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)
Appendices

Kearns B, Rafia R, Leaviss J, Preston L, Wong R, Brazier JE, Ara R

Correspondence to: Ben Kearns , HEDS, ScHARR, University of Sheffield, Regent Court, 30 Regent Street, Sheffield, S1 4DA

RR0044

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.

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.

TABLE OF CONTENTS

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.

APPENDICES

Appendix 1: Literature Search Strategies

1.1 Search strategy for identification of reviews

Medline Search (replication of Cochrane Review)

1. exp Diabetes Mellitus/
2. exp Diabetes Complications/
3. diabet$.tw,ot.
4. (IDDM or NIDDM or MODY or T1DM or T2DM or T1D or T2D).tw,ot.
5. (non insulin$ depend$ or noninsulin$ depend$ or non insulin?depend$ or noninsulin?depend$).tw,ot.
6. (insulin$ depend$ or insulin?depend$).tw,ot.
7. exp Diabetes Insipidus/
8. diabet$ insipidus.tw,ot.
9. or/1-6
10. 7 or 8
11. 9 not 10
12. exp Mood Disorders/
13. exp Depression/
14. depressi* symptom*.tw,ot.
15. dysthymi*.tw,ot.
16. ((depressi* or mood or affectiv* or cognitiv* or bipolar) adj3 disorder*).tw,ot.
17. exp Antidepressive Agents/
18. (antidepress* or anti-depress*).tw,ot.
19. or/12-18
20. randomized controlled trial.pt.
21. controlled clinical trial.pt.
22. randomi?ed.ab.
23. placebo.ab.
24. drug therapy.fs.
25. randomly.ab.
26. trial.ab.
27. groups.ab.
28. or/20-27
29. Meta-analysis.pt.
30. exp Technology Assessment, Biomedical/
31. exp Meta-analysis/
32. exp Meta-analysis as topic/
33. hta.tw,ot.
34. (health technology adj6 assessment$).tw,ot.
35. (meta analy$ or metaanaly$ or meta?analy$).tw,ot.
36. ((review$ or search$) adj10 (literature$ or medical database$ or medline or pubmed or embase or cochrane or cinahl or psycinfo or psyclit or healthstar or biosis or current content$ or systemat$)).tw,ot
37. or/29-36
38. (comment or editorial or historical-article).pt.
39. 37 not 38
40. 39 or 28
41. 11 and 19 and 40

42. (animals not (animals and humans)).sh.
43. 41 not 42

1.2 Search strategies for identification of individual studies for diabetes complications and depression.

Medline and Medline in Process: Ovid. 1946 to Present

1. exp Diabetes Mellitus/
2. diabet$.tw.
3. (insulin$ depend$ or insulin?depend$).tw.
4. (insulin$ defic$ adj2 absolut$).tw.
5. (IDDM or T1DM or T1D).tw.
6. exp Insulin Resistance/
7. Glucose Intolerance/
8. (impaired glucos$ toleranc$ or glucos$ intoleranc$ or insulin resistan$).tw.
9. (non insulin$ depend$ or noninsulin$ depend$ or non insulin?depend$ or noninsulin?depend$).tw.
10. (NIDDM or MODY or T2DM or T2D).tw.
11. exp Diabetes Insipidus/
12. or/1-11
13. exp Mood Disorders/
14. Depression/
15. ((depressi$ or affective) adj symptom$).tw.
16. dysthymi$.tw.
17. ((depressi$ or mood or affectiv$ or cognitiv$ or bipolar or adjustment) adj3 disorder$).tw.
18. exp Antidepressive Agents/
19. (antidepress$ or anti-depress$).tw.
20. or/13-19
21. 12 and 20
22. exp Heart Failure/
23. (congestive adj2 heart).tw.
24. (heart adj3 failure$).mp.
25. (cardiac adj3 failure$).mp.
26. (chf or ccf).tw.
27. or/22-26
28. 21 and 27
29. Myocardial Ischemia/
30. Coronary Disease/
31. ((isch?emi$ or atherosclerotic or coronary) adj3 heart disease).tw.
32. coronary artery disease.tw.
33. (cad or chd or ihd).tw.
34. or/29-33
35. 21 and 34
36. exp Myocardial Infarction/
37. ((heart or cardiac or myocardial or isch?emi$) adj2 (failure or infarc$ or attack$)).tw.

38. myocard$ isch?emi$.tw.
39. heart attack$.tw.

40. or/36-39
41. 21 and 40
42. exp Stroke/
43. stroke$.tw.
44. ((cerebrovasc$ or cerebral vasc$) adj2 accident).tw.
45. (cva or transient isch?emic attack$ or tia$).tw.
46. exp Brain ischemia/
47. ((brain or cerebr$) adj2 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$ or hypoxi$)).tw.
48. or/42-47
49. 21 and 48
50. exp Blindness/
51. blind$.tw.
52. ((vision or visual$ or sight) adj3 (impair$ or loss)).tw.
53. or/50-52
54. 21 and 53
55. Diabetes Foot/
56. Foot Ulcer/
57. (diabet$ adj3 ulcer$).tw.
58. (diabet$ adj3 (foot or feet)).tw.
59. ((leg or foot or feet) adj3 ulcer$).tw.
60. or/55-59
61. 21 and 60
62. Amputation/
63. amputat$.tw.
64. Amputation, Traumatic/
65. Amputation Stumps/
66. Disarticulation/
67. (disarticulat$ or exarticulat$).tw.
68. Amputees/
69. amputee$.tw.
70. or/62-69
71. 21 and 70
72. Diabetes Nephropathies/
73. diabetes nephropath$.tw.
74. Renal Insufficiency/
75. (renal failure or kidney failure).tw.
76. (renal insufficiency or kidney insufficiency).tw.
77. or/72-76
78. 21 and 77
79. 28 or 35 or 41 or 49 or 54 or 61 or 71 or 78
80. limit 79 to yr="2001 -Current"
81. limit 80 to english language

PsycINFO: Ovid. 1806 to Week 5 2013

1. Diabetes Mellitus/
2. exp diabetes/
3. diabet$.tw.
4. (insulin$ depend$ or insulin?depend$).tw.
5. (insulin$ defic$ adj2 absolut$).tw.
6. (IDDM or T1DM or T1D).tw.
7. (impaired glucos$ toleranc$ or glucos$ intoleranc$ or insulin resistan$).tw.
8. (non insulin$ depend$ or noninsulin$ depend$ or non insulin?depend$ or noninsulin?depend$).tw.
9. (NIDDM or MODY or T2DM or T2D).tw.
10. Diabetes Insipidus/
11. or/1-10
12. exp major depression/
13. atypical depression/
14. affective disorders/
15. seasonal affective disorder/
16. ((depressi$ or affective) adj symptom$).tw.
17. dysthymi$.tw.
18. ((depressi$ or mood or affectiv$ or cognitiv$ or bipolar or adjustment) adj3 disorder$).tw.
19. antidepressant drugs/
20. (antidepress$ or anti-depress$).tw.
21. or/12-20
22. 11 and 21
23. (congestive adj2 heart).tw.
24. (heart adj3 failure$).mp.
25. (cardiac adj3 failure$).mp.
26. (chf or ccf).tw.
27. or/23-26
28. 22 and 27
29. heart disorders/
30. ((isch?emi$ or atherosclerotic or coronary) adj3 heart disease).tw.
31. coronary artery disease.tw.
32. (cad or chd or ihd).tw.
33. or/29-32
34. 22 and 33
35. myocardial Infarctions/
36. ((heart or cardiac or myocardial or isch?emi$) adj2 (failure or infarc$ or attack$)).tw.
37. myocard$ isch?emi$.tw.
38. heart attack$.tw.
39. or/35-38
40. 22 and 39

41. cerebrovascular accidents/
42. stroke$.tw.
43. ((cerebrovasc$ or cerebral vasc$) adj2 accident).tw.
44. (cva or transient isch?emic attack$ or tia$).tw.
45. cerebral ischemia/
46. ((brain or cerebr$) adj2 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$ or hypoxi$)).tw.
47. or/41-46
48. 22 and 47
49. blind/
50. blind$.tw.
51. ((vision or visual$ or sight) adj3 (impair$ or loss)).tw.
52. or/49-51
53. 22 and 52
54. (diabet$ adj3 ulcer$).tw.
55. (diabet$ adj3 (foot or feet)).tw.
56. ((leg or foot or feet) adj3 ulcer$).tw.
57. or/54-56
58. 22 and 57
59. Amputation/
60. amputat$.tw.
61. (disarticulat$ or exarticulat$).tw.
62. amputee$.tw.
63. or/59-62
64. 22 and 63
65. kidney diseases/
66. diabetes nephropath$.tw.
67. (renal failure or kidney failure).tw.
68. (renal insufficiency or kidney insufficiency).tw.
69. or/65-68
70. 22 and 69
71. 28 or 34 or 40 or 48 or 53 or 58 or 64 or 70
72. limit 71 to yr="2001 -Current"
73. limit 72 to english language

Cochrane Library

#1	MeSH descriptor: [Diabetes Mellitus] explode all trees
#2	diabet*:ti,ab,kw
#3	(insulin* depend* or insulin*depend*):ti,ab,kw
#4	(insulin* defic* next/2 absolut*):ti,ab,kw
#5	(IDDM or T1DM or T1D):ti,ab,kw
#6	MeSH descriptor: [Insulin Resistance] explode all trees
#7	MeSH descriptor: [Glucose Intolerance] this term only
#8	(impaired glucos* toleranc* or glucos* intoleranc* or insulin
#9	resistan*):ti,ab,kw
#10	(non insulin* depend* or noninsulin* depend* or non insulin*depend* or noninsulin*depend*):ti,ab,kw

#11	(NIDDM or MODY or T2DM or T2D):ti,ab,kw MeSH descriptor: [Diabetes Insipidus] explode all trees
#12	{or #1-#11}
#13	MeSH descriptor: [Mood Disorders] explode all trees
#14	MeSH descriptor: [Depression] this term only
#15	((depressi* or affective) next/2 symptom*):ti,ab,kw
#16	dysthymi*:ti,ab,kw
#17	((depressi* or mood or affectiv* or cognitiv* or bipolar or adjustment) next/3 disorder*):ti,ab,kw
#18	MeSH descriptor: [Antidepressive Agents] explode all trees
#19	(antidepress* or anti-depress*):ti,ab,kw
#20	{or #13-#19}
#21	#12 and #20
#22	MeSH descriptor: [Heart Failure] explode all trees
#23	(congestive next/2 heart):ti,ab,kw
#24	(heart next/3 failure*):ti,ab,kw
#25	(cardiac next/3 failure*):ti,ab,kw
#26	(chf or ccf):ti,ab,kw
#27	{or #22-#26}
#28	#21 and #27
#29	MeSH descriptor: [Myocardial Ischemia] this term only
#30	MeSH descriptor: [Coronary Disease] this term only
#31	((isch*emi* or atherosclerotic or coronary) next/3 heart disease):ti,ab,kw
#32	coronary artery disease:ti,ab,kw
#33	(cad or chd or ihd):ti,ab,kw
#34	{or #29-#33}
#35	#21 and #34
#36	MeSH descriptor: [Myocardial Infarction] explode all trees
#37	((heart or cardiac or myocardial or isch*emi*) next/2 (failure or infarc* or
#38	attack*)):ti,ab,kw
#39	myocard* isch*emi*:ti,ab,kw heart attack*:ti,ab,kw
#40	{or #36-#39}
#41	#21 and #40

#42	MeSH descriptor: [Stroke] explode all trees
#43	stroke*:ti,ab,kw
#44	((cerebrovasc* or cerebral vasc*) next/2 accident):ti,ab,kw
#45	(cva or transient isch*emic attack* or tia*):ti,ab,kw
#46	MeSH descriptor: [Brain Ischemia] explode all trees
#47	((brain or cerebr*) next/2 (isch*emi* or infarct* or thrombo* or emboli* or occlus* or hypoxi*)):ti,ab,kw
#48	{or #42-#47}
#49	#21 and #48
#50	MeSH descriptor: [Blindness] explode all trees
#51	blind*:ti,ab,kw
#52	((vision or visual* or sight) next/3 (impair* or loss)):ti,ab,kw
#53	{or #50-#52}
#54	#21 and #53
#55	MeSH descriptor: [Diabetes Foot] this term only
#56	MeSH descriptor: [Foot Ulcer] explode all trees
#57	(diabet* next/3 ulcer*):ti,ab,kw
#58	(diabet* next/3 (foot or feet)):ti,ab,kw
#59	((leg or foot or feet) next/3 ulcer*):ti,ab,kw
#60	{or #55-#59}
#61	#21 and #60
#62	MeSH descriptor: [Amputation] this term only
#63	amputat*:ti,ab,kw
#64	MeSH descriptor: [Amputation, Traumatic] this term only
#65	MeSH descriptor: [Amputation Stumps] explode all trees
#66	MeSH descriptor: [Disarticulation] this term only
#67	MeSH descriptor: [Amputees] this term only
#68	amputee*:ti,ab,kw
#69	{or #62-#68}
#70	#21 and #69
#71	MeSH descriptor: [Diabetes Nephropathies] this term only
#72	diabetes nephropath*:ti,ab,kw
#73	MeSH descriptor: [Renal Insufficiency] this term only
#74	(renal failure or kidney failure):ti,ab,kw
#75	(renal insufficiency or kidney insufficiency):ti,ab,kw
#76	{or #71-#75}
#77	#21 and #76
#78	#28 or #35 or #41 or #49 or #54 or #61 or #70 or #77
#79	#78 from 2001 to 2013

Appendix 2: Summary tables of characteristics of reviews by topic.

A2.1 Table of reviews identified for interventions.

Paper	Category	Inclusion criteria	Ns	Intervention	Outcomes	Evidence Synthesis
Baumeister 2012 (Cochrane)	Interventions	RCTs. Studies of adults with T1DM or T2DM and depression, diagnosed through standard criteria and assessed through interviews, self-reports, medical records or physicians diagnosis.	19 trials, with 1592 participants. Psychological interventions: 8 trials with 1122 participants. Pharmacological interventions: versus placebo 8 trials, 377 participants.	Psychological interventions including CBT, psychodynamic therapy, interpersonal psychotherapy, non-directive or supportive therapy and counselling. Pharmacological interventions including all antidepressant medications and other drug therapies used for treating depressive disorders.	Primary outcomes: Reduction in depressive symptoms or remission of clinically significant depression. Glycaemic control. Secondary outcomes: HRQoL Healthcare costs Adherence to diabetes treatment regimen. Diabetes complications. Death from any cause.	Mean differences with 95% CIs for glycaemic control. Standardised mean differences with 95% CI for all other continuous outcomes.
Markowitz 2011	Interventions	Studies evaluating treatments for depression in patients with diabetes. Pre-post or controlled designs.	17 trials: 6 psychosocial; 8 pharmacologic; 3 collaborative care.	Treatments for depression in people with diabetes, including psychological, pharmacological and collaborative care.	Depression or depressive symptoms	No pooled analyses. P values reported for individual trials.

Paper	Category	Inclusion criteria	Ns	Intervention	Outcomes	Evidence Synthesis
Piette 2004	Interventions	No methods described. Reviews literature on comorbid depression and diabetes.	N/R	Discusses the effectiveness of some depression treatments in patients with diabetes.	Quality of Life and functioning; level of physical activity; communication with providers; healthcare use.	No pooled data. Narrative description with some data given for treatment effectiveness, physical activity. Useful discussion of optimising care for depressed patients with diabetes.
Van der Feltz-Cornelius 2010	Interventions	RCTs. Crossover designs or waiting list as control. Studies of adult patients with with T1DM or T2DM with comorbid depressive disorders including major depressive disorder, minor depressive disorder, dysthymic disorder or significant depressive disorders as assessed by a validated questionnaire or diagnostic interview.	14 trials, with 1724 patients.	Psychotherapeutic interventions, pharmacotherapeutic interventions, or health services interventions such as collaborative care.	Glycaemic control (HbA1c or FBG/FPG) and depressive symptom severity.	Meta-analysis of standardised effect sizes (Cohens *d*).
Ye 2011	Interventions	Studies examining the metabolic effects of fluoxetine for T2DM. Placebo-controlled RCTs.	5 trials.	Fluoxetine	Body weight loss, fasting plasma glucose, HbA1c, triglyceride, total cholesterol	Meta-analysis (meta-regression).

