TITLE

Prevalence and Incidence of Dementia in People with Diabetes Mellitus in the United Kingdom

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Running title

Prevalence and Incidence of Dementia in People with Diabetes Mellitus in the UK

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ABSTRACT

Background: Few studies have shown that an increased risk of dementia is associated with diabetes mellitus. *Objective:* To estimate the prevalence and incidence of dementia in people with diabetes in primary care in the UK. *Methods:* We conducted a descriptive study using the UK The Health Improvement Network (THIN) database. People diagnosed with diabetes from 2000 to 2016 were included in the study. Prevalence and incidence rates of dementia were calculated annually, stratified by age and gender. *Results:* The prevalence of dementia was 0.424% [95%CI (0.420% - 0.427%)] in 2000 and 2.508% [95% CI (2.501% - 2.515%)] in 2016. The highest prevalence was in those aged 85+ from 2.9% [95%CI (2.890% - 2.974%)] in 2000 to 11.3% [95% CI (11.285% - 11.384%)] in 2016. The incidence of dementia increased 3.7 times, from 0.181 cases per 100 persons [95% CI (0.179 – 0.183)] in 2000 to 0.683 cases per 100 persons [95%CI (0.679-0.686)] in 2016, respectively. Women had a higher prevalence and incidence of dementia than men 3.138% [95% CI (3.127% - 3.150%)] vs 2.014% [95% CI (2.006% - 2.022%)] and 0.820 [95% CI (0.814 – 0.826)] vs 0.576 cases per 100 persons [95%CI (0.571-0.580)] in 2016, respectively. *Conclusion:* There was a trend of increasing prevalence and incidence of dementia in people with diabetes over the period of 2000 to 2016. This study adds to the evidence on dementia prevalence and incidence, particularly in the diabetic population.

Key words: Prevalence; Incidence; Epidemiology; Dementia; Diabetes Mellitus; THIN Database

BACKGROUND

Diabetes and dementia are major global health concerns. Diabetes is characterised by an abnormally high blood glucose level. It can lead to complications in several organ systems,

including cardiovascular diseases, retinopathy, nephropathy and cognitive decline [1, 2]. In the UK, there are more than 4.5 million people with diabetes, including those who are unaware of their condition (Public Health England, 2016, NICE, 2015). This accounts for around 6.2% of the UK adult population and is three times higher within the elderly population (>75 years) [3, 4].

Dementia is an irreversible progressive deterioration in cognitive functions that affects memory, thinking and behaviour. It also leads to a loss of independent functional ability that has a wide-ranging impact on individuals, their families and healthcare systems [5]. In 2013, the prevalence of dementia was 7.1% of the UK's older population aged 65+ years [6].

There is evidence from observational studies that diabetes mellitus is associated with an increased risk of developing cognitive impairment and dementia [7]. The link between diabetes and dementia among older people is controversial, and some studies found an association, while others did not [8, 9]. The disease burden related to diabetes and dementia is high and rising worldwide, fed by the rapid global growth of unhealthy lifestyles and ageing [10, 11]. In addition to the progression of the disease, the life-threatening complications may lead to reduced quality of life [12] and increased mortality rate [13], and the cost of diabetes and dementia management makes these conditions an important public health issue [14, 15]. There is still a gap in knowledge about the epidemiology of dementia, and there are currently no data available on the prevalence and incidence of people with diabetes living with dementia in the UK. Therefore, in this study, we aimed to report on the prevalence and incidence of dementia diagnoses in people with diabetes aged 18 or above in the UK primary care setting.

METHODOLOGY

Study design and data source

This was a population-based descriptive study conducted to investigate the prevalence and incidence of dementia in the diabetes population, using the data from The Health Improvement Network (THIN) database from 2000 to 2016. THIN database is one of the largest UK primary care databases [16]. It contains anonymised data from over 744 practices on more than 13 million individuals, covering about 6% of the UK population, and is broadly representative in terms of demographic and health variables [16-18]. THIN has information on prescriptions issued by the GPs, which has been widely used to study various conditions including dementia [19, 20], and prescribing patterns for different mental health conditions [21-25].

