Effect of pioglitazone medication on the incidence of dementia

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Abstract

Objectives: PPARγ activating drugs show various salutary effects in preclinical models of neurodegenerative disease. The decade-long clinical usage of these drugs as antidiabetics now allow for evaluation of patient-oriented data sources.

Methods: Using observational data from 2004-2010, we analyzed the association of pioglitazone and incidence of dementia in a prospective cohort study of 145,928 subjects aged 60 years or above who, at baseline, were free of dementia and insulin-dependent diabetes mellitus. We distinguished between non-diabetics, diabetics without pioglitazone, diabetics with prescriptions of less than eight calendar quarters of pioglitazone and diabetics with eight and more quarters. Cox proportional hazard models explored the relative risk of dementia incidence dependent on pioglitazone use adjusted for sex, age, use of rosiglitazone or metformin and cardiovascular comorbidities.

Results: Long-term use of pioglitazone was associated with a lower dementia incidence. Relative to non-diabetics, the cumulative long-term use of pioglitazone reduced the dementia risk by 47% (RR=0.53, p=0.029). If diabetes patients used pioglitazone less than eight quarters, the dementia risk was comparable to those of non-diabetics (RR=1.16, p=0.317), and diabetes patients without a pioglitazone treatment had a 23 % increase in dementia risk (RR=1.23, p<0.001). We did not find evidence for age effects, nor for selection into pioglitazone treatment due to obesity.

Interpretation: These findings indicate that pioglitazone treatment is associated which a reduced dementia risk in initially non-insulin dependent diabetes mellitus patients. Prospective clinical trials are needed to evaluate a possible neuroprotective effect in these patients in an ageing population.

Introduction (336)

Activation of the nuclear hormone receptor peroxisome proliferator activated receptor gamma (PPARγ) has emerged as a therapeutic target for the treatment of non-insulin dependent diabetes mellitus (NIDDM). PPARγ activators, the thiazolidinedione class of drugs (TZDs), have been developed as antidiabetics; and two TZDs, pioglitazone (Actos™) and rosiglitazone (Avandia™) were approved and marketed for NIDDM treatment[1]. The underlying molecular mechanisms include transcriptional regulation of genes, which control insulin, amino acid and lipid metabolism[2]. Activation of PPARγ also antagonizes pro-inflammatory signals in a variety of cells. The hypothesis that peripheral insulin resistance and a neuroinflammatory component contribute to the pathogenesis of neurodegenerative disease, prompted preclinical evaluations of TZDs in animal models of Alzheimer's disease (AD) and other neurodegenerative disorders[3]. These experiments identified several ways in which TZDs interfere with disease-relevant pathogenesis and indicated that sustained TZD medication could provide beneficial effects[4]. Most of these preclinical studies suggested that TZDs act preventively rather than therapeutically, because their neuroprotective effects were detected primarily when treatment was initiated prior to the development of major neuropathological or behavioral signs. The decade-long use of these antidiabetic drugs now allows us to address this question through the evaluation of patient-oriented information from health care institutions and data sources generated by health insurance.

NIDDM is an established risk factor for the development of dementia[5,6] and AD, in particular[7]. Recent evidence suggests that the choice of drug treatment may further influence the risk of NIDDM patients to develop AD[8,9]. Therefore, the identification of a modifying action of TZDs or any other antidiabetic drug may have direct implications for the future treatment of NIDDM patients and dementia prevention[7]. While any observation is potentially related to the antidiabetic efficacy of the respective drug, the comparison of TZDs to other antidiabetic drugs, such as the biguanidine derivative metformin, may help to distinguish treatment effects independent of blood glucose

regulation. Metformin is an established NIDDM medication and currently represents the most frequently used drug for this indication in Germany with equal potential for blood sugar regulation compared to TZDs.

Methods (1214)

Sample and study design

Analyses were based on a longitudinal 2.18 % -sample of the largest German mandatory public health insurance, Allgemeine Ortskrankenkassen (AOK), from the year 2004 to 2010. The sample included 250,000 persons born in or prior to 1954 with at least one day of insurance in the first quarter of 2004. The observational data provided information on sex, age, all inpatient and outpatient diagnoses coded by International Classification of Diseases-10 (ICD-10) as well as all filled prescriptions of medications on a quarterly basis. An overview about the advantages and disadvantages of the use of medical observational data for epidemiological studies has been previously given[10,11].

