Title:

Different Glycaemia-Related Risk Factors for Incident Alzheimer's Disease in Men and Women with Type 2 Diabetes – A Sex-Specific Analysis of the Hong Kong Diabetes Database

Short running title:

Glycaemic risk factors and AD

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Abstract

Aims

Sexual dimorphism has been reported in the epidemiology, neurobiologic susceptibility and clinical presentation of Alzheimer's disease (AD). As poor glycaemic control is associated with increased risks of AD, we aimed to investigate whether glycaemia-related risk factors also differ between men and women, using a retrospective, sex-specific analysis of a large Chinese cohort with diabetes.

Materials & Methods

A total of 85514 Chinese individuals with Type 2 diabetes (T2D) (46783 women and 38731 men), aged ≥60 years, were identified from electronic health records and observed for incident AD. Multivariable Cox regression analysis was used to evaluate the associations with incident AD of several glycaemia-related risk factors, including severe hypoglycaemia, mean HbA1c and indices of HbA1c variability, in men and women separately.

Results

Over a median follow-up of 6 years, women had a higher incidence of AD than men (2.3% vs. 1.2%, $p<0.001$). Both men and women shared the same independent non-

glycaemic clinical predictors, which included older age, lower body mass index and longer duration of diabetes. However, for glycaemia-related risk factors, we observed that severe hypoglycaemia and indices of HbA1c variability were independent predictors of incident AD in women but not in men, and the associations were irrespective of their baseline glycaemic control and duration of diabetes.

Conclusions

Our findings highlighted that glycaemia-related risk factors for incident AD differ between men and women with T2D. Strategies to maintain glycaemic stability and avoid severe hypoglycaemia might be especially important to preserve healthy cognition in older women with diabetes.

Introduction

Diabetes is associated with an increased risk of dementia.[1] Notably, previous prospective studies have shown that individuals with type 2 diabetes (T2D) had a 1.2 to 2.3-fold greater risk of developing Alzheimer's disease (AD), over a follow-up of 2 to 7 years, compared to those without diabetes.[2] A recent meta-analysis also reported a 1.64-fold increased risk of AD with diabetes, even after adjustments for obesity, stroke and other vascular risk factors.[3] Moreover, among individuals with T2D, in contrast to the decline in cardiovascular mortality observed in recent years,[4] mortality due to AD had not significantly improved over the last decade.[5]

Women have a higher prevalence and lifetime risk of AD than men,[6] and it has been argued that this could not be explained by differences in longevity alone. Importantly, sexual dimorphism had been observed in various risk factors of AD,[7] and recently in the AD pathological trajectory.[8] On the other hand, whereas various glycaemia-related parameters, such as baseline and mean glycated haemoglobin (HbA1c), hypoglycaemic events, and glycaemic variability, have been reported as risk factors for cognitive decline and/or dementia, most studies were of relatively small sample size and some were based on surrogate markers of cognitive dysfunction [9] Furthermore, whether these glycaemia-related risk factors differ between men and women is not known. Therefore, we performed this sex-specific analysis to investigate

the associations of various glycaemia-related risk factors with incident AD in men and women, using a large clinical database of Hong Kong Chinese with T2D.

Materials & Methods

Study Population

The Hong Kong Hospital Authority is the only public-funded health care provider in Hong Kong, with almost comprehensive coverage for 90% and 80% of our local inpatient and outpatient care, respectively. The current study utilized anonymized data extracted from electronic health records of the Hong Kong Hospital Authority, which has been demonstrated to be a useful platform for epidemiological studies of diabetes and its related complications in Hong Kong.[10] Individuals with T2D who received regular diabetes complications screening at the Hospital Authority public health clinics from 1 January 2008 to 31 December 2012 were identified, with their glycaemic and health status ascertained at baseline. T2D was diagnosed by physicians, based on clinical history, biochemical and/or immunological findings. The index date was defined as the earliest date at which all baseline variables from diabetes complications screening were available. Other inclusion criteria comprised being Chinese and aged ≥60 years. Moreover, only individuals who had at least 3 HbA1c measurements in the preceding 2 years before the index date, and with comprehensive data available at

