

# Diabetes mellitus and risk of dementia: A meta-analysis of prospective observational studies

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## ABSTRACT

**Aims/Introduction:** The aim of the present study was to investigate the association between diabetes and the risk of all type dementia (ATD), Alzheimer's disease (AD) and vascular dementia (VaD).

**Materials and Methods:** Prospective observational studies describing the incidence of ATD, AD and VaD in patients with diabetes mellitus were extracted from PubMed, EMBASE and other databases up to January 2012. Pooled relative risk (RR) estimates and 95% confidence intervals (CIs) were calculated using the random-effects model. Subgroup analyses and sensitivity analysis were also carried out.

**Results:** A total of 28 studies contributed to the analysis. Pooled RR of developing ATD ( $n = 20$ ) was 1.73 (1.65–1.82,  $I^2 = 71.2\%$ ), AD ( $n = 20$ ) was 1.56 (1.41–1.73,  $I^2 = 9.8\%$ ) and VaD ( $n = 13$ ) was 2.27 (1.94–2.66,  $I^2 = 0\%$ ) in patients with diabetes mellitus. Higher and medium quality studies did not show any significant difference for pooled RR for ATD, AD or VaD. Sensitivity analyses showed robustness of pooled RR among ATD, AD and VaD, showing no single study had a major impact on pooled RR.

**Conclusions:** The results showed a 73% increased risk of ATD, 56% increase of AD and 127% increase of VaD in diabetes patients. (J Diabetes Invest, doi: 10.1111/jdi.12087, 2013)

**KEY WORDS:** Dementia, Diabetes mellitus, Meta-analysis

## INTRODUCTION

The *Dementia UK* report predicts that 34 million people worldwide will have dementia by 2050, and 71% of these people will live in developing countries<sup>1</sup>. Currently, nearly 18 million people have dementia worldwide<sup>1</sup>. The diagnosis of dementia and especially Alzheimer's disease (AD) is usually retrospective, based on clinical phenomenology and exclusion of other medical problems<sup>2</sup>. The current management of dementia targets symptoms only and not the disease course<sup>2</sup>. In view of the emergence of risk factors playing key roles in the disease pathology of AD, such as age, obesity, diabetes mellitus, stroke and apolipoprotein  $\epsilon 4$  (APOE  $\epsilon 4$ ), it has become important to generate stronger evidence to strengthen the role of such risk factors, and aim to prevent such risk factors.

Diabetes mellitus is associated with changes in cognition<sup>3</sup>. A number of *in vivo* studies postulate a correlation between the mechanism of insulin resistance, and the pathogenesis of plaque formation and impaired neuronal signalling in AD<sup>4</sup>. Several longitudinal epidemiological studies over the past two decades have

linked diabetes mellitus, particularly type 2 diabetes mellitus, with an increased risk of cognitive impairment and dementia. If these studies have correctly predicted the association, then the future burden of dementia might be even greater than that estimated as the prevalence of diabetes mellitus continues to rise<sup>5</sup>. Early data that linked diabetes mellitus with cognitive impairment came from cross-sectional studies of poor methodological quality<sup>6</sup>. A recent meta-analysis on a similar topic was carried out, and concluded that there is an association between diabetes and dementia<sup>3</sup>. The studies assessing the link between type 2 diabetes mellitus and all type dementia (ATD; includes AD, vascular dementia [VaD] and dementia of other etiologies)<sup>7–26</sup>, AD<sup>7–11,14–16,19–21,23–25,27–32</sup> and VaD<sup>9–11,14–16,19–21,23,24,33,34</sup> have given conflicting results. Some epidemiological studies have reported that diabetes is independently implicated in the development of dementia<sup>26</sup>. However, these findings are inconsistent for its subtypes. Some studies have found an association between diabetes and both AD and VaD<sup>9,33</sup>, whereas others found an association with either only VaD<sup>11</sup> or AD<sup>15,16</sup>. The risk quantification is available only for AD<sup>2</sup>, but not for ATD and VaD. There has been no consensus in regards to the incidence of ATD, AD and VaD in diabetes mellitus as compared with the general population. In the present pooled meta-analysis of published prospective studies, we aim to investigate whether diabetes mellitus increases the risk of dementia, and whether diabetes is differentially related to the main subtypes of dementia, that is AD and VaD.

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## MATERIALS AND METHODS

### Literature Search

A comprehensive literature search was carried out using PubMed, EMBASE and other databases (up to January 2012) for observational cohort studies investigating an association between diabetes and ATD, AD and VaD using keywords dementia or Alzheimer's or cognition or vascular dementia and diabetes or diabetes mellitus. We searched for additional studies in bibliographies and citation sections of retrieved articles.

The present study was reported in accordance with the Meta-analysis of Observational Studies in Epidemiology guidelines for meta-analysis of observational studies.

### Study Selection

Two members (GK and FS) of the study group independently reviewed the titles and abstracts of all identified citations as per the inclusion criteria. An abstract was judged relevant if it reported original data, was published in English, was from epidemiological studies (cohort studies only), the outcome variable was ATD, AD and VaD, and the predictor variable was diabetes (both type 1 and 2 diabetes). Cohort studies reporting risk ratios (RR) or hazard ratios (HR) with 95% confidence interval (CI) were included in the meta-analysis. The manuscripts were excluded if the exposure was not diabetes; the outcome was not incidence of dementia, AD or VaD; if the study participants were cognitively impaired during baseline assessment; if no effect estimates were reported; or if not enough raw data was reported for a RR value to be calculated. We also excluded case-control and cross-sectional studies, as the age of onset of one or both of the diseases are often unknown. In such cases, only the comorbidities are described. Thus, in order to draw inferences about diabetes as a risk factor for developing dementia, longitudinal information (prospective follow up) about age at disease onset is critical. If a manuscript included data on risk factors other than diabetes, we extracted the data on diabetes only. Any discrepancies were resolved by consensus in-group conference. When there were multiple publications for the same population, we included the data from which ever study reported detailed and updated data.

The diagnostic criteria applied were similar across studies, which is probably because of the narrow time frame (1997–2012). Any dementia was generally defined according to the criteria from the Diagnostic and Statistical Manual of Mental Disorders, third edition (DSM-III) or the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV)<sup>35</sup>. AD was diagnosed according to the National Institute of Neurological and Communicative Diseases and Stroke, and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria<sup>36</sup>, including both cases of probable and possible AD. VaD was mostly diagnosed according to the National Institute of Neurological Disorders and Stroke, and the Association Internationale pour la Recherche et L'Enseignement en Neurosciences criteria<sup>37</sup>, including both probable and possible cases.