Dementia incidence was measured in the five-year period from the first quarter of 2006 through the last quarter of 2010 for all persons who were not diagnosed with dementia and did not receive insulin prescriptions in the years 2004 and 2005. Dementia is defined as having been given one of the ICD-10 codes G30, G31.0, G31.82, G23.1, F00, F01, F02, F03, and F05.1. We did not differentiate by subtype of dementia as over 50% of all incident diagnoses were coded as "unspecified dementia" (F03) and no information about the etiology is available. All cases without a valid dementia diagnosis (see section "Validation of diagnoses" below) in the years 2004 and 2005, and a first valid dementia diagnosis in 2006 or later are assumed to be incident dementia cases. Of the 250,000 subjects in the original sample 145,928 persons aged 60 years and above were found to be dementia-free and received no prescription of insulin until the beginning of 2006.

To explore the potential impact of pioglitazone prescription on the incidence of dementia, we summed up the number of quarters of pioglitazone prescriptions given between the first quarter of 2004 and diagnosis of dementia, death, exit from the AOK insurance, or the end of the follow-up, whichever occurred first. The prescription quarters did not have to be consecutive.

We implemented the cumulative number of quarters with pioglitazone prescriptions as a time-dependent variable. We distinguished between the states of (1) not having a diabetes diagnosis, (2) having a diabetes diagnosis receiving no pioglitazone, (3) having a diabetes diagnosis and having received pioglitazone for less than eight quarters (PIO<8) and (4) having a diabetes diagnosis and having received pioglitazone for at least eight quarters (PIO>=8). Diabetes was defined as having at least one ICD-10 codes of E10 to E14 or as having a prescription of antidiabetic medication (ATC-code: A10) and was implemented as a time-dependent variable. We know the baseline diabetes status of the patients based on the two previous years 2004 and 2005. From the first diabetes diagnosis or antidiabetic prescription on the patient's status was set to be a diabetic. We controlled for age, sex and the confounding effects of rosiglitazone, metformin, insulin, and each patient's history of cardiovascular comorbidities, including cerebrovascular diseases[12] (ICD-10: I60-I69), hypertension (ICD-10: I10-I15), ischemic heart diseases[13] (ICD-10: I20-I25), atrial fibrillation[14] (ICD-10: I48), and hypercholesterolemia (ICD-10: E78). With the exception of sex all covariates were defined as time-dependent variables. The variables covering the prescription of rosiglitazone, metformin and insulin, and the comorbidities take the value of one from the first time the patient was on this medication or a comorbidity was noted in the data, and zero otherwise. Age was entered as a time-dependent polynomial variable with a linear and quadratic term.

Validation of diagnoses

Since routine data of public sickness funds are created for the purpose of cost calculation and reimbursement and are subject to legal changes and to changes in the data-handling procedures of the health insurers a two-stage validation procedure was applied in order to internally validate the diagnosis of dementia. For more details see[11]. This procedure excludes false positive diagnoses of dementia which otherwise would lead to an overestimation of the true dementia incidence[10]. First, diagnoses from the outpatient sector were taken into account only if the physician had indicated them as verified. Diagnoses from the inpatient sector had to be either discharge or secondary

diagnoses. Second, dementia diagnoses had to be confirmed by co-occurrence. Diagnoses were considered valid if they occurred simultaneously in the inpatient and outpatient sectors, or if at least two physicians made a diagnosis of dementia in the same quarter. Furthermore, dementia diagnoses were considered valid by a co-occurrence over time, with all five years of study being used as the validation period. If the patient died within the quarter with the first dementia diagnosis, the case was considered valid even though the initial diagnosis could not be confirmed by a second diagnosis.

Statistical analyses

We calculated the incidence of dementia dependent on the number of quarters with pioglitazone; incidence refers to 1000 person-years. We applied extended Kaplan-Meier estimators[15] to study the dementia-free survivor functions dependent on the use of pioglitazone, rosiglitazone and metformin. For the test of equality of the survivor functions we used the Log-rank test. We distinguished each quarterly record of a subject whether a diabetes diagnosis was present or not and if they had prescriptions of less than eight quarters of pioglitazone (PIO<8) or of eight and more quarters of pioglitazone (PIO>=8). The cut-off point in the number of quarters of pioglitazone use was based on the Akaike Information Criteria (AIC). The AIC rates the goodness of fit of the estimated model on the available empirical data dependent on the number of implemented variables. The lower the AIC, the better the fit of the model[16]. With a cut-off point of eight quarters the AIC had the lowest value. Rosiglitazone and metformin were differentiated into use and nonuse.