Paper	Category	Inclusion criteria	Ns	Intervention	Outcomes	Evidence Synthesis
					decrement.	

HRQoL: Health related quality of life

A2.2 Table of reviews identified for epidemiology and/or comorbidity

Paper	Category	Inclusion criteria	Ns	Intervention	Outcomes	Evidence Synthesis
Ali 2006	Comorbidity	Studies examining the prevalence of clinically relevant depression in adults with T2DM. Depression identified through self-report or diagnostic interview.	10 studies included in review, with 51331 people.	None	Depression in diabetes.	Meta-analysis of 9 trials, giving Odds Ratio. Prevalence reported overall and by gender. Subgroup analyses for method of depression diagnosis; gender; country of study; primary care or population setting.
Ali 2010	Comorbidity	Studies examining the influence of depression in people with T2DM on Health-Related Quality of Life. Depression and HRQoL identified using validated assessment method/tool. Quantitative report of cross-sectional association between depression and HRQoL had to be reported.	14 studies reported.	None	HRQoL, with definition as subjective patient-reported construct encompassing multiple dimensions including physical, emotional and social functioning domains, using eg (SF12/36, WHO-DAS11, ADDQoL).	No pooled analyses. Data from individual studies reported, mostly ORs or multiple regression beta coefficients.
Anderson 2001	Comorbidity	Studies of the odds and prevalence of	42 studies with 21351	None	Odds and prevalence of	Meta-analyses, both combined and controlling for

Paper	Category	Inclusion criteria	Ns	Intervention	Outcomes	Evidence Synthesis
		clinically relevant depression in adults with T1DM and T2DM. Major, minor or subsyndromal depression.	subjects. Included 20 studies with non-diabetes control group.		clinically relevant depression in people with diabetes.	sex, type of diabetes, subject source, assessment method. Prevalence and Odds Ratios given.
Bowser 2010	Epidemiology	Studies and reviews on four topics relating to free clinics and missed appointments in low-income, uninsured, racially heterogeneous adults with diabetes and depression.	8 papers on the importance of keeping appointments; 23 papers on depression; 10 on free clinics; 9 on missed appointments.	None	A range of outcomes discussed relating to people with depression in diabetes, including prevalence, costs, association between the 2 conditions, effect of depression on diabetes self-care, availability of and access to free clinics.	No pooled data. Individual data available for listed outcomes. US costs.
Lustman 2000	Epidemiology	Studies examining the association of depression with poor glycaemic control. Adults with T1DM or T2DM. Studies had to assess glycaemic	24	None	Depression or glycaemic control.	Meta-analysis reports Z scores. Subsets analysed: cross-sectional study design; depression per symptom scales; depression for diagnostic criteria; T1DM, T2DM or mixed sample;

Paper	Category	Inclusion criteria	Ns	Intervention	Outcomes	Evidence Synthesis
		control using a measure glycohaemoglobin (GHb). Measure of depression and GHb had to be coincident to the study evaluation. Dependent variable could be either depression or glycaemic control, or studies could be correlational.				depression as IV; HbA as IV.
Lustman 2005	Epidemiology	Articles evaluating outcomes, relationships and/or management of comorbid depression and diabetes.	N/R	Not focus of paper but discusses psychotherapy and pharmacotherapy in diabetes, including CBT and SSRIs.	Outcomes (of depression in diabetes): metabolic control; adherence to medication and diet regimens; quality of life; health care expenditure. Outcomes (of poor metabolic control): depression severity; response to antidepressants.	Discussion paper, no synthesis.

Paper	Category	Inclusion criteria	Ns	Intervention	Outcomes	Evidence Synthesis
Nouwen 2010	Epidemiology	Studies examining the association of diabetes and the onset of depression. Longitudinal studies with sufficient data to estimate relative risk.	11 studies with 48808 cases.	None	Onset of depression.	Meta-analysis, pooled Risk Ratios, with subgroup analyses for method of diagnosis.
Renn 2011	Epidemiology	Studies that examined the relationship, directionality, comorbidity, and/or prevalence of diabetes and depression (including depressive symptomatology). Studies that assessed depression and/or depressive symptomatology in adults with T2DM or in mixed samples of T2DM and Type 1 Diabetes Mellitus (T1DM).	14 studies	None	Depression as a cause of diabetes; depression as a risk factor for diabetes.	No meta-analysis, narrative review, with data for individual studies reported.
Albers 2011	Comorbidity	Longitudinal cohort studies of depression in diabetes	8 studies, 6 population based and 2	None	Predictors of depression in diabetes:	Meta-analysis (step-wise regression).

Paper	Category	Inclusion criteria	Ns	Intervention	Outcomes	Evidence Synthesis
		populations.	based on clinical population groups		Sociodemographic variables eg marital status, employment status, income, education, lifestyle (smoking, alcohol, physical activity, calorie intake); comorbidities and diabetes-related complications e.g. heart disease, cancer, rheumatoid disease, obesity, hypertension, lung disease, retinopathy, nephropathy, neuropathy, amputations and disabilities.	
Astle 2007	Comorbidity	Studies relating to diabetes and depression.	22 papers	None.	Prevalence of depression in people with diabetes.	No pooled analyses. Individual data reported for prevalence of depression in diabetess.
Rotella 2013	Comorbidity	Longitudinal studies assessing the	16 studies, with 497223	None	Risk of depression.	Meta-analysis, pooled prevalence rates (Odds

Paper	Category	Inclusion criteria	Ns	Intervention	Outcomes	Evidence Synthesis
		incidence of clinical depression or depressive symptoms and reporting comparisons in incidence of depression between people with diabetes versus those without diabetes. T1DM or T2DM.	people.			Ratios and Risk Ratios).
De Groot 2001	Comorbidity	Studies examining the association between depression (lifetime and current) and diabetes complications. Adults with T1DM or T2DM.	27 studies.	None.	Association between depression and diabetes complications.	Meta-analyses for association between depression and diabetes complications (pearsons *r*). Separate meta-analyses comparing ratings for those with and without complications; type of diabetes; specific diabetes complications (diabetes retinopathy; neuropathy; nephropathy; sexual dysfunction; macrovascular complications).
Egede 2010	Comorbidity	Studies examining the association between diabetes and depression.	Not reported.	None.	No methods reported. Paper focuses on the global burden of diabetes and	No pooled data. Data on individual papers on self-care behaviours; health care use; health care expenditure; effect of depression on all-

Paper	Category	Inclusion criteria	Ns	Intervention	Outcomes	Evidence Synthesis
					depression; screening for depression; prevalence of depression in individuals with diabetes; causal pathways between depression and diabetes; effect of depression on glycaemic control and self-care behaviours; effect of depression on risk for diabetes complication; effect of depression on disability, work productivity and quality of life in individuals with diabetes; effect of depression on healthcare utilisation and costs; effect of depression on	cause mortality (hazard ratios).

Paper	Category	Inclusion criteria	Ns	Intervention	Outcomes	Evidence Synthesis
					mortality in individuals with diabetes; effectiveness of treating depression in individuals with diabetes; cost of treating depression in individuals with diabetes	
Mezuk 2008	Comorbidity	Studies of the association between depression and diabetes; prospective design, including cases of probable T2DM in adults >30 years; providing enough data to generate a relative risk estimate; excluding prevalent cases of either depression (for diabetes predicting depression onset) or diabetes (for depression predicting	13 studies with 6916 patients looked at depression as a predictor of the onset of T2DM; 7 studies with 6414 patients looked at diabetes as a predictor of the onset of depression.	None	Development of depression or diabetes. Review looks at the bi-directional relationship of diabetes and depression.	Meta-analysis. Pooled relative risks.

Paper	Category	Inclusion criteria	Ns	Intervention	Outcomes	Evidence Synthesis
		diabetes onset).				

HRQoL: Health related quality of life, WHO-DAS11: World Health Organisation Disability Assessment Schedule; ADQoL: Audit of Diabetes-Dependent Quality of Life.

A2.3 Table of reviews identified for quality of life

Paper	Category	Inclusion criteria	Ns	Intervention	Outcomes	Evidence Synthesis
Wandell 2005	Quality of Life	Studies using generic questionnaires to analyse HRQoL in diabetes patients. Studies performed or recruited in primary health care. T1DM and type 2 patients.	19 studies included.	None.	Association between diabetes and HRQoL. Comparison between T1DM and T2DM, age, depression, psychiatric disorders, users of psychoactive drugs, heart disease.	No pooled effects reported.
Schram 2009	Quality of Life	Studies evaluating the effect of depressive symptoms on quality of life in adult individuals with diabetes and depression.	20 studies: 18 cross-sectional and 2 longitudinal.	None.	Association between depressive symptoms and quality of life. Quality of life measured by generic, disease specific and domain specific questionnaires. Depression assessed by diagnostic	No pooled effects reported.

Paper	Category	Inclusion criteria	Ns	Intervention	Outcomes	Evidence Synthesis
					interview or screening questionnaires.	

HRQoL: Health related quality of life

A2.4 Table of reviews identified for antidepressants and weight

Paper	Category	Inclusion criteria	Ns	Intervention	Outcomes	Evidence Synthesis
Serretti 2010	Antidepressants and Weight	Studies regarding the effect of body weight potentially exerted by the most common antidepressant drugs employed for clinical purposes. Adult patients, administered in monotherapy.	116 studies.	None.	Weight change associated with antidepressant treatment. Acute and maintenance periods.	Pooled analyses, and pooled analyses for individual drugs.

A2.5 Table of reviews for identified for screening

Paper	Category	Inclusion criteria	Ns	Intervention	Outcomes	Evidence Synthesis
Meader 2011	Screening	Studies assessing the validity of case-identification instruments for depression in chronic physical health problems. Not specific to diabetes. Reference standard was diagnoses according to DSM or ICD.	113 studies with 20826 participants.	None.	Diagnostic accuracy.	Pooled estimates of sensitivity, specificity and likelihood ratios. No subgroup analyses for diabetes.

DSM: Diagnostic and Statistical Manual of Mental Disorders; ICD: International Classification of Diseases.

A2.6 Table of reviews identified for adherence

Paper	Category	Inclusion criteria	Ns	Intervention	Outcomes	Evidence Synthesis
Gonzales 2008	Adherence	Children, adolescents, or adults with T1DM or T2DM. Studies reporting the relationship between depression and treatment adherence in people with diabetes.	47 study samples with 17319 participants.	None.	Relationship between depression and non-adherence in diabetes. Aggregated self-care and broken down by: appointment keeping; composite measures; diet; medication; exercise; glucose monitoring; foot care.	Meta-analysis, weighted *r*.

A2.7 Table of reviews excluded at stage 1

Paper	Category	Inclusion criteria	Ns	Intervention	Outcomes	Evidence Synthesis
Barnard 2006	Comorbidity	Studies examining the cross-sectional prevalence of clinical depression in adults with T1DM. Major, minor and dysthymic disorder.	14 studies: 3 controlled and 6 uncontrolled.	None	Prevalence and odds of depression in people with T1DM.	Meta-analyses and individual data reported. Combined Odds Ratios for controlled studies only. Mean prevalence rates.
Cosgrove 2008	Comorbidity	Cohort, case-control or cross-sectional studies of adults in community or occupational settings. Major depressive disorder or raised depression on a validated scale. Depression should be identified at time of screening or prior to diagnosis of diabetes.	14 studies.	None	Subsequent development of T2DM in people with existing depression.	Meta-analysis. Pooled least-adjusted estimates of risk ratios.
Dziemidok 2011	Comorbidity	No methods described.	N/R	None	Occurrence of anxiety and depression in diabetes patients, particularly those with complications.	No data reported, discussion paper.
Gavard 1993	Comorbidity	Studies examining	20 studies:	None.	Prevalence rates of	No meta-analyses. Individual

Paper	Category	Inclusion criteria	Ns	Intervention	Outcomes	Evidence Synthesis
		the prevalence rates of depression in adults with diabetes.	9 controlled, 11 uncontrolled.		depression in adults with diabetes.	prevalence rates with p values given for diabetess versus non diabetess and sex for controlled studies. Individual prevalence rates for uncontrolled studies.
Katon 2007	Comorbidity	Studies examining the effects of anxiety and depression comorbidity in patients with chronic medical illness. Cross-sectional and longitudinal studies and RCTs measuring impact of improving anxiety and/or depression on medical symptoms outcomes.	Total 31 studies, with 16922 patients, of which 7 studies are for diabetes, with 5943 patients.	None.	Physical symptoms	No meta-analysis, section on diabetes reports some comorbidity data for individual studies.
Knol 2006	Comorbidity	Studies that longitudinally examined the relationship between depression and onset of T2DM, irrespective of their	9 studies.	None	Risk of developing T2DM in people with depression.	Meta-analysis – pooled Relative Risk.

Paper	Category	Inclusion criteria	Ns	Intervention	Outcomes	Evidence Synthesis
		study design.				
Korczak 2011	Comorbidity	Biological link between T1DM and major depressive disorder in children and adolescents – exclude (not adults).	N/A	N/A	N/A	N/A
Popkin 2001	Comorbidity	No methods described.	N/R	None	Discussion paper, focusing on the association between diabetes and schizophrenia, diabetes and depression, and diabetes-related complications and their links to psychiatry.	Narrative discussion only.
Sobel 2005	Comorbidity	No methods described.	N/R	None	Discussion paper. Focuses on anxiety and depression for several chronic illnesses, section on diabetes.	Narrative discussion only, no data in diabetes section.
Beardsley 1993	Epidemiology	Papers examining the effects of psychological disorders on the	Not reported	None	Psychological factors affecting onset of illness; psychological	No pooled analyses. Mostly descriptive, occasional individual data.

Paper	Category	Inclusion criteria	Ns	Intervention	Outcomes	Evidence Synthesis
		onset, exacerbation and perpetuation of endocrine disease.			factors affecting course of illness; relationship between personality and coping strategies in the course of diabetes; relationship between psychosocial factors and the course of diabetes	
Egede 2010	Comorbidity	Studies examining the association between diabetes and depression.	Not reported.	None.	No methods reported. Paper focuses on the global burden of diabetes and depression; screening for depression; prevalence of depression in individuals with diabetes; causal pathways between depression and diabetes; effect of depression on	No pooled data. Data on individual papers on self-care behaviours; health care use; health care expenditure; effect of depression on all-cause mortality (hazard ratios).

Paper	Category	Inclusion criteria	Ns	Intervention	Outcomes	Evidence Synthesis
					glycaemic control and self-care behaviours; effect of depression on risk for diabetes complication; effect of depression on disability, work productivity and quality of life in individuals with diabetes; effect of depression on healthcare utilisation and costs; effect of depression on mortality in individuals with diabetes; effectiveness of treating depression in individuals with diabetes; cost of treating depression in individuals with diabetes	
Khoza 2011	Epidemiology	Case reports	17 case	None	Glucose control	No pooled data. Narrative

Paper	Category	Inclusion criteria	Ns	Intervention	Outcomes	Evidence Synthesis
		associating the use of antidepressant agents and glucose dysregulation.	reports		disturbances following antidepressant therapy.	summary of each case report.
McIntyre 2011	Epidemiology	Articles examining the effects of depression with comorbid medical conditions in the workplace. Not specific to diabetes.	7 articles including reviews	Some interventional studies discussed.	Work productivity, disability, economic cost, absenteeism, presenteeism.	No synthesis, narrative discussion.
McIntyre 2007	Epidemiology	Studies examining relationship between Major Depressive Disorder and Diabetes type 2.	N/R	None	Neurocognitive deficits, neuroimaging abnormalities, potential mediators linking MDD with DM2.	Narrative discussion only.
Musselman 2003	Epidemiology	Studies investigating pathophysiological alterations related to glucose intolerance and diabetes in depressed patients.	N/R	Some interventions discussed e.g. pharmacological therapies.	Medical risk factors for depression in diabetes; sociocultural risk factors; impact; antecedent depression and subsequent risk of T2DM.	No synthesis, narrative discussion.
Nouwen 2011	Epidemiology	Studies reporting the prevalence of	13 studies, with 1483	None	Depression in individuals with	Meta-analysis, Odds Ratios.