### Data Extraction and Quality Assessment

The following data were extracted from each study: author; study location; date the study was carried out; date of publication; journal; title; number and age of participants; study design; inclusion and exclusion criteria; and methods of diagnosis of diabetes, dementia, AD and VaD. For all included studies, we extracted the source cohort, follow-up period, RR or HR with 95% CI, and confounders adjusted for in the statistical analysis.

Two reviewers (GK and AB) assessed the quality of each selected study using the Newcastle Ottawa Scale (NOS)<sup>38</sup>. We defined studies of high quality as those that scored the maximum nine stars on the NOS; studies of medium quality scored seven or eight stars. Any discrepancy in quality assessment was discussed and resolved by the two reviewers.

### Data Synthesis and Statistical Analysis

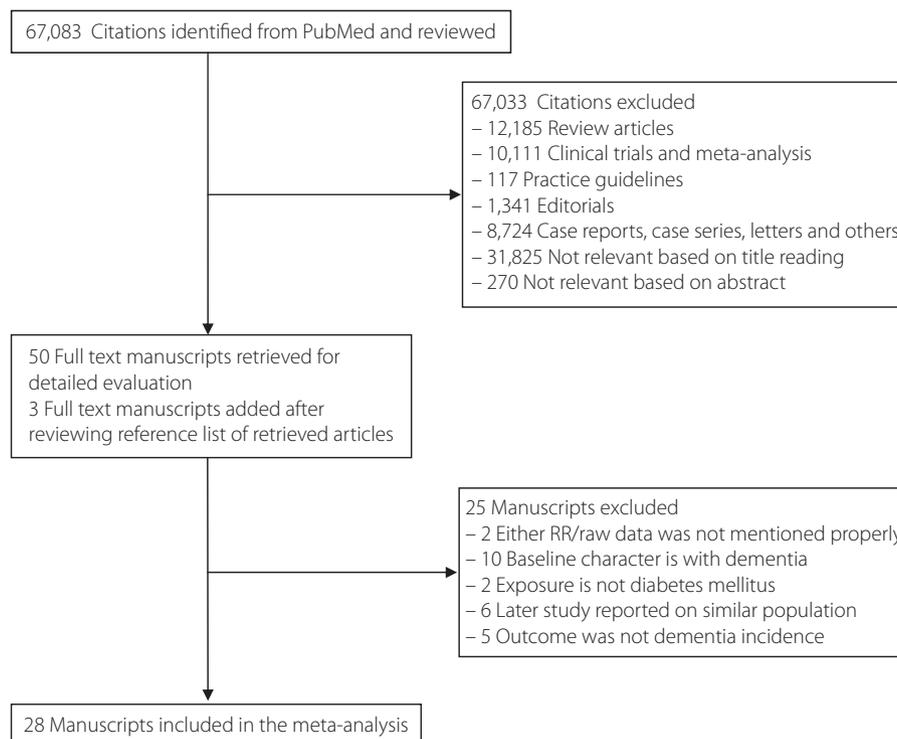
The primary outcome measure was to calculate the RR of dementia, AD and VaD individually. To assess the differential effect of diabetes on risk of AD and VaD, separate analysis was carried out for each category of dementia. To assess the significance of pooled effect estimate, we used a Z-test; a *P*-value <0.10 was considered to be statistically significant. To assess heterogeneity among studies, we used the Cochran Q and *I*<sup>2</sup> statistics; for the Q statistic, a *P*-value <0.10 was considered statistically significant for heterogeneity; for *I*<sup>2</sup>, a value >50% was considered as a measure of severe heterogeneity. If heterogeneity was present, risk ratios were pooled using a random effects model (DerSimonian and Laird method<sup>39</sup>), otherwise a fixed effects model (Hedges-Olkin method<sup>39</sup>) was used.

Prespecified subgroup analysis was carried out to assess the source of heterogeneity, according to: (i) quality of study by NOS; (ii) follow-up period (<6 and >6 years); (iii) adjustment for body mass index (BMI); (iv) adjustment for cardiovascular risk factors; and (v) adjustment for APOE ε4 allele. Tests for interaction using summary estimates were carried out using the method described by Altman and Bland<sup>39</sup>. To assess the robustness of the association, we also carried out sensitivity analysis by excluding the outliers. The publication bias was assessed using both funnel plot and Begg's test. If a publication bias in the pooled estimate was identified, we applied the Trim and Fill method<sup>39</sup>, which negotiates the lack of studies on a particular side of the funnel. When data were not uniformly reported to allow formal statistical analysis, we presented the data in a narrative format. All statistical tests were two-sided, and *P* < 0.05 was considered statistically significant, except where otherwise specified. Data were analyzed using STATA version 11.0 (StataCorp, College Station, TX, USA).

## RESULTS

### Search Results

A total of 67,083 citations were identified during the initial search (Figure 1). After reviewing the citations, 67,033 citations



**Figure 1** | Flow chart showing the number of citations retrieved by individual searches and the number of studies included in review. RR, risk ratio.

were considered ineligible as they were reviews, editorials, case reports and so on, and did not meet the inclusion criteria. After reviewing the reference list of the remaining 50 studies, three more studies were considered. After detailed evaluation of 53 potential manuscripts, 25 manuscripts were excluded for reasons shown in Figure 1.

### Study Characteristics

We identified 28 manuscripts reporting data on diabetes mellitus and the risk of one or more types of dementia in patients with diabetes as compared with non-diabetes patients published between 1997 and 2011. Among these, 20 studies reported the risk of ATD, 20 reported the risk of AD and 13 reported the risk of VaD. The present meta-analysis includes 1,148,041 participants, of whom 89,708 participants were having diabetes and 1,058,333 were non-diabetics. Participants were followed up for 2–30 years, reporting a total of more than 15,039 incident cases of ATD, 4592 AD and 1002 VaD. Information on source population, method of ascertainment of exposure, diagnosis of dementia and adjustment for confounders is presented in Table 1.

