



**QUEEN'S
UNIVERSITY
BELFAST**

Associations between depression and cognition, mild cognitive impairment and dementia in persons with diabetes mellitus: A systematic review and meta-analysis

Chow, Y. Y., Verdonschot, M., McEvoy, C. T., & Peeters, G. (2022). Associations between depression and cognition, mild cognitive impairment and dementia in persons with diabetes mellitus: A systematic review and meta-analysis. *Diabetes Research and Clinical Practice*, 185, Article 109227. <https://doi.org/10.1016/j.diabres.2022.109227>

Published in:
Diabetes Research and Clinical Practice

Document Version:
Publisher's PDF, also known as Version of record

Queen's University Belfast - Research Portal:
[Link to publication record in Queen's University Belfast Research Portal](#)

Publisher rights

Copyright 2022 the authors. Published by Elsevier B.V.
This is an open access article published under a Creative Commons Attribution License (<https://creativecommons.org/licenses/by/4.0/>), which permits unrestricted use, distribution and reproduction in any medium, provided the author and source are cited.

General rights

Copyright for the publications made accessible via the Queen's University Belfast Research Portal is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy

The Research Portal is Queen's institutional repository that provides access to Queen's research output. Every effort has been made to ensure that content in the Research Portal does not infringe any person's rights, or applicable UK laws. If you discover content in the Research Portal that you believe breaches copyright or violates any law, please contact openaccess@qub.ac.uk.

Open Access

This research has been made openly available by Queen's academics and its Open Research team. We would love to hear how access to this research benefits you. – Share your feedback with us: <http://go.qub.ac.uk/oa-feedback>



Review

Associations between depression and cognition, mild cognitive impairment and dementia in persons with diabetes mellitus: A systematic review and meta-analysis

Yeng Yan Chow^a, Milou Verdonschot^a, Claire T. McEvoy^{b,c}, Geeske Peeters^{a,b,*}

^a Department of Geriatric Medicine, Radboud Institute for Health Sciences, Radboud University Medical Centre, Reinier Postlaan 4, 6500 HB Nijmegen, the Netherlands

^b Global Brain Health Institute, Trinity College Institute of Neuroscience, Trinity College Dublin, Llyod Building, Dublin 2, Ireland

^c Centre for Public Health, Queen's University Belfast, Grosvenor Road, Belfast, BT12 6 BJ Northern Ireland, United Kingdom



ARTICLE INFO

Keywords:

Executive function
Cognitive function
Depressive symptoms
Type 1 diabetes
Type 2 diabetes

ABSTRACT

Aims: This systematic review aimed to examine whether persons with diabetes and depression had poorer cognition and higher dementia risk than persons with diabetes only. Moreover, the impact of timing, frequency of depressive episodes throughout life, and antidepressant treatment were examined.

Methods: PubMed, Embase and PsycINFO were searched to obtain observational studies between August 2015 and June 2021 that examined the association between depression and cognition, mild cognitive impairment or dementia in people with diabetes. Studies published before August 2015 were retrieved from a previous systematic review. Findings were pooled using meta-analyses.

Results: 10 out of 19 included articles were appropriate for the meta-analyses. Persons with diabetes and depression experienced greater declines in executive function (SMD = -0.39 (-0.69 , -0.08)), language (SMD = -0.80 (-1.52 , -0.09)), memory (SMD = -0.63 (-1.12 , -0.14)) and overall cognition (SMD = -0.77 (-1.33 , -0.20)), and greater dementia risk (HR = 1.82 (1.79, 1.85)) than persons with diabetes only. No significant differences were observed for complex attention. No studies examined the role of timing and frequency of depressive episodes and antidepressant treatment.

Conclusion: In persons with diabetes, depression is associated with worse cognition and higher dementia risk. The potential mitigating effect of antidepressant treatment remains unclear.

1. Introduction

The psychosocial impact of diabetes mellitus (DM) is considerable. Evidence shows that the prevalence of depression is nearly twice as high in people with DM than in those without DM [1,2]. Recognizing symptoms of depression in persons with DM is important, as depression comorbid with DM produces greater health decrements due to an additive interaction [3,4]. Given that both DM types and depression are independently associated with worse cognition, mild cognitive impairment (MCI), and dementia, it is possible that persons with both DM and depression have a greater risk of worse cognitive outcomes than persons with DM only [5–10].

This hypothesis was supported by the systematic review of Danna

(2016) which indicated that depression in persons with DM was associated with poorer cognition and higher dementia risk than in persons with DM only [11]. An important limitation of this review, however, was that a meta-analysis was precluded due to a high degree of heterogeneity between included studies. Moreover, the majority of included studies were cross-sectional, making it difficult to derive temporal relationships. More studies on the association between depression and cognitive outcomes in persons with DM have now been published, including several longitudinal studies [12–18].

Prior research in the general population indicated that depression is highly recurrent [3] and depressive episodes in midlife are a risk factor for worse cognition and dementia in late-life [19–22]. However, it is still not known whether antidepressant treatment improves cognition and

* Corresponding author at: Department of Geriatric Medicine, Radboud Institute for Health Sciences, Radboud University Medical Centre, Reinier Postlaan 4, Postbus 9101 (route 925), 6500 HB Nijmegen, the Netherlands.

E-mail addresses: yengyanchow@hotmail.com (Y.Y. Chow), m.verdonschot@student.ru.nl (M. Verdonschot), c.mcevoy@qub.ac.uk (C.T. McEvoy), geeske.peeters@radboudumc.nl (G. Peeters).

<https://doi.org/10.1016/j.diabres.2022.109227>

Received 27 September 2021; Received in revised form 26 January 2022; Accepted 28 January 2022

Available online 2 February 2022

0168-8227/© 2022 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

lowers dementia risk [8,23,24]. Moreover, it remains unclear whether these findings apply to persons with DM. The review of Danna (2016) only focused on current depression and did not explore the impact of recurrent depression and depressive episodes earlier in life on cognitive outcomes [11]. Furthermore, they did not examine whether the association between depression and cognition, MCI or dementia risk in persons with DM is modified by antidepressant treatment.

Therefore, the aim of this review is to update the evidence supporting the relationships between current depression and cognition, MCI and dementia in persons with DM with novel studies published after the systematic review by Danna (2016) [11]. In addition, we will investigate the impact of recurrent depression, depressive episodes in early life (<30 years) or midlife (30–65 years) on this relationship. Lastly, we will explore whether the association between depression and cognitive outcomes is modified by antidepressant treatment in persons with DM.

2. Methods

This review was conducted according to recommendations in the PRISMA statement [25]. The study protocol was registered on the PROSPERO database (CRD42020196874).

2.1. Search

An electronic literature search was conducted using PubMed (Medline), Embase and PsycINFO. A basic search strategy was developed for PubMed including both medical subject headings and free-text terms (e.g., “depression”, “depressive disorder”, “diabetes mellitus”, “insulin resistance”, “dementia”, “cognitive dysfunction”, “MCI”) and translated into Embase and PsycINFO (Supplementary file 1). The current review used the review of Danna (2016) as a starting point, in which the search was conducted up to August 6, 2015 [11]. Therefore, we applied a date restriction from this date up to June 13, 2021.

