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Diabetes mellitus and risks of cognitive impairment and dementia: A systematic review and meta-analysis of 144 prospective studies

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ABSTRACT

Background: : Uncertainties persist about the associations of diabetes with risk of cognitive impairment and dementia. We aimed to illuminate these associations from various aspects.
Methods: : We identified relevant prospective studies by searching PubMed up to Jun 2019. Summary relative risks (RR) were estimated using random-effects models. Credibility of each meta-analysis was assessed. Meta-regression and subgroup analyses were conducted.
Results: : Of 28,082 identified literatures, 144 were eligible for inclusion in the systematic review, among which 122 were included in the meta-analysis. Diabetes conferred a 1.25- to 1.91-fold excess risk for cognitive disorders (cognitive impairment and dementia). Subjects with prediabetes also had higher risk for dementia. As for diabetes-related biochemical indicators, fasting plasma glucose (FPG) was non-linearly related to cognitive disorders; the elevated levels of 2 -h postload glucose (2h-PG), glycosylated hemoglobin (HbA1c), low and high levels of fasting plasma insulin (FPI) were associated with an increased risk of dementia. Encouragingly, the use of pioglitazone exhibited a 47% reduced risk of dementia in diabetic population.
Conclusions: : Diabetes, even prediabetes and changes of diabetes-related biochemical indicators, predicted increased incidence of cognitive impairment and dementia. The protective effects of pioglitazone warrant further investigation in randomized trials.

1. Introduction

With a global ageing population, dementia has become one of the most common, disabling and costly condition in modern societies. According to the World Alzheimer Report 2015, there was an estimated 46.8 million incident cases worldwide in 2015, with numbers nearly doubling every 20 years to 75.6 million in 2030 and 135.5 million in 2050. The worldwide economic costs due to dementia have been estimated at 818 billion in 2015, and the threshold of 1 trillion will be crossed by 2018 (Wimo et al., 2017). Dementia accounted for 10.0 million Disability Adjusted Life Years (DALYs) in older people in 2010, which was forecast to an increase by 86% by 2030 (Prince et al., 2015). However, no effective strategies are currently available for treating dementia or delaying the cognitive decline. Thus far, the population trends for dementia are very similar to those observed in diabetes mellitus (Biessels and Despa, 2018) and established evidences suggest considerable overlap in the risk factors and putative pathophysiological mechanisms for the diabetes and cognitive impairment and dementia (Arnold et al., 2018). Determining the relationship between diabetes and its related factors and cognitive disorders may help identify individuals who are at risk of developing cognitive decline and inform preventive strategies.

A growing body of meta-analyses now demonstrates the adverse effects of diabetes on cognition (Cheng et al., 2012; Sadanand et al., 2016; Zhang et al., 2017). However, since the conclusion comes mainly from observational studies that are vulnerable to various biases (included selection bias, information bias, and confounding bias), the credibility of current evidence urgently needs to be assessed. Large differences have been observed in the size of the risk estimates ranging from 0.7 to 2.6 among the published studies, thus detailed meta-regression analyses and subgroup analyses are necessary to clarify whether the strength of the association differ by study characteristics (e.g. the age of the participants, geographic location, study quality of the studies, etc.). In addition, much more prospective observational studies

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on diabetes and risk of dementia and cognitive impairment have since been published, so we could have much more statistical power and consequently higher precision in the summary estimates, and therefore we could conduct meaningful subgroup and sensitivity analyses and make a detailed analysis of diabetes mellitus and the damage of different cognitive domains. Some studies also investigated the association between prediabetes and cognitive disorders, with some reporting a positive association (Marseglia et al., 2018; Rawlings et al., 2014) and others finding no association (Geijselaers et al., 2017; Tuligenga et al., 2014; Zheng et al., 2018). With regard to studies on diabetes-related biochemical indicators (such as FPG, 2h-PG, HbA1c, and fasting plasma insulin (FPI)) and cognitive disorders, the results are also inconsistent. To our knowledge, there has been no pervious meta-analysis on prediabetes or glucose and insulin levels and the risk of dementia, and the dose-response relationship between blood glucose and risk of cognitive disorders has not been established. Furthermore, diabetes is strongly recommended as a target for intervention to prevent cognitive disorders (Xu et al., 2015), and several studies have suggested that anti-diabetic drugs could potentially modulate disease progression and cognitive decline. Some studies, however, reported different conclusions (Biessels et al., 2014). In view of the mixed results, the effect of glucose-lowering drugs on cognition remains to be further explored. Therefore, we performed a systematic review and meta-analysis with rigorous quality evaluation of each meta-analysis to ascertain the association of diabetes, prediabetes, diabetes-related biochemical indicators, and glucose-lowering drugs with risk of cognitive impairment and dementia and to investigate sources of heterogeneity by conducting sensitivity and meta-regression analyses.

2. Methods

2.1. Search strategy and selection criteria

We systematically searched PubMed till June 20, 2019, using the terms “diabetes”, “glucose”, “fasting”, “fasting glucose”, “2 -h post-load glucose”, “impaired fasting glucose”, “IFG”, “impaired glucose tolerance”, “IGT”, “insulin”, “fasting insulin”, “hemoglobin A1c”, “HbA1c”, “dementia”, “Alzheimer”, “Alzheimer’s”, “cognition”, and “cognitive”. Bibliographies of relevant articles and reviews were hand-searched for supplement. The literature screening was done by MX, WX and YNO.

Studies would be included if they: a. were prospective studies (cohort, case-cohort, and nested case-control studies); b. investigated the relationship of diabetes (mixed diabetes and type 2 diabetes) or related metabolic factors with cognitive disorders (cognitive impairment and dementia); c. were published in English. Considering duplicates, we included the most recent publication or the one with the longest follow-up period.