Most of the studies used standard methods NINCDS<sup>36</sup> to diagnose various types of dementia; however, some studies have used ad-hoc criteria<sup>14–16,19</sup> or were registry based<sup>13,18,20,24</sup>. Most of the studies assessed diabetes based on self-report<sup>13,14,30</sup>, registry based<sup>24,32</sup> and antidiabetic medication usage<sup>22</sup>.

### Main Analyses and Subgroup Analyses

#### All Type Dementia

As significant heterogeneity was found between studies ( $P_{heterogeneity} < 0.01$ ,  $I^2 = 71.2\%$ ), a random-effects model was chosen over a fixed-effect model (Table 2). Patients with diabetes were found to be at a significantly higher risk of ATD compared with the non-diabetic population (pooled RR 1.73 (95% CI 1.65–1.82,  $P \leq 0.001$ ). The multivariable-adjusted RR of dementia for each study and all studies combined are shown in Figure 2. Visual examination of the funnel plot showed minimal asymmetry, further confirmed by Egger's test ( $P = 0.83$ ), indicating little or no publication bias in our analysis. Sensitivity analyses showed robustness of pooled RR, as RR values lay within the range of 1.57–1.63, thus clearly showing no major impact of any single study on pooled RR. Table 3 presents the results of subgroup analyses stratified by quality rating and adjustment for risk factors. There was no statistically significant difference observed among studies reporting the incidence of ATD subgrouped on the basis of follow up ( $P_{interaction} = 0.13$ ), adjustment for BMI ( $P_{interaction} = 0.49$ ), cardiovascular disease ( $P_{interaction} = 0.84$ ) and APOE  $\epsilon 4$  allele ( $P_{interaction} = 0.16$ ). When studies were analyzed according to study quality assessed using NOS, high-quality studies reported a stronger association (pooled RR 1.61, 95% CI 1.43–1.81,  $P \leq 0.001$ ) as compared with medium quality studies (pooled RR 1.54, 95% CI 1.10–2.15,  $P \leq 0.001$ ). We did not find a significant difference

**Table 1** | Descriptive characteristics of the studies included in the analysis

Author (year of publication)	Study site	Study name	Age at baseline (years)	Follow up (years)/start-end year	Total population/with diabetes (n)	With dementia (n)	With Alzheimer's disease (n)	With vascular dementia (n)	QR
Leibson (1997) <sup>7</sup>	USA	NR	≥45	15 (1970-1984)	1,455/1,455	101	77	NR	Medium
Ott (1999) <sup>8</sup>	Netherlands	The Rotterdam study	≥55	2.1 (1991-1994)	6,370/692	126	89	NR	High
Tyas (2001) <sup>27</sup>	USA	Manitoba Study of Health and Aging	≥65	5 (1991-1996)	694/44	NR	36	NR	High
Posner (2002) <sup>33</sup>	USA	Washington Heights-Inwood	≥65	7 (1991-1998)	1,259/NR	NR	157	56	Medium
MacKnight (2002) <sup>9</sup>	Canada	Columbia Aging Project	≥65	5 (1991-1996)	5,574/503	NR	267	NR	High
Pella (2002) <sup>10</sup>	USA	Canadian Study of Health and Aging	≥65	2.9 (NR)	2,574/900	76	68	33	High
Hassing (2002) <sup>11</sup>	Sweden	The Honolulu-Asia Aging Study	≥80	9 (1991-1999)	702/108	187	105	50	High
Honig (2003) <sup>28</sup>	USA	Origins of Variance in the Old-Old	≥65	7 (1991-1998)	1,766/NR	NR	181	NR	Medium
Beerl (2004) <sup>12</sup>	Israel	Washington Heights-Inwood	40-65	> 30 (1965-1999)	1,892/867	309	NR	NR	Medium
Arvanitakis (2004) <sup>29</sup>	USA	Columbia Aging Project	≥55	5.5 (1994-2003)	824/127	721	151	NR	High
Whitmer (2005) <sup>13</sup>	USA	Israeli Ischemic Heart Disease study	40-44	9 (1994-2003)	8,845/1,004	NR	NR	NR	High
Borenstein (2005) <sup>30</sup>	USA	Religious Orders Study	≥65	9 (1992-2001)	1,859/NR	NR	90	NR	Medium
Hayden (2006) <sup>14</sup>	USA	Kaiser Permanente Medical Care Program	≥65	3.2 (1995-1999)	3,264/322	185	104	37	High
Akomolafe (2006) <sup>15</sup>	USA	The Cache County Study	70 mean age	12.7 (1977-1990)	2,210/202	319	237	32	High
Lin (2006) <sup>34</sup>	Taiwan	Framingham Study	NR	2 (2003-2005)	345/93	NR	NR	155	Medium
Irie (2008) <sup>16</sup>	USA	The Cardiovascular Health Study	NR	5.4 (1992-1999)	2,547/320	411	207	58	High
Peters (2009) <sup>17</sup>	UK	Cognition Study	≥80	2 (NR)	3,336/518	263	NR	NR	Medium
Alonso (2009) <sup>18</sup>	USA	Hypertension in the Very Elderly Trial	45-64	13 (1991-2004)	11,151/1,444	203	NR	NR	High
Raffaini (2009) <sup>19</sup>	France	Atherosclerosis Risk in Communities study	≥65	4 (1999-2004)	7,087/539	208	134	40	High
Toro (2009) <sup>31</sup>	Germany	The Three-City study	75	NR	381/77	NR	26	NR	Medium
Xu (2009) <sup>20</sup>	Sweden	Interdisciplinary Longitudinal Study on Adult Development and Aging	≥75	9 (1988-1997)	1,248/75	420	320	47	High
		Kungsholmen project							

Table 1 (Continued)

Author (year of publication)	Study site	Study name	Age at baseline (years)	Follow up (years)/start-end year	Total population/with diabetes (n)	With dementia (n)	With Alzheimer's disease (n)	With vascular dementia (n)	QR
Ahtiluoto (2010) <sup>21</sup>	Finland	Vantaa85 + Study	≥85	9 (1991–2001)	NR/NR	106	NR	NR	High
Hsu (2011) <sup>22</sup>	Taiwan	NR	≥50	7 (2000–2007)	229,025/29,748	7835	NR	NR	High
Ohara (2011) <sup>23</sup>	Japan	The Hisayama Study	≥60	15 (1988–2003)	1,017/150	156	71	39	High
Kimm (2011) <sup>24</sup>	Korea	NR	40–95	14 (1993–2006)	848,505/51,611	3252	1851	610	High
Cheng (2011) <sup>25</sup>	USA	Columbia Aging Project	≥65	9 (1999–2007)	1,488/253	161	149	NR	Medium
Creavin (2011) <sup>26</sup>	UK	Caerphilly Prospective Study	45–59	10 (1983–1993)	2,512/NR	NR	NR	NR	High
Li (2011) <sup>32</sup>	China	NR	≥55	5 (2004–09)	837/136	NR	298	NR	High

NR, not reported; QR, quality rating.

