THE DEPLETION OF SUSCEPTIBLES EFFECT IN THE ASSESSMENT OF BURDEN-OF-ILLNESS: THE EXAMPLE OF AGE-RELATED MACULAR DEGENERATION IN THE COMMUNITY-DWELLING ELDERLY POPULATION OF QUEBEC

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ABSTRACT

Background
With the aging of the population, age-related macular degeneration (AMD) is becoming a public health concern. Few studies have assessed its consequences on morbidity and mortality, and the findings are conflicting.

Objectives
To assess the risk of depression, fracture, institutionalization, and death among elderly patients with suspected exudative AMD and the impact of the depletion of susceptibles effect in a burden-of-illness study.

Methods
A population-based retrospective cohort study was conducted in the community-dwelling elderly population of Quebec. The cohort was assembled through the Quebec medical claims database (RAMQ). Among patients age 65 and older with a claim involving a diagnosis of AMD over the years 2000 to 2004, those with suspected exudative AMD (n=2,071) were retained, using fluorescein angiography as a marker. The reference cohort consisted of a sample of 16,932 elderly without a claim involving AMD or visual impairment.

Results
Suspected exudative AMD was associated with an increased risk of depression (hazard ratio HR=1.3, 95%CI 1.18-1.43) and fracture (HR=1.19, 95%CI 1.03-1.37), but a decreased risk of institutionalization (HR=0.55, 95%CI 0.42-0.71) and death (HR=0.68, 95%CI 0.59-0.78). After adjustment for the incident/prevalent status of the AMD, the association between suspected exudative AMD and institutionalization was no longer statistically significant (HR=0.75, 95%CI 0.5-1.12).

Conclusions
These findings enhance the need to detect visual loss and to consider patients' ability to adapt to AMD, to maintain their quality of life. Failure to account for duration of illness and the depletion of susceptibles effect may bias results of burden-of-illness studies.

Key words: *Macular degeneration, burden-of-illness, elderly, depletion of susceptibles*

Burden-of-illness (BOI) addresses adverse consequences and health services use associated with a given disease. It is assessed in economic studies to estimate cost of illness (direct and indirect) and its impact on society (i.e., health and productivity), as well as in clinical studies (benefit/risk ratio determination, treatment decision). BOI data may be obtained through claims databases, such as those of the general drug plan and universal health care program of Quebec (RAMQ databases). However, duration and onset of illness may be difficult to determine using such databases, particularly when diseases are chronic and gradual. Such conditions most likely have started for some time prior to a formal diagnosis and events occurring during this time period should be considered as potential risk modifiers in non-experimental risk assessment of current outcomes.[1] Failure to account for these past events may confound risk comparisons across patient groups, due to the "depletion of susceptibles" effect.

Many reviews have highlighted the need to assess the BOI of age-related macular degeneration (AMD).[2-4] AMD is progressive, severe, and irreversible. It results in a degeneration of the central portion of the retina and is the most common cause of legal blindness among people 65 years and older in industrialized countries. It affects approximately 10 million people in North America.[5-7] The number of persons with blindness or poor vision is predicted to double by the year 2020.[8,9] AMD increases dramatically with age, affecting 8% of persons aged 43 to 54 years, 10% of those aged 65 to 74 years, and 30% of those aged 75 and older.[7,10-12] Nearly one fifth of subjects with AMD aged 85 and older are legally blind.[5] Furthermore, the diagnosis of AMD appears to have increased over the last decade[13,14]; the exudative form being the most serious and rapidly progressing type of AMD.[15]

Vision loss associated with AMD typically manifests itself as a central field loss and varies according to the seriousness of the disease and the extent of the complications.[16] It is a major cause of disability that substantially decreases quality of life and performance in activities of daily living.[11,16] It may have serious consequences for the patient such as: accidents, fractures, psychosocial effects (i.e., depression or institutionalization), and death. Independence may also be dramatically affected.[17]

