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Cognitive changes in people with diabetes with lower extremity complications compared to people with diabetes without lower extremity complications: a systematic review and meta-analysis

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Abstract

Background Recent evidence suggests that diabetes-related lower-extremity complications (DRLECs) may be associated with cognitive changes in people with diabetes. However, existing literature has produced inconsistent findings, and no systematic reviews have been conducted to investigate whether DRLECs impact the cognition of people with diabetes. This systematic review evaluated existing studies that investigated cognition in people with diabetes with DRLECs and without DRLECs.

Method Seven databases; MEDLINE, PubMed, CINAHL, EMBASE, Cochrane, PsycINFO and Web of Science were searched from inception until 22/8/2022 for studies that compared cognition in people with diabetes with and without DRLECs. Results were independently screened for eligibility and assessed for methodological quality by two authors, with key data extracted. Studies were eligible for meta-analysis if the studies reported similar cases, controls, and outcome measures.

Results Thirteen studies were included in the review, with eleven of medium methodological quality, one of high quality, and one of low quality. Four studies found significant differences in cognition between those with and without DRLECs, four found significant associations between diabetes-related lower-extremity complications and cognition, and five found no differences or associations. One small meta-analysis of eligible studies found that there was no statistically significant difference in cognition in people without, compared to with, peripheral neuropathy (Mean difference = -0.49; 95%CI: -1.59–0.61; $N=3$; $n=215$). Leave-one-out sensitivity analyses further confirmed that there was no significant difference in cognition among people with and without peripheral neuropathy ($p>0.05$).

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Conclusion DRLECs may be related to cognition in people with diabetes, however, existing evidence is unclear due to variability in used methodologies that may challenge concluding the findings. Future high-quality studies investigating cognition among people with and without DRLECs are needed.

Keywords Cognition, Diabetes mellitus, Diabetic foot, Diabetes complications, Meta-analysis, Systematic review

Background

Diabetes is now the eighth leading cause of the global disease burden [1, 2]. Diabetes-related lower extremity complications (DRLECs) are the leading cause of the global diabetes disability burden, and the cause of poor quality of life, increased costs and mortality compared to people with diabetes without DRLECs [3–6]. DRLECs are defined as one or more of the following conditions: peripheral neuropathy (PN), peripheral artery disease (PAD), diabetes-related foot ulcers (DFUs), foot infections, and/or amputations in people with diabetes [3, 6]. Recently, a relationship between DRLECs and cognitive impairment has been observed in people with diabetes [7–10].

Cognition is defined as the brain's ability to acquire, process, store, and retrieve information [11]. Whereas, cognitive impairment is a disruption of cognitive functions in the main cognitive sub-domains [12]. Cognitive impairment in people with diabetes may be related to systemic inflammation [13–15], vascular changes [16, 17], and neuropathy [18, 19]. Furthermore, cognitive changes associated with diabetes have mainly been reported to impact the cognitive sub-domains of memory, mental flexibility, processing speed, psychomotor speed, executive function and general intelligence [20, 21]. Thus, these cognitive changes could impact self-care management and treatment adherence in people with diabetes [22, 23].

Some studies report that DRLECs are also associated with cognitive impairment, while others report no associations [9, 10, 24, 25]. A recent systematic review found some evidence of cognitive impairment in people with diabetes PN, but also found high heterogeneity in the methodologies used by existing studies [19]. However, to our knowledge, no systematic reviews have investigated other DRLECs and their impact on cognition in people with diabetes. Thus, to better understand the relationship between cognition and DRLECs, this systematic review aimed to evaluate existing studies that have investigated cognition for people with diabetes with DRLECs compared to people with diabetes without DRLECs.

Materials and methods

The protocol for this systematic review was registered with PROSPERO (CRD42021292571) and was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [26].

Search strategy

The search was performed from inception to 22nd August 2022 and included studies in the English language published from seven electronic databases: MEDLINE, PubMed, CINHAL, EMBASE, PsycINFO, Cochrane and Web of Science. Search strings that included the keywords and MeSH terms for diabetes, diabetes-related lower extremity complications AND cognition were used to identify relevant studies. The search strings for each database are shown in Supplementary Table 1.

Eligibility assessment

The inclusion criteria for this systematic review were studies that included people with diabetes (population) with DRLECs (exposure) or without DRLECs (comparator) that measured cognition (outcome). The diabetes population of interest was defined as adults (over the age of 18 years) diagnosed with type 1 or type 2 diabetes mellitus. The DRLEC exposures of interest were defined as one or more of the conditions of PN, PAD, DFUs, foot infections, and/or amputations in people with diabetes [3, 6]. The comparators of interest were defined as people with diabetes without any of the above-defined DRLECs. All forms (i.e., continuous or categorical) of cognition outcomes which were assessed by cognitive assessment tools were included. Original observational, experimental, and systematic review study designs were included; while case reports, case series, review articles, editorials, conference proceedings, and commentaries were excluded. Studies that investigated cognition in people with diabetes or DRLECs with participants who had depression, anxiety, dementia, delirium, alcoholism, or neurodegenerative diseases were also excluded as those conditions are known to impact cognition and may confound findings [27].

Study selection

Two authors [NK and CP] independently screened all titles and abstracts identified by the search based on the inclusion and exclusion criteria and Cohen's kappa was calculated for agreement between the two authors. Any disagreements were then discussed with a third author [KF] until a consensus was reached. All studies deemed eligible after screening were included in the full-text assessment.