( $P_{interaction} = 0.80$ ) in the two pooled RR, as the studies were grouped according to the study quality.

#### Alzheimer's Disease

Because no significant heterogeneity ( $P_{heterogeneity} = 0.30$ ,  $I^2 = 9.8\%$ ) was found, the fixed-effects model was chosen over a random-effects model (Table 2). The pooled result of 20 studies showed that diabetes was found to be associated with a significantly higher risk of AD compared with non-diabetic population (pooled RR 1.56, 95% CI 1.41–1.73,  $P = 0.00$ ). The multivariable-adjusted RRs of AD for each study and all studies combined are shown in Figure 3. Visual examination of the funnel plot revealed minimal asymmetry, further confirmed by Egger's test ( $P = 0.93$ ), indicating little or no publication bias in our analysis. Sensitivity analysis showed robustness of pooled RR and that RR values lay within the range of 1.54–1.59, and this clearly showed that no single study had a major impact on pooled RR. We did not find a significant difference ( $P_{interaction} = 0.43$ ) in the two pooled RR, as the studies were grouped according to quality assessment (Table 3).

#### Vascular Dementia

As we found no significant heterogeneity ( $P_{heterogeneity} = 0.61$ ,  $I^2 = 0\%$ ), a fixed-effects model was chosen over a random-effects model (Table 2). The pooled result of 13 studies showed that diabetes was associated with a significantly higher risk of VaD compared with the non-diabetic population (pooled RR 2.27 [95% CI 1.94–2.66]). The multivariable-adjusted RRs of VaD for each study and all studies combined are shown in Figure 4. Visual examination of the funnel plot showed minimal asymmetry, further confirmed by Egger's test ( $P = 0.41$ ), indicating little or no publication bias in our analysis. Sensitivity analyses showed robustness of pooled RR and that RR values lie within the range of 2.0–2.3, and this clearly showed that no single study had a major impact on pooled RR. We did not find a significant difference ( $P_{interaction} = 0.48$ ) in the two pooled RR, as the studies were grouped according to the quality assessment (Table 3).

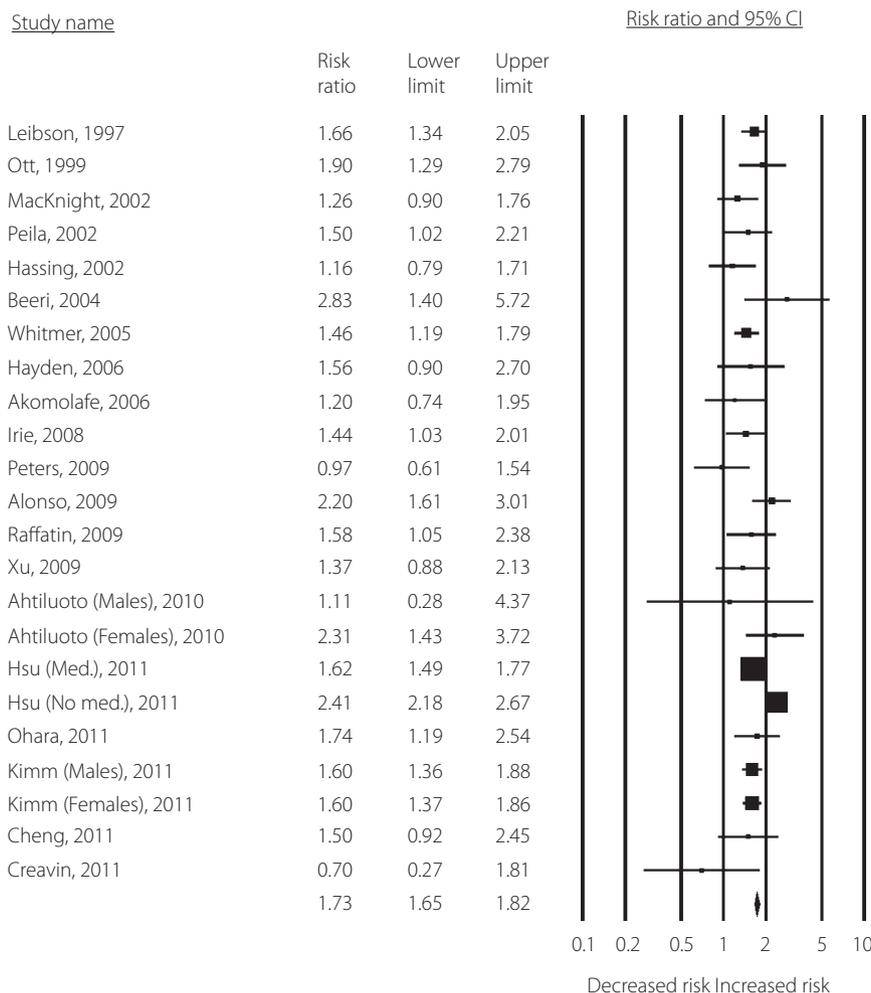
## DISCUSSION

The present meta-analysis of 28 observational studies showed a 73% increased risk of ATD, 56% increase in AD and 127% increase in VaD in patients with history of diabetes as compared with non-diabetic people. Some biological mechanisms have been postulated through which diabetes might increase the risk of AD<sup>4,10</sup>; vascular mechanisms, toxic effects of hyperglycemia, insulin resistance of the brain, formation of advanced glycation end-products (AGE) and competition for insulin-degrading enzyme (IDE) resulting in reduced degradation of  $\beta$  amyloid, but none of these have been proven unequivocally. As diabetes is known to increase the risk of cerebrovascular disease, its association with VaD is understandable<sup>40</sup>. Hyperglycemia in diabetes is usually associated with accelerated AGE formation. The mechanism behind the increased risk of AD might possibly be due to

**Table 2** | Pooled risk ratios of all type dementia, Alzheimer's disease and vascular dementia

Type of dementia	No. studies pooled	Pooled estimate		Level of significance of pooled RR	Tests of heterogeneity			Tests of publication bias
		RR	95% CI		Q value (d.f.)	P-value	I <sup>2</sup> (%)	
All type dementia	20	1.73	1.65–1.82	<0.001	76.5 (22)	<0.01	71.25	0.12
Alzheimer's disease	20	1.56	1.41–1.73	<0.001	23.3 (21)	0.32	9.8	0.93
Vascular dementia	13	2.27	1.94–2.66	<0.001	12.0 (12)	0.52	0	0.41

CI, confidence interval; d.f., degrees of freedom; RR, relative risk.

