The Association Between Diabetes and Age-Related Macular Degeneration Among the Elderly in Taiwan

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OBJECTIVE

To investigate the relationship between diabetes and future development of age-related macular degeneration (AMD).

RESEARCH DESIGN AND METHODS

Longitudinal, retrospective cohort study data for the period between 1997 and 2012 were obtained from the Longitudinal Health Insurance Database (LHID) of Taiwan. The final available 71,904 patients with diabetes and 270,213 patients without diabetes ≥50 years of age were further matched by age, sex, and Charlson comorbidity index. In the end, 54,616 study subjects in each of the diabetes and nondiabetes groups were recruited. The stratified populations of patients with diabetes with diabetic retinopathy (DR) (*n* = 7,119) versus those with diabetes who do not have DR (*n* = 7,119) and populations of patients with proliferative DR (PDR) (*n* = 2,134) versus those with nonproliferative DR (NPDR) (*n* = 2,134) were also obtained. Competing risk regression models were used to assess the adjusted hazard ratio (HR) and 99% CI. The main outcome measures were the first-ever diagnosis of AMD during the observational period.

RESULTS

The incidences of nonexudative AMD (HR 1.23; *P* = 0.108) and exudative AMD (HR 1.37; *P* = 0.023) were not significantly associated with cohorts of persons with diabetes compared with cohorts without diabetes. The stratified analysis showed that nonexudative AMD (HR 3.89; *P* = 0.001) and exudative AMD (HR 3.42; *P* < 0.001) were significantly correlated to diabetes with DR cohorts, compared with diabetes without DR cohorts. The incidences of nonexudative AMD (HR 0.53; *P* = 0.277) and exudative AMD (HR 2.27; *P* = 0.058) were not significantly different between PDR cohorts compared with NPDR cohorts.

CONCLUSIONS

This study provides large-scale, population-based evidence that diabetes with retinopathy is independently associated with an increased risk of subsequent AMD development.

Age-related macular degeneration (AMD) is the most common cause of visual loss in elderly people all over the world (1). There are two types of AMD: nonexudative (dry) and exudative (wet). Nonexudative AMD is the most frequent type of AMD, whereas

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exudative AMD represents ~10% of all AMD cases, and it is also responsible for the majority of cases with severe visual impairment and legal blindness. The global prevalence of diabetes among adults over 18 years of age rose from 4.7% in 1980 to 8.5% in 2014 (2), and the number of people who have received diagnoses of this disease is increasing rapidly worldwide. Diabetic retinopathy (DR), a common complication of diabetes, is also a major cause of visual impairment and the leading cause of blindness among working-age adults. Both AMD and DR impact patients' visual acuity and their quality of life enormously (3).

Vascular endothelial growth factor (VEGF) is a signal protein produced by cells that stimulates vasculogenesis and angiogenesis. Although the cause of disease and the typical source of neovascularization differ between AMD and DR, VEGF plays important roles in both diseases, and anti-VEGF pharmaceutical agents have proven useful in the treatment of both diseases. Although the analysis of claims data is not designed with biological conclusions in mind, these results raise the thesis that DR and AMD may share similar pathogenic features and that improving the control of diabetes may further reduce the development of AMD.

AMD is a complex disease not only with demographic and environmental risk factors but also genetic risk factors (4). Previous studies have reported various risk factors for AMD, including old age (1), white race (5), family history of AMD (1), and smoking (5). Also, it has been suggested that maintaining a normal BMI and preventing hypertension may reduce the risk of the development of AMD (5). However, to date, most of the epidemiological studies have been inconsistent regarding the association of diabetes with AMD. Some reports (5–8) have suggested an increased risk in either nonexudative or exudative AMD with diabetes; some have described the uncommon coexistence of advanced AMD and diabetes or DR; but some other studies (9–11) have found no significant correlation. Because both AMD and DR are VEGF mediated and represent the leading blindness-causing disease in the world, additional large-scale longitudinal studies, which stratify AMD into exudative and nonexudative subtypes and focus on the relationship between AMD and diabetes, may be helpful to further clarify this controversial issue. Therefore, we used the Taiwan National Health Insurance Research Database (NHIRD) in this nationwide study with a retrospective cohort design to investigate the relationship between AMD subtypes with diabetes and subsequent retinopathy.

RESEARCH DESIGN AND METHODS

Data Sources

Study data for the period January 1997 to December 2012 was obtained from the Longitudinal Health Insurance Database (LHID) of Taiwan. The database contains all of the registration files and details about the original claims data for 1 million beneficiaries randomly sampled from the NHIRD, where registration data of everyone who was a beneficiary of the National Health Insurance program during the period of 1 January 2010 to 31 December 2010 were drawn for random sampling. There are ~27.38 million individuals in this registry. All data in the database are encrypted to protect the privacy of individuals. The database provides the detailed outpatient and inpatient claims data including patient identification number; birth date; sex; diagnostic codes according to the ICD-9-CM; treatment information; medical cost; dates of hospital admission and discharge; and date of death. All data sets can be interlinked through patient identification number.