2.2. Inclusion and exclusion criteria

Observational studies with participants aged ≥ 18 years of any race and ethnicity, diagnosed with DM type 1 or 2, were considered eligible for inclusion. Diagnostic criteria used for DM and depression, and instruments to measure cognitive outcomes had to be described. Depression should be the exposure of interest, and cognition, MCI and dementia the outcomes. Studies using early onset Alzheimer’s disease as an outcome were excluded due to a different pathophysiology of this disease, as well as animal studies and studies published in other languages than English and Dutch.

2.3. Study selection

After deduplication of search results, two reviewers (MV, YYC) performed the title-/abstract screening of the remaining articles. Full texts of relevant studies were screened to assess whether they qualified for inclusion. The studies included in the review of Danna (2016) were also screened on our predefined eligibility criteria [11]. Reasons for exclusion were recorded. Reference lists of all included articles were screened to detect other potentially relevant articles. Discrepancies between the two reviewers were resolved by consensus or a third reviewer (GP) was consulted.

2.4. Data extraction

Two reviewers (MV, YYC) independently extracted data using a custom-made electronic template. Disagreements were resolved by consensus. Data extracted included: 1) study characteristics (country, sample size, study design (including total follow-up in case of cohort studies), age, sex, number of participants with DM only/DM and comorbid depression); 2) diagnostic criteria used for DM (including DM

type), depression and assessment of the primary outcomes. Results extracted included: 1) the most relevant statistical analysis conducted; 2) the outcome measure; 3) adjustment for confounders; 4) outcome in participants with DM only and in participants with DM and comorbid depression. If available, the 95% confidence interval or p-value was reported. Authors were contacted by email in case of missing data.

2.5. Quality assessment

The quality of each included study was independently assessed by two reviewers (MV, YYC) using the Newcastle-Ottawa Scale (NOS) [26]. For cross-sectional studies, an adapted scale from a previous review was used [27]. Each study was assessed on three domains: the selection and comparability of study groups, and the ascertainment of outcome. Based on the number of quality criteria met in different domains, each study was assessed as good, fair or poor quality.

2.6. Statistical analysis

A meta-analysis was performed if three or more studies with similar study designs and outcome measures could be combined. The meta-analysis was conducted using RevMan 5.4 [28]. Regarding cognition, studies were grouped per cognitive domain to calculate a pooled standardized mean difference (SMD) with a random-effects model. With respect to dementia risk, a pooled hazard ratio (HR) was calculated using the fixed-effects model, as the included studies were characterized by homogeneous methodological approaches. The range of effects was presented in forest plots including 95% confidence intervals. Between study heterogeneity was assessed using the I^2 -statistic [29]. We considered an I^2 -value $> 75\%$ as indicative of high heterogeneity [30]. In case of high heterogeneity, sensitivity analyses were conducted by excluding one study at a time to explore if an individual study explained the heterogeneity. If 10 or more studies could be included in the meta-analysis, funnel plot asymmetry was examined to evaluate publication bias.

3. Results

3.1. Study selection

Our search identified 4886 unique articles, of which 26 were considered relevant for our systematic review in the title-/abstract screening. As shown in the PRISMA flow chart (Supplementary file 2), 12 articles were eligible for inclusion after full text screening of these publications. No additional relevant publications were identified after searching the reference lists. Eight articles from the review of Danna [11] were excluded as they either did not meet the eligibility criteria or included the same sample as other studies [13,31]. In this case, the study which provided the longest follow-up was selected. In total, 19 articles were included in this systematic review [12–18,32–41], of which 10 were eligible for meta-analyses [15–18,32,34,36,37]. Other results were reported qualitatively. Funnel plots were excluded as the meta-analyses included an insufficient number of studies.

3.2. Study characteristics

Regarding cognition, eight cross-sectional studies [32–38,42], two prospective cohort studies [12,14] and one retrospective cohort study [13] were included (Table 1). The research area was distributed among the United States [13,14,33,34,37], United Kingdom [12], Israel [32], Singapore [35], China [38,42] and Canada [14]. Four studies assessed both types of DM [13,35,37,38], the remaining six studies only assessed type 2 DM [12,14,32–34,36,42]. Studies provided data on executive function [12,14,32–34,36,37], complex attention [14,32,34,36,42], language [32,34,37], memory [12,14,32,34,36,37,42] and overall cognition [13,32,34–38]. Moreover, one study explored whether

Table 1
Study characteristics.

Author	Year	Sample size	Persons with DM and depression (%)	Country	Age ¹	Sex (% female) ¹	Study design (follow-up)	DM type and measurement	Depression criteria (cut-points)	Cognitive outcomes measured
Outcome: cognition										
Demakakos et al. [12]	2017	10,524	1.6	United Kingdom	mean = 68.4 ± 9.1	38.6	Prospective cohort (8–10 yrs)	2; self-report, validated with medication data	CES-D 20-item measure (≥16)	Memory (10-word list), executive function (SFT)
Downer et al. [13]	2016	672	29.5	United States	mean = 72.7 ± 5.9	54.0	Retrospective cohort (11 yrs)	1 + 2; self-report	CES-D 20-item measure (≥16)	Overall cognition (MMSE)
Guerrero-Berroa et al. [32]	2018	738	8.9	Israel	mean = 72.7 ± 4.6	37.2	Cross-sectional	2; American Diabetes association criteria	GDS-15 (>5)	Memory (WLM/R/R), complex attention (DS), language (LF, AF), executive function (TMT, CERAD-constructional praxis, DSST), overall cognition (average z-scores)
Raffield et al. [34]	2016	655	15.9	United States	mean = 66.8 ± 9.7	47.51	Cross-sectional	2; medication reviews and HbA1c measurements	CES-D 10 item measure (>10)	Overall cognition (3MSE), executive function (ST), complex attention (DSST), memory (RAVLT), language (SFT)
Subramaniam et al. [35]	2017	798	9	Singapore	GP: range = 60+	GP: 57.0	Cross-sectional	1 + 2; self-report or earlier doctor diagnosis and treatment	GMS-AGECAT	Overall cognition (COGSCORE)
Wei et al. [37]	2019	741	34.5	United States	≥80 (n = 405)	47.4	Cross-sectional	1 + 2; questionnaire	PHQ-9 (5–14 CRD, ≥15 CSD)	Memory (DVRT), language (AF), executive function (DSST), overall cognition (average z-scores)
Xiu et al. [38]	2019	2,626	10.9	China	GP: mean = 71.2 ± 7.4	GP: 62.95	Cross-sectional	1 + 2; fasting plasma glucose ≥ 7.0 mmol/l, earlier diagnosis, antidiabetic therapy	GDS-15 (>5)	Overall cognition (MMSE)
Munshi et al. [33]	2012	145	NI	United States	GP: mean = 77.0 ± 5.0	GP: 52.0	Cross-sectional	2; doctor diagnosis	GDS-15 (>5)	Executive function (DEX)
Sullivan et al. [14]	2013	2,977	18	United States, Canada	mean = 62.7 ± 5.9	44.7	Prospective cohort (3.3 yrs)	2; NI	PHQ-9 (≥10)	Executive function (ST), memory (RAVLT), complex attention (DSST)
Watari et al. [36]	2006	40	50	United States	mean = 58.9 ± 9.2	65.0	Cross-sectional	2; doctor diagnosis	DSM-IV + HAM-D (≥15)	Overall cognition (MMSE), executive function (ST, TMT), memory (RMT, CVLT), complex attention (ST, TMT, DSST)