**Figure 2** | Diabetes and risk of all type dementia. CI, confidence interval.

the fact that AGE-mediated cross-linking of extracellular proteins accelerates amyloid- $\beta$  aggregation<sup>41</sup>. AGEs might also be involved in microtubule associated tau protein stabilization and tangle formation. AGE-related modifications might also contribute by decreasing protein solubility and increased protease

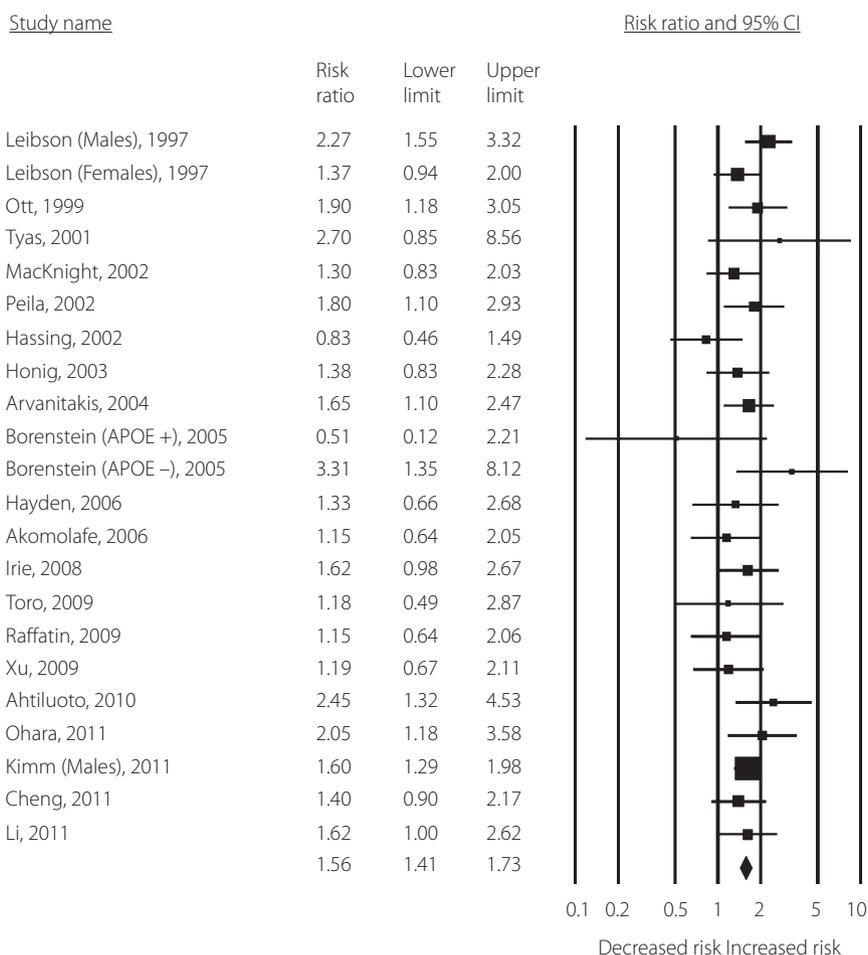
resistance of several proteins involved in pathological lesions associated with AD<sup>42</sup>.

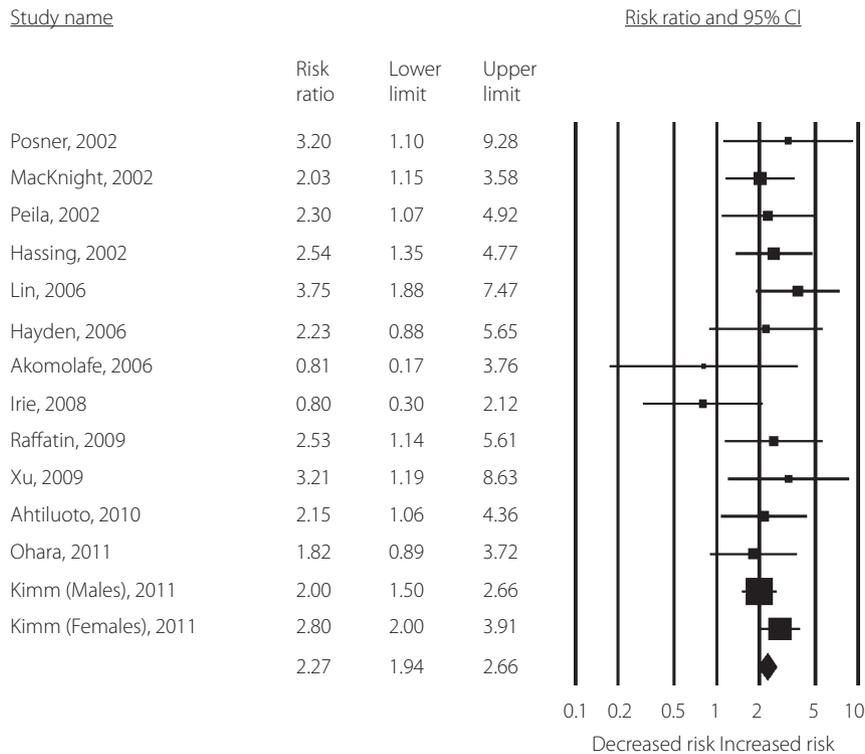
Advanced glycation end-products and APOE  $\epsilon$ 4 allele has been found colocalized in senile plaques, and neurofibrillary tangles of patients with AD and other types of dementia<sup>43</sup>. The

**Table 3** | Overall risk ratios between diabetes and all type dementia, Alzheimer's disease and vascular dementia according to study characteristics

