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Authors	Morrissey, Hana;Bibi, NASREEM;Wara, Bahta;Ball, Patrick;Mughal, Saqib
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Original Article

A CRITICAL LITERATURE REVIEW AND AUDIT OF REAL WORLD DATA TO INFORM THE RELATIONSHIP BETWEEN MENTAL ILL-HEALTH AND TYPE-2 DIABETES FAVOURABLE PROGNOSIS

NASREEM BIBI, BAHTA WARA, SAQIB MUGHAL, HANA MORRISSEY, PATRICK BALL

School of Pharmacy, University of Wolverhampton, Wulfruna Street, Wolverhampton, WV1 1LY, United Kingdom

Email: hana.morrissey@wlv.ac.uk

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ABSTRACT

Objective: The aim of this scoping study was to identify gaps in the current literature and understand the T2DM and MIH comorbidity trends in the local population from the West Midlands, UK to inform future studies.

Methods: This project was a scoping study of two parts; a critical review and a clinical audit. A thematic approach was used to group studies based on their overall study outcome. The clinical audit data was used to compare the local patient population to the patterns identified in the literature reviewed.

Results: The reviewed studies reported a relationship between T2DM control and both depression and anxiety, but did not agree on its significance. The clinical audit of 71 patients diagnosed with T2DM showed that 73% of males presented with poor diabetes control (HbA1c>7) compared to females (46%). Conversely, females exhibited a higher prevalence of MIH (45%) compared to males (31%).

Conclusion: From both this audit of the literature and local data, it remains unclear whether mental-ill health is a major driver for medication non-adherence behaviour and uncontrolled diabetes. Further studies are recommended to further understand this comorbidity.

Keywords: Anxiety, Depression, Type 2 diabetes mellitus, Mental ill-health, Real-world data

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INTRODUCTION

Type 2 Diabetes mellitus (T2DM) and its complications are increasing nationally and globally, consuming a large and increasing portion of health system expenditure [1, 2]. Depression and anxiety are mental health disorders that are frequently diagnosed in T2DM patients. Depression is referred to as a condition that 'negatively affects how you feel, the way you think and how you act' [3]. It may also impact on an individual's emotional and physical state [3]. Anxiety, on the other hand, is defined as 'feeling 'uneasy' or 'on edge', with overwhelming unrealistic worries and fear that can range between mild and severe' [4]. In a systematic review, it was reported that 'diabetic patients were twice as likely to be diagnosed with depression compared to people who do not have diabetes' [5]. On the other hand, poor diabetes control was found to worsen the patient's anxiety, which further worsened the diabetes control leading to further complications including depression [6, 7]. Jia *et al.*, (2016) reported that a family history of depression and/or diabetes increases the possible association between the two conditions later in life, compared to the general population [8]. This highlighted the importance of screening for mental ill-health (MIH) in all patients diagnosed with diabetes [8]. Research has shown that a close focus on one condition can lead to other co-morbid conditions being overlooked. A study by Gonzalez *et al.*, (2007) looked at depression, self-care and medication adherence in T2DM patients. They concluded that adherence to pharmacological therapy is important; suggesting that even low levels of depression may be associated with increased non-adherence to important aspects of diabetes self-care [9]. Another meta-analysis which also looked at the association between MIH and T2DM concluded there is a connection between MIH and T2DM [10].

MATERIALS AND METHODS

This scoping study focused on depression and anxiety in T2DM patients. A total of 17 studies were critically reviewed (part 1) and the records of 71 patients were audited (part 2) to inform whether the local population shares the reported trends of T2DM, depression

and anxiety found in the reviewed literature. Ethical approval was granted by the IRAS/HRA on 9/9/2019.

RESULTS AND DISCUSSION

Part 1-critical literature review

A literature search was conducted using search engines such as Science Direct®, and Medline®. Search terms used were 'anxiety' 'depression' and type 2 diabetes.' The search was limited to literature from 2008-2019. The articles were screened for selection for further review. Fig. 1 shows the breakdown of how articles were selected during the preliminary search.

All of the articles compared T2DM against occurrence of depression and or anxiety. A total of 20174 articles were identified; these were then further screened using the exclusion criteria, resulting in 17 studies suitable for the part 1 critical review (Appendix 1).