Two authors [NK and CK] then independently assessed all included full texts using the same criteria and any disagreements were discussed with a third author [KF] until

consensus was reached. Finally, the reference lists of all included full-text studies were hand-searched to determine any additional relevant studies. All studies remaining eligible after full-text assessments were the final included studies for this systematic review.

Methodological quality

The methodological quality of all included studies was assessed independently by two authors [NK and PC] using the five-item Mixed Method Appraisal Tool (MMAT; 2018 version) [28]. Due to this study potentially including different methodologies, the MMAT was chosen as it provides an appraisal of several methodological designs including qualitative, randomised controlled trials, non-randomised studies, and quantitative descriptive designs [28]. Any disagreements were resolved by discussion and if unable to be resolved, a third reviewer decided [KF]. The overall methodological quality of studies was categorised as low if scoring yes for <3 items, medium for 3–4 items, and high for 5 items [29].

Data extraction

Key data for all included studies were extracted by one author [NK] into tables and the first 50% of data extraction were checked by a second author [PAL] until both authors were in agreement with the data extracted. The extraction of the remaining studies was completed by the first author [NK]. Data extracted for each study included: aim, setting, design, period, population(s), exposure(s)/case(s), control(s) of interest, population characteristics, outcome(s) of interest, and findings.

Data analysis

The summary outcome measures used for each outcome of interest included proportions for categorical data and means (standard deviations (SD)) for continuous data. Where three or more studies included similar populations, exposures/cases, controls and outcome measures, a meta-analysis was eligible to be considered. Meta-analysis was performed using Mantel-Haenszel's statistical method and random effect models, with results reported as risk ratios (RR) with 95% confidence intervals (CI). For continuous outcomes, meta-analysis was performed using the inverse variance method and random effect models, with results reported as mean differences (MD) with 95% CIs. The I^2 statistic was used to test for heterogeneity and categorised as low (0–49%), moderate (50–74%) or high heterogeneity (75–100%). Forest plots were used to visualise outcomes and funnel plots to assess potential publication bias [30]. Leave-one-out sensitivity analyses were performed to determine the influence of each study on the overall estimate of the effect [30]. The meta-analysis was performed according to the Cochrane handbook using Revman 5.4.1 version [30]. Any eligible studies with continuous data that did not report means (SD) were transformed to mean (SD) for the purpose of including in the meta-analysis by using an online calculator [31, 32].

Results

Overall, 1,278 records were identified from the initial search, including 709 unique records after duplicates were removed (Fig. 1). After title and abstract screening, 135 records were eligible for full-text assessment. The agreement between the two authors was substantial (Cohen's kappa=0.715). After the full-text assessment, 13 studies were included and made up the final included studies of this systematic review. All 13 included studies were observational designs with no experimental or systematic review studies included. No additional studies were identified in hand-searching reference lists.

Data extraction

Supplementary Table 2 displays all extracted data of the 13 included studies. Three studies were conducted in China [33–35], and one each in United States of America [36], Egypt [37], Sweden [38], Denmark [39], Netherlands [40], Saudi Arabia [41], Philippines [42], Belgium [43], Israel [9] and Brazil [44]. Seven studies used case-control designs [9, 33–35, 37, 39, 44], five cross-sectional designs [36, 38, 41–43] and one was a cohort design [40] (Table 1; Supplementary Table 2).

Ten studies included participants with type 2 diabetes [9, 34–37, 40–44], and three with type 1 diabetes [33, 38, 39]. DRLEC exposures included 11 studies investigating PN [9, 34, 35, 37–44], two DFUs [9, 41], and one amputation [41], with two also investigating multiple DRLECs [9, 41]. Controls in the seven case-control studies included six investigating people with diabetes without PN [33–35, 37, 39, 44] and one without DFU [9] (Table 1; Supplementary Table 2).

The cognitive assessment tools used to assess cognitive outcomes included the Mini-Mental State Examination (MMSE) in five studies [33–35, 43, 44], the Montreal cognitive assessment (MoCA) [33, 34, 41, 42] and the Trail marker test (TMT) in four studies each [34, 38, 40, 44].

Methodological quality

Eleven studies were rated of medium methodological quality [9, 33–36, 38–41, 43, 44], with one each rated low [37] and high quality [42] (Table 2). Nearly all studies had appropriate statistical analysis (100%), outcome measures (100%) and representative samples (92%), but few had a relevant sampling strategy (15%) and low response bias (23%).