(continued on next page)

Table 1 (continued)

Author	Year	Sample size	Persons with DM and depression (%)	Country	Age ¹	Sex (% female) ¹	Study design (follow-up)	DM type and measurement	Depression criteria (cut-points)	Cognitive outcomes measured
Zhang et al. [42]	2021	94	52.1	China	mean = 50.47 ± 8.83 (DM only), 53.84 ± 8.23 (DM + depression)	46.7 (DM only), 42.9 (DM + depression)	Cross-sectional	2; ICD-10	ICD-10	Memory (RBANS list recall and recognition, story memory/recall, figure recall), attention (RBANS DS, coding)
Outcome: MCI										
Atif et al. [39]	2017	400	67.5	Pakistan	mean = 64 ± 5.5	53.8	Cross-sectional	2; ≥6 months DM, HbA1C tests	GDS-15 (≥5)	MCI (MoCA; cut-point: <26)
Outcome: dementia										
Gilsanz et al. [15]	2018	3,742	20.1	United States	mean = 56.1 ± 8.5	47.4	Prospective cohort (6.3 yrs)	1; diagnostic codes, insulin prescription, insulin use	ICD-9	Dementia (ICD-9)
Yu et al. [18]	2019	1,917,702	6.5	Korea	mean = 59.1 ± 10.3;	41.1;	Prospective cohort (5.1 yrs)	2; anti-diabetic drugs, ICD-10, fasting glucose	ICD-10	Dementia ≥ 60 years (anti-dementia medication, ICD-10)
Bruce et al. [40]	2003	223	13.9	Australia	mean = 76.5 ± 4.3	49.8	Cross-sectional	1 + 2; NI	EBAS-DEP (≥4)	Dementia (MMSE; cut-point < 24 + IQCODE; cut-point > 3.61)
Umegaki et al. [41]	2007	907	NI	Japan	NI	NI	Cross-sectional	1 + 2; HbA1c levels, hypertension, obesity, dyslipidaemia	GDS-15 (cut-point unclear)	Dementia (MMSE; cut-point < 24)
Katon et al. [17]	2010	3,837	11.9	United States	mean = 63.2 ± 13.2	47.9	Prospective cohort (5 yrs)	1 + 2; fasting plasma glucose, medication, doctor diagnosis	PHQ-9 (≥10)	Dementia (ICD-9)
Katon et al. [16]	2012	19,239	19.6	United States	mean = 58.8 ± 10	49.0	Prospective cohort (5 yrs)	2; doctor diagnosis, medical records	PHQ-8 (≥10), ICD-9, use of antidepressants, self-report	Dementia (ICD-9)
Carr et al. [43]	2020	1064	11.8	Scotland	mean = 67.9 ± 4.2	48.7	Prospective cohort (median: 10.6 yrs)	2; DM registry	HADS (≥8)	Dementia (ICD-10, electronic medical records system, death certificate records, prescription data for dementia medication)

3MSE Modified Mini Mental State Examination, AF Animal fluency, CERAD Consortium to Establish a Registry for Alzheimer's dementia, CES-D Center for Epidemiological Studies Depression Scale, CRD Clinically relevant depression, CSD Clinically significant depression, CVLT California verbal learning test, DEX Dysexecutive Questionnaire, DM Diabetes mellitus, DS Digit Span, DSST Digit symbol substitution test, DWRT Delayed word recall test, EBAS-DEP Even Briefer Assessment Scale for Depression, GDS-15 15-item Geriatric Depression Scale, GMS-AGECAT Geriatric Mental State-Automated Geriatric Examination for Computer Assisted Taxonomy, GP General population, HADS Hospital Anxiety and Depression Scale, HAM-D Hamilton Rating Scale for Depression, ICD International Classification of Diseases, IQCODE Informant Questionnaire on Cognitive Decline in the Elderly, LF Letter fluency, MMSE Mini Mental State Examination, MoCA Montreal Cognitive Assessment, NI No information, PHQ-9 9-item Patient Health Questionnaire, RAVLT Rey Auditory-Verbal Learning Task, RBANS Repeatable battery for the assessment of neuropsychological status, RMT Recognition memory test, SFT Semantic fluency test, ST Stroop task, TMT Trail making test, WLM/R/R Word list memory/recall/recognition.

¹ If the characteristics were not presented for the diabetes mellitus population, then the characteristics for the general population (GP) were provided.

antidepressant treatment modified the association between depression on cognition [32].

With respect to MCI and dementia, we included five prospective cohort studies [15–18,43] and three cross-sectional studies [39–41] (Tables 1 and 3). Studies were conducted in the United States [15–17], Pakistan [39], Korea [18], Australia [40], Scotland [43] and Japan [41].

Three studies included both types of DM [17,40,41], four studies only included type 2 DM [16,18,39,43] and one study only included type 1 DM [15]. Seven studies examined the outcome dementia [15–18,40,41,43], one study the outcome MCI [39].

3.3. Quality assessment

Of eight cross-sectional studies which examined cognition as primary outcome [32–38,42], four were assessed as good quality, one as fair quality and three as poor quality. Of three cross-sectional studies which assessed dementia and MCI as an outcome [39–41], one was considered as good quality and two as fair quality (Supplementary file 3a, Table 1). Common limitations were lacking information about the comparability between respondents and non-respondents, non-representative samples [32,33,42], insufficient sample sizes [33,36,42,44], no adjustment for

potential confounders [33,36,39,40,42] and incomplete description of statistical analyses [33,36,40].

Three cohort studies which examined the outcome cognition were all assessed as fair quality [12–14]. Of five cohort studies which assessed the outcome dementia [15–18,43], two studies were assessed as good quality and three as fair (Supplementary file 3b, Table 1). Main limitations were the ascertainment of exposure as depression was measured using self-report questionnaires [12–14,16,17], lacking information about the adequacy of follow-up [14,16–18] and insufficient follow-up time [12–14,16–18].