The few studies that have assessed the psychosocial effects of AMD led to conflicting findings. Overall, AMD has been shown to be associated with affective distress but few studies considered depressive disorders with adequate diagnostic scales, and most were cross-sectional in design.[18-23] Yet, depression is a serious medical condition and has significant health consequences in older patients. To our knowledge, the number of admissions to nursing homes associated with AMD has not been quantified.[24] However, it has been shown in a prospective study that nursing home placement was associated with poor visual function among middle and older age groups (43 to 86 years of age).[25] Furthermore, in this study, visual impairment was associated with fractures of any type, particularly in women. In the prospective Beaver Dam Eye study, an association between poor vision function and hip fracture was also reported among patients aged 60 years and older.[26] In contrast, falls were associated with visual impairment, but not with AMD in the cross-sectional Blue Mountain Eye study.[27] Similarly, mortality has been shown to be associated with visual impairment in the elderly population[28-30], but the association with AMD remains controversial. Relative to other eye conditions, AMD has not been associated with decreased survival in two population-based studies published in the literature.[31,32] However, in another study, AMD was related to increased mortality after statistical adjustment for various mortality risk factors.[33] An association between AMD and mortality was found in women but not men.[34] In another study, advanced AMD was found to be associated with an increased risk of all-cause mortality as well as cardio-vascular death.[35] One reason that could lead to such conflicting results is the heterogeneity in the forms and severity of AMD in the population.

In the absence of comprehensive BOI data that are specific to AMD, we conducted a study that aimed at assessing: the risk of depression, fracture, institutionalization, and death over a five-year period, in a cohort of community-dwelling elderly patients diagnosed with exudative AMD.

A secondary objective was to address the impact of the depletion of susceptibles effect due to prior diagnosis of AMD on BOI data.

METHODS

Overview of the Design

A population-based retrospective cohort study was conducted using the Quebec prescription and medical claims databases (RAMQ). The hazard rates of depression, fracture, institutionalization, or death in a cohort of community-dwelling patients 65 and older who received an outpatient diagnosis of AMD, suspected of being exudative, were compared to the hazard rates in a cohort of elderly who had not received a diagnosis of AMD or of any visual impairment at the time of diagnosis of the case. Suspected exudative AMD was retained to select AMD cases that were most likely serious.

Study Population

The source population consisted of all outpatient elderly residents of the province of Quebec who are members of the public drug coverage programs, i.e., the great majority of community-dwelling elderly (>94%) (population size of approximately 800,000). The following algorithm was used to ascertain the presence of suspected exudative AMD. First, a random sample of patients aged 65 and older with a medical claim that involved a diagnosis of macular degeneration (ICD 9 code 362.5 in the RAMQ medical services database) in the period ranging from January 1st, 2000 to December 31st, 2004 was selected. Out of these patients, those with suspected exudative AMD were ascertained through the presence of a claim for a fluorescein angiography in the RAMQ medical services database (ICD-9 code 537) that was submitted within two years after the first claim for AMD. When exudative AMD is suspected, a fluorescein angiography is performed to confirm the diagnosis. Patients entered the AMD cohort on the date of the first angiography during the study period (i.e., the index date). Given that health care is universal in Quebec, all medical services rendered on a fee-for-service are recorded in this database, regardless of patient's age, income level, or complementary coverage by private insurance. For each medical claim, a diagnosis coded using the ICD-9 classification is recorded. The reference population consisted of a random sample of elderly community-dwelling residents present in the drug program during the same index year, and without any history of AMD or any visual impairment. For each AMD patient, a reference subject was randomly sampled among those without visual impairment and the same index date as the case was ascribed to these subjects. A patient included as a referent could have also entered the AMD cohort if he/she had received a diagnosis of AMD later in the study period. The following inclusion and exclusion criteria were applied:

1. Resident of Quebec for at least two years prior to index date;
2. Continuous coverage of pharmaceutical services for at least two years prior to index date; and
3. Patients already institutionalized on the index date were excluded.

Follow-up Period

Patients were followed from the index date up until the first of the following event:

1. Occurrence of the outcome of interest (i.e., claims involving a diagnosis of depression, fractures, institutionalization, or death); or
2. End of study period (December 31st, 2004).