baseline, were included. Individuals who had AD at baseline were excluded on the basis of diagnostic code 331.0 of the Ninth Revision of International Classification of Diseases (ICD-9), or the use of pharmacological agents for treatment of AD, which included acetylcholinesterase inhibitors (Rivastigmine, donepezil and galantamine), N-methyl-D-aspartate (NMDA) receptor antagonist (Memantine) and Tacrine. Ethical approval has been obtained from the institutional review board of the University of Hong Kong/ Hospital Authority Hong Kong West Cluster.

Clinical and biochemical assessments during diabetes complications screening in Hong Kong

During each diabetes complications screening, individuals with diabetes were assessed clinically and had laboratory investigations to determine their control of diabetes, its related cardiovascular risk factors, and the presence of diabetic complications. Demographic data, which included age, sex, smoking and alcohol consumption, as well as anthropometric parameters, which included body weight, height, body mass index (BMI), waist circumference (WC), and blood pressure (BP) were obtained. In addition, fasting blood was drawn for plasma glucose, lipids and HbA1c levels, with serum creatinine measured and the estimated glomerular filtration

rate (eGFR) calculated using the Modification of Diet in Renal Disease (MDRD) study equation.[11]

Glycaemia-Related Parameters

In the current study, since anonymized data was used and adjudication of individual event was not possible, severe hypoglycaemia was defined based on hard events, which were those episodes requiring hospital attendance or admission, instead of the conventional definition of events requiring external assistance for recovery. [12] Both mean HbA1c and HbA1c variability were determined for each included individual using serial HbA1c values obtained during the 5-year period before the index date. HbA1c variability was assessed using: 1) Standard deviation (SD) of serial HbA1c measurements; 2) Coefficient of variation (CV) of HbA1c, which was the ratio of SD to mean HbA1c; and 3) Adjusted SD of HbA1c, which took into consideration the differences in frequency of HbA1c measurements among individuals with diabetes, and was calculated using the formula $SD / \sqrt{[N/(N-1)]}$ where N referred to the number of HbA1c measurements.[13]

Definitions of clinical variables and outcomes

In the current study, we defined dyslipidaemia as fasting triglycerides (TG) ³ 1.69 mmol/L, high-density lipoprotein cholesterol (HDL-C) <1.04 mmol/L in men and <1.29 mmol/L in women, and low-density lipoprotein cholesterol (LDL-C) ³ 2.6 mmol/L, or on lipid-lowering agents. Hypertension was defined as one blood pressure ³ 140 / 90 mmHg or on anti-hypertensive medications.

Incident AD, the primary outcome of interest, was defined on the basis of ICD9 code 331.0 or the use of pharmacological agents for treatment of AD, which included acetylcholinesterase inhibitors (Rivastigmine, donepezil and galantamine), NMDA antagonist (Memantine) and Tacrine, as of 31 May 2018.

Statistical analysis

All data were analyzed with SAS version 9.4 (SAS Institute, Cary, NC). Values were reported as means ± SD, medians with interquartile range for skewed data, or percentages, as appropriate. Multivariable Cox regression analysis was first used to identify the independent non-glycaemic clinical predictors of AD in T2D, and then to evaluate the associations of various glycaemia-related parameters (severe hypoglycaemia, mean HbA1c and indices of HbA1c variability [SD, adjusted SD and CV of HbA1c]) with incident AD independent of the non-glycaemic clinical predictors. Only variables that were statistically significant in univariate analysis were included in

multivariable Cox regression analyses. Moreover, in order to minimize the possibility of reverse causality, sensitivity analyses were performed to examine the associations between HbA1c variability and incident AD among individuals with duration of diabetes more than 5 and 10 years. In all statistical tests, two-sided p-values <0.05 were considered significant.