Study Cohort and Patient Selection

This study was approved by the Ethics Committee and Human Subjects Institutional Review Board of Tzu Chi Hospital, Hualien, Taiwan (TCH IRB103-39-C+). Among a total of 999,991 subjects between 1 January 1997 and 31 December 2012 in the NHIRD, 104,079 subjects with the diagnosis of diabetes (ICD-9-CM code 250) and 895,912 subjects without diabetes were initially enrolled into diabetes and nondiabetes groups, respectively, for the main study cohort. Subjects were excluded from the diabetes group if they were <50 years old (n = 32,046) or had AMD (n = 130) before the diagnosis of diabetes. On the other hand, 625,699 subjects <50 years of age were excluded from the nondiabetes group. To avoid confounding effect of subjects' characteristics and comorbidities, the resulting available 71,904 patients with diabetes and 270,213 patients without diabetes were further matched in a 1:1 ratio by age, sex, and Charlson comorbidity index (CCI); finally, 54,616 study subjects in each of the diabetes and nondiabetes groups were obtained. The index date was defined as the onset date of diabetes. In addition to the main study cohort (i.e., diabetes vs. nondiabetes groups), the stratified populations with diabetes with DR (ICD-9-CM codes 362.01, 362.02; n = 7,119) versus diabetes without DR (CD-9-CM codes 362.01, 362.02; n = 7,119), and proliferative DR (PDR) (ICD-9-CM code 362.01; n = 2,134) versus nonproliferative DR (NPDR) (ICD-9-CM code 362.02; n = 2,134) were also obtained via similar exclusion criteria and matching procedures for the subsequent stratified analysis. The detailed study data flows are described in Fig. 1.

Outcomes Measures

The study end points were nonexudative AMD (ICD-9-CM codes 362.50, 362.51) and exudative AMD (ICD-9-CM code 362.52), as identified by the corresponding ICD-9-CM codes. When both eyes of a participant had lesions of different severities, the grade assigned for the participant was that of the more severely involved eye. All outcomes were assessed during the entire follow-up period between the index date and 31 December 2011. Baseline comorbidities were identified via ICD-9 codes, which included CCI, hypertension (codes 401.X–405.X, 437.2, 362.11), and hyperlipidemia (code 272.X).

Statistical Analysis

Patient demographic data, including age (51–60, 61–70, and ≥71 years), sex, hypertension, hyperlipidemia, and the CCI score were compared between the study cohort and control groups via standard difference. The demographic variables with a standard difference of >0.1 were considered to represent clinically meaningful differences. The 10,000 person-year incidence of both study groups and control groups were calculated. Competing risk-adjusted Cox regression models were used to assess adjusted hazard ratios (HRs) and 99% CI. SAS statistical software (SAS System for Windows, version 9.3; SAS Institute,