2.2. Data extraction

Data were systematically extracted by two independent researchers, including study characteristics (name of the first author, publication year, project name, study design), sample characteristics at baseline (e.g. age, gender, race, and education level), definition and measurement of exposure, definition and measurement of outcome, follow-up duration, follow-up rate, sample size, case number for analysis, statistical models, measures of effect size, and confounders adjusted for. Any disagreement was resolved by discussion. MX extracted the data, and it was checked for accuracy by YNO.

2.3. Statistical analyses

We calculated summary RRs and 95% CI of diabetes mellitus and related metabolic disorders and risk of dementia (all-cause dementia, AD, and VD) and cognitive impairment (MCI and deficits of memory, executive function, processing function, language, attention, visuo-spatial ability and reasoning). Hazard ratio (HR) was directly considered as RR. Odds ratio (OR) and β with Standard Error (SE) or 95% CI were converted to RR (Ronksley et al., 2011). The RRs and 95%CIs were synthesized using a random effects model (Dersimonian-Laird model), which incorporated between-study heterogeneity into the measurement (Thompson et al., 2010). I^2 value was used to assess heterogeneity, and $I^2 < 40\%$ was considered to be possibly low heterogeneity. For potential heterogeneity, sensitivity analysis excluding one study at a time was conducted to examine if any individual study has a significant impact on the pooled RR. When the meta-analysis included at least 10 studies, we conducted the meta-regression analyses to investigate potential moderators (publication year, age, sex, education years, geographical region, follow-up duration, quality score of studies, attrition, different diagnostic subgroups (mixed diabetes or type 2 diabetes), studies controlling CVD (cerebrovascular or cardiovascular diseases) as a confounder in the model or not, and studies controlling depression as a confounder in the model or not). If meta-analyses found significant mediators, further subgroup analyses would be carried out. Publication bias was examined via the Begg’s test and the Egger’s test. The contour-enhanced funnel plot and trim-and-fill method were employed to distinguish whether the asymmetry was due to publication bias (Peters et al., 2008). “Meta”, “metagene”, “dosresmeta”, and “rms” packages of R software (version 3.5.1.) were used to perform all the above analyses. MX, WX and MST conducted the statistical analyses.

Studies with at least three categories of exposure and with sufficient data for the distribution of cases and person-time across different categories were included in the dose-response analysis. We depicted the dose-response curve of fasting glucose level (FPG) versus risk of dementia using a two-stage generalized least squares regression (Orsini et al., 2012). We performed a sensitivity analysis utilizing percentiles 10, 50, and 90% of the distribution as knots. The midpoint between the upper and lower boundaries of each category was assigned to the corresponding risk estimate. For open-ended categories, lower boundary was divided by 1.25, while upper boundary was multiplied by 1.25 (Xu et al., 2016).

2.4. Assessment of study quality and credibility of meta-analyses

Newcastle-Ottawa Quality Assessment Scale (Stang, 2010) containing eight items (categorized into three dimensions including selection, comparability, and outcome) was employed to evaluate the quality of studies included in the meta-analysis (Supplementary file 1). The NOS total score was regarded as a proxy for measuring the overall risk of bias for each single study. The score for each item was used to assess the risk of bias from different sources. MX and YNO independently evaluated the included studies, and discrepancies were resolved through discussion.

The credibility of each meta-analysis result was categorized into four levels: good (G), acceptable (A), suspicious (S) and poor (P) based on three domains: risk of bias, inconsistency, and imprecision. The risk of bias is based on the weighted quality score; The rating for inconsistency is according to the heterogeneity (estimated by calculating the I^2), variability of point estimates, and overlapping of confidence interval; The rating for imprecision is majorly based on 95% CI (Supplementary file 2). “G” level, “A” level, and “S/P” level were regarded as evidence of high, moderate, and low credibility, respectively.

3. Results

Of 28,082 identified literatures, 144 were eligible for inclusion in the systematic review (Supplementary file 3–4), among which 122 were included in the meta-analysis (Fig.1). Other relevant studies that have been retrieved were presented in the figure of systematic review (Supplementary file 3). Data available for the meta-analysis were collected from 9,359,005 individuals (49.9% women). The mean age of participants ranged from 40.4 to 87.8 years, and the mean duration of

