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Economic aspects of the association between diabetes and depression: A systematic review

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ABSTRACT

Background: The importance of co-morbid diabetes and depression is gaining increased attention. Quantifying the socio-economic and clinical impacts of co-morbidity is important given the high costs of these diseases. This review synthesised evidence on the economic impact of co-morbidity and potential cost-effectiveness of prevention and treatment strategies.
Methods: 11 databases from 1980 until June 2011 searched. In addition, websites and reference lists of studies scrutinised and hand search of selected journals performed. Reviewers independently assessed abstracts, with economic data extracted from relevant studies.
Results: 62 studies were identified. 47 examined the impact of co-morbidity on health care and other resource utilisation. 11 of these included productivity losses, although none quantified the impact of mortality. Most demonstrated an association between co-morbidity and increasing health service utilisation and cost. Adverse impacts on workforce participation and absenteeism were found. 15 economic evaluations were also identified. Most focused on primary care led collaborative and/or stepped care, suggesting actions may be cost effective. We did not identify any studies looking at actions to reduce the risk of diabetes in people with depression.
Limitations: Most studies are set in the US, which may be due to focus on English language databases. Few studies looked at impacts beyond one year or outside the health care system.
Conclusion: There is an evidence base demonstrating the adverse economic impacts of co-morbid diabetes and depression and potential for cost effective intervention. This evidence base might be strengthened through modelling studies on cost effectiveness using different time periods, contexts and settings.

1. Background

Diabetes mellitus and depression are debilitating and costly. In the US in 2008 the prevalence of clinically significant depression was estimated to be 9%, with severe depression reaching 3.4% (Centres for Disease Control, 2010). By 2030 depression is expected to be the leading contributor to the global burden of disease (WHO, 2008). The prevalence of diabetes has also been increasing, as in the UK where population prevalence rose from 2.8% in 1996 to 4.3% in 2005 (Gonzalez et al., 2009a) and is predicted to reach 9.5% of the adult population by 2030 (Holman et al., 2011).

Across much of Europe depressive disorders were estimated to cost €113 billion in 2010 (Gustavsson et al., 2011). Around one third of costs fall on health systems, estimated in the UK as £1.7 billion per annum in 2007 (McCrone et al., 2007). Diabetes and its complications also have substantive economic impacts, accounting for 10% (£9 billion) of the National Health Service budget (NHS) in England and Wales in 2008 (Diabetes UK, 2008) and 9% ($11 billion) of this budget in Italy in 2010 (Giorda et al., 2011). Both conditions have many economic impacts beyond the health system, including poor performance at work, high levels of absenteeism and premature retirement (Das-Munshi et al., 2007; Egede, 2004b; Thomas and Morris, 2003)

1.1. Impacts of co-morbidity

A recent review reported a 1.2–2.6 increase in relative risk of diabetes in people with depression compared to those without (De Hert et al., 2011). People with diabetes also are at greater risk of depression compared to those without, with one recent meta-analysis reporting a 24% increased risk of depression in people with type 2 diabetes (Nouwen et al., 2010).

Co-morbidity exacerbates the adverse impacts of diabetes and depression. It increases the risk of non-adherence to self-care practices, such as maintenance of diet, regular physical activity and use of medications. This poor adherence may cause difficulties

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over time in achieving appropriate metabolic control (Ismail et al., 2004), promoting development and progression of micro and macro vascular complications and functional disabilities (Brown et al., 2006; Egede, 2004b; Egede, 2004a; Ismail et al., 2004; Leichter and See, 2005). Co-morbidity also increases mortality risk, reported to be up to 38% higher in individuals with diabetes and depression compared to those with diabetes alone, regardless of socio-demographic characteristics, lifestyle or health status (Katon et al., 2005b; Katon et al., 2008a).

However, while much is known about the economic impacts of diabetes or depression in isolation, less attention has focused on co-morbidity. Additional to impact on health service use, co-morbidity could exacerbate many adverse social and economic outcomes. The case for investing in promotion, prevention, diagnosis and treatment will be strengthened by having more information on both the costs of co-morbidity and cost effectiveness of interventions. This paper sets out to map systematically what is known about the economic impacts of co-morbidity and value for money of interventions to address the issue.

2. Methods

Our objective was to identify studies examining the costs of co-morbidity between any type of diabetes and depressive disorder. We also searched for economic evaluations of interventions to prevent the onset of and/or alleviate co-morbidity.

2.1. Search strategy

For the period January 1980 to June 2011 we searched 11 health, economic and social science databases: PubMed/MEDLINE, EMBASE, PsychINFO, CINAHL, EconLit, IBSS, ASSIA, NHS Economic Evaluation Database (NHS EED), European Network of Health Economic Evaluation Databases (EURONHEED), Western Pacific Region Index Medicus and the Cochrane Library. A range of search terms related to economics, costs, resourcing, diabetes and depression were used. We also hand searched a number of journals, websites and conducted a limited Google freetext search.

Any empirical studies that looked at the association between co-morbid unipolar or bipolar disorder and any type of diabetes and health system and/or other costs were eligible for inclusion. All types of study design were eligible for inclusion. In the case of economic evaluations of interventions to address or prevent co-morbidity, both empirical and modelling studies were included. Abstracts were screened independently by three reviewers. Papers meeting inclusion criteria were retrieved; their reference lists and citations were also examined.

3. Results

2,398 citations were initially identified. Ultimately, 62 studies were included (Fig. 1). 47 studies looked at the impact of co-morbid diabetes and depression on health care and/or other resource utilisation. Unless otherwise stated these were US studies. Many did not report variations in cost, but examined changes in resource utilisation. 11 studied the impact of co-morbidity on employment, but only five reported both health and non-health sector economic impacts. Another 15 papers looked at the cost effectiveness of interventions to address co-morbidity.

3.1. Studies looking at impact on health care resource utilisation

41 studies examined the economic impact of co-morbid diabetes and depression on health care systems (Table 1). Most report co-

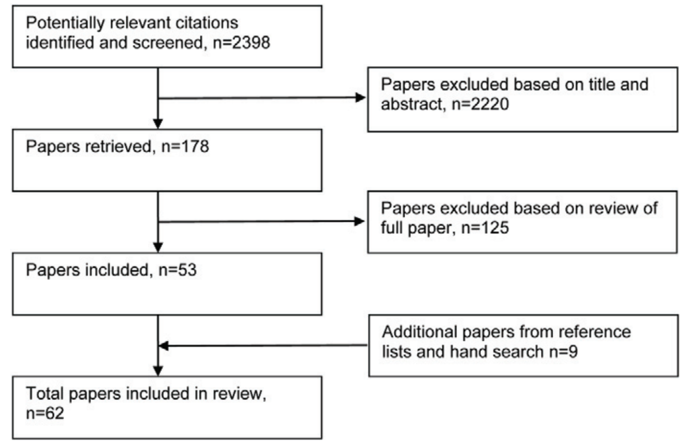

Fig. 1. Flowchart of included/excluded studies.

morbidity leading to statistically significant higher rates of health care utilisation than seen with a single morbidity. Much is due to additional use of general health services to manage and treat complications of diabetes and other somatic health conditions rather than additional mental health services.

3.1.1. Survey data

Several studies use survey data to point to some increased health service use due to co-morbidity. The 1996 US Medical Expenditure Panel Survey (MEPS), which included data on ambulatory care, emergency visits, inpatient care and drug prescriptions, was used to compare costs for 85 people with diabetes and depression with 740 people with diabetes alone (Egede et al., 2002). The co-morbid group used more ambulatory care and prescriptions ($P < 0.0001$). Total costs were 4.5 times greater ($P < 0.0001$), but this estimate may be excessive due to lack of control for disease severity and health risk behaviours. 176 individuals with co-morbid diabetes and depression in the US National Health Interview Survey had significantly more complications and were more likely to visit a mental health practitioner or attend an emergency room compared to 1,810 people with diabetes alone (Egede and Zheng, 2003).

Analysis using the 2003 US MEPS examined the impact of co-morbid minor depression and diabetes (Nichols et al., 2007). Compared with diabetes alone, co-morbidity increased the risk of diabetes complications ($P < 0.05$). Another study comparing self-care practices among 16,000 people with diabetes found that those with minor or major depression were significantly less likely to have eye examinations and 30% to 50% less likely to be physically active (Egede et al., 2009). Recent prospective longitudinal studies have however indicated that minor depression may not be associated with statistically significant increased risks of complications and mortality (Lin et al., 2010).

Some studies emphasize poor adherence to diabetes therapies and lifestyle advice as an explanation for increased costs. In Washington State, adherence to dietary regimens was significantly poorer for people with medium and high severity depression in a small survey (Ciechanowski et al., 2000). Costs in the high and medium severity groups were 88% and 54% higher than for respondents with low severity depression ($P < 0.05$). Another survey of members of a health maintenance organisation with diabetes in Washington State measured the relationship between diabetes, depression and adherence to self-care, and use of oral hypoglycaemic medications (Lin et al., 2004). Members with depression and diabetes were less likely to eat healthily or exercise regularly ($P < 0.0001$) but more likely to smoke ($P < 0.04$). They were also more likely not to adhere to medications, including oral hypoglycaemic antihypertensive and lipid lowering medications ($P < 0.0005$). Subsequent analysis

Table 1
Impact of co-morbidity on health system resource use and cost.