Dependent Variables

Four outcomes were assessed: depression, fractures, institutionalization, and death. Depression was identified through the presence of claim with an ICD-9 code corresponding to depression (codes 311.0 to 311.9) in the RAMQ medical services database and an antidepressant dispensing in the RAMQ prescription database. For this outcome, the follow-up period ended on the date of the first of the two records. Fractures were identified through claims with ICD-9 codes that correspond to fractures (codes 800.0 to 829.9) present in the medical services database (which also includes emergency room visits). Although a given patient could have several fractures during the study period, only the first occurrence was considered in the analysis; the patient being censored from the analysis of this outcome on the date of the first event. Occurrence of institutionalization was determined from the location of service (code corresponding to a long-term care institution) present in the medical services claims database.

Four different types of institutions were considered: public nursing home, private nursing home, admission in long-term care unit, and nursing care in long-term care unit. Death and date of death were identified in the RAMQ medical services database through a physician claim for death certification.

Independent Variables

The main independent variable was the presence of suspected exudative AMD or the absence of AMD. The following covariates were also considered:

1. Age group (categorized as: 65-69, 70-74, 75-79, 80-84, and 85+);
2. Gender;
3. Year of entry in the cohort;
4. History of depression in the two years prior to index date (assessed through the presence in the RAMQ databases of a diagnosis of depression and an antidepressant prescription);
5. History of fractures in the two years prior to index date;
6. History of AMD or visual impairment (ICD-9 codes 369.0 to 369.9) in the two years prior to index date, to distinguish between prevalent and incident cases; and
7. Chronic Disease Score (CDS) as a marker for overall health status, assessed from drug dispensing in the year prior to index date (categorized into four categories: 0, 1-4, 5-9, 10+).[36] The scores are weighted according to the probability of death in the following year.

For patients with AMD, the age at index date was available from RAMQ. For the reference population, the RAMQ provided only age on January 1st 2000, expressed in 5-year age intervals. Consequently, when the index date of the AMD patient was ascribed to the referent, it was necessary to infer age from the available information. The following algorithm was used: if the time interval between the index date and January 1st 2000 was superior to 2.5 years (half of an age interval), the referent moved up to the next age interval and if the interval was below 2.5 years, he/she remained in the same age interval.

Statistical Analysis

The characteristics of patients in each cohort were compared using bivariate analyses (t-test for continuous variables and Chi-square for categorical variables). A Cox proportional hazard model was used to assess the effect of suspected exudative AMD on the occurrence of depression, fracture, institutionalization, and death; each outcome being considered in a separate model. The following covariates were included in the multivariate models: age group, gender, Chronic Disease Score, and year of entry in the cohort. For depression as an outcome, history of depression was added to the model. For fractures, history of fractures was included. Patients and their matched referents that were recruited in earlier years had a longer follow-up period than those included at the end of the study period, and adjustment for varying lengths of follow-up was made in the analysis. Statistical significance was set at .05, and analyses were conducted using the SAS statistical package, version 9.1.3. A sub-analysis was conducted that included the prevalence/incidence status, i.e., presence/absence of a diagnosis of AMD or visual impairment in the two years prior to index date. By design, this sub-analysis could only be performed in patients who entered the cohort in 2000. Hence, only patients recruited in 2000 may have been prevalent cases since diagnoses prior to the start of the study period was not taken into account in the sampling process.

As AMD was ascertained through the presence of two medical claims (i.e., a claim involving a diagnosis of AMD and a claim for a fluorescein angiography), there was an opportunity for immortal time bias in the definition of our study cohorts.[37] AMD patients must have survived until the second claim to be included in the cohort. Such immortal time bias would correspond to the period of time between the first and second claim. Hence, a sensitivity analysis was conducted, whereby follow-up started on the second claim as opposed to the first.

RESULTS

Study Population

Over the study period, 11,770 patients with a claim involving a diagnosis of AMD were identified in the RAMQ database. A fluorescein angiography has subsequently been performed for 17.6% of these patients (n=2,071). The characteristics of the study population, defined as "suspected exudative AMD", are shown in Table 1.

