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Severe Psychiatric Disorders in Mid-Life and Risk of Dementia in Late-Life (Age 65-84 Years): A Population Based Case-Control Study

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Abstract: *Objective:* To examine the association of mid-life exposure to several psychiatric disorders with the development of late-life dementia. *Methods:* A matched case-control study using Western Australian state-wide hospital inpatient, outpatient mental health and emergency records linked to death records. Incident dementia cases (2000-2009) aged 65 to 84 years were sex- and age-matched to an electoral roll control. Records as far back as 1970 were used to assess exposure to medical risk factors before age 65 years. Candidate psychiatric risk factors were required to be present at least 10 years before dementia onset to ensure direction of potential causality. Odds ratios were estimated using conditional logistic regression. *Results:* 13, 568 dementia cases (median age 78.7 years, 43.4 % male) were matched to a control. Depression, bipolar disorder, schizophrenia, anxiety disorder and alcohol dependence were found to be significant and independent risk factors for late-life dementia after adjusting for diabetes, heart disease, cerebrovascular disease and smoking risk factors. The effect of a history of depression, schizophrenia and alcohol dependency on dementia risk varied with age, being strongest for earlier onset late-life dementia and waning at older ages. *Conclusion:* Severe depression, anxiety disorder, bipolar disorder, schizophrenia and alcoholic dependency disorder treated by specialists in psychiatric facilities in mid-life are important risk factors for late-life dementia. These psychiatric conditions need to be considered in future studies of the risk and prevention of late-life dementia.

Keywords: Alzheimer's disease, anxiety disorder, bipolar disorder, case-control studies, dementia, depression, risk factors, schizophrenia.

INTRODUCTION

Successful prevention and treatment strategies are needed to cope with the expected world-wide increases in the prevalence of dementia and Alzheimer's disease. Given the lack of an effective treatment, there is need for a greater understanding of potentially modifiable risk factors for dementia from population based studies [1]. Most studies to date have focused on medical risk-factors but there is also evidence to support a potential role for several psychiatric disorders.

Depression is frequently associated with dementia [2, 3]. A 2001 meta-analysis by Jorm *et al*., including both case-control and prospective studies, suggests that a history of depression nearly doubles the risk of dementia [3]. Whether a history of depression leads to an increased risk of dementia, however, remains controversial. This is because evidence from a population-based longitudinal study found a higher risk of dementia only for depressive episodes developing for the first time in close proximity to the onset of dementia symptoms [4]. This suggests that depression is a prodromal feature of dementia, rather than a risk factor. A 2006 meta-analysis concluded that depression was likely to be a risk factor rather than a prodromal feature of dementia [5] although only two of the thirteen studies in the meta-analysis demonstrated that depression more than 10 years prior was associated with a higher risk for dementia. In one of these [6] the researchers had to rely on informant retrospective reports that are subject to recall bias [7] and in the second [8], the effect of early onset depression, i.e. before age 65 years, was only seen in individuals with a low level of education.

A 2011 review by Byers *et al.* also argues that earlier life depression is associated with dementia while findings are mixed with respect to late life depression. Their review included an additional three studies examining 'early life' depression exposure to contribute to the debate. In the first, which relied on patient recall for history of depression, depression before age 60 was associated with an almost 4-fold increase risk of dementia in a cohort of 503 persons [9]. The second study observed an increase in the risk for dementia as a function of the number of depressive episodes [10]. The third reported that while mid-life depression was associated with dementia after adjustment for other risk factor, there was insufficient evidence for an association with Alzheimer's or vascular dementia and concluded that more studies are needed to examine depression occurrence over the life-course [11].

The controversy over prodrome versus risk factor was highlighted in a 2013 comprehensive systematic review by da Silva *et al.* [12] which examined evidence for depression and bipolar disorder as risk factors for dementia. They concluded that most of the 51 studies found an increased risk of

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developing dementia in individuals with depression, however only three [6, 9, 13] of nine studies that examined effect of early onset depression found a statistically significant association with late onset dementia.

The evidence for associations between bipolar disorder and dementia is sparse, the recent review citing five papers published between 1991 and 2004 [14-18]. The latest, a Danish study of 4,248 patients with bipolar disorder showed, that the risk of getting a diagnosis of dementia was affected significantly by the number of prior episodes leading to admission for bipolar disorder [18]. Three of the studies reporting a positive association between bipolar disorder and dementia originated from Denmark [16-18] so evidence from other populations are needed to build on these early reports.

A recent review [19] identified three studies that examined whether patients with late-onset schizophrenia (i.e. after age 40 years) were at increased risk of dementia [20-22]. The Danish study reported a 2.4-fold increased risk of dementia after almost 5-years of follow-up in 1,206 late-onset schizophrenia patients when compared to normal controls [20]. In an Australian study, nine of the 27 late-onset schizophrenia patients developed dementia while all 34 normal controls remained dementia free after 5-year follow-up [21]. In a US study without a normal control group, half of the 28 patients with late-life schizophrenia developed dementia in the 10-year follow-up, significantly more than the authors' expected 20% 10-year incidence rate [22]. The variability in the above study designs together with a lack of control for known risk factors for dementia in these studies limits our ability to draw any conclusions as to whether there is a positive relationship between mid-life schizophrenia and late-onset dementia.

