THE IMPACT OF TYPE 2 DIABETES ON THE INCREASE OF FRAILTY AMONG ELDERLY: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Objectives: Type 2 diabetes is a widespread chronic condition among the elderly, and its impact on frailty is a growing concern in the context of an aging population. Understanding the association between diabetes and frailty is crucial for implementing effective preventive measures and tailored interventions to enhance the quality of life and well-being of older adults. This study aimed to investigate the association between type 2 diabetes with frailty among older populations.

Methodology: To achieve these objectives, we executed a meticulous systematic review and meta-analysis, sifting through a pool of 9311 studies, ultimately qualifying 8 for inclusion in our analysis. The assessment of these studies was conducted with the RevMan 5.3 software. We also undertook a subgroup meta-analysis, stratifying our analysis by setting, and computed the adjusted odds ratio (aOR) along with a 95% confidence interval (CI) to gauge the correlation between type 2 diabetes and frailty. Our statistical criteria for significance were established with a threshold of $p < 0.0001$.

Results: Our results demonstrated a notable elevation in the risk of frailty among elderly individuals with type 2 diabetes when contrasted with their counterparts who do not have type 2 diabetes (adjusted odds ratio [aOR] = 1.58; 95% confidence interval [CI] = 1.43 to 1.75; $p < 0.0001$).

Conclusion: In conclusion, this study provides strong evidence supporting a significant relationship between Type 2 diabetes and increasing frailty among the elderly. Early detection and effective diabetes management are crucial steps to mitigate the impact of frailty in elderly. Moreover, further studies are expected to focus on exploring targeted interventions and assessing long-term effects to enhance geriatric care and inform evidence-based policies.

Keywords: Aging population, Chronic disease, Frailty, Elderly, Type 2 diabetes

Citation: Adriani, R. B., Murti, B., & Adriana, N. P. THE IMPACT OF TYPE 2 DIABETES ON THE INCREASE OF FRAILTY AMONG ELDERLY: A Systematic Review and Meta-Analysis. Pak Heart J. 2023;56(4).

INTRODUCTION

Frailty has gained more and more attention in the past couple of decades as a distinct and significant predictor of unfavorable outcomes in older persons, regardless of their pre-existing medical illnesses. Frailty is defined by a decreased ability to recover from diverse stresses as a result of the aging-related, progressive loss in several physiological systems. According to Clegg et al. (2013), this increased state of vulnerability can lead to adverse outcomes like death, hospitalization, long-term institutionalization, falls, and increased disability. Globally, the prevalence of diabetes is rising, especially among older people. This is mainly due to longer life expectancies. Frailty is becoming a prominent and serious consequence of diabetes in the aged population (A. Sinclair et al., 2020; A. J. Sinclair et al., 2017).

When compared to elderly people without diabetes, those with diabetes have a higher chance of becoming feeble, according to a number of research studies (Cacciatore et al., 2013; Hubbard et al., 2010; Jang, 2016; Ottenbacher et al., 2009). With prevalence rates of 25% and 18.2%, respectively, it is clear from the analysis of data from the National Health and Nutrition Examination Survey (NHANES) and the Cardiovascular Heart Study (CHS) that people with diabetes exhibit noticeably higher rates of frailty and pre-frailty. The frequency of frailty among those 65 and older as a whole is 6.9%, in comparison. This convincing evidence underlines the significance of more study and the adoption of intervention techniques to reduce these heightened risks. Diabetes is associated with frailty.

The accumulation of research findings from various studies highlights a consistent trend: elderly individuals with diabetes are more susceptible to developing frailty, and this association is supported by concrete data gleaned from large-scale surveys like NHANES and CHS. These findings underscore the pressing need for comprehensive investigations and targeted interventions aimed at addressing the complex interplay between diabetes and frailty in older populations, ultimately promoting better health outcomes and quality of life for this vulnerable demographic.