Paper	Category	Inclusion criteria	Ns	Intervention	Outcomes	Evidence Synthesis
		depression in individuals with impaired glucose metabolism or undiagnosed diabetes relative to each other. Compares rates to normal glucose metabolism and/or previously diagnosed diabetes.	subjects with UDD, 6236 with IGM, and 2121 with PDD.		UDD, IGM, PDD and NGM.	
Ramasubbu 2002	Epidemiology	No methods described.	N/R	None	Relevance of IR as a link between depressive disorder and atherosclerotic vascular diseases	No pooled analysis. Data from individual studies reported.
Jacobson 2002	Epidemiology	Methods not described.	N/R	None	Factors affecting psychiatric illness in diabetess (social and demographic characteristics); lifetime prevalence estimates; hypoglycaemia and cognitive function; diabetes, brain structure and brain	No pooled data, some data from individuals studies reported for listed outcomes. Hypothesised model of relationship of depression and diabetes.

Paper	Category	Inclusion criteria	Ns	Intervention	Outcomes	Evidence Synthesis
					function; depression/depression and medical complications.	
Jakovljevic 2007	Epidemiology	Papers with original data looking at the association between metabolic syndrome and psychiatric disorders and pathophysiologic mechanisms that link these disorders.	N/R	None.	Prevalence of metabolic syndrome and schizophrenia, bipolar disorder, depression, PTSD, personality disorders; mechanisms linking metabolic disorders and metabolic syndrome: hypothalamic-pituitary-adrenal (HPA) activity, autonomic nervous system imbalance, inflammation, central serotonergic (5-HT) responsivity, lifestyle disorders, medication.	No pooled data. Prevalence rates given for metabolic syndrome and schizophrenia.
McIntyre	Epidemiology	Pre-clinical and	Not	None	Blood	No pooled effects. Data from

Paper	Category	Inclusion criteria	Ns	Intervention	Outcomes	Evidence Synthesis
2006		clinical investigations with priority given to RCTs. Studies exploring the effect of antidepressants on glucose-insulin homeostasis	reported		glucose/insulin levels in antidepressant users (diabetes and non-diabetes)	individual papers for blood glucose/insulin levels.
Cimpean 2011	Interventions	RCTs of outpatient interventions addressed to people with comorbid specific chronic medical illness (including diabetes) and anxiety/depression disorders.	14 trials: 6 complex interventions based on CCM; 8 RCTs of psychosocial interventions	Includes IMPACT, PROSPECT, PATHWAYS; COPES; ENRICHD; CREATE.	Quality of Life; satisfaction; morbidity; mortality; use of services.	No pooled analyses. Reports %s and p values for individual trials.
Gill 2000	Interventions	Antidepressants in medical illness – not specific to diabetes. Only 1 study included relevant to diabetes, exclude.	N/A	N/A	N/A	N/A
Iwata 2009	Epidemiology	Studies evaluating cognitive or psychosocial aspects in elderly patients with diabetes.	N/R	None	Association between diabetes and cognitive function; cognitive impairment in	No pooled data, occasional reporting of effects sizes from individual papers or meta-analyses.

Paper	Category	Inclusion criteria	Ns	Intervention	Outcomes	Evidence Synthesis
		Methods not described.			diabetes; glycaemic control and cognitive dysfunction; vascular dementia, Alzheimers and diabetes; depression and diabetes; relevance to diabetes care: screening for psychosocial barriers; individualised management for patients with diabetes and cognitive and social problems.	
Snoek 2002	Interventions	Studies evaluating psychological interventions in diabetes.	11 RCTs	Psychosocial interventions; counselling; psychotherapy.	Improvements relating to: Depression, eating disorders, anxiety/stress; self-destructive behaviour; interpersonal/family conflicts.	No pooled evidence. Limited reporting of individual data. No effect sizes.
Steed 2003	Interventions	Studies evaluating	36 studies	Educational self-	Quality of Life or	No pooled data. P values for

Paper	Category	Inclusion criteria	Ns	Intervention	Outcomes	Evidence Synthesis
		the provision of educational self-management or psychological interventions in adults with T1DM or T2DM. Pre-post controlled trial design only.		management or psychological interventions.	psychological well-being (general well-being, depression, anxiety, or emotional adjustment)	individual studies for listed outcomes.
Wang 2008	Interventions	Studies examining non-pharmacological treatments for depression in individuals with T2DM. Interventions included psychological therapy, non-pharmacological therapies. RCTs only.	3 trials	Interventions included CBT, self-management, collaborative treatment (problem-solving and antidepressants).	Depressive symptoms and glycaemic control (HbA1c).	Meta-analysis for changes in depression and HbA1c (Odds ratios).
Goodnick 1995	Epidemiology	Studies relating to epidemiology, neurochemicals and glucose control, antidepressants and factors of importance to diabetes	Epidemiology 20 papers; neurochemicals: 15 papers; antidepressants: 28 papers.	None	Prevalence rates of depression in diabetes; impact of depression on diabetes management; biochemical effects of antidepressant	No pooled analyses. Data reported for individual studies for listed outcomes.

Paper	Category	Inclusion criteria	Ns	Intervention	Outcomes	Evidence Synthesis
					pharmacological treatment of depression in diabetes patients	
Joss 1999	Interventions	Not available	N/A	N/A	N/A	N/A
McIntyre 2005	Epidemiology	Papers describing the cross-sectional and longitudinal epidemiological associations between bipolar disorder and diabetes.	N/R	None	Bipolar disorder and glucose metabolism – etiology and pathophysiology.	No pooled data. Only bipolar so exclude.
Rustad 2011	Epidemiology	No methods described. Reviews multiple topics around depression in people with diabetes.	N/R	Small section on interventions for depression in diabetes.	Epidemiology of depression/diabetes, antecedent depression and depressive symptoms as an independent risk factor for development of T2DM; prevalence of functional disability for diabetes/depression; all cause mortality; nonadherence to	No original meta-analyses, but reports some data from individuals studies and existing meta-analyses for listed outcomes.

Paper	Category	Inclusion criteria	Ns	Intervention	Outcomes	Evidence Synthesis
					diabetes self-care; missed medical appointments; pathophysiology of depression/diabetes; diagnosis of depression in patients with diabetes; treatments for depression in patients with diabetes.	
Agius 2010	Shared Care	Trials, systematic reviews and metaanalyses carried out on shared care in the treatment of depression.	Ns not given. Discussion paper based on literature review.	None	N/A	Narrative discussion of selected results. No data.
Smith 2007 (Cochrane)	Shared Care (not specifically depression and diabetes)	RCTs, controlled clinical trials, controlled before and after studies, interrupted time series analyses of shared care interventions for chronic disease	20 studies	Any type of intervention that involved continuing collaborative clinical care between primary and specialist care physicians in the management of patients with pre-specified chronic diseases.	Patient health outcome; patient behaviour including measures of medication adherence and utilization of health services; provider behaviour;	Absolute difference, relative percentage difference, absolute change from baseline, difference in absolute changes from baseline. No pooled data.

Paper	Category	Inclusion criteria	Ns	Intervention	Outcomes	Evidence Synthesis
		management. People or populations with a specified chronic disease who were enrolled in a defined shared care service provided by primary and specialty care practitioners.			efficiency and cost; acceptability of the service to patients and providers if this was reported using validated measures.	
Sajatovic 2010	Prevention	Methodology not described.	Not reported.	None.	Prevention of depression in a range of populations.	Descriptive review, no data. Short paragraph on prevention of depression in diabetes, contains some refs that may be useful.
Lysy 2008	Physical Activity	Cross-sectional or RCTs. Adults with T2DM, depression, major depression, mood disorder.	12 studies: 10 cross-sectional, 2 RCTs.	RCTs: Depression-specific management.	Diabetes care outcomes, including level of physical activity.	For cross-sectional studies, estimate of likelihood of depressed mood in inactive versus active and/or inactivity in the depressed versus non-depressed (Relative Risk or adjusted Odds Ratios). No pooled analyses.
Breitscheidel 2010	Economics	Unavailable	Unavailable	Unavailable	Unavailable	Unavailable
Lehnert 2011	Economics	GERMAN	GERMAN	GERMAN	GERMAN	GERMAN
Egede 2006	Economics	No methods described	N/A	Contains a narrative review of depression	Costs. Some data from individual	No pooled analyses.

Paper	Category	Inclusion criteria	Ns	Intervention	Outcomes	Evidence Synthesis
				treatment interventions in individuals who have depression.	studies for: worldwide burden of depression; prevalence of depression in individuals with diabetes; effect of glycaemic control and risk for diabetes-related complications; effect of depression on disability, work productivity and QoL; effect of depression on health care costs; effect of depression on medication adherence; effect of depression on diabetes self-care behaviours; effect of depression on mortality; causal pathways between diabetes and	

Paper	Category	Inclusion criteria	Ns	Intervention	Outcomes	Evidence Synthesis
					depression; barriers to effective treatment of depression.	

PTSD: Post Traumatic Stress Disorder; QoL: Quality of Life

Appendix 3: Summary tables of information used for decision-making for inclusion of reviews

Prevalence of Depression in Individuals with Diabetes

3.2.1 Summary of review findings for prevalence rates

Review	Pooled prevalence of depression in individuals with diabetes
Anderson 2001	31% OR 2.0 (95% CI 1.8 to 2.2). Results differed by study type.
Nouwen 2010	OR 1.24 (95% CI 1.09 to 1.40)
Mezuk 2008	Depression associated with 60% increased risk of T2DM RR 1.15 (95% CI 1.02 to 1.30) for incidence ofdepression associated with baseline diabetes. RR 1.60 (95% CI 1.37 to 1.88) for incidence of diabetes associated with baseline depression.
Ali 2006	17.6% OR 1.6 (95% CI 1.2 to 2.0) (but notes sex confounded this results)
Rotella 2013	1.6% incidence of depression in diabetes subjects

OR: Odds Ratio; RR: Risk Ratio; CI: Confidence Interval

3.2.2. Reported prevalence rates from individual studies reported in the reviews

Study	**Prevalence of depression in diabetes**
Ciechanowski 2001	30.2%
Mauksch 2001	51%
Katon 2004	12%
De Groot 2006	25.3%
Mims 2006	27%
Anderson 2007	31.4%
Olvera 2007	32.3%
Campayo 2010	Depression associated with 65% increased risk of T2DM
Gale 2010	Men with undiagnosed diabetes: OR 1.80 for diagnosis of MDD; Men with diagnosed diabetes OR 3.82.
Knol 2006	Adults with depression 37% increased risk of developing T2DM
Knol 2007	29.7% for diagnosed type 2, 20% for undiagnosed type 2
Aarts 2009	HR 1.26 (95%CI 1.12 to 1.42)
Brown 2006	HR 1.04 (95% CI 0.94 to 1.15)
De Jonge 2006	OR 1.42 (95% CI 1.04 to 1.93) (age-sex adjusted) OR 1.26 (95% CI 0.90 to 1.77) (fully adjusted)
Engum 2007	OR 1.24 (95% CI 0.78 to 1.98)
Golden 2008	OR 0.75 (95% CI 0.44 to 1.27) in untreated diabetes OR 1.54 (95% CI 1.13 to 2.09) in treated diabetes
Maraldi 2007	OR 1.31 (95% CI 1.07 to 1.61)
O'Connor 2009	OR 1.46 (95% CI 1.19 to 1.80) in patients with few physician visits OR 0.95 (95% CI 0.77 to 1.17) in patients with lots of physician visits
Palinkas 2004	OR 0.73 (95% CI 0.41 to 1.30)
Stein	7.2%
Blazer	9.6%
Katon	Ns given for major and minor.
Sacco	16%

Kessing	29.03%
Bruce	31.5%
De Groot	25.3%

OR: Odds ratio; HR: Hazard ratio; MDD: Major Depressive Disorder

Appendix 3.2.3 Summaries of reviews not considered for inclusion within the model.

Lustman et al 2000 [1] conducted a systematic review and meta-analysis of the relationship between depression and glycaemic control. Studies of adults with either T1DM or T2DM were included. Direction of the relationship between depression and glycaemic control was not an exclusion factor. Studies using depression as the independent variable were considered, as were studies where depression was the dependent variable. Depression was defined by self-report instrument. Pearson's r was calculated to determine the relationship between depression severity and glycaemic level, as defined by HbA1c. 26 cross-sectional studies were identified and 5 RCTs. 24 studies were included in the meta-analysis, which showed a significant association between depression and hyperglycaemia ($Z=5.4$, $p<0.0001$). The effect size was small to moderate, and was of similar size when T1DM was compared to T2DM. Based on the results of the conceptual modelling, it was decided that the economic model used for this project would not directly model any relationship between depression and glycaemic control. Hence this study was deemed to not be required for the economic model.

A further review by Lustman and Clouse 2005 [2], searched for studies evaluating the relationship, outcomes, and/or management of depression in diabetes. No review methods were presented therefore it was not possible to identify specific inclusion/exclusion criteria. The paper provided a narrative overview of different aspects of comorbid depression and diabetes. Evidence is presented from individual studies that show that depression in diabetes is associated with a decrease in metabolic control, poor adherence to medication and diet regimens, a reduction in quality of life, and an increase in health care expenditures. The review highlights studies that show psychological and pharmacological interventions are effective in treating depression in diabetes. As the review did not contain pooled data, it was excluded from further consideration.

Bowser et al 2010 [3] conducted a systematic review of the literature on the relationship between the diagnosis of diabetes and depression and missed appointments in a low-income uninsured racially heterogeneous population. Inclusion criteria included studies relevant to 4 topic areas: diabetes management, depression, free clinics for a low-income uninsured racially homogenous adult population, and missed appointments. 50 papers were identified, 23 for diabetes management, 10 to describe the concept of free clinics, 23 studies on depression and 9 describing missed appointments. The review presents the information on these studies in a narrative synthesis.

Whilst the review provides a useful overview of these topic areas, no statistical synthesis is conducted and the study was therefore excluded from further consideration.

Renn et al 2011 [4] conducted a systematic review of the literature regarding the bi-directional relationship of diabetes and depression. Studies were included if they examined this relationship, including directionality, comorbidity, and/or prevalence of diabetes and depression. The review focused on adults with T2DM. Results of the review were presented as a narrative synthesis, and provided an overview of this area, including depression as a risk factor for diabetes, depression as a consequence of diabetes, and evidence for a bi-directional relationship. As no statistical synthesis was conducted, the review was excluded from further consideration.

Albers et al 2011 [5] conducted a systematic review of diabetes and incidence of depression, with a focus on whether this association is mediated or moderated by sociodemographic factors or comorbidities. Searches looked specifically for articles focused on longitudinal studies which evaluated the appearance of depression in individuals with and without diabetes. These data were analysed to identify interactions or additional influences of potential modifying factors. Eight studies were identified, these were from the US, Netherlands, Norway and Spain. Only 3 of the studies analysed interaction using interaction terms in multiple regressions. No significant effect was found for modifying factors of interest. As the focus of this review was very narrow, few studies were identified. Broader reviews as described above were considered to contain more useful pooled data for the model.

Ali et al 2010 [6] reviewed the relationship between depression and HRQoL in people with T2DM. Searches were conducted up to 2007. HRQoL was defined as a subjective patient-reported construct encompassing multiple dimensions including physical, emotional, and social functioning. Studies had to include adults with T2DM, with depression identified through a previously validated instrument. HRQoL was identified through a previously validated instrument. Studies with fewer than 25 participants were excluded. Fourteen studies with 14,605 participants were included in the review. A recurring theme for these reviews was the lack of UK data available. No UK studies were identified for this review, with the majority of studies conducted in the US, and the remaining studies conducted in Croatia and Finland. Results of the review were presented in a narrative synthesis, with summary characteristics for each study reported. The authors report evidence that comorbid depression in T2DM has detrimental associations with HRQoL. As no pooled data were reported, the review was excluded from further consideration.