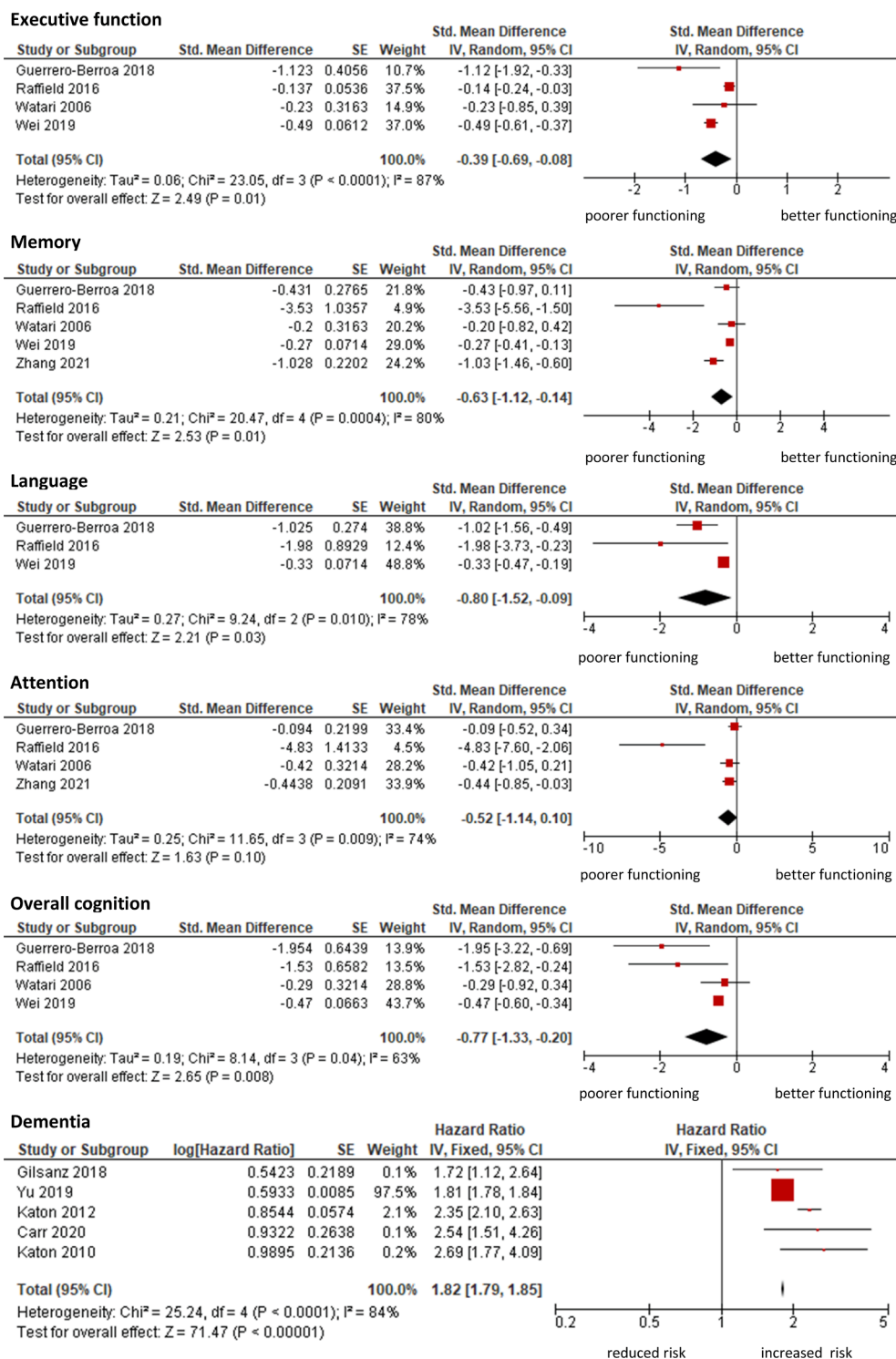


Fig. 1. Forest plots for the associations between depression and cognitive outcomes in persons with diabetes mellitus (DM).

3.4. Association between depression and cognition in persons with DM

3.4.1. Complex attention

Five studies (four cross-sectional [32,34,36,42], one cohort [14]) examined the outcome complex attention. Meta-analysis of cross-sectional studies showed that participants with DM and depression scored similar on complex attention compared with participants with DM only (n = 1,527, SMD = -0.52 (-1.14, 0.10)), but the heterogeneity was high (I² = 74%) (Fig. 1). Sensitivity analyses suggested that the heterogeneity was fully explained by Raffield (2016) (SMD = -0.30 (-0.57, -0.03), I² = 0% after excluding Raffield) [34]. The prospective cohort study, however, found a significant greater decline in complex attention over three years in persons with DM and depression compared with persons with DM only (mean difference = 0.72 (0.25, 1.19)) (Table 2) [14].

3.4.2. Memory

Seven studies (five cross-sectional [32,34,36,37,42], two cohort [12,14]) reported on the memory outcomes. Meta-analysis of cross-sectional studies suggested in persons with DM, those with depression had slightly worse memory than those without (n = 4,628, SMD = -0.63 (-1.12, -0.14)), but the heterogeneity was considerable (I² = 80%) (Fig. 1). Sensitivity analyses suggested that the heterogeneity was explained by Raffield (2016) and Zhang (2021) (SMD = -0.28, (-0.41, -0.14), I² = 0% after excluding Raffield and Zhang) [34,42].

Of the two prospective cohort studies, one study showed that compared with healthy controls, persons with DM and comorbid depression experienced more memory decline than persons with DM only (respectively β = -0.74 (-1.28, -0.20); β = -0.39 (-0.67, -0.10)) [12]. The second study found that in participants with DM, those with depression scored worse on memory over three years than those without (mean difference = 0.18 (0.07, 0.29)) [14] (Table 2).

3.4.3. Executive function

Seven studies (five cross-sectional, two cohort) provided data on executive function. Meta-analysis based on four cross-sectional studies showed that executive dysfunction was more common in persons with DM and depression than in persons with MD only (n = 4534, SMD = -0.39, (-0.69, -0.08)), but the heterogeneity was substantial (I² = 87%) (Fig. 1) [32,34,36,37]. Sensitivity analyses suggested that Raffield (2016) might be the source of heterogeneity (SMD = -0.52 (-0.84, -0.20), I² = 36% after excluding Raffield) [34]. The remaining cross-sectional study was not included in the meta-analysis as executive function was measured with a subjective test [33]. This study found that depressive symptoms in persons with DM were associated with increased self-reported dysexecutive symptoms (β = 0.94 (SE = 0.32), p < 0.004).

Of the prospective cohort studies [12,14], one study found that compared with healthy controls, persons with only DM as well as persons with DM and comorbid depression scored worse on executive function over eight years [12]. However, the association was stronger in persons with DM and comorbid depression (β = -1.60 (-2.57, -0.63)) than in persons with DM only (β = -0.53 (-1.04, -0.02)). The second study found that in participants with DM, those with depression had a greater decline in executive function over three years than those without (SMD = -1.06 (-1.93, -0.18)) (Table 2) [14].