Ethics approval

This study was approved by the THIN Scientific Review Committee in July 2018 (reference: 18THIN054).

Study population

All individuals in the THIN database aged 18 or above who had a recorded diagnosis of diabetes from 1st January 2000 to 31st December 2016 were identified by Read Codes. Individuals entered the study at the date of first record of diabetes. If individuals had a diabetes record 12 months prior to 1st January 2000, their entry date was defined as 1st January 2000. Individuals who had a record of dementia prior to 1st January 2000 were only included in the prevalence calculation. Figure 1 illustrates the study population in this study.

Figure 1 Study Population

STATISTICAL ANALYSIS

The overall prevalence and incidence of dementia over the 16-year study period were calculated. Descriptive analyses of the study were carried out and presented to show the basic demographics of the population. The annual prevalence of dementia was calculated by

dividing all the prevalent diabetic cases with a diagnosis of dementia in a particular year, by the total number of cases with a diabetes diagnosis available in the database in the same year. The prevalence is expressed as per 100 persons, with 95% confidence intervals estimated using the Poisson method. The incidence of dementia diagnosis per 100 persons in that year was estimated by computing the number of persons with a first record indicative of dementia diagnosis in a particular year, by the total number of persons with a diabetes diagnosis but without records of dementia diagnosis prior to or at the start of that particular year, with 95% confidence intervals using the Poisson method. Both annual prevalence and incidence were stratified by gender, age groups (18- 65 years old, 65-74 years old, 75-84 years old and ≥ 85 years old) and diabetes types (T1DM and T2DM). We formally tested any differences in sex and various comorbidities between patients diagnosed with 1) diabetes only and 2) diabetes plus dementia, using chi-squared tests. Differences with a P-value <0.05 were considered significant, P-values were added to Table 1. All analyses were performed using SAS version 9.4[26].

RESULTS

Cohort demographics

The source population comprised 544,162 people with diabetes [(Type 1 diabetes (T1DM): 22,668 individuals (4.2%); Type 2 diabetes (T2DM): 350,314 individuals (64.4%); Unspecified DM type: 171,180 individuals (31.4%)]. 55.2% of the diabetic population were males. The mean age at diabetes mellitus diagnosis was 59.4 years (SD: 15.0).

Among the diabetic population, 28,772 people had a record of dementia diagnosis during the 16-year period. Of the 28,722 patients with dementia, 27.9% were diagnosed with vascular dementia and 21.4% with Alzheimer's disease (see Table 1). The majority of dementia patients were diagnosed with T2DM [19,531 (67.9%)], T1DM [501 (1.7%)] and [8,740 (30.4%)]

unspecified. 19,046 people developed dementia during the study period, and 10,855 of the people with dementia were females. Table 1 shows the characterisitics for individuals with diabetes who had a diagnosis of dementia and no dementia diagnosis, and Table 2 shows the characteristics of individuals with incident dementia during the study period.