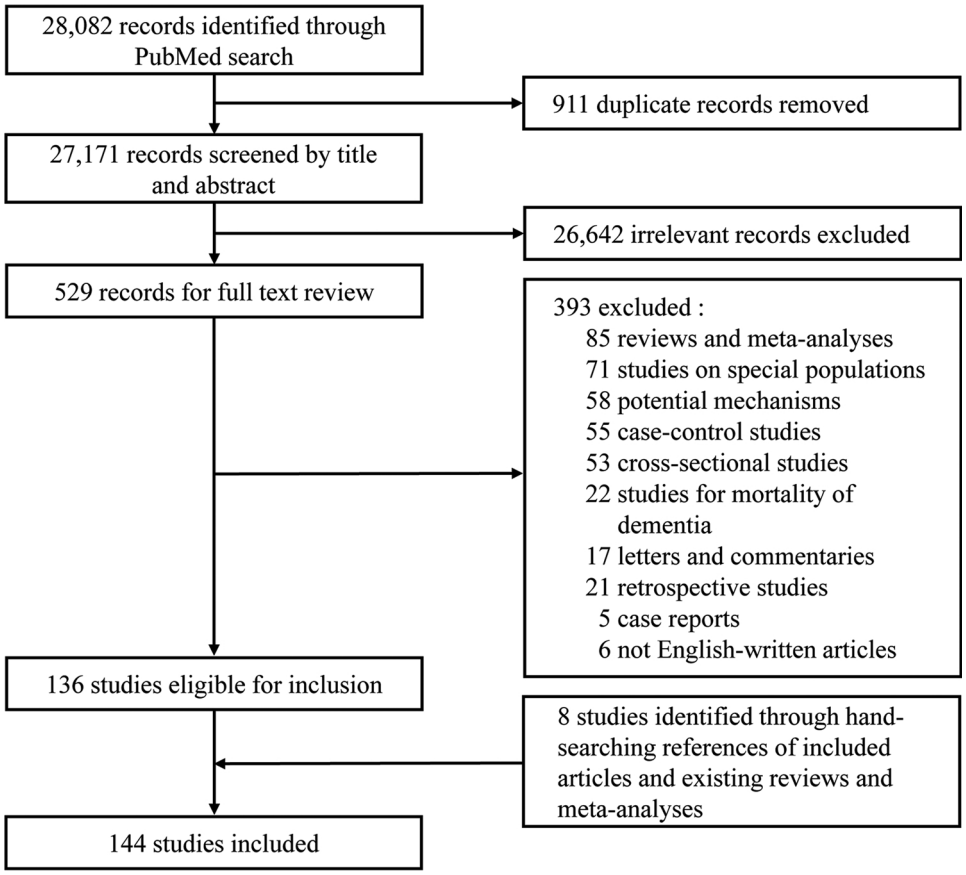


Fig. 1. Flowchart for identifying eligible studies.

follow-up ranged from 1.5 to 32 years (Supplementary file 5). The mean quality score of the studies included in the meta-analysis was 7.75 ± 1.0 (Supplementary file 6). Forest plots of each meta-analysis and the funnel plots were showed in supplementary file 8. Definitions and methods of measurement of diabetes variables and neuropsychological tests assessing cognitive domains were presented in supplementary file 9 and 10.

3.1. Diabetes

3.1.1. Diabetes and risk of cognitive impairment

Low-moderate quality evidence showed that individuals with diabetes had increased risk of cognitive decline compared to those without diabetes. For twenty studies that reported on diabetes and global cognitive decline the pooled multi-adjusted RR was 1.25 (95% CI:1.12–1.39, I^2 = 31%). Ten studies were included in analysis of diabetes in relation to executive function decline and the pooled multi-adjusted RR was 1.44 (95% CI:1.23–1.69, I^2 = 38%). Ten studies were included in the analysis of diabetes and memory function impairment and the pooled multi-adjusted RR was 1.27 (95% CI:1.16–1.39, I^2 = 0%). The meta-regression analyses did not find any valid moderators and there was no evidence of publication bias. Positive associations were also observed between diabetes and lower performance in processing function, language, and attention/reasoning. (Fig.2)

3.1.2. Diabetes and risk of MCI

Nine studies were identified on diabetes and risk of MCI and provided moderate quality evidence. Compared with non-diabetes, diabetes was associated with 49% increased risk of MCI (RR:1.49, 95% CI:1.26-1.77, I^2 = 30, grade A+). Three studies provided separate information of RR for amnestic MCI (aMCI) and nonamnestic MCI (naMCI). The meta-analysis yielded a pooled effect size of 1.50 (95% CI: 1.17–1.92; I^2 = 0, grade G) for aMCI and a pooled effect size of 1.34 (95% CI:1.04–1.73; I^2 = 0, grade G) for naMCI. Furthermore, the meta-analysis of nine studies providing moderate quality evidence indicated that diabetes was associated with nearly a doubled risk of progression from MCI to dementia (RR: 1.91, 95%CI:1.54-2.36; I^2 = 11%). (Fig.2)

3.1.3. Diabetes and risk of dementia

The meta-analysis of thirty-one studies showed a significant association between diabetes and increased risk of all-cause dementia (RR:1.43, 95%CI:1.33–1.53, I^2 = 79%, grade A+). Sensitivity analyses which reduced the heterogeneity or limited the review to the studies with high-quality (score ≥8) had no appreciable effect on the pooled RR. The funnel plot showed the existence of publication bias. After correcting the potential publication bias with the trim-and-fill method, the pooled analysis continued to show a statistically significant association between diabetes and all-cause dementia (RR:1.25, 95% CI:1.17–1.34). The meta-regression analyses revealed that whether controlling CVD as a confounder in the model was a significant moderator (p = 0.011). The pooled RR of studies not controlling CVD in the model was significantly higher (RR1.66, 95% CI:1.53-1.80, I^2 = 0%) than that in studies controlling CVD (RR1.28, 95% CI:1.20-1.36, I^2 = 66%). (Fig.2)

Twenty-four studies reported data for diabetes and the risk of AD. Grade A + evidence implied that diabetes could increase the risk of AD (RR:1.43, 95% CI:1.25-1.62, I^2 = 81%). Sensitivity analyses which reduced the heterogeneity or limited the review to the studies with high-quality (score ≥8) had no appreciable effect on the pooled RR. There was no evidence of publication bias. The meta-regression showed that whether controlling CVD as a confounder in the model was a significant moderator (p = 0.039). The pooled RR of studies not controlling CVD in the model was significantly higher (RR1.61, 95% CI:1.39-1.85, I^2 = 9%) than that in studies controlling CVD (RR1.30, 95% CI:1.11-