There was no significant difference across patients with respect to the year of entry in the cohort (p=0.08). As expected, there was a significantly higher proportion of females among patients with AMD than in the referent group (p<0.001). AMD patients were also older (p<0.001) and had poorer health status (i.e., higher CDS scores, p<0.001) than the referent patients. They more often had a fracture history (p<0.001), but there was no difference with respect to depression history (p=0.9).

TABLE 1 Description of the Study Population

	Exudative Macular Degeneration N=2,071, n (%)	**Reference N=16,932, n (%)**
Index Year		
2000	631 (30.5)	5,387 (31.8)
2001	367 (17.7)	3,243 (19.2)
2002	362 (17.5)	2,861 (16.9)
2003	161 (17.4)	2,637 (15.6)
2004	350 (16.9)	2,705 (16.0)
Age Group		
60-64	-	2,555 (15.1)
65-69	288 (13.9)	3,997 (23.6)
70-74	481 (23.2)	3,489 (20.6)
75-79	566 (27.3)	2,866 (16.9)
80-84	434 (21.0)	1,909 (11.3)
85-89	302 (14.6)	1,472 (8.7)
90+	-	574 (3.4)
Gender (male)	808 (39.0)	7,288 (43.0)
Chronic Disease Score		
0	489 (23.6)	7,979 (47.1)
1-4	613 (29.6)	4,068 (24.0)
5-9	699 (33.8)	3,675 (21.7)
10+	270 (13.0)	1,210 (7.1)
Depression History *	52 (2.5)	412 (2.4)
Fractures History*	154 (7.4)	824 (4.9)

* In the 2 years prior to index date

Association between AMD and Depression

As shown in Table 2, suspected exudative AMD was independently associated with an increased risk of depression (hazard ratio HR=1.30, 95%CI 1.18-1.43, p<0.0001), although the strongest predictor of depression during the follow-up was a recent history of depression. Males were less likely than females to present with depression during the study period. In the eldest patients (age 85+), the risk of depression was decreased, which might be due to the adjustment for the Chronic Disease Score (CDS) since patients with the worst overall health status (i.e., CDS scores 10 and over) had a higher risk of depression.

TABLE 2 Association between Exudative Age-related Macular Degeneration and Depression

	Hazard Ratio*	**95% Confidence Limits**	**P**
Macular Degeneration	1.30	1.18-1.43	< 0.0001
No visual impairment	*Reference*		
Age 70-74	1.01	0.92-1.11	0.8
75-79	1.06	0.96-1.17	0.2
80-84	1.07	0.95-1.20	0.3
85+	0.84	0.73-0.97	0.02
60-64	*Reference*		
Male	0.60	0.56-0.65	< 0.0001
Female	*Reference*		
Von Korff CDS 1-4	2.49	2.25-2.74	< 0.0001
5-9	2.67	2.41-2.94	< 0.0001
10+	3.47	3.06-3.93	< 0.0001
0	*Reference*		
Year of entry in cohort 2001	1.01	0.92-1.11	0.9
2002	0.97	0.87-1.07	0.5
2003	0.97	0.86-1.09	0.6
2004	1.09	0.96-1.23	0.2
2000	*Reference*		
History of Depression**	9.42	8.42-10.53	< 0.0001

* Adjusted for all the covariates listed in the table
** In the 2 years prior to index date

Association between AMD and Fractures

As shown in Table 3, suspected exudative AMD may be associated with a slightly increased risk of fracture (HR=1.19, 95%CI 1.03-1.37, p=0.02). As with depression, the strongest predictor of fracture during the follow-up was a recent history of fracture. Males were less likely than females to present with a fracture during the study period. The poorer the overall health status and the older the patient, the higher the risk of fracture was, although the trends were not statistically significant.

Association between AMD and Institutionalization

As shown in Table 4, suspected exudative AMD was associated with a decreased risk of institutionalization over the study period (HR=0.55, 95%CI 0.42-0.71, p<0.0001). As expected, there was a relationship between the risk of institutionalization and overall health status and age, the higher the risk of institutionalization, the poorer the overall health status or the older the patient.

