

Nefs et al 2012 [116] report results from a cohort study (DiaDDZoB) of 2,460 primary care patients with T2DM. The study aimed to examine the course (incidence, recurrence/persistence) of depressive symptoms. Depression was identified by a score of >12 on the Edinburgh Depression Scale (EDS). Incidence of depression was determined in a subgroup who scored <12 at baseline. Individuals with a subsequent score of >12 on the EDS were considered incident cases. Depression was labelled as recurrent/persistent if patients had at least one other high EDS score at either follow-up. 630/2460 (26%) of individuals met the criteria for depression at one or more assessments. Prevalence of depression at baseline and each yearly follow-up were as follows: baseline: 320/2460; year 1: 343/2460; year 2: 389/2460. For those with no depression at baseline, incidence of

depression at follow-up was 14% (n=310). Recurrence/persistence in the group with baseline depression was 66% (n=212).

This was a large-scale well-conducted study, providing useful data for the progression of depression in individuals with T2DM.

2.3.4.3 Screening and case-finding

Finally, two individual studies were retrieved that focused on screening and case-finding.

Fleer et al [111] 2012 investigated the willingness of patients with diabetes to participate in a screening program to identify depression. This was an observational study of 499 patients with diabetes. The main outcome of interest was the number of people participating in the screening program. Depressive symptoms were identified by the CES-D, and diabetes distress identified by the Problem Areas in Diabetes (PAID) questionnaire. Patients scoring above cut-off level on the screening questionnaire were offered a diagnostic interview. Three hundred and forty seven completed the screening questionnaire. Out of 499 eligible patients, there were 152 non-responders. 104/347 who were screened scored above cut-off on CES-D or PAID. 70/104 were identified as at risk of clinical depression. 28/104 were identified as at high risk for both depression and diabetes distress. 35/104 were not interested in further screening. 8/104 had received further help already. 5/104 did not show for their appointment. 4/104 cancelled their appointment. 45/104 accepted the invitation to diagnostic interview. 36/104 had an unmet need for which they would like a referral for psychosocial care. For the comparison group who received no formal screening, 6/528 patients were referred for psychosocial care. This study not only provides useful data on the effectiveness of screening programs for identifying depression, but also on willingness to attend for these appointments.

Pouwer et al 2011 [112] tested the effectiveness of an online screening procedure for depression, versus care as usual. The study was a multi-centre parallel RCT. Participants were 223 outpatients with T2DM who had an elevated depression score. One hundred and seven participants received care as usual, 116 were in the screening group. Depression was identified using the Composite International Diagnostic Interview (CIDI), and was assessed at baseline and 6 months follow-up. 2% of men and 21% of women with diabetes were diagnosed with a depressive disorder. 18% of the care as usual group received treatment for depression during the study period. 28% of the screening group received treatment for depression during this period. At 6 months follow-up there was no

significant difference between the groups on depression scores (68% of the care as usual group and 75% of the screening group had an elevated depression score).

These individual studies report data for the progression of depression in diabetes, and the effectiveness of screening for depression in people with diabetes. However several limitations restrict the usefulness of the data for the model, the main one of these being small sample sizes.

2.4 Review 3: Review of the literature on the relationship between diabetes complications and depression

The relationship between depression and diabetes is the "key" component of the economic model linking the diabetes and depression sub-model through complications; therefore a review was conducted to identify evidence on this relationship.

2.4.1 Identification of studies

Search strategy

The scoping search for reviews (Review 1) produced one review of diabetes complications in people with depression (de Groot 2001 [23]). A search was therefore conducted aimed at identifying all studies published since the de Groot review relating to the relationship between diabetes complications and presence/absence of depression, with specific search terms for: congestive heart failure (CHF); ischaemic heart disease (IHD); myocardial infarction (MI); stroke; blindness; ulcer; amputation and renal failure.

Sources Searched

3 electronic bibliographic databases were searched: Medline; PsychInfo and the Cochrane Library.

Search Terms

A combination of free-text and thesaurus terms was used. The previous review of diabetes complications in people with depression was used to develop keyword strategies (de Groot 2001[23]). 'Population' search terms (e.g. diabetes, non-insulin dependent, mood disorders, depression, dysthymia) were used to identify any references related to this population. Searches were not restricted by diabetes type and papers relating to T1DM were excluded at sifting stage. Copies of the search strategies used in each database are included in Appendix 1. The searches were undertaken in October 2013.

Search Restrictions

Searches were restricted to human studies, by English language, and by date (only studies published after the de Groot [23] review were included). There were no restrictions by study design.

Inclusion and exclusion criteria

The initial search was broad, and intended to retrieve studies examining the relationship between diabetes-related complications and depression.

Population: Adults with T2DM and comorbid depression. Studies of only T1DM were excluded as were studies involving just adolescents and children. Studies that included both T1DM and T2DM were included.

Outcomes: The relationship between depression and diabetes complications. Complications could include individual microvascular or macrovascular complications, including but not exclusively CHF, coronary heart disease (CHD); IHD; MI; stroke; blindness; ulcer; amputation; renal failure. Studies where microvascular or macrovascular complications were reported as composite measures were also included. Studies were considered eligible for inclusion if the odds, risk, or prevalence of complications was reported for people with diabetes and depression versus those with diabetes without depression. Studies where depression was the dependent variable were excluded.

Study design: Reviews, RCTs; non-RCTs; cross-sectional studies, and longitudinal studies were eligible for inclusion.

Data extraction strategy

Titles and abstracts of all retrieved papers were read by one reviewer, who excluded papers that did not meet the initial inclusion criteria. Full papers of the remaining potentially relevant papers were then retrieved. Summary characteristics for the studies considered to be potentially relevant were extracted by the reviewer, and a summary of these study characteristics was synthesised and is presented in Appendix 5. A further sift of these full papers was conducted by the reviewer. Papers that did not fit the initial inclusion criteria on scrutiny of the full papers were excluded. The remaining full papers were subsequently examined in regard to the more narrow inclusion criteria.. Papers that satisfied the narrow inclusion criteria were identified, and a full summary of these papers is presented below.

Quality assessment

Due to time and resource constraints, no formal quality assessments of individual reviews were conducted.

2.4.2 Results of systematic search for complications

Quantity of research available

For the initial search for papers examining the association between diabetes-related complications a total of 54 full papers were identified for further scrutiny. A table of summary characteristics of all 54 studies assessed at full paper stage can be found in Appendix 5. One paper was a systematic review (de Groot et al 2001 [23]). A summary of this paper was presented previously. After scrutiny of the remaining full papers, a further 33 papers were excluded. Reasons for exclusion are given in the summary table in appendix 5. Briefly, reasons for exclusion were: protocol only n=1 (Du Burgos [122]-Lunar et al 2012); no link analysed between depression and diabetes i.e. data reported separately for complications n=1 (Dogdu et al 2012 [123]); dependent variable is HRQoL n=3 (Chyun et al 2006 [124], Wexler et al 2006 [125], Verma et al 2010 [126]); dependent variable is healthcare costs n=1 (Boulanger et al 2009 [127]); dependent variable is mortality rate for complication only n=4 (Bot et al 2012 [128], Pan et al 2011 [129], Winkley et al 2012 [130], Egede 2005a [131]; complication and depression or diabetes analysed separately n=4 (Windle et al 2013 [132], Shehatah et al 2010 [133], Huang et al 2010 [134], Al Snih et al 2005 [135]); outcome is too specific n=2 (Wagner et al 2012 [136] for endothelial functioning, Vedhara et al 2010 for ulcer healing only); depression is the dependent variable n=12 (Vileikyte et al 2009 [137], Vileikyte et al 2005 [138], Trento et al 2012 [139], Pan et al 2012 [140], Labad et al 2010 [141], Iversen et al 2009 [142], Icks et al 2013 [143], Findley et al 2001 [144], Egede et al 2005b [145], Willrich et al [146] et al , Savli et al 2005 [147], Shen et al 2010 [148]); focus of study is screening not complications n=1 (Taylor et al 2008 [149]); focus of paper is cognitive function not depression n=1 (Kloos et al 2009 [150]); only T1DM n=1 (Gendelman et al 2009 [151]); paper unavailable n=2 (Williams et al 2010[152], Monami et al 2008 [153]). Figure 2 shows the PRISMA flowchart for the search.