Studies included into the review were those that had their primary outcome as diabetes and non-adherence, diabetes and depression, diabetes and anxiety or diabetes and those including two or each of the three outcomes. Other studies were excluded. MIH is a broad term that fits a range of conditions. The CONSORT® (<http://www.consort-statement.org/>) and CASP® (<https://casp-uk.net/>) checklists were used as appropriate to determine the appropriateness and the quality of the studies for the inclusion in this review.

The articles were further analysed to identify relationships reported between the comparators. Appendix 1 provides an overview of the studies' designs and populations. A total of 17 articles were reviewed to assess the relationships reported between MIH and the effects of MIH on T2DM prognosis. The Cochrane® Handbook for Systematic Reviews of Interventions was used to guide the design of this review. Studies were analysed based on ten comparators (table 1), however, it was found that the study designs and primary outcomes varied widely, with no specific approach applied to investigate depression, anxiety with diabetes and non-adherence primary outcome. This indicates that a future multicentre large study is required to establish a better starting point with a robust and reproducible methodology.

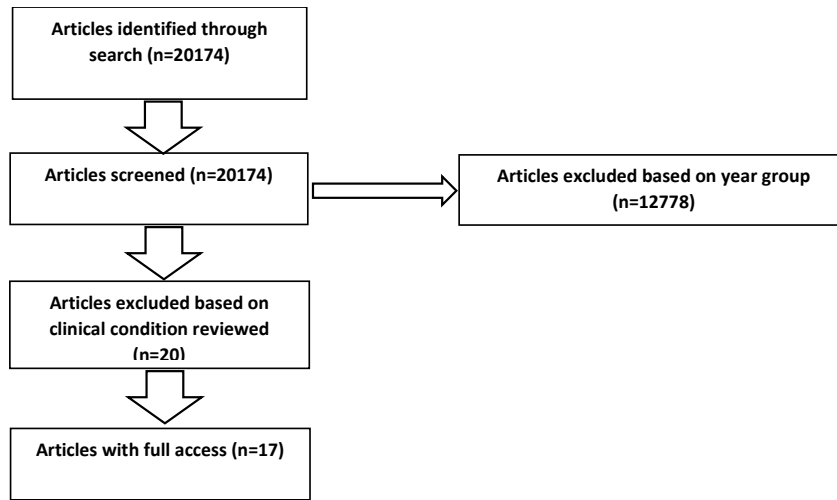


Fig. 1: Inclusion and exclusion criteria or literature used

Table 1: Selected papers compared (Yes: Y, No: N)

First authors and reference number	Sample size (>1500)	Single study	Age > 50	Depression, anxiety with diabetes and non-adherence primary outcome	Non-adherence	Diabetes and depression	Diabetes causes depression	Diabetes and anxiety	Diabetes causes anxiety	Depression and/or anxiety cause diabetes
Gonzalez (9)	N	Y	Y	Y	Y	Y	N	Y	N	N
Engum (10)	Y	Y	Y	Y	N	Y	Y	Y	Y	Y
Lunghi (11)	Y	Y	N	Y	N	Y	Y	N	N	N
Mezuk (12)	Y	Y	Y	Y	N	Y	Y	Y	Y	N
Ivanova (13)	Y	Y	Y	N	N	Y	Y	N	N	N
Collins (14)	Y	Y	N	N	N	Y	Y	Y	Y	N
Rachdi (15)	N	Y	Y	N	N	Y	N	N	N	N
Edwards (16)	Y	Y	Y	Y	N	N	N	N	N	N
Safren (17)	N	Y	N	Y	Y	Y	N	N	N	N
Khuwaja (18)	N	Y	Y	Y	N	Y	N	N	N	N
Ganasegeran (19)	N	Y	N	Y	N	Y	N	N	N	N
Naicker (20)	Y	Y	Y	Y	N	Y	Y	Y	Y	Y
Ayman (21)	N	Y	N	Y	Y	Y	N	N	N	N
Kivimaki (22)	Y	Y	N	N	N	N	N	N	N	Y
Pan (23)	Y	Y	N	N	N	N	N	N	N	Y
Pan (24)	Y	Y	Y	Y	Y	Y	N	N	N	N
Roopan (25)	N	N	N	Y	Y	Y	Y	N	N	N

Eight out of the 17 studies included five or more of the ten identified comparators; however, the score was made up of different comparators, making it not possible to deem them to be comparable studies (fig. 2).