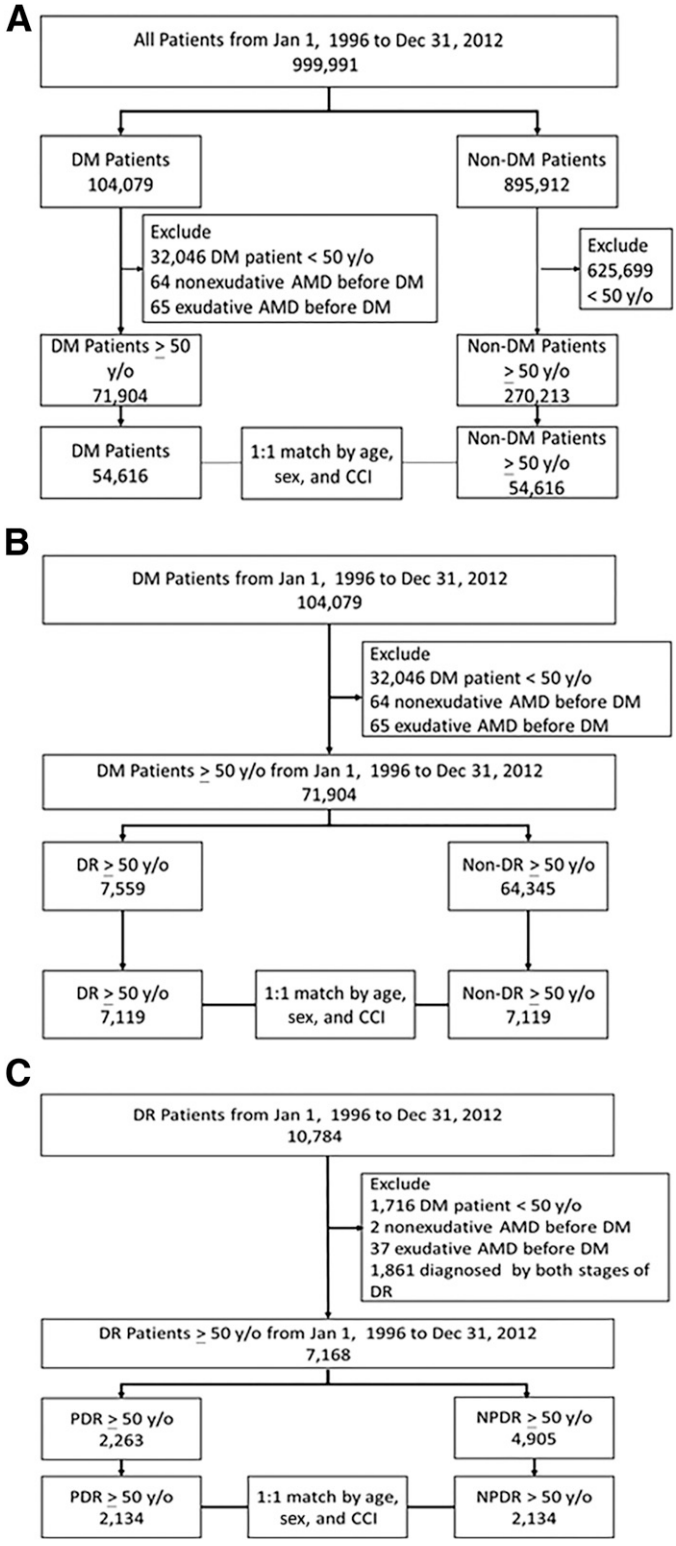

Figure 1—Study protocol and profile. *A*: The selection flow chart and selected populations for diabetes group and the control cohort. *B*: The stratification flow chart and the stratified populations for diabetes with DR vs. diabetes without DR. *C*: The stratification flow chart and the stratified populations for PDR vs. nonPDR. DM, diabetes mellitus; y/o, years old.

Cary, NC) was used for the statistical analysis. All statistical tests were two sided, and a *P* value of <0.01 was considered to be statistically significant.

RESULTS

Diabetes Versus Nondiabetes

After matching by sex, age, and CCI, the final analysis included 54,616 patients with diabetes and 54,616 patients without diabetes (Fig. 1*A*). The distributions of demographic characteristics and comorbidities for these two cohorts are shown in Table 1. Patients with diabetes were more likely to have claims for chronic comorbidities, including hypertension (52.5% vs. 27.9%) and hyperlipidemia (31.6% vs. 12.5%), with standard differences of 0.52 and 0.47, respectively. During the follow-up period of 15 years, the overall mean annual incidence of nonexudative AMD was higher in patients with diabetes than in patients without diabetes (33.7/10,000 person-years to 23.5/10,000 person-years in the period of 1996–2012; incidence ratio 1.4). Similar trends were also observed in exudative AMD (3.5/10,000 person-years to 2.5/10,000 person-years; incidence ratio 1.4) (Table 2).

In multivariate survival analysis, patients with diabetes did not show significantly increased risk of subsequent nonexudative AMD development (HR 1.23; 99% CI 0.88–1.70; $P = 0.108$) except for CCI total (HR 1.27; 99% CI 1.20–1.34; $P < 0.001$), which was independently associated with increased risk of subsequent nonexudative AMD. For exudative AMD, CCI total (HR 1.23; 99% CI 1.13–1.35; $P < 0.001$) and male sex (HR 1.65; 99% CI 1.19–2.30; $P < 0.001$) both had a significantly higher incidence of subsequent exudative AMD. Although diabetes seemed to add to the risk of exudative AMD development, the statistical analysis result was not significant (HR 1.37; 99% CI 0.96–1.97; $P = 0.023$). In contrast, the difference in the risk of the development of subsequent either nonexudative or exudative AMD was not significantly associated with hypertension or hyperlipidemia (Table 3).

Diabetes With DR Versus Diabetes Without DR

After including control subjects matched 1:1 by sex, age, and CCI, the final analysis included 7,119 patients with diabetes with retinopathy and 7,119 patients with diabetes without retinopathy (Fig. 1*B*). The distributions of demographic characteristics and comorbidities for these two cohorts are shown in Table 1. Patients with diabetes with DR were more likely to have claims for chronic comorbidities, including hypertension (74.8% vs. 65.1%) and hyperlipidemia (52.0% vs. 42.0%) than those without

DR. During a follow-up period of 17 years, the overall mean annual incidence of nonexudative AMD was significantly correlated to patients with diabetes with DR, compared with patients with diabetes without retinopathy (8.7/10,000 person-years to 2.2/10,000 person-years in the period of 1996–2012; incidence ratio 4.0). Similar trends can also be observed in patients with exudative AMD (12.1/10,000 person-years to 3.1/10,000 person-years; incidence ratio 3.9) (Table 2).

In multivariate survival analysis, we found that diabetes with DR was independently associated with an increased risk of subsequent nonexudative AMD (HR 3.89; 99% CI 1.35–11.23; $P = 0.001$). However, the difference in the risk of the development of subsequent nonexudative AMD was not significant for sex, CCI total, hypertension, or hyperlipidemia variants. Similarly, patients with DR also showed an increased risk of subsequent exudative AMD (HR 3.42; 99% CI 1.48–7.90; $P < 0.001$). Male sex also had a significantly higher incidence of subsequent exudative AMD (HR 2.05; 99% CI 1.06–3.99; $P = 0.005$) as a variant; whereas CCI total, hypertension and hyperlipidemia did not (Table 3).