Nineteen papers remained eligible for further consideration for inclusion in the model, with a total of 1,248,163 participants. Five papers studied multiple microvascular complications (Bajaj et al 2012 [154], Sullivan et al 2012 [155], van Steenbergen-Weijenburg et al 2010 [156], Raval et al 2010 [157], Poongothai et al 2011 [158]); six papers studies multiple macrovascular complications (Clouse et al 2003 [159], Sullivan et al 2012 [155], Bhattarai et al 2013 [160], van Steenbergen-Weijenburg et al 2010 [156], Raval et al 2010 [157], Poongothai et al 2011 [158]); five papers reported composite macrovascular complications (Black et al 2003 [161], Sullivan et al 2012 [155], van Steenbergen-Weijenburg et al 2010 [156], Raval et al 2010 [157], Lin et al 2010 [162]); and four papers reported composite microvascular complications (Black et al 2003 [161], Sullivan et al 2012 [155], Raval et al 2010 [157], Lin et al 2010). Of those papers reporting single complications, one paper studied

neuropathy (Kloos et al 2009 [150]); five papers studied coronary-related complications (including MI, CAD, CVD, IHD, systolic heart failure) (Albert et al 2009 [163], Guruprasad et al 2012 [164], Angerman et al 2011 [165], Scherrer et al 2011 [166], Rowan et al 2005 [167]); three papers studied foot ulcers (Altenburg et al 2010 [168], Gonzalez et al 2010 [169], Williams et al 2010 [170],); one paper studied amputation (Williams 2011[171]; and one paper studied renal disease (Young et al 2010 [172]).

All included papers related to adults, with participants aged from 18 to 100. One paper only studied older participants (Black et al 2003 [161]). Clouse et al 2003 [159] only studied women, whilst Black et al 2003 [161] only studied a narrow ethnic group (Mexican-Americans), and Williams et al 2011 [171] only studied US veterans. Eleven studies were of T2DM only (Bajaj et al 2012 [154], Altenburg et al 2010 [168], Guruprasad et al 2012 [164], Black et al 2003 [161], Williams et al 2010 [170], Scherrer et al 2011 [166], , Sullivan et al 2012 [155], van Steenbergen-Weijenburg et al 2010 [156], Raval et al 2010 [157], Lin et al 2010 [162], Poongothai et al 2011 [158]); Four studies were of both T1DM and T2DM (Young et al 2010 [172], Gonzalez et al 2010 [169], Clouse et al 2003 [159], Bhattarai et al 2010 [160]); Three studies did not specify the type of diabetes (Angerman et al 2011 [165], Rowan et al 2005 [167], Williams et al 2011 [171]); and one study specified only insulin-dependent diabetes (Albert et al 2009 [163]).

Nine papers used a cross-sectional study design (Bajaj et al 2012 [154], Angerman et al 2011 [165], Altenburg et al 2010 [168], Albert et al 2009 [163], Guruprasad et al 2012 [164], Bhattarai et al 2010 [160], van Steenbergen-Weijenburg et al 2010 [156], Raval et al 2010 [157], Poongothai et al 2011 [158]); with the remaining ten papers using a longitudinal study design (Lin et al 2010 [162], Young et al 2010 [172], Gonzalez et al 2010 [169], Black et al 2003 [161], Williams et al 2011 [171], Scherrer et al 2011 [166], Rowan et al 2005 [167], Williams et al 2010 [170], Clouse et al 2003 [159], Sullivan et al 2012 [155]). Most papers used a prospective design, with only Williams et al 2011 [171]using a retrospective design.

Depression was diagnosed with a number of different instruments and approaches. Three studies used the BDI (Bajaj et al [154], Altenburg et al 2010 [168], Guruprasad et al 2012 [164]); Eight studies used the PHQ-9 (Angerman et al 2011 [165], Young et al 2010 [163], Williams et al 2010 [170], Williams et al 2011[171], Sullivan et al 2012 [155], van Steenbergen-Weijenburg et al 2010 [156], Raval et al 2010 [157], Lin et al 2010 [162]); two studies used the CIDI (Altenburg et al 2010 [168], Black et al 2003 [161]); two studies used the CES-D (Black et al 2003 [161], Rowan et al 2005 [167]);

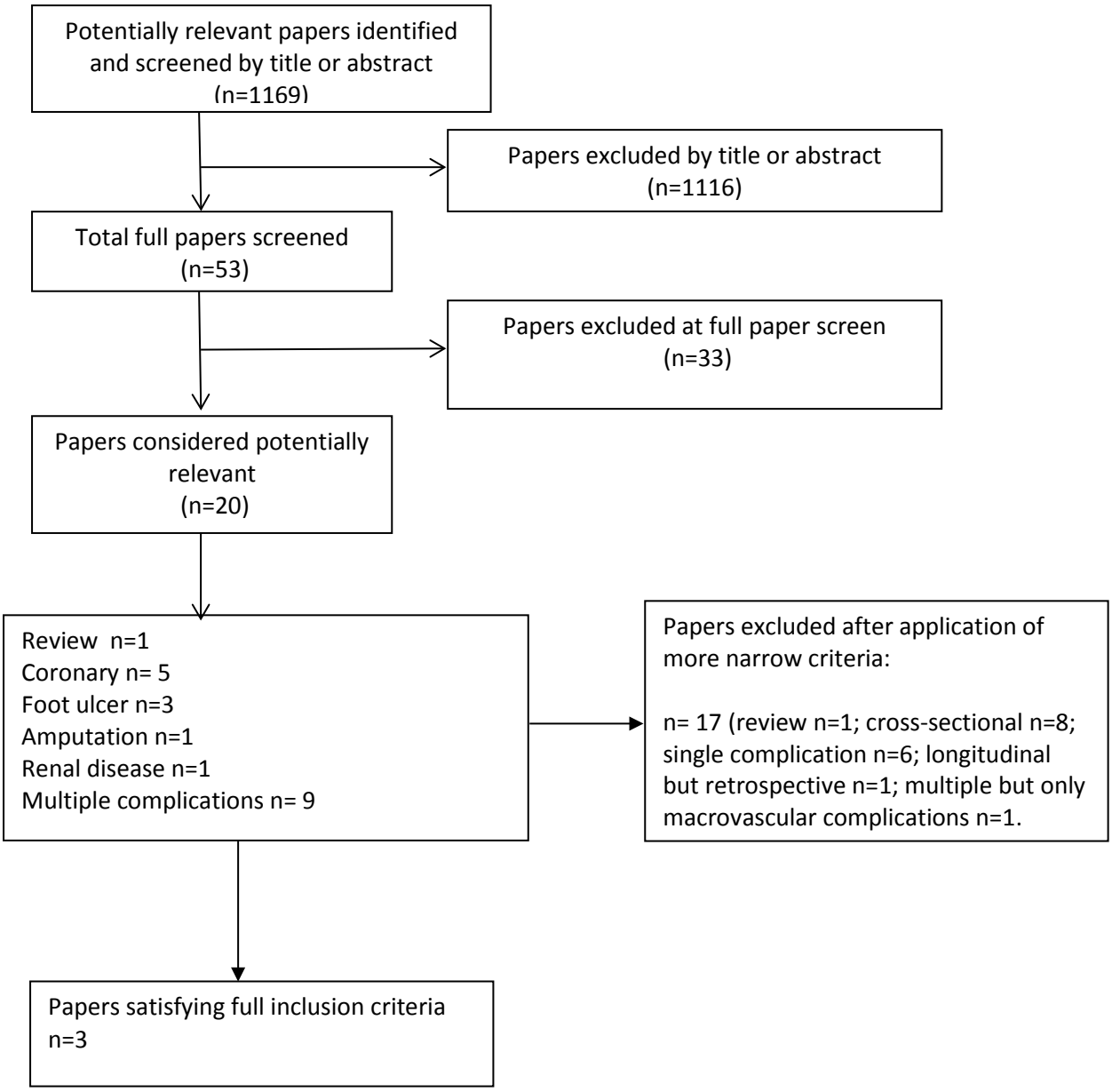
one study used HADS (Gonzalez et al 2010 [169]); one study used a diagnostic interview (Clouse et al 2003 [159]); and one study used the PHQ-12 (Poongothai et al 2011 [158]). four studies reviewed existing medical records to identify depression (Albert et al 2009, Scherrer et al 2011 [166], Williams et al 2011[171], Bhattarai et al 2010 [160]). five papers distinguished between minor and major depression (Black et al 2003 [161], Williams et al 2010 [170], Lin et al 2010 [162]).

Most studies reported the association between depression and diabetes complication as odds ratios or hazard ratios (Gonzalez et al 2010 [169], Black et al 2003 [161], Williams et al 2010[170], Scherrer et al 2011 [166], Rowan et al 2005 [167], Lin et al 2010 [162], Raval et al 2010 [157], Clouse et al 2003 [159], Sullivan et al 2012 [155], Williams et al 2011[171], Bhattarai et al 2010 [160], van Steenbergen-Weijenburg et al 2010 [156], Poongothai et al 2011 [158]); whilst four papers reported prevalence rates of complications as percentages for depressed and non-depressed groups (Bajaj et al 2012 [154], Albert et al 2009 [163], Young et al 2010 [172], Guruprasad et al 2012 [164]). Angerman et al 2011 [165] and Altenburg et al 2010 [168] used linear regression to analyse this relationship.