Results

A total of 85514 individuals (55% women and 45% men) with T2D, aged ≥60 years and without AD at baseline, were included in our study (Supplemental Figure 1). Table 1 summarizes the differences in baseline characteristics between men and women. Compared with men, women were significantly older (71.8±7.7 vs. 70.7±7.3 years, p<0.001), with higher BMI (25.1±3.9kg/m^2 vs. 25.1±3.5kg/m^2, p<0.001), longer duration of diabetes (12.2±7.9 vs. 11.4±7.5 years, p<0.001), and with higher prevalence of hypertension (85.3% vs. 82.7%, p<0.001) and dyslipidaemia (90% vs. 82.2%, p<0.001). There were significantly more users of metformin and dipeptidyl peptidase 4 inhibitors (DPP4i) in women than men (75.5% vs. 71.6%, p<0.001; 1.0% vs. 0.8%, p=0.007, respectively), and women had significantly higher baseline eGFR than men (73.2±23.6 ml/min/1.73m^2 vs 72.8±22.7 ml/min/1.73m^2, p=0.044). On the other hand, there were significantly more ever-smokers in men than women (58.7% vs. 6.1%,

p<0.001), as with users of sulphonylureas (54.9% vs. 51.6%, p <0.001) and insulin (14.5% vs. 12.6%, p<0.001). Among the insulin users, most were on daytime premixed insulin (47.5%), followed by combination therapy (35.7%) and multiple injections (16.8%). Moreover, men had significantly higher prevalence of stroke (11.8% vs. 9.3%, p <0.001) and coronary heart disease (16.6% vs. 10.9%, p <0.001) than women. At baseline, HbA1c were just marginally different between men and women (7.33±1.28% vs. 7.32±1.18%, p=0.049), and no significant differences were observed in the rates of severe hypoglycaemia between men and women (p=0.186).

Non-glycaemic clinical predictors of incident AD in men and women

Over a median follow-up of 6 years, 1535 of the 85514 individuals developed AD, with a cumulative incidence of 2.83 per 1000 person-years. Women had a higher incidence of AD than men (2.3% in women vs. 1.2% in men, p<0.001). When included individuals were stratified into three groups by their age at baseline, the incidence of AD significantly increased progressively with age (0.6%, 2.3% and 3.9% for baseline age 60-69 years, 70-80 years and ≥80 years, respectively, p for trend <0.001), with similar trends observed in men and women. Importantly, women had consistently a higher incidence of AD than men in each age group (all p<0.001). (Table 2)

In univariable analysis, use of metformin, sulphonylureas, pioglitazone, DPP4i and insulin were all not associated with incident AD in both men and women. In multivariable Cox regression analyses, men and women shared the same non-glycaemic independent clinical predictors, which included older age, lower BMI and longer duration of diabetes. (Table 3)

The associations of different glycaemia-related parameters with incident AD in men and women

In women with T2D, those who developed AD had significantly lower mean HbA1c, as well as higher rates of severe hypoglycaemia and indices of HbA1c variability, compared to those who did not. (Table 4) This was in contrast to findings in men in whom none of the glycaemia related parameters were significantly different between individuals who developed AD and those who did not.

In multivariable Cox regression analyses (Table 4), severe hypoglycaemia, as well as all indices of HbA1c variability were independently associated with incident AD in women. The adjusted HR was 1.69 for severe hypoglycaemia (95%CI 1.14 – 2.52, p=0.010); 1.14 for SD of HbA1c (95%CI 1.02 – 1.27, p=0.023); 1.15 for adjusted SD of HbA1c (95%CI 1.02 – 1.30, p=0.028); 1.01 for CV of HbA1c (95%CI 1.00 – 1.02, p=0.004), in a model adjusted for significant non-glycaemic clinical risk factors

of AD. In both men and women, however, mean HbA1c was not associated with the development of AD. Moreover, when mean HbA1c levels were also included in the regression model, all indices of HbA1c variability remained independently associated with incident AD in women (Adjusted HR for SD of HbA1c: 1.27, 95%CI 1.12 – 1.45, p<0.001; Adjusted SD of HbA1c: 1.31, 95%CI 1.13 – 1.52, p<0.001; CV of HbA1c: 1.02, 95%CI 1.01 – 1.03, p<0.001) but not in men.