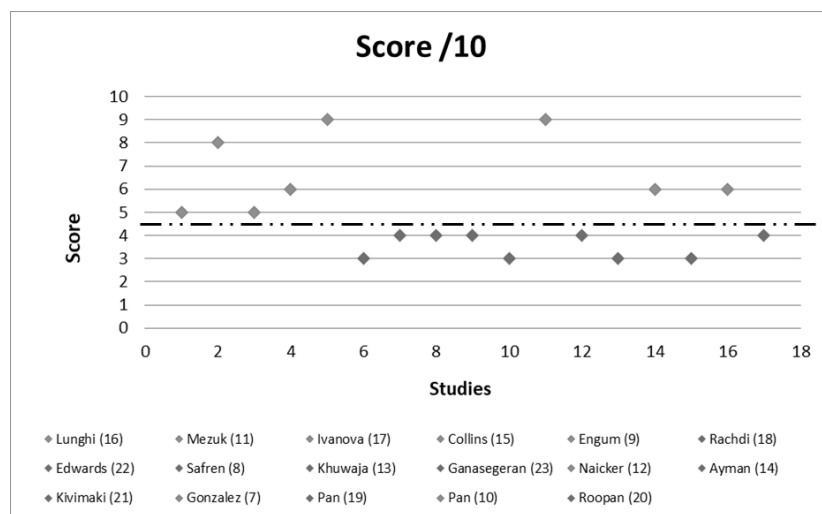


Fig. 2: Journal bias total score

Four studies [9-12] reached similar conclusions: 'MIH has a substantial effect on T2DM prognosis and clinical deterioration of both conditions. These four studies demonstrate the association between MIH and T2DM has a negative impact on T2DM control and prognosis.

Gonzalez *et al.*, [9] stated that 'depression increases the risk of poorer diabetes-specific outcomes such as hyperglycaemia and increased diabetic complications.' The authors suggested that depression has a negative impact on T2DM when untreated. The authors added that 'major depression is significantly associated with poorer diabetes self-care behaviour' [9]. Engum *et al.*, [10] in their study discussed the hypothesis that 'symptoms of depression and anxiety are considered as significant risk factors for the onset of T2DM independent of all other known diabetes physical risk factors'. They asserted that people with untreated depression or anxiety will later potentially develop T2DM, noting the prevalence of depression is observed to be higher in the diabetic than the general population. Interestingly, this group suggested that 'mood disturbance is a manifestation of the direct physiological effects of diabetes.' Safren, *et al.*, [11] added that cognitive behavioural therapy (CBT) improved adherence to medications for diabetes in patients diagnosed with depression and poorly controlled T2DM. This appears to support that MIH may have a deleterious effect on T2DM and that CBT may be an effective intervention for improving medication-taking behaviour. Pan *et al.*, [12] concurred with Engum *et al.*, [10] and added that patients with high depressive symptoms score had elevated risk of T2DM. Pan *et al.*, [12] discussed finding that the incidence of depression was twice as high in diabetic patients as that in non-diabetic people and how 'depression was associated with a 60% increased risk for T2DM.' Additionally, the authors reported that 'the two conditions can cause or worsen each other.

Six studies [13-18] discussed T2DM causing or worsening MIH such as depression and anxiety. Mezuk *et al.*, [13] discussed the relationship of generalised anxiety disorder and its link with T2DM. The authors stated that 'Major depression often co-occurs with chronic medical conditions such as T2DM'. Naiker *et al.*, (2017) [14] found that the mortality rate increased dramatically when both conditions co-existed. They stated that 'the relationship may alternately be conceptualised as an accumulation of risk over an individual's lifetime through trajectories or chains of risk precipitated by psychiatric symptoms.' Khawaja *et al.*, (2010) [15] echoed Mezuk *et al.*, [13] and Naiker *et al.*, [14] and agreed that T2DM influences the occurrence of MIH. Khawaja *et al.*, [15] demonstrated that clinicians need to identify and treat anxiety and depression as 'common components of diabetes care.' They also stated that 33% of people with diabetes experience clinical anxiety and 25% have clinical depression. Edwards LE [16] and Ayman *et al.*, [17] also reported the association between T2DM and MIH, stating that in their study, anxiety and depression were twice as common among diabetic patients compared with matched control subjects without diabetes.

