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Survival of patients with incident dementia who had a pre-existing psychiatric disorder: a population-based 7-year follow-up study

Xiangfei Meng[1,2,†], Carl D'Arcy[1,3,†], Raymond Tempier[1], Changgui Kou[1], Debra Morgan[2] and Darrell D. Mousseau[1]

[1]Department of Psychiatry, College of Medicine, University of Saskatchewan, Canada
[2]Canadian Centre for Health and Safety in Agriculture, University of Saskatchewan, Canada
[3]School of Public Health, University of Saskatchewan, Canada
Correspondence to: X. Meng, E-mail: xim443@mail.usask.ca; C. D'Arcy, E-mail: carl.darcy@usask.ca

[†]These authors contributed to the work equally.

Objectives: Although it is widely accepted that psychiatric disorders and dementia coexist and survival data for dementia patients have been published, there is a paucity of information regarding the survival of patients with a psychiatric disorder who develop dementia. This study fills this information gap providing survival data on patients with such comorbidity and identifies mortality risk factors.

Methods: All residents of Saskatchewan, a Canadian province, diagnosed with psychiatric problems and/or dispensed a psychiatric drug in 2000 and without dementia were followed through to 31 December 2006; the development of incident dementia was noted. Median survival time (in months) and selected predictors of mortality were measured. Analyses used Cox's proportional hazard model. Incidence density of dementia for the year 2000 was also computed.

Results: By December 2006, 5,583 subjects with psychiatric disorders in 2000 had been diagnosed with incident dementia, and 60.65% of them died. Dementia-incidence density in this population for 2000 was 0.01 per 1000 person years at risk among those aged 18–64 years and rapidly increased to 3.13 per 1000 person years at risk among those aged 75 to 84 years. The median survival time from dementia onset to death was 32.66 months (interquartile range 31.21–34.14). Being male, later age of onset of dementia, having a lower income, and a high chronic disease score predicted shorter survival.

Conclusions: The comorbidity of psychiatric disorders and dementia resulted in shorter survival compared with that reported for patients with dementia only. These findings can be used for prognosis for patients, caregivers, and service providers. Copyright © 2011 John Wiley & Sons, Ltd.

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Introduction

According to the World Health Organization 2004 update (World Health Organization, 2008), there are 24.2 million people suffering from dementia and 207 million people with psychiatric disorders worldwide. Globally, 4.6 million new dementia cases are diagnosed every year; the number of people with dementia will approach to 81.1 million in 2040 (Ferri *et al.*, 2005). The increasing prevalence and incidence of dementia and its consequent disability will place additional burden on patients, caregivers, and society (England, 2010). Mental disorders contribute 14% of global disease burden, mainly because of their chronicity and comorbidity (Prince *et al.*, 2007).

Neuropsychiatric symptoms such as apathy, depressed mood, anxiety, and agitation are prevalent in dementia and Alzheimer's disease (Mega *et al.*, 1996; Burns *et al.*, 1990; Lyketsos *et al.*, 2000, 2002; Craig *et al.*, 2005; Tatsch *et al.*, 2006; Okura *et al.*, 2010).

Complementing these reports, others have suggested that a diagnosis of depression is a risk factor for dementia. Jorm (2001), in a systematic review, found that a history of depression almost doubles the risk of dementia in both case–control and prospective cohort studies. There is growing interest in the comorbidity between dementia and depression. Bolland's (2000) review concluded that the depression associated with dementia arises from damages that were part of the neuro-pathological course of dementia. Butters *et al.* (2008) reviewing epidemiological, neuroimaging, post-mortem neuropathologic studies, and animal models concluded that prior depression increases the risk of subsequent cognitive decline and dementia. Wuwongse *et al.* (2010) in a concise review about the neurodegenerative link between depression and Alzheimer's disease pointed out that these two disorders share similar neurodegenerative mechanisms, including inflammatory processes, shrinking neurotrophic factors, and changing neuronal plasticity. However, Tsuno and Homma (2009) more cautiously suggested that depressive symptoms may represent either a risk factor, a symptom of neurodegeneration, or a reaction to early cognitive loss. A recent study using Swedish twin record data found that depression in early life was not a risk factor for dementia but that depression in later life was, suggesting that depression was prodromal for dementia (Brommelhoff *et al.*, 2009). The authors of that study also observed that the association between depression and dementia may not be unique to depression and that future studies need to examine the impact of psychiatric history in general. Recently, Yaffe *et al.* (2010) in a stratified retrospective cohort study of US veterans found that those diagnosed as having post-traumatic stress disorder were nearly twice as likely to develop dementia in comparison with those without a history of post-traumatic stress disorder.

