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SYSTEMATIC REVIEWS

Diabetes mellitus and risk of falls in older adults: a systematic review and meta-analysis

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Abstract

Background: intensive or very loose glycemic control may contribute to the risk of falls in diabetic patients. However, studies on diabetes mellitus and the risk of falls have yielded conflicting results. Our objective was to investigate the effect of diabetes mellitus on the risk of falls in older adults by conducting a systematic review and meta-analysis.
Methods: the PubMed and Embase databases were searched for relevant studies published until November 2015. Only prospective cohort studies reporting at least age-adjusted risk estimate of falls compared diabetic to non-diabetic individuals were selected. Diabetes mellitus was ascertained by a combination of medical history and laboratory tests or use of anti-diabetic drugs.
Results: a total of six studies involving 14,685 participants were identified. The number of falls in diabetic and non-diabetic individuals was 423 of 1,692 (25.0%) and 2,368 of 13,011 (18.2%), respectively. Diabetes mellitus was associated with an increased risk of falls (risk ratio [RR] = 1.64; 95% confidence intervals [CI] 1.27–2.11) in a random-effects model. Subgroup analyses showed that the risk of falls seemed more pronounced among both gender groups (RR = 1.81; 95% CI 1.19–2.76) than among women (RR = 1.52; 95% CI 1.04–2.21). Diabetes increased 94% (RR = 1.94; 95% CI 1.42–2.63) and 27% (RR = 1.27; 95% CI 1.06–1.52) risk of falls in insulin-treated and no-insulin-treated patients, respectively.
Conclusions: this meta-analysis reveals that older adults with diabetes mellitus are associated with greater risk of falls, and this association is more pronounced in insulin-treated patients.

Keywords: *diabetes mellitus, risk factors, falls, meta-analysis, older people, systematic review*

Introduction

Falls is a leading cause of injury in older population [1] and affect one-third of adults aged 65 and older per year in the USA [2]. Falls is associated with fracture risk and cause of hospital admission for trauma. Recurrent falls may significantly reduce the social and physical activities and quality of life. Therefore, identification of modifiable risk factors is of urgent need.

Diabetes mellitus is a global public health burden [3]. Diabetes is estimated to affect at 8.3% of adulthood, and this number will increase by 55% over the next two decades [4]. Falls is a major concern for elderly adults with diabetes mellitus [5, 6]. The annual incidence of falls in elderly diabetic individuals was up to 39% [7]. Approximately 30.6% of individuals with diabetes and 19.4% of individuals without diabetes experienced recurrent falls in the Longitudinal Ageing Study [8]. Declines in sensory function caused by neuropathy or retinopathy may lead to increased risk of falls in diabetic persons [9]. Intensive glycemic control associated with hypoglycemia may be another possible reason for falls [10, 11].

Studies on the association between diabetes mellitus and the risk of falls in older people have yielded conflicting results [8, 12–17]. These inconsistent findings may correlate to the presence of diabetic complications, long duration of disease, gender or age difference or the study design. However, no previous a systematic review and meta-analysis has evaluated the association between diabetes mellitus and the risk of falls in older people.

Here, we conducted a comprehensive systematic review and meta-analysis of prospective observational studies to

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investigate whether diabetes was an independent risk factor for falls in community-dwelling individuals aged 60 and over.

Methods

Search strategy

This meta-analysis was conducted in accordance with the checklist of the Meta-Analysis of Observational Studies in Epidemiology [18]. We searched the PubMed and Embase databases from their inception to November 2015 using a combination of the following medical subject headings terms: (falls OR falling) AND (diabetes mellitus OR diabetic) AND (follow-up OR prospective OR longitudinal OR cohort). The study protocol was present in Supplementary data, Figure S1, available in *Age and Ageing* online. In addition, the reference lists of included studies and relevant reviews were manually screened to identify additional eligible articles. Two reviewers (Y. Yang and Q. Zhang) independently made literature search.