Subgroup	All type dementia			Alzheimer's disease			Vascular dementia		
	No. studies	Risk ratio (95% CI)	$P_{interaction}$	No. studies	Risk ratio (95% CI)	$P_{interaction}$	No. studies	Risk ratio (95% CI)	$P_{interaction}$
Quality rating									
High	16	1.61 (1.43–1.81)	0.80	15	1.48 (1.33–1.64)	0.43	11	2.19 (1.86–2.58)	0.48
Medium	4	1.54 (1.10–2.15)		5	1.62 (1.33–1.99)		2	3.2 (1.1–9.2)	
Follow-up period (years)									
<6	7	1.43 (1.23–1.66)	0.13	10	1.57 (1.33–1.87)	0.78	5	1.95 (1.39–2.75)	0.41
≥6	13	1.66 (1.46–1.89)†		10	1.52 (1.29–1.78)		8	2.29 (1.91–2.75)	
Adjustments for confounders									
Body mass index									
Yes	7	1.53 (1.33–1.77)	0.49	4	1.52 (1.21–1.91)	0.95	6	1.82 (1.26–2.62)	0.25
No	13	1.64 (1.43–1.88)†		16	1.51 (1.36–1.67)		7	2.31 (1.93–2.77)	
Cardiovascular diseases									
Yes	11	1.61 (1.35–1.91)†	0.84	7	1.46 (1.21–1.75)	0.50	7	1.88 (1.38–2.55)	0.22
No	9	1.58 (1.45–1.71)		13	1.57 (1.40–1.75)		6	2.35 (1.94–2.80)	
APOE gene									
Yes	8	1.79 (1.52–2.12)	0.16	4	1.57 (1.27–1.95)	0.83	4	2.36 (1.57–3.57)	0.72
No	12	1.54 (1.35–1.75)†		16	1.53 (1.38–1.72)		9	2.18 (1.83–2.60)	

$P < 0.05$ . †Heterogeneity present ( $I^2 > 50\%$ ). APOE, apolipoprotein; BMI, body mass index.

**Figure 3** | Diabetes and risk of Alzheimer's disease. CI, confidence interval.



**Figure 4** | Diabetes and risk of vascular dementia. CI, confidence interval.

APOE  $\epsilon 4$  allele has a reduced ability to repair neuronal damage and a decreased anti-oxidant activity<sup>44</sup>, and promotes stabilization of  $\beta$ -amyloid deposits<sup>45</sup>. The APOE  $\epsilon 4$  allele also stimulates A $\beta$  deposition and accelerates conversion of A $\beta$  protein to insoluble deposits in the brain by binding to it<sup>46</sup>. Peila *et al.*<sup>10</sup> have also reported a high association (a fivefold increase) between AD and diabetes, particularly among carriers of the APOE  $\epsilon 4$  allele.

Regarding the genetic predisposition, an association between the APOE  $\epsilon 4$  allele and dementia is well known<sup>24</sup>. It has been reported that APOE  $\epsilon 4$  allele carriers have an increased incidence of AD<sup>21</sup>. In several observational studies, it has been reported that the presence of the APOE  $\epsilon 4$  allele in diabetic patients synergistically increased the incidence of AD and other types of dementia as compared with non-diabetic patients<sup>10,16,21</sup>.

The other postulated mechanism is that in the brain, insulin is involved in various cognitive functions. A large number of insulin receptors are located in the hippocampus and cerebral cortex, which play a central role in memory. Insulin induces the release of  $\beta$ -amyloid peptide (Ab) to the cell exterior, and also promotes the expression of IDE. IDE is also involved in the degradation of Ab. Thus, a lack of insulin will promote Ab accumulation<sup>47–49</sup>.

In the case of hyperinsulinemia or insulin-resistance, as a result of downregulation, there is a fall in insulin receptors and less entry of insulin into the brain. Also, in the

hyperinsulinemic state, the amount of IDE falls due to its higher consumption, resulting in an increase in Ab causing accelerated cognitive impairment. In this regard, a cohort study on middle-aged adults reported an association between hyperinsulinemia and cognitive decline<sup>50</sup>. Also, in the Hisayama study, autopsy findings showed that hyperinsulinemia and hyperglycemia enhanced neuritic plaque formation<sup>51</sup>. Furthermore, Ronnema *et al.*<sup>52</sup> reported that a reduction in insulin secretion was associated with the onset of AD. Thus, insulin seems to be definitely connected with the AD pathology and insulin resistance to be associated with VaD through atherosclerosis.

In the present analysis also, we have found that diabetes causes an increased risk of both AD 1.56 (95% CI 1.41–1.73) and VaD 2.27 (95% CI 1.94–2.66). Differentiation between the underlying pathology of these two categories of dementia with diabetes is not very well elucidated.

The present findings are consistent with two previous systematic reviews assessing the risk of ATD in patients with type 2 diabetes mellitus<sup>47,53</sup>. Seven out of 10 studies by Biessels *et al.*<sup>47</sup> and five out of nine studies by Kloppenborg *et al.*<sup>53</sup> reported a higher risk of dementia in patients with diabetes. The present pooled analysis quantifies the data from 20 cohort studies, including 15,039 incident dementia cases reporting a strong association between ATD and its subtypes and diabetes (1.73 [95% CI 1.65–1.82]).

The possible reasons for variation in the results could arise from methodological differences; for example, different criteria of

diagnosis and categorization of dementia<sup>26,29,32</sup>, varying diagnostic criteria of diabetes through different times<sup>54,55</sup>, different follow-up times<sup>14,17,23</sup>, sample sizes<sup>11,22,24</sup>, specific populations<sup>17,21,25</sup> and so on. The most important factor is the cut-off value of fasting plasma glucose for the diagnosis of diabetes. In the Prospective Study of Pravastatin in the Elderly at Risk and the Rotterdam study, although a decline in cognitive function was observed in diabetic patients as compared with non-diabetic subjects, no significant association was noted between fasting blood glucose levels and cognitive impairment in non-diabetics<sup>56</sup>.

Thus, it has been argued that there is a certain threshold above which abnormal blood glucose levels cause cognitive impairment or the involvement of factors other than hyperglycemia is greater in diabetic patients<sup>57</sup>. Diabetes treatment that minimizes dementia will be of growing importance, although the place of insulin is still controversial<sup>8</sup>.