1) Papers retrieved through this initial sift were examined in more depth, and inclusion criteria were subsequently narrowed in order to retrieve studies more relevant to the model. Inclusion criteria after the first sift were narrowed to include only studies with a prospective longitudinal design, in order to explore causation, and examine the effect of depression on diabetes-related complications over time.
2) Only studies of multiple complications.
3) Only studies where both microvascular and macrovascular complications were assessed, in order to ensure that study design was not a confounding factor when comparing microvascular and macrovascular data.

After application of the more narrow inclusion criteria, sixteen of these papers were excluded, with three satisfying the criteria (i.e. prospective longitudinal, reporting multiple micro- and macrovascular diabetes-related complications). Reasons for exclusion of the remaining papers are included in the summary characteristics table in appendix 5. The final three studies (Lin et al 2010 [162], Sullivan et al 2012 [155], and Black et al 2003 [161]) are summarised below.

Figure 2: PRISMA flowchart for complication search



2.4.4 Summary of papers considered for further inclusion

Three studies remained eligible for inclusion, and were considered for the model. These are summarised briefly below.

Black et al 2003 [161] report a 7 year longitudinal study examining the main effects and interaction effects of diabetes and depressive symptoms on the development of both microvascular and macrovascular complications. Microvascular complications included nephropathy, neuropathy, retinopathy, and amputations. Macrovascular complications included cardiovascular disease, stroke, and kidney disease. Participants were 2,830 Mexican Americans aged 65 or over. Depression was measures in two ways: firstly, depressive symptoms were measured at baseline using the CES-D. Depression was categorised into minimal (subthreshold depressive syndrome); minor, and those without any depressive symptoms. At first follow-up, depressive symptoms were assessed again using the CIDI. Survival analyses indicated that participants with diabetes and minor depression had a risk over 7 years of developing macrovascular complications of HR 2.40, (95% CI 1.71-3.36), compared with a risk for those with diabetes but no depression of HR 1.35, (95% CI 1.06-2.27). For microvascular complications the risk for those with diabetes with minor depression was HR 8.63 (95% CI 5.40-13.79), compared with HR 2.31 (95% CI 1.58-3.39) for those with diabetes with no depressive symptoms.

Sullivan et al 2012 [155] report a 4 year study examining the effects of depression on cardiovascular disease outcomes in people with T2DM. 2,053 participants of the ACCORD HRQL substudy were included in the study. The PHQ-9 was used to identify participants with depression. Major depression was defined as those reporting a score of ≥2 for 5 symptoms, at least one of which is depressed mood or lack of pleasure. A category of a PHQ-9 score of ≥10 was also included. This score has been shown to have 77% sensitivity and 94% specificity to diagnosis of major depression by structured psychiatric interview. 20% of participants were identified at baseline as meeting the criteria for depression. Depression was not found to be associated with the composite outcome of cardiovascular death, nonfatal heart attack or stroke (HR 1.53; 95% CI 0.85 to 2.73), or to the 'microvascular' composite outcome (fatal or non fatal renal failure, retinal photocoagulation, or vitrectomy for diabetes retinopathy) (HR 0.93; 95% CI 0.53 to 1.62). All cause mortality was significantly increased both in those with major depression (HR 2.24; 95% CI 1.24 to 4.06), and those scoring ≥10 on the PHQ-9. (HR 1.84; 95% CI 1.17 to 2.89). Limitations of the study were the method of diagnosis using the PHQ-9, which has high sensitivity but low specificity. Early onset microvascular complications were not measured.

Lin et al 2010 [162]conducted a 5 year longitudinal prospective study to examine the relationship between depression as risk of advanced macrovascular and microvascular complications. This was part of the PATHWAYS follow-up study, where surviving members of the original cohort of patients with T2DM were followed-up after 5 years. Outcomes of interest were advanced macro and micro vascular complications, as identified by medical chart and depression, as identified by the PHQ-9. 3,723 patients were included in the analysis. Depression was broken down into minor and major. Hazard ratios were calculated for the risk of microvascular and macrovascular complications by depression group. Major depression was associated with significantly higher risk of adverse microvascular outcomes (HR 1.36; 95% CI 1.05 to 1.75) and macrovascular outcomes (HR 1.24, 95% CI 1.0 to 1.54). This was a large-scale longitudinal study which presents robust 5 year follow-up data.

Table 5: Summary of the main characteristics for the three studies of diabetes-related complications

Study	**Lin 2010 [162]**	**Sullivan 2012 [155]**	**Black 2003 [161]**
Country	USA	USA	USA
Study duration	5 years	4 years (follow-up at 1, 3 and 4 years)	7 years
Total N	3,723	2,053	2,830
Diabetes type (N)	T2DM	T2DM	T2DM
Duration of diabetes Mean (SD)	8.8 years (+/- 8.4)	10 years (median)	N/R
Sex (F/M)	1,782/1,941	805/1,248	1,657/1,173
Setting	Primary care (from PATHWAYS study)	Participants recruited from ACCORD study (at risk of cardiovascular events)	Hispanic EPESE epidemiological study of community-dwelling Mexican-Americans
Depression assessment method	PHQ-9 at baseline and 5 year follow-up to ascertain probable major and minor depression. Probable major depression required a positive response to one of the two core symptoms (depressed mood or loss of interest) and a total of	PHQ-9 at baseline, year 1, year 3, and year 4. PHQ-9 ≥10; probable major depression; probable minor depression; continuous PHQ-9 score. Rates at which patients met any depression criteria at any time point ('ever depressed') versus not meeting any depression	Depressive symptoms: measured at baseline with the CES-D. 3 categories of depression: minor depression (CES-D score ≥16; minimal depression (CES-D score 1-15); no depressive symptoms (CES-D score of 0). Depressive diagnosis:

Study	Lin 2010 [162]	Sullivan 2012 [155]	Black 2003 [161]
	five positive symptoms for at least the last 2 weeks. Probable minor depression required at least one core symptom and a total of two to four positive symptoms for at least the last 2 weeks.	criteria at any time point ('never depressed').	assessed at first follow-up interview) using modified version of the depression module of the CIDI. Depressive diagnosis included reporting of any lifetime major depressive episode, or lifetime dysthymia.
Complication: Microvascular (assessment method)	End-stage renal disease; low vision or blindness; proliferative retinopathy or photocoagulation procedures for diabetes; foot ulcers; amputations (physician diagnosis; automated laboratory, pharmacy data; chart review).	Fatal or non-fatal renal failure; retinal photocoagulation; or vitrectomy for diabetes retinopathy (N/R)	Nephropathy; retinopathy; neuropathy; amputations (self-report).
Complication: Macrovascular (assessment methods)	Myocardial infarction; stroke; congestive heart failure; cardiovascular procedures (percutaneous coronary artery intervention; coronary artery bypass grafting; abdominal aortic aneurysm repair); revascularization of the lower extremity (physician diagnosis; automated laboratory, pharmacy data; chart review).	Major coronary artery disease events, specifically fatal events; nonfatal myocardial infarction; unstable angina.	Cardiovascular disease; stroke; kidney disease (self-report or physician diagnosis)
All-cause mortality	Not studied	All-cause mortality reported	Not studied
Statistical method used	Proportional hazard ratios to estimate the	Proportional hazards regressions models	Survival analyses to estimate hazard ratios

Study	Lin 2010 [162]	Sullivan 2012 [155]	Black 2003 [161]
	association between depression and adverse outcomes, comparing individuals with minor or major depression to those without depression at baseline.	where outcome is time until first occurrence of each event and predictor of interest is the measure of depression. 4 measures of depression studied: PHQ-9 ≥10; probable major depression; probable minor depression; continuous PHQ-9 score.	and survival function estimates associated with diabetes/depressive symptoms classes: no diabetes/no depressive symptoms; no diabetes/minimal depressive symptoms; no diabetes/minor depressive symptoms; diabetes/no depressive symptoms; diabetes/minimal depressive symptoms; diabetes/minor depression. Diabetes/depressive diagnosis classes: no diabetes/no lifetime depressive diagnosis; no diabetes/lifetime depressive diagnosis; diabetes/no lifetime depressive diagnosis; diabetes/lifetime depressive diagnosis.

PHQ-9: 9-item version of Patient Health Questionnaire; CES-D: Center for Epidemiological Studies – Depression; CIDI: Composite International Diagnostic Interview.

Tables 6-8 summarise the main outcomes reported in these studies.