Dementia significantly shortens life expectancy. In community studies, being male, older, separated, widowed, divorced, or unmarried, and having physical health comorbidities predicted increased mortality and decreased survival time (Molsa *et al.*, 1995; Aguero-Torres *et al.*, 1999; Xie *et al.*, 2008; Jotheeswaran *et al.*, 2010). Lee and Chodosh (2009) systematically reviewed 48 studies on survival of dementia patients, which covered all types of observational study designs; they found that getting older, being male, dysfunctional status, and physical comorbidity were associated with increased mortality. Zeki AI Hazzouri *et al.* (2011) analyzed the relationship between dementia and socio-economic status and found that lower socio-economic status significantly increases the risk of dementia and shortens survival. Dementia patients living in rural areas are much more vulnerable than urban patients in terms of health status and access to services (Forbes *et al.*, 2006).

Although we have rich data on mortality and survival in dementia patients, there are very few studies on survival of dementia patients with a pre-existing psychiatric disorder. Given their potential impact on caregivers and long-term care facilities as well as their economic impact, it is important to draw attention to this component of the population who suffer psychiatric disorders and subsequently develop dementia.

The aim of this study are as follows: (i) to examine the incidence of dementia among those with pre-existing psychiatric disorders and/or who were dispensed a psychiatric medication in a population; (ii) to determine survival and mortality among those with pre-existing psychiatric disorders who develop incident dementia; and (iii) to identify risk factors associated with decreased survival.

Methods

Context

Canada has a predominantly publicly financed health system with the delivery of services carried out through private (for-profit and not-for-profit) and public (arm's length and direct) modes. Approximately 70% of total health expenditures occur in the public sector largely through provincial and territorial governments who are responsible for hospital care, nursing homes, some home care, and community care as well as administrating prescription drugs plans, and paying physicians for their public health care services. Provinces and territories vary in terms of financing, administration, delivery modes, and range of services provided. The remaining 30% of health expenditures are in the private sector, paid for either out-of-pocket or through private health insurance. Most of these expenditures include dental, vision care, some prescription drug care, and virtually all complementary and alternative therapies and medicines as well as some home care, community care, and long-term care (Marchildon, 2005).

The government of Saskatchewan is responsible for the majority of health services delivered in the province. These services include almost all hospital and physician services as well as a significant portion of nursing home care, home care, prescription drug subsidies, and public health (Marchildon and O'Fee,

2007). One by-product of this provision of services is extensive linkable health care utilization data files that are available for research (Rawson *et al*., 2011). The data files involved, with the exception of the outpatient prescription drug database, cover health services (e.g. hospital discharge and physician services) delivered to all beneficiaries, notably almost 99% of the provincial population. The drug data file includes information for only those eligible for prescription drug benefits, which covers 91% of the provincial population.