The current meta-analysis presents with a few strengths. As the present analysis was carried out on prospective studies, our findings are unlikely to be biased by recall bias and selection bias. We included 28 studies, with a total of 89,708 diabetes patients, which further strengthens our results. We also carried out sensitivity analysis to investigate whether any particular study explained the results, and the overall findings were robust. These are important determinants of the increased risk of dementia in people with diabetes, and likely to help in understanding the factors that are associated in diabetes patients, which can then be better regulated.

The study also had some limitations. Many, but not all, of the studies were adjusted for potential confounding factors, such as age and sex. Most studies did not assess a premorbid intelligence quotient in their study populations, but did adjust the RR for the possible effects of education. We also did not search for unpublished studies, and excluded studies published in languages other than English. This might also have influenced the results.

To summarize, the present meta-analysis suggests that patients with diabetes are at higher risk of ATD. Further studies should report more detailed results, including those for subtypes of antidiabetic medications usage, along with the class of drugs, and the results should also be stratified by other risk factors in order to rule out residual confounding. Further assessment of the impact of measurement errors on the risk estimates is also warranted. Future studies are required to determine the role of good glycemic control among diabetes patients in lowering the risk of dementia.

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## REFERENCES

1. Alzheimer's Disease International. The Prevalence of Dementia Worldwide. Alzheimer's Disease International, London, 2008.
2. Profenno LA, Porsteinsson AP, Faraone SV. Meta-analysis of Alzheimer's disease risk with obesity, diabetes, and related disorders. *Biol Psychiatry* 2010; 67: 505–512.
3. Cheng G, Huang C, Deng H, et al. Diabetes as a risk factor for dementia and mild cognitive impairment: a meta-analysis of longitudinal studies. *Intern Med J* 2012; 42: 484–491.
4. Cole AR, Astell A, Green C, et al. Molecular connexions between dementia and diabetes. *Neurosci Biobehav Rev* 2007; 31: 1046–1063.
5. Strachan MW, Price JF, Frier BM. Diabetes, cognitive impairment, and dementia. *BMJ* 2008; 336: 6.
6. Kimura R, Tomiyasu H, Takeuchi T, et al. Prevalence of Alzheimer's disease with diabetes in the Japanese population. *Psychogeriatrics* 2008; 8: 73–78.
7. Leibson CL, Rocca WA, Hanson VA, et al. Risk of dementia among persons with diabetes mellitus: a population-based cohort study. *Am J Epidemiol* 1997; 145: 301–308.
8. Ott A, Stolk RP, van Harskamp F, et al. Diabetes mellitus and the risk of dementia: the rotterdam study. *Neurology* 1999; 53: 1937–1942.
9. MacKnight C, Rockwood K, Awalt E, et al. Diabetes mellitus and the risk of dementia, Alzheimer's disease and vascular cognitive impairment in the Canadian Study of Health and Aging. *Dement Geriatr Cogn Disord* 2002; 14: 77–83.
10. Peila R, Rodriguez BL, Launer LJ. Type 2 diabetes, APOE gene, and the risk for dementia and related pathologies. The honolulu-Asia aging study. *Diabetes* 2002; 51: 1256–1262.
11. Hassing LB, Johansson B, Nilsson SE, et al. Diabetes mellitus is a risk factor for vascular dementia, but not for Alzheimer's disease: a population-based study of the oldest old. *Int Psychogeriatr* 2002; 14: 239–248.
12. Beeri MS, Goldbourt U, Silverman JM, et al. Diabetes mellitus in midlife and the risk of dementia three decades later. *Neurology* 2004; 63: 1902–1907.
13. Whitmer RA, Sidney S, Selby J, et al. Midlife cardiovascular risk factors and risk of dementia in late life. *Neurology* 2005; 64: 277–281.
14. Hayden KM, Zandi PP, Lyketsos CG, et al. Vascular risk factors for incident Alzheimer disease and vascular dementia. *Alzheimer Dis Assoc Disord* 2006; 20: 93–100.
15. Akomolafe A, Beiser A, Meigs JB, et al. Diabetes mellitus and risk of developing alzhemiers disease. Results from the framingham study. *Arch Neurol* 2006; 63: 1551–1555.
16. Irie F, Fitzpatrick AL, Lopez OL, et al. Enhanced risk for Alzheimer disease in persons with type 2 diabetes and APOE e4. The cardiovascular health study cognition study. *Arch Neurol* 2008; 65: 89–93.
17. Peters R, Poulter R, Beckett N, et al. Cardiovascular and biochemical risk factors for incident dementia in the hypertension in the very elderly trial. *J Hypertens* 2009; 27: 2055–2062.
18. Alonso A, Mosley TH, Gottesman RF, et al. Risk of dementia hospitalisation associated with cardiovascular risk factors in