Table 1 Cohort characterisiticcs

Variables	Total individuals Diabetes mellitus 544,162 (100%)	Individuals Diabetes without Dementia 515,390 (100%)	Individuals Diabetes with Dementia 28,772 (100%)	P-value
Mean age at first Diabetes mellitus diagnosis (SD)	59.4 years (15.0)	58.7 years (14.9)	73.1 years (10.0)	-
Mean age at first Dementia diagnosis (SD)	-	-	80.4 years (7.9)	-
Gender (%)				
Male	300,157 (55.2)	288,093 (55.9)	12,064 (41.9)	<0.0001
Female	244,005 (44.8)	227,297 (44.1)	16,708 (58.1)	<0.0001
Comorbidities (%)				
Chronic Kidney Disease	111,349 (20.5)	100,824 (19.6)	10,525 (36.6)	<0.0001
Hypertension	332,921 (61.2)	313,811 (60.8)	19,110 (66.4)	<0.0001
Arrhythmias	69,674 (12.8)	63,479 (12.3)	6,195 (21.5)	<0.0001
Myocardial Infarction	160,216 (29.4)	149,583 (29.2)	10,633 (37.0)	<0.0001
Stroke	52,174 (9.6)	45,558 (8.8)	6,616 (23.0)	<0.0001
Depression	160,093 (29.4)	150,547 (29.2)	9,546 (33.2)	<0.0001
Heart failure	52,216 (9.6)	48,316 (9.3)	3,900 (13.6)	<0.0001
Diabetic retinopathy	179,649 (33.0)	170,735 (33.1)	8,914 (31.0)	<0.0001
Diabetic nephropathy	4,563 (0.8)	4,369 (0.8)	194 (0.7)	0.0014
Diabetic neuropathy	81,362 (14.9)	77,150 (14.9)	4,212 (14.6)	0.5729
Diabetic foot	395,101 (72.6)	376,972 (73.1)	18,129 (63.0)	<0.0001
Types of diabetes (%)				
Type 1 diabetes mellitus	22,668 (4.2)	22,167 (4.3)	501 (1.7)	<0.0001
Type 2 diabetes mellitus	350,314 (64.4)	330,783 (64.2)	19,531 (67.9)	<0.0001

Unspecified diabetes	171,180 (31.4)	162,440 (31.5)	8,740 (30.4)	0.0004
Types of dementia (%)				
Unspecified dementia	-	-	14,125 (49.1)	-
Vascular Dementia	-	-	8,034 (27.9)	-
Alzheimer's Disease	-	-	6,162 (21.4)	-
Dementia with Lewy bodies	-	-	290 (1.0)	-
Parkinson's Dementia	-	-	139 (0.5)	-
Frontotemporal Dementia	-	-	22 (0.1)	-

Table 2 Characteristics of diabetic individuals with incident dementia

Variables	**Diabetic individuals with incident dementia** **19,046 (100%)**
Mean age at first Diabetes mellitus diagnosis (SD)	72.5 years (10.1)
Mean age at first Dementia diagnosis (SD)	80.4 years (7.9)
Gender (%)	
Male	8,191 (43.0)
Female	10,855 (57.0)
Comorbidities (%)	
Chronic Kidney Disease	7,538 (39.6)
Hypertension	13,488 (70.8)
Arrhythmias	4,332 (22.7)
Myocardial Infarction	7,802 (40.9)
Stroke	4,364 (22.9)
Depression	6,807 (35.7)
Heart failure	2,807 (14.7)
Diabetic retinopathy	6,978 (36.6)
Diabetic nephropathy	161 (0.8)
Diabetic neuropathy	3,581 (18.8)
Diabetic foot	13,650 (71.7)
Types of diabetes (%)	
Type 1 diabetes mellitus	284 (1.5)

Type 2 diabetes mellitus	11,707 (61.5)
Unspecified diabetes	7,055 (37.0)
Types of dementia (%)	
Unspecified dementia	9,473 (49.7)
Vascular Dementia	5,178 (27.2)
Alzheimer's Disease	4,123 (21.6)
Dementia with Lewy bodies	164 (0.9)
Parkinson's Dementia	92 (0.5)
Frontotemporal Dementia	16 (0.1)

Prevalence of dementia in the diabetes population by calendar year

The overall prevalence of dementia increased over time from 0.424% to 2.508 % (Table 3), and the prevalence estimates increased with increasing age. The prevalence estimate increased approximately five-fold, from 0.031 per 100 persons in 2000 to 0.153 per 100 persons in 2016 in individuals aged 18 – 65, and from 0.857 per 100 persons in 2000 to 4.223 per 100 persons in 2016 in individuals aged above 65 (Figure 2A).

We found that the prevalence of dementia in female patients with diabetes was approximately 1.5 times higher compared to the male diabetic patients, being 3.138% and 2.014% in 2016 for women and men respectively (Figure 2B). The prevalence rate of dementia was three times higher in patients diagnosed with T2DM (2.410 per 100 persons) compared to the rate in patients diagnosed with T1DM in 2016 (0.777 per 100 persons, see Figure 2C).