Few studies have focused on the role of anxiety as a risk factor for dementia. Two studies, both with three years of follow-up, found that anxiety and distress in the elderly increases risk of Alzheimer's disease [23, 24]. One study, restricted to men with 17 years of follow-up, reported that mid-life anxiety was associated with increased incidence dementia in later life [25].

There are several established non-psychiatric clinical risk factors for dementia, including diabetes, cardiovascular risk factors and head injury [26-28]. Many studies, although not all [29, 30], have assessed these risk factors during later life but this can be problematic as older age can modulate their association with dementia. For example, hypertension and hyperlipidaemia during midlife predict late life dementia whereas their impact appears reduced when assessed during later life [31]. Similar considerations may apply to diabetes although the duration of diabetes may be a more potent dementia risk factor [32].

The aim of the present study was to examine the impact of exposure during mid-life to a range of psychiatric disorders and medical conditions that have been associated with late-life dementia. We used linked administrative health data from the state of Western Australia to conduct a case-control study in a large population. Steps were taken to ensure both long follow-up and a clear gap between exposure (risk factor) onset and outcome (incident dementia). We first explored risk factors for all dementia cases combined and then investigated dementia sub-types.

MATERIAL AND METHODS

Source of Data

The state of Western Australia occupies the western third of Australia and has a population of 2.3 million persons, including 285,221 persons aged over 65 years (2011 Census data). The Western Australian Data Linkage System is a validated, population-based, data linkage system that creates links among state health-related data sets [33, 34]. The Hospital Morbidity Data Collection (HMDC) has recorded all inpatient discharge summaries from all Western Australian acute hospitals (private and public) since 1970. Public outpatient mental health services are provided by psychiatric clinics, community health centres, psychiatric day centres, outreach programs and rehabilitation programs. The Western Australian Mental Health Information System (MHIS) commenced linking all public and private inpatient and public outpatient mental health services contacts in 1966. The Emergency Department Data Collection (EDDC) commenced linking public and private hospital emergency department activity in 2002. All Western Australian deaths are registered in the Death Registry. For the present study, the Data Linkage Branch of the Western Australian Department of Health [34] used the Western Australian Data Linkage System to provide a de-identified extraction of linked data from the HMDC (1970-2009), MHIS (1966-2009), EDCC (2002-2009) and Death Registry (2000-2009) for all persons with an index record of dementia in any of these datasets between 2000 and 2009 (cases) and their matched electoral roll controls. Each record in the linked datasets contained the encrypted patient identification, age and sex of the patient. Data fields in the HMDC and inpatient MHIS records also included: date of separation, International Classification of Disease (ICD) code of principle and additional diagnoses (maximum of 21 diagnosis codes per admission). Data fields in outpatient MHIS and EDDC also included: date of contact and principle diagnosis ICD code. Data fields in the Death records included: date of death and ICD codes for cause of death, antecedent causes relating to death and other significant conditions contributing to death. Study data were obtained in December 2010 following approval from the Curtin University Human Research Ethics Committee and the Western Australian Department of Health Human Research Ethics Committee.

Study Design

In order to account for the temporal nature of mid-life risk exposure relative to developing late-life dementia, a matched case-control study was performed. Matching by age and sex allowed a reference date for each matched pair to be defined which ensured that a similar length of exposure history (look-back period) was available for cases and controls. For each matched pair of case and control, the reference date was defined as the date of the case's incident dementia (index) record. The look-back period was defined as the number of years between each subject's first available linked health record and the reference date. Individuals with an index record of dementia age > 84 years were excluded because their linked administrative health records did not extend back far enough in calendar years to identify risk factors in middle life. Individuals with early-onset dementia (i.e.

symptoms before age 65) were excluded because of known clinical and neurological differences between early-onset and late-onset Alzheimer's disease [35, 36].

Selection of Dementia Cases

Cases included all patients diagnosed and registered in the Western Australian HMDC, EDDC, MHIS or Death Registry with first (index) dementia record from 1 January 2000 to 31 December 2009. Dementia was defined using the following ICD-10-AM codes: Alzheimer's disease (F00, G30), vascular dementia (F01) and unspecified dementia (F03). Excluded from the study were cases with (i) index dementia age <65 years, (ii) index dementia age > 84, (iii) dementia in other diseases (1988-1999, ICD-9-CM codes 294.1 331.1, 46.1, 333.4; 1999-2009, ICD-10-AM codes F02, 81.0, G10, G31.0) and (iv) controls who were identified during cleaning and preparation of data-extracts as not meeting control inclusion/exclusion criteria as defined in next paragraph. The above ICD codes were used previously to study dementia associated hospitalization and death rates in the Western Australian population between 1990 and 2005 [37, 38]. Dementia sub-diagnoses were those documented by the wide range of treating physicians from both specialist and general settings and the largest sub-group was non-specific dementia, followed by Alzheimer's and vascular dementia, and a relatively small number with mixed dementia (where coding included both Alzheimer and vascular dementia categories at different times). Because the diagnostic accuracy of dementia sub-diagnoses is likely to be low, we chose to explore risk factors for all cases of dementia before exploring the three largest categories (non-specific dementia, Alzheimer's disease, vascular dementia).