The association between HbA1c variability and incident AD in men and women

In order to evaluate if our observed associations between HbA1c variability and incident AD were related to the overall glycaemic control, we further divided our individuals with T2D into two groups by their mean HbA1c of <7.5% and ≥7.5%, a cut-off generally suggested for older adults with comorbidities.[14] We found that in women, both SD and CV of HbA1c remained significantly associated with incident AD in both subgroups. (Supplemental Table 1) For SD of HbA1c, the adjusted HR was 1.29 (95%CI 1.05 – 1.60, p=0.018) for mean HbA1c<7.5% and 1.17 (95%CI 1.01 – 1.36, p=0.040) for mean HbA1c ≥7.5%. For CV of HbA1c, the adjusted HR was 1.02 (95%CI 1.01 – 1.04, p=0.008) for mean HbA1c <7.5% and 1.02 (95%CI 1.00 – 1.03, p=0.025) for mean HbA1c ≥7.5%. In men, no significant association between HbA1c variability and development of AD was found in both subgroups. Moreover, all three indices of

HbA1c variability predicted incident AD in women even when limited to individuals with duration of diabetes more than 5 or even 10 years, which suggested against the possibility of reverse causality. (Figure 1)

Discussion

Our study provided the novel observation that there was significant sexual dimorphism in the associations between different glycaemia-related risk factors and incident AD in T2D, and both severe hypoglycaemia and indices of HbA1c variability independently predicted the development of AD in women but not in men, over a median follow-up of 6 years.

One of the strengths of our study was the large sample size compared to those in previous studies, which enabled further sex-specific analysis in a disease in which sexual dimorphism has been well reported.[7] Indeed, longitudinal studies from the Alzheimer's Disease Neuroimaging Initiative (ADNI) using structural magnetic resonance imaging (MRI) had demonstrated that women experienced faster brain atrophic rates than men [15], and this sexual dimorphism was observed across the spectrum from elderly with normal cognition, mild cognitive impairment (MCI) to AD.[16] Moreover, among individuals with MCI, women also had higher rates of clinical decline than men.[17] Recently, it was also shown that women who had normal or zero

score on global clinical dementia rating score had greater regional tau deposition than men with similar amyloid burden, which provided further support to the presence of sexual dimorphism in the AD pathologic trajectory.[8] In our large cohort of Chinese individuals with T2D, we also observed that women had a significantly and consistently higher cumulative risk of incident AD than men across each age group. Notably, although pioglitazone has recently been proposed to have protective effects on the risk of developing dementia among individuals with T2D,[18 19] there was no significant difference in the use of pioglitazone between men and women in our study at baseline. In both men and women, lower BMI were independent predictors of incident AD, which was in keeping with our previous report that late-life BMI decreased with decline in cognition. [20]

Hypoglycaemia is associated with the development of dementia in T2D.[21] In our study, we found that severe hypoglycaemia was an independent predictor of AD in women but not in men. Moreover, all indices of HbA1c variability, including HbA1c CV, SD and adjusted SD, were also associated with incident AD in women only. Although men had significantly greater use of insulin and sulphonylurea than women at baseline, there was no significant difference in the rates of severe hypoglycaemia between men and women. However, we also observed that, in contrast to men, women with incident AD tended to have lower mean HbA1c compared to those without.

281 Therefore, although HbA1c variability remained independently associated with
282 incident AD even after adjustments for severe hypoglycaemia and baseline glycaemic
283 control, it is still possible that the women in this study might have experienced more
284 episodes of mild hypoglycaemia than men, which could also negatively impact on
285 cognition in the long run.