Table 3 Annual prevalence of dementia in diabetes population

Year	Total number of individuals with Dementia and Diabetes	Total number of individuals with Diabetes	Dementia prevalence per 100 persons (%)	95% Confidence interval
2000	631	148,822	0.424	(0.420-0.427)
2001	830	169,371	0.490	(0.486-0.493)

2002	1,087	190,860	0.570	(0.566-0.573)
2003	1,335	211,072	0.632	(0.629-0.636)
2004	1,596	229,774	0.695	(0.691-0.698)
2005	1,873	246,155	0.761	(0.757-0.764)
2006	2,373	261,446	0.908	(0.904-0.911)
2007	2,773	274,213	1.011	(1.007-1.015)
2008	3,033	285,674	1.062	(1.057-1.065)
2009	3,511	295,513	1.188	(1.184-1.192)
2010	3,984	300,175	1.327	(1.323-1.331)
2011	4,585	303,180	1.512	(1.507-1.517)
2012	5,191	305,749	1.698	(1.693-1.702)
2013	5,823	304,749	1.911	(1.905-1.916)
2014	6,267	287,330	2.181	(2.176-2.187)
2015	6,367	262,455	2.426	(2.419-2.432)
2016	5,502	219,366	2.508	(2.501-2.515)

Figure 2A.

Figure 2B.

Figure 2C.

Figure 2 Annual prevalence of dementia in diabetes population 2A. stratified by age groups. 2B. stratified by gender 2C. stratified by diabetes mellitus type.

The incidence of dementia in the diabetes population by calendar year

The incidence of dementia in the diabetes population is illustrated in Table 4. The results showed that the incidence estimates were highest for the elderly (≥ 85) (Figure 3A). When the data were stratified by gender, the incidence estimates were shown to be much higher among females than among males (Figure 3B). Similar to the prevalence estimates, the overall incidence estimates increased over the study period, from 0.181 in 2000 to 0.683 per 100

persons in 2016, with a peak in 2015 at 0.693 per 100 persons (Table 4). The incidence rate was higher among individuals with T2DM (0.684 per 100 persons) compared to T1DM (0.172 per 100 persons) in 2016 (Figure 3C).

Table 4 Annual Incidence of Dementia in Diabetes population

Year	Total number of individuals with diabetes and newly diagnosed dementia	Total number of individuals with diabetes (at risk population)	Dementia Incidence per 100 persons per year (%)	95% Confidence interval
2000	269	148,353	0.181	(0.179-0.183)
2001	350	168,740	0.207	(0.205-0.209)
2002	432	190,030	0.227	(0.225-0.229)
2003	527	209,985	0.251	(0.248 -0.253)
2004	597	228,439	0.261	(0.259-0.263)
2005	668	244,559	0.273	(0.271-0.275)
2006	907	259,573	0.349	(0.347-0.351)
2007	922	271,840	0.339	(0.336-0.341)
2008	943	282,901	0.333	(0.331-0.335)
2009	1,213	292,480	0.415	(0.412-0.417)
2010	1,340	296,664	0.452	(0.449-0.454)
2011	1,492	299,196	0.499	(0.496-0.501)
2012	1,654	301,164	0.549	(0.546-0.551)
2013	1,873	299,558	0.625	(0.622-0.628)
2014	1,971	281,507	0.700	(0.697-0.703)
2015	1,847	256,188	0.721	(0.717-0.724)
2016	1,454	212,999	0.683	(0.679-0.686)

Figure 3A.

Figure 3B.

Figure 3C.

Figure 3 Annual incidence of dementia in diabetes population 3A. stratified by age groups 3B. stratified by gender 3C. stratified by diabetes mellitus type.

DISCUSSION

To the best of our knowledge, this is the first study to estimate the prevalence and incidence of dementia among the diabetes population in a nationally representative sample in the UK. Our results showed that the incidence and prevalence of dementia have increased sharply from 2000 to 2016 among the diabetic population. The prevalence and incidence of dementia were greater in women than men across all age groups.