Study cohorts

The psychiatric patient cohort studied included all Saskatchewan residents who, in 2000, were eligible for health coverage, including provincial prescription drug benefits, and had a physician service claim for treatment of a psychiatric disorder, or a hospital separation record with a primary diagnosis for a psychiatric problem, or a prescription drug dispensed claim for a psychotropic medication. Cohort members also had to have been eligible for health services in the province in the year prior to the first eligible service in 2000. Data on cohort members' record of physician services use, hospital stays, and medication prescriptions were collected from 1 January 2000 to 31 December 2006 or to when the cohort member ceased to be eligible for coverage or death. This cohort is a natural population cohort of a defined geographic area. When individuals were no longer covered or died, there is a record of the date of their termination of health benefit coverage and/or death.

The incident dementia sub-cohort included all individuals from the psychiatric patient cohort, with a physician or hospital record reporting a diagnosis of dementia during the period 1 January 2000 to 31 December 2006 or to when the cohort member died or coverage ceased and who had no record of dementia in the year preceding the index date.

Data sources

The data for this study were taken from five Saskatchewan Ministry of Health data files. The data released to researchers by the Saskatchewan Ministry of Health are subject to restraints and dummy identification to ensure confidentiality. The *Person Registry File* contains data on persons eligible for coverage in Saskatchewan in any given year. This file was used to compile demographic information on the study subjects, including sex, year of birth, coverage dates, date of death, marital status, residence, and receipt of income security benefits. The *Physician Visits File* contains data on the details of doctor's visits. Data retrieved include the date of the visit and the diagnosis recorded. The *Outpatient Prescription Drug File* records data on medications dispensed. Data on medications dispensed and date of dispensing were retrieved. The *Hospital Separation File* contains hospital discharge data. Date of admission and associated primary and secondary diagnoses were also retrieved. The *Vital Statistics Death File* contains date and cause of death.

Measures

The data on socio-demographic variables were standard information retrieved from the *Person Registry File*. Date of birth and entry and exit dates are recorded on a perpetual calendar basis. Marital status was recorded as follows: single, married or common-law, separated, divorced or widowed, and unknown. Residence location was recorded as urban (the cities of Regina and Saskatoon) or rural (the rest of the province). Whether subjects were in receipt of income security benefits was also recorded. This is a rudimentary measure of low income. Residents of the province with lower incomes may apply for both family and individual-based income security benefits. A targeted program was also available for low-income seniors. The benefits and eligibility criteria for these programs have varied over time.

For inclusion in the *Psychiatric Patient Cohort*, subjects had to have a psychiatric diagnosis recorded in the *Physician Visits File* or a primary psychiatric diagnosis recorded in the *Hospital Separation File* or a prescription for a psychotropic medication in *Outpatient Prescription Drug File* during the period 1 January to 31 December 2000. The *Physician Visits File* and the *Hospital Separation File* used ICD-9, DSM-IV, and ICD-10-CA codes to record diagnoses. Incident dementia was considered to have occurred if a subject had such a diagnosis in the *Physician Visits File* and/or the *Hospital Separation File*. The date of the visit or hospitalization was used to indicate the date of onset of disease.

A chronic disease score (von Korff *et al*., 1992) was calculated at index date on the basis of prescriptions dispensed in the previous year. The chronic disease score is seen as a stable measure of chronic disease status. von Korff *et al*. (1992) noted that the score was associated with physician-rated disease severity, patient-rated health status, and predicted subsequently mortality and hospitalization.

Because dementia is an age-related disease and those over 65 years of age have an increasing risk of occurrence and that rate increases significantly with age (Chen *et al*., 2009), in reporting incidence rates, we classified the population into three age categories: 16–64, 65–74, and 75+ years.

Analyses

Incidence density is a more precise measure of incidence because it takes into account the sum of the population's time at risk. It was used to measure the incidence of dementia among those with pre-existing psychiatric disorders in 2000. We calculated the incidence of dementia within age groups for men and women separately. The Kaplan–Meier estimator was used to estimate the survival function for incident dementia cases to death during the follow-up period. We censored subjects, who survived or were lost to follow-up during the period. The factors associated with the hazard of mortality were examined with a Cox proportional model. Schoenfeld's residual test was used to evaluate the proportional hazard assumption and checked interactions between explanatory variables. STATA (StataCorp LP, College Station, TX) version 11 was used for the statistical analyses.