Association between AMD and Mortality

As shown in Table 5, suspected exudative AMD was associated with a decreased risk of death over the study period (HR=0.68, 95%CI 0.59-0.7 p<0.0001). There was a strong association between death and male gender, age, and higher CDS scores (with a statistically significant dose-response relationship for age and CDS). The latter finding was particularly expected since this score has been created and validated using death as the outcome, and scores are weighted according to their probability of inducing death in the following year.[36]

TABLE 3 Association between Exudative Age-related Macular Degeneration and Fractures

	Hazard Ratio*	95% Confidence Limits	P
Macular Degeneration	1.19	1.03-1.37	0.02
No visual impairment	*Reference*		
Age 70-74	1.19	1.02-1.38	0.02
75-79	1.33	1.15-1.56	0.0002
80-84	1.74	1.48-2.04	<0.0001
85+	2.15	1.82-2.55	<0.0001
60-64	*Reference*		
Male	0.66	0.60-0.72	<0.0001
Female	*Reference*		
Von Korff CDS 1-4	1.33	1.16-1.52	<0.0001
5-9	1.46	1.28-1.67	<0.0001
10+	1.52	1.25-1.84	<0.0001
0	*Reference*		
Year of entry in cohort 2001	0.91	0.79-1.04	0.15
2002	0.92	0.78-1.07	0.26
2003	0.94	0.78-1.13	0.50
2004	0.86	0.66-1.10	0.23
2000	*Reference*		
Fractures History**	2.68	2.30-3.12	<0.0001

* Adjusted for all the covariates listed in the table ** In the 2 years prior to index date

TABLE 4 Association between Exudative Age-related Macular Degeneration and Institutionalization

	Hazard Ratio*	95% Confidence Limits	P
Macular Degeneration	0.55	0.42-0.71	<0.0001
No visual impairment	*Reference*		
Age 70-74	1.73	1.31-2.27	<0.0001
75-79	3.03	2.35-3.89	<0.0001
80-84	5.02	3.89-6.46	<0.0001
85+	9.59	7.58-12.13	<0.0001
60-64	*Reference*		
Male	0.95	0.81-1.11	0.5
Female	*Reference*		
Von Korff CDS 1-4	0.77	0.62-0.96	0.02
5-9	1.10	0.91-1.33	0.4
10+	1.62	1.26-2.09	0.0002
0	*Reference*		
Year of entry in cohort 2001	1.01	0.83-1.23	0.9
2002	1.03	0.82-1.28	0.8
2003	0.77	0.58-1.02	0.07
2004	0.69	0.49-0.97	0.03
2000	*Reference*		

* Adjusted for all the covariates listed in the table

TABLE 5 Association between Exudative Age-related Macular Degeneration and Mortality

	Hazard Ratio*	95% Confidence Limits	P
Macular Degeneration	0.68	0.59-1.18	<0.0001
No visual impairment	*Reference*		
Age 70-74	1.58	1.37-1.84	<0.0001
75-79	2.40	2.09-2.77	<0.0001
80-84	3.81	3.29-4.41	<0.0001
85+	6.78	5.90-7.80	<0.0001
60-64	*Reference*		
Male	1.52	1.39-1.66	<0.0001
Female	*Reference*		
Von Korff CDS 1-4	1.31	1.15-1.49	<0.0001
5-9	2.09	1.86-2.36	<0.0001
10+	3.83	3.33-4.40	<0.0001
0	*Reference*		
Year of entry in cohort 2001	1.04	0.93-1.17	0.5
2002	0.91	0.79-1.05	0.2
2003	0.86	0.73-1.03	0.1
2004	0.99	0.79-1.25	0.9
2000	*Reference*		

* Adjusted for all the covariates listed in the table

Association between AMD and the Four Outcomes According to the Prevalence/ Incidence Status

Among the patients with suspected exudative AMD included in 2000, 219 (34.7%) had received a diagnosis of AMD or of visual impairment in the two years prior to index date and were considered as prevalent AMD cases, while 412 (65.3%) had not received such a diagnosis and were categorized as incident AMD cases.