We compared the observed and predicted hazard rates of dementia dependent on the numbers of quarters with pioglitazone prescriptions. The predicted hazard rates derived from a proportional hazard model with piecewise exponential baseline over the time period of the study and the number of quarters with pioglitazone use. The baseline was split at quarter 1 and quarter 8 (predicted hazard rates are shown in Figure 1A). Further, we performed Cox proportional hazard models to explore the transition into dementia and to calculate the relative risk of dementia dependent on the use of pioglitazone, rosiglitazone, metformin, and the covariates. We distinguished the prescription of

rosiglitazone and metformin only between use and nonuse because all records without a diabetes diagnosis are comprised in one category of the variable describing the pioglitazone use Model 1 covers the whole study population. Models 2 to 4 are age-specific models to account for age-specific prescription patterns of pioglitazone. Analysis time was time in months starting on January 1st, 2006, as the years 2004 and 2005 are by definition free of any dementia diagnosis. Analysis time ended at the time of the first dementia diagnosis. In the case of no dementia diagnosis, analysis time was censored at the time of death, leaving health insurance or the end of the study period, December 31st, 2010, whichever occurred first. As we had information on diagnoses on a quarterly basis, the incidence of dementia was set in the middle of the respective quarter (which corresponded to 1.5 months in terms of analysis time) for purposes of analysis. In the case of death, the time of death was assumed to be in the middle of the respective month (0.5 months in terms of analysis time).

Results (532)

Descriptive results

Our sample consisted of 633,418 person-years and 13, 177 patients developed dementia during the follow-up observation. The mean time of follow-up per subject was 4.3 years. Characteristics of the study population as well as of the dementia incidence are given in Table 1. The use of pioglitazone significantly reduced the incidence of dementia. Compared to non-diabetics with 18 new dementia cases per 1000 person-years, diabetics without pioglitazone prescription had the highest dementia incidence with 28 new cases. Patients with less than eight quarters of pioglitazone (PIO<8) had 20 new cases and did not differ statistically from non-diabetics. Patients with eight or more quarters of pioglitazone (PIO>=8) had seven new cases and thus the lowest dementia incidence. Analysis of single quarters of pioglitazone revealed that the incidence of dementia decreased from 28 cases among diabetics without pioglitazone to 3 cases for 14 and more quarters of pioglitazone users (Figure 1A), corresponding to a risk reduction of 90.1 %. Despite small case numbers long-term users of pioglitazone (PIO>=8) had a lower dementia incidence than diabetic patients without pioglitazone ($p<0.001$). Rosiglitazone users had a lower dementia incidence than diabetics without rosiglitazone but did not differ significantly from non-diabetics. Diabetics without metformin as well as diabetics with metformin showed a significantly higher dementia incidence than non-diabetics.

The extended Kaplan-Meier estimators (Figures 1B-D) confirmed above findings: at the end of the observation period 91.7 % of the non-diabetics were dementia-free, compared to 86.7 % of the diabetics without pioglitazone, 90.4 % of PIO<8 users, and 95.5 % of PIO>=8 users ($p<0.001$). Among the rosiglitazone users 92.1 % were still dementia-free compared to 86.9 % among the diabetic nonusers ($p<0.001$); 89.5 % of the metformin users and 85.5 % of the nonusers remained dementia-free ($p<0.001$).

Model results

Table 2 presents the relative risks (RR) of dementia estimated by Cox regression. The long-term use of pioglitazone was significantly associated with a lower dementia risk. Relative to non-diabetics, the dementia risk of PIO>=8 users was reduced by 47 % (Model 1, RR=0.531, p=0.029). PIO<8 users had a

dementia risk comparable to those of the non-diabetics (RR=1.161, p=0.317), and diabetes patients without a pioglitazone treatment had a 23 % increased dementia risk (RR=1.234, p<0.001). All age - specific models showed the protective effect of the long-term use of pioglitazone. Due to sample size, however, the effect was only significant among the 70 to 79 year old (RR=0.457, p=0.081).

