Title: Cognitive frailty in older adults with diabetes: prevalence and risk factors.

Authors: Mohamed Mansoor[1], Joanna Harrison[2], James Hill[2]

[1] Guy's and St Thomas' NHS Foundation Trust

[2] Synthesis, Economic Evaluation and Decision Science (SEEDS) group, University of Central Lancashire

Abstract

In older adults living with diabetes, there is a higher prevalence of frailty and a greater risk of cognitive impairment. Cognitive frailty is defined by the presence of both and is associated with an increased risk of mortality. A systematic review was undertaken to estimate the prevalence of cognitive frailty in community-dwelling older adults living with diabetes and associated risk factors. This commentary critically appraises the review and explores the implications of the findings for community practice.

Acknowledgement/Disclaimer

This research was partly-funded by the National Institute for Health and Care Research Applied Research Collaboration North-West Coast (NIHR ARC NWC). The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, or the Department of Health and Social Care.

Commentary on:

Lyu Q, Guan CX, Kong LN, Zhu JL. 2023. Prevalence and risk factors of cognitive frailty in community-dwelling older adults with diabetes: A systematic review and meta-analysis. Diabet Med. 40(1):e14935.

Key Points

- The pooled prevalence of cognitive frailty among community-dwelling older adults with diabetes was estimated at 11%, indicating a substantial burden of this condition.
- The risk factors of depression, HbA1c (average blood glucose level) ≥8.5%, age over 75 years, and sleep duration <5 hours were associated with cognitive frailty.

- To support timely identification of cognitive frailty and treatment in the community, integrated mental health assessments, optimisation of glycaemic control, and promoting good sleep hygiene may be beneficial.
- There is a need for a comprehensive geriatric assessment for cognitive frailty in the community.

Introduction

In the UK, 4.3 million people live with diabetes and a further 850,000 could be living with the condition unaware (Diabetes UK 2023). Type 2 diabetes mellitus is a chronic metabolic disorder, characterised by hyperglycaemia, and associated with greater risks of heart disease, stroke, peripheral neuropathy, renal disease, blindness and amputation (Hurtado & Vella, 2019). Middle-aged and older adults with diabetes have a higher prevalence of frailty (Hanlon et al. 2018), an increased vulnerability associated with ageing and a decline in the body's physical and psychological reserves (Turner 2014). Both diabetes and frailty are independently associated with low self-rated health, depressive symptoms and low quality of life (O'Donovan et al. 2021).

In addition to physical frailty, cognitive impairment is increasingly recognised as a potential complication of diabetes, which may reflect a direct effect on the brain of hyperglycaemia or the effects of associated comorbidities such as hypertension (Luchsinger et al. 2018). Diabetes that is poorly controlled in older adults is also associated with double the risk of cognitive impairment-no dementia (CIND) and triple the risk of CIND progressing to dementia (Dove et al. 2021).

Cognitive frailty is a clinical condition defined by the presence of both mild cognitive impairment and physical frailty (Yoshiura et al. 2022). Older adults with cognitive frailty are at higher risk of adverse health outcomes including death, disability, hospitalisation and incident dementia (Sugimoto et al. 2022). In older people with diabetes, cognitive frailty is also associated with an increased risk of

mortality, greater than from either physical frailty or cognitive impairment alone (Abdelhafiz & Sinclair 2019). A systematic review and meta-analysis (Lyu et al. 2023) aimed to identify the prevalence of cognitive frailty and associated risk factors in community-dwelling older adults with diabetes.

Aim of commentary

This commentary aims to critically appraise the methods used within the review (Lyu et al. 2023) and expand upon the findings in the context of clinical practice and further research.

Methods

This systematic review and meta-analysis used a specific multi-database search from date of inception until February 10th, 2022. Additional hand searching was undertaken of included studies and relevant systematic reviews. Only cross-sectional, longitudinal, and cohort studies which reported the prevalence of cognitive frailty in community dwelling older adults (60+ years), with a diagnosis of diabetes were included. Screening of included studies and assessment of quality were carried out by two reviewers independently. It was indicated that two reviewers carried out data-extraction, but it was not stipulated that this was independent. A random effects meta-analysis was used to estimate the prevalence rates for cognitive frailty. Individual moderating risk factors were assessed using a pooled odds ratio (OR). Heterogeneity was assessed using the I^2 statistic. Subgroup and meta-regression was undertaken to explore causes of heterogeneity. Publication bias was examined using visual inspection of funnel plot and relevant statistical tests.