In 2013 a meta-analysis of 28 prospective observational studies investigated the association between diabetes and the risk of dementia, and found that diabetes was associated with a 73% increased risk of all types of dementia compared to non-diabetic people [7]. The prevalence of diabetes and dementia has been increasing from 1980 to 2018 [27-29]. However, the prevalence of dementia in people with diabetes has not been reported or estimated yet [30]. There is an growing body of evidence demonstrating various mechanisms that may contribute to the development of dementia in patients with diabetes, including brain vascular lesions, oxidative distress and insulin resistance, and hyperglycaemia causing inflammation [30].

Given the impact of diabetes on the risk of dementia, the most important goal is to identify its individual risk factors and reduce dementia occurrence. Effective intervention strategies including early treatment of diabetes, physical exercise, and nutritional approaches may play a key role in overall dementia risk reduction [31].

Comparison with previous studies

The majority of previous cohort studies have reported age-adjusted dementia incidence over time in the general population. This included a large UK-based population which found a

stable incidence of dementia diagnosis (3 - 4 per 1,000 persons per year) in primary care between 1990 and 2007 [32]. Another study of people aged ≥65 from a UK community-based cohort reported a 20% decline in dementia incidence over two decades, with an overall incidence of 17.7 / 1000 persons per year between 2008 and 2011 [33]. Finally, a recently published study has compared the incidence of dementia diagnosis among ethnic groups in a nationally representative sample using THIN data, and evaluated whether ethnicity is associated with the likelihood of people with dementia receiving a diagnosis. They found that the overall incidence of dementia increased over time, from 3.75 per 1,000 person-years from 2007 to 5.65 per 1,000 person-years in 2015, and that the black UK ethnic group were more likely to be diagnosed with dementia compared to the white group [34].

Our study results may reflect the effects of the National Dementia Strategy drive (published in 2009) to increase diagnosis rates by improving awareness, facilitating assessment through early diagnosis, and providing higher quality care services to improve diagnosis rates by introducing a new dementia toolkit, which has helped GPs to provide additional services between 2014 and 2015 to further increase diagnosis rates up to 67% in 2015 [35, 36]. We believe this had a major impact on the increase of known cases of dementia in primary care [37] in terms of resource allocation for the medical and social care support for patients with dementia and their families.

Strengths and limitations

The strengths of this study include the large, UK representative study sample, which is a particularly suitable database for chronic disease prevalence work [17]. The data were based on recorded dementia diagnoses in general practice records; people with suspected dementia or with symptoms of dementia and no diagnosis would not have been included in our sample, and our results would not apply to these groups. We know from previous work that dementia

tends to be under-recorded in general practice records, and that some general practitioners believe that they are not skilled or confident enough to make a diagnosis alone, and seek specialist advice first [38, 39]. Moreover, most codes entered were non-specific and did not allow for the differentiation of subtypes. We would, therefore, anticipate the diagnosis of dementia in general practice records to have low sensitivity but high specificity, which may have led to lower results [40].

Future work

Further work is needed to explore the risk factors underlying the diagnosis of dementia, and understanding the relationship between diabetes and dementia will be important in teasing apart the risks and causes that lie behind these two conditions. The findings of this study can assist future studies in the estimation of the workload and costs of dementia, and evaluate the effect of dementia on health and social care services.

CONCLUSION

The results revealed a trend of increasing prevalence and incidence of dementia in the diabetic population of the UK over the period from 2000 to 2016. Further studies are required to determine how dementia prevalence and incidence may be influenced by diabetes mellitus.