The results of the control variables followed our expectations, confirming the validity of our results. The incidence of dementia was lower for women than for men aged 60 to 69 (Model 2), whereas in the highest age group women had a higher incidence than men (Model 4). There was no significant effect of the use of rosiglitazone and metformin, however, user of insulin had a significantly higher dementia risk than nonusers. A diagnosis of cerebrovascular diseases, hypertension, ischemic heart diseases or atrial fibrillation significantly increased the risk of dementia[12–14,17–19]; a diagnosis of hypercholesterolemia reduced the dementia risk, the latter likely being caused by the concomitant treatment with statins[20,21]. For sensitivity analysis, we applied the approach of Fewell and colleagues to accommodate time-dependent confounding and did not find evidence of it[22].

Discussion (1303)

Dementia represents a growing threat to our health care systems due to the costs for care and treatment of an increasing number of patients. AD is the major cause for dementia followed by vascular dementia, together accounting for approximately 80% of cases. NIDDM patients have an increased risk to develop dementia and in particular AD. The identification of risk modifiers in such populations is likely to improve therapeutic approaches in future. Recent evidence suggests that a decade-long clinically silent period precedes the onset of AD, which is characterized by short-term memory decline and beginning cognitive dysfunction. Important pathogenetic mechanisms may determine the brain's fate during these pre-stages of AD. Likewise, therapeutic windows may remain unused. Preclinical studies had suggested that long-term medication with PPARγ activating drugs prevent AD like neuropathological and behavioural changes. Two PPARγ activators, pioglitazone and rosiglitazone, have been prescribed and monitored by health care insurances for a decade. This information now allows for an epidemiological analysis of possible drug effects. Analyzing observational data, which were generated from 2004-2010 by the largest German public health care insurance AOK, we performed a prospective analysis of the incidence of dementia dependent on the use or non-use of pioglitazone. We were not able to distinguish types of dementia by etiology, however, since recent evidence from post-mortem autopsies showed that the "pure" forms of dementia, such as Alzheimer's disease, become rarer while mixed dementia forms prevail[23], this may not be disadvantageous. Further, the data source allowed us to control for potential confounders including the use of rosiglitazone, metformin and insulin as well as the existence of cerebrovascular diseases, hypertension, atrial fibrillation, hypercholesterolemia and ischemic heart diseases.

A total of 145,928 patients with 633,418 person-years of survival at 60 years of age or older were analyzed from which 13,177 (9 %) developed dementia during the observation period. Confirming previous observations, patients with NIDDM showed a higher risk of developing dementia[5]. This phenomenon may be attributed to a variety of factors including an increased number of comorbidities, changes in cerebral insulin and amyloid metabolism as well as cerebrovascular

pathology. Pioglitazone treatment was associated with a significantly reduced incidence of dementia in NIDDM patients over the observation period. This protection was dependent on the duration of pioglitazone therapy and increased with each quarter of prescription. Medication for up to eight quarters was associated with a reduced risk of dementia nearly to the levels of people without diabetes, while pioglitazone prescription for eight or more quarters lowered the risk for dementia significantly further. Rosiglitazone showed a similar trend, which however did not reach the level of statistical significance, likely in part due to the much lower number of NIDDM patients receiving rosiglitazone. This lower rate of rosiglitazone prescription follows several studies, which revealed that rosiglitazone therapy is associated with an increased risk of myocardial infarction[24] and a subsequent black box warning by the FDA in 2007[25]. Prescription of rosiglitazone has been halted in Germany since 2010 for this reason. It is important to note that pioglitazone medication does not show the same risk profile and both drugs, despite acting via PPARγ ligation, activate or repress different gene sets. In the present study, pioglitazone therapy of NIDDM patients was not associated with any increase in mortality. Bladder cancer was increased for all NIDDM patients, but there was no additional excess risk for pioglitazone users as previously suggested by other studies[26,27]. Importantly, similar data were obtained from an analysis of 142,328 Department of Veterans Affairs patients. Miller and colleagues reported a 20% decrease of AD incidence in patients treated either with pioglitazone or rosiglitazone when compared to patients treated with metformin or insulin[28]. The period of observation in this study was 24 months. Thus, these data are entirely consistent with the present findings obtained from an entirely different data source[8,9]. The principal findings of this study confirmed previous observations, however, these data need to be interpreted with caution. First, the primary aim of medical observational data is cost calculation and reimbursement, thus only those diagnoses are included that lead to treatment. Incidence may be underestimated as doctors may refrain from diagnosing mild dementia cases due to a lack of awareness, as well as dementia cases in the very high ages due to the lack of therapeutic options. However, confirming the validity of our data source, we found that age-specific dementia incidence rates are comparable to previous studies (see Appendix Figure 2).