286 Hyperglycaemic excursions, on the other hand, have also been linked with
287 cognitive decline. Recently, glucose peaks, as determined by 1,5-anhydroglucitol levels,
288 predicted cognitive decline in T2D over a median follow-up of 21 years.[22] It has been
289 suggested that advanced glycation end-products (AGE) are present in neurofibrillary
290 tangles and amyloid beta plaques, two pathological hallmarks of AD.[23] Moreover, *in*
291 *vitro* studies have also shown that AGE can induce apoptosis in cultured cortical
292 neuronal cells.[24] Increased HbA1c variability and fluctuating glycaemia promote
293 oxidative stress, [25 26] which in the presence of chronic hyperglycaemia, enhances AGE
294 production and therefore can potentially contribute to the development of AD in
295 diabetes.[27] Indeed, HbA1c variability has been increasingly recognized as an
296 independent predictor of multiple diabetic complications such as cardiovascular disease
297 that are also mediated in part through oxidative stress and AGE formation.[28] Increased
298 HbA1c variability predicted incident cardiovascular and renal complications[29,30],
299 incident hip fractures [31], as well as all-cause mortality in T2D.[32-34] Recently, glycaemic

variability, as determined by CV of fasting glucose and HbA1c, was also demonstrated to be associated with the development of AD in a Taiwan study which did not include sex-specific analysis.[35]

Interestingly, previous studies had suggested that women with T2D were more susceptible to develop both fatal and non-fatal coronary events and stroke than men, which some authors attributed to a multitude of biological and psychosocial factors.[36] It appears that women may also progress from mild cognitive impairment (MCI) to AD at a faster rate. While AD prevalence is higher in women, an early study from the Mayo Clinic actually showed a higher MCI prevalence in men, [37] whereas a meta-analysis in 2017 showed a higher prevalence of non-amnesic MCI in women but no gender difference in amnesic MCI. [38] In our study, we could not exclude patients having MCI or undiagnosed AD at baseline. Therefore, it is possible that undiagnosed AD at baseline may be more prevalent among the women in our study. Moreover, high carer burden [39 40] and depression [41] were more commonly found in women, which both could lead to less attention being paid to their personal needs. Collectively, these may have contributed to a more irregular intake of meals and medications, resulting in increased HbA1c variability and liability to hypoglycaemia of varying severity. The lack of information on these psychosocial factors in our study is a distinct limitation.

Our findings that women might be more susceptible to the effect of severe hypoglycaemia and HbA1c fluctuations in terms of cognitive impairment, might also be explained by several other unmeasured confounders, which included apolipoprotein E Ɛ4 allele (APOE4) status. HbA1c variability has been significantly associated with higher white matter hyperintensities, a marker of cortical and subcortical atrophy, in APOE4 carriers but not in non-carriers.[42] A recent meta-analysis also demonstrated that women aged 65-75 years who were APOE Ɛ3/Ɛ4 had a higher risk of developing AD compared to men with APOE Ɛ3/Ɛ4.[43] Therefore, it remains possible that these APOE genotype-phenotype interactions might also contribute to the sexual dimorphism observed in the relationship between glycaemic variability and risk of AD. Some other potential mechanisms such as variations in sleep disordered breathing, which has been associated with both cognitive decline and glycaemic variability, [44] [45] could also play a role.

Furthermore, there are several other limitations in our study. First, the diagnosis of AD was based on ICD codes (i.e. clinical diagnosis) and the use of pharmacotherapy instead of the recently proposed research definition employing ATN biomarkers of β-amyloid plaques, fibrillar tau and neuro-degeneration.[46] There was also possibility of dementia due to mixed etiologies, for instance AD together with vascular dementia. Second, the inclusion of exclusively Chinese individuals with T2D could have limited

generalizability to other populations such as those with type 1 diabetes or other ethnic groups. Third, a proportion of individuals with T2D was not included in our analysis because of an inadequate number of HbA1c values prior to the index date. This could be related to variations in the clinical experience of the attending clinicians in the field of diabetes, which might have affected their adherence to guidelines on HbA1c monitoring during follow-up. Moreover, our duration of follow-up might also be relatively short for the observations of incident AD.