Results

The Saskatchewan population was approximately one million in 2000. The covered population, from which our cohort was drawn, numbered 930,965. Of that population, 164,025 (17.62%) were diagnosed with a psychiatric disorder and/or prescribed a psychotropic medication in 2000. This cohort of patients was followed through to 31 December 2006.

During this period, a total of 5,583 (3.4%) of all the psychiatric patients in Saskatchewan were diagnosed with incident dementia. Of these, 18 subjects had missing data on time in their incidence record and were excluded from the analyses; the remaining 5,565 subjects were included in the survival analysis. For the incidence density analysis, we only calculated incident cases that occurred during the calendar year 2000.

Table 1 shows the basic demographic characteristics of the cohort of the population with pre-existing psychiatric conditions who developed an incident dementia in 2000 ($N = 1{,}374$). Those psychiatric patients with low income, higher chronic disease score, and who were separated, widowed or divorced, were more likely to be diagnosed with dementia ($p < 0.001$). Of the psychiatric patients aged 65+ years in 2000, some 1,329 (2.84%) developed incident dementia in that year. The incidence density of dementia among those

Table 1 Baseline characteristics of the Saskatchewan population (by gender) with a pre-existing psychiatric disorder who developed incident dementia in the year 2000 ($N = 1{,}374$)

	Males		Females		Total			
Characteristics	*N*	%	*N*	%	*N*	%	χ^2	*p*
Age (years)							4.14	0.126
18–64	20	3.78	25	3.00	45	3.28		
65–74	72	13.61	88	10.41	160	11.64		
75+	437	82.61	732	86.63	1169	85.08		
Residence							0.84	0.358
Urban	167	31.57	287	33.96	454	33.04		
Rural	362	68.43	558	66.04	920	66.96		
Marital status							220.08	<0.001
Single	68	12.85	62	7.34	130	9.46		
Married/common law	312	58.98	201	23.79	513	37.34		
Separated[a]	149	28.17	580	68.64	729	53.06		
Unknown	0	0	2	0.23	2	0.15		
Income indicator							37.19	<0.001
Not low	258	48.77	273	32.31	531	38.65		
Low income	271	51.23	572	67.69	843	61.35		
Chronic disease score							19.19	<0.001
<0	134	25.33	141	16.67	275	20.01		
1–3	136	25.71	201	23.79	337	24.53		
4–5	92	17.39	177	20.95	269	19.58		
6–24	167	31.57	326	38.58	493	35.88		

[a]Separated, divorced, and widowed.

aged 18–64 years in 2000 was 0.01 per 1000 person years at risk, with this incidence density rapidly increasing to 0.33 per 1000 person years at risk among those aged 65 to 74 years. Subjects aged 75+ years had an almost 10-fold higher incidence compared with people between 65 and 74 years of age (Table 2).

Over the 7-year follow-up period to 31 December 2006, two thirds of incident dementia cases ($N = 5,565$) were women (3,621, 65.07%). Among the 3,386 deceased cases, the median age at death was 80 years for men and 82 years for women ($p < 0.001$). Compared with deceased men, deceased women were more likely to have a higher chronic disease score (79.21% vs. 85.65%, $p < 0.001$), be older (75+) (81.09% vs. 89.92%, $p < 0.001$), more likely widowed, separated and divorced (27.29% vs. 59.82%, $p < 0.001$), and have received low income benefits (46.18% vs. 59.82%, $p < 0.001$).