Study selection

Articles were eligible if: (i) prospective cohort studies investigated the association between diabetes and the risk of falls; (ii) participants were aged 60 and over; (iii) diabetes mellitus was ascertained by a combination of medical history and laboratory tests or use of anti-diabetic agents and (iv) studies provided at least age-adjusted risk estimates of falls compared diabetes to non-diabetes individuals. A falls was defined as 'an unintentional change in position resulting in coming to rest at a lower level or on the ground' [19]. Participants were grouped as fallers if they experienced at least one fall during the follow-up period. We excluded articles of retrospective, case-control or cross-sectional design. In addition, we also excluded studies that did not provide unadjusted risk estimate.

Data extraction and quality assessment

Two reviewers (Y. Yang and Q. Zhang) independently carried out the literature search, study selection and data extraction process. The following data were extracted from the included studies: 1st author's name, year of publication, study design, origin of study, sample size, participant information (mean age or age range, percentage of females), number of participants, definition of diabetes and falls, most fully adjusted hazard ratio (HR) or odds ratio (OR) together with 95% confidence intervals (CI), follow-up duration and adjustments for covariates. Two reviewers (Y. Yang and Q. Zhang) independently assessed the quality of included studies using the Newcastle Ottawa Scale (NOS) for the non-randomised observational study [20]. The overall scores for methodological quality range from zero to nine.

Statistical analysis

As for variation in the report and adjustment for confounding factors in each study, we only selected the most fully adjusted risk estimate. HR and OR were assumed to approximate the same relative risk and are collectively described as the risk ratio (RR) in this meta-analysis. If the studies provided the separate risk estimate by the subgroup, we pooled these separate risk estimates in this study. In order to measure heterogeneity, the Cochran Q test and I^2 statistic were used, with I^2 value >50% or P-value in Cochran Q test less than 0.10 indicated statistically significant heterogeneity [21]. A random-effect model was applied with statistically significant heterogeneity across the studies; otherwise, we selected a fixed-effect model. Subgroup analyses were conducted by the geographic region (Europe vs. USA), gender (female vs. both gender), insulin treated (yes vs. not), follow-up duration (>3 years vs. ≤3 years), adjustment for body weight (yes vs. not), risk estimate (HR vs. OR) and number of diabetic participants (≥500 vs. <500). Sensitivity analyses were performed by omitting a single study in each turn to test the robustness of our results. Statistical tests for publication bias were conducted if the number of the included studies was less than the recommended arbitrary minimum number of 10 [22]. All analyses were done using STATA version 12.0 statistical software (Stata, College Station, TX).

Results

Literature search

Based on the initial search strategies, 685 potentially relevant citations were retrieved. Among these studies, 679 citations were removed mainly because they did not report the outcome interesting or not provide adjusted risk estimate. Finally, six prospective observational studies [8, 12–15, 17] met the inclusion criteria. The study selection process is presented in Figure 1.

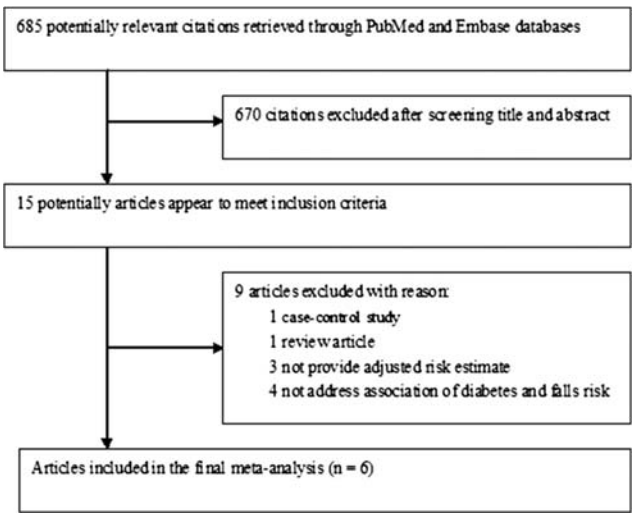

Figure 1. Flow chart of studies selection process.