Social selection into pioglitazone treatment may play a role with patients from higher social strata having a higher likelihood of receiving pioglitazone. Since observational data do not contain information about social status we used the diagnosis of obesity, which is closely linked to socioeconomic and educational background[29]. We did not find evidence of selection into pioglitazone treatment by obesity. It should be noted that our data source allowed for the estimation of the daily drug intake, but not on the patient´s compliance with their doctor's recommendation for intake. Moreover, the number of dementia cases among pioglitazone long-term users is small. This finding, however, may also be caused by a protective effect of pioglitazone on dementia incidence. Finally, we cannot exclude that known contra-indications for pioglitazone use including heart failure and liver dysfunction may have selected for patients, who had a primarily reduced dementia risk.

Several clinical studies have tested the efficacy of rosiglitazone treatment in AD patients, mostly reporting failure to prevent or improve cognitive and functional decline: While one study reported positive effects of rosiglitazone in APOEε4 non-carrieres[30], this finding was not replicated in the larger Phase III trial [31]. Similarly, rosiglitazone did not improve cognition or global function when tested as an adjunct therapy to acetylcholine-esterase inhibitors[32]. Two studies, so far have evaluated the therapeutic potential of pioglitazone, albeit with very small patient numbers, which do not allow for any conclusion[33,34]. Still, it seems noteworthy that the study, which enrolled NIDDM patients already suffering from mild AD found positive effects[34], while the study in non diabetic probable AD patients yielded negative results[33]. Another principle difference between both drugs is the lower cerebral availability of rosiglitazone due to a reduced blood brain barrier permeability and active export by p-glycoprotein mediated transport. The limited efficacy found in these clinical studies may also result from the late time of intervention, as they employed patient populations with diagnosed AD, similar to other therapeutic approaches in AD, e.g. the anti-beta amlyoid vaccination strategy. In preclinical models, PPARγ activation has been shown to prevent the deposition of beta-amyloid by transcriptional suppression of BACE1[35,36] , the rate-limiting enzyme of the amyloidogenic pathway and by positively regulating phagocytic clearance of beta-amyloid by microglia[37,38]. In

murine AD models pioglitazone treatment reduced inflammation and lowered beta-amlyoid deposition[39]. Additionally, TZDs including pioglitazone have been shown to exert positive effects on cerebrovascular dysfunction[40], mitochondrial biogenesis and antioxidative enzymes[41], all of which could contribute to the observed beneficial effect. While compromized clearance of beta-amyloid has been suggested as major cause for the sporadic form of AD[42], it seems evident, that any therapy directed against beta-amyloid will benefit from an early time point of intervention. Thus, the TZDs may be well effective as preventive measure, when taken prior to major pathological changes in AD. Possibly, such a positive action is limited to NIDDM patients. They may, however be of no or only limited value, when given to already clinically symptomatic AD patients. A first hint may come from an ongoing clinical trial (NCT01931566), which will test the efficacy of pioglitazone to delay the onset of mild cognitive impairment due to AD in cognitively normal participants.

The findings from this analysis suggest that medication with pioglitazone is associated which a lower risk of dementia for NIDDM patients. Prospective clinical trials with NIDDM patients and non diabetics are needed to evaluate whether a possible neuroprotective effect can be verified in NIDDM patients and beyond.

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Figure legends

Figure 1: Dementia incidence rate by number of quarters with pioglitazone (A) and extended Kaplan-Meier estimators of time to the first dementia diagnosis dependent on the use of pioglitazone (B), rosiglitazone (C) and metformin (D).

Source: AOK Observational Data 2004-2010

Table 1: Characteristic s of the study population and dementia incidence rate per 1000 person-years, 95 % confidence interval