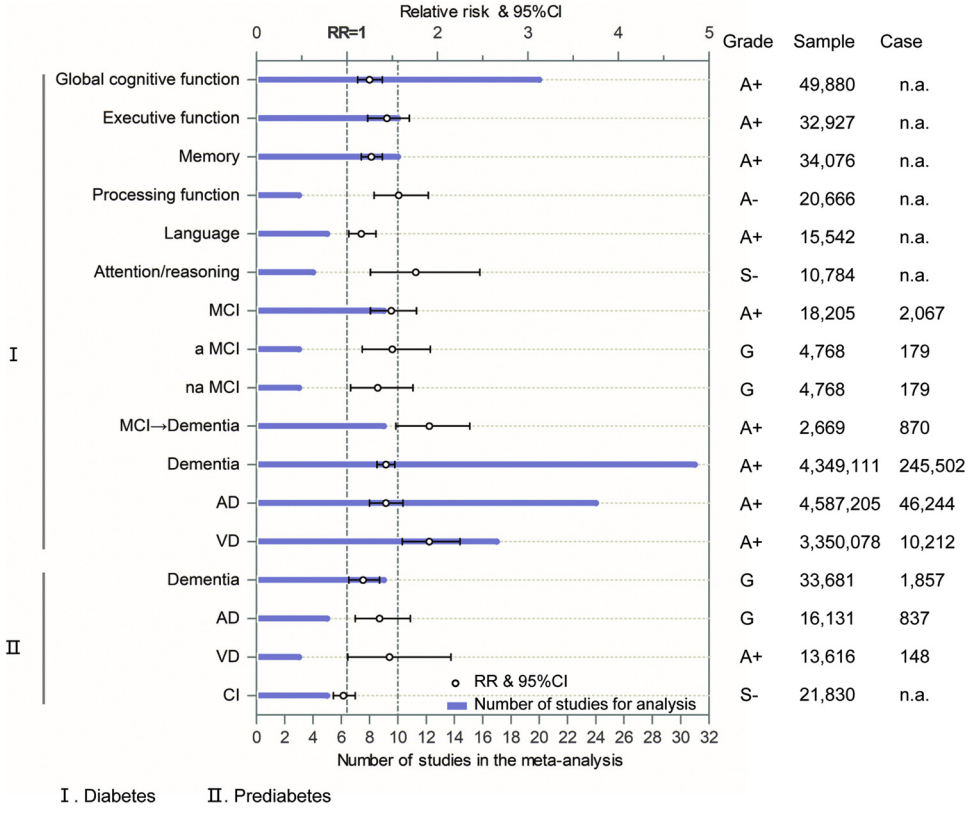


Fig. 2. Meta-analyses of the association of diabetes and prediabetes with different cognitive outcomes. Low-moderate quality evidence showed that diabetes increased risk of cognitive decline in global cognition, executive function, memory, processing function, language and attention /reasoning. Moderate to high quality evidence implied that diabetes was a risk factor for MCI and dementia (all-cause dementia, AD, VD) and accelerated the progression from MCI to dementia. Moderate-high quality evidence indicated positive associations between prediabetes and the risk of dementia, AD and VD. Abbreviations: AD, Alzheimer's disease; VD, vascular dementia; MCI, mild cognitive impairment; aMCI, amnestic mild cognitive impairment; naMCI, nonamnestic mild cognitive impairment; n.a. the number of people with cognitive impairment is not available.

1.53, I^2 = 86%). (Fig.2)

Seventeen studies were included in the meta-analysis of diabetes and VD risk. The multiple-adjusted pooled RR indicated that diabetes approximately doubled the risk of VD (RR:1.91, 95% CI:1.61-2.25, I^2 = 33%, grade A+). Sensitivity analyses limited the review to the studies with high-quality (score ≥8) had no appreciable effect on the pooled RR. There was no evidence of publication bias. The meta-regression analyses indicated the impact of studies controlling CVD or depression as a confounder in the model or not (p_{CVD} = 0.033, $p_{depression}$ = 0.001) on the pooled RR. The pooled RR of studies not controlling CVD in the model was significantly higher (RR2.32, 95% CI:1.89-2.85, I^2 = 0%) than that in studies controlling CVD (RR1.58, 95% CI:1.48-1.69, I^2 = 0%). Similarly, the pooled RR of studies not controlling depression in the model was significantly higher (RR2.19, 95% CI:1.88-2.56, I^2 = 0%) than that in studies controlling CVD (RR1.54, 95% CI:1.44-1.66, I^2 = 0%). (Fig.2)

3.2. Prediabetes

Nine studies assessed the risk of all-cause dementia in prediabetes. Grade G evidence indicated that prediabetes was associated with an increased risk of dementia overall (RR:1.18, 95% CI:1.02-1.36, I^2 = 22%). The risks were also significant when prediabetes was defined as an IFG 5.6–6.9 mmol/l (RR: 1.27, 95% CI:1.08-1.49, I^2 = 0%) and IGT (RR:1.40, 95% CI:1.03-1.91). Five studies were included in the analysis of prediabetes and AD, whereas three studies were included in the analysis of prediabetes and VD. Prediabetes was related to a higher risk of AD (RR: 1.36, 95% CI:1.09-1.70, I^2 = 14%, grade G) and a higher risk of VD (RR: 1.47, 95% CI:1.01–2.15, I^2 = 0%, grade A+). Five studies were identified on prediabetes and risk of cognitive impairment and found no association (RR:0.96, 95% CI:0.85–1.09, I^2 = 0%, grade S-). (Fig.2)