Table 6: Hazard ratios (95% CIs) for microvascular and macrovascular outcomes from Lin et al 2010

Covariate adjustment	Microvascular complications		Macrovascular complications	
	Minor depression	Major depression	Minor depression	Major depression
Unadjusted	1.54 (1.16-2.03)	1.48 (1.16-1.88)	1.17 (0.92-1.47)	1,20 (0.98-1.47)
Adjusted for any prior event	1.49 (1.13-1.97)	1.47 (1.15-1.87)	1.09 (0.86-1.37)	1.13 (0.92-1.38)
Adjusted for any prior event, demographic characteristics,	1.31 (0.98-1.74)	1.36 (1.05-1.76)	1.00 (0.79-1.27)	1.25 (1.00-1.54)

clinical characteristics, self-care and diabetes control measures				

Table 7: Hazard ratios for macrovascular and microvascular complications from Black et al 2003

Diabetes and depression assessment	Macrovascular complications HR (95% CI)	Microvascular complications HR (95% CI)
Diabetes with no depressive symptoms	1.35 (1.06-2.27)	2.31 (1.58-3.39)
Diabetes with minimal depressive symptoms	3.56 (1.21-2.00)	2.43 (1.90-3.14)
Diabetes with minor depressive symptoms	2.40 (1.71-3.36)	8.63 (5.40-13.79)
Diabetes and lifetime depression	2.64 (1.73-4.04)	11.32 (8.76-15.43)

Table 8: Proportional hazard models of depression predicting macrovascular and microvascular outcomes from Sullivan et al 2012

Predictor	HR (95% CI)	P	HR (95% CI)	P
Composite macrovascular complications				
Major depression	1.42 (0.99-2.04)	0.0552	1.36 (0.95-1.95)	0.0960
Minor depression	1.23 (0.85-1.78)	0.2762	1.23 (0.85-1.78)	0.2762
PHQ continuous	1.02 (1.00-1.04)	0.0247	1.02 (1.00-1.04)	0.0635
PHQ score ≥10	1.14 (0.88-1.49)	0.3261	1.10 (0.84-1.44)	0.4882
Composite microvascular complications				
Major depression	0.93 (0.53-1.62)	0.7929	0.97 (0.56-1.70)	0.9229
Minor depression	1.14 (0.70-1.85)	0.6011	1.14 (0.70-1.86)	0.5972
PHQ continuous	1.01 (0.98-1.04)	0.5197	1.01 (0.99-1.04)	0.3168
PHQ score ≥10	1.27 (0.90-1.79)	0.1804	1.31 (0.93-1.86)	0.1273

PHQ: Patient Health Questionnaire. HR: Hazard ratio. The first set of HRs presented are for the model adjusted for demographic, trial, and clinical variables. The second set of HRs presented are further adjusted for behavioural variables.

The utility of the Black et al [161] study is limited by its use of only elderly (over 65) participants, and of only one ethnic group (Hispanics). The study is however strengthened by its use of both interview and survey for the assessment of depression, and the length of the study, which follows participants for 7 years, the longest of the three studies. Neither Lin et al [173], Sullivan et al [155] nor Black et al [161] consider the treatment of depression in their methods or analyses, therefore it is not known whether or how many participants were receiving psychotherapy/pharmacotherapy for their depression over the course of the studies and how this may have affected the incidence of complications. All 3 studies controlled for baseline characteristics in their analyses, with Lin et al

[173] and Sullivan et al [155] presenting both adjusted and unadjusted hazard ratios. Lin et al [162] studies a greater range of both micro and macrovascular complications than Sullivan et al [155] or Black et al [161]. However, depression diagnosis was limited to one assessment in Lin et al's [162] analyses, whilst Sullivan et al [155] assessed depression over 4 time points in the study, and conducted analyses on a more comprehensive range of diagnoses/incidence of depression. However, participants in the study by Sullivan et al [155] were all at high-risk of cardiovascular disease (because of existing CVD or additional risk factors) and this may affect the interpretation of the macrovascular results when compared to the other studies. All studies used composite outcome measures for micro- and macrovascular complications, rather than reporting data for specific complications. However the review by de Groot et al [23] provided analyses for individual complications and noted that effect sizes were similar for these complications.

2.5 Discussion

The scoping search for reviews of depression in T2DM retrieved 60 reviews, which focused on a diverse range of themes. Whilst the scoping review was not an exhaustive search of the literature, these searches together with studies identified through supplementary targeted searches and the consultation with experts provide an indication of the nature of the current research in this area. Many of the reviews attempted to estimate the prevalence of depression in people with diabetes, producing wide variation in results. None of the pooled data identified in the scoping search related to UK prevalence, and supplementary searches were necessary to attempt to identify such data from individual studies. Further studies conducted in the UK may enhance this body of knowledge, providing an indication of how the UK compares with other countries with regard to estimates of the prevalence of depression in diabetes.

A number of studies relating to the treatment of depression in people with diabetes provided data for two systematic reviews with meta-analyses (Baumeister et al 2012 [18]) and Van der Feltz-Cornelius 2010 [76]) identified in the scoping review. Results from these reviews indicate that both psychological and pharmacological interventions have a positive effect on depressive symptoms in people with diabetes. Future reviews may focus on the mechanisms underlying these observed effects, for example glycaemic control, which was shown by Baumeister et al to improve after pharmacological therapy for depression, and has been implicated as a potential influence in a number of individual studies. Both Van der Feltz-Cornelius et al (2010) and Baumeister (2012) investigated whether treatment for depression had an impact on glycaemic control. Previous studies have indicated a relationship between depression and impaired glycaemic control (Lustman 2000 [71]). Whilst Baumeister et al (2012) found a short-term improvement in depression for pharmacological interventions, Van der Feltz-Cornelius (2010) found only sertraline had an effect on glycaemic control, but this conclusion was based on only one study. There is insufficient evidence to date to conclude that psychological interventions impact upon glycaemic control. Good quality trials with a low risk of bias are suggested in order to explore these issues further.

Direct comparisons for the effectiveness of depression interventions for people with diabetes and/or other long term conditions and people without such conditions are difficult due to different methodologies that have been utilised in such meta-analyses. However, results from the Van der Feltz-Cornelius review [174] showed an effect size of -0.37 for all therapies (psychological, pharmacological or collaborative care) on depressive symptoms in people with diabetes; -0.47 for pharmacological therapies; and -0.58 for psychological therapies. This compares with reported effect

sizes of 0.3 for SSRIs and 0.6 for TCAs on depressive symptoms in people with a range of chronic physical health problems (Taylor et al 2011 [175]), which are similar to effect sizes found in a Cochrane review by Raynor et al 2010 [176] for antidepressants in physically ill people. For depression not associated with physical illness, Turner et al 2008 [177] report effect sizes of 0.2 to 0.6 for antidepressants. For psychological therapies for depression not associated with physical illness, effect sizes of 0.34, 0.32 and 0.31 have been reported by Cuijpers et al 2013 [178], Turner et al 2008 [177], and Kirsch et al 2008 [179] respectively.

The scoping review did not identify sufficient pooled data to populate all model parameters. In particular, little pooled data was identified relating to the progression of depression in T2DM i.e. incidence, recurrence, and relapse, or relating to screening for depression in T2DM. Supplementary targeted searches identified 12 studies that reported data that may be useful for these parameters, although these are individual studies rather than pooled data from meta-analyses. As the papers identified by the current review do not represent an exhaustive search of the literature, it is not possible to conclude that these few studies are representative of the whole literature, however, more large-scale prospective longitudinal studies that track the trajectory of depressive symptoms in people with diabetes over time may usefully add to the current evidence.

The review of the complications literature looked for studies published after the de Groot et al (2001)[180]review of the association between depression and diabetes-related complications. Meta-analyses conducted by the authors only included cross-sectional studies, and therefore whilst the results showed a positive association between depression and both micro- and macrovascular complications, no conclusions with regards to causality can be drawn. The current review showed that since 2001, the literature has progressed in the area, with a number of prospective longitudinal studies published, for a range of both micro- and macrovascular complications. Whilst no pooling of data was attempted for the current review, results from three individual studies suggest that depression may predict a number of these complications. Future studies may improve understanding further by use of diagnostic interview for the assessment of depression rather than reliance of self-report questionnaires, and there appear to be only a few studies that assess depression over multiple time points. Such studies are needed in order to further explore the nature of this relationship over time.

Limitations

Limited time and resources meant that no formal quality assessment of studies was undertaken. Data extraction was limited to key outcomes only, and, for individual studies identified during targeted searching and for the complications search, no attempt at evidence synthesis was undertaken. In addition, searching for individual studies was not exhaustive. However, in line with requirements of the NICE reference case, data used for parameters relating to the effectiveness of interventions was drawn from pooled data where such evidence was available [181].

3. Review of existing health economic literature

A review of the literature of existing economic evaluations of interventions/policy targeted at patients with both diabetes and comorbid depression was carried out, with the aim of identifying existing health economic models that could be used to inform the development of the de-novo economic model, inform model parameters and/or provide some indication of the effects of interventions targeted at patients with both diabetes and comorbid depression.

3.1 Methods

The authors were aware of two recent systematic reviews of economic evaluations that considered interventions for depression in patients with diabetes [182;183].

Molosankwe et al. (2012) [182] performed a systematic review of the economic aspects of the association between diabetes and depression. Eleven databases (PubMed/MEDLINE, EMBASE, PsychINFO, CINAHL, EconLit, IBSS, ASSIA, NHS Economic Evaluation Database (NHS EED), European Network of Health Economic Evaluation Databases (EURONHEED), Western Pacific Region Index Medicus and the Cochrane Library) were searched from 1980 until June 2011. The authors identified 62 papers, of which 47 examined the impact of having comorbid depression on health care and other resource utilisation, and 15 were economic evaluations. Of the 15 identified economic evaluations, one study was conducted in the UK, 3 studies were conducted in Germany (but the studies were ongoing and only the protocols were available), 2 studies were conducted in the Netherlands and 9 studies were US-based.