Colins *et al.*, [18] also concluded that the prevalence of anxiety and depression symptoms in patients with diabetes in their study sample was considerably higher than that in the general population. They noted that patients with diabetes complications who had poor medication adherence behaviour in their study, experienced higher levels of anxiety and/or depression; therefore, further affecting the primary condition.

Lunghi *et al.*, [19] described how T2DM and depression comorbidity was associated with worse self-care behaviour and poorer glycaemic control. The authors illustrated how diabetes and MIH affect each other's prognosis causing further deterioration. Within their study sample, the incidence of a diagnosis of depression was higher during the first year after oral antidiabetic treatment was initiated. This demonstrates that the diagnosis of the T2DM may have been traumatic.

Six studies [19-24] discussed the effect of antidepressant medications on T2DM diagnosis and prognosis due to their side effect of predisposing to metabolic disorders. Lunghi *et al.*, [19] showed that patients prescribed antidepressant medications had a

higher BMI (average 32.6, SD+/- 6.5) compared with those who did not take them (29.2, SD+/- 5.7).

Ivanova *et al.*, [20] described how weight gain linked to both antidiabetic and antidepressant medications are known risk factors in worsening T2DM outcome. Rachdi [21] agreed that antidepressants can have a major metabolic impact and can cause T2DM, suggesting that the use of sertraline as an antidepressant in patients with T2DM may reduce weight gain.

Pan *et al.*, [22] evaluated this relationship in a cohort study and concluded that antidepressants caused considerable weight gain and induced impaired glucose homeostasis. The authors concluded that the use of antidepressant medications moderately increased the risk of T2DM diagnosis regardless of the intensity of weight gain. A systematic review by Roopan *et al.*, [23] stated that specific antidepressants can have a greater or lesser metabolic effect. They noted that when a tricyclic antidepressant was used, closer glycaemic monitoring was required to prevent further metabolic complications, recommending that the use of selective serotonin reuptake inhibitor (SSRI) was preferred in a T2DM patient. Kivimaki *et al.*, [24] concurred that the weight gain caused by high doses of antidepressants was associated with a doubling of the risk of developing T2DM in their study sample. They also highlighted that the hyperglycaemic effects of the noradrenergic activity of antidepressants increase the risk of diabetes.

Part 2-real world clinical audit

A de-identified condition report was gathered from a Medical General Practice (GP) in West Midlands, UK, where the GP carried out a search on T2DM patients prescribed medications used to treat MIH conditions. Total population registered at the practice is 5500. Total MIH patients registered in the clinic is 291 patients (alone or with co-morbidity), 5.5% of the total clinic population. Total T2DM patients registered in the clinic is 71 patients (excluding patients who were diet-controlled and those treated with injectable for T2DM). There were 28 of these patients (39.5%) identified as receiving treatment for MIH condition which is higher than the general population (1 in 4 people or 25% experience MIH). This data was analysed and compared to the findings from the critical review in part 1.

The population of this practice is diverse in age and ethnicity (fig. 3) with Asian being the highest ethnic group (70% vs 30% all others). The data showed that in the audited population T2DM diagnosis was made at the age of 30 y or over.

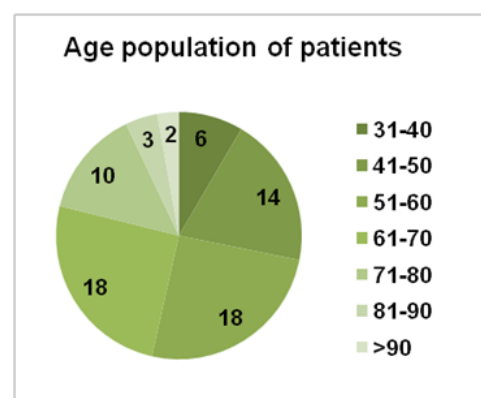


Fig. 3: T2DM patients' population by age

The data was further analysed to count the frequencies of conditions repeated more than once (table 2). Cardiovascular diseases (CVD) were the highest after diabetes followed by neuropathic pain and MIH. While erectile dysfunction was reported in four, there was only one case of vaginal atrophy in women.