Nonetheless, we have demonstrated for the first time that sexual dimorphism is present in the associations between various glycaemia-related risk factors and incident AD in T2D. With a global aging population, which is accompanied by improved overall standards of care and cardiovascular mortality, patients with diabetes are living longer and cognitive decline would emerge as an important diabetic complication in the years to come. From a clinical perspective, while we strive to optimize glycaemic control to HbA1c targets, our findings should inform clinicians of the importance of maintaining glycaemic stability and minimizing hypoglycaemia in order to prevent the development of AD, especially in older women with T2D, whose apparently faster deterioration from MCI to AD might also involve an increased liability or susceptibility to the damaging effects of glycaemic risk factors. Further studies should examine if newer anti-diabetes

medications with potentially less glycaemic variability[47] may be associated with a decreased risk of incident AD in patients with T2D.

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Contribution Statement

C.H.L. researched the data and wrote the manuscript. D.T.W.L., C.Y.Y.C., Y.C.W. and M.M.A.Y. researched the data. C.H.Y.F. performed statistical analyses. Y.F.S., D.C.W.S. and K.H.C. critically reviewed and edited the manuscript. W.S.C. and K.S.L.L. supervised the study, edited the manuscript and take responsibility for the integrity of the data and the accuracy of the data analysis.

Data availability statement

The datasets generated during and/or analysed during the current study are not publicly available but are available from the corresponding author upon reasonable request.

Figure legends

Figure 1. The associations between indices of HbA1c variability and incident Alzheimer's disease in men and women, stratified by their duration of type 2 diabetes

Abbreviations: T2D, type 2 diabetes; HR, hazard ratio

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Table 1. Baseline characteristics of study individuals with type 2 diabetes

Baseline variables	All	Women	Men	p-value
N	85,514	46,783	38,731	--
Age, years	71.3±7.6	71.8±7.7	70.7±7.3	**<0.001**
Ever smoker, %	29.9	6.1	58.7	**<0.001**
Duration of diabetes, years	11.8±7.7	12.2±7.9	11.4±7.5	**<0.001**
SBP, mmHg	138.0±18.2	139.0±18.4	137.0±18.0	**<0.001**
DBP, mmHg	72.0±10.4	70.9±10.3	73.4±10.3	**<0.001**
BMI, kg/m^2	25.1±3.7	25.1±3.9	25.1±3.5	**0.013**
Severe hypoglycaemia, %	1.0	1.0	0.9	0.186
Hypertension, %	84.1	85.3	82.7	**<0.001**
Dyslipidaemia, %	86.5	90.0	82.2	**<0.001**
Stroke, %	10.4	9.3	11.8	**<0.001**
CHD, %	13.5	10.9	16.6	**<0.001**
Use of insulin, %	13.5	12.6	14.5	**<0.001**
Use of metformin, %	73.8	75.5	71.6	**<0.001**
Use of sulfonylurea, %	53.1	51.6	54.9	**<0.001**
Use of pioglitazone, %	0.4	0.3	0.4	0.270
Use of DPP4i, %	0.9	0.8	1.0	**0.007**
Anti-hypertensive medication, %	80.9	81.2	80.6	0.178
Lipid-lowering medication, %	49.4	51.0	47.4	**<0.001**
HbA1c, %	7.33±1.22	7.32±1.18	7.33±1.28	**0.049**
HDL-C, mmol/L	1.28±0.36	1.34±0.36	1.19±0.33	**<0.001**
LDL-C, mmol/L	2.57±0.77	2.62±0.79	2.51±0.75	**<0.001**
TG†, mmol/L	1.25 (0.90-1.78)	1.33 (0.98-1.87)	1.15 (0.83-1.64)	**<0.001**
eGFR, $ml/min/1.73m^2$	73.0±23.6	73.2±23.6	72.8±22.7	**0.044**

Data were presented as mean±standard deviation or median (25^{th} – 75^{th} percentile);

†log-transformed before analysis.

SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; CHD, coronary heart disease; DPP4i, dipeptidyl peptidase 4 inhibitors; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; TG, triglyceride; eGFR, estimated glomerular filtration rate.