More recently, Jeeva et al. (2013) [183] conducted a review of the literature to identify economic evidence of psychological treatments for depression amongst people with diabetes. Five datasets (MEDLINE, EMBASE, PsycINFO, CINAHL, and NHS EED) were searched from January 2000 to May 2012. The authors identified four economic evaluations alongside or integrated with RCT. All studies were conducted in the United States and evaluated collaborative care.

The searches undertaken within these reviews included publications up to May 2012. The references identified from these two reviews were examined.

Given the purpose of this review (to inform the model conceptualisation and/or model parameters), only UK-based economic evaluations conducted alongside clinical trials, or “model-based” economic evaluation of depression treatment in diabetes were considered.

3.2 Results

All four studies included in the recent Jeeva review [183] (Katon et al., 2006 [184], Katon et al., 2012 [185], Simon et al., 2007 [186] and Hay et al., 2012 [187]) were included in the Molosankwe review [182], leading to 15 citations in total.

All but one study (King et al., 2011 [188]) were economic evaluations conducted alongside or integrated with an RCT. They were non-UK based, used short time horizons (usually less than 2 years), and most studies evaluated the impact of collaborative or stepped care.

The final study, conducted by King et al [189] was a "model-based" economic evaluation and evaluated the cost-effectiveness of collaborative care (CC) for patients with diabetes and comorbid depression in the UK. It was not possible to critically appraise this study as little detail was provided on the model structure, evidence and assumption used. The authors were contacted for further details regarding model structure and inputs, but no response was received at the time of writing of this report.

In the King study, both CC and usual care (UC) were assumed to include general practitioner (GP) advice and care, the use of antidepressants and CBT. The difference between CC and UC was the addition of a case manager (a GP practice nurse). The intervention (CC) was assumed to be given for six months for patients newly diagnosed with T2DM who screened positive for depression. Due to a lack of evidence, the authors assumed that CBT would be received by 20% of individuals under CC and by 15% of individuals under UC. It was also assumed that 20% of individuals with newly diagnosed T2DM would have depression. Costs were reported in 2009 UK £. The six month costs of CC and UC were taken from the NICE guideline CG91[13] and were assumed to be £682 and £346 respectively. The impact of CC on depression-free days was taken from a US study [184].

Assuming a cohort of 119,150 newly diagnosed T2DM in England, of which 20% screen positive for depression, the authors reported that CC leads to an increase in depression-free days during years 1 and 2 (Table 9). CC was associated with higher costs during year 1, but during year 2 (Table 9) the intervention was cost saving. The authors estimated the incremental cost-effectiveness ratio (ICER) to be £3,614 per quality adjusted life years (QALY) gained.

Table 9: Incremental costs of CC compared to UC (assuming 119.150 new cases of T2DM).

	During Year 1	During year 2
Health and social care costs (£)	7,298,860	-385,240
Productivity losses costs (£)	-331,170	-314,330
Depression-free days	117,850	111,860

CC: Collaborative care, UC: Usual care.

The authors reported that results were conservative as the analysis did not include productivity losses due to premature mortality, or the impact associated with avoidance of complications.

3.3 Discussion

In summary, only one "model-based" economic evaluation for intervention/policies targeted at patients with both diabetes and comorbid depression was identified [189]. The evaluation compared CC with UC. No economic evaluations were identified that considered alternative service designs or changes to other parts of the depression pathway (for example, screening or case-finding) for patients with diabetes.

No critical appraisal was conducted as little detail was provided on the model structure, evidence and the assumption used. The model also used a short time horizon and relied on simplifying assumptions with regard to the differences in CBT given, limiting the interpretation of results. The study also did not consider the impact of any interventions at different parts of the care pathway, which limits the usefulness of their findings to the current project. As reported by the authors, the study also did not include the impact of avoiding depression on diabetes-related complication.

Due to the lack of evidence on the economic impact of interventions/policies targeted at patients with T2DM and comorbid depression in England, a *de novo* economic evaluation was constructed.

4. Conceptual modelling

Prior to the construction of the economic model, a conceptual modelling exercise was undertaken to:

- Gain an understanding of the natural history of diabetes
- Gain an understanding of the natural history of depression
- Understand the current pathway of care for diabetes in England
- Understand the current pathway of care for depression in England
- Gain an understanding of the relationship between diabetes and depression
- Understand where efficiencies may be possible through integrating the current pathways of care for diabetes and depression.

The conceptual model, which is described in more detail below, was developed with the aid of the advisory group (composed of 2 GPs, 2 clinical psychologists, 2 consultant psychiatrists, 1 consultant diabetologist, 1 mental health nurse, 1 nurse consultant in psychotherapy and research, 1 senior clinical lecturer in diabetes, and 1 Professor in Diabetes and Endocrinology) through a series of interactive meetings, teleconferences and email exchanges, supplemented by a review of the published literature (section 2). A draft version of the conceptual model was presented to service users (composed of three patients who had experience of both diabetes and depression) during an internal project team meeting prior to finalising the mathematical model.

The conceptual modelling was based on the framework developed by Tappenden et al (2013)[190] which includes two conceptual model types:

- Disease-level conceptual modelling to describe the underlying disease events and processes that an individual with the particular condition might experience
- Service-level conceptual modelling to describe the services of care (or care pathways) that an individual with the disease would experience.

The inter-relationships between these two types of conceptual models are described using design-orientated conceptual models.

Tappenden et al's [190] framework was developed for use when modelling a single disease. As the current project considers two comorbid diseases (diabetes and depression), initial conceptual model types (disease-level and service-level) were developed for diabetes and depression separately, with additional conceptual modelling to understand how the two diseases/pathways interact.

The design-orientated conceptual model brought together both the two initial conceptual model types and the two diseases. This resulted in a total of six conceptual models:

1. Disease-level conceptual model for diabetes
2. Disease-level conceptual model for depression
3. Disease-level conceptual model for diabetes with comorbid depression
4. Service-level conceptual model for diabetes
5. Service-level conceptual model for depression
6. Service-level conceptual model for diabetes with comorbid depression

Each of these conceptual models is discussed in turn.

4.1 Disease-level conceptual model for diabetes

There are a variety of existing mathematical models that replicate the natural history of T2DM and associated microvascular and macrovascular complications [191].

For this project, the T2DM conceptual model was informed by the UK Prospective Diabetes Study (UKPDS) outcome model (OM) v2. This model framework was chosen as it was informed by relatively recent (up to 2007) English data and has been validated in a UK population [192].

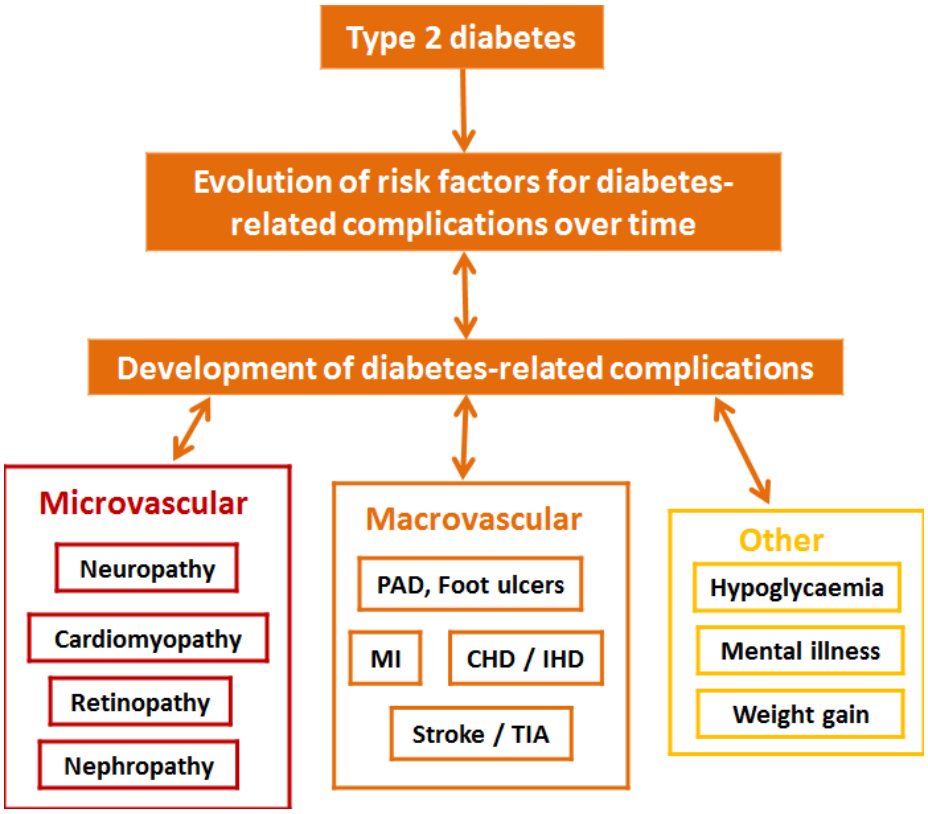
T2DM is a lifelong condition and the risk of diabetes-related complications increases with duration of the disease and progression of risk factors. The UKPDS OMv2 includes demographic (e.g. age, gender, ethnicity, time with diabetes) and clinical (e.g. HbA1c, systolic blood pressure (SBP), BMI, cholesterol) risk factors for diabetes-related complications. With the UKPDS OMv2, these risk factors evolve over time, and an individual may develop multiple diabetes-related complications over their lifetime. Patients with existing diabetes-related complications are also at higher risk of developing further complications. For instance, individuals with an amputation may be more likely to develop a stroke.