Author	Year	Sample size (*N*)	Time horizon for economic analysis	Country of study	In-patient resource use	Out-patient, ambulatory visits, and primary care	Emergency services	Prescription drugs	Mental health care services	Key conclusions
Atlantis et al.	2011	9,059 people aged 15+. 4% diabetes; 7.2% major depression; 0.8% DD	1 month in 3 surveys over 10 years	Australia	N/S	N/S	N/S	N/S	N/S	Health service use higher (49%) in co-morbid group compared to diabetes alone ($P < 0.05$).
Banerjea et al.	2008	390,253 veterans with diabetes; including 35,408 DD or DB	12 months	USA	Y	Y	N/S	N/S	N/S	Mean annual inpatient/outpatient health expenditure in 2000 was $6,185 for diabetes alone, vs $9,871 co-morbid depression or bipolar disorder group. Depression/bipolar disorder accounted 9% health care costs.
Black	1999	636 and 2,196 Mexican Americans aged 65+ with/without diabetes; 31% and 24% had depressive symptoms	12 months	USA	Y	Y	N	Y	N/S	Co-morbid group 2.6 times more likely to be hospitalised. Non-depressed more likely to have shorter hospitalisations ($P < 0.01$), physician visits ($P < 0.001$) and make use of oral hypoglycaemic agents ($P < 0.05$) and less use insulin ($P < 0.001$).
Boulanger et al.	2009	Adults with diabetic peripheral neuropathic pain in Medicare 11,854 (65+) and Private insurance (18–64) 11,685. Plus 1,512 and 2,728 with co-morbid depression/anxiety.	12 months	USA	Y	Y	Y	Y	N/S	Greater utilisation of medications, inpatient visits and emergency care ($P < 0.01$) in co-morbid group. Mean annual costs of co-morbid patients greater: $9,134 greater in Medicare and $11,085 in private insurance group ($P < 0.01$).
Boulanger et al.	2009	34,036 adults with diabetic neuropathy (DN) alone. 4,804 with DN and depression/anxiety.	12 months	USA	Y	Y	Y	Y	N/S	Mean healthcare costs for co-morbid patients$26,718 vs. $17,483 for Medicare patients; $29,775 vs. $19,386 for private insurance patients (18–64) ($P < 0.05$).
Chou et al.	2005	182 people aged 60+ with diabetes only; 64 with DD	6 months	China (Hong Kong)	N	N	Y	N	N	Co-morbid group had more ER visits (20.3% vs 8.2%) and poor self-rated health (60.9% vs 28.0%). Less likely to have personal monthly income of more than US $577 (12.5% vs 31.3%).
Ciechanowski et al.	2000	119, 119 and 121 adults with Type 1 or Type 2 diabetes with low, medium or severe levels of depression.	12 months for adherence; 6 months for utilisation	USA	Y	Y	Y	Y	Y	Six month average health care costs for low, medium and high severity depression groups were $2,094, $2,653 and $3,654 (1999 prices). Costs in high and medium depression groups, 88% and 54% higher than low severity group ($P < 0.05$). Primary care cost 51% higher ($P = 0.002$) in high severity group.
Cradock-O'Leary et al.	2002	47,516 Veterans with psychiatric diagnosis, including 3,694 bipolar disorder; 6,295 depressive disorders.	12 months	USA	N	Y	N	N	Y	Patients with bipolar disorder and diabetes significantly likely > 1 outpatient visit than those without bipolar disorder. No significant different for co-morbid DD group
Das-Munshi et al.	2007	8,580 adults 16–74; 249 diabetics	12 months	UK	Y	N	N/S	Y	N/S	No significant difference in hospital admissions or non-adherence to medications. DD group 3 times more likely to consult with doctor over physical health issues ($P < 0.05$)
Desai et al.	2002	38,020 Veterans. 27,503 diabetes alone. 9,025 any psychiatric problem (including psychosis and PTSD as well as major affective disorders). 2,931 major affective disorders.	12 months	US	Y	Y	N/S		Y	Co-morbid psychiatric problem associated with more outpatient and medical specialist visits and inpatient stays than group without psychiatric problems ($P < 0.0001$).
Druss et al.	2000	15,153 employees, including 412 depression; 203 diabetes. 100 depression plus physical co-morbidity	12 months	USA	Y	Y	N/S	Y	Y	Individuals with co-morbidity had health care costs 1.7 times greater than individuals with one condition ($P < 0.001$).
Egede et al.	2002	85 individuals with DD; 740 diabetes alone	12 months	USA	Y	Y	Y	Y	N/S	DD use more ambulatory care and prescriptions ($P < 0.0001$). Total health care costs 4.5 times greater($P < 0.0001$)
Egede et al.	2003	1,634 adults with diabetes; 176 with DD	12 months	USA	N	Y	Y	N	Y	51% DD group had diabetes complications compared to 39% in diabetes alone group. ($P < 0.02$). 29% vs 4% visited mental health professional ($P < 0.0001$). 41% vs 26% attended ER ($P < 0.0001$). No difference in primary care visits

Table 1 (continued)

Author	Year	Sample size (*N*)	Time horizon for economic analysis	Country of study	In-patient resource use	Out-patient, ambulatory visits, and primary care	Emergency services	Prescription drugs	Mental health care services	Key conclusions
Egede et al.	2009	16,754 adults with diabetes including 3,323 with minor depression and 2,463 with major depression.	12 months	USA	N	Y	N	Y	N	Minor and major depression group less likely to have more than one eye examination compared to no depression group ($P < 0.001$). Influenza vaccination less likely for minor depression ($P < 0.001$). No significant differences in foot examinations, AC1 testing or pneumonia shots.
Finkelstein et al.	2003	218,000 Medicare claimants with diabetes; 19,600 with major depression; 4,023 with DD	12 months	USA	Y	N/S	N/S	N	N/S	Annual mean costs for DD population $25,360 vs $10,358 and $13,153 in diabetes or major depression alone groups.
Fortney et al.	1999	16, 270 Veterans with alcohol, diabetes or depressive disorders	48 months	USA	Y	Y	N	N	N	Costs of co-morbid alcohol and diabetes lower than costs of DD.
Garis et al.	2002	1,027 people with diabetes; 4,077 depression; 48 DD	12 months	USA	N/S	N/S	N/S	N/S	N/S	Co-morbid group mean annual costs $4,253. Diabetes with other co-morbidities higher mean costs: psychosis and diabetes $9,947 (35 people); acid peptic illness and diabetes $7,749 (30 people). Co-morbid depression with psychosis $18,136 (238 people). No significance reported.
Gilmer et al.	2005	1694 Medicare claimants with diabetes	3 years	USA	N/S	N/S	N/S	N/S	N/S	Depression a significant independent predictor of health care costs in people with diabetes. Overall 3 year costs were 50% higher than diabetes only (US $31,967 vs. US $21,609, 2002 prices) ($P < 0.05$).
Harley et al.	2007	8,555 adults with bipolar disorder; 904 DB	18 months	USA	Y	Y	Y	Y	Y	DB had higher one year all-cause costs (US $11,317 vs $6,351.36) No significant cost difference in treating bipolar disorder.
Himmelhoch et al.	2004	Adults 65+. 180,065 diabetes only. 13,491 DD.	12 months	USA	Y	N	Y	N	N	Co-morbid group had 2.83 and 3.42 times more emergency department visits and hospital inpatient admissions'
Husaini et al.	2004	Low income African Americans. 88 diabetes (17.2% had major depressive symptoms); 215 without diabetes (13% had major depressive symptoms)	12 months	USA	Y	Y	Y	N	N	Co-morbidity increased use of emergency care / inpatient days ($P < 0.01$). 2.75 and 3times more emergency visits and more inpatient days. No impact on physician visits.
Hutter et al.	2009	146 people with diabetes. 40 also any mood, anxiety, substance abuse or somatoform disorder in previous month.	12 months	Germany	Y	Y	N	N	Y	No significant difference in health care resource utilisation.
Jones et al.	2004	26,020 people aged 18–64 with diabetes; 6,627 also had mental disorder; including 2,701 with mood disorder	Up to 6years	USA	Y	Y	N	N	N	Median number of (non-mental) inpatient days and visits to primary care providers greater for any co-morbid mental health disorder group – 25 vs 12 days ($P < 0.001$).
Kalsekar et al.	2006	1,525 DD; 2,769 diabetes alone	4 years	USA	Y	Y	Y	Y	N	Co-morbid group costs 65% higher than diabetes only. Also had greater numbers of office visits (mean 10.95 vs 6.62); more than twice ER/hospitalisation events. More prescriptions. Higher total costs (US $12,353 vs. US $8131; 2002 prices)
Krein et al.	2006	18,273 Veterans with diabetes and serious mental illness. 18% DB. Plus 18,273 veterans with diabetes only	12 months	USA	Y	Y	N/S	N	Y	Co-morbid diabetes and serious mental illness group 2.8 times more likely to have inpatient stay. Length of stay 12 vs 8.2 days. Also double number of outpatient visits.
Lawrence et al.	2006	2,672 people aged 10 to 21 85% had Type 1 diabetes. 14% had mild and 8.6% had moderate/severe depressed mood.	6 months	USA	Y	N	Y	Y	N	Mean visits to emergency departments per man with moderate/severe depression were 0.53 versus 0.27 in minimal depressed state ($P < 0.01$). For women 1.02 versus 0.34 ($P < 0.001$). Hospitalisations significantly higher in moderate/severe depressed female group ($P < 0.05$).
Le et al.	2006	55,972 with diabetes alone; 2,146 with diabetic neuropathy (DN); 2,136 with DD ; 683 with DN and depression	12 months	USA	Y	Y	Y	Y	N/S	Mean costs significantly higher in co-morbid group compared with diabetes only: $19,398 vs. $4,819, $P < 0.0001$, 2003 prices. Inpatient, outpatient, emergency care and medication costs all significantly greater. Total costs for DN and depression group double those in DN group alone ($48,281 vs. $18,665, $P < 0.0001$) and triple costs of individuals with DD ($47,214 vs.$14,785, $P < 0.0001$).

Table 1 (continued)