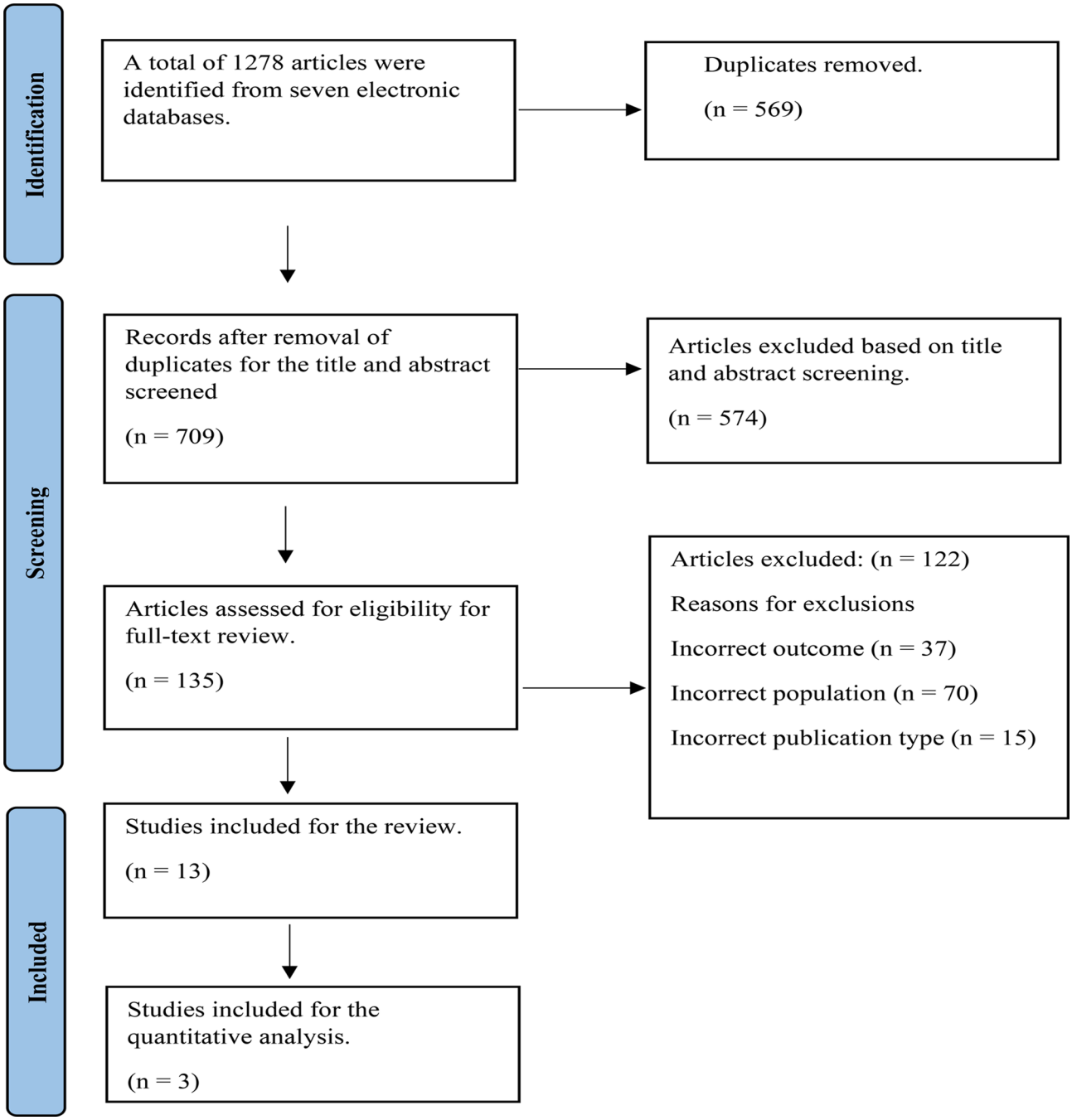

Fig. 1 PRISMA flow diagram

Cognition outcomes

Of the 13 included studies [9, 33–44], four (three case-control and one cross-sectional) reported a significant decrease in cognition (in at least one cognitive subdomain) among people with diabetes with DRLECs compared to people with diabetes without DRLECs ($p<0.05$) [9, 34, 37, 43], and reported DRLECs of such studies were PN [9, 34, 37, 43] and DFUs [9]. Four other studies (one cross-sectional and three case-control) reported a significant association [33, 39] or negative correlation [36, 38] between cognition and DRLECs among people with diabetes ($p<0.05$) and reported DRLECs of such studies were PN (33,36,38.39). Two further case-control studies and the remaining three studies (one cohort and two cross-sectional) found no significant differences or associations among people with diabetes with and without DRLECs ($p>0.05$) [36, 41–43] and PN was the

Table 1 Evidence tables of data extracted of included studies

Reference (Author/ Year)	Study setting	Study design	Population(s) control(s) of interest	Population Charecteristics	Exposure(s)	Outcome(s) of interest reported	Main findings – Cognition changes with/without DRLECs
Althbuaity et al., 2021	Saudia Arabia	Cross-sectional study	Population(s) Type 2 diabetes Control(s) Not applicable (NA)	Numbers: 179 Mean Age: 58.6 ± 9.6 yrs. Male: Reported as "almost equally distributed according to gender" Diabetes type: 179 (100%) T2 Diabetes duration: 11–16 yrs. -84 (47.0%) Diabetes-related lower extremity complications (DRLECs): PN: 123 (68.7%) Peripheral arterial disease (PAD): Not reported (NR) DFU History: NR DFU: 75 (47.5%) AMP: 7 (3.9%) Other: NR	Diabetic polyneuropathy (DPN)	Montreal Cognitive Assessment (MoCA)-Arabic version	No association found
Blanquisco et al., 2017	Philippine	Cross-sectional study	Population(s) Type 2 diabetes Control(s) - NA	Numbers: 179 (With MCI – $n = 60$; Without MCI – $n = 73$) Mean Age: 67 ± 4.8 yrs. Male: 40 (29.1%) Diabetes type: 179 (100%) T2 Diabetes duration (IQR) 12 ± 12 yrs. DRLECs: PN: $n = 22$ (16.5%) PAD: NR DFU History: NR DFU: NR AMP: NR Other: NR	Peripheral neuropathy (PN)	MoCA – Philippine version	No association found
Brismar et al., 2007	Sweden	Cross-sectional study	Population(s) Type 1 diabetes Control(s) - NA	Numbers: 150 Mean Age: 43 ± 7.8 yrs. Male: 44.0% Diabetes type: $n = 150$ (100%) T1 Diabetes duration – 26.6 ± 11.4 yrs. DRLECs: PN – Neurological impairment assessment (NIA score) > 7 (70%) PAD: NR DFU History: NR DFU: NR AMP: NR Other: NR	NA	The 10 cognitive sub-domains domains and global cognition score	Correlation found [Neurological impairment assessment (NIA - PN) vs. Cognition scores]