- midlife and older age: the Atherosclerosis Risk in Communities (ARIC) study. *J Neurol Neurosurg Psychiatry* 2009; 80: 1194–1201.
19. Raffaitin C, Gin H, Empana JP, *et al.* Metabolic syndrome and risk for incident Alzheimer's disease or vascular dementia. *Diabetes Care* 2009; 32: 169–174.
  20. Xu WL, Qiu CX, Wahlin A, *et al.* Diabetes mellitus and risk of dementia in the Kungsholmen project: a 6-year follow-up study. *Neurology* 2004; 63: 1181–1186.
  21. Ahiluoto S, Polvikoski T, Peltonen M, *et al.* Diabetes, Alzheimer disease, and vascular dementia. A population-based neuropathologic study. *Neurology* 2010; 75: 1195–1202.
  22. Hsu CC, Wahlqvist ML, Lee MS, *et al.* Incidence of dementia is increased in type 2 diabetes and reduced by the use of sulfonylureas and metformin. *J Alzheimers Dis* 2011; 24: 485–493.
  23. Ohara T, Doi Y, Ninomiya T, *et al.* Glucose tolerance status and risk of dementia in the community. The Hisayama Study. *Neurology* 2011; 77: 1126–1134.
  24. Kimm H, Lee PH, Shin YJ, *et al.* Mid-life and late-life vascular risk factors and dementia in Korean men and women. *Arch Gerontol Geriatr* 2011; 52: e117–e122.
  25. Cheng D, Noble J, Tang MX, *et al.* Type 2 diabetes and late onset Alzheimer's disease. *Dement Geriatr Cogn Disord* 2011; 31: 424–430.
  26. Creavin ST, Gallacher J, Bayer A, *et al.* Metabolic syndrome, diabetes, poor cognition, and dementia in the caerphilly prospective study. *J Alzheimers Dis* 2011; 28: 1–10.
  27. Tyas SL, Manfreda J, Strain LA, *et al.* Risk factors for Alzheimer's disease: a population-based, longitudinal study in Manitoba, Canada. *Int J Epidemiol* 2001; 30: 590–597.
  28. Honig LS, Tang MX, Albert S, *et al.* Stroke and the risk of alzheimer disease. *Arch Neurol* 2003; 60: 1707–1712.
  29. Arvanitakis Z, Wilson RS, Bienias JL, *et al.* Diabetes mellitus and risk of alzheimer disease and decline in cognitive function. *Arch Neurol* 2004; 61: 661–666.
  30. Borenstein AR, Wu Y, Mortimer JA, *et al.* Development and vascular risk factors for alzheimer's disease. *Neurobiol Aging* 2005; 26: 325–334.
  31. Toro P, Schonknecht P, Schroder J. Type II diabetes in mild cognitive impairment and Alzheimer's disease: results from a prospective population-based study in Germany. *J Alzheimers Dis* 2009; 16: 687–691.
  32. Li J, Wang YJ, Zhang M, *et al.* Vascular risk factors promote conversion from mild cognitive impairment to Alzheimer disease. *Neurology* 2011; 76: 1485–1491.
  33. Posner HB, Tang MX, Luchsinger J, *et al.* The relationship of hypertension in the elderly to ad, vascular dementia, and cognitive function. *Neurology* 2002; 58: 1175–1181.
  34. Lin JC, Hsu CW, Hsu HP, *et al.* Risk factors for vascular dementia: a hospital-based study in Taiwan. *Acta Neurol Taiwan* 2006; 17: 22–26.
  35. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th edn. American Psychiatric Association, Washington, DC, 2000.
  36. McKhann G, Drachman D, Folstein M, *et al.* Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* 1984; 34: 939–944.
  37. Roman GC, Tatemichi TK, Erkinjuntti T, *et al.* Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. *Neurology* 1993; 43: 250–260.
  38. Wells G, Shea B, O'Connell D, *et al.* The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. [Cited 2012 March 27]. Available at: [http://www.evidencebasedpublichealth.de/download/Newcastle\\_Ottawa\\_Scale\\_Pope\\_Bruce.pdf](http://www.evidencebasedpublichealth.de/download/Newcastle_Ottawa_Scale_Pope_Bruce.pdf)
  39. Higgins JP, Thompson SG, Deeks JJ, *et al.* Measuring inconsistency in meta-analyses. *BMJ* 2003; 327: 557–560.
  40. Bruce DG, Davis WA, Casey GP, *et al.* Predictors of cognitive impairment and dementia in older people with diabetes. *Diabetologia* 2008; 51: 241–248.
  41. Dickson DW, Sinicropi S, Yen SH, *et al.* Glycation and microglial reaction in lesions of Alzheimer's disease. *Neurobiol Aging* 1996; 17: 733–743.
  42. Selkoe DJ, Ihara Y, Salazar FJ. Alzheimer's disease: insolubility of partially purified paired helical filaments in sodium dodecyl sulfate and urea. *Science* 1982; 215: 1243–1245.
  43. Sasaki N, Fukatsu R, Tsuzuki K, *et al.* Advanced glycation end products in Alzheimer's disease and other neurodegenerative diseases. *Am J Pathol* 1998; 153: 1149–1155.
  44. Ma J, Yee A, Brewer HB, *et al.* Amyloid-associated proteins alpha 1-antichymotrypsin and apolipoprotein E promote assembly of Alzheimer beta-protein into filaments. *Nature* 1994; 372: 92–94.
  45. Beffert U, Danik M, Krzywkowski P, *et al.* The neurobiology of apolipoproteins and their receptors in the CNS and Alzheimer's disease. *Brain Res Brain Res Rev* 1998; 27: 119–142.
  46. Dolev I, Michaelson DM. A nontransgenic mouse model shows inducible amyloid-beta (Abeta) peptide deposition and elucidates the role of apolipoprotein E in the amyloid cascade. *Proc Natl Acad Sci USA* 2004; 101: 13909–13914.
  47. Biessels GJ, Staekenborg S, Brunner E, *et al.* Risk of dementia in diabetes mellitus: a systematic review. *Lancet Neurol* 2006; 5: 64–67.
  48. Kodl CT, Seaquist ER. Cognitive dysfunction and diabetes mellitus. *Endocr Rev* 2008; 29: 494–511.
  49. Craft S. Insulin resistance syndrome and Alzheimer's disease: age- and obesity-related on memory, amyloid, and inflammation. *Neurobiol Aging* 2005; 26: S65–S69.
  50. Young SE, Mainous AG, Carnemolla M. Hyperinsulinemia and cognitive decline in a middle-aged cohort. *Diabetes Care* 2006; 29: 2688–2693.

51. Matsuzaki T, Sasaki K, Tanizaki Y, *et al.* Insulin resistance is associated with the pathology of Alzheimer disease. The Hisayama Study. *Neurology* 2010; 75: 764–770.
52. Rönneenmaa E, Zethelius B, Sundelof J, *et al.* Impaired insulin secretion increased the risk of Alzheimer disease. *Neurology* 2008; 71: 1065–1071.
53. Kloppenborg RP, van den Berg E, Kappelle LJ, *et al.* . Diabetes and other vascular risk factors for dementia: which factor matters most? A systematic review. *Eur J Pharmacol* 2008; 585: 97–108.
54. Seino Y, Nanjo K, Tajima N, *et al.* Report of the committee on the classification and diagnostic criteria of diabetes mellitus. *J Diabetes Invest* 2010; 1: 212–228.
55. Kashiwagi A, Kasuga M, Araki E, *et al.* International clinical harmonization of glycated hemoglobin in Japan: from Japan Diabetes Society to National Glycohemoglobin Standardization Program values. *J Diabetes Invest* 2012; 3: 39–40.
56. Euser SM, Sattar N, Wittman CM, *et al.* A prospective analysis of elevated fasting glucose levels and cognitive function in older people. Results from PROSPER and the Rotterdam study. *Diabetes* 2010; 59: 1601–1607.
57. Kawamura T, Umemura T, Hotta N. Cognitive impairment in diabetic patients: can diabetic control prevent cognitive decline? *J Diabetes Invest* 2012; 3: 413–423.