Astle et al 2007 [7] conducted a systematic review of the literature concerning depression in diabetes. Studies were not excluded for population, study design or diabetes type. The review provides a narrative overview of the topic, and presents summary characteristics for included studies. Results are presented as a narrative synthesis, and as no pooled data was available, this review was excluded from further consideration.

Egede and Ellis 2010 [8] conducted a systematic review of the literature on the relationship between diabetes and depression. Review methods are not described therefore it is not possible to give an overview of inclusion/exclusion criteria. A broad range of literature in presented in a narrative synthesis. Topics identified as important issues for comorbid depression and diabetes and discussed within the paper include the global burden of both diabetes and depression; screening for depression; the prevalence of depression in individuals with diabetes; causal pathways between depression and diabetes; the effect of depression on glycaemic control and self-care behaviours; the effect of depression on risk for diabetes complications; the effect of depression on disability, work productivity and quality of life in individuals with diabetes; the effect of healthcare utilization and costs in individuals with diabetes; the effect of depression on mortality in individuals with diabetes; the effectiveness of treating depression in individuals with diabetes; the cost of treating depression in individuals with diabetes. No pooled data was presented therefore the review was excluded from further consideration.

Serretti and Mandelli 2010 [9] conducted a systematic search and meta-analysis of the evidence to explore the effect of the most common types of antidepressant medication on weight gain. The review was not focused on weight gain in people with diabetes. Placebo-controlled and non-placebo-controlled trials were included. Individual and global mean differences were calculated for meta-analysis of data. The primary outcome was weight change. 116 studies were included in the analysis. Meta-analysis indicated that amitriptyline, mirtazapine, and paroxetine were associated with a greater risk of weight gain (MDs amitriptyline short-term 1.52; 95% CI 1.08 to 1.95; mirtazapine short-term 1.74; 95% CI 1.28 to 2.20), (MD paroxetine medium-term 2.73; 95% CI 0.78 to 4.68). Fluoxetine and bupropion were associated with weight loss (MDs fluoxetine short-term -0.94; 95% CI -1.24 to -0.65; bupropion -1.13; 95% CI -1.41 to -0.84). Whilst this large review offers useful data on the association of weight change with antidepressant use, it was not specific to diabetes and therefore it was excluded from further consideration. In addition, based on advice from

clinical experts it was felt that it was not necessary to consider weight change after antidepressant use within the economic model.

Appendix 4 Costs associated with depression in diabetes (data from individual studies retrieved from reviews)

Study	Finding
Ciechanowski 2000	Increased annual cost of $2100 for patients with diabetes and depression versus diabetes alone
Egede 2002	X4.5 increase cost of care for patients with diabetes and depression
Finkelstein 2003	Mean Medicare payments x2 as great and median payments x3 as great for patients with diabetes and depression
Von Korff 2005	19% had significant work disability (12% unemployed and 7% missed >5 days of work in past month); 50% of unemployed were depressed
Simon 2005	70% increase in health service costs with diabetes and depression
Stein 2006	50% of cost of chronic disease is related to depression; x2 health care utilisation with patients who are both chronically ill and depressed versus chronic illness alone

NB: Not UK data

Appendix 4: Summary of results of studies retrieved from targeted searches

Outcome	Paper	Aim of Study	Type of Study	N	Main outcomes	Data
Prevalence of depression amongst T2DM	Ali 2009	Identify prevalence of depression amongst patients with diabetes. (UK)	Cross-sectional study	Total N 6230, of which 1405 T1DM and 4781 T2DM.	Depression, as identified through case documentation or being in receipt of antidepressant medication. Also data collected for demographic variables, comorbidities (one or more of CHD, cerebrovascular disease, asthma, chronic obstructive pulmonary embolism, heart failure, peripheral vascular disease, inflammatory bowel disease, irritable bowel syndrome, epilepsy, hypothyroidism, transient ischaemic attack, fibromyalgia, malignant neoplasm) and complications (one or more of peripheral neuropathy, diabetes	No. and %. Prevalence rate for depression amongst patients with T2DM = 9.3% (435). Of those 253 had complications. 252 had comorbidities. Data also available broken down by South Asian versus White European. No distinction made for depression severity.

Outcome	Paper	Aim of Study	Type of Study	N	Main outcomes	Data
					retinopathy, nephropathy, neuropathy, microalbuminuria)	
	Skinner 2010	Data on prevalence of depression in T2DM from DESMOND trial (UK)	Post hoc analysis of data from an RCT	824 individuals newly diagnosed with T2DM	Depression during first year of diagnosis, identified by HADS. Not depressed, not depressed on antidepressants, mild depression, severe depression.	% of T2DM with depression for baseline and 4, 8 and 12 months post T2DM diagnosis. Prevalence 18%-22% over the first year. No significant effect over time for depressive symptoms over 1 year.
	Das-Munshi 2007	To determine the association between diabetes and common mental disorders	Cross-sectional survey	249 individuals with diabetes	Psychiatric morbidity assessed using the Revised Clinical Interview Schedule.	People with diabetes more likely to suffer common mental disorders (OR = 1.5; 95% CI 1.1-2.2, p<.05
Depression progression: Incidence rates; relapse rates; recovery rates; progression rates.	Lustman 1997	Recurrence or persistence of depression in diabetes patients. (US)	5 year follow-up study of diabetes patients who had participated in an 8 week depression trial	25 diabetes patients followed-up from a previous trial.	At 5 year reevaluation, depression assessed using DSM-III-R criteria, broken down by severity.	Recurrence or persistence of depression occurred in 23/25 patients, with an average 4.8 depression episodes over 5 year period. Duration of longest epidose averaged 16 months. Year 1 all subjects 20/25 depressed; nortiptyline responders 4/7 depressed; nortriptyline nonresponders 5/5 depressed; placebo

Outcome	Paper	Aim of Study	Type of Study	N	Main outcomes	Data
						responders 3/5 depressed; placebo non responders 8/8 depressed. Year 5 all subjects 23/25 depressed; nortriptyline responders 6/7 depressed; nortryptaline nonresponders 5/5 depressed; placebo responders 4/5 depressed; placebo non-responders 8/8 depressed.
	Lustman 2006	Effect of sertraline on depression recurrence in T2DM (US)	Randomized double-blind placebo-controlled trial	152 patients with T2DM who had previously recovered from depression (43.3% of those originally sampled for a previous study)	Recurrence of depression. See previous Lustman study for recovery rates. Major depression defined by DISH scale (Depression Interview and Structured Hamilton Scale – designed and validated specifically to diagnose depression in patients who are medically ill). BDI scores at timepoints during induction and maintenance phases.	Time to recurrence for treatment group and placebo. Proportional hazard for recurrence on sertraline 0.51 (95% CI 0.31-0.85). At 1 year, the calculated rate of non-recurrence was 65.8% for sertraline group compared with 47.9% for placebo group. Time to recurrence 57 days for placebo group, 226 days for sertraline group. Median time to recurrence 251 days for placebo group, exceeding 365 days (maximum follow-up) for sertraline group.
	Ell 2012	Depressive	Sub-cohort of	193 diabetes	Major Depressive	Depressive symptom

Outcome	Paper	Aim of Study	Type of Study	N	Main outcomes	Data
		symptom deterioration in diabetes patients (NB patients are predominantly Hispanic) (US)	diabetes patients following completion of a clinical intervention trial.	patients with major depression symptoms at baseline who had received collaborative care intervention or enhanced usual care, who no longer met depression criteria at 12 months, and who were subsequently observed over 18-24 months.	Disorder (MDD) as defined by at least one of the two cardinal depression symptoms more than half the days to nearly every day over the past 2 weeks and PHQ-9 score ≥10. Symptom deterioration over a one-year post-intervention period defined as meeting MDD at 18 or 24 months among those who did not meet PHQ-9 criteria for MDD at 12 month follow-up. NB: standard definitions define relapse as occurring prior to 6 months after reaching symptom remission and recurrence as occurring ≥ 6 months after symptom remission. However, in most depression treatment trials, only a minority of	deterioration in enhanced usual care group 30/85 (35.5%), in intervention group 38/108 (35.2%).

Outcome	Paper	Aim of Study	Type of Study	N	Main outcomes	Data
					patients meet remission criteria at study completion, with the majority having residual symptoms. Therefore the term 'symptom deterioration' is used.	
	Peyrot 1999	To determine the level and pattern of persistent depressive symptoms amongst adults with diabetes. (US)	Self-report depression inventory at 2 follow-up time points.	245 adults with diabetes who completed a 1 week diabetes education program.	CESD depression scale used to identify depression. Considered persistently depressed only if patients met criterion for disturbance at all 3 time points.	Pre-intervention: 93/245 depressed, 152/245 not depressed. Post-intervention 44/93 depressed still depressed, 49/93 not depressed. 9/152 not depressed now depressed, 143/152 not depressed still not depressed. Follow-up: 32/44 depressed still depressed, 12/44 depressed no longer depressed. 18/49 not depressed now depressed, 31/49 not depressed still not depressed. 3/9 depressed still depressed, 6/9 not depressed were depressed, 15/143 depressed were not depressed, 128/143 not depressed, were not depressed.

Outcome	Paper	Aim of Study	Type of Study	N	Main outcomes	Data
	Nefs 2012 (Netherlands)	Examine the course (incidence, recurrence/persistence) of depressive symptoms)	Cohort study (DiaDDZoB)	2460 primary care patients with T2DM.	Depression as identified by ≥12 on Edinburgh Depression Scale. No depression/depression groups. Incidence of depression determined in the subgroup with an EDS score, 12 at baseline. Patients with EDS score ≥12 from this group at either follow-up were considered incidences. Rates of recurrence/persistence examined for those scoring ≥12 on EDS at baseline. Depression labelled recurrent/persistent if patients had at least one other high EDS score at either follow-up.	630/2460 (26%) of T2DM patients met criteria for depression at one of more assessments. Prevalence of depression at baseline and each yearly follow-up: Baseline – 320/2460, year 1 – 343/2460, year 2 – 389/2460. No baseline depression: incidence of depression at follow-up = 14% (n=310). Recurrence/persistence in group with baseline depression = 66% (n=212).
	Fisher 2008	To report the prevalence and correlates of mood disorders in adults with	Longitudinal study	506 patients with T2DM	MDD (CES-D), dysthymia (CIDI), depressive affect (and other mood disorders) and diabetes distress	Prevalence % and SE for all outcomes at T1, prevalence over 18 months condition present at any of three waves. Persistence - % of

Outcome	Paper	Aim of Study	Type of Study	N	Main outcomes	Data
		T2DM over time. (US)			(DDS) assessed 3 times over 18 months.	patients with a condition at: only a single wave, at any 2 waves, at all 3 waves.
	Bot 2010	Effect of stepped care intervention on depressive symptoms in diabetes patients with subthreshold depression (Netherlands)	Follow-up of STEPPED (RCT of stepped care intervention for diabetes patients with elevated depression symptoms	114 at baseline, 73 at 2 year follow-up.	Incidence of major depression during 2 year follow-up. Determined by MINI. Severity after 2 years assessed with CES-D.	Incidence of major depression at follow-up 42%. Baseline depression severity related to onset of major depression (OR = 1.08, 95% CI 1.00-1.18, p=0.02). Type of intervention not related to incidence of major depression during 2 year follow-up (OR = 1.25, 95% CI 0.49-3.18,p=0.64).
Screening and Case-finding	Fleer 2012 (Netherlands)	Investigate the willingness of patients with diabetes to participate in a screening programme, the extent to which patients with diabetes who screen positive endorse the need for psychosocial care, rate of	Observational study.	499 patients with diabetes were eligible for the screening questionnaire. 347 completed the screening questionnaire.	Depressive symptoms as measured by the CES-D scale. Diabetes distress measured using the PAID scale. Patients scoring above cut-off for depressive symptoms on the screening questionnaire were followed-up with an interview.	152 non-responders, of which 113 did not turn up for screening appointment. 104/347 who were screened scored above cut-off on CES-D or PAID. 70/104 identified as at risk of clinical depression. 28/104 identified as high risk for both depression and diabetes distress. 6/104 identified as high risk for diabetes distress. 35/104 not interested in further screening. 8/104 had already received further help.

Outcome	Paper	Aim of Study	Type of Study	N	Main outcomes	Data
		referral to psychosocial care during screening versus usual care.				5/104 did not show up for appointment. 4/104 cancelled appointment. 1/104 forgot and was not interested in new appointment. 45/104 accepted invitation for diagnostic interview. 36/104 had unmet need for which they would like a referral for additional psychosocial care. In comparison, 1 year after cessation of formal screening, 528 patients met inclusion criteria, of which 6 were referred for additional psychosocial services.
	Pouwer 2011 (Netherlands)	Test the effectiveness of online screening procedure for depression versus care as usual.	Multicentre parallel randomised controlled trial	223 outpatients with diabetes who had an elevated depression score. 107 CAU group, 116 SCR group (CIDI with written feedback).	Depression, as identified through the Composite International Diagnostic Interview (CIDI). Baseline and 6 month follow-up depression measured using CES-D and the PAID.	2% of men and 21% of women with T2DM diagnosed with a depressive disorder. % of patients receiving depression treatment during study period 18% CAU, 28% SCR. At6 month follow-up, no significant difference between groups on depression scores (% with elevated depression score CAU 68%, SCR 75%).

PHQ-9: 9-item Patient Health Questionnaire; OR: Odds Ratio; CI: Confidence Interval; DSM-III-R: Diagnostic and Statistical Manual-111-Revised; HADS: Hospital Anxiety and Depression Scale; CES-D: Center for Epidemiological Studies – Depression; EDS: Edinburgh Depression Scale; CIDI: Composite International Diagnostic Interview; MDD: Major Depressive Disorder; DDS: Diabetes Distress Scale; MINI:Mini International Neuropsychiatric Interview; PAID: Problem Areas in Diabetes Questionnaire; CAU: Care As Usual; SCR: Screening.