Variable	Person-years (N=633,418)	Subjects with dementia (N=13,177)	Dementia incidence rate per 1000 person-years	
	Number (percent)	Number (percent)	Rate	95% CI
Sex				
Male	256,292 (40.5)	4,310 (32.7)	16.82	16.32 - 17.33
Female	377,126 (59.5)	8,867 (67.3)	23.51	23.03 - 24.01
Age group				
60-64	56,894 (9.0)	194 (1.5)	3.41	2.96 - 3.93
65-69	160,655 (25.4)	771 (5.9)	4.80	4.47 - 5.15
70-74	161,281 (25.5)	1,595 (12.1)	9.89	9.42 - 10.39
75-79	121,014 (19.1)	2,665 (20.2)	22.02	21.20 - 22.87
80-84	80,531 (12.7)	3,416 (25.9)	42.42	41.02 - 43.87
85-89	39,047 (6.2)	2,845 (21.6)	72.86	70.23 - 75.59
90-94	10,630 (1.7)	1,210 (9.2)	113.83	107.60 - 120.43
95+	3,366 (0.5)	481 (3.7)	142.89	130.68 - 156.25
Diabetes				
No diabetes	443,559 (70.0)	7,845 (59.5)	17.69	17.30 - 18.08
Pioglitazone				
Diabetes & no pioglitazone	185,864 (29.3)	5,273 (40.0)	28.37	27.61 - 29.15
Diabetes & PIO<8	2,375 (0.4)	47 (0.4)	19.79	14.87 - 26.34
Diabetes & PIO>=8	1,620 (0.3)	12 (0.1)	7.41	4.21 - 13.04
Rosiglitazone				
Diabetes & no rosiglitazone	187,868 (29.7)	5,299 (40.2)	28.21	27.46 - 28.98
Diabetes & rosiglitazone	1,991 (0.3)	33 (0.3)	16.58	11.78 - 23.32
Metformin				
Diabetes & no metformin	122,036 (19.3)	3,854 (29.3)	31.58	30.60 - 32.59
Diabetes & metformin	67,822 (10.7)	1,478 (11.2)	21.79	20.71 - 22.93
Insulin				
Diabetes & no insulin	179,221 (28.3)	4,868 (36.9)	27.16	26.41 - 27.94
Diabetes & insulin	10,638 (1.7)	464 (3.5)	43.62	39.82 - 47.77
Cerebrovascular diseases				
No	512,119 (80.9)	6,945 (52.7)	13.56	13.25 - 13.88
Yes	121,298 (19.1)	6,232 (47.3)	51.38	50.12 - 52.67
Hypertension				
No	162,047 (24.4)	1,995 (15.1)	12.31	11.78 - 12.86
Yes	471,371 (75.6)	11,182 (84.9)	23.72	23.29 - 24.17
Ischemic heart diseases				
No	409,042 (64.6)	6,281 (47.7)	15.36	14.98 - 15.74
Yes	224,376 (35.4)	6,896 (52.3)	30.73	30.02 - 31.47
Atrial fibrillation				
No	557,115 (88.0)	9,526 (72.3)	17.10	16.76 - 17.45
Yes	76,303 (12.0)	3,651 (27.7)	47.85	46.32 - 49.43
Hypercholesterolemia				
No	438,360 (69.2)	9,464 (71.8)	21.59	21.16 - 22.03
Yes	195,057 (30.8)	3,713 (28.2)	19.04	18.43 - 19.66

Source: AOK Observational Data 2004-2010

Table 2: Relative risks of dementia

Variable	Model 1 Age 60+ RR	95% CI	p-value	Model 2 Age 60-69 RR	95% CI	p-value	Model 3 Age 70-79 RR	95% CI	p-value	Model 4 Age 80+ RR	95% CI	p-value
Females (Ref. Males)	1.016	0.978-1.054	0.415	0.775	0.681-0.882	<0.001	1.005	0.945-1.069	0.874	1.081	1.027-1.139	0.003
Age	1.097	1.094-1.100	<0.001	1.097	1.059-1.137	<0.001	1.138	1.126-1.151	<0.001	1.070	1.064-1.077	<0.001
Age*Age	0.998	0.998-0.998	<0.001	1.005	0.992-1.017	0.475	1.000	0.995-1.004	0.871	0.997	0.996-0.998	<0.001
Diabetes & no pioglitazone (Ref. No diabetes)	1.234	1.186-1.283	<0.001	1.607	1.372-1.883	<0.001	1.267	1.179-1.362	<0.001	1.178	1.121-1.239	<0.001
Diabetes & PIO<8	1.161	0.867-1.553	0.317	1.139	0.464-2.792	0.777	0.874	0.530-1.442	0.599	1.468	0.933-2.171	0.054
Diabetes & PIO>=8	0.531	0.301-0.936	0.029	0.408	0.057-2.921	0.372	0.457	0.189-1.102	0.081	0.664	0.298-1.482	0.318
Rosiglitazone (Ref. Nonuse)	0.842	0.597-1.188	0.328	0.356	0.088-1.435	0.147	0.917	0.567-1.482	0.723	0.865	0.510-1.467	0.592
Metformin (Ref. Nonuse)	0.966	0.908-1.027	0.270	0.987	0.798-1.220	0.903	0.954	0.863-1.055	0.358	0.948	0.870-1.033	0.223
Insulin (Ref. Nonuse)	1.608	1.459-1.773	<0.001	2.389	1.741-3.278	<0.001	1.713	1.459-2.011	<0.001	1.452	1.270-1.661	<0.001
Cerebrovascular diseases (Ref. No)	2.440	2.354-2.530	<0.001	5.000	4.364-5.728	<0.001	3.102	2.913-3.304	<0.001	1.989	1.901-2.081	<0.001
Hypertension (Ref. No)	1.043	0.989-1.100	0.118	0.832	0.712-0.972	0.021	1.058	0.965-1.160	0.228	1.042	0.970-1.119	0.261
Ischemic heart diseases (Ref. No)	1.061	1.023-1.101	0.001	1.032	0.892-1.192	0.675	1.056	0.989-1.126	0.102	1.054	1.006-1.104	0.028
Atrial fibrillation (Ref. No)	1.552	1.491-1.615	<0.001	1.356	1.108-1.660	0.003	1.632	1.516-1.757	<0.001	1.536	1.462-1.612	<0.001
Hypercholesterolemia (Ref. No)	0.917	0.882-0.953	<0.001	0.958	0.834-1.100	0.540	0.891	0.835-0.951	0.001	0.914	0.868-0.962	0.001
Exposures in person-years	633,418			217,549			282,295			133,574		
Cases	13,177			965			4,260			7,952		