Results

After duplicate removal, 1295 citations were identified, of which 15 full papers were included after screening. Studies included 6391 community dwelling older adults with diabetes and took place in China (n= 6), Italy (n=1), Japan (n=2), Malaysia (n=1), Mexico (n=1), Singapore (n=2) and the United States (n=2). Most included studies were deemed to be of high quality (n=11) and the remaining four studies were classified to be of moderate quality.

The pooled prevalence of cognitive frailty within community dwelling older adults with diabetes was 11% (95% confidence interval [Cl, 7.9% to 14%). There was statistically significant heterogeneity across studies (I^2 = 95%). Using a take one away analysis, there was no significant difference from the removal of any single study for the estimated prevalence of cognitive frailty. There was no evidence of publication bias for both Eggers and Becks tests. When assessed using either subgroup analysis or meta-regression, there was no evidence of significant association for the factors of study design, sex, frailty instrument, cognition instrument, geographic region and study quality.

Exploration of the risk factors of cognitive frailty in community dwelling adults with diabetes showed an increased odds for those who: have depression (OR 3.18, 95% CI: 1.99 to 5.07), HbA1c (average blood glucose level) of ≥8.5% (OR 2.13, 95% CI: 1.13 to 4.01), are aged >75 years (OR 2.10, 95% CI: 1.15 to 3.82), or have sleep duration <5h (OR 1.98, 95% CI: 1.08 to 3.61). Furthermore, there was a reduced odds of cognitive frailty for individuals who exercised (OR = 0.56, 95% CI: 0.36 to 0.88). There was no evidence of increased odds of cognitive frailty for sex, educational level, unmarried status, living alone, BMI of ≥24kg/m^2, disease duration greater than 10 years, HbA1c <7.0%, smoking and night sleep duration >8h.

Commentary

Using the Joanna Briggs critical appraisal checklist for systematic reviews and research syntheses (JBI 2017), 10 out of 11 criteria were judged to be satisfactory for this review. In the criterion for data extraction, it was unclear if the two reviewers undertook this task independently. The authors also note that due to limitations within the included study methodology, results should be treated cautiously due to the high heterogeneity between studies, e.g. several assessment tools for cognitive frailty were used across studies. Furthermore, a limited number of studies reported risk factors in a uniform format and some studies failed to specify between type 1 or type 2 diabetes or whether

participants were on medications. Overall however, the systematic review is deemed to provide a comprehensive synthesis of the available evidence.

1. Is the review question clearly and explicitly stated?	Yes.
2. Were the inclusion criteria appropriate for the review question?	Yes.
3. Was the search strategy appropriate?	Yes, the search was conducted using Medical Subject Headings (MeSH) and free terms including frail, cognition and diabetes. Manual searching of relevant studies was also undertaken.
4. Were the sources and resources used to search for studies adequate?	Yes, systematic searches of: PubMed, Web of Science, Cochrane Library, Embase, Cumulative Index of Nursing and Allied Health, Proquest, China National Knowledge Infrastructure and China Biology Medicine.
5. Were the criteria for appraising studies appropriate?	Yes, the quality of included studies was assessed using Hoy's tool for assessing risk of bias in prevalence studies (Hoy et al. 2012).
6. Was critical appraisal carried out by two or more reviewers independently?	Yes, quality assessment was undertaken by two independent investigators and disagreements settled by discussion.
7. Were there methods to minimize errors in data extraction?	Unclear, data extraction by two reviewers is stated but it is unclear if this was undertaken independently.
8. Were the methods used to combine studies appropriate?	Yes, a random-effects model was used to combine data because of the heterogeneity present.
9. Was the likelihood of publication biased assessed?	Yes, publication bias was assessed using funnel plot inspection, Begg's test, and Egger's test.
10. Were recommendations for policy and/or practice supported by the reported data?	Yes, recommendations for screening of cognitive frailty, standardisation of assessments, and targeted interventions were supported by the data.
11. Were the specific directives for new research appropriate?	Yes, recommendations were made for future high-quality study to explore risk factors for cognitive frailty.