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FIGURES

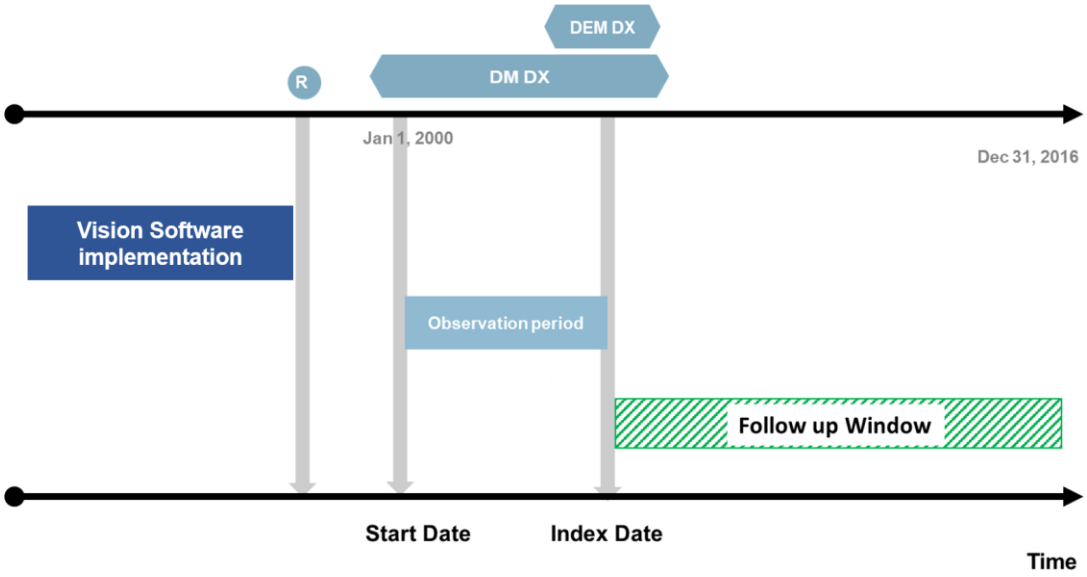

Figure 4 Study Population

Vision System *is a computerised clinical management system used by the general practices to collect patients' data,* **R** *the date of patient's registration in the GP,* **DM DX** *Diabetes mellitus diagnosis,* **DEM DX** *Dementia diagnosis.*

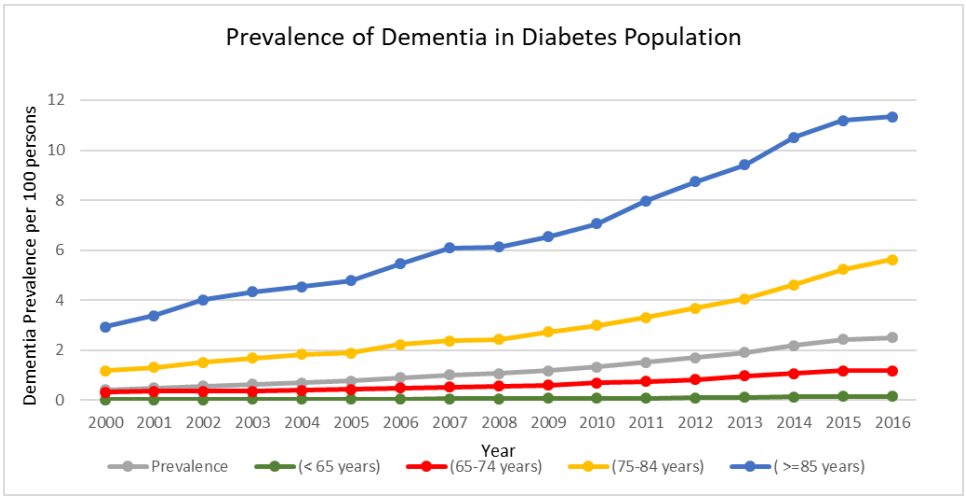

Figure 2A.

Figure 2B.