Development of AMD in Different Stages of DR

We further stratified patients with DR by the presence or lack of retinal neovascularization into NPDR and PDR. After matching by sex, age, and CCI, the final analysis included 2,134 patients with NPDR and 2,134 patients with PDR (Fig. 1*C*). The distributions of demographic characteristics and comorbidities of these two cohorts are shown in Table 1. The overall mean annual incidences of nonexudative AMD were lower with patients with PDR compared with patients with NPDR (4.2/10,000 person-years to 7.3/10,000 person-years; incidence ratio 0.6), but multivariate analysis did not show any difference between patients with PDR and those with NPDR. In contrast, the annual incidence of exudative AMD was significantly higher in patients with PDR than in patients with NPDR (14/10,000 person-years to 4.6/10,000 person-years; incidence ratio 3.0) (Table 2). However, in multivariate survival analysis, the trend toward the development of exudative AMD in patients with PDR was not statistically significant (HR 2.27; 99% CI 0.74–6.92; $P = 0.058$).

Table 1—Characteristics of the study population

			Diabetes vs. nondiabetes			Diabetes w/DR vs. diabetes w/o DR			PDR vs. NPDR		
Variable	Category	Statistic	Diabetes	Nondiabetes	Standard Diff.	Diabetes w/ DR	Diabetes w/o DR	Standard Diff.	PDR	NPDR	Standard Diff.
Sex	Female	*n* (%)	27,581 (50.5)	27,581 (50.5)	0.00	4,089 (57.4)	4,089 (57.4)	0.00	1,147 (53.1)	1,147 (53.1)	0.00
	Male	*n* (%)	27,035 (49.5)	27,035 (49.5)		3,030 (42.5)	3,030 (42.5)		987 (46.2)	987 (46.2)	
Age, years	Mean ± SD		62.3 ± 9.0	62.3 ± 9.0	0.01	66.4 ± 7.9	66.4 ± 7.9	0.001	63.3 ± 8.1	63.3 ± 8.1	0.00
	50 < age ≤ 60	*n* (%)	26,109 (47.8)	26,154 (47.9)	0.11	1,632 (22.9)	1,624 (22.8)	0.02	856 (40.1)	862 (40.3)	0.00
	60 < age ≤ 70	*n* (%)	17,219 (31.5)	17,148 (31.4)		3,181 (44.6)	3,195 (44.8)		804 (37.6)	797 (37.3)	
	age >70	*n* (%)	11,288 (20.6)	11,314 (20.7)		2,306 (32.3)	2,300 (32.3)		474 (22.2)	475 (22.2)	
CCI total		Mean ± SD	2.8 ± 1.0	2.7 ± 0.9	0.044	4.8 ± 4.7	4.8 ± 4.7	0	4.4 ± 1.9	4.4 ± 1.9	0.00
Hypertension		*n* (%)	28,687 (52.5)	15,259 (27.9)	0.52	5,331 (74.8)	4,637 (65.1)	0.21	1,570 (73.5)	1,567 (73.4)	0.00
Hyperlipidemia		*n* (%)	17,270 (31.6)	6,871 (12.5)	0.47	3,706 (52.0)	2,994 (42.0)	0.20	1,106 (51.8)	1,237 (57.9)	−0.12

Diff., difference; w/o, without; w/, with.

Table 2—Incidence of events (10,000 person-years)

Outcome	Diabetes vs. nondiabetes						Diabetes w/DR vs. diabetes w/o DR						PDR vs. NPDR					
	Diabetes			Nondiabetes			Diabetes w/ DR			Diabetes w/o DR			PDR			NPDR		
	PY	Event	Rate	PY	Event	Rate	Ratio	PY	Event	Rate	PY	Event	Rate	Ratio	PY	Event	Rate	Ratio	PY	Event	Rate	Ratio
Nonexudative AMD	458,966	1,549	33.7	468,355	1,099	23.5	1.4*	49,693	43	8.7	50,982	11	2.2	4.0*	14,329	6	4.2	15,103	11	7.3	0.6*
Exudative AMD	466,970	165	3.5	475,451	121	2.5	1.4*	49,579	60	12.1	50,991	16	3.1	3.9*	14,243	20	14.0	15,110	7	4.6	3.0*

Event, number of events; PY, total person-years; Rate, incidence; Ratio, incidence ratio; w/o, without; w/, with. *Statistically significant at $P < 0.01$.

CONCLUSIONS

The first clinical feature of early nonexudative AMD is the presence of drusen, which are extracellular deposits below the retinal pigmented epithelium (RPE) and composed of lipid- and protein-rich debris. Small, isolated drusen do not affect visual function, but their expansion and coalescence are hallmarks of AMD progression. The two main advanced forms of AMD are as follows: exudative AMD (also known as wet AMD or neovascular AMD), which is characterized by the invasion of abnormal choroidal (or occasionally retinal) blood vessels and fluid leakage into the retina; and nonexudative AMD (also known as dry AMD or atrophic AMD). AMD and DR are among the leading causes of vision loss in the world. Surprisingly, the relationship between these two diseases is poorly understood, with inconsistent conclusions in previous clinical and epidemiological studies. There is limited population-based evidence supporting a positive association between diabetes and AMD (5–8,12–14).