3.4.4. Language

Meta-analysis of three cross-sectional studies suggested that in participants with DM, those with depression scored lower on language than those without (n = 4494, SMD = -0.80 (-1.52, -0.09)) [32,34,37]. The heterogeneity was high (I² = 78%) (Fig. 1). Sensitivity analyses strongly indicated that Wei (2019) explained this heterogeneity (SMD = -1.12 (-1.70, -0.55)), I² = 4% after excluding Wei) [37].

Table 2
Study results.

Authors	Adjustment for main variables ¹	Outcome in persons with DM alone (95 % CI; p-value)	Outcome in persons with DM and depression (95 %CI; p-value)	Quality assessment
Outcome: cognition				
Demakakos et al. [12]	Yes	MM: β = -0.39 (-0.67, -0.10; p ≤ 0.01) EF: β = -0.53 (-1.04, -0.02; p ≤ 0.05) OC: β = -0.19 (SE 0.05; p < 0.01)	MM: β = -0.74 (-1.28, -0.20; p ≤ 0.01) EF: β = -1.60 (-2.57, -0.63; p ≤ 0.001)	Fair
Downer et al. [13]	Yes	[Reference]	OC: β = -0.26 (SE 0.09; p < 0.01)	Fair
Guerrero-Berroa et al. [32]	Yes	[Reference]	CA: β = -0.094 (-0.525, 0.336; p > 0.05) EF: β = -1.123 (-1.918, -0.329; p = 0.006) LG: β = -1.025 (-1.562, -0.487; p < 0.001) MM: β = -0.431 (-0.973, 0.111; p = 0.119) OC: β = -1.954 (-3.216, -0.692; p = 0.002)	Fair
Raffield et al. [34]	Yes	[Reference]	CA: β = -4.83 (-7.60, -2.06; p < 0.001) EF: β = 0.137 (0.032, 0.242; p = 0.011) LG: β = -1.98 (-3.73, -0.231; p = 0.027) MM: β = -3.53 (-5.56, -1.50; p < 0.001) OC: β = -1.53 (-2.82, -0.246; p = 0.020)	Good
Subramaniam et al. [35]	Yes	[Reference]	OC: β = -0.002 (-0.041, 0.036; p = 0.901)	Good
Wei et al. [37]	Yes	EF: β = -0.22 (-0.30, -0.13) LG: β = -0.03 (-0.13, 0.07) MM: β = -0.09 (-0.19, 0.02) OC: β = -0.15 (-0.24, -0.05)	EF: β = -0.49 (-0.61, -0.37) LG: β = -0.33 (-0.47, -0.19) MM: β = -0.27 (-0.41, -0.14) OC: β = -0.47 (-0.60, -0.34)	Good
Xiu et al. [38]	Yes	[Reference]		Good

(continued on next page)

Table 2 (continued)

Authors	Adjustment for main variables ¹	Outcome in persons with DM alone (95 % CI; p-value)	Outcome in persons with DM and depression (95 %CI; p-value)	Quality assessment
Munshi et al. [33]	Yes	[Reference]	OC: AOR = 1.64 (1.06, 2.54; p = 0.03) EF: $\beta = 0.94$ (SE 0.32; p = 0.004)	Poor
Sullivan et al. [14]	Yes	CA: MD = 0.72 (0.25, 1.19; p = 0.003) EF: MD = -1.06 (-1.93, -0.18; p = 0.02) MM: MD = 0.18 (0.07, 0.29; p = 0.001)	[Reference]	Fair
Watari et al. [36]	No	CA: mean = -0.04 (SD 1.34) EF: mean = -0.31 (SD 1.14) MM: mean = -0.07 (SD 1.06) OC: mean = -0.13 (SD 0.95)	CA: mean = -0.62 (SD 1.36) EF: mean = -0.58 (SD 1.16) MM: mean = -0.29 (SD 1.08) OC: mean = -0.42 (SD 0.98)	Poor
Zhang et al. [42]	No	CA: mean = 92.16 (SD 14.07) MM: mean = 92.16 (SD 14.43)	CA: mean = 85.20 (SD 16.80) MM: mean = 75.76 (SD 17.00)	Poor
Outcome: MCI				
Atif et al. [39]	Yes	[Reference]	MCI risk: OR 42.50 (20.99, 86.06; p < 0.001)	Fair
Outcome: dementia				
Gilsanz et al. [15]	Yes	[Reference]	HR 1.72 (1.12, 2.65; p < 0.05)	Good
Yu et al. [18]	Yes	[Reference]	HR 1.81 (1.78, 1.85)	Fair
Bruce et al. [40]	No	NI	Spearman's $\rho = -0.17$, p = 0.012	Fair
Umegaki et al. [41]	Yes	[Reference]	OR 1.139 (1.045, 1.243; p = 0.003)	Good
Katon et al. [17]	Yes	[Reference]	HR 2.69 (1.77, 4.07)	Fair
Katon et al. [16]	Yes	[Reference]	HR 2.35 (2.10, 2.63; p < 0.001)	Fair
Carr et al. [43]	Yes	[Reference]	HR 2.54 (1.51, 4.26)	Good

CA Complex attention, CI Confidence interval, EF Executive function, LG Language, MD Mean difference, MM Memory, OC Overall cognition.

¹ Adjustment for age, sex, education, diabetes characteristics and cardiovascular risk factors.

3.4.5. Overall cognition

Seven studies (six cross-sectional, one cohort) provided results on overall cognition. Meta-analysis of four cross-sectional studies [32,34,36,37] showed that participants with DM and depression had lower overall cognition than participants with DM only (n = 4,534, SMD = -0.77 (-1.33, -0.20)). The heterogeneity was moderate ($I^2 = 63%$) (Fig. 1). Of the cross-sectional studies that were not included in the meta-analysis due to incompatible design, one study showed that persons with DM and depression scored similar on overall cognition as persons with DM only ($\beta = -0.002$ (-0.041, 0.036)) [35]. The second study performed a logistic regression analysis, which suggested that in persons with DM, depressive symptoms are a risk factor for cognitive decline (adjusted odds ratio (OR) = 1.64 (1.06, 2.54)) [38]. The retrospective cohort study found that both persons with DM only and persons with DM and comorbid depression had worse overall cognition compared with healthy controls [13]. This association was slightly stronger in persons with DM and comorbid depression ($\beta = -0.26$ (SE = 0.09), p < 0.01) than in persons with DM only ($\beta = -0.19$ (SE = 0.05), p < 0.01) (Table 2).

3.5. Association between depression and MCI in persons with DM

Only one study examined the outcome MCI, which found that participants with DM and depression had a higher risk of MCI than participants with DM only (n = 400, adjusted OR = 42.50 (20.99, 86.06)) (Table 2) [39].

3.6. Association between depression and dementia risk in persons with DM

Seven studies (two cross-sectional, five cohort) examined the outcome dementia risk. One cross-sectional study showed a significant correlation between depression and dementia ($\rho = -0.17$, p = 0.012) [40]. A second cross-sectional study found that dementia risk was higher in persons with depression and DM than in persons with DM only (OR = 1.14 (1.05, 1.24)) [41] (Table 2).