Additional supporting data comes from the Beijing Longitudinal Study of Aging II, which shows that people with diabetes had the greatest prevalence of frailty, at 19.3%, when compared to both pre-diabetic and non-diabetic groups (Chhetri et al., 2017). This extensive body of research highlights the complex interactions between frailty and diabetes in older persons and highlights the pressing need for specialized healthcare strategies and interventions for this at-risk group. According to a previous systematic review and meta-analysis (Abdelhafiz et al., 2021; Hanlon et al., 2020), there is a favorable correlation between frailty and diabetes mellitus.

Although several reviews have already explored the topic of the impact of type 2 diabetes with frailty among the elderly, there is a pressing need for a more extensive and collaborative review. By incorporating a broader range of studies and pooling together data from various research endeavors, a comprehensive meta-analysis can offer a deeper and more nuanced understanding of the relationship between these two complex health conditions. A collaborative approach will allow for the inclusion of diverse perspectives, methodologies, and datasets, leading to more robust conclusions and facilitating the identification of potential research gaps. Therefore, undertaking a further collaborative review is essential to unveil new insights, validate existing findings, and guide the development of effective interventions that can better address the intricate challenges posed by the coexistence of type 2 diabetes and frailty in the elderly population. Hence, the primary objective of this study was to explore the link between type 2 diabetes and frailty.

METHODOLOGY

Data sources

The reporting standards selected for this investigation were carefully followed to comply with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations (Hutton et al., 2015). A thorough electronic search covering their beginnings up to July 31, 2023 was conducted across databases, including EBSCO, PubMed/Medline, and Science-Direct. This thorough search focused only on books written in the English language. The used search term was "(frailty) AND (type 2 diabetes OR diabetes mellitus) AND (elderly OR aging population OR older people)." In order to find pertinent research, we also manually reviewed the references listed in prior meta-analyses and review papers as part of our search approach. This rigorous methodology was employed to ensure the thoroughness and comprehensiveness of our study's data collection, drawing upon both electronic database searches and the wealth of knowledge encapsulated within the references of established meta-analyses and review articles.

Study selection

The primary studies analyzed in this research adhered to specific criteria, which comprised: (a) investigating the connection between frailty and type II diabetes, (b) utilizing observational research designs such as case-control, cohort, or cross-sectional methodologies, (c) evaluating relationships through adjusted odds ratios, and (d) including participants aged 60 years or older. The research methodology was structured in accordance with the PECOS framework, outlined as follows: 1) Population: adults aged 50 years or older; 2) Exposure: type 2 diabetes; 3) Control: individuals without type 2 diabetes; 4) Outcome: frailty; and 5) Studies: observational studies published in the English language.

Data extraction

In this research, two reviewers autonomously carried out electronic database searches, and then transferred the located studies to Mendeley, where they meticulously reviewed and eliminated any duplicate records. Simultaneously, these two reviewers independently collected data from the chosen studies and performed an extensive evaluation of the research's caliber. The assessment of the quality of all identified observational studies centered around the application of the Newcastle-Ottawa Scale (NOS).

Table 1. Quality assessment of cross-sectional studies through the application of the Newcastle-Ottawa Scale (NOS)

Studies	Selection				Comparability	Outcome		Total Score
	Representa-tiveness of the sample	Sample size	Ascer-tainment of expo-sure	Non-respon dents	The study design or analysis ensures comparability between subjects in different outcome groups, and measures are taken to control for confounding factors.	Assessment of outcome	Statistical Test	
Au Yong et al., (2021)	1	1	1	1	1	1	1	Good
Hayakawa et al., (2021)	1	1	1	1	1	1	1	Good
Takeuchi et al., (2018)	1	1	1	1	1	1	1	Good

Table 2. Assessment of the quality of cohort studies employing the Newcastle-Ottawa Scale (NOS)