3.3. Diabetes-related biochemical indicators

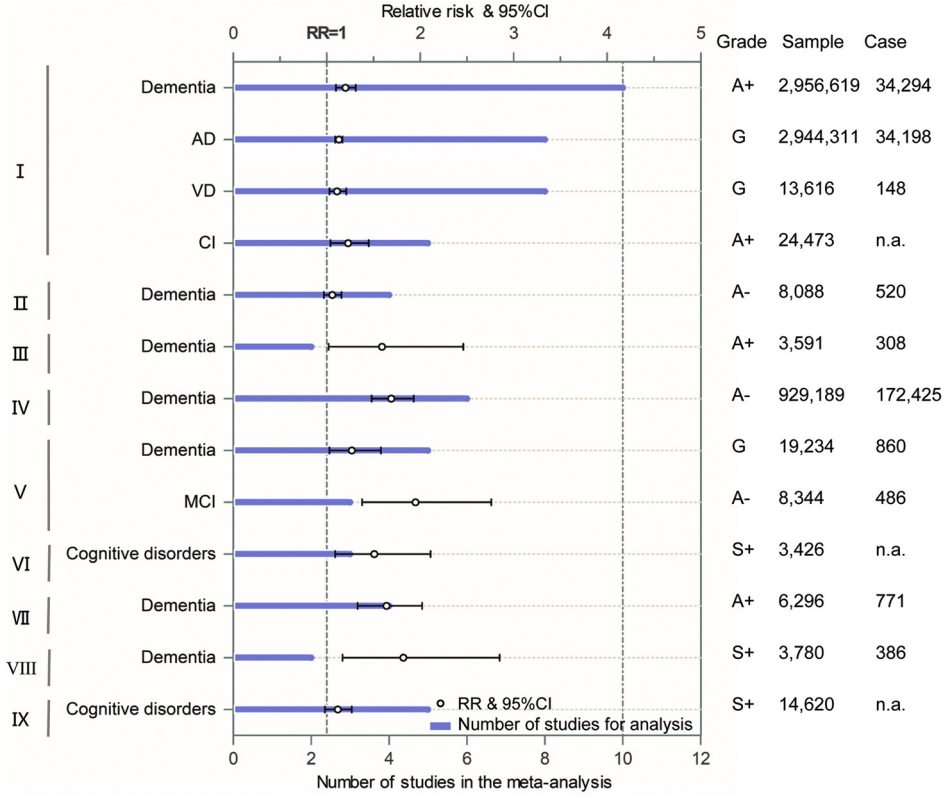
3.3.1. FPG and 2h-PG

Ten population-based cohort studies were included in the meta-analysis of high fasting plasma glucose and the risk of all cause dementia. The pooled RR was 1.20 (95% CI:1.10-1.31, I^2 = 36%, grade A+). There was no evidence of publication bias. In subgroup analysis, the risks were also significant when FPG > 5.6 mmol/L versus FPG < 5.6 mmol/L (RR: 1.22, 95% CI:1.06-1.41, I^2 = 16%), FPG > 6.1 mmol/L versus FPG < 6.1 mmol/L (RR: 1.49, 95% CI:1.10-2.03, I^2 = 0%), FPG > 7.0 mmol/L versus FPG < 7.0 mmol/L (RR: 1.21, 95% CI:1.06-1.37, I^2 = 0%). Eight studies were included in the analysis of fasting plasma glucose and AD and the pooled RR was 1.13 (95% CI:1.09-1.17, I^2 = 0%, grade G). Also, eight studies were included in the analysis of fasting plasma glucose and VD and the pooled RR was 1.11 (95% CI:1.03-1.21, I^2 = 0%, grade G). Additionally, high FPG was a risk factor for cognitive impairment (RR: 1.23, 95% CI:1.04-1.45, I^2 = 37%, grade A+). When we considered FPG as a continuous variable, we found no association of FPG with the risk of dementia (RR: 1.06, 95% CI:0.97-1.16, I^2 = 0%, grade A+). Moderate quality evidence showed that high 2h-PG level was associated with a 59% increased risk of dementia. Furthermore, six studies reported the association between hypoglycemia and dementia and the pooled RR was 1.69 (95% CI:1.48-1.93, I^2 = 47%, grade A-). (Fig.3)

Four studies were included in the dose-response analysis exploring the relationship between FPG and risk of cognitive disorders (Fig.4). There was evidence of a non-linear dose–response association (p for model = 0.0063, p for heterogeneity = 0.0116, p for non-linear trend = 0.0063); the risk of cognitive disorders increased by 20% with FPG above 7.75 mmol/L.

3.3.2. HbA1c

The positive relation of high HbA1c value with dementia was proved by the meta-analysis of five studies (RR: 1.27, 95%CI:1.03-1.58, I^2 = 26%, grade G). For three studies that reported on HbA1c and



Ⅰ. Fasting plasma glucose (FPG) high vs. low Ⅱ. FPG Ⅲ. 2h-Postprandial plasma glucose (2h-PG) high vs. low
Ⅳ. Hypoglycemia Ⅴ. HbA1c high vs. low Ⅵ. HbA1c Ⅶ. Hyperinsulinemia Ⅷ. Low fasting plasma insulin (FPI) Ⅸ. FPI

Fig. 3. Meta-analyses of the association of glucose and insulin levels with different cognitive outcomes. Moderate to high quality evidence indicated that elevated FPG, 2h-PG, HbA1c value and hypoglycemia were related to increased risk of dementia. Both low and high levels of fasting insulin are associated with an increased risk of developing dementia. "High vs low" means we compare the high level of the corresponding variable versus the low level. Cognitive disorders included all cause dementia, AD, VD, and cognitive impairment. Abbreviations: AD, Alzheimer's disease; VD, vascular dementia; MCI, mild cognitive impairment; CI, cognitive impairment; n.a. the number of people with cognitive impairment is not available.

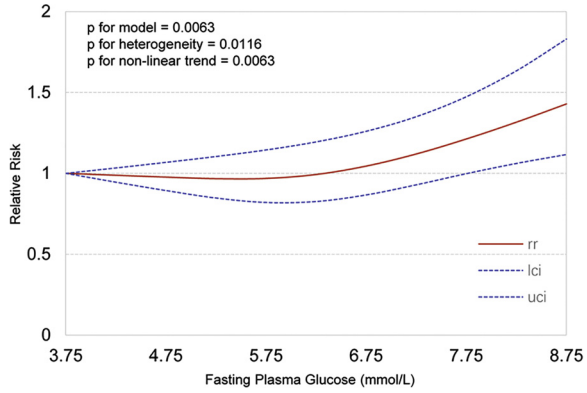


Fig. 4. Dose-response relation between FPG and cognitive disorders. There was a non-linear relationship between FPG and the risk of cognitive disorders. When FPG exceeds 7.75 mmol/L, the risk of cognitive disorders may increase by more than 20%.