Meta-analysis of prospective cohort studies indicated that in persons with depression and DM, dementia risk was higher than in persons with DM only (n = 1,945,584, HR = 1.82 (1.79, 1.85)), but the heterogeneity was substantial ($I^2 = 84%$) (Fig. 1) [15-18,43]. Sensitivity analyses suggested that the heterogeneity was explained by Yu (2020) (HR = 2.33 (2.11, 2.59), $I^2 = 0%$ after excluding Yu) [18].

3.7. Frequency and timing of depressive episodes

No studies were found that examined the role of frequency and timing of depressive episodes over the adult life course in the association between depression and cognitive outcomes.

3.8. Antidepressant treatment as an effect modifier

One study examined whether antidepressant use modified the association between depression and cognitive functioning. They found that among anti-depressant users, there were no statistically significant differences in people with (n = 28) and without depression (n = 164) in the five cognitive domains measured (p > 0.18, effect sizes ≤ 0.27). Among non-antidepressant users, people with depression (n = 490) had poorer executive function (p = 0.04, effect size = 0.38) and semantic categorization (p = 0.01, effect size = 0.49) than people without depression (n = 33) [32].

4. Discussion

To our knowledge, this is the first meta-analysis that examined the association between depression and cognitive outcomes in persons with DM. The current findings in persons with DM are largely in line with

previous observations in the general population. In persons with DM, we found that depression was associated with a 1.82 (1.79, 1.85) times higher risk of developing dementia, which is in the same range as the 2–3 times higher dementia risk reported in the general population [8,19,21,45]. However, the one paper that examined the association between depression and MCI in persons with DM found a much higher MCI risk (OR = 42.50 (20.99, 86.06)) [39] than reported in the general population (HR = 1.48 (1.23, 1.77); relative risk (RR) = 1.97 (1.53, 2.54)) [7,9]. No clear explanation was provided for this exceptionally high odds ratio. Additional studies are required to verify this association in persons with DM. We also found that depression was associated with poorer global cognition, executive function, memory and language. These associations have also been demonstrated in the general population, but additional associations were found between depression and attention and episodic memory [6,46]. Although we found no statistically significant associations with complex attention, the pooled estimate points toward negative associations (Fig. 1). The consistency in findings in cross-sectional and prospective studies and across the general and DM populations support the robustness of the association between depression and cognitive outcomes. These collective findings show that monitoring of cognitive functions is required in people with depression regardless of presence of DM. Note, however, that depression may be a precursor to dementia or dementia may lead to depression [47,48].

The current results support that depression further increases the risk of cognitive decline or dementia up and above the risk associated with having DM. Two potential mechanisms may explain this interaction between DM and depression. First, both DM [47–49] and depression [50–53] have been associated with white matter changes in the brain, which result in cognitive decline and dementia. Given the shared pathophysiological pathway, the risk of worse cognitive outcomes may be greater in people who have both conditions than in people with DM only. Second, DM is known as a risk factor for cognitive decline of both neurodegenerative as well as vascular etiology [49]. In persons with DM, depression is associated with poor glycaemic control, unhealthy lifestyle habits and increased risk of microvascular and macrovascular complications [14,50,51], which may further aggravate cognitive decline.

No studies were found on whether recurrence and timing of depressive episodes throughout life were associated with cognitive outcomes in persons with DM. A 2008-review conducted in the general population reported that the odds of having white matter changes was four-fold higher in people with late-life depression than in people with depression earlier in life [52]. These findings are supported by later studies, which showed that the dementia risk was higher in people with depression in mid-life than in early life [20] and was higher in people with depression in late life than in mid-life [21]. Thus, it seems that the risk of cognitive decline and dementia increases as the onset of depression occurs later in life. A narrative review published in 2019 suggested that early-onset depression may be associated with declines in memory and processing speed and reversible changes in the hippocampus, whereas late-onset depression may be indicative of neurodegeneration [53]. Furthermore, in the general population, the risk of cognitive decline or dementia seems to be higher in people with recurrent episodes than in people with a single episode or no depression [22,54,55]. Given the consistency in findings across the groups, it seems likely that recurrence and timing of episodes play a similar role in people with diabetes as in the general population, but direct evidence is lacking.

Only one study included in this review examined whether antidepressants modified the association between depression and cognitive outcomes in persons with diabetes [32]. The results suggested that antidepressant use could mitigate the negative effects of depression on cognitive function. However, this was only one cross-sectional study and the numbers per group were relatively small. Thus, further research is required to verify these findings. Nevertheless, these results are hopeful and in line with a meta-analysis of studies conducted in the general population showing that antidepressant use was associated with better functioning on several cognitive domains, including executive function

(Hedges' $g = 0.28$, $p < 0.01$), recent memory (Hedges' $g = 0.18$, $p = 0.02$) and sustained attention (Hedges' $g = 0.19$, $p < 0.01$) [56].

A strength of this review was the ability to perform meta-analyses following the best practice guidelines for the conduct of systematic reviews and meta-analyses [25]. There are several limitations that should be acknowledged. Firstly, the degree of heterogeneity in the meta-analyses was substantial. This may be explained by variations in cognitive tests, tests for depression, adjustment for different confounders, different sample sizes and types of DM across studies [18,36,37]. Sensitivity analyses stratified for type of DM were not possible as only few studies presented results for type 1 DM alone. However, the estimates of these studies were in the same range as for the 11 studies presenting results for type 2 DM (Fig. 1). Further subgroup analyses were precluded as the sensitivity analyses and comparison of study characteristics did not show which differences were most likely to explain the heterogeneity. Therefore, we decided to accept the degree of heterogeneity and results of the meta-analyses must be interpreted with caution. Although the direction of the effect is generally consistent across studies, the magnitude of the effect remains uncertain. Comparing studies that used different cognitive tests remains a well-known difficulty. Core outcome sets, an agreed standardized collection of outcome measures for a specific domain, could possibly reduce the heterogeneity [57]. Second, the literature suggests that diabetes and depression in later life are risk factors for dementia, and that the risk increases with longer disease duration [8]. Thus, age difference, follow-up duration and disease duration may explain some of the heterogeneity between studies. More studies per outcome are required for reliable meta-regression analyses to better understand the role of age and disease duration. Differences in metabolic state could also play a role, however, most studies adjusted for this in their analyses. Third, the results may have been affected by several sources of bias. None of the cross-sectional studies included a non-response analyses and thus the representativeness of the samples is unclear. It is important to recognize potential misclassification bias, as several studies relied on self-report to assess depression [16,17,32,34,37]. Moreover, as depression could adversely affect the ability to complete cognitive tests, the actual cognitive function may have been underestimated. Also, three of the five prospective studies that examined the outcomes MCI or dementia did not have a sufficiently long follow-up, which may have led to underestimation of the true association [16–18]. Finally, there were too few studies per outcome to reliably test publication bias using Funnel plots and Egger's test, hence it is unclear if the results were affected by publication bias.