Survival from incident dementia to death was 24.05 months for men and 37.32 months for women with a significantly shorter survival with increasing age (Table 3). Figure 1 shows Kaplan–Meier survival probability curves, men and women separately. Table 4 shows the univariate and multivariate mortality hazard ratios for selected socio-demographic and health characteristics in the study cohort. Being male, later age of onset of dementia, having a lower income, and a higher chronic disease score each independently

Table 2 Incidence density of dementia with pre-existing psychiatric conditions, by age and gender, Saskatchewan, 2000 ($N = 1,374$)

	Females				Males				Total			
Age (years)	*N*	Person years at risk	Incidence[a]	95% CI	*N*	Person years at risk	Incidence[a]	95% CI	*N*	Person years at risk	Incidence[a]	95% CI
18–64	25	2,054,582	0.01	0.01–0.02	20	2,093,608	0.01	0.01–0.02	45	4,148,190	0.01	0.01–0.02
65–74	88	255,776	0.34	0.27–0.42	72	235,175	0.31	0.24–0.38	160	490,951	0.33	0.28–0.38
75+	732	216,103	3.39	3.14–3.63	437	157,409	2.78	2.52–3.04	1169	373,512	3.13	2.95–3.31

[a]Incidence density of dementia per 1000 years at risk.

Table 3 Median survival time (months) of incident dementia cases among residents of Saskatchewan with pre-existing psychiatric disorders diagnosed in 2000 and followed through to 31 December 2006, by selected socio-demographic characteristics and chronic disease score ($N = 5,565$)

	Females		Males		All	
	Median	95% CI	Median	95% CI	Median	95% CI
Gender	37.32	35.58–39.42	24.05	21.62–26.61	32.66	31.21–34.14
Age of onset (years)						
18–64	NA	NA	NA	NA	NA	NA
65–74	73.17	NA	43.14	34.78–51.49	50.33	42.01–58.66
75+	35.09	33.11–37.07	19.98	17.77–22.18	29.77	28.26–31.27
Marital status						
Single	38.70	29.34–45.80	29.86	23.85–38.87	33.87	27.83–39.82
Married/common law	48.03	43.43–5319	22.77	19.09–26.84	34.33	31.34–36.53
Separated[a]	33.22	31.44–35.94	23.06	18.69–27.79	31.51	29.90–33.22
Unknown	41.59	23.72–NA	NA	NA	41.59	23.72–NA
Residence						
Urban	36.96	34.07–41.10	22.83	18.76–27.17	33.31	29.44–35.71
Rural	37.55	35.48–40.24	24.54	21.49–27.96	32.42	31.01–34.63
Income indicator						
Not low	41.13	36.60–44.78	27.07	22.90–29.77	34.66	32.36–36.67
Low income	35.78	32.85–38.01	21.49	17.74–24.57	31.24	29.24–32.99
Chronic disease score						
0	46.13	42.48–53.19	28.06	23.43–36.24	41.86	35.71–44.55
1–3	42.84	38.18–46.55	30.09	25.23–34.73	37.85	35.55–40.87
4–5	35.55	31.44–40.18	26.12	19.58–31.01	32.30	29.34–35.55
6–24	31.01	28.02–33.54	17.48	14.98–19.48	25.79	23.79–28.35

[a]Separated, divorced, and widowed.

predicted shorter survival. Variables with *p*-values less than 0.20 in the univariate analyses were put into a multivariate Cox's proportional hazards regression model. After model fitting and proportional assumption test, being male, age of onset of dementia, lower income, and higher chronic disease score were consistently significantly associated with decreasing survival. Marital status and residence location were not associated with survival. Figure 2 shows Kaplan–Meier survival probability curves for men and women separately taking into account age of onset, lower income status, and chronic disease score. After adjusted with other risk factors, gender differences in survival were substantially reduced.