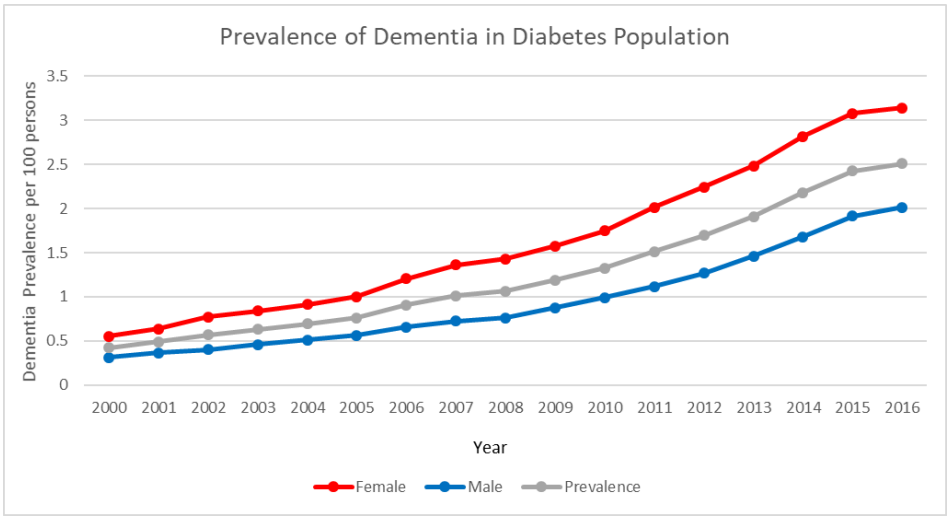

Figure 2C.

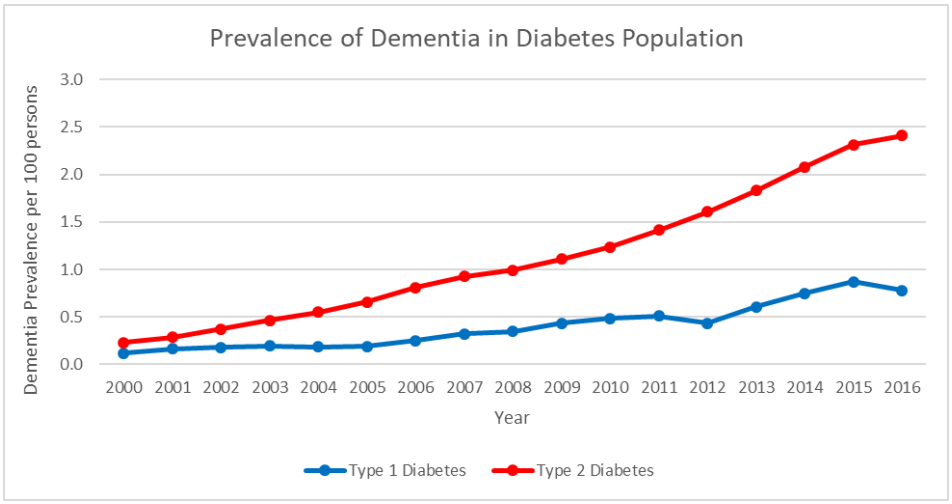

Figure 5 Annual prevalence of dementia in diabetes population A. stratified by age groups. B. stratified by gender C. stratified by diabetes mellitus type.

Figure 3A.

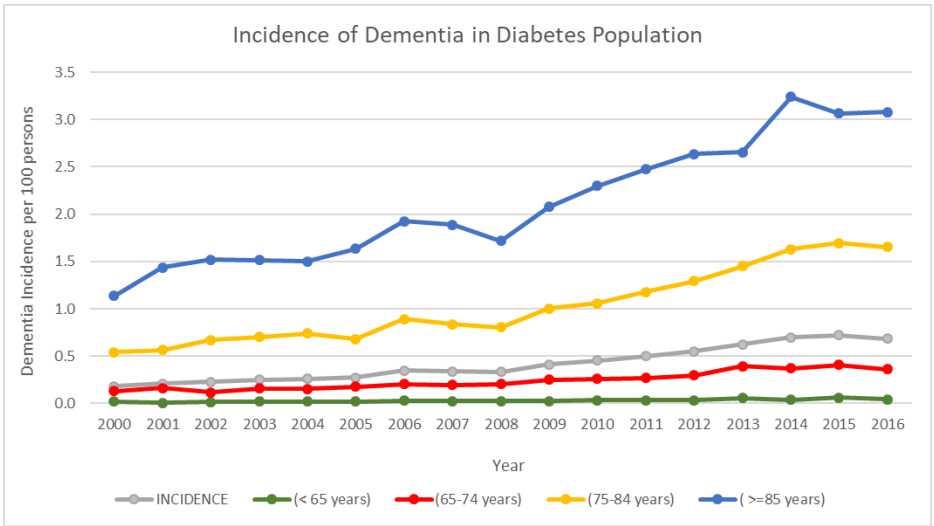

Figure 3B.