Author	Year	Sample size (*N*)	Time horizon for economic analysis	Country of study	In-patient resource use	Out-patient, ambulatory visits, and primary care	Emergency services	Prescription drugs	Mental health care services	Key conclusions
Le et al.	2011	404,348 adults with diabetes. 5,826 also DD.	12 months	USA	Y	Y	Y	Y	Y	Mean costs for DD $19,707 vs $11,237 diabetes only. Average visits to inpatient, outpatient and emergency care greater for DD ($P<0.0001$).
Lin et al.	2004	4,493 adults individuals with diabetes. 12% DD	12 months	USA	N	N	N	Y	N	Co-morbid cohort had average 3.62 additional days non-adherence to oral hypoglycemics ($P<0.005$); 6.79 additional days non adherence to lipid lowering therapies ($P<0.0005$); 5.59 days non-adherence to ACE inhibitors ($P=0.01$). Twice as likely not to have HbA1c test in year.
Nichols et al.	2007	435 individuals with minor depression and diabetes; 1497 with diabetes alone.	12 months	USA	Y	Y	Y	Y	N/S	Co-existing diabetes and minor depression had higher prescriptions and ambulatory care visits than diabetes only group. In multivariate analysis depression not linked to increased resource use or expenditure.
Pawaskar et al.	2007	792 65+ with Type 2 diabetes. 137 DD	36 months	USA	Y	N/S	Y	Y	N/S	DD group had more self-reported hospitalisations and ER visits ($P<0.05$).
Rosenweig et al.	2002	347 people with Type 1 diabetes; 161 with Type 2 diabetes. 92 DD.	12 months	USA	Y	Y	N/S	Y	Y	Mean annual costs in co-morbid group $8,061 vs $4,832 in diabetes only. Medical costs $5,613 vs $3,086; pharmaceutical costs $2,459 vs 1,784. (Significance not reported).
Simon et al.	2005	4,398 individuals with diabetes. 517 major depression; 371 sub-threshold depression.	6 months	USA	Y	Y	Y	Y	Y	DD associated with 50–75% increase in health costs. Mean healthcare costs $5,361 versus $3,120 ($P<0.001$; Price year not stated). 15% ($275) of increased costs for mental health services. Healthcare costs increased significantly with diabetes complications in co-morbid group.
Stein et al.	2006	130,880 adults; 9,739 had major depression; 4.1% diabetes;	12 months	Canada	N/S	N/S	N/S	N/S	N/S	Compared to depression only DD associated with higher rates of healthcare utilisation ($P<0.005$)
Stewart et al.	2005	231 outpatients aged 11–18 with Type 1 diabetes. 33% DD.	7 months to 2 years	USA	Y	N	N	N	N	54% of those hospitalised for diabetes complications previously diagnosed with depression compared with 30% non-hospitalised ($P<0.05$). Young people diagnosed with depression 2.5 times more likely to be hospitalised than non-depressed.
Subramanian et al.	2009	537 adults aged 21 plus attending a diabetes centre	12 months	Singapore	Y	Y	Y	N	Y	Co-morbid group had more hospitalisations than diabetes alone ($P<0.05$). No significant difference in hospitalisation for psychiatric disorders. Average inpatient days higher 1.9 vs 0.3 ($p<0.05$). Emergency visits for non-diabetes related medical conditions higher ($P<0.05$).
Sundaram et al.	2007	385 people with Type 2 diabetes. 39% depressive symptoms; 8.3% DD	12 months	USA	Y	Y	Y	N	N/S	Co-morbid group had more diabetes complication scores and greater number of hospitalisations and ER visits ($p<0.001$).
Trief et al.	2006	14,438 male veterans with diabetes. 649 had PTSD and depression; 480 PTSD only; 1,696 DD.	12 months	USA	N	Y	N	Y	N/S	Co-morbid PTSD and/or depression had more primary care visits than diabetes alone group ($P<0.001$). Patients with depression and PTSD more likely to be on insulin compared with diabetes alone: 24% vs 16% ($P<0.001$).
Unutzer et al.	2009	14,902 individuals aged 65+ with diabetes (11,590) or congestive heart failure or both; 2,108 had depression; 1,081 probable depression	12 months	USA	Y	Y	Y	N	Y	Annual mean costs of $15,750 vs $10,673 for co-morbid and no depression groups ($P<0.01$). Costs increased with severity of co-morbidity
Vamos et al.	2009	12,643 adults; 526 diabetes alone; 1404 depression alone; 218 DD	12 months	Hungary	Y	N	Y	N	N	Co-morbid group 2.6 times more likely to have hospital stays > 20 days $p<0.001$, and 1.8 times more likely to have multiple hospital admissions $P<0.01$. Increasing Becks Depression Inventory Scores associated with prolonged length of stay ($P<0.001$), emergency calls ($P<0.03$), and hospital admissions ($P<0.003$).
Welch et al.	2009	618,780 adults with private health insurance. 20, 843 had diabetes, including 5,091 with formal diagnosis of depression and/or on antidepressants.	12 months	USA	Y	Y	Y	Y	Y	No cost data provided, but series of diagrams examine differences in cost between co-morbid chronic condition and depression versus depression alone. Costs significantly higher – in DD group circa $2,000 per annum – in 10 of 11 co-morbidity groups.

Key: N/S, not specified; Y, Yes N, No; ER, Emergency Room; DD, Co-morbid Diabetes and Depression; DB, Co-morbid Diabetes and Bipolar Disorder.

reported a 70% increase in all (non-psychiatric) health care costs in people with diabetes and co-morbid major depression compared to non-depressed counterparts (Simon et al., 2005). Total mean health care costs over six months were $5,361 versus $3,120 ($P<0.001$; price year not stated). Only 15% ($275) of this cost increase was for mental health services.

Some survey-based studies have taken place outside the US. In South Australia, in three population surveys over ten years health service use was 49% higher for those with diabetes and depression compared to diabetes alone ($P<0.05$) (Atlantis et al., 2012). Although there was no significant difference in hospital admissions or adherence to medications, people with diabetes and depression in the 2000 UK Psychiatric Morbidity Survey were three times more likely to consult a doctor about physical health compared to those with depression alone ($P<0.05$) (Das-Munshi et al., 2007). A Canadian survey of 130,000 people reported higher rates of health care utilisation by those with co-morbidities ($P<0.005$) compared to those with no health problems (Stein et al., 2006). In Hungary people with depression co-morbidity were 2.6 times more likely to have hospital stays of 20 plus days ($P<0.001$) and 1.8 times more likely to have multiple hospital admissions ($P<0.01$) compared to people with diabetes alone (Vamos et al., 2009). This study also found that increased severity of depression was associated with increased length of stay ($P<0.001$), emergency calls ($P<0.03$) and hospital admissions ($P<0.003$). In contrast, analysis of the German National Health Interview and Examination Survey observed no significant difference in physician contact or inpatient days between 100 people with diabetes alone and 40 with a co-morbid mood, substance abuse or somatoform disorder (Hutter et al., 2009).

3.1.2. Analysis of medical record data

Medical record/claims data have been used for economic analysis of co-morbidity, again with a trend towards significantly increased costs. Medicaid claims data indicate higher annual health care costs in a low income population with diabetes and depression compared to those with diabetes alone ($12,353 vs. $8131; 2002 prices) (Kalsekar et al., 2006). Private insurance claims data for 404,000 adults with diabetes reported mean annual health care costs for people with diabetes with and without major depression of $19,700 and $11,200 respectively (2006 prices) (Le et al., 2011). The number of visits to inpatient, outpatient and emergency care was significantly greater in those with co-morbid depression ($P<0.0001$).

Co-morbid diabetes and depression was also compared with co-morbidity between depression and ten other chronic conditions in 618,000 medical claims records (Welch et al., 2009). Nearly all co-morbid conditions had significantly higher costs, which for diabetes were around $2,000 per annum. Another analysis of claims data reported individuals with bipolar disorder and diabetes had double the one year all-cause costs of those with bipolar disorder alone (Harley et al., 2007). Analysis of 20,000 insured people with diabetes, including 2,700 with a mood disorder, also reported higher inpatient and primary care utilisation for the co-morbid group (Jones et al., 2004). Higher medical costs were also observed in small studies comparing diabetes and depression with diabetes alone (Rosenzweig et al., 2002; Sundaram et al., 2007). In a Singapore study, diabetes clinic attendees with depression had more emergency visits, hospitalisations and longer inpatient stays ($P<0.05$) (Subramaniam et al., 2009).

1995 Oklahoman Medicaid data found co-morbid diabetes with psychosis or acid peptic illness to have annual costs $3,000–$5000 (1995 prices) greater than for diabetes and depression (Garis and Farmer, 2002). Health care costs of co-morbid diabetes and depression for a manufacturing company's staff were also 1.7 times greater than for employees with one condition at $7,407 (1995 prices) ($P<0.001$) (Druss et al., 2000).

Few of these studies report economic impacts beyond one year. One found mean Medicare costs between 1999 and 2002 to be 50% higher for people with diabetes and different co-morbidities, including depression, compared with diabetes only (Gilmer et al., 2005) (US $31,967 *vs.* US $21,609; $P<0.05$; 2002 prices). One study suggested that quality improvement strategies emphasising pharmaceutical therapy for depression would increase costs of care by $2,962, $P=0.038$; 2002 prices) (Gilmer et al., 2006). This finding contradicts most studies we have reviewed where improvements in quality of care and outcomes tend to lower total health care costs compared to usual care.

3.1.3. Analysis for population sub-groups

Some studies have focused on specific age or ethnic groups. Analysing 1.3 million Medicare records, mean annual non-mental health care costs of people with co-morbid diabetes and major depression in 1997 were $25,360 compared to $10,358 and $13,153 for groups with diabetes or major depression alone (2001 prices) (Finkelstein et al., 2003). In the US 13,000 Medicare recipients with co-morbid diabetes and depression were 2.83 and 3.42 times more likely to have emergency department visits, or hospital inpatient admissions respectively, compared to people with diabetes alone (Himelhoch et al., 2004). Similar findings were seen in a survey of Medicare enrolees with diabetes and depression, compared to people with diabetes only in a Health Maintenance Organisation (Pawaskar et al., 2007).

The presence of co-morbid depression alongside diabetes or congestive heart failure in 15,000 Medicare claimants in Florida increased annual mean costs to $15,750 versus $10,673 ($P<0.01$). Mental health services accounted for just 1% of costs (Unutzer et al., 2009). Costs also increased with severity of co-morbidity in those with or without a diagnosis of depression: $37,392 versus $21,940 for quartile with severest co-morbidity. We only found one study looking at older people with diabetes and depression outside the US. In Hong Kong, compared with people with diabetes alone, they were three times more likely to use emergency care services (Chou et al., 2005).

Several US studies examined military veteran data. Mean annual inpatient and outpatient health expenditure in 2000 was $6,185 and $9,871 for 355,000 and 35,000 veterans with diabetes only or co-morbid depression or bipolar disorder respectively (Banerjea et al., 2008). Mental health treatment of depression or bipolar disorder covered just 9% of these costs. In another study of 47,000 veterans, those with either bipolar disorder or depression alongside diabetes were less likely to have more than one outpatient visit to a Veterans Affairs (VA) clinic per annum compared to veterans without psychiatric illness (Cradock-O'Leary et al., 2002).

In contrast, analysis of 146 VA clinics over one year reported significantly higher use of primary care, specialists and inpatient stays in people with diabetes and any mental health problem (Desai et al., 2002). Similarly, higher rates of outpatient and inpatient service use were seen in those with co-morbid diabetes and serious mental illness, including bipolar disorder (Krein et al., 2006). Of 14,000 New York veterans with diabetes, those with co-morbid post-traumatic stress disorder and/or depression had more primary care visits and were more likely to be treated with insulin than veterans with diabetes alone ($P<0.001$) (Trief et al., 2006).

There has been also been some analysis of the impact of co-morbidity for minority groups. Survey data from five southern US states highlighted excessive rates of diabetes complications in over 600 older Mexican-Americans with diabetes and depressive symptoms versus those without depression (Black, 1999). They were less likely to use oral hypoglycaemic agents, but had more aggressive insulin therapy. Higher complication rates, and adverse impacts on activities of daily living and mortality were seen over seven years (Black et al., 2003). A study of a low-income African

American primary care population reported that people over 40 with co-morbid diabetes and depression had 2.75 and 3 times more emergency visits and inpatient days than those with neither condition ($P<0.01$) (Husaini et al., 2004).