Appendix 5: Table of summary characteristics of papers considered after first sift for complications

Paper	Complication	Aim of Study	Type of Study	N	Main outcomes	'Include' (for further consideration) or reason for exclusion
Al Snih 2005	Lower body disability	To examine the relationship between diabetes mellitus and incidence of lower body disability	7 year prospective cohort study	1835 Mexican-Americans, non-disabled at baseline. Of which 347 had diabetes (type not specified), 1488 had no diabetes.	Incidence of lower body disability, rates for heart attack, stroke, hypertension, near vision impairment, distant vision impairment, arthritis and obesity for diabetes and non-diabetes. Depressive symptoms for diabetes and non-diabetes. Multi-variate analysis for listed outcomes to predict hazard of lower body disability.	Depressive symptoms by diabetes group, complications by diabetes group, but no analyses to link depression to diabetes symptoms.
Albert 2009	Heart failure	To examine outcomes in hospitalised heart failure patients with a documented history of depression.	Cross-sectional study	48612 patients with heart failure	Rates of depression in heart failure patients, association of depression with hospital treatments and mortality, early post-discharge mortality, emergency care and rehospitalisation. Rates of depression in diabetes comorbidity.	Single complication, cross-sectional
Altenburg 2010	Foot ulcers	To characterise bio-psycho-social	Case controlled cross-sectional	47 diabetes patients with	Depression as identified through CIDI and BDI. Cross-	Single complication, cross-sectional

Paper	Complication	Aim of Study	Type of Study	N	Main outcomes	'Include' (for further consideration) or reason for exclusion
		factors associated with the development of diabetes foot ulcers.	study	foot ulcers, 47 diabetes patients without foot ulcers. All type 2 diabetes.	sectional associations between biological, psychological and social factors and the presence of diabetes foot ulcers.	
Angermann 2011	Systolic heart failure	To investigate somatic correlates of comorbid depression in patients with heart failure.	Prospective cross-sectional study.	702 patients hospitalised for heart failure.	Depression as identified through the PHQ-9. Numbers for diabetes mellitus, type not specified. Multivariate regression analysis to identify associations with major depression.	Single complication, cross-sectional
Bajaj 2012	Microalbuminuria (nephropathy) Raised serum creatinine Dyslipidemia Retinopathy ECG abnormalities	To study the association of depression with diabetes and its complications in newly diagnosed type 2 diabetes.	Single point cross-sectional case controlled study.	60 newly diagnosed type 2 diabetes patients, and 60 age and sex matched normal healthy volunteers.	Prevalence of depression as identified through the BDI. Rates of complications in newly diagnosed diabetess for those with depression compared with those without depression.	Cross-sectional
Bhatterai	CHD	To determine	Cohort study	299,912	Includes prevalence rates for	Cross-sectional

Paper	Complication	Aim of Study	Type of Study	N	Main outcomes	'Include' (for further consideration) or reason for exclusion
2013	Stroke	whether depression in patients with long term conditions is associated with the number of morbidities or type of comorbidity		participants aged 30-100	Type 2 diabetes and comorbid CHD, T2DM and stroke, and T2DM, CHD and stroke. Also health care utilization and costs.	
Black 2003	Macrovascular complications (cardiovascular disease, stroke and kidney disease), microvascular complications (nephropathy, neuropathy, retinopathy, amputations)	To examine the separate and combined effects of depression and diabetes on the incidence of adverse health outcomes among older Mexican Americans.	Longitudinal study over 7 years	2830 Mexican Americans aged >65 years	Prevalence of diabetes and depression and rates of adverse outcomes.	Include
Bot 2012	Myocardial infarction	To examine the joint association of diabetes and depression with	Data from two multicentre cohort studies	2704 patients hospitalised for MI	Depression as diagnosed by BDI, diabetes and mortality rates post MI.	Mortality rates only

Paper	Complication	Aim of Study	Type of Study	N	Main outcomes	'Include' (for further consideration) or reason for exclusion
		mortality in MI patients.				
Boulanger 2009	Neuropathy, Cardiovascular disease, Cerebrovascular /peripheral vascular disease, Infections, Nephropathy, Obesity, Retinopathy, Hypoglycaemic events Skin problems, Leg amputation	To examine and quantify factors associated with healthcare costs among patients with diabetes neuropathy with or without a comorbid diagnosis of depression or anxiety	Retrospective cohort study using administrative claims data.	16,831 DN only, 1699 DN-DA patients in Medicare supplemental cohort, 17,205 DN and 3105 DN-DA in commercially insured cohort	Prevalence of diabetes-related comorbidities (cardiovascular disease, cerebrovascular/peripheral vascular disease, nephropathy, obesity, hypoglycaemic events) in patients with or without comorbid depression, and related costs.	Main outcome is healthcare resource costs
Chyun 2006	Microvascular complications: (retinopathy, nephropathy, neuropathy) Cardiac risk factors	To determine the relationship between sociodemographic influences, diabetes-related factors, including diabetes-related	Observational study	116 participants with Type 2 diabetes age 50 to 75 years, with no subjective or objective	Multivariate linear regression to determine factors associated with eight QoL domains on SF-36 and two on D-QoL.	Dependent variable is quality of life

Paper	Complication	Aim of Study	Type of Study	N	Main outcomes	'Include' (for further consideration) or reason for exclusion
		microvacular complications (retinopathy, nephropathy, and neuropathy); CAD risk factors; and psychological factors with QoL.		evidence of CAD		
Clouse 2003	Coronary Heart Disease	To examine the relationship between depression, diabetes and CHD.	10 year observational study	76 female diabetes patients, T1DM and T2DM.	The development of CHD manifestations in diabetes women, with survival analyses to compare rates in a subset with major depression established by psychiatric interview. Also examined effects of depression on the appearance of other macrovascular complications – peripheral vascular disease and cerebrovascular disease.	Only macrovascular complications
De Groot 2001	Retinopathy Nephropathy Sexual dysfunction Neuropathy	To examine the association between depression and diabetes	Systematic review and meta-analysis	27 studies of T1DM and T2DM adults.	Association between depression and diabetes complications.	Included from reviews

Paper	Complication	Aim of Study	Type of Study	N	Main outcomes	'Include' (for further consideration) or reason for exclusion
	Macrovascular	complications.				
Dogdu 2012	Coronary Artery Disease	To investigate the association between emotional conditions and Left Ventricular Systolic Functions in CAD. Reports prevalence of diabetes in preserved and impaired groups.	Prospective cross-sectional study.	168 patients with stable angina and multivessel disease in coronary angiography.	Relationship between depression, anxiety and systolic dysfunction in CAD patients. Prevalence of diabetes reported.	No data for depression with diabetes
Du Burgos-Lunar 2012	Cardiovascular mortality	To examine the effect of depression on cardiovascular events in T2DM	3 year observational prospective cohort study	Protocol stage only	Protocol stage only	Protocol stage only
Egede 2005a	Coronary heart disease	To evaluate the effect of depression on all-cause and coronary heart disease mortality	8-year population-based cross-sectional longitudinal study.	10,025 participants. 4 groups: no diabetes no depression (reference	Multivariate-adjusted hazard ratios of death for each group compared to reference group. Depression identified through CES-D.	All-cause and coronary mortality

Paper	Complication	Aim of Study	Type of Study	N	Main outcomes	'Include' (for further consideration) or reason for exclusion
		among adults with and without diabetes.		group); no diabetes depression; diabetes present no depression; diabetes present, depression present. Diabetes type not specified.		
Egede 2005b	Hypertension Coronary artery disease Chronic arthritis Stroke COPD End-stage renal disease	To determine the effect of coexisting chronic conditions on prevalence and odds of depression in individuals with diabetes.	Cross-sectional study.	1794 adults with diabetes (type not specified). 4 groups: diabetes alone; diabetes plus 1 condition; diabetes plus 2 conditions; diabetes plus	Prevalence of major depression by number of chronic conditions and for each condition. Adjusted Odds Ratios.	Depression is dependent variable

Paper	Complication	Aim of Study	Type of Study	N	Main outcomes	'Include' (for further consideration) or reason for exclusion
				3 or more conditions.		
Findley 2001	Heart disease Hypertension	To investigate the association between multimorbidity and persistent depression in veterans with diabetes, heart disease or hypertension.	Cohort study	1,383,950 veterans with diabetes, heart disease or hypertension	Prevalence rates for diabetes and heart disease, diabetes and hypertension, and diabetes and HD and HTN. Logistic regressions for relationship between listed variables and depression.	Rates of depression main outcome in diabetes patients with complications.
Gendelman 2009	Retinopathy Blindness Neuropathy Amputation Kidney or pancreas transplantation	Prevalence of depression in adults with T1DM and association between depression and diabetes complications	T1DM exclude N/R	N/R	N/R	Only T1DM included
Gonzales 2010	Foot ulcer	To examine the relationship between symptoms of depression an	2 year longitudinal study	333 patients with T1DM or T2DM with diabetes peripheral	Regression to test whether depression was an independent predictor of foot ulcer over 18 months.	Single complication

Paper	Complication	Aim of Study	Type of Study	N	Main outcomes	'Include' (for further consideration) or reason for exclusion
		diabetes foot ulcers		neuropathy but without peripheral vascular disease.		
Guruprasad 2012	Ischemic heart disease Hypertension	To study the association between depression, demographic and socio-medical factors in type 2 diabetes.	Cross-sectional epidemiological study	210 type 2 diabetes patients	Prevalence of depression as defined by BDI, prevalence of IHD and hypertension in T2DM with and without depression.	Cross-sectional
Huang 2010	Coronary artery disease	To examine the relationships between depression, coronary artery disease, type 2 diabetes, metabolic syndrome and quality of life.	Cross-sectional descriptive correlational study.	140 individuals recruited from a hospital cardiovascular department. Participants both with or without CVD or type 2	Rates of metabolic syndrome, CVD, T2DM, depression. Correlations between variables, and regression for predictors of QoL.	No analyses of data for CAD in people with diabetes and depression

Paper	Complication	Aim of Study	Type of Study	N	Main outcomes	'Include' (for further consideration) or reason for exclusion
				diabetes or depression >16 on CES-D		
Icks 2013	Cardiovascular disease Myocardial infarction Stroke Retinopathy Blindness Proteinuria Renal failure Renal replacement therapy Neuropathy Amputation	To determine the risk of the development of high depressive symptoms in diagnosed and previously undetected diabetes compared to those without diabetes.	5 year prospective population-based cohort study	3,633 participants, of which 7% diagnosed diabetes, 5.3% previously undiagnosed diabetes, and the remaining without diabetes.	Numbers for listed complications for diabetes groups. Logistic regression for the relationship between diagnosed and undetected diabetes and the development of depressive symptoms. Regression includes MI and stroke.	Development of depressive symptoms, not development of complications by depression.
Iversen 2009	Foot ulcer	To compare levels of anxiety and depression, psychological well-being and perceived health between persons with diabetes,	Cross-sectional study	65,126 participants, of which 63,632 did not have diabetes, 1339 had diabetes	Levels of anxiety and depression as defined by HADS, and psychological well-being, in non-diabetess, diabetess without foot ulcer, and diabetess with a history of foot ulcer. Multiple regressions.	Depression is dependent variable

Paper	Complication	Aim of Study	Type of Study	N	Main outcomes	'Include' (for further consideration) or reason for exclusion
		with or without a foot ulcer, and persons without diabetes.		without a foot ulcer, 155 had diabetes with history of a foot ulcer.		
Kloos 2009	Foot ulcers	To study whether there is an association between cognitive impairment and the relapse rate of foot ulcers in diabetes patients with previous foot ulcers.	Prospective study	59 patients with diabetes, peripheral neuropathy and a history of foot ulceration	Prevalence of comorbidities/complications by ulcer relapse/no ulcer relapse (includes depression, retinopathy, nephropathy, dialysis, microvascular complications, peripheral vascular disease. Logistic regression for cognitive function as predictor of foot ulcer relapse.	Focus is cognitive function not depression
Labad 2010	Cardiovascular disease	To identify risk factors for depression and anxiety in a cohort of individuals with type 2 diabetes	Cohort study	1066 participants from the Edinburgh Type 2 Diabetes study.	Anxiety and depression measured by HADS, obesity, cardiovascular disease. Linear regression to explore relationships between variables.	Depression is dependent variable
Lin 2010	Microvascular	To examine the	Prospective	4,623	Hazard ratios to report the	Include

Paper	Complication	Aim of Study	Type of Study	N	Main outcomes	'Include' (for further consideration) or reason for exclusion
	complications: Blindness End-stage renal disease Amputations Renal failure deaths Macrovascular complications: Myocardial infarction Stroke Cardiovascular procedures Death	association of depression with risks for advanced macrovascular and microvascular complications among patients with type 2 diabetes.	cohort study	primary care patients with T2DM.	association between baseline depression and risks of adverse outcomes (see complications).	
Monami 2005	Foot ulcer	To assess the role of depressive symptoms in healing and recurrence of diabetes foot ulcers	Cohort observational study	80 type 2 diabetes patients 60 years and older with foot ulcers. Patients who healed within 6 months of enrolment	The association between depressive symptoms and foot ulcer healing and recurrence.	Single complication

Paper	Complication	Aim of Study	Type of Study	N	Main outcomes	'Include' (for further consideration) or reason for exclusion
				were included in a 12 month follow-up study of foot ulcer recurrence.		
Pan 2011	Cardiovascular disease	To evaluate the individual and joint effects of depression and diabetes on all-cause and CVD mortality	Prospective cohort study	78,282 women with or without depression or type 2 diabetes	All-cause and CVD mortality rate. Adjusted Risk Ratios for depression and diabetes.	Only CVD deaths or all-cause mortality as dependent variable
Pan 2012	Macrovascular complications	Contribution of macrovascular complications and hip fracture to depression onset in elderly patients with diabetes.	Longitudinal cross-sectional study over 8 years	144,216 elderly diabetes participants	Cumulative risk of depression in relation to diabetes macrovascular complications and hip fracture. Hazard ratios for association of diabetes with CVD, hip fracture and lower limb amputation.	Depression is dependent variable
Poongothai 2011	Retinopathy Neuropathy Nephropathy Peripheral	To assess the relationship between depression and	Cross-sectional study	847 patients with T2DM	Prevalence of depression defined by PHQ-12. Prevalence of diabetes complications. Odds Ratios for association of	Cross-sectional

Paper	Complication	Aim of Study	Type of Study	N	Main outcomes	'Include' (for further consideration) or reason for exclusion
	vascular disease Coronary artery disease	diabetes complications in T2DM patients in India.			depression with microvascular and macrovascular complications. Prevalence of depression in relation to number of diabetes complications.	
Raval 2010	Neuropathy Nephropathy Peripheral vascular disease Diabetes foot ulcer	To investigate the prevalence and determinants of depression in patients with type 2 diabetes	Cross-sectional study	300 patients with type 2 DM	Binary logistic regression analyses showing risk factors associated with depression in T2DM patients, including complications: neuropathy, nephropathy, retinopathy, microvascular complications (any), CAD, peripheral vascular disease, cerebrovascular accident, diabetes foot, macrovascular complications (any).	Cross-sectional
Rowan 2005	Coronary heart disease	To test a gradient risk for depressive symptoms on CHD incidence .	Population-based prospective study	1302 random sample, 45 years or older.	Risk of CHD event in people with depression as measured by CES-D. Diabetes entered as a covariate.	Single complication
Savli 2005	Microvascular complications Diabetes foot	To determine psychological well-being in diabetes	Cross-sectional study	100 patients with diabetes	The effect of complications on general well-being.	Depression is dependent variable

Paper	Complication	Aim of Study	Type of Study	N	Main outcomes	'Include' (for further consideration) or reason for exclusion
	(others, not clear from abstract)	patients				
Scherrer 2011	Cardiovascular disease	To investigate the association of major depressive disorder with risk of cardiovascular disease in depressed patients with type 2 diabetes compared with non-depressed patients with type 2 diabetes.	Cohort study	4 level risk groups: neither diabetes nor MDD, n=214,749; MDD alone n=77,568; type 2 diabetes alone n=40,953; Comorbid MDD and type 2 diabetes n=12,679.	Hazard ratios for risk of MI for all groups.	Single complication
Shehatah 2010	Retinopathy Blindness Neuropathy Amputation Transplantation	To assess the prevalence of depressive symptoms and antidepressant	Cross-sectional survey	458 participants with type 2 diabetes, and 546	Prevalence of depressive disorder as defined by BDI-II >14 and/or use of antidepressants. Self-reported occurrence of diabetes	No analyses for depression and specific complications

Paper	Complication	Aim of Study	Type of Study	N	Main outcomes	'Include' (for further consideration) or reason for exclusion
		medication use among elderly people with and without diabetes, and the association between depression and diabetes complications		participants without diabetes.	complications.	
Shen 2010	Heart disease Hypertension	To compare rates of major and minor depression in cohorts of women veterans with diabetes or heart disease or hypertension and examine variations in these rates by demographic, socioeconomic and health status.	Retrospective cross-sectional study.	13,430 women veterans with diabetes or heart disease or hypertension who were diagnosed with depression.	Prevalence rates of depression for each condition (abstract only, unclear if there is more specific data that links these conditions)	Depression is dependent variable
Sullivan 2012	Cardiovascular disease	To examine the effect of	4 year longitudinal	2053 participants	Hazard ratios for time-varying impact of depression on clinical	Include

Paper	Complication	Aim of Study	Type of Study	N	Main outcomes	'Include' (for further consideration) or reason for exclusion
	Composite Macrovascular outcome. Composite microvascular outcome.	cardiovascular disease outcomes in type 2 diabetes	study	from ACCORD study.	outcomes including cardiovascular death, nonfatal heart attack, stroke and macrovascular composite outcome (CAD events, nonfatal MI, unstable angina), microvascular composite outcome (fatal or nonfatal renal failure, retinal photocoagulation, vitrectomy for diabetes retinopathy) .	
Taylor 2008	Not complications	N/R	N/R	N/R	N/R	Focus is screening for depression
Trento 2012	Foot ulcers Retinopathy Microalbuminuria	To evaluate the prevalence of depression in patients with type 2 diabetes and its possible correlation with anxiety, cognitive function and clinical variables	Cross-sectional survey	249 non-insulin-treated and 249 insulin-treated outpatients with type 2 diabetes	Rates of depression in diabetes groups. Rates of complications for diabetes groups.	Depression is dependent variable
Van Steenberge	Nephropathy Retinopathy	To study the association	Cross-sectional survey	596 patients with Type 2	Logistic regression for association of number and type	Cross-sectional