4.1. Conclusion

The current systematic review and meta-analyses suggest that persons with DM and depression are more likely to suffer from worse overall cognition, deficits in language, memory and executive function and a 1.8 times higher risk of developing dementia than persons with DM only. Whether the risk of MCI is increased as well, remains unclear but seems likely given the associations with cognitive decline and dementia. The detrimental effects of depression on cognition may be mitigated by antidepressant treatment, but further research is required to confirm this. The question whether the timing and frequency of depressive episodes throughout the life course influences the association between depression and cognitive outcomes in persons with DM remains unanswered. If future research confirms that depression is a modifiable risk factor for cognitive decline in persons with DM, strategies can be developed to adequately prevent or treat depression in persons with DM and subsequently prevent or delay cognitive decline and dementia in later life.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.diabres.2022.109227>.

References

- [1] Roy T, Lloyd CE. Epidemiology of depression and diabetes: a systematic review. *J Affect Disord* 2012;142(Suppl):S8–21.
- [2] Anderson RJ, Freedland KE, Clouse RE, Lustman PJ. The prevalence of comorbid depression in adults with diabetes: a meta-analysis. *Diabetes Care* 2001;24(6):1069–78.
- [3] Moussavi S, Chatterji S, Verdes E, Tandon A, Patel V, Ustun B. Depression, chronic diseases, and decrements in health: results from the World Health Surveys. *Lancet* (London, England). 2007;370(9590):851–8.
- [4] Zhang Y, Chen Y, Ma L. Depression and cardiovascular disease in elderly: current understanding. *J Clin Neurosci: Off J Neurosurg Soc Austral* 2018;47:1–5.
- [5] Monette MCE, Baird A, Jackson DL. A meta-analysis of cognitive functioning in nondemented adults with type 2 diabetes mellitus. *Can J Diabetes* 2014;38(6):401–8.
- [6] Rock PL, Roiser JP, Riedel WJ, Blackwell AD. Cognitive impairment in depression: a systematic review and meta-analysis. *Psychol Med* 2014;44(10):2029–40.
- [7] Gallagher D, Kiss A, Lancot KL, Herrmann N. Toward prevention of mild cognitive impairment in older adults with depression: an observational study of potentially modifiable risk factors. *J Clin Psychiatry* 2018;80(1).
- [8] Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet* (London, England). 2020;396(10248):413–46.
- [9] Gao Y, Huang C, Zhao K, Ma L, Qiu X, Zhang L, et al. Depression as a risk factor for dementia and mild cognitive impairment: a meta-analysis of longitudinal studies. *Int J Geriatric Psychiatry* 2013;28(5):441–9.
- [10] Luchsinger JA, Reitz C, Patel B, Tang MX, Manly JJ, Mayeux R. Relation of diabetes to mild cognitive impairment. *Arch Neurol* 2007;64(4):570–5.
- [11] Danna SM, Graham E, Burns RJ, Deschênes SS, Schmitz N, Ginsberg SD. Association between depressive symptoms and cognitive function in persons with diabetes mellitus: a systematic review. *PLoS ONE* 2016;11(8):e0160809.
- [12] Demakakos P, Muniz-Terrera G, Nouwen A, Ginsberg SD. Type 2 diabetes, depressive symptoms and trajectories of cognitive decline in a national sample of community-dwellers: a prospective cohort study. *PLoS ONE* 2017;12(4):e0175827.
- [13] Downer B, Vickers BN, Al Snih S, Raji M, Markides KS. Effects of comorbid depression and diabetes mellitus on cognitive decline in older Mexican Americans. *J Am Geriatr Soc* 2016;64(1):109–17.
- [14] Sullivan MD, Katon WJ, Lovato LC, Miller ME, Murray AM, Horowitz KR, et al. Association of depression with accelerated cognitive decline among patients with type 2 diabetes in the ACCORD-MIND trial. *JAMA Psychiatry*. 2013;70(10):1041. <https://doi.org/10.1001/jamapsychiatry.2013.1965>.
- [15] Gilsanz P, Schnaider Beerli M, Karter AJ, Quesenberry CP, Adams AS, Whitmer RA. Depression in type 1 diabetes and risk of dementia. *Aging Mental Health*. 2019;23(7):880–6.
- [16] Katon W, Lyles CR, Parker MM, Karter AJ, Huang ES, Whitmer RA. Association of depression with increased risk of dementia in patients with type 2 diabetes: the Diabetes and Aging Study. *Arch Gen Psychiatry* 2012;69(4):410–7.
- [17] Katon WJ, Lin EHB, Williams LH, Ciechanowski P, Heckbert SR, Ludman E, et al. Comorbid depression is associated with an increased risk of dementia diagnosis in patients with diabetes: a prospective cohort study. *J. Gen. Int. Med.* 2010;25(5):423–9.
- [18] Yu JH, Han K, Park S, Cho H, Lee DY, Kim J-W, et al. Incidence and risk factors for dementia in type 2 diabetes mellitus: a nationwide population-based study in Korea. *Diabetes Metab J*. 2020;44(1):113. <https://doi.org/10.4093/dmj.2018.0216>.
- [19] Zilkens RR, Bruce DG, Duke J, Spilbury K, Semmens JB. Severe psychiatric disorders in mid-life and risk of dementia in late- life (age 65–84 years): a population based case-control study. *Curr Alzheimer Res* 2014;11(7):681–93.
- [20] Skogen JC, Bergh S, Stewart R, Knudsen AK, Bjerkeset O. Midlife mental distress and risk for dementia up to 27 years later: the Nord-Trøndelag Health Study (HUNT) in linkage with a dementia registry in Norway. *BMC Geriatrics* 2015;15:23.
- [21] Barnes DE, Yaffe K, Byers AL, McCormick M, Schaefer C, Whitmer RA. Midlife vs late-life depressive symptoms and risk of dementia: differential effects for Alzheimer disease and vascular dementia. *Arch Gen Psychiatry* 2012;69(5):493–8.
- [22] Dotson VM, Beydoun MA, Zonderman AB. Recurrent depressive symptoms and the incidence of dementia and mild cognitive impairment. *Neurology* 2010;75(1):27–34.
- [23] Wagner S, Doering B, Helmreich I, Lieb K, Tadić A. A meta-analysis of executive dysfunctions in unipolar major depressive disorder without psychotic symptoms and their changes during antidepressant treatment. *Acta Psychiatr Scand* 2012;125(4):281–92.
- [24] Wang Y-C, Tai P-A, Poly TN, Islam MM, Yang H-C, Wu C-C, et al. Increased risk of dementia in patients with antidepressants: a meta-analysis of observational studies. *Behav Neurol* 2018;2018:1–8.
- [25] Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009;339(jul21 1):b2535.
- [26] Wells GA SB, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses 2019 [Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