Table 1 (continued)

Reference (Author/ Year)	Study setting	Study design	Population(s) control(s) of interest	Population Charecteristics	Exposure(s)	Outcome(s) of interest reported	Main findings – Cognition changes with/without DRLECs
de Bresser et al., 2010	Netherland	Not reported (NR) (Cohort study with 4-year follow-up)	Population(s) Type 2 diabetes Control(s) - NA	Numbers: 68 Mean Age: 65.6 ± 5.6 yrs. Male: 32 (47.0%) Diabetes type: 68 (100%) T2 DRLECs: PN = 24 (36%) PAD: NR DFU History: NR DFU: NR AMP: NR Other: NR	PN	Composite cognition score: 11 verbal and nonverbal tasks that cover five cognitive sub-domains	No association found at baseline & No difference found between baseline & follow-up.
Dejgaard et al., 1991	Denmark	NR (Case-control study)	Population(s) Type 1 diabetes (Long duration with PN vs. Short duration without PN) Control(s) - Healthy non-diabetes subjects	Numbers: 159 Ca: LD – 20 SD – 19 Co: 120 Mean Age: Ca: LD – 44.0 ± 9.0 yrs. SD – 23.0 ± 8.0 yrs. p = NR Co: NR Male: Ca: NR for both LD and SD but was reported as sex-matched Co: NR Diabetes type: Ca: LD – 20 (100%) T1 SD – 19 (100%) T1 Diabetes duration Ca: LD – 26.0 ± 9.0 yrs. SD – 2.0 ± 2.0 yrs. DRLECs: (Ca only reported) PN – Ca: LD = 20 (100%) SD = 0 PAD: NR DFU History: NR DFU: NR AMP: NR Other: NR	PN	17 Neuropsychological examination for intelligence and cognition	Association found

Table 1 (continued)

Reference (Author/ Year)	Study setting	Study design	Population(s) control(s) of interest	Population Charecteristics	Exposure(s)	Outcome(s) of interest reported	Main findings – Cognition changes with/without DRLECs
Ding et al., 2019	China	Case-control study	Population(s) Type 1 diabetes Control(s) - Healthy volunteers	Numbers: 118 Ca: 70 Co: 48 Mean Age: Ca: 32.1 ± 9.5 yrs. Co: 31.5 ± 7.1 yrs. $p = 0.108$ Male: Ca: 37 (52.9%) Co: 25 (52.1%) $p = 0.934$ Diabetes type: Ca: 70 (100%) T1 Co: 0 DRLECs: (Ca) PN = NR PAD: NR DFU History: NR DFU: NR AMP: NR Other: NR	NA	Mini-Mental State Examination (MMSE) and MoCA	Association found nerve conduction velocity (NCV) of Sural Nerves for PN and cognitive impairment
El-Tamawy et al., 2022	Egypt	Case-control study	Population: People with T 2 diabetes Control(s): Age, sex and education level matched people with T2 diabetes without DPN	Numbers: 40 Ca: 20 Co: 20 Mean Age: Ca: NR Co: NR p = NR Male: Ca: 11 (55.0%) Co: 13 (65.0%) $p > 0.05$ Diabetes type: Ca: 20 (100%) T2 Co: 20 (100%) T2 DRLECs: Ca PN – 20 (100%) PAD: NR DFU History: NR DFU: Excluded AMP: Excluded Other: NR	DPN	RehaCom procedure	Difference found

Table 1 (continued)

Reference (Author/ Year)	Study setting	Study design	Population(s) control(s) of interest	Population Charecteristics	Exposure(s)	Outcome(s) of interest reported	Main findings – Cognition changes with/without DRLECs
Moreira et al., 2015	Brazil	Case-control study	Population: People with T 2 diabetes Control(s): Age, sex and education level matched healthy cohort	Numbers: 148 Ca: 94 (DPN^+ – 45/ DPN^- – 48) Co: 54 Median Age: Ca: 65.8 (61–84) yrs. Co: 66.4 (60–75) yrs. $p = 0.210$ Male: Ca: 2 (3.7%) Co: 7 (7.4%) $p = 0.480$ Diabetes type: Ca: 94 (100%) T2 Co: 0 DRLECs: Ca PN – 45 (47.8%) - PAD: NR DFU History: NR DFU: NR AMP: NR Other: NR	DPN	MMSE - Portuguese Version. Trail marker test - TMT (A & B) Verbal Fluency Test (VFT - Animals)	No difference found

Table 1 (continued)

Reference (Author/ Year)	Study setting	Study design	Population(s) control(s) of interest	Population Charecteristics	Exposure(s)	Outcome(s) of interest reported	Main findings – Cognition changes with/without DRLECs
Natovich et al., 2016	Israel	Case-control study	Population: People with T2 diabetes Control(s): Sex and duration of diabetes matched people with T2 diabetes without DFUs	Numbers: 194 Ca: 99 Co: 95 Mean Age: Ca: 58.0 ± 6.9 yrs. Co: 61.3 ± 7.0 yrs. $p < 0.001$ Male: Ca: 76 (77%) Co: 76 (80%) $p > 0.05$ Diabetes type: Ca: 99 (100%) T2 Co: 95 (100%) T2 DRLECs: PN – Ca – 88.9% Co – 15.8% PAD: NR DFU History: NR DFU: Ca – 100% Co – 0% AMP: NR Other: Macrovascular - Ca – 88.9% Co – 51.6%	DFU	Computerised neuropsychological battery of tests (NeuroTrax) and paper-and-pencil tests GCS (Global cognitive score)	Difference found