Previous studies examining the relationship between diabetes and AMD have been contradictory (Table 4). Among these studies, different staging systems of AMD classification were applied. Some studies were divided into early and late AMD subgroups by using the Age-Related Eye Disease Study (AREDS) Research Group classification system (15). In brief, early AMD was defined by either the presence of any soft drusen (distinct or indistinct) and pigmentary abnormalities (either increased retinal pigment or RPE depigmentation), the presence of a large soft drusen $\geq$125 μm in diameter with a large drusen area ($\geq$500-μm-diameter circle), or large soft instinct drusen in the absence of signs of late AMD. Although late AMD is defined as the presence of the signs of exudative AMD or geographic atrophy. The other studies were divided into nonexudative and exudative AMD subgroups by the presence of choroidal neovascularization and its sequelae. We performed a meta-analysis for the studies with the same comparison in Table 4 to assess whether diabetes is a risk factor for AMD. Statistical analysis was recalculated using 95% CI for our study to match the same comparisons of other study. The results (Fig. 2) showed nonsignificant association between diabetes and nonexudative AMD (HR 1.04; P = 0.23) or early AMD (odds ratio [OR] 0.99; P = 0.92), whereas there was significant association between diabetes and exudative AMD (HR 1.55, P = 0.01; OR 1.14, P = 0.04) or late AMD (OR 2.10; $P < 0.01$). Our findings are consistent with the results of the study conducted by Chen et al. (16), which indicated that diabetes is a potential risk factor for late AMD, whereas no clear association between diabetes and early AMD is identified. Examination of those large population-based cross-sectional and longitudinal studies, such as the Beaver Dam Eye Study (BDES) (17), the Blue Mountains Eye Study (BMES) (18), the European Eye (EUREYE) Study (8), the AREDS (19), and the Barbados Eye Studies (BES) (7), reveals an increased risk of AMD with diabetes. However, these studies did not further differentiate the incidence between different types of AMD or diabetes, with or without retinopathy. In addition, the cross-sectional designs limited causal inference. These studies were contrary to other case control–type studies (20,21), which indicate a lower prevalence of AMD among patients with diabetes. Still other reports have demonstrated no association between AMD and diabetes. Some of these investigations have been small case-control studies (22–24) or small prospective cohort studies (25) that might not have been sufficiently powered to detect any difference. The Framingham Eye Study (26) also did not reveal an association between AMD and diabetes, but this study was likely limited by different criteria and/or less sensitive methods for the detection of AMD than those in current practice.

By analyzing a 5% sample of claims data from American beneficiaries of Medicare (age >69 years), Hahn et al. (12) conducted a longitudinal cohort study and revealed that newly diagnosed NPDR was associated with significantly increased risk of incident diagnosis of nonexudative AMD (HR 1.24; 95% CI 1.08–1.43) and exudative AMD (HR 1.68; 95% CI 1.23–2.31). Newly diagnosed PDR was associated with significantly increased risk of exudative AMD only (HR 2.15; 95% CI 1.07–4.33). These results were in line with those of our studies. Of note, AMD is a common eye condition and a leading cause of vision loss among people $\geq$50 years of age.

Table 3—Predictors of two types of AMD by multivariate analysis

		Diabetes vs. nondiabetes		Diabetes w/ DR vs. diabetes w/o DR		PDR vs. NPDR	
Outcome	Effect	HR (99% CI)	*P* value	HR (99% CI)	*P* value	HR (99% CI)	*P* value
Nonexudative AMD	Group	1.23 (0.88–1.70)	0.108	3.89 (1.35–11.23)	0.001	0.53 (0.12–2.36)	0.277
	Sex (ref.: female)	1.34 (0.98–1.82)	0.015	1.45 (0.70–3.01)	0.189	0.78 (0.21–2.90)	0.624
	CCI total	1.27 (1.20–1.34)	<0.001	1.08 (0.90–1.31)	0.282	0.81 (0.52–1.27)	0.234
	Hypertension	1.15 (0.83–1.60)	0.277	1.16 (0.45–2.97)	0.693	1.31 (0.32–5.28)	0.621
	Hyperlipidemia	1.19 (0.80–1.78)	0.265	0.72 (0.34–1.52)	0.253	1.17 (0.30–4.50)	0.766
Exudative AMD	Group	1.37 (0.96–1.97)	0.023	3.42 (1.48–7.90)	<0.001	2.27 (0.74–6.92)	0.058
	Sex (ref.: female)	1.65 (1.19–2.30)	<0.001	2.05 (1.06–3.99)	0.005	2.54 (0.82–7.92)	0.034
	CCI total	1.23 (1.13–1.35)	<0.001	1.06 (0.92–1.22)	0.318	1.00 (0.81–1.24)	0.975
	Hypertension	0.99 (0.68–1.43)	0.919	0.83 (0.39–1.77)	0.519	0.87 (0.26–2.88)	0.761
	Hyperlipidemia	1.12 (0.72–1.75)	0.512	1.30 (0.70–2.40)	0.275	1.06 (0.36–3.08)	0.898

Groups: Diabetes vs. nondiabetes: diabetes (reference: nondiabetes); diabetes w/DR vs. diabetes w/o DR: diabetes w/DR (reference: diabetes w/o DR); PDR vs. NPDR: PDR (reference: NPDR). w/, with; w/o, without.