History of AMD or visual impairment in the two years prior to index date was not associated with any of the four outcomes. After adjustment for the incident/prevalent status, the risks of depression, fracture, and death associated with suspected exudative AMD were similar to the risks found in the overall exudative AMD population (respectively, HR=1.28, 95%CI 1.07-1.54, p=0.008; HR=1.35, 95%CI 1.07-1.72, p=0.01; and HR=0.72, 95%CI 0.57-0.90, p=0.004). Conversely, after adjustment for the incident/prevalent status, the association between suspected exudative AMD and the risk of institutionalization was no longer statistically significant (HR=0.75, 95%CI 0.5-1.12, p=0.2).

Sensitivity Analyses

Because exudative AMD was ascertained through the presence of a marker, there was opportunity for misclassification. We conducted a sensitivity analysis whereby hazard ratios for the various outcomes investigated were also obtained for

patients with less serious and more gradual forms of AMD (i.e., without fluorescein angiography in the two years after index date). Such patients presented with slightly increased risks of depression and fractures (HR=1.24, 95%CI 1.17-1.32, p<0.0001 and HR=1.11, 95%CI 1.02-1.22, p=0.02, respectively) compared to the reference group. However, their risks of institutionalization and death were similar to the ones observed in the reference group (HR=0.96, 95%CI 0.85-1.09, p=0.5 and HR=0.98, 95%CI 0.91-1.06, p=0.6, respectively).

A sensitivity analysis was also conducted to assess the potential impact of immortal time bias on the lower rates of institutionalization or death in subjects with suspected exudative AMD. The index date of the cases was modified; the new index date being the date of the fluorescein angiography. On average, this date occurred 33 days later than the date of first diagnosis. Given that the overall follow-up period was long, this modification did not have any effect on the associations between AMD and the study outcomes [Depression: HR 1.4 (95%CI 1.2-1.5) vs. HR 1.3 (95%CI 1.2-1.4); Fracture: HR 1.3 (95%CI 1.1-1.5) vs. HR 1.2 (95%CI 1.0-1.4); Death: HR 0.5 (95%CI 0.4-0.6) vs. HR 0.7 (95%CI 0.6-0.8); and Institutionalization: HR 0.6 (95%CI 0.5-0.8) vs. HR 0.5 (95%CI 0.4-0.7)].

DISCUSSION

Suspected exudative AMD was associated with an increased risk of depression and fracture, but unexpectedly with a decreased risk of institutionalization and death. After adjustment for the incident/prevalent status, the association between suspected exudative AMD and institutionalization was no longer statistically significant. These counter-intuitive findings may be attributable to the depletion of susceptibles effect.[1] Indeed, in previous studies conducted in patients with visual impairment, even a moderate visual loss may have a significant impact on daily life, morbidity, and mortality.[38,39] Thus, patients with advanced disease may have already experienced dangerous events and functional loss in the past. Hence, they may have adapted their lifestyle to cope with the disability and reduce the risks of institutionalization or death (i.e., decreased mobility, stopped driving a car, or had assistance at home). Past experience related to a disease and its duration may modify the risk of current adverse events associated with the disease. Patients who are susceptible select themselves out of the population at risk. This interpretation was supported by the fact that the association between suspected exudative AMD and institutionalization disappeared after adjustment for the incident/prevalent status.

AMD was associated with increased risks of depression and fracture whatever the incident/prevalent status. In previous studies, one third of patients with AMD presented with depression, and the association between AMD and depression appeared mediated through functional impairment and loss of valued and enjoyable activities.[18,22] Overall, AMD patients with unilateral legal blindness or shorter duration of disease reported a higher level of emotional distress than those with bilateral blindness or longer duration.[22,23] Patients with only one eye affected or shorter duration of disease may anticipate future vision worsening, while those with both eyes affected and longer duration of disease may have a better adaptation and a greater acceptance of the condition.[11,16] Visual impairment has also been strongly associated with falls and fractures in older subjects.[27,40,41] Similar to depression, the risk of fracture was increased even for patients with moderately impaired vision and in the first years of the disease but not over a longer period.[42,43] Visual impairment has been shown to be a risk factor for fracture mainly in women.[43] Among patients with vision loss and hip fracture, very few appeared to be under ophthalmic care at the time of the fall.[44] As older people often do not complain about visual disorders to their general practitioners, intervention strategies, such as regular eye examination, may prevent falls and fractures.[41,45-47]