Table 1 (continued)

Reference (Author/ Year)	Study setting	Study design	Population(s) control(s) of interest	Population Charecteristics	Exposure(s)	Outcome(s) of interest reported	Main findings – Cognition changes with/without DRLECs
Perlmuter et al., 1984	America	Cross-sectional study	Population: People with T2 diabetes Control(s): People without diabetes with normal fasting glucose, normal random blood sugar and normal HbA1c levels	Numbers: 178 Ca: 140 Co: 38 Mean Age: Ca: 64.3 ± 5.4 Co: 63.1 ± 5.2 Male: Ca: 54% Co: 43% Diabetes type: Ca: 140 (100%) T2 Co: 0 DRLECs: PN - NR PAD: NR DFU History: NR DFU: NR AMP: NR Other: NR	NR	Serial Learning Task Digit Span Test	Correlation found (Percentage words correct) vs. PN
Roman de et al., 2013	Belgium	Cross-sectional study	Population: People with T2 diabetes (including with and without PN) Control(s): Age and sex-matched healthy older adults (without T2 diabetes)	Numbers: 101 Ca: 56 (PN^+= 28; PN^-= 28) Co: 45 Mean Age: Ca: PN^+= 74.8 ± 7.5 yrs. PN^- = 74.1 ± 8.2 yrs. Co: 71.3 ± 8.1 yrs. $p > 0.05$ Male: Ca: PN^+ – 15 (53.6%) PN^- – 10 (35.7%) Co: 20 (44.4%) $p > 0.05$ Diabetes type: Ca: 101 (100%) T2 Co: 0 DRLECs: Ca PN – 28 (50%) PAD: NR DFU History: NR DFU: NR AMP: NR Other: NR	PN	MMSE The clock drawing test (CDT) MMSE-CDT	Difference found

Table 1 (continued)

Reference (Author/ Year)	Study setting	Study design	Population(s) control(s) of interest	Population Charecteristics	Exposure(s)	Outcome(s) of interest reported	Main findings – Cognition changes with/without DRLECs
Zhang et al., 2021	China	Case-control study	Population: People with T2 diabetes Control(s): Demographically matched healthy control	Numbers: 108 Ca: 67 (T2_C: 37; T2_NC: 30) Co: 41 Mean Age: Ca: T2_C: 53.8 ± 1.1 yrs. T2_NC: 55.0 ± 1.0 yrs. Co: 53.9 ± 0.8 yrs. $p = 0.467$ Male: Ca: T2_C: 19 (51%) T2_NC: 17 (56%) Co: 22 (53%) $p = 0.442$ Diabetes type: Ca: 67 (100%) T2 Co: 0 DRLECs: Ca PN – T2_C: 37 (100%) PAD: NR DFU History: NR DFU: NR AMP: NR Other: NR	With and without diabetes-related Complications (PN)	MMSE MoCA CDT TMT	Difference found

Table 1 (continued)

Reference (Author/ Year)	Study setting	Study design	Population(s) control(s) of interest	Population Charecteristics	Exposure(s)	Outcome(s) of interest reported	Main findings – Cognition changes with/without DRLECs
Zhao et al., 2021	China	Case-control study	Population: People with T 2 diabetes Control(s): Age and sex-matched healthy control	Numbers: 106 Ca: 66 (DPN^+= 29; DPN^-= 37) Co: 40 Mean Age: Ca: DPN^+= 56.7 ± 11.3 yrs. DPN^- = 56.1 ± 9.4 yrs. Co: 52.4 ± 1.3 yrs. $p > 0.05$ Male: Ca: 19 (46.9%) Co: 31 (47.5%) $p > 0.05$ Diabetes type: Ca: 101 (100%) T2 Co: 0 DRLECs: Ca PN: 29 (100%) PAD: NR DFU History: NR DFU: NR AMP: NR Other: NR	DPN	MMSE	No difference found

AMP – Amputation Ca – Cases CDT - Clock drawing test, Co – Controls Diabetic foot, DFU - Diabetic foot ulcer, DPN - Diabetic polyneuropathy, DRLECs - Diabetes-related lower extremity complications, LD - Long duration, MMSE - Mini-mental state examination, MoCA - Montreal Cognitive Assessment, NA – Not applicable, NIA - Neurological impairment assessment, NR – Not reported, NVC - Nerve conduction velocity, PAD - Peripheral arterial disease, PN – Peripheral neuropathy, SD - Short duration, T1 - Type I diabetes, T2 - Type 2 diabetes, T2_C - Type two diabetes with complications, T2_NC - Type two diabetes without complications, TMT - Trail marker test, VFT - Verbal fluency test, GCS – Global cognitive score,

Table 2 Quality assessment of included studies, as scored using the mixed Method Appraisal Tool