About 0.4% of people between 50 and 60 years of age have the disease, whereas it occurs in 0.7% of people between 60 and 70 years of age, 2.3% of those 70–80 years of age, and nearly 12% of those >80 years of age (25). Patients with AMD in the study by Hahn et al. (12) were >69 years of age, which neglected patients 50–69 years of ages and might not fully represent the distribution of AMD patients. According to the Centers for Disease Control and Prevention reports on 2012, adults 45–64 years of age were the age group receiving the most diagnoses of diabetes. Patients with newly diagnosed diabetes in the study by Hahn et al. (12) were >69 years of age, which might not completely represent the incidence of AMD in patients with diabetes. Considering the younger onset of diabetes, we included subjects as young as 50 years of age and those without AMD before the onset of diabetes. Furthermore, we took follow-up time and censored cases into consideration, and used a Cox regression model to analyze the longitudinal data.

In our study, patients with diabetes had a 1.4-fold increased the incidence of nonexudative and exudative AMD over matched patients without diabetes, but the difference did not reach significance in multivariate survival analysis. In contrast, patients with diabetes with DR had a 4-fold increased incidence of nonexudative AMD, and a 3.9-fold increased incidence of exudative AMD over patients with diabetes without DR. The HR of the development of nonexudative AMD was 3.89 for patients with diabetes with DR compared with patients with diabetes without DR ($P = 0.001$). The HR of the development of exudative AMD was 3.42 for patients with diabetes with DR compared with patients with diabetes without DR ($P < 0.001$).

DR is generally considered to be a disease of the inner retina, in contrast to the outer retinal involvement in AMD, but there may be features common to both diseases. Macular RPE abnormalities and increased area of drusen have been correlated with increased blood glucose levels, impaired glucose tolerance, and advanced glycation end products (27). Moreover, both exudative AMD and DR appear to be VEGF mediated, and the use of anti-VEGF pharmaceutical agents has proven useful in the treatment of both diseases. Similar observations in component molecules of extracellular depositions and clinical progression courses between AMD and diabetes give support to the hypothesis that AMD is significantly associated with diabetes. Furthermore, a high dietary glycemic index (dGI) was found, in a cross-sectional analysis of the AREDS cohort, to be associated with an increased risk of early and late AMD in subjects without diabetes (28). The dGI is a weighted average of the glycemic index of foods in the diet. High dGI is an indicator of poor quality dietary carbohydrate intake and has been implicated in the development of diabetes and cardiovascular disease. It may increase the risk of AMD through several common etiological factors of diabetes and cardiovascular disease, including the formation of advanced glycation end products and increases in oxidative stress, inflammation, and hyperlipidemia.

Diabetes-related changes in the function and structure of the RPE, Bruch membrane, and the choroidal circulation have been hypothesized to increase the risk of AMD. Histopathological studies in the eyes of subjects with long-term diabetes have shown thickening of the basement membrane of the choriocapillary walls, luminal narrowing, dropout of the choriocapillaries, and thickening of the Bruch membrane, all of which are factors that may predispose a subject to the development of AMD (29). Subfoveal choroidal blood flows have been found to be reduced in patients with both NPDR and PDR (30).

It has been demonstrated that systemic inflammation is an intrinsic response to overfeeding, obesity, and diabetes. The latter increases the release of retinal inflammatory mediators (interleukin [IL]-1β, tumor necrosis factor-α [TNF-α], intercellular adhesion molecule [ICAM-1], MCP-1, and angiotensin II) (31) and activation of microglial cells (32) in early retinopathy. Similarly, several studies have found an association between AMD and inflammation. Cellular remnants and debris from degenerated RPE, sequestered between the RPE basal lamina and Bruch membrane, may constitute a chronic inflammatory stimulus (33). A number of inflammatory cytokines have been found to be elevated either systemically in the serum or locally in the ocular tissue or fluids of patients with AMD. Systemic levels of IL-6, IL-8, and TNF-α correlated with complement factor H haplotypes in AMD patients. Concentrations of MCP-1 and ICAM-1 are significantly

Table 4—Review of studies investigating the relationship between diabetes or DR and AMD

	Study name	Type of study	Enrollees, *n*	Age, years	Major findings
Longitudinal	AREDS (5)	Prospective cohort study	3,294	55–80	Increased incidence of diabetes in patients at risk for development of advanced AMD in each eye (OR 1.88)
	BES (7)		2,793	40–84	Trend toward increased 9-year incidence of late AMD in patients with diabetes vs. control subjects (age-adjusted relative risk 2.7; $P = 0.054$)
	Voutilainen-Kaunisto et al. (25)		277	45–64	No association between 10-year incidence of AMD and diabetes
	Hahn et al. (12)	Retrospective cohort study	16,174	>69	Increased 10-year incidence of dry AMD in NPDR vs. control subjects (HR 1.24); increased 10-year incidence of wet AMD in NPDR vs. control (HR 1.68) and PDR vs. control subjects (HR 2.15); diabetes without retinopathy did not affect risk of dry or wet AMD; there was no difference in risk of wet AMD in PDR compared with NPDR
	He et al. (current study)		109,232	≥50	A tendency toward a greater risk of dry AMD (HR 1.23; $P = 0.108$) and wet AMD (HR 1.37; $P = 0.023$) in patients with diabetes vs. those without diabetes, but the difference did not reach significance at a significance level of 1%; dry AMD (HR 3.89) and wet AMD (HR 3.42) were significantly correlated to patients with diabetes with DR, compared with those with diabetes without DR at a significance level of 1%
Cross-sectional	BDES (6)	Cross-sectional population based	4,695	43–86	Increased prevalence of wet AMD in male patients with diabetes >75 years of age (OR 10.2) compared with control subjects
	EUREYE Study (8)		4,522	>65	Increased prevalence of diabetes in exudative AMD vs. control subjects (OR 1.81)
	BMES (18)		3,228	49–97	No significant association between patients with or without diabetes for exudative AMD (OR 1.2) and early AMD (OR 1.0)
	Framingham Eye Study (26)		2,477	52–85	No association between patients with diabetes and those with AMD
	Choi et al. (13)		3,008	50–87	Patients with diabetes were more likely to have early AMD (OR 1.87) than those without diabetes
	Klein et al. (14)	Observational analysis of a randomized clinical trial	4,288	≥63	No significant association between patients with and without diabetes for early AMD (OR 0.87); significant association between patients with and without diabetes for late AMD (OR 2.43) and exudative AMD (OR 2.49)
Case-control	Borrone et al. (20)	Retrospective descriptive observational case control	399	>65	Lower prevalence of late AMD in patients with diabetes vs. control subjects in persons >75 years of age
	Maltzman et al. (22)	Case-control studies	60	52–88	No association between patients with diabetes and those with AMD
	Hyman et al. (23)		465		
	Blumenkranz et al. (24)		49		
	Cackett et al. (40)		1,790	>60	Diabetes was not significantly associated with wet AMD (OR 0.9)