Paper	Complication	Aim of Study	Type of Study	N	Main outcomes	'Include' (for further consideration) or reason for exclusion
n-Weijenburg 2010	Neuropathy Macrovascular	between diabetes with multiple complications and depression in patients with type 2 diabetes		diabetes	of complications and depression in patients with Type 2 diabetes	
Vedhara 2010	Foot ulcer	To examine the role of coping style and psychological distress in the healing of diabetes foot ulcers	Prospective observational study	93 patients with neuropathic or neuroischaemic diabetes foot ulcers	Ulcer status at 24 weeks, healed versus not healed. Predictors of ulcer healing (coping and depression).	Focus is healing of foot ulcer, not incidence
Verma 2010	Stroke Retinopathy Coronary artery disease	To examine the association between depression and HRQOL in patients with diabetes, and to identify additional medical factors associated with HRQOL	Cross-sectional survey	537 adults with T1DM or T2DM	Multiple regression to identify associations between depression and HRQOL in diabetes. Also reports association between stroke, retinopathy and CAD.	CAD, stroke, retinopathy with depression as predictors of HRQoL.
Vileikyte	Peripheral	To examine the	Cross-sectional	494 patients	Multiple regression to identify	Depression is

Paper	Complication	Aim of Study	Type of Study	N	Main outcomes	'Include' (for further consideration) or reason for exclusion
2005	neuropathy	association between severity of diabetes peripheral neuropathy and depressive symptoms	survey	with T1DM or T2DM	associations between depressive symptoms as measured by HADS, and diabetes neuropathy symptoms	dependent variable
Vileikyte 2009	Peripheral neuropathy	To determine whether diabetes peripheral neuropathy is a risk factor for depressive symptoms	18 month longitudinal study	338 patients with diabetes peripheral neuropathy	Temporal relationships between DPN severity and depressive symptoms as measures by HADS-D. Also gives numbers for active foot ulcer, number of diabetes complications, number of concomitant disorders, numbers on antidepressants.	Depression is dependent variable
Wagner 2012	Coronary heart disease	To determine whether acute stress and lifetime history of major depressive disorder are associated with functional and biochemical	Cross-sectional survey	215 post-menopausal women with no known or suspected CAD. 103 had T2DM, 108 had lifetime major	Effect of history of depression or T2DM on endothelial functioning	Outcome is too specific – endothethial functioning

Paper	Complication	Aim of Study	Type of Study	N	Main outcomes	'Include' (for further consideration) or reason for exclusion
		markers of endothelial function and whether this relationship varies by diabetes status.		depression.		
Wexler 2006	Coronary heart disease Stroke Peripheral vascular disease Microvascular complications Symptomatic microvascular complications Hypertension Heart failure Hyperlipidaemia COPD	To assess the impact of medical comorbidities, depression and treatment intensity on QoL in Type 2 diabetes	Primary care cohort study	909 primary care patients with type 2 diabetes	Rates of complications in T2DM. Effect of complications on QoL.	Dependent variable is quality of life. No data for complications for depression and diabetes.
Williams 2010	Foot ulcer	To test whether depression is associated with an increased risk of	Prospective cohort study	3474 adults with type 2 diabetes and no prior	Incidence of diabetes foot ulcers, hazard ratios for incidence of diabetes foot ulcers, comparing patients with	Single complication

Paper	Complication	Aim of Study	Type of Study	N	Main outcomes	'Include' (for further consideration) or reason for exclusion
		incidence of diabetes foot ulcer.		history of diabetes foot ulcers or amputations	minor and major depression and those without depression.	
Williams 2010	Foot checks Eye examinations Haemoglobin checks	To evaluate relationship between Type 2 diabetes, serious psychological distress and diabetes care.	Population based cross-sectional survey	1,516,171 adults with diabetes, of which 108,621 had comorbid SPD.	Odds ratios for foot checks, eye examinations, and haemoglobin checks.	Cross-sectional
Williams 2011	Lower limb amputation	To examine the association between diagnosed depression and incidence of non-traumatic lower limb amputations in veterans with diabetes	Retrospective cohort study	531,973 veterans with diabetes	Incidence of lower limb amputation (major and minor) (Hazard Ratios), comparing veterans with and without diagnosed depression.	Include
Willrich	Foot ulcer or amputation	To determine if there is a relationship between HRQoL	Cross-sectional study with control group	20 participants undergoing treatment	Depression prevalence or cognitive impairment, HRQoL.	Depression is dependent variable

Paper	Complication	Aim of Study	Type of Study	N	Main outcomes	'Include' (for further consideration) or reason for exclusion
		following diabetes foot ulcers, foot infection, Charcot foot anthropathy and lower extremity amputation, and cognitive impairment or clinical depression.		for diabetes foot ulcers or active Charcot foot anthropathy, and 20 patients undergoing treatment for lower extremity amputation. 20 diabetes people without foot-related morbidity but with evidence of peripheral neuropathy were the control group.		

Paper	Complication	Aim of Study	Type of Study	N	Main outcomes	'Include' (for further consideration) or reason for exclusion
Windle 2013	Cardiovascular disease (heart attack, MI, stroke, angina)	To investigate the concurrent and prospective relationships between single and recurrent depression and CVD and diabetes in middle and older aged women.	5 year longitudinal study	557 women	Depression (recurrent or single episode) as a predictor of CVD risk and diabetes.	CVD and diabetes considered as separate variables
Winkley 2012	Foot ulcer	To determine whether depressive disorder is associated with increased mortality in people with diabetes foot ulcers.	5 year cohort study	253 patients presenting with their first diabetes foot ulcer. Type T1DM and T2DM.	Prevalence of depressive disorder; mortality rate over 5 years; rates of microvascular and macrovascular complications in depressed and non-depressed (not specific).	Main outcome is foot ulcer mortality
Young 2010	Chronic kidney disease	To determine the association of major depression with mortality	Longitudinal prospective cohort study, mean duration	4128 participants enrolled in Pathways	Association of depression with risk of all-cause mortality in diabetes patients with CKD. Depression identified through	Single complication

Paper	Complication	Aim of Study	Type of Study	N	Main outcomes	'Include' (for further consideration) or reason for exclusion
		among diabetes patients with late stage chronic kidney disease.	4.4. years. (Pathways study).	study. Of which, 110 identified with stage 5 CKD at baseline. Of these, 34 had depression.	PHQ-9. Hazard ratios.	

PHQ-9: 9-item Patient Health Questionnaire; QoL: Quality of Life; CAD: Coronary Artery Disease; COPD: Chronic Obstructive Pulmonary Disease; HRQoL: Health Related Quality of Life; CVD: Cardiovascular Disease; MI: Myocardial Infarction; CHD: Coronary Heart Disease; BDI: Beck Depression Inventory; CKD: Chronic Kidney Disease; CES-D: Center for Epidemiological Studies- Depression; HADS-D: Hospital Anxiety and Depression Scale-Depression.

Appendix 6 – Depression definitions used for this project

There are two different diagnostic criteria that may be used to define depression; DSM-IV and ICD-10. Both require an assessment of duration, severity and course. For duration, both require at least 2 weeks of depressive symptoms before a diagnosis can be made. Both also include two core symptoms, and additional symptoms that can be used to categorise severities of depression.

The two core symptoms are:

1. Depressed mood for at least 2 weeks
2. Loss of interest or pleasure in life activities for at least 2 weeks

DSM-IV is the classification system recommended by NICE. It requires at least one of the above two core symptoms for a diagnosis of depression.

1. Depressed mood most of the day.

2. Diminished interest or pleasure in all or most activities.

3. Significant unintentional weight loss or gain.

4. Insomnia or sleeping too much.

5. Agitation or psychomotor retardation noticed by others.

6. Fatigue or loss of energy.

7. Feelings of worthlessness or excessive guilt.

8. Diminished ability to think or concentrate, or indecisiveness.

9. Recurrent thoughts of death

Severity is assessed based on a count of the above symptoms:

- Minor depression: fewer than five symptoms of depression
- Mild depression: few, if any, symptoms in excess of five, and symptoms result in only minor functional impairment
- Moderate depression: symptoms or functional impairment are between 'mild' and 'severe'
- Severe depression: most symptoms, and the symptoms markedly interfere with functioning; can occur with or without psychotic symptoms.

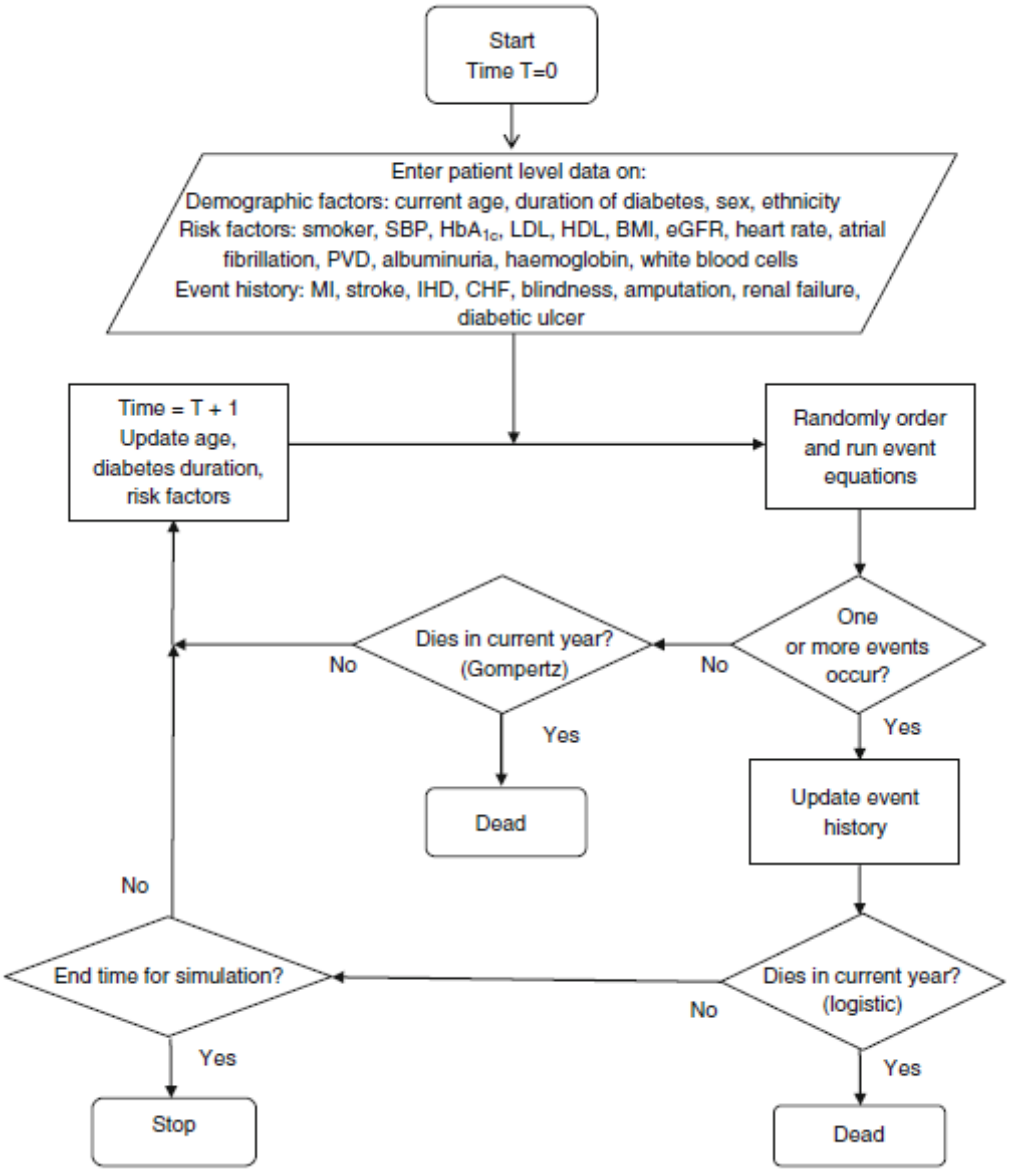
ICD-10 requires both of the core-symptoms to be present. It has a slightly different list of symptoms (in total there are 10), with different cut-offs for severities of depression: minor is defined as fewer than four, mild depression requires few, if any, in excess of four. The remaining definitions are the same as DSM-IV.

Appendix 7: Details of the UKPDS Outcomes Model.

Version 1 of the UKPDS OM was published in 2004 [10], and uses data from the UKPDS trial [11]. Recruitment for this RCT ran between 1977 and 1991. The objective of the trial was to compare the effects of different blood-glucose control strategies on the risk of developing diabetes-related complications. The RCT had 3 arms comparing conventional treatment with intensive blood-glucose control, which included either sulphonylureas or insulin. The patient population was individuals aged between 25 and 65 with newly diagnosed T2DM, and without any existing diabetes-related complications [11]. A total of 5,102 patients entered the trial, which had a median follow-up of 10.0 years. Clinical parameters measured during the trial were used to estimate the relationship between diabetes risk factors and the probability of developing a diabetes-related complication.

Version 2 of the UKPDS OM updates version 1 by including additional 10 years of observational post-trial monitoring (PTM) data. The PTM data was collected for all 4,031 participants who had entered the original RCT and were still alive when it concluded in 1997. During PTM, no active attempts were made to maintain the treatment received during the RCT, instead patients returned to their usual care providers. The UKPDS OMv2 includes data from both the RCT and the PTM, and updates both the set of risk factors considered and the set of diabetes-related complications considered.

Figure A7.1: Schematic of the UKPDS OM2 Reproduced from Hayes et al 2013



The UKPDS OMv2 uses an annual Markov cycle. Instead of health states, patient characteristics (diabetes risk factors and diabetes-related complications) are captured using 'tracker variables'; and updated every year using regression models. An annual probability of mortality is also calculated using regression models. The impact of diabetes-related complications on health-related quality of life was calculated using longitudinal data from the UKPDS RCT and PTM data [12]. Data on costs and resource use were based on inpatient and outpatient hospital appointments incurred during the UKPDS RCT [13].

It should be noted that the UKPDS OMv2 does not explicitly consider treatment care pathways. Instead the progression of diabetes risk factors and the development of diabetes-related

complications are modelled. Data sources for the UKPDS v2 OM are a mixture of trial-based and observational. Based on advice from clinical experts, the 'intensive' treatment management strategies included in the UKPDS RCT are now part of standard care, hence the UKPDS v2 OM may be assumed to reflect the progression of diabetes risk factors and the development of diabetes-related complications under standard care. However, clinical experts also noted that since the UKPDS RCT concluded, further advances in the treatment and prevention of diabetes-related complications have occurred, and so the rates of diabetes-related complications observed in the UKPDS OMv2 may not reflect the rates observed in clinical practice.