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Study characteristics

All the included studies were prospective design and published from 2002 to 13. The sample size of the individual studies varied from 139 to 9,249. A total of 14,685 participants were identified and analysed. The follow-up duration ranged from 299 days to 10.1 years. Two studies were [13, 17] consisted of female participants, whereas the other four studies [8, 12, 14, 15] included both genders. Three studies [13, 15, 17] reported the risk estimates by insulin treated or not. Diabetes was ascertained by self-report of a physician's diagnosis, anti-diabetic medication use or laboratory findings. Falls was monitored by the postcard, telephone or review of the daily report. The baseline characteristics of the included studies are listed in Table 1. The overall NOS stars of the included studies ranged from 6 to 8 (Supplementary Table S1, available in *Age and Ageing* online).

Association between diabetes mellitus and risk of falls

Six studies involving 1,691 diabetic patients reported the risk of any falls. The number of falls in diabetic and non-diabetic participants was 423 of 1,692 (25.0%) and 2,368 of 13,011 (18.2%), respectively. As shown in Figure 2, older persons with diabetes are associated with an increased risk of falls (RR 1.64; 95% CI 1.27–2.11) compared with healthy controls. A random-effects model was selected because the significant heterogeneity (I^2 = 60.1%; P = 0.020) was observed. Subgroup analyses showed that the excessive risk of falls was consistently observed in each subgroup (Table 2 and supplementary figures are available in *Age and Ageing* online). Particularly, insulin-treated diabetic patients were associated with a greater risk of falls (RR 1.94; 95% CI 1.42–2.63) than those without insulin treatment. The number of falls in insulin-treated and without insulin-treated patients was 82 of 255 (32.2%) and 259 of 1,229 (21.1%), respectively. The risk of falls appeared to be lower in women than both gender subgroups.

Sensitivity analyses

Sensitivity analyses indicated that the pooled RR ranged from 1.46 to 1.75 and low 95% CI ranged from 1.20 to 1.28 when any single study was removed. Moreover, the pooled RR of falls was 1.49 (95% CI 1.28–1.73) when we changed to a fixed-effect model. When we removed two studies that only investigated the recurrent falls [8] and injurious falls [15], the pooled RR of any falls was 1.88 (95% CI 1.27–2.78) in a random-effects model.

Discussion

To the best of our knowledge, this is the 1st meta-analysis to investigate the relationship between diabetes mellitus and the risk of falls in older adults. Our meta-analysis revealed that (i) older adults with diabetes mellitus were associated with a 64% greater risk of falls; (ii) diabetes increased 94 and 27% risk of falls in insulin-treated and without insulin-treated patients, respectively. This systematic review and meta-analysis reinforced the effect of diabetes as an independent risk factor for falls in older adults.

Falls is one of the greatest health challenges, particularly in diabetic adults [23]. The consequences of falls, such as fractures, poorer rehabilitation and increased number of falls were said to be more severe in the elderly with diabetes [24]. Subgroup analysis revealed that diabetes increased by 52 and 81% the risk of falls in women and both genders. Men with diabetes had a higher frequency of falls has been reported in a previous study [25]. The pronounced risk of falls in men may be attributed to the effects of body weight or body mass index [26]. However, gender-specific effect of diabetes on falls risk needs to be further investigated. Subgroup analysis revealed that studies involving over 500 cases of diabetic individuals had a lower risk estimate than those sample sizes less than 500 cases (RR 1.54 vs. 1.80). Moreover, the effects of diabetes on falls risk were not affected by the duration of follow-up, geographical regions or publication year.