B, black; H, Hispanic; M, Mexican.

associated with exudative AMD, even in the presence of normal VEGF concentrations (34).

Several inflammatory mediators such as ICAM-1, MCP-1, IL-1β, IL-8, and TNF-α play a part in both DR and AMD, and the release of these cytokines into the intraocular tissue in DR patients may promote the development of AMD.

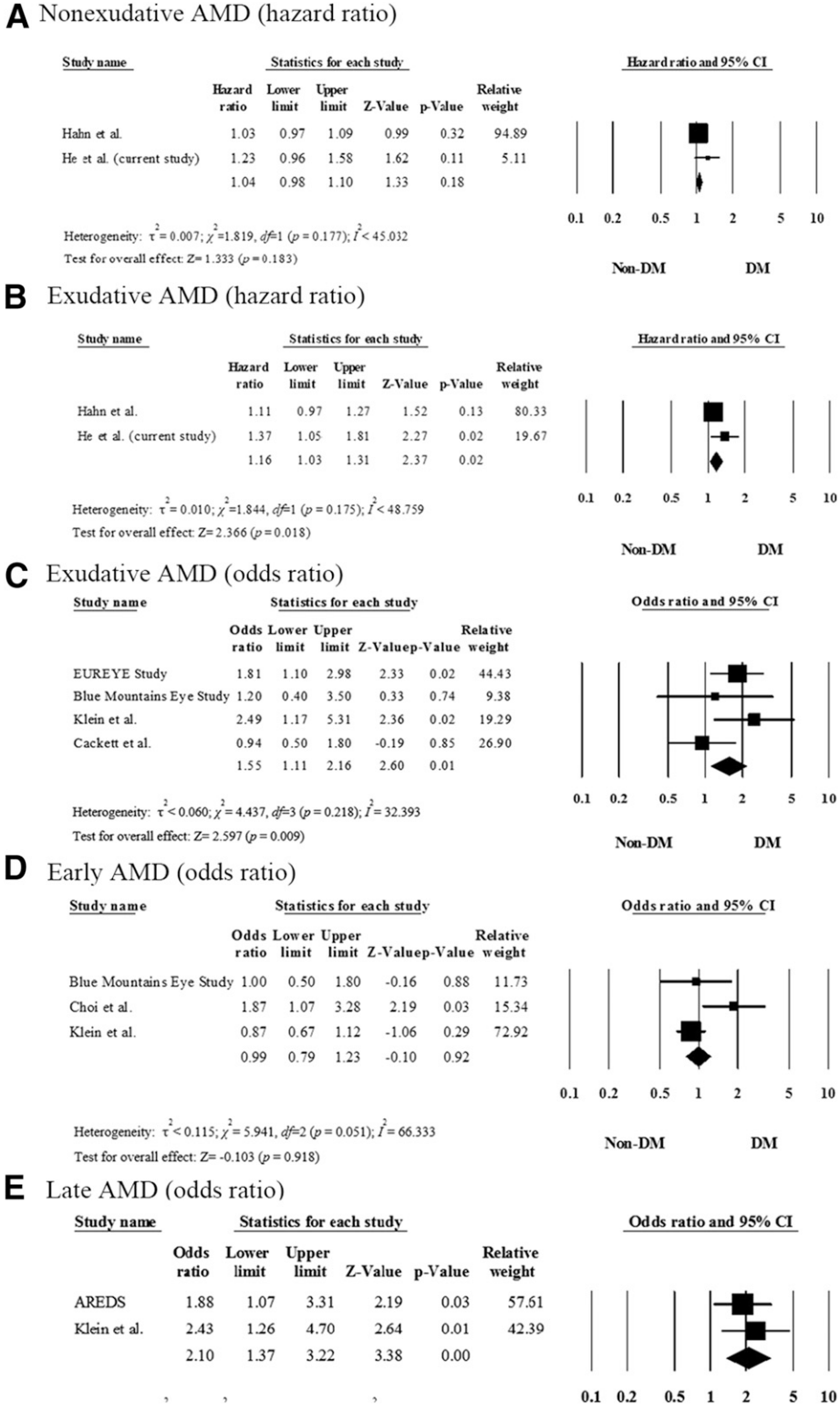

Figure 2—Meta-analysis for the selected studies with the same comparison between patients with diabetes and control subjects in Table 4. *A*: The HR for nonexudative AMD. *B*: The HR for exudative AMD. *C*: The OR for exudative AMD. *D*: The OR for early AMD. *E*: The OR for late AMD. DM, diabetes mellitus. AREDS (5), Blue Mountains Eye Study (18), Cackett et al. (40), Choi et al. (13), EUREYE Study (8), Hahn et al. (12), Klein et al. (14).