Studies	**Selection**				**Comparability**	**Outcome**			**Total Score**
	Representa-tiveness of the exposed cohort	Selection of the non-exposed cohort	Ascer-tainment of expo-sure	Evidence indicating that the outcome of interest was absent at the beginning of the study	The cohorts are made comparable through the study design or data analysis, with appropriate measures taken to control for confounding variables.	Assess ment of outcome	Ensuring an adequate duration of follow-up to allow for the occurrence of outcomes	The sufficiency of follow-up within the cohort	
García-Esquinas et al., (2015)	1	1	1	1	1	1	1	1	Good
Johansen et al., (2007)	1	1	1	1	1	1	1	1	Good
Veronese et al., (2016)	1	1	1	1	1	1	1	1	Good
Brunner et al., (2018)	1	1	1	1	1	1	1	1	Good
Espinoza et al., (2010)	1	1	1	1	1	1	1	1	Good

Statistical analysis

For our statistical analyses, we utilized Review Manager version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) as our chosen software tool. To amalgamate the collected data, we applied a fixed-effects model. To evaluate the results, we relied on the Adjusted Odds Ratio (AOR) along with its corresponding 95% confidence intervals (CI). In line with the guidelines proposed by Higgins et al., we assessed heterogeneity based on specific criteria: I2 values falling within the range of 25-60% were considered indicative of moderate heterogeneity, 50-90% denoted substantial heterogeneity, and values between 75-100% were classified as considerable heterogeneity. Additionally, a p-value of less than 0.1 was considered as an indicator of significant heterogeneity (Higgins et al., 2003). For all our analyses, we maintained a significance threshold of $p < 0.05$.

The choice of Review Manager version 5.3 for our statistical analyses ensured a robust and standardized approach to data synthesis. We employed the AOR and its associated confidence intervals to accurately assess and quantify the results. Furthermore, our stringent criteria for evaluating heterogeneity, following the guidelines proposed by Higgins and colleagues, allowed us to gauge the consistency and reliability of the included studies. We maintained a significance level of $p < 0.05$ throughout our analyses to ensure that our findings met established statistical standards.

RESULTS

Upon the initial search of three electronic databases, a total of 9,311 potential studies were identified. After reviewing the titles and abstracts, 129 studies were deemed worthy of further evaluation. Out of these, 8 articles underwent a comprehensive review and were chosen for quantitative analysis. The literature search results are shown in Figure 1.

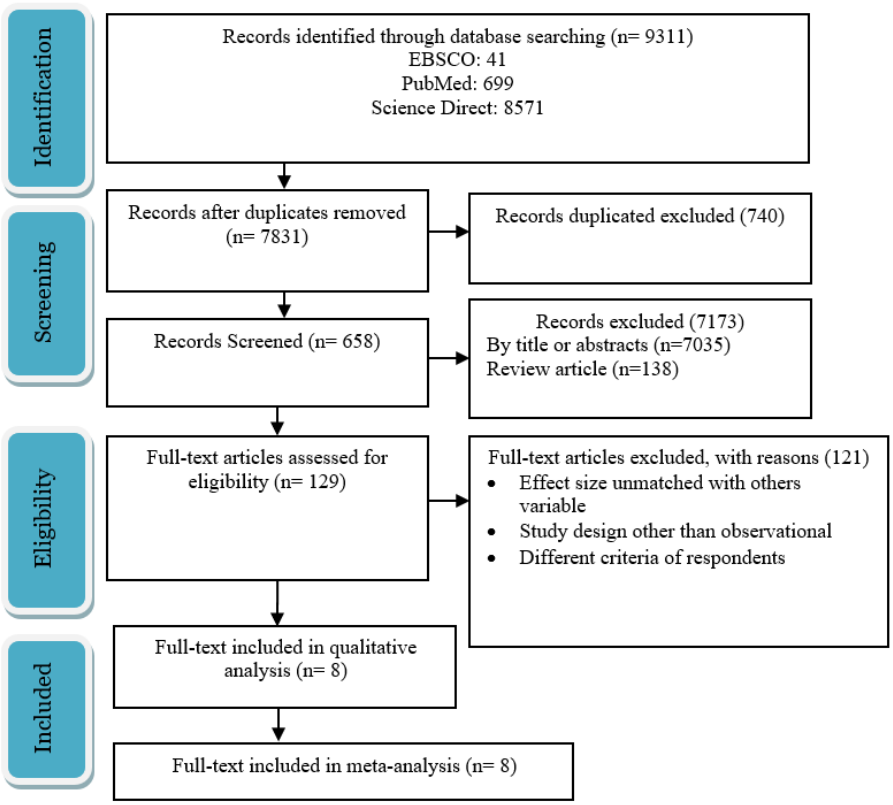

Figure (1) PRISMA flowchart for database searches and systematic reviews and meta-analysis