The pooled prevalence of cognitive frailty was estimated at 11%, highlighting the substantial burden of this condition within the older adult population with diabetes. It has previously been identified that

cognitive frailty is a significant predictor of dementia and mortality in older adults living in the community and yet there is no uniform assessment available to evaluate this syndrome (Bu et al. 2021). Evidence therefore suggests there is a need for a comprehensive and multi-dimensional geriatric assessment that helps identify cognitive frailty in vulnerable older adults in both clinical and community settings (Sugimoto et al. 2022). In the absence of a gold standard, community practitioners can utilize validated tools to assess for cognitive impairment such as the Mini-Mental State Examination (MMSE) (Creavin et al. 2016) or the Montreal Cognitive Assessment (MoCA) (Wei et al. 2022) in combination with a measure of physical frailty such as the FRAIL scale (Thompson et al. 2020), the Clinical Frailty Scale (Rockwood et al. 2020) or Fried's Frailty Phenotype Approach (Fried et al. 2001). Identifying cognitive frailty early, besides prevention and intervention measures, is recommended to reduce the occurrence of adverse outcomes caused by cognitive frailty (Bu et al. 2021).

Several factors were found to be associated with an increased risk of cognitive frailty. Individuals with depression, HbA1c ≥8.5%, age over 75 years, and night sleep duration <5 hours exhibited higher odds of cognitive frailty. These findings highlight the importance of addressing comorbidities in the community setting such as depression and optimizing glycaemic control. Given the association between depression and cognitive frailty in older adults with diabetes, it may be beneficial to integrate mental health assessments routinely through standardized depression scales such as the Patient Health Questionnaire-9 (Levis et al. 2019) or the 15 item Geriatric Depression Scale (Shin et al. 2019).

The association between HbA1c levels ≥8.5% and cognitive frailty underscores the importance of glycemic control in mitigating the risk of cognitive decline. Diabetic patients over 50 years old with uncontrolled blood glucose levels are at higher risk of cognitive decline then individuals with controlled blood glucose levels (Koh et al. 2022). As such, community professionals should aim to educate patients about the relevance and importance of glycaemic control and testing as there is a positive association between HbA1c self-awareness and blood glucose control (Almutairi et al, 2022).

The National Institute for Health and Care Excellence guidelines (NICE 2022) recommends measuring HBA1c in adults with type 2 diabetes every 3-6 months until stable and subsequently every 6 months. Additionally, they recommend targets of 6.5% for individuals whose diabetes is managed by lifestyle/diet and 7.0% for those who take medication associated with hypoglycaemia.

Older adults with diabetes and those with shorter sleep durations also demonstrated increased odds of cognitive frailty. There is a bidirectional relationship between mild cognitive impairment and sleep disorders (Randhi et al. 2023). In addition to increased odds of cognitive frailty, later sleep timing and greater sleep variability may also be associated with other adverse health outcomes including risk to cardiometabolic health (Chaput et al. 2020). There is a need to identify sleep disorders in older adults as soon as possible and not just regard them as a sign of aging (Randhi et al. 2023). To address difficulties with sleeping, patients in the community could be supported through information on maintaining good sleep hygiene, the importance of sleep (Randhi et al. 2023), and keeping sleep diaries or questionnaires to be more aware of sleep habits and sleep quality (Ibanez et al. 2018).

The review also found that individuals who exercised showed a decreased odds of cognitive frailty, although it was unclear whether the act of exercising provided protection or some aspect of a physical lifestyle. The World Health Organisation (WHO) recommend that older adults aged 65 years and above should do at least 150 minutes of moderate intensity aerobic physical activity throughout the week (WHO 2010). This includes recreational, leisure, transport, occupational, household or exercise activity. A higher level of physical activity is also associated with a lower odds of frailty in community dwelling older adults (Zhao et al. 2022). Furthermore, physical exercise for community dwelling older adults with frailty, promotes benefits in global cognition and mental flexibility (Rossi et al. 2021). Promotion of the benefits of physical activity to those in the community is therefore supported. NICE guidance suggests that tailored exercise and physical activity programmes of moderate intensity, including walking schemes, are recommended in the community setting to promote mental well-being in the over 65s (NICE 2008).

Future research would benefit from a focus on longitudinal studies that explore the trajectory of cognitive frailty and its relationship with diabetes management strategies. Such studies would enable the identification of temporal associations and causal relationships between cognitive frailty and risk factors such as glycaemic control, depression, sleep duration, and exercise, helping to inform targeted interventions. A focus on developing a uniform assessment for cognitive frailty would also be welcomed.