Our results revealed that patients with diabetes had a tendency toward a greater risk of nonexudative and exudative AMD than the matched control subjects. This trend was intensified when DR developed in these patients with diabetes. The development of DR means the breakdown of the blood-retina barrier. A large amount of evidence supports the role of proinflammatory cytokines, chemokines, and other inflammatory mediators in the pathogenesis of DR as leading to persistent low-grade inflammation, and subsequent influx of leukocytes as further contributing to the

damage of the retinal vasculature and neovascularization. These released inflammatory mediators in DR may further trigger the pathogenesis of AMD, thus increasing the likelihood of AMD in this group.

We also found that the overall mean annual incidence of nonexudative AMD was significantly lower with PDR patients compared with NPDR patients (incidence ratio 0.6), although this did not show a significant difference in multivariate analysis (P = 0.277). In contrast, exudative AMD had a trend toward association with PDR patients compared with NPDR patients (incidence ratio 3.0), and multivariate analysis also showed the tendency, but it was not statistically significant (HR 2.27; 99% CI 0.74–6.92; P = 0.058). Retinas or vitreous from patients with PDR have been found to contain elevated levels of a variety of inflammatory mediators, including TNF-α, IL-6, VEGF, and matrix metalloproteinase (MMP)-9 (35,36). MMPs and their tissue inhibitors also play a central role in the pathogenesis of AMD (37). The expression of MMP-9, TNF-α, IL-6, and VEGF in patients with PDR may further expose the eye to development of choroidal neovascularization, thus increasing the coincidence of exudative AMD. Since patients with PDR have more severe pathology and inflammation than patients with NPDR, it is reasonable that our study revealed a tendency for development of exudative AMD in patients with PDR compared with patients with NPDR. The results are also consistent with a large longitudinal cohort analysis by Hahn et al. (12), which showed an association between newly diagnosed NPDR and an increased risk of incident diagnosis of dry AMD and wet AMD; whereas newly diagnosed PDR was associated with a significantly increased risk of wet AMD only.

This study exhibits several strengths. First, the NHIRD contains all claims data that were recorded electronically, ensuring accuracy and avoiding recall bias. Second, analyzing data from the NHIRD provided us with population-based and representative claims information of insured people in Taiwan and reduced the likelihood of selection bias. Third, the large size of the data set and longitudinal study design provided considerable statistical power and enabled us to detect differences between the AMD and control cohorts more effectively.

Study Limitations

First, the NHIRD is an administrative database and lacks direct imaging and laboratory results. Although the proportion of exudative AMD among overall AMD in our study is consistent with previous findings (10–15%) in the published literature (38), the identification accuracy for AMD is still a concern. The AMD cases identified on the basis of ICD-9 codes were less accurate than those identified individually through standardized procedures. Polypoidal choroidal vasculopathy (PCV), a distinct variant of type 1 choroidal neovascularization, is considerably prevalent in East Asian populations (39). In addition, without an ICD-9 diagnosis code specific for PCV, the identification of the patients with PCV from among those with exudative AMD was almost impossible in the NHIRD data set. Second, although the current retrospective cohort study is more efficient than a prospective design study because it makes use of the retrospective data. However, unlike a prospective study, some of potential risk factors cannot be obtained since it is based on the retrospective data. Some important factors, such as educational level, drinking and smoking habits, BMI, visual acuity, severity of comorbid diseases, family history of diabetes, are not available in the NHIRD, which might confound our results. Third, early AMD might be asymptomatic, and the individuals with early AMD might not have received diagnosis, which could lead to a misclassification bias in this study. However, this nondifferential misclassification would bias our results toward the null and dilute the real difference in AMD incidence between these two cohorts. Fourth, early-stage diabetes might also be underdiagnosed, which could result in group misclassification in both cohorts. Finally, most of our study subjects were ethnically Chinese people from Taiwan, and the generalizability of our results to other ethnic groups needs to be further confirmed.

Conclusion

Our study provides large-scale, population-based evidence in support of an independent relationship between overall diabetes and incident AMD in Taiwan. An important strength of our study is the large, nationally representative sample size, which yielded ample statistical power and allowed us to distinguish between diabetes and different types of retinopathy. Furthermore, the stratified analysis showed that patients with DR were at significantly greater risk of subsequent development of AMD than the matched control subjects. These results raise the possibility that DR and AMD may share pathogenic features and that preventing DR in patients with diabetes may reduce further development of AMD. Further studies should be undertaken to gain a better understanding of these disease processes.

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