3.1.4. Type 1 diabetes and depression

Few costing studies focused on type 1 diabetes. One rare example examined depressive symptoms as a predictor of hospitalisation for diabetes-related events in 231 outpatients with type 1 diabetes aged 11 to 18 over two years (Stewart et al., 2005). They were 2.5 times more likely to be hospitalised than in non-depressed counterparts. Another cross-sectional study of people aged 10–21 in six US states, 85% with type 1 diabetes, reported more emergency department visits over six months by those with higher levels of self-reported depressed mood (Lawrence et al., 2006).

3.1.5. Diabetes complications and depression

There has been some analysis of the additional costs of diabetes complications, including diabetic neuropathy, with co-morbid depression. Using eight years of claims data (Le et al., 2006), one study found not only significantly higher mean costs for diabetes and depression versus diabetes alone: $19,398 vs. $4,819 ($P<0.0001$ 2003 prices), but costs tripled for those with diabetic neuropathy and depression, compared to individuals with diabetes and depression ($47, 214 vs $14,785, $P<0.0001$).

Another study assessed 4,800 individuals with depression or anxiety and diabetic neuropathy compared with 34,000 people with diabetic neuropathy alone (Boulanger et al., 2009a). Again, annual mean healthcare costs were higher for co-morbid patients: $26,718 vs. $17,483 for patients aged 65+ and $29,775 vs. $19,386 (2006 prices) for those aged 18–64 ($P<0.05$). The co-morbid group had greater utilisation of medications, inpatient visits and emergency care ($P<0.01$) (Boulanger et al., 2009b).

3.2. Impacts on productivity

It is important to look at impacts on productivity. Individuals may have higher rates of absenteeism or prematurely retire from work (Von Korff et al., 2005; Friis and Nanjundappa, 1986; Egede, 2004b). Co-morbidity may hamper the ability to do household tasks or voluntary work, all of which contribute to economic output. Relatives may need to cut back on paid and unpaid activities to provide informal care (Jonkers et al., 2009).

Mortality also contributes to productivity losses. Mortality risk is higher in individuals with diabetes and depression compared with diabetes alone (Bogner et al., 2007; Zhang et al., 2005; Ismail et al., 2007; Katon et al., 2005b). Adverse impacts of depression on self-care could also increase the risk of cardiovascular disease, itself the leading cause of mortality in people with diabetes (Black et al., 2003; Rush et al., 2008).

Table 2 summarises findings of 11 studies, five US and six non-US, on productivity losses, although only two assign these a monetary value and none include premature mortality or informal care. The omission of these aspects of productivity loss is remarkable given that they are often reported in studies looking solely at diabetes or depression (Chatterjee et al., 2011; Gonzalez et al., 2009b; Hogan et al., 2003; Hu et al., 2007; Salvador-Carulla et al., 2011; Thomas and Morris, 2003).

Five studies used survey data. UK Psychiatric Morbidity Survey data indicate that over a year individuals with diabetes and depression were 7.7 and 5.3 times more likely to take sick days and have work/regular activities impaired by poor health respectively compared to people with diabetes alone ($P<0.05$) (Das-Munshi et al., 2007). A national survey in Hungary found that people with diabetes and depression had significantly lower rates of employment compared to those with diabetes alone – 7.4% vs 24% ($P<0.001$) (Vamos et al., 2009). They were 3.3 and 2.7 times respectively to lose more than 10 workdays ($P<0.05$) or spend more than 20 days in bed ($P<0.001$).

In the 1999 US National Health Interview Survey, 170 people with diabetes and depression were three, five and seven times more likely to have work loss days, bed disability days and functional disabilities respectively compared to those with neither condition (Egede, 2004b; Egede, 2004a). Further analysis, examining depression and several chronic conditions, including diabetes, concluded that co-morbid major depression is associated with significant increases in lost productivity and functional disability (Egede, 2007). In a Canadian survey of 130,000 adults however, no significant differences in work absence over just one week or on activities of daily living over six months were found between co-morbid and diabetes or depression alone groups. Co-morbidity did predict increased risk of disability in the two weeks prior to the survey ($P<0.005$) (Stein et al., 2006).

Two studies examined employee experiences. One linked certified sickness absence to health status in 33,000 public sector employees in Finland. Non-cardiovascular co-morbid conditions for employees with diabetes, including depression, accounted for over 50% of excess risk of sickness absence (Kivimaki et al., 2007). A US study of a manufacturing company with 15,000 employees reported 13.48 sick days per annum on average due to depression and physical co-morbidity (diabetes, heart disease, hypertension or back problems) compared to 6.64 and 8.79 days for those with a physical condition or depression alone. Total mean costs, including health care and disability, per employee with co-morbidity were $7,906 (1995 prices). This is conservative: the costs of poor performance at work were not included (Druss et al., 2000).

Three studies examined the experience of different groups of people with a primary diagnosis of diabetes. In one cross-sectional study in Washington State (Von Korff et al., 2005), 26% of those with depressive co-morbidity were unemployed. Even co-morbid minor depression increased the risk of being disabled or unemployed by 70% ($P<0.05$). Major depression doubled risk and increased the risk of severe difficulty with work tasks fivefold (all $P<0.01$). Analysis of 56 people with diabetes compared to matched controls illustrated that those in employment were significantly less likely to be depressed (Friis and Nanjundappa, 1986). A study of diabetes centre attendees in Singapore highlighted that people with co-morbid depression lost an extra half day of work over three months compared to those with diabetes alone (1.9 vs. 1.4, $P=0.001$) (Subramaniam et al., 2009).

Finally an econometric study examined the association between annual income and depression in individuals with diabetes (Dismuke and Egede, 2010). Using the 2006 US MEPS, mean annual incomes for those with diabetes alone versus diabetes and depression were $33,391 and $17,786. Accounting for confounding factors such as education or ethnicity, co-morbid major depression was independently associated with a $2,838 reduction in mean annual income, with a decrease in income of $1,235 for each additional depressive symptom.

3.3. Economic evaluations of interventions for prevention or treatment of co-morbidity

It is not enough to know the health care costs associated with co-morbidity, it is important to explore whether potential investments in tackling co-morbid diabetes and depression represent better value for money than alternative actions in the health system or other sectors. Economic evaluation can help with this question. It compares the costs and effectiveness of two or more actions. Different techniques are available; all value cost in the same way but differ on outcome measurement. Cost effectiveness and cost consequences analyses use condition specific outcome measures

Table 2
Impact of co-morbidity on productivity losses.

Author	Year	Sample size (*N*)	Time horizon	Country of study	Monetary value of costs reported	Summary conclusions
Das-Munshi et al.	2007	8,580 adults 16–74; 249 with diabetes	12 months	UK	N	No difference in unemployment or economic inactivity. DD 7.7 and 5.3 times more likely to take days off work sick and have work/regular activities impaired by health ($P < 0.05$)
Dismuke et al.	2010	1,818 individuals aged 18+ with diabetes. 18.1% DD; a further 45% had at least one depressive symptom.	12 months	USA	Y	As depressive symptoms increase annual income decreases. Major depression associated with $2,838 income reduction. Each additional symptom of depression associated with $1,235 income reduction.
Druss et al.	2000	15,153 employees, including 412 depression; 203 diabetes. 100 depression plus physical co-morbidity	12 months	USA	Y	Co-morbid group mean 13.48 sick days per annum vs 6.64 for physical condition or 8.79 for depression only. Total mean health and productivity costs per employee with co-morbidity $7,906.
Egede	2004a	30, 022 adults; 1,852 depression; 1,624 diabetes; 170 DD.	12 months	USA	N	Compared to no diabetes or no depression groups functional disability 7.15 times higher in DD group.
Egede	2004b	30, 022 adults; 1,852 depression; 1,624 diabetes; 170 DD.	12 months	USA	N	Co-morbid group 3.25 times more likely to have work loss days vs no condition group. 5.61 times more likely to have bed disability days. Productivity losses greater than for diabetes or depression alone.
Friis et al.	1986	56 adults with and 56 without diabetes.	One day	USA	N	Individuals with DD in employment had higher levels of depression than those without diabetes. More likely to be depressed if had diabetes and unemployed.
Kivimaki et al.	2007	33,148 public sector employees. 638 had diabetes, including 20% DD.	12 months	Finland	N	DD had 1.98 increased risk of certified sickness absence vs no diabetes.
Stein et al.	2006	130,880 adults; 9,739 had major depression; 4.1% diabetes;	1week for work; 2 weeks for disability; 6 months for activities of living	Canada	N	No significant differences in work absence or in reduction in activities of daily life compared to those without illness. Co-morbidity was predictor of increased risk of disability in previous two weeks ($P < 0.005$).
Subramanian	2009	537 adults aged 21 plus attending a diabetes centre	3 months	Singapore	N	DD group lost more working days vs diabetes alone (1.9 vs. 1.4, $P = 0.001$).
Vamos et al.	2009	12,643 adults; 526 had diabetes alone; 1404 depression alone; 218 DD	12 months	Hungary	N	DD group had lower employment vs diabetes alone – 7.4% vs 24% ($P < 0.001$). They had more days lost from work (78.5 vs 18.1 ($P < 0.001$) and more days spent in bed (87 vs 21) ($P < 0.001$).DD 3.3 times more likely to have 10+ lost workdays vs those without diabetes or depression ($P < 0.05$). Also 2.7 times more likely to have 20+ days in bed ($P < 0.001$).
Von Korff et al.	2005	1,642 adults with diabetes ≤62 and employed, disabled or unemployed.	One month for work disability.	USA	N	Co-morbid minor depression increased risk of being disabled or unemployed by 70% relative to diabetes alone ($P < 0.05$); also had threefold risk of severe difficulty with work tasks ($P < 0.05$). Major depression doubled risk of being disabled or unemployed, increased risk of five plus days out of work threefold, and risk of severe difficulty with work tasks 4.5 times (all $P < 0.01$).

Key: N/S, not specified; Y, Yes; N, No; DD, Co-morbid Diabetes and Depression.

while cost utility analyses may use quality adjusted life years (QALYs), allowing easier comparison of investments within the health care system. Cost benefit analysis places a monetary value on benefits, making it possible to compare investment in health with investments in other sectors, such as education.