Appendix 8: Equations used for modelling the development of diabetes-related complications and for mortality

Complication	Congestive heart failure		Ischaemic heart disease		1st Myocardial infarction male		1st Myocardial infarction Female		2nd Myocardial infarction		1st Stroke		2nd Stroke	
Patient-years	77941		75163		43032		32093		4799		77332		2368	
Patients	4977		4967		2910		2042		1012		4981		506	
No. of events	334	**7%**	721	**15%**	619	**21%**	334	**16%**	169	**17%**	490	**10%**	78	**15%**
Functional form	Weibull		Weibull		Exponential		Weibull		Exponential		Weibull		Weibull	
Parameters	**Mean**	**SE**	**Mean**	**SE**	**Mean**	**SE**	**Mean**	**SE**	**Mean**	**SE**	**Mean**	**SE**	**Mean**	**SE**
Lambda	-12.332	0.859	-6.709	0.503	-8.791	0.486	-8.708	0.844	-4.179	0.262	-13.053	0.722	-9.431	1.569
Rho	1.514	0.096	1.276	0.059	1	0	1.376	0.097	1	0	1.466	0.081	1.956	0.291
Afro-carribean					-0.83	0.237	-1.684	0.506						
Age at diagnosis	0.068	0.008	0.016	0.005	0.045	0.006	0.041	0.008			0.066	0.007	0.046	0.018
Female			-0.532	0.085							-0.42	0.098		
Indian					0.279	0.126								
Atrial Fibrilation	1.562	0.245									1.476	0.201		
BMI	0.072	0.008												
eGFR			-0.053	0.023										
eGFR < 60	-0.22	0.065					-0.28	0.062			-0.19	0.056		
eGFR > 60														
Haemoglobin														
HbA1c					0.108	0.023	0.078	0.03			0.092	0.026		
High-density lipoprotein			-0.065	0.014	-0.049	0.016								
Heart rate														
Low-density lipoprotein (LDL)	0.012	0.005	0.023	0.003	0.023	0.004			0.021	0.007	0.016	0.004		
LDL > 35							0.035	0.007						
Albuminuria	0.771	0.116			0.203	0.094	0.277	0.129	0.344	0.162	0.42	0.101	0.537	0.228
Peripharal vascular disease	0.479	0.136	0.486	0.101	0.34	0.111	0.469	0.132						

Systolic blood pressure			0.058	0.019	0.046	0.022	0.056	0.027	0.17	0.022		
Smoker					0.277	0.091	0.344	0.138	0.331	0.111	0.656	0.263
White blood cell count					0.026	0.013	0.07	0.023	0.04	0.012		
Amputation history	0.658	0.334	0.526	0.266	0.743	0.241			1.09	0.24		
Blindness history												
Congestive heart failure history			0.824	0.168	0.814	0.195	0.853	0.2				
Ischaemic heart disease history					0.846	0.117	0.876	0.163	0.481	0.144		
Stroke history					0.448	0.173						
Ulcer history	0.654	0.291										

Complication	Blindness		Ulcer		1st Amputation; no prior ulcer		1st Amputation; prior ulcer		2nd Amputation		Renal Failure[a]	
Patient-years	77220		51780		77408		861		627		79157	
Patients	4961		5102		4939		93		172		4992	
No. of events	251	**5%**	97	**2%**	140	**3%**	21	**23%**	58	**34%**	109	**2%**
Functional form	Exponential		Logistic		Weibull		Exponential		Exponential		Exponential	
Parameters	**Mean**	**SE**	**Mean**	**SE**	**Mean**	**SE**	**Mean**	**SE**	**Mean**	**SE**	**Mean**	**SE**
Lambda	-11.607	0.759	-11.295	1.13	-14.844	1.205	-0.881	1.39	-3.455	0.565	-10.016	0.939
Rho	1	0			2.067	0.193	1	0	1	0	1.865	0.387
Afro-carribean												
Age at diagnosis	0.047	0.009	0.043	0.014	0.023	0.011	-0.065	0.027				
Female			-0.962	0.255	-0.445	0.189						
Indian												
Atrial Fibrilation					1.088	0.398						
BMI			0.053	0.019								
eGFR												
eGFR < 60												
eGFR > 60												
Haemoglobin												
HbA1c	0.171	0.032	0.16	0.056	0.248	0.042			0.127	0.06		
High-density lipoprotein					-0.059	0.032						
Heart rate	0.08	0.039			0.098	0.05						
Low-density lipoprotein (LDL)												
LDL > 35												
Albuminuria					0.602	0.18						
Peripheral vascular disease			0.968	0.258	1.01	0.189	1.769	0.449				
Systolic blood pressure	0.068	0.032			0.086	0.043					0.404	0.106
Smoker												
White blood cell count	0.052	0.019			0.04	0.017						

Amputation history						
Blindness history					2.082	0.551
Congestive heart failure history	0.841	0.287				
Ischeamic heart disease history	0.61	0.208				
Stroke history			1.299	0.245		
Ulcer history						

[a] From UKPDS OMv1[10]

Worked example:

As a worked example, for an individual who was 43 years old when diagnosed with diabetes, has no atrial fibrillation, BMI of 32, no evidence of kidney damage (eGFR > 60), LDL of 33, albuminuria of 0.14, no PVD, and no history of either amputation or ulcers, the estimated annual probability of congestive heart failure after 11 years in the economic model is calculated by the following steps:

1. Calculate the linear predictor: for a Weibull functional form this is found by multiplying their parameters by their value (for example, using the above patient characteristics, for age at diagnosis multiply 0.068 by 43, for PVD multiply 0.479 by 0), and adding on the value of lambda.
2. Convert the linear predictor into a probability of having congestive heart failure at a specific point in time: 't'. For a Weibull functional form this is found by taking the exponential of the linear predictor and multiplying this value by t raised to the power of rho.
3. Convert the linear predictor into a probability of having congestive heart failure at a specific point in time: 't + one year'
4. Subtract the value calculated at step 2 from that calculated at step 3, to find the estimated annual probability of congestive heart failure after 11 years in the economic model.

Using the above patient characteristics the full calculations are:

1. $0.068 \times 43 + 1.562 \times 0 + 0.072 \times 32 - 0.22 \times 0 + 0.012 \times 33 + 0.771 \times 0.14 + 0.479 \times 0 + 0.658 \times 0 + 0.654 \times 0 - 12.332 = -6.60006$
2. $e^{-6.6006} \times 11^{1.514} = 5.1321\%$
3. $e^{-6.6006} \times 12^{1.514} = 5.8548\%$

4. $5.8548\% - 5.1321\% = 0.7226\%$

The mortality equations used are reproduced over-page.

Event	Death in years with no history or events		Death in 1st year of event(s)*		Death in years with history but not events**		Death in subsequent year/s of event(s)*	
Patient-years	73310		2151		13284		847	
Patients	4993		2151		1612		847	
No. of events	715		683		386		473	
Functional form	Gompertz		Logistic		Gompertz		Logistic	
Parameters	**Mean**	**SE**	**Mean**	**SE**	**Mean**	**SE**	**Mean**	**SE**
Lambda	-10.908	0.304	-6.916	0.591	-9.207	0.534	-4.868	0.828
Rho	0.098	0.004			0.073	0.007		
Female	-0.229	0.077						
Indian			-0.54	0.205				
Diabetes duration			0.042	0.01				
Atrial Fib							1.081	0.396
BMI Cat1					1.083	0.511		
BMI Cat3					-0.293	0.114		
Curr Age			0.058	0.007			0.05	0.01
HDL							0.068	0.03
Heart rate			0.124	0.032				
MMALB					0.348	0.107		
PVD			0.367	0.13			0.352	0.178
Smoker	0.379	0.089	0.444	0.117	0.374	0.133		
WBC					0.048	0.011	0.089	0.038
Amp event			-0.734	0.321			-1.267	0.344
Amp history					0.539	0.198	0.753	0.3
Amp2 event							-1.727	0.467
CHF history					0.632	0.13		
IHD event			0.423	0.168			0.583	0.243
IHD history							-0.507	0.191

MI event	1.309	0.158				0.982	0.23
MI history						0.44	0.186
Renal event	0.584	0.305					
Renal history				1.15	0.197	0.961	0.396
Stroke event	0.547	0.176				-0.619	0.246
Stroke history			if		0.122		

* Excludes blindness or ulcer

** Used when there is a history of any event

Appendix 9: Example calculations for deriving the distribution of baseline age.

The NDA presented distributions by categorised values. For example, for age, 10-year age categories were presented. By assuming a constant distribution within categories, Normal distributions were fit to the NDA data. These Normal distributions were then transformed to Log-Normal distributions for use in the economic model, to ensure that negative values were not possible (this applies to age, time with T2DM and BMI values). A worked example for age is presented below. Table A9.1 displays the data that is presented in the NDA 2011/12 for the age of individuals with T2DM.

Table A9.1: The distribution of individuals with T2DM sourced from the NDA 2011/12

Age	Count	Running Count
0 to 9	83	-
10 to 19	1,212	-
20 to 29	10,409	10,409
30 to 39	58,601	69,010
40 to 49	213,997	283,007
50 to 59	421,503	704,510
60 to 69	602,374	1,306,884
70 to 79	565,845	1,872,729
80 to 89	281,392	2,154,121
90+	35,248	2,189,369

For this project only adults with T2DM were considered, so the age categories '0 to 9' and '10 to 19' were excluded. This leaves data for 2,189,369 individuals. Half of this number is 1,094,684.5. If we ordered the individuals by increasing age and counted them, we would reach the half-way count within the '60 to 69' age category. Column 3 shows that we would pass 704,510 individuals before reaching the '60 to 69' category. This leaves (1,094,684.5 – 704,510 =) 390,174.5 before the half-way point is reached. Assuming that ages are distributed equally within categories, the half-way count is (390,174.5/602,374 =) 64.8% within the '60 to 69' category, which gives a value of (60 + 10*64.8% =) 66.48 for the mean age.

Similar calculations were performed to identify where the 2.5 percentile and 97.5 percentile of counts were located (at ages 37.56 and 88.38 respectively). The difference between these percentiles is equal to (approximately) 3.92 standard deviations, which gives a value for one standard deviation of ([88.38 – 37.56]/3.92 =) 12.96. Hence a Normal distribution with a mean of 66.48 and a standard deviation of 12.96 was fit to the age values. This was transformed to a Log-Normal distribution using the following formulas:

$$\beta = \sqrt{\ln\left(1 + \theta/(\mu^2)\right)}$$

$$\alpha = \ln(\mu) - (\beta^2/2)$$

Where μ, θ are the mean and standard deviation of the Normal distribution(respectively) and α, β are the mean and standard deviation of the Log-Normal distribution (respectively).

Age at diagnosis of T2DM is found by subtracting an individual's time with diabetes from their age.

Appendix 10: Logistic regression models used to derive the baseline probability of having a diabetes-related complication

The 2010/11 NDA presented the parameters of logistic regression models that can be used to estimate the probability that an individual has a diabetic complication (these logistic regression models had not, at the time of writing, been updated for the 2011/12 NDA). These parameters are displayed in Table A10.1.

Table A10.1 Odds ratios for the probability that an individual has a diabetic complication at baseline.

Odds Ratios	CHF	IHD	MI	Stroke	Blindness	Amputation	Renal failure
Age	1.09	1.051	1.058	1.07	0.992	1.02	1.023
Male	1.466	1.264	1.608	1.202	1.228	2.414	1.389
Asian	1.283	1.224	1.62	1.084	0.652	0.25	2.274
Black	0.788	0.386	0.519	0.904	0.824	0.616	2.4
BMI < 18.5	1.013	0.892	1.146	1.231	0.383	1.928	1.409
BMI 25 to 29.9	1.039	1.175	0.988	0.869	1.141	0.846	0.789
BMI 30 to 24.9	1.356	1.412	1.025	0.858	1.164	0.931	0.879
BMI 35 to 39.9	2.09	1.604	1.047	0.867	1.216	1.1	1.054
BMI 40+	3.372	1.736	1.11	0.935	1.2	1.145	1.327

Appendix 11: Baseline characteristics taken from the UKPDS

If evidence for the baseline characteristics could not be obtained from the NDA, they were instead taken from the UKPDS OMv2. The paper describing this model presents means and standard deviations for the following variables:

- HbA1c
- SBP
- HDL
- LDL
- Heart rate
- eGFR
- White blood cell count
- Heamoglobin

These were assumed to follow a Normal distribution. For use in the economic model they were transformed into a Log-Normal distribution using the formulas previously presented.

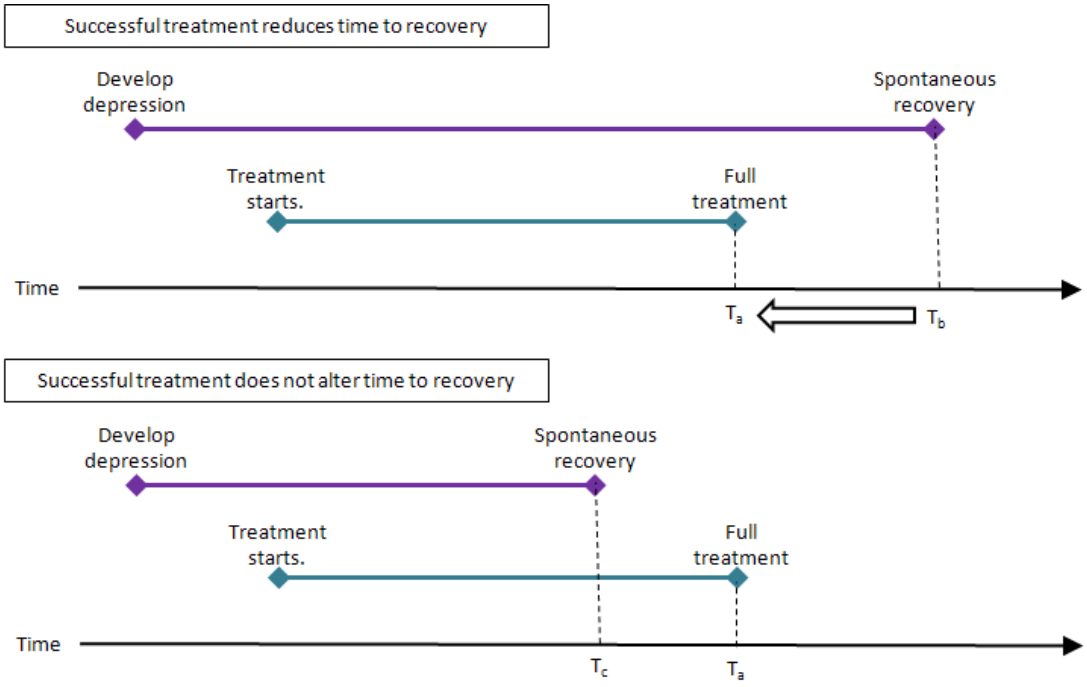
The paper describing the UKPDS OMv2 also presents data on the following:

- Proportion of individuals with T2DM that have micro- or macro-albuminuria,
- Proportion of individuals with T2DM that have atrial fibrillation,
- Proportion of individuals with T2DM that have PVD,
- Proportion of individuals with T2DM that have a history of a foot ulcer.

Appendix 12: Example of how successful depression treatment may shorten the length of a depressive episode

It should be noted that successful treatment may not result in a shorter time to recovery. If an individual was due to spontaneously recover from their depression during their treatment, then successful treatment will not have affected the amount of time spent with depression. This is depicted in Figure A12.1 below, which shows the two possible outcomes for people who respond to treatment. In the top example, the treatment brings-forwards the time to recovery from time 'b' to time 'a'. In the bottom example treatment does not alter the time to recovery. Treatment costs are the same in both examples.

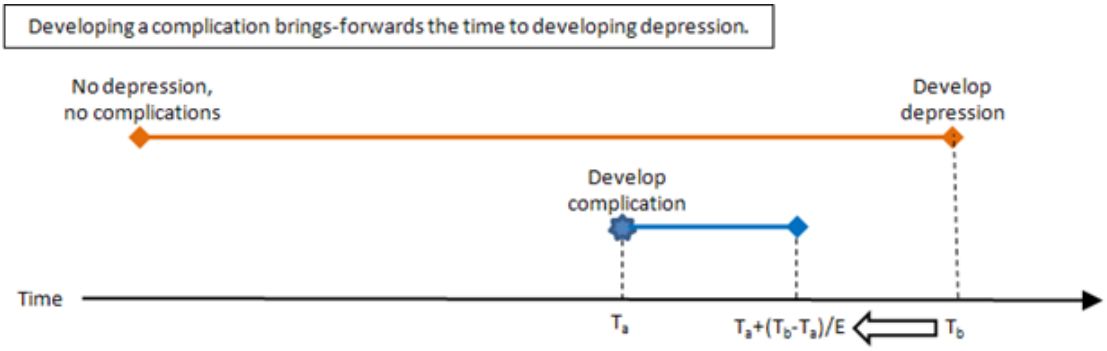
Figure A12.1: Relationship between time spent receiving depression treatment and time spent with depression



Appendix 13: Example of how developing a diabetes-related complication will decrease the time to developing depression.