No	Author & Year	MMAT – 2018 Version[¶]							
		4.1	4.2	4.3	4.4	4.5	Score	%	Rating (29)
1.	Althubaity et al., 2011	0	1	1	0	1	3	60	Medium
2.	Blanquisco et al., 2017	1	1	1	1	1	5	100	High
3.	Brismar et al., 2007	1	1	1	0	1	4	80	Medium
4.	de Bresser et al., 2010	0	1	1	1	1	4	80	Medium
5.	Dejgaard et al., 1991	0	1	1	0	1	3	60	Medium
6.	Ding et al., 2019	0	1	1	0	1	3	60	Medium
7.	El-Tamawy et al., 2016	0	0	1	0	1	2	40	Low
8.	Moreira et al., 2015	0	1	1	1	1	4	80	Medium
9.	Natovich et al., 2016	0	1	1	0	1	3	60	Medium
10.	Perlmuter et al., 1984	0	1	1	0	1	3	60	Medium
11.	Roman de et al., 2013	0	1	1	0	1	3	60	Medium
12.	Zhang et al., 2021	0	1	1	0	1	3	60	Medium
13.	Zhao et al., 2021	0	1	1	0	1	3	60	Medium
Total		2 (15%)	12 (92%)	13 (100%)	3 (23%)	13 (100%)			

0: No or can't tell; 1: Yes

[¶]**4.1** - Is the sampling strategy relevant to addressing the research question? **4.2** - Is the sample representative of the target population? **4.3** - Are the measurements appropriate? **4.4** - Is the risk of nonresponse bias low? **4.5** - Is the statistical analysis appropriate to answer the research question?

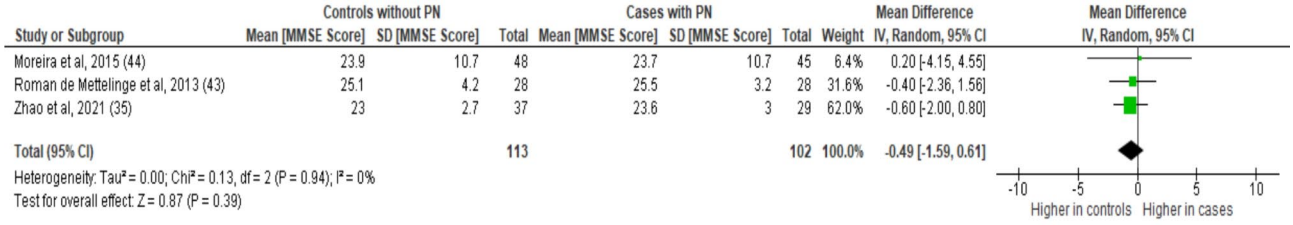

Fig. 2 Forest plot for subgroup meta-analysis[¶] - Differences in cognition between people with diabetes with peripheral neuropathy (cases) compared to people with diabetes without peripheral neuropathy (controls).MMSE: Mini-Mental State Examination; SD: Standard deviation. Higher the cognitive score implies better cognition; Median (IQR) MMSE score of Moreira et al., 2015 converted to Mean (SD) prior to meta-analysis

examined DRLECs of such studies [36, 41–43] (Table 1; Supplementary Table 2).

Eight of the 13 included studies reported cognitive sub-domain scores [9, 34, 36–39, 43, 44]. Three studies reported a significant decrease in executive function [9, 34, 43], two studies reported a significant decrease in memory and reaction time [9, 37], and one study reported a significant decrease in attention, psychomotor speed, and verbal fluency [9] in people with DRLECs (PN, PAD, DFUs or their combinations) compared to people without DRLECs. Two other studies reported significant associations in the sub-domains of memory [36] and psychomotor speed [38], visual perception [38] and visual-spatial ability [38] in people with DRELCs. However, another two studies reported no significant differences in verbal fluency [39, 44], and one study reported no significant differences in memory [39] and one study reported no significant differences in executive functions [44] among people with diabetes with and without PN.

Meta-analysis

Three studies were eligible for inclusion in a meta-analysis, as they all investigated the same populations: participants with type 2 diabetes, cases with DRLEC exposure (PN), controls with no PN; and measured the same outcome (cognition using the mini-mental state examination (MMSE). This meta-analysis included three case-control studies [35, 43, 44], including 215 participants, and found there was no significant difference in cognition in people with diabetes without PN compared to people with diabetes with PN (mean difference (MD) -0.49 MMSE score; 95% CI: -1.59–0.61; $p=0.39$; $N=3$ studies; $n=215$; Fig. 2). Leave-one-out sensitivity analyses further confirmed that the results were remained non-significant, MD range from −0.53 (95% CI: -1.85–0.80)] to -0.30 (95% CI: -2.08–1.48) [35, 43, 44]. (Supplementary Fig. 1). Finally, the funnel plot suggests no major evidence for publication bias (Fig. 3).