The UKPDS OMv2 considers a variety of different diabetes-related complications, which may be classified as either microvascular complications (such as blindness or foot ulcer) or macrovascular complications (such as stroke or IHD).

Of note, neuropathy, cardiomyopathy, nephropathy and retinopathy were considered for inclusion. However, in the UKPDS OMv2, only the final outcomes of these complications are included such as renal failure, chronic heart failure and blindness.

Furthermore, following discussions with advisors, the number of diabetes-related complications considered was also extended compared with the UKPDS OMv2 to include hypoglycaemia, mental illness (including, but not restricted to, depression), and weight gain (Figure 3).

Figure 3: Disease-level conceptual model for T2DM

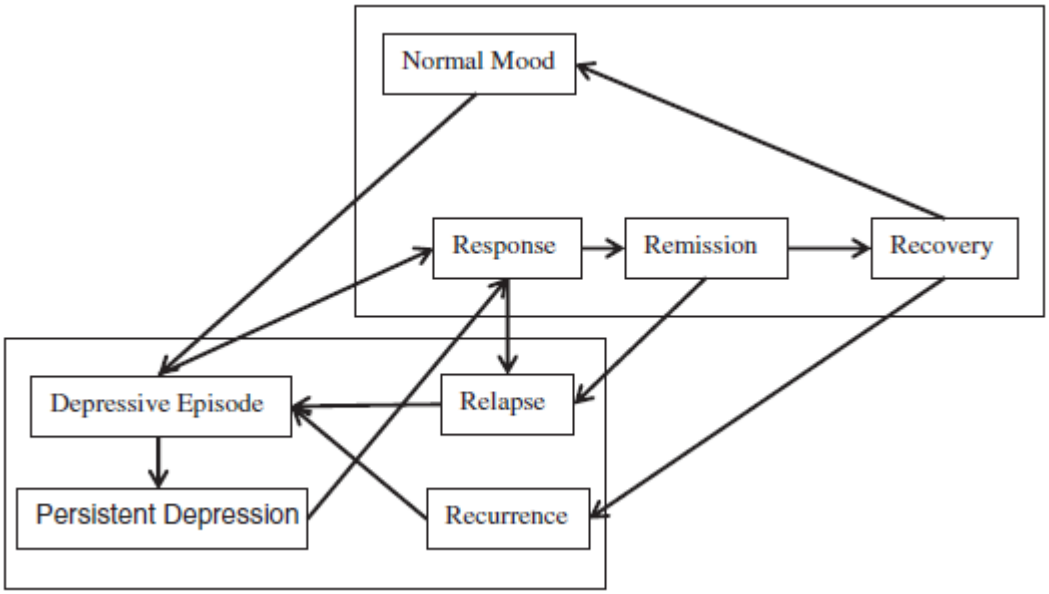


CHD: Coronary heart disease. IHD: Ischaemic heart disease. MI: Myocardial infarction. TIA: Transient ischaemic attack.

4.2. Disease-level conceptual model for depression

There are a number of published models on depression [193;194]. For this project, the depression natural history conceptual model was informed by research conducted by Tosh *et al.* (2013) [194]. Depression was defined as a recovering-relapsing disease, with individuals capable of experiencing multiple episodes of depression across their lifetime. The conceptual model is displayed in Figure 4. Advisors to this project were consulted and felt this was an appropriate representation of the natural history of depression.

Figure 4: Disease level conceptual model for the natural history of depression[1]



[1] Reproduced from Tosh *et al* 2013 [194]

Similarly, discussions with advisors and the review of the literature indicated that there are different levels of depression severity and that patients can progress between these different severities of depression. The least severe level of depression, minor depression, is also known as sub-threshold depression. Patients can then progress to major depression, which can be sub-divided into mild, moderate, and severe depression. Appendix 6 provides details of the depression definitions used in this project. It should be noted that the implemented economic model does not sub-divide major depression due to a lack of available evidence.

4.3. Disease-level conceptual model for diabetes with comorbid depression

No existing economic models or conceptual models were identified that considered disease processes for diabetes with comorbid depression. The conceptual model for diabetes with comorbid depression was therefore developed based on the conceptual models for the single diseases, informed by the evidence identified by the scoping search (see section 2.2 for more details).

The conceptual modelling considered both the impact of diabetes-related complication risk factors (such as HbA1c, BMI) for the development of depression and the impact of depression on diabetes-related complication risk factors (Figure 5).

Single-headed arrows denote a one-way association (for example, age, gender and ethnicity were assumed to affect the development of depression, but were themselves not affected by an

individual's depression status), whilst double-headed arrows denote a two-way association (for example, having a diabetes-related complication was assumed to affect the development of depression, and having depression was assumed to affect the development of diabetes-related complications). Diabetes-related risk factors are labelled as 'patient characteristics' in Figure 5 to illustrate the fact that they are specific to each individual.

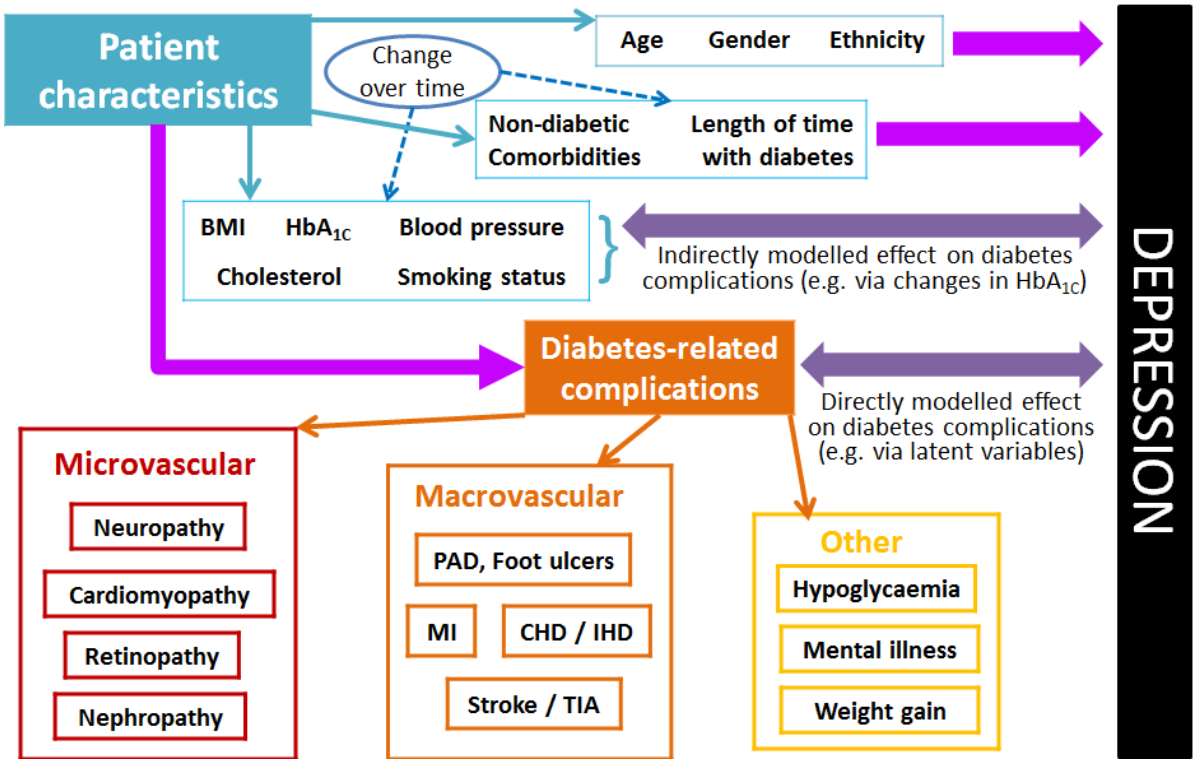
Particular emphasis was placed on the bi-directional association between depression episodes and diabetes-related complications. It was agreed that the presence of diabetes-related complications would have a direct impact on the probability of developing depression on the basis of the evidence from the scoping reviews.