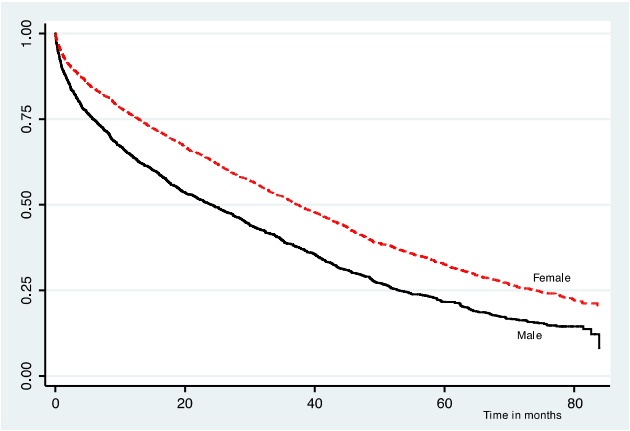

Figure 1 Survival curves from onset of dementia for those with pre-existing psychiatric conditions by gender, Saskatchewan, 2000–2006 ($N = 5{,}565$).

Discussion

This study demonstrated that incidence density of dementia for those patients with pre-existing psychiatric disorders was higher in women and increased with age. In this large population-based cohort, estimated survival after the onset of dementia was 32.66 months among those with pre-existing psychiatric disorders. Being male, having a later age of onset of dementia, being poor, and having a high chronic disease score predicted increasing mortality.

Depression and dementia are important health issues (Tsuno and Homma, 2009). There is evidence to support that depression and dementia share

Table 4 Univariate and multivariate hazard ratios for mortality of patients with pre-existing psychiatric conditions who develop incident dementia by selected socio-demographic and health characteristics ($N = 5{,}565$)

	Univariate		*Final model*	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Sex				
Male	1	<0.001	1	<0.001
Female	0.699 (0.652–0.749)		0.648 (0.603–0.695)	
Age at onset				
18–64 years	1	<0.001	1	<0.001
65–74 years	2.627 (1.891–3.651)		2.522 (1.815–3.506)	
75+ years	4.523 (3.323–6.157)		4.752 (3.489–6.473)	
Marital status				
Single	1	0.168	—	—
Married/common law	0.980 (0.862–1.116)		—	
Separated/widowed/divorced unknown	1.057 (0.932–1.198)		—	
	0.676 (0.252–1.813)		—	
Income indicator				
Not low	1	0.004	1	0.005
Low income	1.105 (1.032–1.182)		1.102 (1.029–1.181)	
Residence				
Urban	1	0.592	—	—
Rural	0.981 (0.914–1.053)		—	
Chronic disease score				
0	1	<0.001	1	<0.001
1–3	1.023 (0.920–1.139)		1.038 (0.933–1.155)	
4–5	1.185 (1.061–1.323)		1.204 (1.077–1.345)	
6–24	1.378 (1.249–1.521)		1.387 (1.256–1.532)	

HR, hazard ratios.
—, not included in the final model.

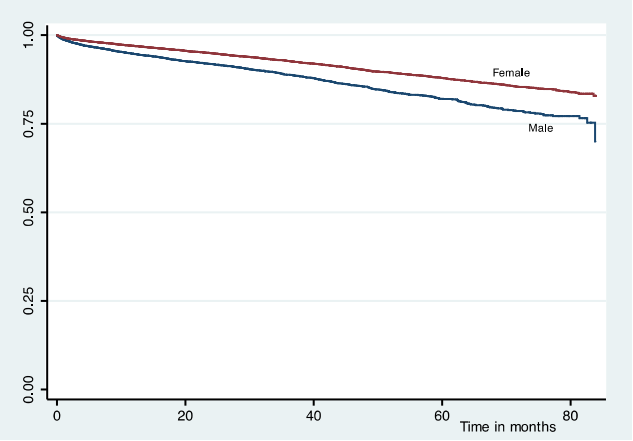

Figure 2 Survival from onset of dementia for those with pre-existing psychiatric conditions adjusted for age of onset, low income, and chronic disease score, by gender, Saskatchewan, 2000–2006 ($N = 5{,}565$).