MCI, the pooled RR was 1.95 (95%CI:1.38–2.76; I^2 = 31%, grade A-). When we considered HbA1c as a continuous variable, we found no association of HbA1c with the risk of cognitive disorders (RR: 1.51, 95% CI:1.09-2.11, I^2 = 61%, grade S+). (Fig.3)

3.3.3. FPI

Four studies were identified on prediabetes and risk of hyperinsulinemia and dementia. Moderate quality evidence indicated that higher levels of FPI were directly associated with dementia (RR:1.64, 95% CI:1.33-2.02, I^2 = 4%). Besides, low levels of FPI are also associated with an increased risk of developing dementia (RR:1.82, 95% CI:1.17-2.15, I^2 = 64%, grade S+). When FPI considered as a continuous variable, there was no association of FPI with the risk of cognitive disorders. (Fig.3)

3.4. Glucose-lowering drugs

3.4.1. Insulin

Eight population-based studies were included in the meta-analysis of infused insulin and the risk of dementia. Low quality evidence indicated that infused insulin in diabetic patients was associated with 1.44 greater likelihood of dementia (RR:1.44, 95% CI:1.16–1.79, I^2 = 95%). In the subgroup meta-analysis of different reference groups, the incidence rate of dementia was increased among diabetics with infused insulin both when compared to non-diabetics (RR:1.83, 95% CI:1.00–3.35, I^2 = 66%) and to diabetic patients without insulin use (RR:1.36, 95% CI:1.00–1.84, I^2 = 96%). Two studies reported data for infused insulin and risk of cognitive impairment and the pooled RR was 3.54 (95%CI:1.75–7.18; I^2 = 0%, grade A+). (Fig.5)

3.4.2. Oral antidiabetic drugs

The meta-analysis of five studies showed that the risk of dementia in diabetic patients treated with oral antidiabetic drugs was higher than that in non-diabetic patients (RR:1.49, 95% CI:1.16-1.92, I^2 = 91%). The sensitivity analysis excluding a study with low quality score showed a more significant association (RR:1.63, 95% CI:1.44-1.85, I^2 = 6%). Three studies reported data for metformin and risk of dementia. No association was identified between the risk of incident dementia and metformin when referenced to non-diabetics (RR:1.42, 95% CI:0.96-2.11, I^2 = 90%, grade S-) or to diabetic patients without metformin use (RR:0.89, 95% CI:0.75-1.06, I^2 = 44%, grade S-). (Fig.5)

Furthermore, the meta-analysis of two studies that provided high quality evidence demonstrated a possible effect of pioglitazone on the prevention of dementia in diabetic population. Compared with diabetics without pioglitazone treatment, use of pioglitazone reduced the dementia risk by 47% (RR:0.53, 95% CI:0.39-0.73, I^2 = 0%). In addition, the pooled RR of four studies for the incidence of dementia was 0.82 (95% CI: 0.57–1.18, I^2 = 83%, grade S+) in diabetics with

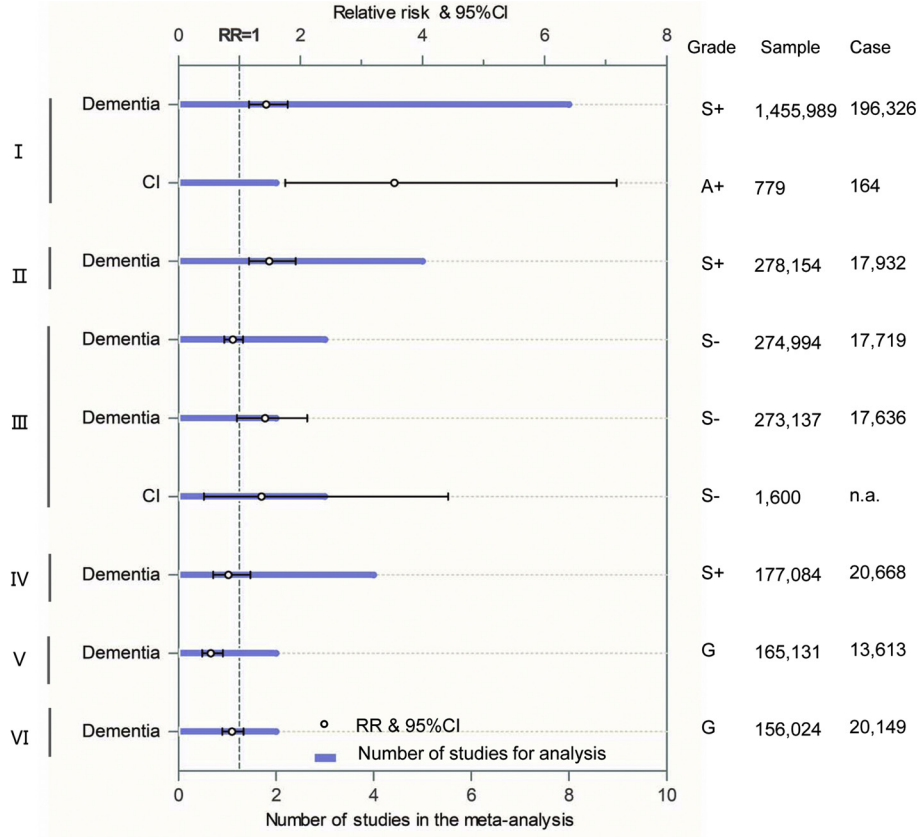


Fig. 5. Meta-analyses of the association of glucose-lowing drugs with different cognitive outcomes. Low quality evidence confirmed that infused insulin in diabetic patients was associated with greater risk of dementia. By contrast, pioglitazone might provide protection against incident dementia. Abbreviations: CI, cognitive impairment; n.a. the number of people with cognitive impairment is not available.

thiazolidinediones, and the pooled RR of two studies for the incidence of dementia was 0.88 (95% CI:0.72–1.07, I^2 = 0%, grade G) in diabetics with rosiglitazone. (Fig.5)

4. Discussion

To our knowledge, we are the first to comprehensively investigate the association of diabetes mellitus, prediabetes, diabetes-related biochemical indicators, and glucose-lowering drugs with the risk of cognitive impairment and dementia. We conducted detailed assessments of each meta-analysis to determine the credibility of the evidence and conducted meaningful sensitivity and meta-regression analyses to investigate sources of heterogeneity.