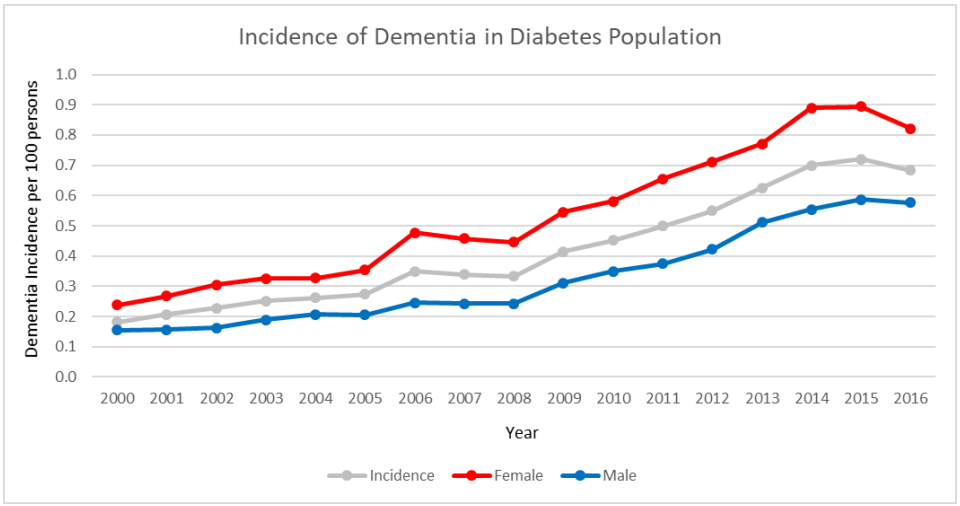

Figure 3C.

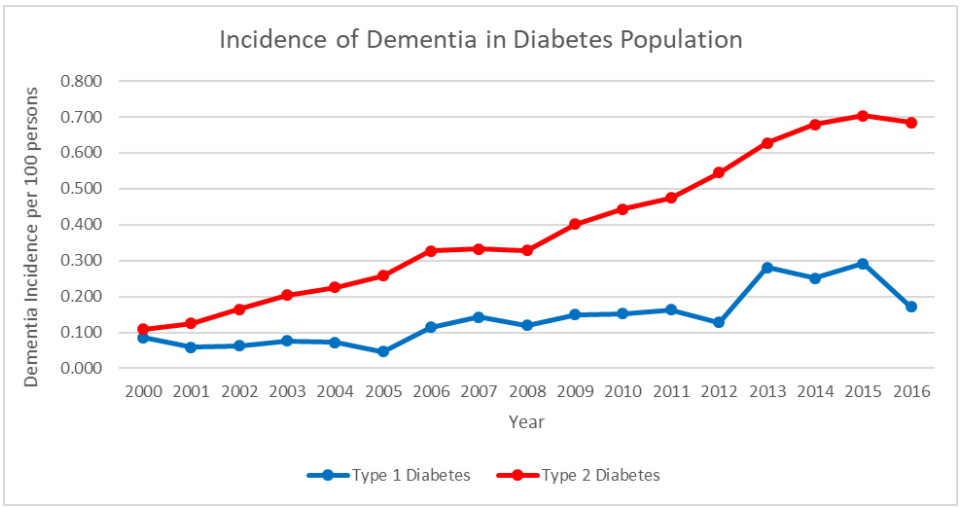

Figure 6 Annual incidence of dementia in diabetes population A. stratified by age groups B. stratified by gender C. stratified by diabetes mellitus type.