Table 2. Incidence of Alzheimer's disease in men and woman with type 2 diabetes

	All	Women	Men	p-value (Women vs. Men)
ALL	85,514	46,783	38,731	--
Number of individuals with AD	1,535	1,069	466	--
Incidence, %	1.8	2.3	1.2	**<0.001**
Cumulative incidence, per 1,000 person-years	2.83	3.59	1.91	**<0.001**
Age: 60-69 years	39,048	20,185	18,863	--
Number of individuals with AD	238	151	87	--
Incidence, %	0.6	0.7	0.5	**0.011**
Cumulative incidence, per 1,000 person-years	0.94	1.15	0.71	**<0.001**
Age: 70-80 years	32,668	18,096	14,572	--
Number of individuals with AD	755	520	235	--
Incidence, %	2.3	2.9	1.6	**<0.001**
Cumulative incidence, per 1,000 person-years	3.65	4.50	2.58	**<0.001**
Age: ≥80 years	13,798	8,502	5,296	--
Number of individuals with AD	542	398	144	--
Incidence, %	3.9	4.7	2.7	**<0.001**
Cumulative incidence, per 1,000 person-years	6.57	7.73	4.64	**<0.001**
P for trend	**<0.001**	**<0.001**	**<0.001**	--

Values in **BOLD** were statistically significant. AD, Alzheimer's disease

Table 3. Associations of clinical variables with incident Alzheimer's disease in type 2 diabetes

Baseline variables	Incidence of AD		Crude HR (95% CI)	Adjusted HR (95% CI)
	Yes	No		
Women				
Age, years	77.0±.6.3	71.6±7.7	**1.09 (1.08-1.10)**	
60-69	14.1	44.4	1	1
70-79	49.0	38.2	**3.93 (3.27-4.70)**	**3.92 (3.26-4.72)**
≥80	36.9	17.5	**6.69 (5.55-8.07)**	**6.68 (5.48-8.13)**
BMI, kg/m^2	24.5±3.8	25.3±4.1	**0.95 (0.93-0.96)**	
<18.5	3.6	2.5	1.20 (0.85-1.68)	1.10 (0.78-1.54)
18.5-22.9	33.1	27.7	1	1
23.0-27.4	44.4	44.3	**0.83 (0.73-0.96)**	**0.89 (0.78-1.02)**
≥27.5	18.9	25.5	**0.62 (0.52-0.74)**	**0.75 (0.63-0.89)**
Ever smoke, %	1.7	1.5	**1.36 (1.09-1.69)**	1.11 (0.89-1.39)
Duration of diabetes, years	12.9±8.6	11.6±8.1	**1.02 (1.01-1.03)**	**1.09 (1.03-1.15)**
Use of insulin, %	12.0	13.6	0.87 (0.73-1.05)	
Use of metformin, %	77.2	75.5	1.09 (0.93-1.24)	
Use of sulphonylurea, %	52.9	51.6	1.06 (0.94-1.19)	
Use of pioglitazone, %	0.0	0.4	0.05 (0.00-4.38)	
Use of DPP4i, %	0.7	0.9	0.79 (0.38-1.66)	
Hypertension, %	85.8	85.3	1.07 (0.90-1.27)	
Dyslipidaemia, %	88.7	90.1	0.86 (0.71-1.04)	
Stroke, %	10.5	8.8	1.20 (0.99-1.45)	
CHD, %	10.2	10.3	1.01 (0.83-1.22)	
eGFR, ml/min/1.73m^2	69.4±21.5	73.7±23.7	**0.99 (0.99-1.00)**	0.99 (0.99-1.01)
Men				
Age, years	75.6±6.7	70.5±7.3	**1.09 (1.08-1.11)**	
60-69	18.9	49.7	1	1
70-79	50.1	37.2	**3.62 (2.93-4.63)**	**3.43 (2.67-4.41)**
≥80	31.0	13.1	**6.44 (4.93-8.40)**	**5.94 (4.50-7.85)**
BMI, kg/m^2	24.1±3.3	25.1±3.5	**0.92 (0.90-0.95)**	
<18.5	2.9	1.8	1.32 (0.75-2.32)	1.20 (0.68-2.11)
18.5-22.9	33.5	25.6	1	1
23.0-27.4	50.7	50.4	**0.77 (0.63-0.95)**	**0.85 (0.69-1.04)**
≥27.5	13.0	22.3	**0.55 (0.32-0.59)**	**0.53 (0.39-0.72)**
Ever smoke, %	8.2	14.6	0.87 (0.73-1.05)	
Duration of diabetes, years	13.8±9.12	10.8±7.59	**1.04 (1.03-1.05)**	**1.21 (1.11-1.31)**
Use of insulin, %	15.2	15.6	0.99 (0.77-1.28)	
Use of metformin, %	69.7	71.6	0.89 (0.73-1.09)	
Use of sulphonylurea, %	57.7	54.9	1.13 (0.94-1.35)	
Use of pioglitazone, %	0.2	0.4	0.55 (0.08-3.90)	
Use of DPP4i, %	0.9	1.0	0.85 (0.32-2.27)	
Hypertension, %	81.6	82.6	0.99 (0.78-1.26)	
Dyslipidaemia, %	80.0	82.2	0.86 (0.68-1.07)	
Stroke, %	15.5	11.2	**1.49 (1.16-1.90)**	1.25 (0.98-1.60)
CHD, %	18.4	15.6	**1.26 (1.01-1.57)**	1.16 (0.92-1.46)
eGFR, ml/min/1.73m^2	69.7±20.8	72.9±22.7	**0.99 (0.99-1.00)**	1.25 (0.98-1.60)