Table 3 provides a summary of 15 studies identified, generally supporting investment in action to tackle co-morbidity. Most focus on collaborative or stepped care, particularly on depression management. With the exception of two studies (King et al., 2011; Jonkers et al., 2009), all 11 completed economic evaluations examined the impact on costs from a health system perspective alone, potentially ignoring productivity losses. Four studies used costs per QALY gained (Hay et al., 2012; Jonkers et al., 2009; Katon et al., 2006; King et al., 2011), while two were cost benefit analyses (Simon et al., 2007; Katon et al., 2006).

Several studies built on the Improving Mood-Promoting Access to Collaborative (IMPACT) trial previously shown to double the effectiveness of depression treatment for older adults in primary care settings (Unutzer et al., 2002). Intervention consisted of stepped collaborative care led by a care manager (usually a nurse) supervised by a psychiatrist. It included behaviour activation and a choice of starting treatment with six to eight sessions of psychotherapy for problem-solving or antidepressant medication. It has been compared to usual primary care services, including use of antidepressants and referral to mental health services. The intervention improved depression and some diabetes outcomes in co-morbid individuals over two years (Williams et al., 2004). It was also cost effective in depression management (Katon et al., 2005c; Unutzer et al., 2008).

An economic evaluation of the above IMPACT diabetes depression sub study reported 115 additional depression free days gained at an increased cost of $25 in outpatient services, with an incremental cost per QALY gained between $198 and $397 (price year unspecified) (Katon et al., 2006). These economic benefits of stepped collaborative care are conservative, as substantial cost savings for inpatient care services if included would mean net costs avoided of $896. Previous analysis had observed a willingness to pay of $11 per depression free day gained (Unutzer et al., 2003). Using this method the intervention would generate a net benefit of $1,129 per patient.

The Pathways study in Washington State was another controlled trial of a stepped collaborative care model for the treatment of depression in individuals with diabetes. Intervention dominated usual care; with 12 months of treatment, the intervention group gained 61 additional depression free days over two years. Additional costs of participating in the programme were offset by a reduction in other outpatient expenditures (Simon et al., 2007). Using a willingness to pay value of $10 per depression free day generated there were net benefits of $952 (2003 prices). No difference in inpatient costs was observed due to small sample size.

A subsequent evaluation of Pathways using the same population sample looked at trends over five years (Katon et al., 2008b); a consistent trend towards lower costs in the intervention group was seen, with mean five-year total savings of US $3,900 per patient, but the small sample size meant no significant differences in costs were identified. The authors noted that the greatest level of cost savings might be realised in the third of the patient sample with the most severe morbidity.

In another trial in Washington State, the integration of disease management programmes for diabetes and cardiovascular disease with collaborative stepped care to tackle depression was associated with significantly improved outcomes for depression and physical co-morbidities over one year (Katon et al., 2010). Average costs per patient were $1,224 (price year not stated), which were offset by savings in total outpatient costs over 24 months. Compared to usual primary care controls, the intervention group showed a total 24-month saving of $594 per patient (Katon et al., 2012). This study is unique because it measured potential gains in QALYs associated with intervention benefits on depression, HbA_{1c} LDL cholesterol and systolic blood pressure and found a 99% probability the intervention would cost less than $20,000 per QALY gained.

Some economic analysis of the IMPACT model was examined in an uncontrolled study of a Spanish speaking population in the US (Gilmer et al., 2008). Implemented alongside a culturally specific diabetes management programme (Project Dulce), 99 of 154 individuals completed the programme at a cost of $512 per person (2008 prices). They had significant reductions in depressive symptoms and improvements in diabetes self-care. The intervention is likely to be cost effective, as Project Dulce had been shown as cost effective for diabetes management in low income populations, with a cost per QALY gained of $10,141 (2007 prices) (Gilmer et al., 2007).

Another evaluation examined a culturally adapted collaborative, stepped care model for diabetes and depression alongside an 18 month randomised controlled trial targeted at 387 low-income Hispanics with diabetes and depression (Hay et al., 2012; Ell et al., 2010). It was compared with enhanced usual care (standard clinical care, pamphlets on depression education and a resource list for relevant services). The intervention group showed greater improvements in depression than controls, with a cost per QALY gained of $4,053 (2009 prices). At a cost per QALY gained threshold of $12,000 the intervention had a 90% chance of being cost effective. There was also significantly less deterioration in the financial circumstances of the intervention group compared with controls over 6 and 12 months (Ell et al., 2010).

A modelling approach was used to synthesise data from US studies on potential depression free days gained through collaborative care with cost data from an English NHS perspective NHS (King et al., 2011). Impacts on productivity losses were also included. Over two years the incremental cost per QALY gained was £3,614 (2009 prices). While changes in the costs of diabetes care were not included, avoidance of some diabetes complications would make the intervention cost saving.

Only one other economic evaluation examined costs beyond the health care system, although this is also examined in three ongoing studies, one in the Netherlands (Horn et al., 2007) and two in Germany (Chernyak et al., 2010; Chernyak et al., 2009; Petrak et al., 2010). The completed study is for a clinical trial of a primary care nurse-led minimal psychological intervention (MPI) compared with usual care in the Netherlands (Jonkers et al., 2009). The intervention group received a combination of home-based cognitive behavioural therapy and self-management therapy, in addition to usual care for three months. Patient diaries captured costs beyond the health care system, such as informal care, domestic help and work absenteeism. No significant differences in depressive symptoms or costs were reported. The intervention had a 63% chance of having lower costs and better outcomes than usual care and an 82% chance of being cost effective given a cost per QALY gained threshold of €20,000.

We also identified a US study that observed a significant association between good adherence to antidepressants and adherence to diabetes management treatments in claims records of 2,500 adults with diabetes and depression (Katon et al., 2005a). Over one year, compared to co-morbid patients with poor adherence to antidepressants, patients with good adherence had 12% lower medical charges; for patients with multiple co-morbidities, total medical charges were 20% lower ($P < 0.05$). The study did not include pharmaceutical costs; better adherence to medication would thus reduce some cost offsets.

Table 3
Economic evaluations of interventions to prevent and/or treat co-morbid diabetes and depression.

Author	Year	Sample size	Country	Time horizon, Study design Economic evaluation type	Intervention (I) and comparator(s) (C)	Outcomes	Perspective	Results
Chernyak et al. and Petrak et al.	2009 2010	315 adults aged 65 to 85 with DD	Germany	15 months RCT CUA, CEA	I: Cognitive behavioural therapy C: Intensified treatment as usual or guided self-help group	QALYs: EQ5D and SF 36 Depression-free years	Statutory health insurance and societal	Study protocol
Chernyak et al.	2010	208 adults with diabetes and sub-threshold depression	Germany	12 months	I: Diabetes specific cognitive behavioural therapy C: Standard diabetes education programme	QALYs: EQ5D and SF 36	Statutory health insurance and societal	Study protocol
Ell et al.	2010	387 adults with DD 97% Hispanic.	USA	18 months RCT Partial CCA	I: Stepped collaborative care including problem solving therapy C: Standard clinical care plus family education leaflets on depression; potential referral to community mental health care	Depression symptoms using Hopkins Symptom Checklist 20	Health care system	Intervention group more likely to have 50% reduction in depressive symptoms at 6, 12 and 18 months ($P < 0.001$.) Intervention group experienced less financial deterioration over 6 and 12 months. Utilisation of depression treatment also better. Per patient intervention costs $820.
Gilmer et al.	2008	154 adults with DD; 99 completed study. 74% Latino and 71% used Spanish as main language	USA	Up to 12 months Before and after study without control CCA	I: Culturally tailored stepped collaborative care led by care manager (usually nurse) for management of DD. Includes behaviour activation and 6–8 sessions of psychotherapy for problem-solving. Integrated with culturally specific diabetes management programme. No comparator	Changes in depression as measured on PHQ-9. Diabetes self-care activities.	Health care system	Intervention cost $512 per person. PHQ-9 scores declined by 7.5 points on average ($P < 0.001$) Diabetes self-care activities related to nutrition increased.
Hay et al.	2012	387 adults with diabetes. 97% Hispanic	USA	18 months RCT CUA	See Ell et al., 2010	Depression-free days – PHQ-9 QALY – SF-12	Health care system	Intervention group had improvements in quality of life and depression free days ($P < 0.001$). Average costs of intervention $515 per patient. Mean cost per QALY gained per recipient $4,053; more than 90% likely to be <$12,000 per QALY.
Horn et al.	2007	126 adults with diabetes, COPD or cardiovascular disease. All have moderate to severe depression	Netherlands	12 months RCT CUA	I: Collaborative care from consultative psychiatric nurse and psychiatrist in outpatient department C: usual care in outpatient department of hospital.	QALYs: EQ5D and SF 36	Societal	Study protocol
Jonkers et al.	2009	Patients aged 60+ with diabetes or COPD; 110 in intervention group, including 57 with diabetes; 118 in control group, including 64 with diabetes.	Netherlands	12 months RCT CUA	I: primary care nurse-led minimal psychological intervention (MPI) C: usual care	Depression-free days: BDI QALYs: EQ5D	Societal	63% probability that MPI less costly and more effective than usual care. 82% probability when willingness to pay per QALY gained £20,000
Katon et al.	2005	2,518 adults with DD; plus 863 with cardiovascular disease and dyslipidemia and DD	USA	12 months Claims database analysis Partial COA	I: Use of antidepressants	Adherence to medication for diabetes and other co-morbid physical illness	Health care costs (excluding cost of pharmacy)	Adherence to antidepressant therapy over 180 days was associated with adherence to co-morbid medication therapy ($P < 0.001$). For DD cohort total medical charges were 12% lower; for diabetes and cardiovascular disease and dyslipidemia group, total medical charges were 20% lower($P < 0.05$).