In patients with AMD, an annual eye examination is recommended to detect vision loss.[48] Furthermore, it appears important to assess a broad array of outcomes in addition to standard ophthalmologic examination and to consider vision loss in the context of patients' ability to adapt and cope.[11,16,49] Patients should be educated about their disease and informed that they can accomplish many activities with assistance.[17]

Rehabilitative and self-management programs would improve quality of life and emotional distress in older patients with AMD.[50-52]

Our study comprised several limitations. Cohorts were defined on the basis of a medical diagnosis and entry in the cohort was based on the date of the diagnosis recorded in the administrative database. AMD being a gradual chronic condition, there is probably extensive misclassification of the index date. Indeed, AMD may have started in the past and only received a formal diagnosis recently. Subjects classified as non-AMD may present AMD not yet diagnosed. However, this would have likely occurred only for subjects who entered the cohort towards the end of the study period. This misclassification bias would have led to an under-estimation of the strength of the associations between AMD and the various study outcomes. Furthermore, patients with such conditions may not be followed-up regularly unless there is a sudden deterioration. This would also lead to misclassification with respect to history (i.e., prevalent/incident status). However, no difference was found between the year of entry in the cohort and the risk of the four outcomes, apart from an association between the last year of entry and the risk of institutionalization. Patients included in the last study year were followed for, at most, one year and the delay of onset for institutionalization following diagnosis may be longer; hence, very unlikely that a patient would be institutionalized during this first year.

One may question the validity of diagnoses in the RAMQ database. Such misclassification may have affected the definition of the cohorts (exudative AMD and non-visually impaired), as well as the outcome measures (depression and fracture). The form of AMD (i.e., exudative or dry) or the extent of visual impairment are not recorded in the RAMQ medical services database, as only one ICD-9 diagnosis is used. AMD was considered exudative if a fluorescein angiography had been performed in the two years after the index date. This marker of exudative AMD appeared valid, as the risks of institutionalization and death in patients with non-exudative AMD were indeed different from those observed in the exudative AMD population and similar to those in the referent population. Depression was assessed through the diagnosis and the prescription of an antidepressant. Two levels of misclassification may have occurred. First, under-diagnosis of depression in the elderly population may lead to underestimation of depression.[53] Second, prescription of antidepressants for conditions other than depression (i.e., anxiety disorders, chronic pain) may lead to overestimation of depression. Whether or not this misclassification is differential across the sub-cohorts of patients is uncertain. However, the prevalence of depression that was found in the referent cohort using this case definition corresponded to the expected prevalence in the elderly population.[54,55] and a good agreement between medical claim database and medical records was found in a previous study.[56]

The other limitations are specific to the RAMQ database. The first was due to the difference in the age data that are provided for patients with AMD and the reference population. Misclassification was more important for the reference than for the AMD group. However, because the trends between age and the various outcomes that were assessed were consistent with results found in the literature, it is likely that misclassification did not play a major role in observed findings.

The present study showed associations between suspected exudative AMD and decreased risks of institutionalization and death, as well as between suspected exudative AMD and increased risks of depression and fracture. These findings are consistent with previous studies that reported a significant impact of moderate visual impairment on daily living, morbidity, and mortality. Assuming that AMD is a continuum that progresses over time from mild, moderate to severe, patients with the most advanced AMD may have already experienced dangerous events in the past and hence the best adaptation to the functional disability and acceptance of the condition. Thus, past experience and disease duration should be considered as potential risk modifiers in non-experimental risk assessment of events associated with AMD. If the objective is to determine the risk of adverse events according to an etiological perspective, failure to account for the depletion of susceptibles effect may bias results. Crude burden-of-illness data are however very relevant in economic evaluations as they include the entire case mix.

Acknowledgments

We are grateful to the members of the Department of Statistical Services at the Régie de l'assurance-maladie du Québec for providing us with the necessary data for this study. Pfizer Canada Inc funded the study. Marie Tournier is a recipient of an award from the Fondation pour la Recherche Médicale of France. We are also very grateful to Lucie Blais for her valuable methodological input in the statistical analyses.

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