Discussions with advisors and evidence from the literature review indicated that the relationship between diabetes-related complications and depression could be considered in a model either indirectly or directly.

- Indirectly involves modelling the effect of depression on diabetes-related complication risk factors. For instance, individuals with depression may have poor glycaemic control and may gain weight. Changes in these diabetes risk factors would then affect the probability of developing diabetes-related complications.
- Directly involves modelling the impact of depression on the probability of developing diabetes-related complications. Modelling a direct effect of depression on diabetes-related complications would treat the role of diabetes risk factors as latent variables for this association. For example, having depression may lead to biological or genetic changes (such as changes to the nervous system) that pre-dispose to developing diabetic complications.

Advisors to the project felt that the true causal pathway between having depression and developing diabetes-related complications was indirect (i.e. depression would affect the progression of diabetes-related risk factors hence increase the risk of diabetes-related complications in turn). However, it was anticipated and confirmed by the scoping review that evidence would be lacking to inform such an "indirect" relationship; therefore the conceptual modelling also included a direct relationship between depression and risk of diabetes-related complications.

Figure 5: Disease level conceptual model for diabetes and comorbid depression



CHD: Coronary heart disease. IHD: Ischaemic heart disease. MI: Myocardial infarction. TIA: Transient ischaemic attack.

4.4 Service-level conceptual model for diabetes

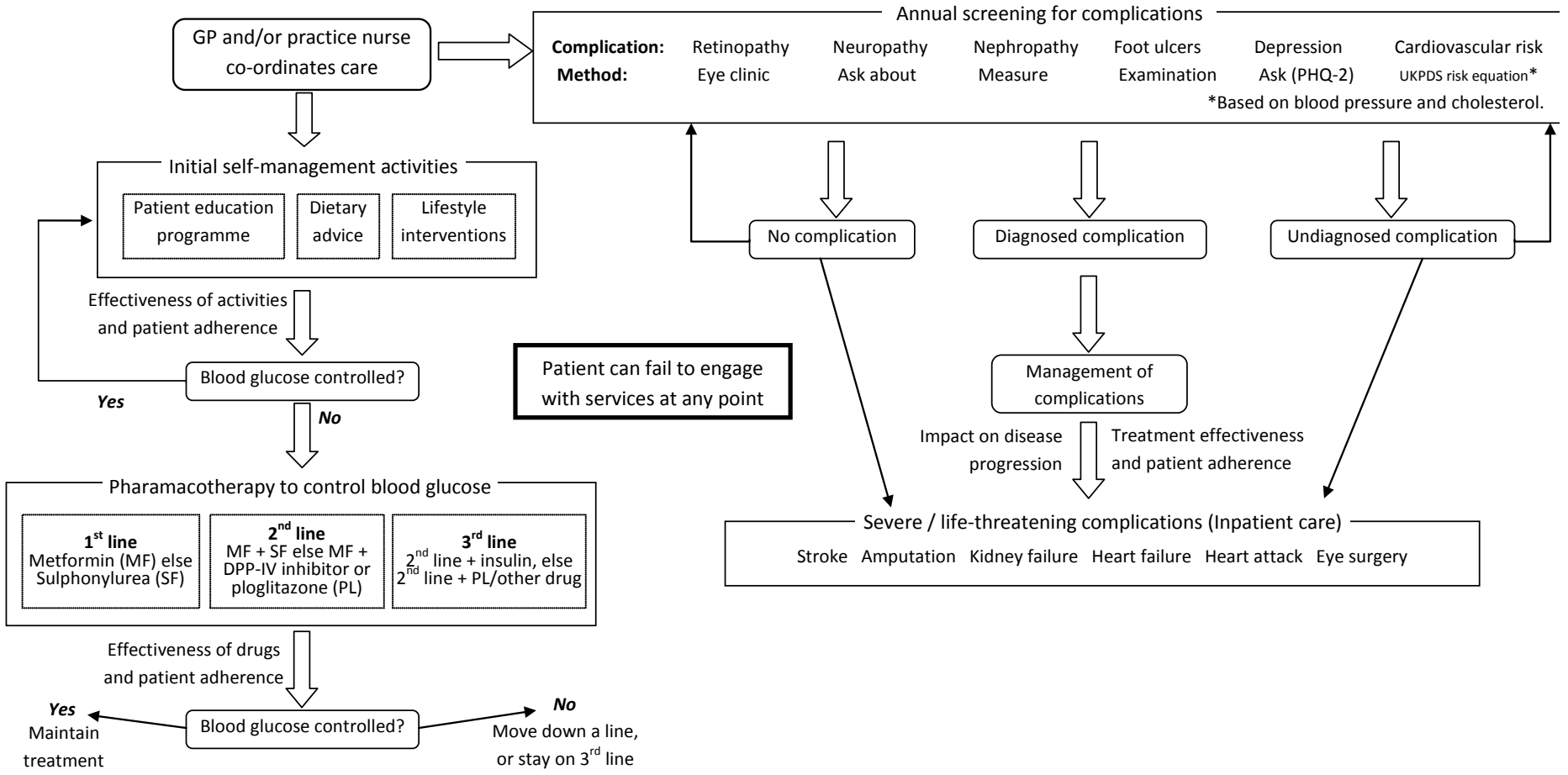
The services of care received by individuals with T2DM were based on those described in NICE Guidance [195]. The extent to which NICE guidance is implemented in the real-world was discussed with clinical advisors, and the service-level conceptual model for diabetes was modified accordingly. Notably, the following points were raised by the advisors:

- There are wide variations in how primary care trusts deliver diabetes care and variation in clinical practice between healthcare professionals.
- Whilst NICE recommends offering patient education programmes to everyone who is diagnosed with T2DM, uptake is generally low. There is also wide variation in the actual programmes offered, and in uptake rates. The two main programmes offered are 'DESMOND' [196]and 'X-PERT'[197]. It was noted that the cost of DESMOND can sometimes prohibit its use.
- Diabetes care is usually provided in primary care by a practice nurse (not a specialist diabetes nurse).
- It was noted that both smoking status and BMI are usually checked during screening for complications.

- Screening for retinopathy differs from screening for the other complications, as this is the only one that cannot be routinely screened within general practice and attendance for retinopathy screening can be an issue. There is now a national screening policy for retinopathy [198] and in some areas mobile screening units are used. Uptake is currently estimated to be about 85%, but it was noted that the 15% who don't have screening are likely to be problematical.

The resulting conceptual model is displayed in Figure 6.

Figure 6: Service-level conceptual model for T2DM



4.5 Service-level conceptual model for depression

The current project considers individuals with T2DM with a history of depression, and individuals with T2DM who have no history of depression. Hence the services that these individuals could receive cover both screening for new or recurrent depression for patients with no history or a history of depression respectively, and the treatment/management of depression for patients with current depression.

4.5.1. Screening for depression

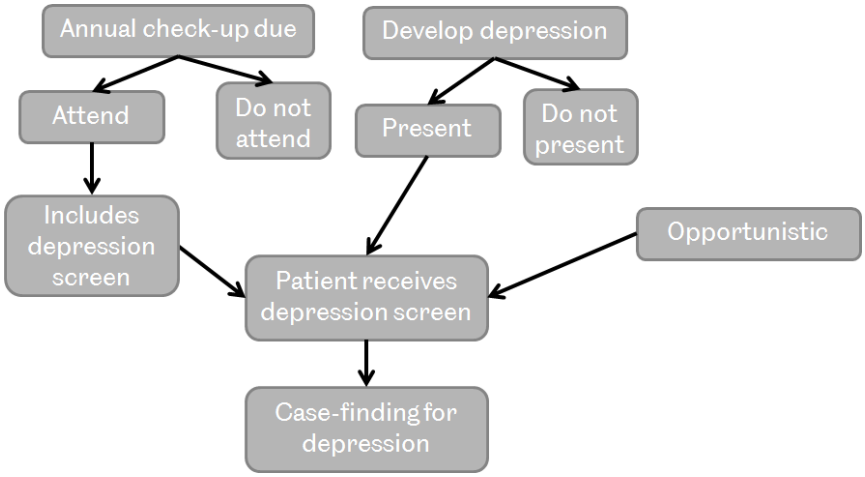
Three main opportunities for depression screening were identified. These were: spontaneous presentation when the individual presents with symptoms of depression, opportunistically (for example, if an individual has a primary care appointment due to backache and is screened for possible depression), and through the annual diabetes review.

The annual diabetes review is intended to cover key aspects in the management of diabetes. It is expected to cover the indicators listed within the diabetes clinical domain of the Quality and Outcomes Framework (QOF) [199]. The 2013/14 QOF lists 15 indicators (Health and Social Care Information Centre, 2013)[199] in the diabetes clinical domain, covering topics such as clinical measurements (e.g. blood pressure, HbA1c, total cholesterol) and screening for diabetes-related complications (e.g. retinal screening, foot examinations). The current diabetes clinical domain does not include screening for depression, but historically the depression clinical domain included an indicator for the number of people with diabetes and/or CHD who were screened for depression. Of note, this indicator has been removed from the 2013/14 QOF.