CPD reflective questions

- Which assessments for cognitive impairment and frailty could be integrated into practice?
- How could patient self-awareness of glycaemic control be improved?
- Are there any exercise or physical activity groups in the local area for older adults?

References

Abdelhafiz AH, Sinclair AJ. 2019. Cognitive Frailty in Older People with Type 2 Diabetes Mellitus: the Central Role of Hypoglycaemia and the Need for Prevention. Curr Diab Rep. 2019. 26;19(4):15.

Almutairi JS, Almigbal TH, Alruhaim HY, Mujammami MH, AlMogbel TA, Alshahrani AM, Al Zahrani AM, Batais MA, & Shaik SA. 2022. Self-awareness of HbA1c and its association with glycemic control among patients with type 2 diabetes: A multicenter study. Saudi Med. J. 43(3):291-300.

Bu Z, Huang A, Xue M, Li Q, Bai Y, Xu G. 2021. Cognitive frailty as a predictor of adverse outcomes among older adults: A systematic review and meta-analysis. Brain Behav. 11(1):e01926.

Chaput JP, Dutil C, Featherstone R, Ross R, Giangregorio L, Saunders TJ, Janssen I, Poitras VJ, Kho ME, Ross-White A, Zankar S, & Carrier J. 2020. Sleep timing, sleep consistency, and health in adults: a systematic review. Appl Physiol Nutr Metab. 45(10 (Suppl. 2):S232–S247.

Creavin ST, Wisniewski S, Noel-Storr AH, Trevelyan CM, Hampton T, Rayment D, Thom VM, Nash KJE, Elhamoui H, Milligan R, Patel AS, Tsivos DV, Wing T, Phillips E, Kellman SM, Shackleton HL, Singleton GF, Neale BE, Watton ME, Cullum S. 2016. Mini-Mental State Examination (MMSE) for the detection

of dementia in clinically unevaluated people aged 65 and over in community and primary care populations. Cochrane Database Syst. Rev. (1):CD011145.

Diabetes UK. 2023. How many people in the UK have diabetes?; [accessed July 23]. https://www.diabetes.org.uk/professionals/position-statements-reports/statistics

Dove A, Shang Y, Xu W, et al. 2021. The impact of diabetes on cognitive impairment and its progression to dementia. Alzheimers Dement.17:1769– 1778.

Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, Seeman T, Tracy R, Kop WJ, Burke G, McBurnie MA, & Cardiovascular Health Study Collaborative Research Group. 2001. Frailty in older adults: evidence for a phenotype. J. Gerontol: Series A. 56(3):M146–M157.

Hanlon P, Nicholl BI, Jani BD, et al. 2018. Frailty and pre-frailty in middle-aged and older adults and its association with multimorbidity and mortality: a prospective analysis of 493 737 UK Biobank participants. Lancet Public Health. 3:e323–e332.

Hoy D, Brooks P, Woolf A, Blyth F, March L, Bain C, Baker P, Smith E, Buchbinder R. 2012. Assessing risk of bias in prevalence studies: modification of an existing tool and evidence of interrater agreement. J Clin Epidemiol. 65(9):934-9.

Hurtado MD, & Vella A. 2019. What is type 2 diabetes?. Medicine. 47(1):10-15.

Ibáñez V, Silva J, Cauli O. A survey on sleep questionnaires and diaries. Sleep Med. 2018. 42:90-96.

Joanna Briggs Institute (JBI). 2017. Checklist for Systematic Reviews and Research Syntheses; [accessed July 2023]. https://jbi.global/sites/default/files/2019-05/JBI_Critical_Appraisal-Checklist_for_Systematic_Reviews2017_0.pdf.

Koh DH, Rho YJ, Lee SY, Kim KN, & Ju YJ. 2022. Association between Blood Glucose Control and Subjective Cognitive Decline in Korean Patients with Diabetes Aged over 50 Years. Int. J. Environ. 19(12):7267.

Levis B, Benedetti A, Thombs BD. 2019. DEPRESsion Screening Data (DEPRESSD) Collaboration. Accuracy of Patient Health Questionnaire-9 (PHQ-9) for screening to detect major depression: individual participant data meta-analysis. BMJ. 365:1476.