Table 3 (continued)

Author	Year	Sample size	Country	Time horizon, Study design Economic evaluation type	Intervention (I) and comparator(s) (C)	Outcomes	Perspective	Results
Katon et al.	2006	418 Adults with DD aged 60+	USA	2 years RCT CEA; CUA; Partial CBA	I: Stepped collaborative care led by care manager (usually nurse) for management of DD. Includes behaviour activation and 6–8 sessions of psychotherapy for problem-solving. C: Usual primary care which could include use of antidepressants and referral to mental health services.	Hopkins Symptom Checklist 20 Depression Score (HSCL-20) to determine number of depression free days. QALYs Willingness to pay for depression free days	outpatient costs only.	Incremental cost per depression free day \$0.25; Incremental cost per QALY gained: \$198–\$397; Incremental net cost benefit \$1,129. 50% chance of intervention being cost effective considering outpatient costs only; 67% if inpatient costs included.
Katon et al.	2008	310 adults with diabetes	USA	5 years RCT CCA	I: Depression screening followed by nurse led stepped care including psychotherapy and pharmacotherapy C: Usual primary care	Depression free days gained using the Hopkins SCL-20 depression scale	Health payer	Consistent trend in lower outpatient and inpatient costs in the intervention group, although not significant. Intervention improves depression outcomes without greater long term costs.
Katon et al.	2010	214 adults with depression; 106 in intervention and 108 in control group; 89% and 82% in groups has diabetes; 23% and 30% had cardiovascular disease.	USA	12 months RCT CCA	I: Integration of programme for cardiovascular disease with collaborative care for depression which included motivational therapy, self help guides and pharmaceutical therapy. C: Enhanced usual primary care, allowing for referral to mental health care.	Four outcomes: depression using SCL-20 score, glycated haemoglobin level, systolic blood pressure and LDL cholesterol level	Health care payer.	Patients in intervention group had significantly greater improvement in all outcomes ($P < 0.001$). Average cost per patient of intervention was \$1,224. No other cost data provided.
Katon et al.	2012	See Katon et al., 2010	USA	2 years RCT CUA	See Katon et al., 2010	Depression free days gained using Hopkins SCL-20 depression scale QALYs gained	Health care system	Compared to controls intervention was dominant with lower costs and better outcomes. Mean 114 depression free days and 0.335 QALYs gained. Mean costs lower by \$594. 99.7% chance of being cost effective if cost per QALY threshold of \$20,000 used.
King et al.	2011	Hypothetical cohort of individuals with diabetes	UK (England)	24 months Decision analytical model CUA	I: Usual care plus collaborative care where practice nurse acts as a case manager for patients receiving care; GPs liaise with practice nurses C: Usual care – GP advice and care, use of antidepressants and cognitive behavioural therapy for some patients.	Depression free days gained QALYs gained	Health care payer, public purse and society	Incremental cost per QALY gained was £3,614. Conservative as impacts on costs of diabetes care/complications not included.
Simon et al.	2007	310 adults with diabetes;	USA	24 months RCT CEA; Partial CBA	I: Depression screening followed by nurse led stepped care including psychotherapy and pharmacotherapy C: Usual primary care	Depression free days gained using the Hopkins SCL-20 depression scale	Outpatient health care costs alone.	Over two years intervention was dominant over usual care, with mean of 61 additional depression free days gained and reduction in outpatient costs of \$314. If willingness tp pay \$10 per depression free day – net benefit of \$952 per patient.

Key: DD, Co-morbid Diabetes and Depression; RCT, Randomised Controlled Trial; CEA, Cost Effectiveness Analysis; CUA, Cost Utility Anaysis; CBA, Cost Benefit Analysis; CCA, Cost Consequences Analysis.

4. Discussion

Despite limitations, this review provides the most comprehensive assessment both of literature measuring the association between co-morbid diabetes and depression and impacts on health and non-health care systems, and in identifying completed and ongoing economic evaluations. The review indicates growing evidence demonstrating the substantial adverse economic impact of co-morbidity. This relationship is complex and will vary depending on factors including severity of co-morbidity and the socio-economic environment where services are delivered. Most studies focused on type 2 diabetes, but adverse economic impacts of co-morbidity with type 1 diabetes and with complications such as diabetic neuropathy were reported. No studies looked at gestational diabetes.

4.1. Limitations

While we did not have any language restrictions in our review, we did not search non- English language databases. This may contribute to the dominance of US literature that may limit the generalisability of findings to non-US settings. We sought to identify more studies by including papers that reported impacts on health system resource utilisation, even if not reporting actual increments in health care costs, but are likely to have missed papers that do discuss resource utilisation, but are not key worded or indicated in their abstracts as having cost or resource relevant information. The limited number of studies found may also reflect the predominance of cross-sectional analysis of datasets, making it difficult to link co-morbidity directly with cost impacts.

4.2. Implications

Despite limitations, these findings are consistent with previous reviews. One review of the costs of co-morbid mental disorders on people with diabetes identified 31 papers, including 27 on diabetes and depression, observing a trend between co-morbidity and increased health care resource use and productivity losses (Hutter et al., 2010). A German language review of economic evaluations could only find US studies (Chernyak et al., 2011).

The importance of the economic impact of co-morbid diabetes and depression is likely to be further strengthened, not only by more analysis of non-US populations, but also if more studies consider economic impacts beyond the health care system. We were only able to identify 11 studies that looked at costs beyond the health care system, yet the impacts of diabetes and depression in isolation on participation in work, in particular, are well known.

Understanding the magnitude of costs is itself an insufficient argument for investment. From a health policy perspective, it is important to identify whether interventions that improve health outcomes are cost effective. We identified 11 completed economic evaluations, mostly conducted alongside clinical trials. While caution must be exercised in their interpretation, all suggest that actions to manage depression in people with diabetes have the potential to improve quality of life and generate economic benefits. In contrast, we were unable to identify any studies on the economic benefits for measures to reduce the risk of diabetes in people with depression. This is one area for analysis in future research.

Stepped/collaborative care is recommended in English guidelines on the management of depression in individuals with chronic physical illness (National Institute for Health and Clinical Excellence, 2009). Favourable cost per QALY ratios or positive net benefits in the US for stepped care and/or collaborative approach to depression management for people with diabetes have been reported. These economic gains may be conservative as most QALY gains have looked solely at the additional utility from depression free days and have not included impacts on diabetes.

The economic case will be more robust if benefits beyond the health sector are considered. Only two studies have looked at productivity losses due to work absenteeism, and none at impacts on premature mortality or informal care. It is also important to consider the cost effectiveness of any screening strategies for diabetes or depression, including any impacts of false positive/negative screenings on cost and quality of life. Long-term analyses are needed: only one economic evaluation examined economic impacts beyond two years, despite the chronic nature of both conditions.

Thus, the challenge for policy makers remains to build up the evidence base on the cost effectiveness of different interventions in different real world settings. We identified three evaluations underway in Europe, but again these are short-term in duration. Longer follow-up and broader perspectives (such as impacts on social services, lost productivity or families) will strengthen the evidence base. One way to do this is through modelling approaches that synthesise data on the effectiveness of interventions and the consequences of not taking action, considering how interventions may need to be adapted for different localities, and attaching local resources and unit costs. We know of only one such modelling study from England (King et al., 2011). This leaves plenty of scope for rapidly building on promising cost effective actions to examine different approaches to tackle co-morbid diabetes and depression in different contexts and settings.

Conflict of interest

There are no conflicts of interest to disclose.

References

Atlantis, E., Goldney, R.D., Eckert, K.A., Taylor, A.W., Phillips, P., 2012. Trends in health-related quality of life and health service use associated with comorbid diabetes and major depression in South Australia, 1998–2008. Soc. Psychiatry Psychiatr. Epidemiol. 47, 871–877. [Epub 2011 May 18]

Banerjea, R., Sambamoorthi, U., Smelson, D., Pogach, L.M., 2008. Expenditures in mental illness and substance use disorders among veteran clinic users with diabetes. J. Behav. Health. Serv. Res. 35, 290–303.

Black, S.A., 1999. Increased health burden associated with comorbid depression in older diabetic Mexican Americans. Results from the Hispanic Established Population for the Epidemiologic Study of the Elderly survey. Diabetes Care 22, 56–64.

Black, S.A., Markides, K.S., Ray, L.A., 2003. Depression predicts increased incidence of adverse health outcomes in older Mexican Americans with type 2 diabetes. Diabetes Care 26, 2822–2828.

Bogner, H.R., Morales, K.H., Post, E.P., Bruce, M.L., 2007. Diabetes, depression, and death: a randomized controlled trial of a depression treatment program for older adults based in primary care (PROSPECT). Diabetes Care 30, 3005–3010.

Boulanger, L., Zhao, Y., Bao, Y., Russell, M.W., 2009a. A retrospective study on the impact of comorbid depression or anxiety on healthcare resource use and costs among diabetic neuropathy patients. BMC Health Serv. Res. 9, 111.

Boulanger, L., Zhao, Y., Foster, T.S., Fraser, K., Bledsoe, S.L., Russell, M.W., 2009b. Impact of comorbid depression or anxiety on patterns of treatment and economic outcomes among patients with diabetic peripheral neuropathic pain. Curr. Med. Res. Opin. 25, 1763–1773.

Brown, L.C., Majumdar, S.R., Newman, S.C., Johnson, J.A., 2006. Type 2 diabetes does not increase risk of depression. CMAJ 175, 42–46.

Centres for Disease Control, 2010. Current depression among adults – United States, 2006 and 2008. MMWR Morb. Mortal Wkly. Rep. 59, 1229–1235.

Chatterjee, S., Riewpaiboon, A., Piyauthakit, P., Riewpaiboon, W., Boupaijit, K., Panpuwong, N., Archavanuntagul, V., 2011. Cost of diabetes and its complications in Thailand: a complete picture of economic burden. Health Soc. Care Community, 19, 289–298.

Chernyak, N., Icks, A., Scheer, M., Giani, G., 2011. Gesundheitsökonomische Evaluation von Interventionen bei Diabetes mellitus und komorbider Depression. Der Diabetologe 7, 88–91.

Chernyak, N., Petrak, F., Plack, K., Hautzinger, M., Muller, M.J., Giani, G., Icks, A., 2009. Cost-effectiveness analysis of cognitive behaviour therapy for treatment of minor or mild-major depression in elderly patients with type 2 diabetes: study protocol for the economic evaluation alongside the MIND-DIA randomized controlled trial (MIND-DIA CEA). BMC Geriatr. 9, 25.

Chernyak, N., Kulzer, B., Hermanns, N., Schmitt, A., Gahr, A., Haak, T., Kruse, J., Ohmann, C., Scheer, M., Giani, G., Icks, A., 2010. Within-trial economic evaluation of diabetes-specific cognitive behaviour therapy in patients with type 2 diabetes and subthreshold depression. BMC Public Health 10, 625.

Chou, K.L., Ho, A.H., Chi, I., 2005. The effect of depression on use of emergency department services in Hong Kong Chinese older adults with diabetes. Int. J. Geriatr. Psychiatry 20, 900–902.

Ciechanowski, P.S., Katon, W.J., Russo, J.E., 2000. Depression and diabetes: impact of depressive symptoms on adherence, function, and costs. Arch. Intern. Med. 160, 3278–3285.

Cradock-O'Leary, J., Young, A.S., Yano, E.M., Wang, M., Lee, M.L., 2002. Use of general medical services by VA patients with psychiatric disorders. Psychiatr. Serv. 53, 874–878.