neurodegenerative links or pathways, which makes them more likely to coexist (Wuwongse *et al.*, 2010; Butters *et al.*, 2008; Tsuno and Homma, 2009; Huang *et al.*, 2010). Brommelhoff *et al.* (2009) and Yaffe *et al.* (2010) have suggested that other psychiatric disorders may also be associated with dementia. The negative impact of dementia on survival has been repeatedly shown both in community and population-based studies (Rait *et al.*, 2010; Rakowski *et al.*, 2006; Rozzini *et al.*, 2005; Williams *et al.*, 2006; Andersen *et al.*, 2010). The presence of mental disorders has also been associated with significantly higher mortality (Saz *et al.*, 1999; Viron and Stern, 2010; Zubenko *et al.*, 1997). The estimated survival time from incident dementia to death ranges from 3 to 10 years, and the median survival time is 5 years (Xie *et al.*, 2008; Rait *et al.*, 2010; Zanetti *et al.*, 2009). To our knowledge, our study is the first to examine survival among patients suffering from both dementia and psychiatric disorders. Given that higher mortality was associated with dementia as well as with psychiatric disorders, it would be reasonable to expect an increased mortality for patients with incident dementia and pre-existing psychiatric disorders. That, in fact, is what we found. The median survival time in this study is 32.66 months (about 2.72 years) from incident dementia to death, which is significantly less than the median survival time for those patients diagnosed with dementia or psychiatric disorders alone (Chen *et al.*, 2010).

Previous studies have suggested that women are not only more likely to develop dementia but also live longer with the disease (Hamid *et al.*, 2010, Rait *et al.*, 2010, Xie *et al.*, 2008). As expected, we found that women had a higher incidence density and a longer survival prior to death. The increased likelihood that women will develop dementia has relevance for service providers and policy makers. In terms of socio-demographic risk factors related to survival of dementia, our findings also are consistent with previous publications regarding the effects of socio-demographic factors (age, gender, social status) and additional physical health problems on survival (Zubenko *et al.*, 1997; Rait *et al.*, 2010). Specifically, male patients, or those who had a later age of onset of dementia, or low income, survived fewer months after the occurrence of dementia.

Our study has certain strengths and limitations. Although our study subjects were based on a community population cohort with psychiatric disorders, we did not have data on a "healthy" control group for comparison purposes. There is a potential for misclassification. For example, a single prescription or diagnosis could bring someone into the cohort, such as would be the case for psychotropic medications, which may be used for other conditions that do not have a primarily mental health component. In addition, these administrative data do not include any measurement regarding the severity of psychiatric conditions. However, the strength of the study is that it is a relatively large population study of patients covering both primary and specialist care settings.

In conclusion, a significant proportion of the population who suffers from psychiatric disorders subsequently develops comorbid dementia. This study reveals that the incidence density of dementia among those with pre-existing psychiatric disorders was higher in women and increased with age. The findings also showed significant survival loss for patients with comorbid dementia and psychiatric disorders compared with that reported for those with dementia only. Being male, having a later age of onset of dementia, having a lower income, and suffering from multiple physical health problems contributed to shorter survival. These findings draw attention to the following: (i) the incidence of dementia among patients with pre-existing psychiatric disorders; (ii) the increased mortality risks for patients with both a psychiatric disorder and dementia; and (iii) the need for the early identification of dementia among psychiatric patients so that appropriate treatment and care can be initiated.

Conflict of interest

None declared.

Key points

- The comorbidity of dementia and psychiatric disorders significantly impacts on clinical treatment and intervention. Early recognition of this phenomenon is important to individuals, families, and societies.
- A significant proportion of population suffers from psychiatric disorders and subsequently develops comorbid dementia.
- There is significant survival loss for patients with comorbid dementia and psychiatric disorder compared with that reported for those with dementia only.
- In this cohort, being male, having a later age of onset of dementia, having a lower income, and suffering from multiple physical health problems increased mortality.

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Disclaimer

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