Table 2: Common medical condition in patient with T2DM

Medical condition	Female	Male
Erectile dysfunction (ED)	0	4
Insomnia	1	1
Parkinson	2	0
Respiratory	4	4
Thyroid	4	0
Dry eye	8	3
Gastro-oesophageal reflux disease (GORD)	17	7
Mental illness combined	20	8
Neuropathic pain	24	6
Cardiovascular diseases (CVD)	38	24
Type 2 diabetes mellitus (T2DM)	45	26

Overall, 73% of the sample audited had 4 or more long-term and chronic conditions (80% of women and 62% of men). The highest numbers of co-existing conditions were seen in 3 women compared to one man (table 3).

Table 3: Diagnosis of medical condition in diabetic patients

Gender	1-3 medical conditions	4-6 medical conditions	>6 medical conditions	Highest comorbidities
Male	10	13	3	8
Female	9	33	3	9

Number of medications per patient was then counted (table 4); with more medications used in men compared to women (42% and 33% respectively).

Table 4: Number of medications per patient

Gender	<5 medications	5-9 medications	>10 medications	Highest polypharmacy
Male	4	11	11	19
Female	6	24	15	18

Table 5 illustrates the frequency of prescribing of the top 35 medications seen in the study sample, with atorvastatin the highest medication prescribed in 65% of all audited records. However, it

was also observed that a large number of medications were prescribed to treat T2DM complications such as dry eye, ED, neuropathic pain and MIH.

Table 5: Frequency of medication prescribing in the study population

Most prescribed medication	Frequency	Most prescribed medication	Frequency
Salbutamol	5	Ca+D	8
Empagliflozin	5	Citalopram	9
Clopidogrel	5	Paracetamol	9
Indapamide	5	Metformin modified release	9
Pregabalin	5	Losartan	11
Senna	5	Dapagliflozin	12
Solifenacin	5	Amlodipine	14
Tramadol	5	simvastatin	14
Thyroxine	6	Pantoprazole	17
Lansoprazole	6	Sertraline	18
Doxazosin	6	Aspirin	21
Duloxetine	6	Amitriptyline	24
Atenolol	6	Linagliptin	24
Bisoprolol	7	Ramipril	25
paracetamol/codeine	7	Gliclazide	26
Omeprazole	8	Metformin	33
ferrous sulfate	8	Atorvastatin	46

Table 6 represents the study population diabetes control using their latest HbA1c results. Female patient shows better diabetes control (53%) compared to male patients (27%) with the higher HbA1c was not significantly different in both genders.

Table 6: Representation of Hba1c in patient with type 2 diabetes

Gender	Number of patients	HbA1c under<7%	HbA1c>7%	highest HbA1c
Male	26	7	19	10%
Female	45	24	21	9.7%

T2DM is the fastest growing clinical condition in many countries and is having a major impact on the UK NHS budget due to high medication use, surgical intervention (amputations) and other

complications such as blindness and renal failure. The data analysed from the literature and the local GP practice shows that T2DM can also affect the individual mental state. Overall a clear association can

be seen between patients with MIH such as depression and anxiety with a diagnosis of T2DM. The studies analysed within this critical review and the real-world data demonstrate a strong relationship between the MIH and T2DM. The data from the general medical practice showed a high prescribing rate of antidepressants. Care is required in interpretation as although amitriptyline is an antidepressant, it was prescribed here for neuropathic pain and the doses used for this indication are general considered inadequate to treat depression. It was also found that gender appears to impact on diagnosis of MIH, as being higher in females than in the male population. However, compared to the general population, mood disorders are known to be higher in females than males.

LIMITATIONS

Whilst all the studies included investigated the modifying effect, or the co-existing effects of the two conditions, the differing study designs and analyses used prevented direct comparison. Interest in this area is growing fast [25, 26] with new studies regularly appearing that should facilitate future meta-analysis.

Additionally, the patient sample audited was limited to one general practice which may not be representative to the entire population of patients diagnosed with type 2 diabetes.

CONCLUSION

MIH and T2DM are interrelated. Females diagnosed with T2DM are at a greater risk of MIH. It is recommended that as soon as a diagnosis of T2DM is made clinicians should take active steps to prevent, diagnose and treat MIH to reduce its negative effect on disease prognosis, patient adherence to pharmacological therapy and motivation to self-care.

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AUTHORS CONTRIBUTIONS

Nasreem Bibi conducted the critical review, Saqib Mughal collated the clinical audit data report, Hana Morrissey, Nasreem Bibi, Bahta Wara analysed the data, Hana Morrissey and Patrick Ball produced the manuscript.

CONFLICTS OF INTERESTS

Declare none

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