- [27] Herzog R, Alvarez-Pasquin MJ, Díaz C, Del Barrio JL, Estrada JM, Gil Á. Are healthcare workers' intentions to vaccinate related to their knowledge, beliefs and attitudes? A systematic review. *BMC Public Health* 2013;13:154.
- [28] Review Manager (RevMan). Version 5.4 ed. Copenhagen: The Nordic Cochrane Centre: The Cochrane Collaboration; 2020.
- [29] Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21(11):1539–58.
- [30] Higgins J, Green S, editors. *Cochrane Handbook for Systematic Reviews of Interventions*. The Cochrane Collaboration; 2011. Version 5.1.0 [updated March 2011].
- [31] Rotkiewicz-Piorun AM, Al Snih S, Raji MA, Kuo YF, Markides KS. Cognitive decline in older Mexican Americans with diabetes. *J Natl Med Assoc* 2006;98(11):1840–7.
- [32] Guerrero-Berroa E, Ravona-Springer R, Schmeidler J, Heymann A, Soleimani L, Sano M, et al. Depressive symptoms are associated with cognitive function in the elderly with type 2 diabetes. *J Alzheimer's Disease : JAD*. 2018;65(2):683–92.
- [33] Munshi MN, Hayes M, Iwata I, Lee Y, Weinger K. Which aspects of executive dysfunction influence ability to manage diabetes in older adults? *Diabet Med*. 2012;29(9):1171–7.
- [34] Raffield LM, Brenes GA, Cox AJ, Freedman BI, Hugenschmidt CE, Hsu F-C, et al. Associations between anxiety and depression symptoms and cognitive testing and neuroimaging in type 2 diabetes. *J Diabetes Complications* 2016;30(1):143–9.
- [35] Subramaniam M, Abidin E, Vaingankar JA, Picco L, Seow E, Chua BY, et al. Comorbid diabetes and depression among older adults - prevalence, correlates, disability and healthcare utilisation. *Ann Acad Med Singapore* 2017;46(3):91–101.
- [36] Watarai K, Letamendi A, Elderkinthompson V, Haroon E, Miller J, Darwin C, et al. Cognitive function in adults with type 2 diabetes and major depression. *Arch Clin Neuropsychol: Off J Natl Acad Neuropsychol* 2006;21(8):787–96.
- [37] Wei J, Ying M, Xie L, Chandrasekar EK, Lu H, Wang T, et al. Late-life depression and cognitive function among older adults in the U.S.: The National Health and Nutrition Examination Survey, 2011–2014. *J Psychiatr Res* 2019;111:30–5.
- [38] Xiu S, Liao Q, Sun L, Chan P. Risk factors for cognitive impairment in older people with diabetes: a community-based study. 204201881983664 *Therap Adv Endocrinol Metabol* 2019;10. <https://doi.org/10.1177/2042018819836640>.
- [39] Atif M, Saleem Q, Scahill S. Depression and mild cognitive impairment (MCI) among elderly patients with type 2 diabetes mellitus in Pakistan: possible determinants. *Int J Diabet Dev Count* 2018;38(3):312–20.
- [40] Bruce DG, Casey GP, Grange V, Clarnette RC, Almeida OP, Foster JK, et al. Cognitive impairment, physical disability and depressive symptoms in older diabetic patients: the Fremantle Cognition in Diabetes Study. *Diabetes Res Clin Pract* 2003;61(1):59–67.
- [41] Umegaki H, Iimuro S, Kaneko T, Araki A, Sakurai T, Ohashi Y, et al. Factors associated with lower Mini Mental State Examination scores in elderly Japanese diabetes mellitus patients. *Neurobiol Aging* 2008;29(7):1022–6.
- [42] Zhang X, wang P, Shi Li, Li Na. Study on caspase-1 and partial cognitive impairment in the comorbidity of type 2 diabetes and MDD. *J Affect Disord* 2021; 290:387–92.
- [43] Carr AL, Sluiman AJ, Grecian SM, Forster R, McLachlan S, Strachan MWJ, et al. Depression as a risk factor for dementia in older people with type 2 diabetes and the mediating effect of inflammation. *Diabetologia* 2021;64(2):448–57.
- [44] Iype T, Shaji SK, Balakrishnan A, Charles D, Varghese AA, Antony TP. Cognition in type 2 diabetes: association with vascular risk factors, complications of diabetes and depression. *Ann Ind Acad Neurol* 2009;12(1):25–7.
- [45] Diniz BS, Butters MA, Albert SM, Dew MA, Reynolds CF. Late-life depression and risk of vascular dementia and Alzheimer's disease: systematic review and meta-analysis of community-based cohort studies. *Brit J Psychiatry: J Ment Sci* 2013; 202(5):329–35.
- [46] McDermott LM, Ebmeier KP. A meta-analysis of depression severity and cognitive function. *J Affect Disord* 2009;119(1-3):1–8.
- [47] Brzezińska A, Bourke J, Riverá-Hernández R, Tsolaki M, Woźniak J, Kaźmierski J. Depression in dementia or dementia in depression? Systematic review of studies and hypotheses. *Curr Alzheimer Res* 2020;17(1):16–28.
- [48] Regan B, Varanelli L. Adjustment, depression, and anxiety in mild cognitive impairment and early dementia: a systematic review of psychological intervention studies. *Int Psychogeriatr*. 2013;25(12):1963–84.
- [49] Munshi MN. Cognitive dysfunction in older adults with diabetes: what a clinician needs to know. *Diabetes Care* 2017;40(4):461–7.
- [50] Sharma G, Parihar A, Talaiya T, Dubey K, Porwal B, Parihar MS. Cognitive impairments in type 2 diabetes, risk factors and preventive strategies. *J Basic Clin Physiol Pharmacol* 2020;31(2).
- [51] Huang Z, Guo Y, Ruan Ye, Sun S, Lin T, Ye J, et al. Associations of lifestyle factors with cognition in community-dwelling adults aged 50 and older. *A Longitudinal Cohort Study*. 2020;12.

- [52] Herrmann LL, Le Masurier M, Ebmeier KP. White matter hyperintensities in late life depression: a systematic review. *J Neurol Neurosurg Psychiatry* 2008;79(6): 619–24.
- [53] Jamieson A, Goodwill AM, Termine M, Campbell S, Szoeki C. Depression related cerebral pathology and its relationship with cognitive functioning: a systematic review. *J Affect Disord* 2019;250:410–8.
- [54] Singh-Manoux A, Akbaraly TN, Marmot M, Melchior M, Ankri J, Sabia S, et al. Persistent depressive symptoms and cognitive function in late midlife: the Whitehall II study. *J Clin Psychiat* 2010;71(10):1379–85.
- [55] Semkowska M, Quinlivan L, O'Grady T, Johnson R, Collins A, O'Connor J, et al. Cognitive function following a major depressive episode: a systematic review and meta-analysis. *Lancet Psychiat* 2019;6(10):851–61.
- [56] Prado CE, Watt S, Crowe SF. A meta-analysis of the effects of antidepressants on cognitive functioning in depressed and non-depressed samples. *Neuropsychol Rev* 2018;28(1):32–72.
- [57] Clarke M, Williamson PR. Core outcome sets and systematic reviews. *Systemat Rev* 2016;5:11.