Study characteristics

Table 4 presents the essential characteristics of the selected studies. Our analysis encompassed a total of 8 published studies, comprising five cohorts and three cross-sectional, and three case-control studies. In total, this analysis involved 25,844 respondents of varying ages. The geographic distribution of the studies included two from USA and Japan and one each from Singapore, UK, Spain, and Italy. The most frequently employed measures of frailty included the Fried Frailty Index derived from the Cardiovascular Health Study, which was used in 7 studies, and the Edmonton Frail Scale, which was utilized in 1 study. The studies exhibited heterogeneity in terms of their settings, with 3 studies conducted in community-based settings, 4 in outpatient-based settings, and 1 in an inpatient-based setting.

Table 3. Key Attributes of Selected Studies

Author	Method	Country	Sample	aOR	CI	Conclusion
Au Yong et al., (2021)	Cross-sectionals	Singapore	1396 (mean age: 75.8)	1.69	1.28-2.24	Factors independently associated with frailty was diabetes mellitus.
Brunner et al., (2018)	Cohort	UK	16,164 (mean age: 69)	1.48	1.26-1·74	Diagnosis of diabetes did not substantially increase the likelihood of frailty.
Espinoza et al., (2010)	Cohort	USA	606 (mean age: 69.6)	1.70	0.89-3.25	Diabetes was not a significant predictor of incident frailty.
García-Esquinas et al., (2015)	Cohort	Spain	1750 (aged 60 years or older)	2.18	1.42-3.37	After accounting for age, gender, and educational background, individuals with diabetes exhibited an elevated susceptibility to frailty.
Hayakawa et al., (2021)	Cross-sectionals	Japan	1357 adults (median age: 77 years)	2.13	1.09-4.14	Diabetes Melitus were associated with frailty in older people.

Johansen et al., (2007)	Cohort	USA	2275 (mean age 58.2)	1.35	1.10-1.65	Only diabetes, stroke, and lower blood albumin concentrations had statistical significance, however individuals with comorbid illnesses were more likely to be frail.
Takeuchi et al., (2018)	Cross-sectionals	Japan	542 adults (mean not frail 63.6 ± 11.2; pre frail 67.5 ± 12.3; frail 71.0 ± 10.2)	2.765	1.081-7.071	The factors independently associated with frailty was diabetes melitus
Veronese et al., (2016)	Cohort	Italy	1754 (older than 65 years)	1.87	1.31-2.13	The presence of frailty was linked to a notably increased occurrence of type 2 diabetes (T2DM).

Publication bias and quality assessment

Since the number of included studies was less than 10, it was not possible to assess publication bias. Nonetheless, all seven studies demonstrated high-quality articles.

Results of the Review

The analysis of eight articles yielded varying degrees of support for the connection between frailty and type 2 diabetes mellitus. Specifically, two of these articles did not offer substantial backing for this association, while the remaining six articles provided compelling evidence in favor of it.

These findings suggest that the majority of the studies reviewed highlight a significant link between type 2 diabetes and frailty among older individuals. It is essential to consider the variation in results from different studies when interpreting the overall findings and addressing potential factors that may contribute to the inconsistencies observed. Understanding this link is vital for tailoring effective interventions and improving the quality of life for older adults facing these health challenges.

Results of the meta-analysis

We conducted a subgroup meta-analysis based on setting from eight studies. All of the analyses used fixed effect because the value of heterogeneity (I2) was ≤50% and they were all statistically significant ($p < 0.05$). A detailed forest plot outlining the association between type 2 diabetes and frailty was interpreted as elderly with diabetes mellitus can increase the odds of having frailty 1.58 times compared to elderly who did not have diabetes mellitus (aOR= 1.58; 95% CI= 1.43 to 1.75; $p < 0.0001$) (Figure 2).