An important issue was the association of falls and glycemic control in diabetic persons. Studies on glycemic control and risk of falls have yielded conflicting results. Tighter glycemic control (HbA1c ≤ 7) was associated with greater risk of falls in a retrospective study [27], but other study did not find such association [28]. Another study showed that only the low-impact falls were significantly increased in patients receiving insulin therapy [29]. The Health, Aging and Body Composition cohort showed that achieving lower HbA1c levels with oral hypoglycaemia agents did not increase more frequent falls, but, HbA1c ≤6% among those insulin-treated patients increased the risk of falls [30]. Irrespective of type of diabetes mellitus, insulin treatment may represent intensive glycemic control of the diseases. In this meta-analysis, diabetic persons who received insulin treatment had a 94% greater risk of falls, while the risk was lower (27%) in those without insulin-treated diabetic individuals. Hypoglycaemia episodes induced by the intensive insulin therapy at least in part explain the excess risk of falls associated with diabetes. In addition, using multiple drugs may increase the risk of falls owing to the occurrence of drowsiness, muscle weakness, balance change, vertigo and hypotension [31]. Among 46,946 type 2 diabetic persons in the Kaiser Permanente Northern California Diabetes Registry, the prescription of four or more medications was associated with greater risk of falls [32]. On the contrary, inadequate glycemic control and conditions associated with peripheral neuropathy and retinopathy also significantly increased risk of falls in diabetic persons. The effect of glycemic control on falls risk needs to further investigated in more well-designed studies.

Mechanisms underlying diabetes and falls risk are not well elucidated. People with diabetes developed peripheral neuropathy and retinopathy, vestibular dysfunction, cognitive impairment, musculoskeletal/neuromuscular lesion of

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Table 1. Baseline characteristics of the included studies

Study/year	Region	Design	Subject (% women)	Age/range or mean ± SD	Diagnosis of DB (number of DB)	Ascertainment of falls	Falls number (%) (DB vs. control)	HR/OR (95% CI)	Follow-up duration	Adjustment for covariates
Schwartz *et al.* (2002) [17]	USA	Prospective cohort study	9,249 (100%)	≥67 years	Self-reported (629)	Any falls by monitored every 4 months by postcard	171 (27.2%) vs.1465 (17%); 35/99 in insulin and 136/530 in without insulin	1.18 (0.87–1.60) no insulin treated; 2.76 (1.52–5.01) insulin treated	7.2 years	Age, tandem walk score, tandem stand, loss of pressure sensitivity, history of CHD, history of stroke, arthritis or fainting, grip strength, positive GDS, near depth perception and sleeplessness or anxiety medications
Maurer *et al.* (2005) [12]	USA	Prospective cohort study	139 (84%)	88 ± 7 years	Prescription of medications used to treat DB (18)	Any falls by interview or from their guardian	14 (78%) vs. 35 (30%)	4.03 (1.96–8.28) total patients	299 days	Berg scale < 45, hypertension, no. of medications, angiotensin-converting enzyme inhibitors
Volpato *et al.* (2005) [13]	Norway	Prospective population-based cohort study	878 (100%)	≥65 years	Algorithm used for diabetes ascertainment (136)	Any falls by interview every 6 months	99 (72.8%) vs. 417 (63.5%); 31/39 in insulin and 68/97 in without insulin	1.38 (1.04–1.81) total patients; 1.35 (0.99–1.84) no insulin treated; 1.45 (0.92–2.27) insulin treated	3 years	Age, race, education, smoking, overweight, obesity, hypertension, antihypertensive drugs, stroke, PAD, peripheral nerve dysfunction, knee osteoarthritis pain, visual impairment, MMSE, fall in per year before interview, ADLs, physical performance and knee strength
Pijpers *et al.* (2012) [8]	The Netherlands	Population-based cohort study	1,145 (49.8%)	≥65 years	Self-reported and use of glucose-lowering medication (85)	Recurrent falls monitored every 4 months by calendar page	26 (30.6%) vs. 206 (19.4%)	1.30 (0.79–2.11) total patients	3 years	Age, sex, education, urbanisation, dogs and cats in household, special adjustments in house, BMI, alcohol, smoking, medication, physical impairments, general health, pain score, self-perceived health, physical activity, grip strength, functional limitations in ADLs, physical performance and MMSE score ≤ 23
Yau *et al.* (2013) [15]	USA	Prospective longitudinal study	3,075 (51.5%)	70–79 years	Glucose measurements as well as self-report (719)	Injurious falls requiring hospitalisation	71 (21.8%) vs. 223 (9.46%); 16/117 in insulin and 55/602 in without insulin	1.41 (1.05–1.88) total patients; 1.30 (0.95–1.78) no insulin treated; 2.24 (1.24–4.03) insulin treated	10.1 years	Age, sex, race, study site, education, BMI, fainting in the past year, standing balance score, cystatin C and number of prescription medications
Roman de Mettelinge *et al.* (2013) [14]	Belgium	Prospective cohort study	199 (63.3%)	76.9 ± 9.4 years	General practitioner or medical specialist (95)	Any falls by monitored by monthly fall calendars	42 (40.8%) vs. 22 (23.4%)	2.03 (1.06–3.88) total patients	12 months	Age, BMI, community-dwelling, walking aids, number of medications, previous falls, grip strength, cognitive, gait and smoking