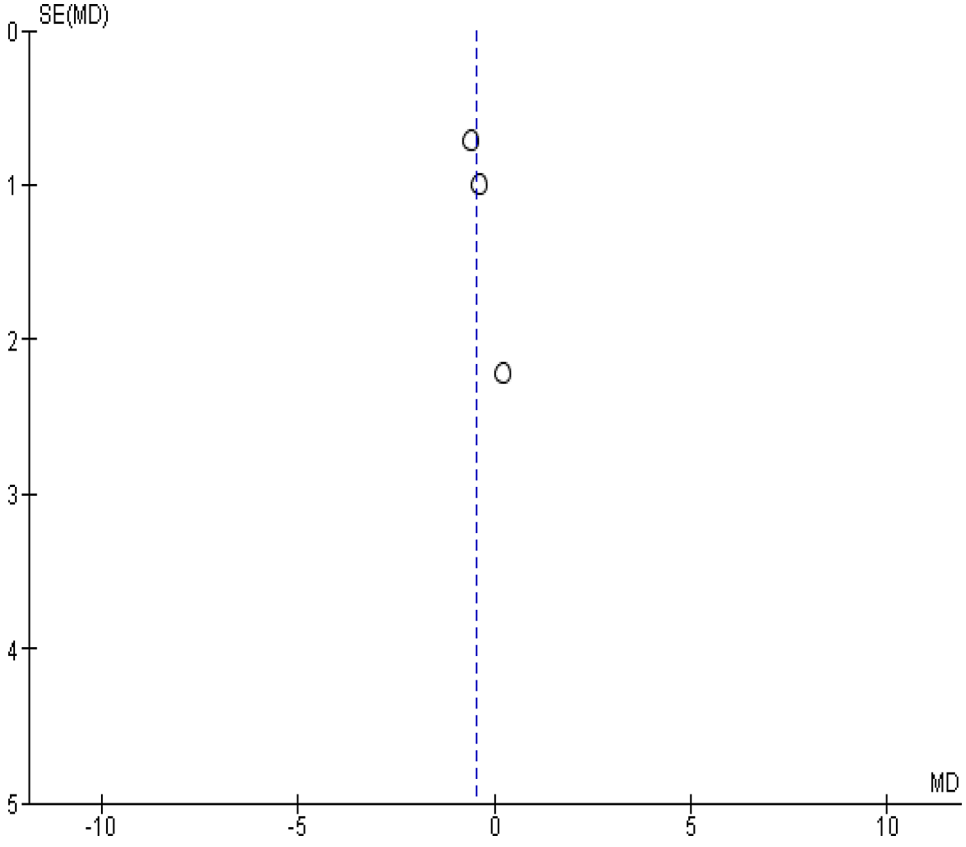

Fig. 3 Funnel plot for publication bias analysis for subgroup meta-analysis on differences in cognition between people with diabetes with neuropathy compared to people with diabetes without neuropathy

Discussion

This is the first systematic review to our knowledge that has investigated cognition in people with diabetes and DRLECs, compared to those without DRLECs. Of the 13 studies identified, eight found a significant relationship between impaired cognition and people with DRLECs, while the other five studies did not find any differences or associations. With regard to the methodological quality of the included studies, eleven were medium and one each high and low methodological quality (Table 1). Eleven of the included studies investigated PN as the DRLEC exposure of interest with the remainder investigating DFU or amputations.

We found only two of the 13 studies investigated DRLECs other than PN, such as DFU and amputation, and these studies also reported conflicting results [9, 41]. The first of these, a case-control study, reported a significant difference between people with diabetes with DFU and people with diabetes without DFUs, across all cognitive sub-domains [9]. The other, a cross-sectional study, did not find any association between cognition and DRLECs (DFU and amputation), however, the difference in cognition scores in those with and without DRLECs in people with type 2 diabetes were not reported [41]. Furthermore, the inconsistent findings found in our review are potentially due to differences in methodology used between included studies, including investigating different diabetes populations, different DRLEC exposures (PN, PAD, DFU, amputation and their combinations) and using different cognition outcome measures. Moreover, the presence of more severe DRLECs such as DFU, infection and amputation (usually accompanied by more severe PN), may have a stronger relationship with cognition compared to people with diabetes with PN only. However, this hypothesis needs further investigation to confirm.

We found only three studies that were similar in methodology and eligible for inclusion in a meta-analysis. This meta-analysis found no significant difference between people with diabetes with and without PN and this difference was not greater than 1.0 MMSE, which would be required to be considered a clinically meaningful cognitive difference [45]. However, this finding was in contrast to a recent meta-analysis that reported significant cognitive impairment in people with type 2 diabetes with PN compared to those without PN [19]. The differences in findings between our review and the recent meta-analysis may be because, unlike our review, the recent meta-analysis did not exclude or control for the effect of depression, dementia, alcoholism and other conditions that are

known to impact cognition and potentially confound the relationship between DRLECs and cognition [19].

The potential mechanisms for cognitive change in people with diabetes are suggested to arise from diabetes, and potentially its complications, causing systemic inflammation [17] and with that increased inflammatory marker concentration in the blood [15, 16], vascular and neurological degeneration, and altered insulin signalling [18, 19]. However, the relationship between cognitive changes and DRLECs is potentially observed as bi-directional, with cognitive changes in people with diabetes possibly contributing to DRLECs, or increased systemic inflammation and DRLECs potentially related to cognitive changes [46]. The present systematic review found that cognitive changes were observed in people with DRLECs in the sub-domains of executive function [9, 34, 43] memory [9, 37], reaction time [9, 37] attention [9], psychomotor speed [9], and verbal fluency [9]. Similarly, recent studies revealed that cognitive changes due to diabetes and its complications may affect memory, executive function, and psychomotor speed. Furthermore, these cognitive changes may occur regardless of the presence of dementia in people with diabetes [22, 23, 47]. Thus, cognitive impairments in people with diabetes may lead to reducing instrumental activities of daily living [48] and eventually may impact self-care management and treatments in people with diabetes and may lead to DRLECs [23, 49]. However, as we excluded studies the did not control for dementia, depression, and other conditions, known to impact cognition, it is more likely that any relationship we found between cognition and DRLECs, is that people with DRLECs and potentially more severe systemic inflammation, may lead to cognitive changes. However, future longitudinal studies are required to identify if this is the case.