To assess the likelihood of publication bias, an examination of the funnel plot (depicted in Figure 3) was conducted. The analysis of this plot reveals an asymmetric distribution, primarily leaning towards the right side. This observed asymmetry suggests the possible existence of selective reporting and a tendency to publish studies with positive findings. Consequently, studies reporting non-significant results might be underrepresented, potentially resulting in an inflated overall effect size within the meta-analysis. It's important to acknowledge that this observed bias could impact the broader conclusions and should be considered when interpreting the association between frailty and type 2 diabetes mellitus.

In summary, the funnel plot analysis indicates an imbalance in the publication of studies, potentially favoring those with positive results. This skew may lead to an overestimation of the overall effect size, which, in turn, has implications for the broader understanding of the relationship between frailty and type 2 diabetes mellitus. It is essential to exercise caution and consider the potential impact of publication bias when drawing conclusions from the meta-analysis results.

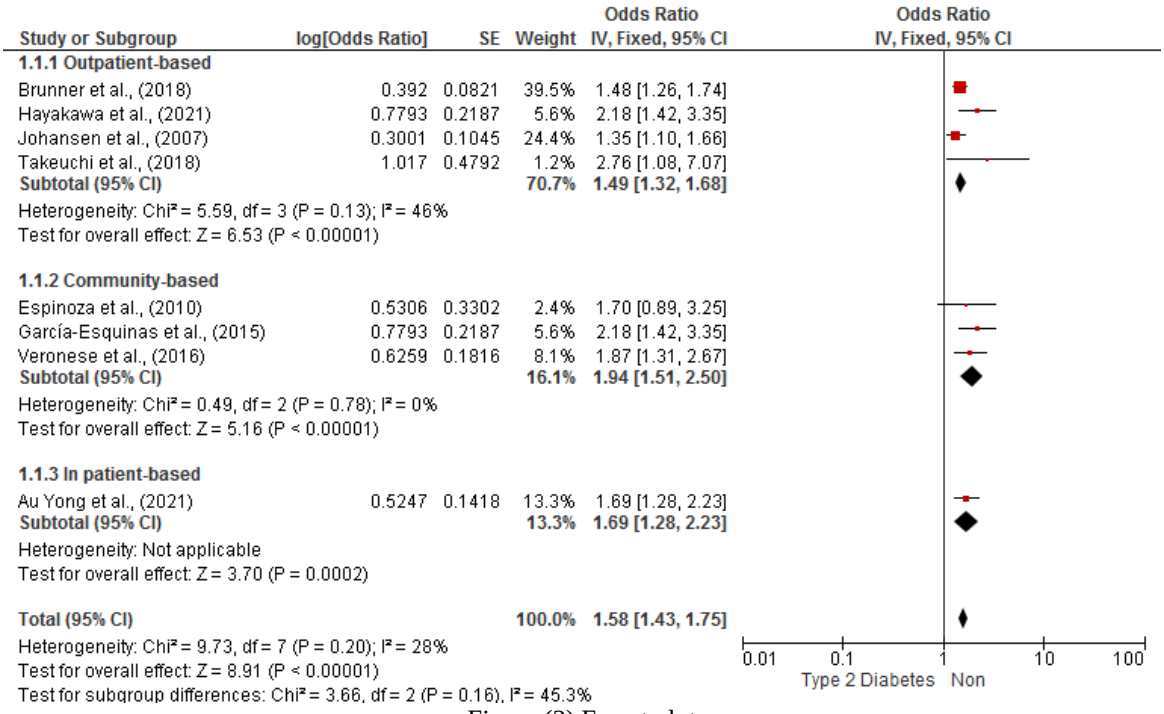

Figure (2) Forest plot

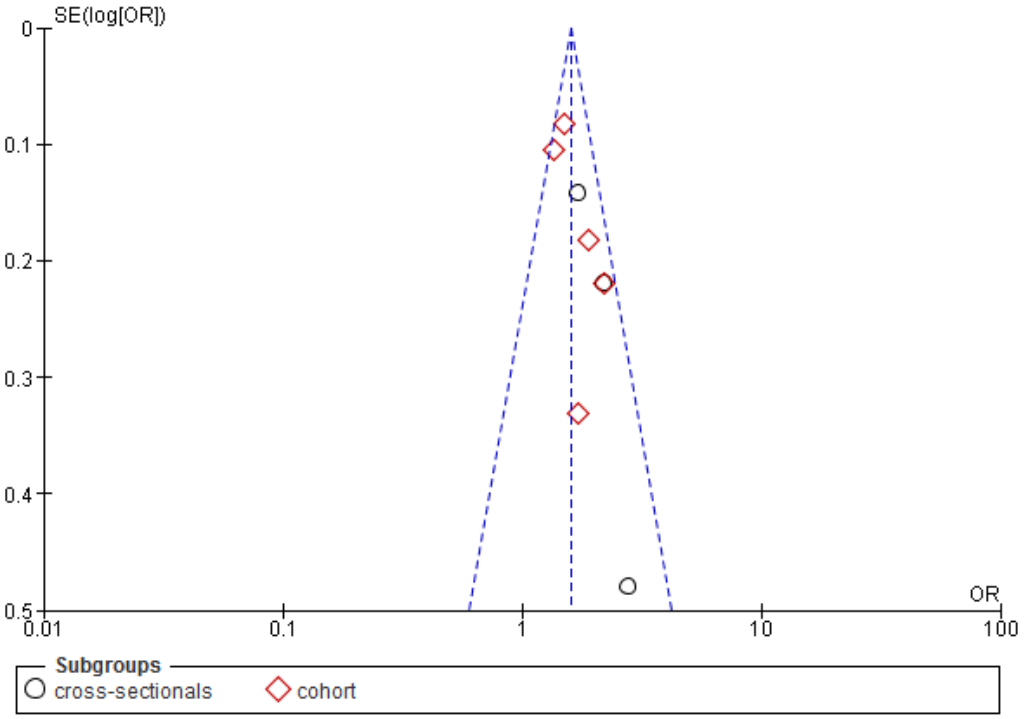

Figure (3) Funnel plot

DISCUSSION

Our primary objective in conducting this study was to investigate the impact of type 2 diabetes on frailty among the elderly population. Through a rigorous and systematic review, we aimed to analyze and consolidate the existing body of research to shed light on the relationship between these common health conditions. Our goal was to acquire a thorough and holistic comprehension of how these two factors interact and influence each other.

By methodically examining the available literature and synthesizing its findings, we aimed to provide valuable