ADLs, activities of daily living; BMI, body mass index; CHD, coronary heart disease; DB, diabetes; GDS, Geriatric Depression Score; HR, hazard ratio; MMSE, Mini-Mental Scale Examination; OR, odds ratio; PAD, peripheral arterial disease.

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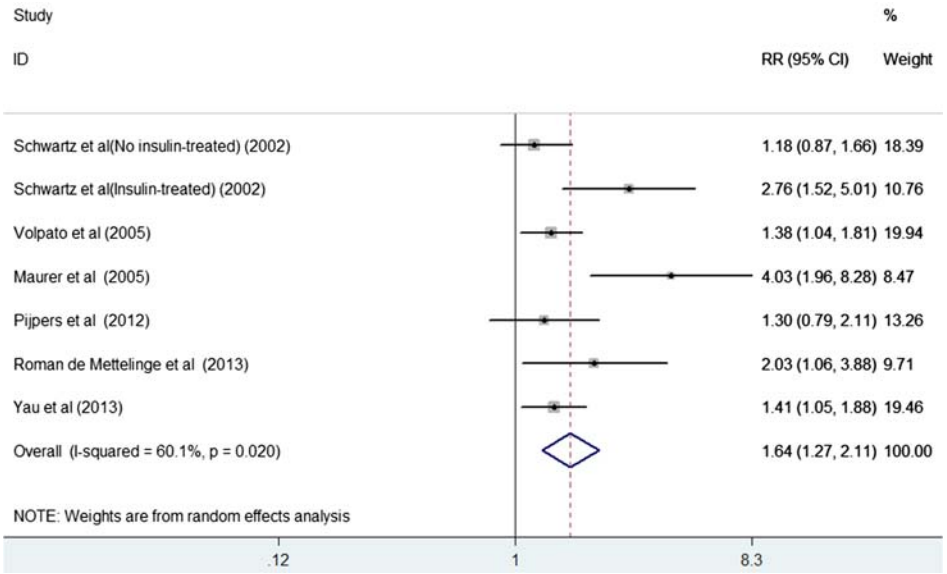

Figure 2. Forest plots showing RR and 95% CI of falls comparing the diabetic individuals to non-diabetes in a random-effect model.