RR: Rate ratios

CI: Confidence intervals

PIO: pioglitazone

Source: AOK Observational Data 2004-2010

APPENDIX

Figure 2: Dementia incidence rates from AOK and previous studies.

Table 3: Relative risks of dementia, rosiglitazone nonusers split up into non-diabetics and diabetics without rosiglitazone

Variable	Model 1b Age 60+ RR	95% CI	p-value
Females (Ref. Males)	1.016	0.978-1.054	0.418
Age	1.097	1.094-1.101	<0.001
Age*Age	0.998	0.998-0.998	<0.001
Diabetes & no rosiglitazone (Ref. No diabetes)	1.219	1.175-1.264	<0.001
Diabetes & rosiglitazone	1.001	0.711-1.412	0.993
Insulin (Ref. Nonuse)	1.589	1.444-1.749	<0.001
Cerebrovascular diseases (Ref. No)	2.441	2.355-2.530	<0.001
Hypertension (Ref. No)	1.042	0.989-1.099	0.127
Ischemic heart diseases (Ref. No)	1.062	1.023-1.101	0.001
Atrial fibrillation (Ref. No)	1.553	1.492-1.616	<0.001
Hypercholesterolemia (Ref. No)	0.916	0.881-0.953	<0.001

RR: Rate ratios
CI: Confidence intervals

Source: AOK Observational Data 2004-2010

Table 4: Relative risks of dementia, metformin nonusers split up into non-diabetics and diabetics without metformin

Variable	Model 1c Age 60+ RR	95% CI	p-value
Females (Ref. Males)	1.016	0.978-1.054	0.417
Age	1.097	1.094-1.100	<0.001
Age*Age	0.998	0.998-0.998	<0.001
Diabetes & no metformin (Ref. No diabetes)	1.231	1.183-1.281	<0.001
Diabetes & metformin	1.178	1.111-1.249	<0.001
Insulin (Ref. Nonuse)	1.604	1.445-1.768	<0.001
Cerebrovascular diseases (Ref. No)	2.441	2.355-2.530	<0.001
Hypertension (Ref. No)	1.043	0.989-1.100	0.119
Ischemic heart diseases (Ref. No)	1.061	1.023-1.101	0.002
Atrial fibrillation (Ref. No)	1.552	1.491-1.616	<0.001
Hypercholesterolemia (Ref. No)	0.916	0.881-0.953	<0.001