A schematic of the relationship between developing a diabetic complication and time to depression is provided in Figure A13.1 below. In this figure, a diabetes-related complication occurs (at time T=a). 'E' is the effect size of developing depression due to developing a complication. For example, if E=2, the remaining time to developing depression is halved. It should be noted that having a complication does not impact on length of depression or time to progression (due to a lack of data).

Figure A13.1: Relationship between developing a diabetes-related complication and developing depression



Appendix 14: Productivity estimates

Societal impact

The societal impact of having T2DM with comorbid depression, along with the effect of any policy change on this, was measured in two ways:

- Probability of being productive in the last week.
- Number of days in the last six weeks spent providing informal care.

The methods used to estimate these were based on previous EEPRU work for the DoH. Full details have been published online for both days off paid work due to sickness [14] and days spent providing informal care[15]. Details relevant to this project are provided below:

Estimating the probability of being productive in the last week

The probability of being productive in the last week was estimated based on an individual's age, gender, EQ-5D index score, and their primary ICD-10 diagnosis. The estimation process consisted of 2 steps:

1. SF-6D preference index values were generated for each individual, based on their age, gender, EQ-5D index score, and their primary ICD-10 diagnosis.
2. The probability that an individual was productive in the last week was estimated based on their age, gender and their estimated SF-6D values.

This two-step approach was used because a relationship between EQ-5D and productivity was required, but only direct data on the relationship between SF-6D and productivity was available. Data for estimating the relationship at step 1 were taken from the Health Outcomes Data Repository, whilst data for estimating the relationship at step 2 were taken from Understanding Society.

For use within this project, each individual's primary ICD-10 diagnosis was set to 'Diabetes', and the impact of any diabetes complications (including depression) was captured via changes in the EQ-5D index score. The regression parameter coefficients used, and a worked example showing the calculation steps for a 45-year old male with T2DM and an EQ-5D index score of 0.59 are provided below.

Step 1: Estimate SF-6D preference index values. Details of the linear regression model used are provided in Table A14.1.

Table A14.1 Coefficients for the linear regression model used to estimate SF-6D

Parameter	Coefficient
Age / 10	0.0031
Female	-0.0164
EQ-5D	0.3664
ICD-group: diabetes	-0.005
Constant	0.4242

Worked example of SF-6D estimate = (45/10) * 0.0031 + 0 * -0.0164 + 0.59 * 0.3664 - 0.005 + 0.4242 = 0.6493

Step 2: Estimate the probability that an individual was productive in the last week. Details of the logistic regression model used are provided in Table A14.2.

Table A14.2. Parameters and coefficients for the logistic regression model used to estimate the probability that an individual was productive in the last week.

Parameter	Coefficient
Age / 10	3.04
$(Age / 10)^2$	-0.36
Female	-0.48
Ln(SF-6D)	3.1
Constant	-3.590

Worked example of productivity estimate (carrying-on from Step 1) Log-odds of being productive = (45/10) * 3.04 + $(45/10)^2$ * -0.36 + 0 * -0.48 + 0.6493 * 3.1 -3.590 = 1.4612
Probability of being productive in the last week = Exp(1.4612) / [1 + Exp(1.4612)] = 81.17%

For this project this probability was interpreted as the proportion of time that the individual was productive in the last week. So for the worked example, the individual was estimated to spend 81.17% of the last working week being productive. Individuals aged over 65 were assumed to not be productive.

Estimating the number of days in the last six weeks spent providing informal care.

The number of days in the last six weeks spent providing informal care was estimated based on an individual's age, gender, EQ-5D index score, and their primary ICD-10 diagnosis. The estimation

process used a zero-inflated negative binomial regression model with variable inflation. Details of the parameter coefficients are provided in Table A14.3.

Table A14.2. Parameters and coefficients for the zero-inflated negative binomial regression model used to estimate the number of days in the last six weeks spent providing informal care.

Parameter	Coefficient
Age	0.0195
Age^2	-0.0001
Female	-0.0227
EQ-5D	-0.8583
Comorbidity	0.1479
ICD-group: diabetes	-0.0209
Constant	2.6541
Inflated variables	
Age	0.0483
Age^2	-0.0004
Female	-0.5629
EQ-5D	4.1226
Comorbidity	-0.3932
Constant	-3.3426

Appendix 15: Results of sensitivity analyses.

Results of the 29 univariate (one-way) sensitivity analyses conducted are displayed in Table A15.1. Calculated ICERs are all relative to current practice.

Table A15.1. Results of sensitivity analyses.

Description		Current practice	Policy 1	Policy 2	Policy 3
Probability of attending annual review and of receiving a depression screen (if not being treated) = 100% for both.	Costs	£31,041,254,920	£32,223,103,720	£35,750,062,800	£37,558,267,520
	QALYs	12,012,643	12,116,321	12,098,838	12,191,842
	ICER	-	£11,399	£54,630	£36,368
Probability that the annual review includes a depression screen = 60% (base-case = 86%)	Costs	£29,392,542,620	£30,470,366,780	£34,495,103,540	£36,389,301,060
	QALYs	12,009,271	12,098,046	12,088,817	12,187,832
	ICER	-	£12,141	£64,146	£39,184
Double the time to relapse.	Costs	£29,993,245,460	£31,527,950,140	£33,965,467,580	£35,318,500,200
	QALYs	11,867,315	11,956,775	12,269,584	12,357,142
	ICER	-	£17,155	£9,875	£10,872
Halve the time to relapse.	Costs	£29,298,806,080	£29,988,665,780	£35,137,628,680	£37,604,440,540
	QALYs	12,206,453	12,290,250	11,936,659	12,035,347
	ICER	-	£8,233	-£21,642	-£48,541
Drop out rates are 15% for all treatments and types of depression (base-case = 30%).	Costs	£30,197,896,080	£31,090,074,520	£35,475,239,160	£37,022,123,720
	QALYs	12,037,733	12,135,934	12,120,061	12,217,133
	ICER	-	£9,085	£64,101	£38,039
Drop out rates are 45% for all treatments and types of depression (base-case = 30%).	Costs	£29,071,665,220	£30,412,342,500	£33,717,108,840	£35,978,472,320
	QALYs	11,972,784	12,072,852	12,045,501	12,147,008
	ICER	-	£13,398	£63,884	£39,643
Average annual number of GP appointments for people with depression = 12 (base-case = 8).	Costs	£30,773,456,760	£31,880,127,580	£35,359,635,120	£37,176,614,600
	QALYs	12,029,283	12,125,173	12,090,057	12,189,334
	ICER	-	£11,541	£75,463	£40,007
Average annual number of GP appointments for people with depression = 4 (base-case = 8).	Costs	£28,244,882,580	£29,207,967,080	£33,377,553,780	£35,397,551,600
	QALYs	11,994,019	12,069,042	12,081,294	12,189,559
	ICER	-	£12,837	£58,811	£36,579

Sensitivity of screening test is 98%, specificity is 86% (basecase values = 95% and 66% respectively).	Costs	£29,290,951,720	£30,428,894,840	£32,477,965,280	£34,280,733,180
	QALYs	12,002,087	12,102,441	12,084,209	12,188,225
	ICER	-	£11,339	£38,808	£26,807
The incidence of minor depression is doubled.	Costs	£29,780,144,380	£30,900,178,220	£34,775,215,040	£36,948,888,680
	QALYs	11,935,180	12,034,558	12,019,161	12,133,930
	ICER	-	£11,270	£59,479	£36,069
The incidence of minor depression is halved.	Costs	£29,448,540,300	£30,475,508,560	£34,459,719,160	£36,126,195,000
	QALYs	12,097,109	12,193,654	12,169,769	12,256,748
	ICER	-	£10,637	£68,968	£41,830
The incidence of both minor and major depression is halved.	Costs	£29,388,654,500	£30,225,678,180	£34,190,139,240	£35,683,432,000
	QALYs	12,174,044	12,253,822	12,235,989	12,321,013
	ICER	-	£10,492	£77,512	£42,830
First-line treatment is 100% pharmacotherapy.	Costs	£29,533,251,440	£30,695,082,420	£34,467,639,800	£36,445,312,920
	QALYs	12,016,516	12,117,946	12,100,536	12,211,283
	ICER	-	£11,455	£58,729	£35,489
Second-line treatment following watchful waiting is 100% pharmacotherapy.	Costs	£29,532,127,360	£30,623,069,540	£34,457,717,920	£36,343,689,680
	QALYs	12,003,174	12,108,641	12,084,484	12,191,477
	ICER	-	£10,344	£60,577	£36,173
Screening cost = £0 (base = £2).	Costs	£29,551,641,800	£30,598,314,460	£34,072,768,940	£36,011,502,620
	QALYs	12,006,264	12,103,498	12,082,254	12,188,107
	ICER	-	£10,765	£59,497	£35,524
Screening cost = £4 (base = £2).	Costs	£29,700,757,320	£30,753,924,260	£34,877,368,280	£36,850,445,740
	QALYs	12,006,264	12,103,498	12,082,254	12,188,107
	ICER	-	£10,831	£68,122	£39,318
Disutility due to major depression = 0.1 (base = 0.3)	Costs	£29,626,199,560	£30,676,119,360	£34,475,068,620	£36,430,974,180
	QALYs	12,375,905	12,446,942	12,431,422	12,497,192
	ICER	-	£14,780	£87,340	£56,104
Disutility due to major depression = 0.5 (base = 0.3)	Costs	£29,626,199,560	£30,676,119,360	£34,475,068,620	£36,430,974,180
	QALYs	11,266,984	11,416,610	11,383,919	11,569,937
	ICER	-	£7,017	£41,466	£22,461
Hazard ratio for diabetic complications affecting depression = 1 for all.	Costs	£29,447,966,500	£30,587,486,160	£34,507,055,500	£36,370,118,740
	QALYs	12,017,445	12,110,721	12,095,820	12,193,722
	ICER	-	£12,217	£64,550	£39,269
Hazard ratio for diabetic complications	Costs	£29,526,189,120	£30,657,825,720	£34,594,004,000	£36,494,474,960

affecting depression = 3 for all.	QALYs	11,993,161	12,101,041	12,076,461	12,173,775
	ICER	-	£10,490	£60,838	£38,581
Hazard ratio for depression = 1 for microvascular complications and 1.5 for macrovascular complications.	Costs	£29,623,904,020	£30,700,009,560	£34,502,553,420	£36,392,876,320
	QALYs	12,006,216	12,114,978	12,091,848	12,191,141
	ICER	-	£9,894	£56,972	£36,604
Hazard ratio for depression = 1.5 for microvascular complications and 1 for macrovascular complications.	Costs	£29,584,247,820	£30,709,064,620	£34,468,679,620	£36,405,809,140
	QALYs	12,016,182	12,109,806	12,085,464	12,191,202
	ICER	-	£12,014	£70,500	£38,976
Hazard ratio for depression affecting diabetic complications = 1 for all.	Costs	£29,411,630,860	£30,523,535,260	£34,479,353,520	£36,402,653,320
	QALYs	12,101,338	12,159,181	12,145,361	12,229,219
	ICER	-	£19,223	£115,115	£54,668
Hazard ratio for depression affecting diabetic complications = 1.5 for all.	Costs	£29,311,515,240	£30,518,841,820	£34,204,597,060	£36,151,701,660
	QALYs	11,787,274	11,935,229	11,907,282	12,049,734
	ICER	-	£8,160	£40,773	£26,062
Hazard ratio for depression affecting diabetic complications = 2 for all.	Costs	£29,229,670,660	£30,338,905,500	£34,056,112,060	£35,935,119,020
	QALYs	11,501,647	11,722,974	11,682,287	11,874,388
	ICER	-	£5,012	£26,719	£17,990
Prevalence of depression (minor and major) doubled.	Costs	£29,855,656,780	£31,019,770,120	£34,692,638,360	£36,868,761,940
	QALYs	11,900,788	11,999,650	11,986,946	12,090,845
	ICER	-	£11,775	£56,141	£36,900
Prevalence of depression (minor and major) halved.	Costs	£29,449,250,540	£30,462,125,960	£34,388,825,140	£36,195,940,100
	QALYs	12,071,403	12,153,721	12,149,589	12,237,159
	ICER	-	£12,304	£63,177	£40,702
Halve cost of collaborative care	Costs	£29,626,199,560	£30,241,201,260	£34,475,068,620	£35,710,135,940
	QALYs	12,006,264	12,103,498	12,082,254	12,188,107
	ICER	-	£6,325	£63,810	£33,457
Double cost of collaborative care	Costs	£29,626,199,560	£31,545,955,560	£34,475,068,620	£37,872,650,660
	QALYs	12,006,264	12,103,498	12,082,254	12,188,107
	ICER	-	£19,744	£63,810	£45,349
Prevalence of depression (minor and major) halved.	Costs	£29,626,199,560	£30,676,119,360	£34,475,068,620	£36,430,974,180
	QALYs	12,006,264	12,103,498	12,082,254	12,188,107
	ICER	-	£10,798	£63,810	£37,421

2. References

Reference List

1. Lustman PJ, Anderson RJ, Freedland KE, de GM, Carney RM, Clouse RE. Depression and poor glycemic control: a meta-analytic review of the literature. Diabetes Care 2000; 23(7):934-942.

2. Lustman PJ, Clouse RE. Depression in diabetic patients: the relationship between mood and glycemic control. [Review] [79 refs]. Journal of Diabetes & its Complications 2005; 19(2):113-122.

3. Bowser DM, Utz S, Glick D, Harmon R. A systematic review of the relationship of diabetes mellitus, depression, and missed appointments in a low-income uninsured population. [Review]. Archives of Psychiatric Nursing 2010; 24(5):317-329.

4. Renn BN, Feliciano L, Segal DL. The bidirectional relationship of depression and diabetes: a systematic review. [Review]. Clinical Psychology Review 2011; 31(8):1239-1246.

5. Albers B, Kruse J, Giani G, Icks A. Diabetes and incident depression: Is the association mediated or modified by sociodemographic factors or co-morbidities? A systematic review. [Review]. Experimental & Clinical Endocrinology & Diabetes 2011; 119(10):591-598.

6. Ali S, Stone M, Skinner TC, Robertson N, Davies M, Khunti K. The association between depression and health-related quality of life in people with type 2 diabetes: a systematic literature review. [Review] [63 refs]. Diabetes/Metabolism Research Reviews 2010; 26(2):75-89.

7. Astle F. Diabetes and depression: a review of the literature. [Review] [36 refs]. Nursing Clinics of North America 2007; 42(1):67-78.

8. Egede LE, Ellis C. Diabetes and depression: global perspectives. [Review] [85 refs]. Diabetes Research & Clinical Practice 2010; 87(3):302-312.

9. Serretti A, Mandelli L. Antidepressants and body weight: a comprehensive review and meta-analysis. [Review]. Journal of Clinical Psychiatry 2010; 71(10):1259-1272.

10. Clarke PM, Gray AM, Briggs A, Farmer AJ, Fenn P, Stevens RJ et al. A model to estimate the lifetime health outcomes of patients with type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model (UKPDS no. 68). Diabetologia 2004; 47(10):1747-1759.

11. Turner RC, Holman RR, Cull CA, Stratton IM, Matthews DR, Frighi V et al. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998; 352(9131):837-853.

12. Alva M, Gray A, Mihaylova B, Clarke P. The Effect of Diabetes Complications on Health-Related Quality of Life: the Importance of Longitudinal Data to Address Patient Heterogeneity. Health Economics 2013.

13. Clarke P, Gray A, Legood R, Briggs A, Holman R. The impact of diabetes-related complications on healthcare costs: results from the United Kingdom Prospective Diabetes Study (UKPDS Study No. 65). Diabetic Medicine 2003; 20(6):442-450.

14. Ara R, Kearns B, Mukuria C, van Hout B, Brazier J. Examining productivity losses associated with health related quality of life using patient and general population data. Report for the Department of Health . 2013.

15. Rowen D, Dixon S, Hernandez M, Mukuria C. Estimating informal care effects associated with EQ-5D tariff values for use in economic evaluation. Report for the Department of Health . 2013.