In general, different cognitive assessment tools, such as MMSE [50], MoCA [51], Modified Mini-Mental Exam (3MS) [52] and Addenbrooke's cognitive examination -III (ACE-III) [53], have been designed to determine subtly different cognitive screening outcomes such as screening of global cognition (MMSE), mild cognitive impairment (MoCA), brief screening of cognition (3MS) and differential diagnosis (ACE-III) [54]. Thus, the use of these different cognitive assessment tools in previous studies investigating cognition in people with diabetes may have also led to different or inconsistent results. Cognitive assessment tools need to be valid, reliable and specific to the population concerned and as such, some of these tools may be too broad or lack the sensitivity to identify cognitive changes in specific populations [54], such as people with DRLECs. As our findings are inconsistent and indicate mostly mild or no cognitive impairments in people with DRLECs [8], we suggest, using a cognitive assessment tool that can detect mild cognitive impairment (i.e. MoCA) might be a more appropriate tool to screen for cognitive impairment in people with DRLECs in future.

However, cognition is also known to be related to several factors that may confound with cognition, such as gender, age and education level [55–57], blood pressure, cholesterol level, presence of carotid plaque [58–62], depression [27, 63], dementia, alcoholism and physical activity and sedentary lifestyle [64–66]. Hence, investigating the true impact on cognition of specific conditions such as DRLECs requires either exclusion or adjustment for such confounders in appropriately powered future samples to evaluate the actual effect size. Whilst, the studies included in this review excluded most conditions known to impact cognition, such as depression, dementia and alcoholism, they did not consider the impact of other factors that can also confound cognition, such as cardiovascular risk factors and physical activity. Hence, properly powered and well-controlled studies with appropriately defined DRLEC exposure and control groups that enable appropriate adjustment for a wide range of potential confounders are recommended in future when investigating cognition in people with DRLECs.

Some limitations of this systematic review should be acknowledged. First, our search strings may not have identified all eligible studies (i.e. – published in non-English) and we did not include grey literature for this review. However, we note high agreement between authors in the screening process which should have minimised the likelihood of missing any eligible studies within the records identified by our search and reference lists of eligible studies. However, there were relatively few studies included in this study to investigate cognition with and without DRLECs, along with a number of different cognitive assessment tools leading to conflicting findings. Second, studies selected for the systematic review have identified considerable heterogenicity, particularly in clinical and methodological heterogeneities. Further, clinical heterogenicity may be due to the variability of outcome measures (i.e. using different cognitive assessment tools for screening cognition) while methodological heterogenicity may be due to the different study designs that may affect the precise conclusion of the findings. Third, there were only three studies eligible for meta-analysis for the current study and therefore interpreted results may have some limitations due to lack of included studies. Fourth, we used the broader MMAT tool to assess methodological quality, rather than more specific tools designed to assess the methodological quality of specific study designs. However, we note the MMAT tool is widely used for such reviews of included studies with a mix of study designs. Fifth, whilst, the accuracy of data extraction of included studies was checked by a second author for half of the included studies, this was not

done for the remainder of included studies and may have resulted in data extraction errors. However, we suggest this would be minimal as we ensured the data extraction process had a high agreement in the first half of included studies before the author extracted data for the second half of included studies. Sixth, It's possible that some participants in the studies may have had depressive symptoms, even if they were not diagnosed or did not have sufficient scores to detect depressive symptoms at the time of data collection. Lastly, the methodological quality of nearly all included studies was considered to be either low or medium and sample sizes small which may have impacted our inconsistent overall findings and our specific meta-analyses findings.

Conclusions

In conclusion, we found relatively few studies that had examined cognition and DRLECs and furthermore, collectively these studies had weak and conflicting findings on cognitive changes in people with diabetes with, and without, DRLECs. Hence, larger more robust studies are required to shed more light on cognition in people with DRLECs to determine if cognition is further impaired in people with DRLECs in comparison to those with diabetes without DRLECs. Such investigations are important to determine if DRLECs specifically may be related to the deterioration of cognition and if any specific deterioration also impacts the self-care and clinical outcomes of people with DLRECs.

Abbreviations

3MS	Modified mini-mental exam
ACE	III-Addenbrooke's cognitive examination-III
CI	Confidence Intervals
DFU	Diabetes-related Foot Ulcer
DRLECs	Diabetes-related Lower Extremity Complications
MD	Mean Differences
MMAT	Mixed Method Appraisal Tool
MMSE	Mini-Mental State Examination
MoCA	Montreal cognitive assessment
PAD	Peripheral Artery Disease
PN	Peripheral Neuropathy
PRISMA	Preferred Reporting Item for Systematic Reviews And Meta-Analyses
RR	Risk Ratio
SD	Standard Deviations
TMT	Trail marker test

Supplementary Information

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Supplementary Material 1

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Author contributions

NK contributed to the conception, design of the study, database search, title and abstract search, full-text screening, quality assessment, data extraction, data analysis, interpretation and manuscript drafting. KF contributed to the conception, design of the study, database search, reviewing disagreement of title and abstract search, full-text screening and quality assessment, interpretation and critically reviewed the manuscript. CP contributed to the conception, design of the study, title and abstract search, interpretation and critically reviewed the manuscript. PAL contributed to the conception, design of the study, data extraction, data analysis, interpretation and critically reviewed the manuscript. CK contributed to the conception, design of the study, full-text screening and critically reviewed the manuscript. PC contributed to the conception, design of the study, quality assessment and critically reviewed the manuscript. MM contributed to the conception, design of the study, interpretation and critically reviewed the manuscript.

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Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Not necessary.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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