Das-Munshi, J., Stewart, R., Ismail, K., Bebbington, P.E., Jenkins, R., Prince, M.J., 2007. Diabetes, common mental disorders, and disability: findings from the UK National Psychiatric Morbidity Survey. Psychosom. Med. 69, 543–550.

De Hert, M., Cohen, D., Bobes, J., Cetkovich-Bakmas, M., Leucht, S., Ndetei, D.M., Newcomer, J.W., Uwakwe, R., Asai, I., Moller, H.J., Gautam, S., Detraux, J., Correll, C.U., 2011. Physical illness in patients with severe mental disorders. II. Barriers to care, monitoring and treatment guidelines, plus recommendations at the system and individual level. World Psychiatry 10, 138–151.

Desai, M.M., Rosenheck, R.A., Druss, B.G., Perlin, J.B., 2002. Mental disorders and quality of diabetes care in the veterans health administration. Am. J. Psychiatry 159, 1584–1590.

Diabetes UK, 2008. Diabetes: Beware the silent assassin. Available at http://www.diabetes.org.uk/Documents/Reports/Silent_assassin_press_report.pdf. Diabetes UK, London.

Dismuke, C.E., Egede, L.E., 2010. Association between major depression, depressive symptoms and personal income in US adults with diabetes. Gen. Hosp. Psychiatry 32, 484–491.

Druss, B.G., Rosenheck, R.A., Sledge, W.H., 2000. Health and disability costs of depressive illness in a major U.S. corporation. Am. J. Psychiatry 157, 1274–1278.

Egede, L.E., 2004a. Diabetes, major depression, and functional disability among U.S. adults. Diabetes Care 27, 421–428.

Egede, L.E., 2004b. Effects of depression on work loss and disability bed days in individuals with diabetes. Diabetes Care 27, 1751–1753.

Egede, L.E., 2007. Major depression in individuals with chronic medical disorders: prevalence, correlates and association with health resource utilization, lost productivity and functional disability. Gen. Hosp. Psychiatry 29, 409–416.

Egede, L.E., Zheng, D., Simpson, K., 2002. Comorbid depression is associated with increased health care use and expenditures in individuals with diabetes. Diabetes Care 25, 464–470.

Egede, L.E., Zheng, D., 2003. Independent factors associated with major depressive disorder in a national sample of individuals with diabetes. Diabetes Care 26, 104–111.

Egede, L.E., Ellis, C., Grubaugh, A.L., 2009. The effect of depression on self-care behaviors and quality of care in a national sample of adults with diabetes. Gen. Hosp. Psychiatry 31, 422–427.

Ell, K., Katon, W., Xie, B., Lee, P.J., Kapetanovic, S., Guterman, J., Chou, C.P., 2010. Collaborative care management of major depression among low-income, predominantly Hispanic subjects with diabetes: a randomized controlled trial. Diabetes Care 33, 706–713.

Finkelstein, E.A., Bray, J.W., Chen, H., Larson, M.J., Miller, K., Tompkins, C., Keme, A., Manderscheid, R., 2003. Prevalence and costs of major depression among elderly claimants with diabetes. Diabetes Care 26, 415–420.

Friis, R., Nanjundappa, G., 1986. Diabetes, depression and employment status. Soc. Sci. Med. 23, 471–475.

Garis, R.I., Farmer, K.C., 2002. Examining costs of chronic conditions in a Medicaid population. Manag. Care 11, 43–50.

Gilmer, T.P., O'Connor, P.J., Rush, W.A., Crain, A.L., Whitebird, R.R., Hanson, A.M., Solberg, L.I., 2005. Predictors of health care costs in adults with diabetes. Diabetes Care 28, 59–64.

Gilmer, T.P., O'Connor, P.J., Rush, W.A., Crain, A.L., Whitebird, R.R., Hanson, A.M., Solberg, L.I., 2006. Impact of office systems and improvement strategies on costs of care for adults with diabetes. Diabetes Care 29, 1242–1248.

Gilmer, T.P., Roze, S., Valentine, W.J., Emy-Albrecht, K., Ray, J.A., Cobden, D., Nicklasson, L., Philis-Tsimikas, A., Palmer, A.J., 2007. Cost-effectiveness of diabetes case management for low-income populations. Health Serv. Res. 42, 1943–1959.

Gilmer, T.P., Walker, C., Johnson, E.D., Philis-Tsimikas, A., Unutzer, J., 2008. Improving treatment of depression among Latinos with diabetes using project Dulce and IMPACT. Diabetes Care 31, 1324–1326.

Giorda, C.B., Manicardi, V., Diago Cabezudo, J., 2011. The impact of diabetes mellitus on healthcare costs in Italy. Expert Rev. Pharmacoecon. Outcomes Res. 11, 709–719.

Gonzalez, E.L., Johansson, S., Wallander, M.A., Rodriguez, L.A., 2009a. Trends in the prevalence and incidence of diabetes in the UK: 1996–2005. J. Epidemiol. Community Health 63, 332–336.

Gonzalez, J.C., Walker, J.H., Einarson, T.R., 2009b. Cost-of-illness study of type 2 diabetes mellitus in Colombia. Rev. Panam. Salud Publica 26, 55–63.

Gustavsson, A., Svensson, M., Jacobi, F., Allgulander, C., Alonso, J., Beghi, E., Dodel, R., Ekman, M., Faravelli, C., Fratiglioni, L., Gannon, B., Jones, D.H., Jennum, P., Jordanova, A., Jonsson, L., Karampampa, K., Knapp, M., Kobelt, G., Kurth, T., Lieb, R., Linde, M., Ljungcrantz, C., Maercker, A., Melin, B., Moscarelli, M., Musayev, A., Norwood, F., Preisig, M., Pugliatti, M., Rehm, J., Salvador-Carulla, L., Schlehofer, B., Simon, R., Steinhausen, H.C., Stovner, L.J., Vallat, J.M., Den Bergh, P.V., Van Os, J., Vos, P., Xu, W., Wittchen, H.U., Jonsson, B., Olesen, J., 2011. Cost of disorders of the brain in Europe 2010. Eur. Neuropsychopharmacol. 21, 718–779.

Harley, C., Li, H., Corey-Lisle, P., L'Italien, G.J., Carson, W., 2007. Influence of medication choice and comorbid diabetes: the cost of bipolar disorder in a privately insured US population. Soc. Psychiatry Psychiatr. Epidemiol. 42, 690–697.

Hay, J.W., Katon, W.J., Ell, K., Lee, P.J., Guterman, J.J., 2012. Cost-effectiveness analysis of collaborative care management of major depression among low-income, predominantly Hispanics with diabetes. Value Health 15, 249–254.

Himelhoch, S., Weller, W.E., Wu, A.W., Anderson, G.F., Cooper, L.A., 2004. Chronic medical illness, depression, and use of acute medical services among Medicare beneficiaries. Med. Care, 42, 512–521.

Hogan, P., Dall, T., Nikolov, P., 2003. Economic costs of diabetes in the US in 2002. Diabetes Care 26, 917–932.

Holman, N., Forouhi, N.G., Goyder, E., Wild, S.H., 2011. The Association of Public Health Observatories (APHO) Diabetes Prevalence Model: estimates of total diabetes prevalence for England, 2010–2030. Diabet. Med. 28, 575–582.

Horn, E.K., Van Benthem, T.B., Hakkaart-Van Roijen, L., Van Marwijk, H.W., Beekman, A.T., Rutten, F.F., Van der Feltz-Cornelis, C.M., 2007. Cost-effectiveness of collaborative care for chronically ill patients with comorbid depressive disorder in the general hospital setting, a randomised controlled trial. BMC Health Serv. Res. 7, 28.

Hu, T.W., He, Y., Zhang, M., Chen, N., 2007. Economic costs of depression in China. Soc. Psychiatry Psychiatr. Epidemiol. 42, 110–116.

Husaini, B.A., Hull, P.C., Sherkat, D.E., Emerson, J.S., Overton, M.T., Craun, C., Cain, V.A., Levine, R.S., 2004. Diabetes, depression, and healthcare utilization among African Americans in primary care. J. Natl. Med. Assoc. 96, 476–484.

Hutter, N., Scheidt-Nave, C., Baumeister, H., 2009. Health care utilisation and quality of life in individuals with diabetes and comorbid mental disorders. Gen. Hosp. Psychiatry, 31, 33–35.

Hutter, N., Schnurr, A., Baumeister, H., 2010. Healthcare costs in patients with diabetes mellitus and comorbid mental disorders – a systematic review. Diabetologia 53, 2470–2479.

Ismail, K., Winkley, K., Rabe-Hesketh, S., 2004. Systematic review and meta-analysis of randomised controlled trials of psychological interventions to improve glycaemic control in patients with type 2 diabetes. Lancet 363, 1589–1597.

Ismail, K., Winkley, K., Stahl, D., Chalder, T., Edmonds, M., 2007. A cohort study of people with diabetes and their first foot ulcer: the role of depression on mortality. Diabetes Care 30, 1473–1479.

Jones, L.E., Clarke, W., Carney, C.P., 2004. Receipt of diabetes services by insured adults with and without claims for mental disorders. Med. Care, 42, 1167–1175.

Jonkers, C.C., Lamers, F., Evers, S.M., Bosma, H., Metsemakers, J.F., Van Eijk, J.T., 2009. Economic evaluation of a minimal psychological intervention in chronically ill elderly patients with minor or mild to moderate depression: a randomized trial (the DELTA-study). Int. J. Technol. Assess. Health Care 25, 497–504.

Kalsekar, I.D., Madhavan, S.M., Amonkar, M.M., Scott, V., Douglas, S.M., Makela, E., 2006. The effect of depression on health care utilization and costs in patients with type 2 diabetes. Manag. Care Interface 19, 39–46.

Katon, W., Cantrell, C.R., Sokol, M.C., Chiao, E., Gdovin, J.M., 2005a. Impact of antidepressant drug adherence on comorbid medication use and resource utilization. Arch. Intern. Med. 165, 2497–2503.

Katon, W.J., Rutter, C., Simon, G., Lin, E.H., Ludman, E., Ciechanowski, P., Kinder, L., Young, B., Von Korff, M., 2005b. The association of comorbid depression with mortality in patients with type 2 diabetes. Diabetes Care 28, 2668–2672.

Katon, W.J., Schoenbaum, M., Fan, M.Y., Callahan, C.M., Williams, J., Jr., Hunkeler, E., Harpole, L., Zhou, X.H., Langston, C., Unutzer, J., 2005c. Cost-effectiveness of improving primary care treatment of late-life depression. Arch. Gen. Psychiatry 62, 1313–1320.