4.1. Diabetes and cognitive disorders

Meta-analyses provided low-moderate quality evidence that diabetes leads to deficits in all measured cognitive abilities. This finding is in line with previous meta-analyses of both cross-sectional studies and prospective studies (Monette et al., 2014; Palta et al., 2014). However, our analyses only included prospective studies with higher level of evidence, so we had more explanatory power and consequently higher credibility. Earlier studies indicate that diabetes affect cognitive subdomains served by the fronto-temporal lobe, resulting in a decline in memory, executive and processing abilities, but the reasons for the susceptibility of these regions to other regions of the brain needs further work (Zhou et al., 2010).

In non-demented population, moderate quality evidence indicated that diabetes conferred a 1.43- to 1.91- fold excess risk for dementia (including all-cause dementia, AD and VD), and the relative risk of developing MCI was 1.49. The positive association of diabetes with various types of dementia and MCI presented here is compatible with a previous meta-analysis (Cheng et al., 2012). However, in that meta-analysis, the authors found relatively few longitudinal studies, and recommended that additional studies needed to be conducted. Since 2012, several large prospective cohort studies have been reported. Therefore, much more high-quality studies were included in the present study, and our results consequently have more statistical power and higher accuracy.

Because of the large number of studies now published, we were able to conduct meaningful meta-regression and subgroup analyses. In our meta-regression analyses, publication year, the age, sex and education years of participants, geographical region, follow-up duration, quality score of studies, attrition, and different diagnostic subgroups (mixed diabetes or type 2 diabetes) were not significant predictors of estimated effect size. A recent study points out that there are bidirectional nature and neurological similarities with respect to diabetes and depression. The combination of diabetes and depression results in synergistic effects on cognition. Individuals with both diabetes and depression may experience greater deficits in cognitive functioning (Black et al., 2018). Therefore, we presented further meta-regression analyses to explore the potential effects of depression on the relationship between diabetes and cognitive impairment and dementia. In meta-analysis of diabetes and risk of VD, the result showed that the pooled RR of studies not adjusted for depression was higher compared with those adjusted for depression. In addition, diabetes is closely related to the cerebrovascular or cardiovascular disease, which is also a risk factor of dementia or cognitive impairment (Haroon et al., 2015). We explored the influence of whether controlling CVD as a confounder in the model by meta-regression and subgroup analysis. We found that when studies not controlling CVD as a confounder in the model, diabetes had a stronger effect on all-cause dementia, AD, and VD, which indicated that CVD as potential factors contributing to the diabetes-dementia associations might make us overestimate the association between the two.

The mechanism by which diabetes modifies the risk of developing dementia possibly involves Alzheimer's type pathology and vascular

type pathology against a background of ageing-related brain changes (Supplementary file 7). Alzheimer's type pathology is the accumulation of abnormally folded amyloid-β peptides (Aβ) and tau proteins in amyloid plaques and neuronal tangles (Scheltens et al., 2016), and vascular type pathology is caused by various forms of vascular damage, such as large vessel atherosclerosis, small vessel arteriosclerosis and other vascular diseases (i.e. cerebral amyloid angiopathy) (O'Brien and Thomas, 2015). With regard to Alzheimer's type pathology, diabetes has been reported to be positively associated with the CSF Aβ1-42 but negatively associated with cortical Aβ (Li et al., 2018) and associated with greater CSF total tau and phosphorylated tau (Moran et al., 2015). With regard to vascular type pathology, diabetes is a risk factor for atherosclerotic changes (Beckman et al., 2002) and is associated with an increased risk of stroke (Luitse et al., 2012).

4.2. Prediabetes and cognitive disorders

We summarized previous studies on prediabetes and cognitive disorders, involving different definitions of prediabetes: an HbA1c level of 5.7%–6.4% (American Diabetes Association, 2017); an FPG level of 5.6 or 6.1 mmol/l to 7.0 mmol/l, a 2h-PG level of 7.8 mmol/l to 11.1 mmol/l (Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 1997, 2003); or a random glucose level of 7.8 mmol/l to 11.1 mmol/l (Xu et al., 2010). High quality evidence disclosed that prediabetes was a risk factor for all-cause dementia, AD and VD, however, no association was found between diabetes and risk of cognitive impairment. The review by Biessels et al. suggested that different markers of prediabetes increased incidence of dementia (Biessels et al., 2014). A previous systematic review also highlighted the need to clarify the relationship between prediabetes and cognitive disorders (Li et al., 2014). Four studies included in their analysis have demonstrated the presence of mild cognitive deficits in people with prediabetes, and the data at the time were insufficient to investigate the effect of prediabetes on the risk of dementia and its major subtypes. A recent prospective cohort study confirmed that prediabetes was associated with accelerated cognitive decline independent of diabetes and prediabetes was related to smaller global brain volume, especially lower white matter volume (Marseglia et al., 2019). Our meta analyses included relatively fewer studies, so further studies with larger sample sizes are needed to validate the relationship between prediabetes and cognitive disorders. Additionally, in view of a positive association between prediabetes and dementia, interventions aimed at early diagnosis and treatment of abnormal glucose metabolism are necessary for the prevention of cognitive disorders.