Luchsinger JA, Ryan C, Launer LJ. Diabetes and Cognitive Impairment. In: Cowie CC, Casagrande SS, Menke A, Cissell MA, Eberhardt MS, Meigs JB, Gregg EW, Knowler WC, Barrett-Connor E, Becker DJ,

Brancati FL, Boyko EJ, Herman WH, Howard BV, Narayan KMV, Rewers M, Fradkin JE, (eds). Diabetes in America. 3rd ed. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases (US); 2018 Aug. CHAPTER 24.

Lyu Q, Guan CX, Kong LN, Zhu JL. 2023. Prevalence and risk factors of cognitive frailty in community-dwelling older adults with diabetes: A systematic review and meta-analysis. Diabet Med. 40(1):e14935.

National Institute for Health and Care Excellence (NICE). 2008. Mental wellbeing in over 65s: occupational therapy and physical activity interventions: Public health guideline [PH16]; [accessed July 2023]. https://www.nice.org.uk/guidance/ph16/chapter/1-Recommendations

National Institute for Health and Care Excellence (NICE). 2022. Type 2 diabetes in adults: management; [accessed July 23]. https://www.nice.org.uk/guidance/ng28/chapter/Recommendations#blood-glucose-management

O'Donovan M, Sezgin D, O'Caoimh R, Liew A. 2021. The relationship between frailty and diabetes: An investigation of self-rated health, depression symptoms and quality of life in the Study of Health Aging and Retirement in Europe. Arch Gerontol Geriatr. 96:104448.

Randhi B, Gutlapalli SD, Pu J, Zaidi MF, Patel M, Atluri LM, Gonzalez NA, Sakhamuri N, Athiyaman S, Hamid P. 2023. Sleep Disorders in Mild Cognitive Impairment. Cureus. 15(3):e36202.

Rockwood K, Theou O. 2020. Using the Clinical Frailty Scale in Allocating Scarce Health Care Resources. Can Geriatr J. 23(3):210-215.

Rossi PG, Carnavale BF, Farche ACS, Ansai JH, de Andrade LP, & Takahashi ACM. 2021. Effects of physical exercise on the cognition of older adults with frailty syndrome: A systematic review and meta-analysis of randomized trials. Arch. Gerontol. 93:104322.

Shin C, Park MH, Lee SH, Ko YH, Kim YK, Han KM, Jeong HG, Han C. 2019. Usefulness of the 15-item geriatric depression scale (GDS-15) for classifying minor and major depressive disorders among community-dwelling elders. J Affect Disord. 259:370-375.

Sugimoto T, Arai H, Sakurai T. An update on cognitive frailty: Its definition, impact, associated factors and underlying mechanisms, and interventions. 2022. Geriatr Gerontol Int. 22(2):99-109.

Thompson MQ, Theou O, Tucker GR, Adams RJ, Visvanathan R. 2020. FRAIL scale: Predictive validity and diagnostic test accuracy. Australas J Ageing. 39(4):e529-e536.

Turner G. 2014. Introduction to frailty. Fit for frailty part 1. British Geriatrics Society; [accessed 2023 July]. https://www.bgs.org.uk/resources/introduction-to-frailty

Wei YC, Chen CK, Lin C, Chen PY, Hsu PC, Lin CP, Shyu YC, Huang WY. 2022. Normative Data of Mini-Mental State Examination, Montreal Cognitive Assessment, and Alzheimer's Disease Assessment Scale-Cognitive Subscale of Community-Dwelling Older Adults in Taiwan. Dement Geriatr Cogn Disord. 51(4):365-376.

Woo J, Leung J, Morley JE. 2012. Comparison of frailty indicators based on clinical phenotype and the multiple deficit approach in predicting mortality and physical limitation. J Am Geriatr Soc. 60(8):1478-1486.

World Health Organisation (WHO). 2010. Global Recommendations on Physical Activity for Health; [accessed 2023 July]. https://www.who.int/publications/i/item/9789241599979

Yoshiura K, Fukuhara R, Ishikawa T, et al. 2022. Brain structural alterations and clinical features of cognitive frailty in Japanese community-dwelling older adults: the Arao study (JPSC-AD). Sci Rep. 12: 8202.

Zhao W, Hu P, Sun W, Wu W, Zhang J, Deng H, Huang J, Ukawa S, Lu J, Tamakoshi A, Liu X. 2022. Effect of physical activity on the risk of frailty: A systematic review and meta-analysis. PLoS One. 17(12):e0278226.