Values in **BOLD** were statistically significant. AD, Alzheimer's disease; HR, hazard ratio; BMI, body mass index; 95%CI, 95% confidence interval; CHD, coronary heart

disease; DPP4i, dipeptidyl peptidase 4 inhibitors; eGFR, estimated glomerular filtration rate.

Table 4 Multivariable Cox regression analysis showing associations of indices of glycaemic variability with incident Alzheimer's disease in type 2 diabetes

HbA1c variability	Incidence of AD			Model	
	Yes	No	Crude HR (95% CI)	Adjusted HR (95% CI)	p-value
Women	1,069	45,714			
Severe hypoglycaemia, %†	2.1	1.0	**2.49 (1.68-3.71)**	**1.69 (1.14-2.52)**	**0.010**
Mean HbA1c, %	7.30±0.98	7.40±1.01	**0.91 (0.85-0.97)**	0.95 (0.90-1.02)	0.152
SD	0.69±0.51	0.65±0.51	**1.12 (1.01-1.25)**	**1.14 (1.02-1.27)**	**0.023**
Adjusted SD	0.61±0.46	0.58±0.46	1.13 (1.00-1.28)	**1.15 (1.02-1.30)**	**0.028**
CV	9.05±5.94	8.53±5.90	**1.01 (1.01-1.02)**	**1.01 (1.00-1.02)**	**0.004**
Men	466	38,265			
Severe hypoglycaemia, %†	1.1	0.9	1.47 (0.66-3.29)	0.93 (0.42-2.9)	0.865
Mean HbA1c, %	7.49±1.08	7.42±1.10	1.06 (0.98-1.15)	1.08 (1.00-1.17)	0.066
SD	0.73±0.58	0.72±0.60	1.04 (0.90-1.20)	1.09 (0.94-1.26)	0.275
Adjusted SD	0.65±0.51	0.64±0.54	1.05 (0.89-1.24)	1.10 (0.93-1.30)	0.272
CV	9.32±6.64	9.23±6.84	1.00 (0.99-1.02)	1.01 (0.99-1.02)	0.351

Values in **BOLD** were statistically significant. HR, hazard ratio; 95%CI, 95% confidence interval; SD, standard deviation; CV, coefficient of variation.

All models for both men and women included age, body mass index, duration of diabetes at baseline

†Model for both men and women included all the above plus mean HbA1c levels at baseline