Table 2. Subgroup analyses of diabetes and risk of falls

Subgroup	No. of studies	Pooled RR	95% confidence interval	Heterogeneity between studies
Region				
Europe	3	1.43	1.14–1.79	$P = 0.515$; $I^2 = 0.0\%$
USA	3	1.89	1.19–2.99	$P = 0.004$; $I^2 = 77.8\%$
Follow-up period				
>3 years	2	1.54	1.05–2.25	$P = 0.049$; $I^2 = 66.9\%$
≤3 years	4	1.80	1.17–2.75	$P = 0.035$; $I^2 = 65.0\%$
No. of diabetes				
<500	4	1.80	1.17–2.75	$P = 0.035$; $I^2 = 65.0\%$
≥500	2	1.54	1.05–2.25	$P = 0.049$; $I^2 = 66.9\%$
Publication year				
<2010	4	1.87	1.18–2.96	$P = 0.003$; $I^2 = 78.1\%$
>2010	2	1.45	1.15–1.83	$P = 0.533$; $I^2 = 0.0\%$
Risk estimate				
HR	3	1.59	1.14–2.20	$P = 0.066$; $I^2 = 58.3\%$
OR	3	1.79	1.04–3.09	$P = 0.022$; $I^2 = 73.9\%$
Gender				
Women	2	1.52	1.04–2.21	$P = 0.048$; $I^2 = 67.0\%$
Women + men	4	1.81	1.19–2.76	$P = 0.041$; $I^2 = 63.6\%$
Insulin treated				
Yes	3	1.94	1.42–2.63	$P = 0.205$; $I^2 = 36.9\%$
No	3	1.27	1.06–1.52	$P = 0.821$; $I^2 = 0.0\%$
Adjusted body weight				
Yes	4	1.42	1.19–1.70	$P = 0.721$; $I^2 = 0.0\%$
No	2	2.25	1.03–4.92	$P = 0.002$; $I^2 = 84.5\%$

RR, risk ratio.

the lower limbs or dizziness and hypoglycaemia events with insulin use [23]. Insulin treatment was associated with excessive risk of falls, possibly owing to more severe disease and/or hypoglycaemia episodes.

This study had several limitations. First, substantial heterogeneity ($I^2 = 60.1\%$) was observed in the overall analysis; differences in severity of diabetes and falls, follow-up duration, gender and adjustment for confounding factors may partly explain the heterogeneity. Second, diabetes ascertaining by self-report but not through a fasting glucose level may underestimate the number of persons with diabetes. Misclassification of participants might underestimate the effect of diabetes on the risk of falls. Moreover, we did not differentiate between single and recurrent falls in this meta-analysis. Third, residual confounding factors, such as prior fall history, chronic musculoskeletal pain or cognitive status,

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could have confounded the findings of this study. Fourth, findings of subgroup analyses should be explained with caution due to the limited number of study available. Fifth, all the included studies were performed in Western countries; generalisation of these findings to other regions should be cautioned. Sixth, we only selected articles that published in peer-reviewed journal and unpublished articles or conference abstracts were not considered in this meta-analysis. Finally, the included studies did not report the risk estimate of falls based on the peripheral neuropathy, retinopathy as well as hypoglycemia induced by intensive glycemic control. Therefore, we cannot distinguish overtreatment or complications as a cause of falls in this meta-analysis.

Conclusions

This meta-analysis reveals that older adults with diabetes are associated with excessive risk of falls compared with non-diabetes. Moreover, the increased risk appears to be greater in insulin-treated patients. Hypoglycemia induced by intensive glycemic control or peripheral neuropathy and retinopathy induced by the loose glycemic control may increase the risk of falls. Future studies should address the association between glycemic control and the severity of falls.

Key points

- Conflicting findings have been reported on diabetes and risk of falls.
- Older adults with diabetes mellitus have an excessive risk of falls.
- This association is more pronounced in insulin-treated patients.
- Intensive or loose glycemic control all may increase the risk of falls.
- Effect of glycemic control on falls risk needs to be further studied.

Supplementary data

Supplementary data mentioned in the text are available to subscribers in *Age and Ageing* online.

Authors' contributions

Y. Yang and Q. Zhang conducted the literature search and data extraction; R. Zou and XH. Hu performed the statistical analysis; XH. Hu draughted the manuscript; Q. Zhang and R. Zou revised the manuscript; Y. Yang designed the study protocol and analysed the results.

Conflicts of interest

None.

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Thromboprophylaxis in atrial fibrillation and association with cognitive decline: systematic review

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Abstract

Objective: atrial fibrillation (AF) is associated with dementia. If AF-related cognitive decline is driven by cerebral embolic events, thromboprophylaxis may impact on this. This systematic review assessed the association between cognitive impairment and AF thromboprophylaxis.

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