Katon, W., Unutzer, J., Fan, M.Y., Williams, J.W., Jr., Schoenbaum, M., Lin, E.H., Hunkeler, E.M., 2006. Cost-effectiveness and net benefit of enhanced treatment of depression for older adults with diabetes and depression. Diabetes Care 29, 265–270.

Katon, W., Fan, M.Y., Unutzer, J., Taylor, J., Pincus, H., Schoenbaum, M., 2008a. Depression and diabetes: a potentially lethal combination. J. Gen. Intern. Med. 23, 1571–1575.

Katon, W.J., Russo, J.E., Von Korff, M., Lin, E.H., Ludman, E., Ciechanowski, P.S., 2008b. Long-term effects on medical costs of improving depression outcomes in patients with depression and diabetes. Diabetes Care 31, 1155–1159.

Katon, W.J., Lin, E.H., Von Korff, M., Ciechanowski, P., Ludman, E.J., Young, B., Peterson, D., Rutter, C.M., McGregor, M., McCulloch, D., 2010. Collaborative care for patients with depression and chronic illnesses. N. Engl. J. Med. 363, 2611–2620.

Katon, W., Russo, J., Lin, E.H., Schmittdiel, J., Ciechanowski, P., Ludman, E., Peterson, D., Young, B., Von Korff, M., 2012. Cost-effectiveness of a Multicondition Collaborative Care Intervention: A Randomized Controlled Trial. Arch. Gen. Psychiatry 69, 506–514.

King, D., Molosankwe, I., McDaid, D., 2011. Collaborative care for depression in individuals with Type II diabetes. In: Knapp, M., McDaid, D., Parsonage, M. (Eds.), Mental Health Promotion and Mental Illness Prevention: The Economic Case. Department of Health, London.

Kivimaki, M., Vahtera, J., Pentti, J., Virtanen, M., Elovainio, M., Hemingway, H., 2007. Increased sickness absence in diabetic employees: what is the role of co-morbid conditions? Diabet. Med. 24, 1043–1048.

Krein, S.L., Bingham, C.R., McCarthy, J.F., Mitchinson, A., Payes, J., Valenstein, M., 2006. Diabetes treatment among VA patients with comorbid serious mental illness. Psychiatr. Serv. 57, 1016–1021.

Lawrence, J.M., Standiford, D.A., Loots, B., Klingensmith, G.J., Williams, D.E., Ruggiero, A., Liese, A.D., Bell, R.A., Waitzfelder, B.E., McKeown, R.E., 2006. Prevalence and correlates of depressed mood among youth with diabetes: the SEARCH for Diabetes in Youth study. Pediatrics 117, 1348–1358.

Le, T.K., Able, S.L., Lage, M.J., 2006. Resource use among patients with diabetes, diabetic neuropathy, or diabetes with depression. Cost Eff. Resour. Alloc. 4, 18.

Le, T.K., Curtis, B., Kahle-Wrobleski, K., Johnston, J., Haldane, D., Melfi, C., 2011. Treatment patterns and resource use among patients with comorbid diabetes mellitus and major depressive disorder. J. Med. Econ. 14, 440–447.

Leichter, S., See, Y., 2005. Problems That Extend Visit Time and Cost in Diabetes Care: 1. How Depression May Affect the Efficacy and Cost of Care of Diabetic Patients. Clin. Diabetes 23, 53–54.

Lin, E.H., Katon, W., Von Korff, M., Rutter, C., Simon, G.E., Oliver, M., Ciechanowski, P., Ludman, E.J., Bush, T., Young, B., 2004. Relationship of depression and diabetes self-care, medication adherence, and preventive care. Diabetes Care 27, 2154–2160.

Lin, E.H., Rutter, C.M., Katon, W., Heckbert, S.R., Ciechanowski, P., Oliver, M.M., Ludman, E.J., Young, B.A., Williams, L.H., McCulloch, D.K., Von Korff, M., 2010. Depression and advanced complications of diabetes: a prospective cohort study. Diabetes Care 33, 264–269.

McCrone, P., Dhanasiri, S., Patel, A., Knapp, M., Lawton-Smith, S., 2007. Paying the price; The cost of mental health care in England to 2026. King's Fund, London.

National Institute for Health and Clinical Excellence, 2009. Depression in adults with a chronic physical health problem. Treatment and management. NICE Clinical Guideline 91. NICE, London.

Nichols, L., Barton, P.L., Glazner, J., McCollum, M., 2007. Diabetes, minor depression and health care utilization and expenditures: a retrospective database study. Cost Eff. Resour. Alloc. 5, 4.

Nouwen, A., Winkley, K., Twisk, J., Lloyd, C.E., Peyrot, M., Ismail, K., Pouwer, F., 2010. Type 2 diabetes mellitus as a risk factor for the onset of depression: a systematic review and meta-analysis. Diabetologia 53, 2480–2486.

Pawaskar, M.D., Anderson, R.T., Balkrishnan, R., 2007. Self-reported predictors of depressive symptomatology in an elderly population with type 2 diabetes mellitus: a prospective cohort study. Health Qual. Life Outcomes 5, 50.

Petrak, F., Hautzinger, M., Plack, K., Kronfeld, K., Ruckes, C., Herpertz, S., Muller, M.J., 2010. Cognitive behavioural therapy in elderly type 2 diabetes patients with minor depression or mild major depression: study protocol of a randomized controlled trial (MIND-DIA). BMC Geriatr. 10, 21.

Rosenzweig, J.L., Weinger, K., Poirier-Solomon, L., Rushton, M., 2002. Use of a disease severity index for evaluation of healthcare costs and management of comorbidities of patients with diabetes mellitus. Am. J. Manag. Care 8, 950–958.

Rush, W.A., Whitebird, R.R., Rush, M.R., Solberg, L.I., O'Connor, P.J., 2008. Depression in patients with diabetes: does it impact clinical goals? J. Am. Board Fam. Med. 21, 392–397.

Salvador-Carulla, L., Bendeck, M., Fernandez, A., Alberti, C., Sabes-Figuera, R., Molina, C., Knapp, M., 2011. Costs of depression in Catalonia (Spain). J. Affect. Disord. 132, 130–138.

Simon, G.E., Katon, W.J., Lin, E.H., Ludman, E., Von Korff, M., Ciechanowski, P., Young, B.A., 2005. Diabetes complications and depression as predictors of health service costs. Gen. Hosp. Psychiatry 27, 344–351.

Simon, G.E., Katon, W.J., Lin, E.H., Rutter, C., Manning, W.G., Von Korff, M., Ciechanowski, P., Ludman, E.J., Young, B.A., 2007. Cost-effectiveness of systematic depression treatment among people with diabetes mellitus. Arch. Gen. Psychiatry 64, 65–72.

Stein, M.B., Cox, B.J., Afifi, T.O., Belik, S.L., Sareen, J., 2006. Does co-morbid depressive illness magnify the impact of chronic physical illness? A population-based perspective. Psychol. Med. 36, 587–596.

Stewart, S.M., Rao, U., Emslie, G.J., Klein, D., White, P.C., 2005. Depressive symptoms predict hospitalization for adolescents with type 1 diabetes mellitus. Pediatrics 115, 1315–1319.

Subramaniam, M., Sum, C.F., Pek, E., Stahl, D., Verma, S., Liow, P.H., Chua, H.C., Abdin, E., Chong, S.A., 2009. Comorbid depression and increased health care utilisation in individuals with diabetes. Gen. Hosp. Psychiatry 31, 220–224.

Sundaram, M., Kavookjian, J., Patrick, J.H., Miller, L.A., Madhavan, S.S., Scott, V.G., 2007. Quality of life, health status and clinical outcomes in Type 2 diabetes patients. Qual. Life Res. 16, 165–177.

Thomas, C.M., Morris, S., 2003. Cost of depression among adults in England in 2000. Br. J. Psychiatry 183, 514–519.

Trief, P.M., Ouimette, P., Wade, M., Shanahan, P., Weinstock, R.S., 2006. Post-traumatic stress disorder and diabetes: co-morbidity and outcomes in a male veterans sample. J. Behav. Med. 29, 411–418.

Unutzer, J., Katon, W., Callahan, C.M., Williams, J.W., Jr., Hunkeler, E., Harpole, L., Hoffing, M., Della Penna, R.D., Noel, P.H., Lin, E.H., Arean, P.A., Hegel, M.T., Tang, L., Belin, T.R., Oishi, S., Langston, C., 2002. Collaborative care management of late-life depression in the primary care setting: a randomized controlled trial. JAMA 288, 2836–2845.

Unutzer, J., Katon, W.J., Russo, J., Simon, G., Von Korff, M., Lin, E., Walker, E., Ludman, E., Bush, T., 2003. Willingness to pay for depression treatment in primary care. Psychiatr. Serv. 54, 340–345.

Unutzer, J., Katon, W.J., Fan, M.Y., Schoenbaum, M.C., Lin, E.H., Della Penna, R.D., Powers, D., 2008. Long-term cost effects of collaborative care for late-life depression. Am. J. Manag. Care 14, 95–100.

Unutzer, J., Schoenbaum, M., Katon, W.J., Fan, M.Y., Pincus, H.A., Hogan, D., Taylor, J., 2009. Healthcare costs associated with depression in medically ill fee-for-service medicare participants. J. Am. Geriatr. Soc. 57, 506–510.

Vamos, E.P., Mucsi, I., Keszei, A., Kopp, M.S., Novak, M., 2009. Comorbid depression is associated with increased healthcare utilization and lost productivity in persons with diabetes: a large nationally representative Hungarian population survey. Psychosom. Med. 71, 501–507.

Von Korff, M., Katon, W., Lin, E.H., Simon, G., Ciechanowski, P., Ludman, E., Oliver, M., Rutter, C., Young, B., 2005. Work disability among individuals with diabetes. Diabetes Care 28, 1326–1332.

Welch, C.A., Czerwinski, D., Ghimire, B., Bertsimas, D., 2009. Depression and costs of health care. Psychosomatics 50, 392–401.

Williams, J.W., Jr., Katon, W., Lin, E.H., Noel, P.H., Worchel, J., Cornell, J., Harpole, L., Fultz, B.A., Hunkeler, E., Mika, V.S., Unutzer, J., 2004. The effectiveness of depression care management on diabetes-related outcomes in older patients. Ann. Intern. Med. 140, 1015–1024.

World Health Organization, 2008. The Global Burden of Disease: 2004 update. World Health Organization, Geneva.

Zhang, X., Norris, S.L., Gregg, E.W., Cheng, Y.J., Beckles, G., Kahn, H.S., 2005. Depressive symptoms and mortality among persons with and without diabetes. Am. J. Epidemiol. 161, 652–660.