insights into the connection between type 2 diabetes and frailty in elderly individuals. This research endeavor was motivated by the need to contribute to a deeper understanding of the intricate dynamics between these prevalent health issues and their implications for the well-being of older adults.

Our findings are consistent with previous research that has identified a link between type 2 diabetes mellitus and frailty. Recent systematic reviews and meta-analyses conducted by Abdelhafiz et al. (2021) and Hanlon et al. (2020) have firmly established a direct association between frailty and diabetes mellitus, with specific attention to the role of low blood sugar levels. In contrast, Yanagita et al. (2018) reported conflicting results, suggesting an association between frailty and elevated blood sugar levels, or hyperglycemia. Nevertheless, this comprehensive study draws a distinct conclusion, indicating that the relationship between HbA1c levels and frailty does not exhibit a U-shaped pattern. This suggests that maintaining relatively stable glycemic control is more crucial for managing frailty in elderly individuals with type 2 diabetes mellitus when compared to individuals with poorly controlled blood sugar levels.

Our research builds upon and supports the existing body of knowledge regarding the connection between frailty and type 2 diabetes mellitus. Notably, it underscores the significance of glycemic control in addressing frailty among elderly patients with diabetes, a crucial aspect that can contribute to their overall well-being. Furthermore, Abd.Ghafar et al., (2022) argued that frailty and diabetes mellitus are age-related conditions that frequently co-occur. Frailty influences the advancement of diabetes mellitus, the level of control required, and the choice of treatment approaches. Moreover, diabetes mellitus is associated with unfavorable outcomes, including heightened mortality rates, especially in the context of frailty.