RR: Rate ratios
CI: Confidence intervals

Source: AOK Observational Data 2004-2010

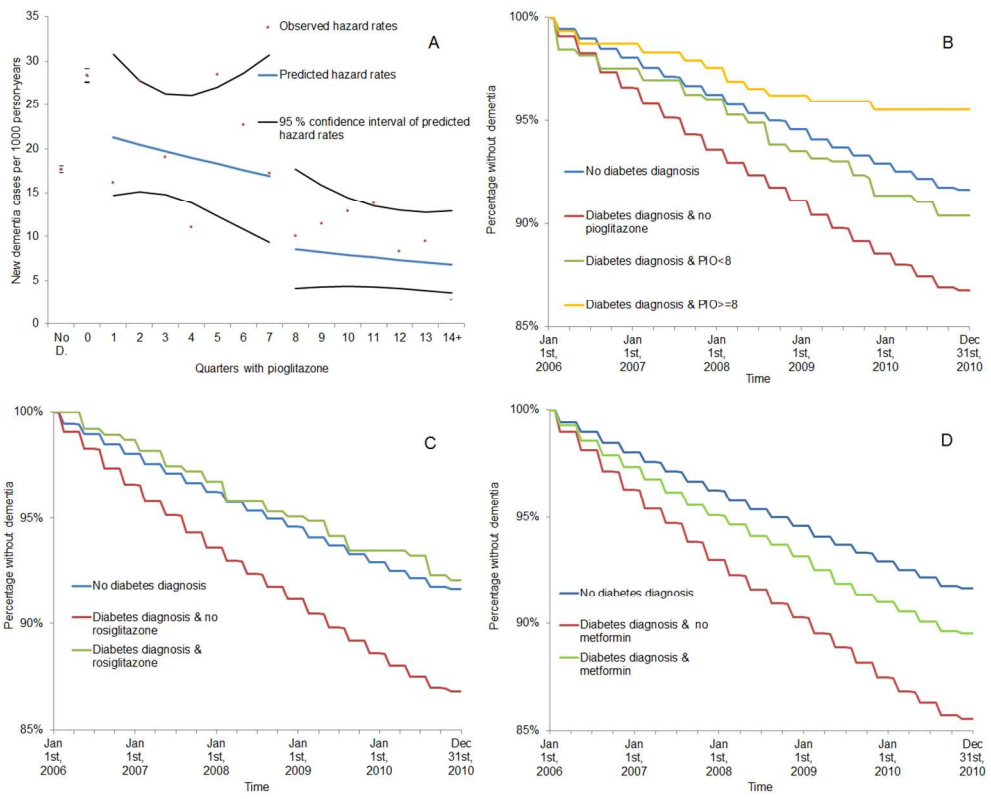

Figure 1: Dementia incidence rate by number of quarters with pioglitazone (A) and extended Kaplan-Meier estimators of time to the first dementia diagnosis dependent on the use of pioglitazone (B), rosiglitazone (C) and metformin (D).

Source: AOK Observational Data 2004-2010

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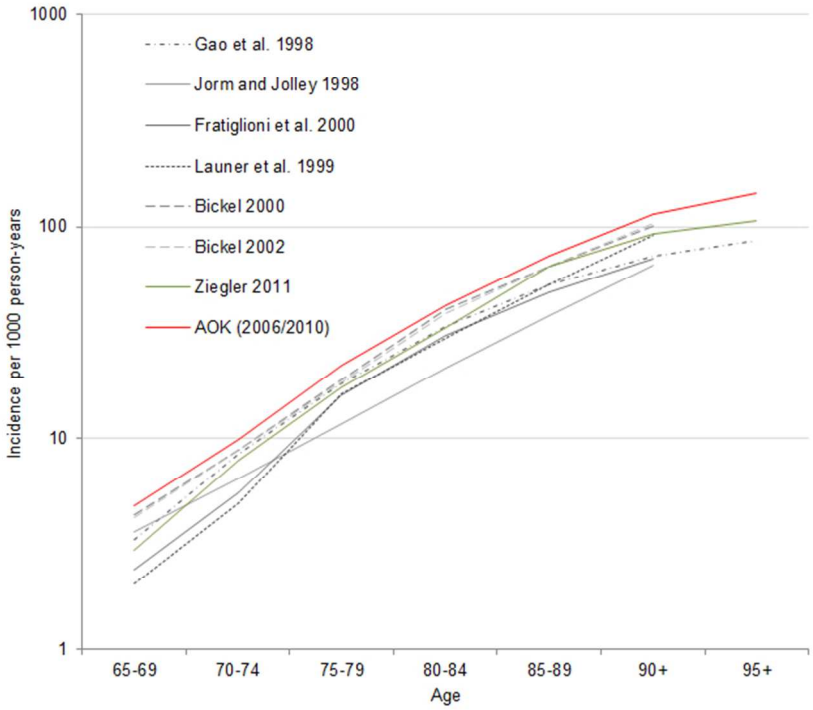

Figure 2: Dementia incidence rates from AOK and previous studies.
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