4.3. Diabetes-related biochemical indicators and cognitive disorders

Moderate-to-high quality evidence implied that elevated levels of FPG, 2h-PG, HbA1c and hypoglycemia were closely associated with increased risk of dementia. Dose-response curves illustrated a nonlinear positive relationship between FPG and the risk of cognitive disorders. Our results are consistent with a previous review, indicating that high glycosylated hemoglobin concentration and glucose variability are negatively correlated with cognitive function (Geijselaers et al., 2015). As far as we know, we are the first to conduct meta-analysis of glycemia and cognitive function, as well as the first to establish the dose-response relationship. Mechanisms underlying the relationship between glycemia and cognitive function might involve glucose-related increased oxidative stress and toxic effect of accumulation of advanced glycation end-products, leading to diverse microvascular and macrovascular pathologies, resulting in clinical and subclinical strokes and subsequent cerebral volume loss (Brownlee, 2001; Kerti et al., 2013). Additionally, as previous studies reported, higher average glucose levels might be a risk factor for dementia, even among people without diabetes (Crane et al., 2013); elevated glucose fluctuation evaluated through a continuous glucose monitoring system (CGMS) was significantly related to cognitive impairment, independent of FPG, 2h-PG, and HbA1c (Rizzo et al., 2010; Zhong et al., 2012).

Moderate quality evidence suggested that both low and high levels of FPI levels were associated with a higher risk of dementia. Mechanisms underlying hyperinsulinemia/hypoinsulinemia on the development of dementia are not fully elucidated. Insulin can cross the blood brain barrier and insulin receptors are found in several areas of the brain, including the hippocampus. Therefore, abnormal insulin levels might directly affect cognitive function (Biessels et al., 2014). Moreover, hyperinsulinemia usually corresponds to insulin resistance. Insulin resistance could result in a reduction of insulin sensitivity at the cellular level and a modification of insulin transport into the brain. Thus, it is possible that both hypoinsulinemia and hyperinsulinemia lead to reduced insulinization in the brain, affecting the function of cells associated with cognition (Peila et al., 2004). Insulin also can play a part in the amyloid metabolism. Aβ is decomposed by insulin degrading enzyme and the increased concentrations of insulin compete for this enzyme, thereby reducing the degradation of Aβ (Banks et al., 2012; Biessels et al., 2014).

4.4. Glucose-lowering drugs and cognitive disorders

Moderate quality evidence confirmed that infused insulin in diabetic patients was associated with greater risk of cognitive disorders. Since patients with insulin treatment may have more severe diabetes or a longer history, this higher risk for the insulin-treated patients might be interpreted like a mark of the length or severity of diabetes (Areosa and Grimley, 2002). Besides, insulin exerts its effect on increasing the risk of dementia either directly or indirectly via causing hypoglycaemia (Lin and Sheu, 2013). High quality evidence suggested that pioglitazone might provide protection against incident dementia. Pioglitazone, an agonist of the nuclear receptor peroxisome proliferator-activated receptor gamma (PPARγ), may reduce the risk of dementia by lowering peripheral insulin and enhancing insulin sensitivity. In addition, PPARγ agonists have been shown to reduce amyloid-β accumulation and inflammatory reactants and confer neuroprotective effects (Landreth, 2007). The study by Lu et al. demonstrated that pioglitazone might exert a better protective effect on reducing dementia risk compared with other second-line glucose-lowering drugs when added to metformin (Lu et al., 2017). Additionally, the pilot trials provide preliminary support that glucose-lowering drugs (including intranasal insulin, metformin, pioglitazone, rosiglitazone, and liraglutide) may be a novel strategy for the treatment of cognitive disorders (Craft et al., 2012; Gejl et al., 2016; Hanyu et al., 2009; Luchsinger et al., 2016; Watson et al., 2005).

4.5. Limitations

The study has several limitations. First, we did not attempt to identify unpublished studies and we only included studies in PubMed, which were published in English. Therefore, some studies may have been missed. Second, in view of the small numbers of studies in some analyses, we cannot rule out the publication bias that may exist. Third, not all the included studies attempted to control for various known confounding factors. Even if these known confounding factors are controlled, the possibility of residual or unmeasured confounding cannot be ruled out. Fourth, the analysis with low quality evidence should be interpreted with great caution. Fifth, the data available are not sufficient to assess the relationship of diabetes duration and glucose control with the risk of cognitive disorders.

5. Conclusion

In summary, moderate to high quality evidence demonstrated that diabetes and prediabetes were associated with increased risk of dementia, suggesting that early glycemic control, perhaps in the

prediabetic stage, may be promising therapeutic targets for the prevention of cognitive decrements. Dose-response curves illustrated a nonlinear positive relationship between FPG and the risk of cognitive disorders. As data from the epidemiological studies included in the dose-response analysis was inadequate, the relation between FPG and cognitive disorders needs to be further clarified. Moderate to high quality evidence indicated that abnormal FPG, 2h-PG, HbA1c and FPI levels were related to a higher risk of cognitive disorders. Further studies with detailed assessment of cognition as well as detailed assessment of additional markers of dysglycaemia and insulin resistance, are expected to be carried out. High quality evidence showed that the application of pioglitazone might prevent dementia in the diabetic population. Good-quality randomized controlled trials with large samples should be conducted to confirm this conclusion and provide more information for prevention strategies.

Contributors

JTY and LT conceptualized and designed the study. MX, WX and YNO conducted the study. YNO, WX and MX, and MST analyzed and extracted data. MX, WX and JTY wrote the first draft of the manuscript. All authors reviewed the manuscript.

Declaration of Competing Interest

None authors have financial disclosures and conflicts of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.arr.2019.100944.

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