Frail elderly individuals with diabetes mellitus may encounter challenges in effectively managing their insulin levels, determining optimal medication schedules, adhering to dietary plans, adapting to new technologies, and recognizing hypoglycemic symptoms. Consequently, it becomes imperative to simplify treatment plans and place a heightened emphasis on caregiver involvement in managing these health conditions. Education emerges as a pivotal tool with the potential to reduce healthcare expenditures for both patients and caregivers. Healthcare professionals should seize every available opportunity to provide patients with comprehensive education on this intricate subject. Moreover, it is crucial for healthcare staff, particularly those working in long-term care and rehabilitation facilities, to undergo regular training to enhance their expertise in managing diabetes and frailty, as advocated by the American Diabetes Association (2022); A. Sinclair et al., (2012).

The challenges faced by frail elderly individuals with diabetes underscore the need for streamlined and accessible healthcare strategies. These challenges encompass insulin regulation, medication adherence, dietary choices, technology adoption, and hypoglycemia recognition. As a result, simplification of treatment plans and active involvement of caregivers in disease management becomes paramount. Educating patients and caregivers takes on a central role in not only improving health outcomes but also in reducing healthcare costs. It is incumbent upon healthcare practitioners to proactively engage in patient education, and continuous training, particularly for professionals working in long-term care and rehabilitation settings, is essential. These recommendations align with the guidance provided by the American Diabetes Association (2022); A. Sinclair et al., (2012) in addressing the complex healthcare needs of frail individuals with diabetes mellitus.

When dealing with advanced frailty and eldery care, the emphasis should transition toward symptom management and ensuring the patient's comfort. Utilizing supported telemedicine and remote blood glucose monitoring could be practical alternatives when in-person assessments become challenging (Isaković et al., 2016; Tan et al., 2020). Maintaining blood glucose levels within an acceptable range is crucial to prevent both hypoglycemia and the acute complications that can arise from hyperglycemia (American Diabetes Association, 2022). To respect patient preferences and prevent unnecessary or unsuitable interventions, it is strongly advised to engage in advance planning that includes patients and their caregivers.

This review study stands apart from previous research in two significant aspects. Firstly, unlike previous studies that might have lacked subgroup analysis due to limited data, our review incorporates a comprehensive subgroup analysis, enabling a more nuanced understanding of the association between diabetes and frailty across different category. Secondly, our review includes additional recent studies that were not part of previous analyses, enriching the available evidence and offering more up-to-date insights into the relationship between diabetes and frailty among older individuals. These enhancements contribute to a more comprehensive and refined examination of the topic, yielding valuable implications for future research and clinical practice.

Limitation

There are several constraints associated with this study. Firstly, the meta-analysis incorporated a relatively limited number of primary studies. Additionally, the scope of the literature search was confined to just three databases, and it exclusively considered studies published in English,

potentially resulting in the omission of pertinent information. Furthermore, due to limited data from the primary studies, we only performed a subgroup analysis based on study design. Future research should aim for a larger pool of primary studies and consider additional criteria for conducting subgroup analyses.

CONCLUSION

The meta-analysis findings indicate a significant association between diabetes mellitus in individuals aged 60 years and older and an increased incidence of frailty. The study's eligibility evaluation adhered to predetermined criteria and was independently performed by two researchers, ensuring thorough scrutiny of the study quality. This study highlights the vital aspects to be taken into account when creating health promotion initiatives, emphasizing the need for the creation of health literacy, counseling, and educational programs in both clinical and community environments.

AUTHORS' CONTRIBUTION

ARB: Conceptualization and structure, data collection, interpretation, and drawing are all included in the list of responsibilities. MB and ANP: Acquisition of data, interpretation, agreement to accept responsibility for all parts of the task, and final approval.

Conflict of interest: The authors of this article have not disclosed any competing interests.

Source of Funding: This research did not receive specific funding from public, commercial, or nonprofit sources.

Ethical Approval: Not needed.

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