The clinical experts advised that not all annual diabetes reviews include a depression screen. The main reason given was time constraints. In addition, there were mixed views on the impact of dropping the depression-screening indicator from the QOF. Some felt that this would make little difference since screening for depression amongst diabetes was routine practice. Others felt that, due to the time-limited nature of the annual diabetes review, only indicators included within the QOF would be considered (as these determine payments). These mixed views reflected those reported in the literature.[200]

The resulting conceptual model for depression screening is displayed in Figure 7.

Figure 7: Service-level conceptual model for depression screening



Patients who receive a depression screen enter the case-finding sub-model. Patients are assumed to be screened for depression using the Whooley questions along with an additional 'help' question (as recommended in the QOF) [199]. These questions are:

1. During the last month, have you often been bothered by feeling down, depressed or hopeless?
2. During the last month, have you often been bothered by having little interest or pleasure in doing things?
3. Is this something with which you would like help?

The answers to the first two questions may be either 'Yes' or 'No'. For the help question an additional response of 'Yes, but not today' is also possible. Individuals are defined as receiving a positive screen if they answer 'Yes' to either of the first two questions, and do not answer 'No' to the third help question.

There are two possible outcomes to this: a positive screen (which indicates that the individual may have depression), or a negative screen (which indicates that the individual may not have depression). Following a positive depression screen (from any of the three opportunities for screening), patients receive a follow-up structured diagnostic interview as the sensitivity/specificity of screening is not 100%.

Advisors were consulted, and felt this was a reasonable representation of clinical practice in England. It was however suggested that in practice, GPs/nurses tend to not use the Whooley questions directly, but ask the patients these questions informally. It was also suggested that screening for depression was done by both GPs and nurses and that there was variation in clinical practice.

4.5.2. Treatment for depression

There are a number of different possible treatments for depression. The conceptual modelling initially considered the treatments included in the economic model of depression care pathways (amongst the general population) described by Tosh *et al*. (2013) [194]:

- Antidepressant medication (pharmacotherapy) provided in primary care
- Low-intensity psychological interventions offered by Improving Access to Psychological Therapies (IAPT) teams in primary care
- High-intensity psychological interventions offered by IAPT teams in primary care
- Treatment by Community Mental Health Teams (CMHT)
- Treatment by Specialist Psychotherapy Services (SPS)

The Tosh *et al*. (2013) [194] model implemented the treatments as part of a stepped-care model whereby all individuals started on antidepressant medication, followed by CMHT, with the highest step being SPS. An element of stratification was included whereby local IAPT data were used to determine the proportion of patients who received either low or high intensity psychological interventions after stepping-up from antidepressant medication. Informed by discussions with clinical experts, it was agreed that treatment delivered by CMHT and SPS were to be excluded, as it was noted that the volume of individuals who access these services was very small; the evidence profile for these individuals was likely to be very weak; and these individuals were likely to be excluded from clinical trials (for example if they are acutely suicidal).

It was also noted that in the conceptual modelling of Tosh *et al*. (2013) [194], services delivered by charities and private sectors were excluded. It was decided that these services should remain excluded, but it was noted that the demographics of individuals accessing depression services of care via these routes may be different to those who access depression services provided in primary care. It was further noted that the stepped care model used in Tosh *et al*. (2013) [194] was based on a local implementation. It was agreed that for the current project different treatments at each step should be considered, to better reflect the variation in implementations of stepped care nationally.

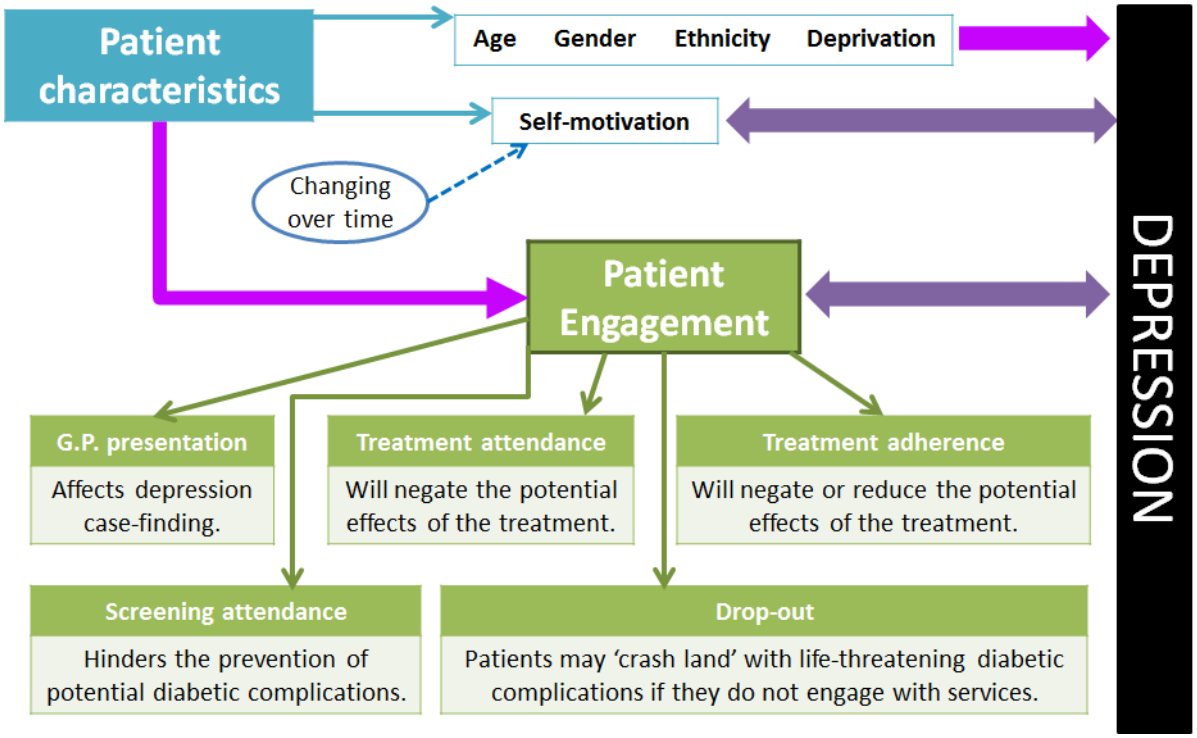
Discussion with clinical experts also indicated that whilst IAPT is widely available in England, not all the English population have access to IAPT services. Finally, it was noted that ‘watchful waiting’ was a (passive) treatment option, and that this should be included.

4.6. Service-level conceptual model for diabetes with comorbid depression

The conceptual model for diabetes with comorbid depression considered which risk factors for developing depression were also risk factors that may affect an individual's view of, and hence engagement with, the services of care that they receive.

The conceptual model is shown in Figure 8 and was informed by discussions with clinical advisors and the results from the scoping searches (section 2.2). Single-headed arrows denote a one-way association (for example, age, gender, ethnicity and deprivation were assumed to affect the development of depression, but were themselves not affected by an individual's depression status), whilst double-headed arrows denote a two-way association (for example, an individual's self-motivation was assumed to affect the development of depression, and having depression was assumed to affect an individual's self-motivation).

Figure 8: Service-level conceptual model for diabetes and comorbid depression



Advisors suggested that the link between depression and experience of services was very important. It was felt that by offering continuity, GPs could improve the patient experience, but some patients seen by specialist mental health services (including community services) anecdotally expressed a poor experience of primary care. It was felt that for some patients their only contact was with a mental health team, meaning that there was no healthcare professional to treat any physical

problems. However, it was noted that this project considered depression comorbid to T2DM, where the T2DM was already identified (and so treated) in primary care.

It was further mentioned that telephone counselling may be useful for improving compliance and treatment adherence. Finally, it was pointed out that the patient's experience of services may be very different to those providing the services and that patient engagement could also impact on their diabetes care.

4.7 Service user input

As indicated earlier in the report, the conceptual model was used as the basis for discussions in a meeting with service users. The users provided valuable input into the project by sharing their experience of the services they currently received in relation to the clinical pathways portrayed in the conceptual models. While all three service users agreed with the primary structures of the different conceptual models, the meeting discussions highlighted huge variations in the level and types of services and care they received.

In addition to having both T2DM and depression, all three users had at least one other long term health condition, such as cancer. The duration of diabetes ranged from 2 years to 12 years, and there was a wide variation in the duration of history of depression with two initially being diagnosed before the onset of T2DM and one being diagnosed after the onset of T2DM. All three indicated they initially self-presented with symptoms of depression, were not currently screened opportunistically, and generally self-presented to the GP when experiencing early symptoms of recurrence of depression.

There was a general agreement that the health care for depression was treated as secondary to the physical care related to T2DM. There was also a consensus that management of T2DM and depression was totally separate and that a holistic approach with a key worker taking responsibility might improve communication and should be beneficial to the patient in the long term.

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