Selection of Controls

Population controls were randomly drawn from the Western Australian state electoral roll in a country where voting is mandatory for all citizens over age 18 years. Citizens are required to notify the Australian Electoral Office if they change their address. Therefore some controls may only be resident in Western Australia for a short period of time and may have had minimal contact with Western Australian hospitals (this also applies to cases). Persons with dementia are required to have their name removed from the electoral roll by a relative provided there is written evidence from a medical provider. In 2011, 254,013 Western Australian citizens aged 65 years and over were registered on the electoral roll (i.e. 89% of all residents aged 65 years and over [39]. One sex and age-matched (+/- 3 years) control was selected from the Western Australian electoral roll for each case by the Data-Linkage Unit of the Western Australian Department prior to extraction of the health data for the controls. Excluded from the study were controls with (i) any history of dementia prior to 2000 [ICD-8 code 290; ICD-9 and ICD9-CM codes 290.0-290.4, 331.0] or index dementia record between 2000 and 2009 or (ii) death prior to their reference date.

Mid-Life Risk Factor Exposure

Mid-life risk factors were considered to be present if documented in the administrative health datasets between age 30 and 65 years. Factors shown in previous studies to be potentially associated with the development of dementia were included where available. These included unipolar (major) and/or dysthymia/neurotic depression, bipolar disorder [18], schizophrenia spectrum disorder [20], anxiety disorder [25], alcohol dependence syndrome [40], heart disease [41] , cerebrovascular disease [42], diabetes mellitus [43, 44], hypertension [31], smoking history [45], hyperlipidemia /hypercholesterolemia [31] and head injury [28]. The ICD-8, ICD-9, ICD-9-CM, and ICD-10-AM codes used to identify risk factor exposure documented in health records for years 1966-2009 are provided in eAppendix 1.

Temporal Relationship of Risk Factors Exposure

In addition to being present during the mid-life period, all risk factors, (except for atrial fibrillation, heart failure, cerebrovascular events, and smoking history) were required to be documented at least 10 years prior to the reference date. In the case of the non-psychiatric risk factors, such as ischaemic heart disease and hypertension, this was done because the mechanisms for increasing dementia risk are likely to require long-term exposure. In the case of psychiatric risk factors this was also done to eliminate the possibility that they were a consequence of prodromal/early dementia. This was based on the assumption that the prodromal phase of all relevant dementias is shorter than 10 years. The 10 year prior restriction was not applied to atrial fibrillation, heart failure and cerebrovascular events because it was considered likely that they act to impair cognition via mechanisms within a shorter time-frame. Hence, cases and controls aged 65 years at time of reference date had most risk factors assessed only for age span 30 to 55 years.

Statistical Analysis

Paired t-test was used to examine differences in continuous variables between cases and controls. Dementia outcomes were defined as all dementias (including Alzheimer's dementia, vascular dementia, mixed dementia and non-specific dementia) and then by separate diagnostic subgroups.

The relative risks of developing late-life dementia following exposure to mid-life risk factors were estimated using odds ratios obtained from conditional logistic regression models that accounted for the matched design. Univariate conditional logistic regression models were used to estimate the relative odds of mid-life risk factor exposures in cases compared to controls. All significant ($p<0.001$) univariate risk factors categories (14 in total) were used to construct four multivariate conditional logistic regression models, one for all dementias and one for each of the three dementia subgroups. Regression model building included all significant two-way interactions between the risk factors and case-control matching variables (age at index dementia record and sex). Using backward selection all non-significant two-way terms and non-significant risk factors were removed from the model (p stay <0.05). All explanatory variables in the final logistic model for 'all dementia' were included in the three subgroup models. Multicollinearity diagnostics were performed using the Tolerance option in SAS conditional logistic regression analysis [46]. We concluded that there were no multicollinearity issues in any models because all tolerance values were greater than 0.7. SAS Version 9.3 (SAS Institute, Inc., Cary, NC) was used for statistical analysis.

Sensitivity Analyses

Three sensitivity analyses using the same set of explanatory variables as those used in the adjusted model for 'All dementia' were conducted to examine the robustness of the adjusted odds ratio estimates for 'All Dementia'.

Sensitivity Analysis 1: Persons aged 65-74 years at index reference date with less than 10 years look-back and persons aged 75-84 without any linked health records prior to age 65 years may have lived outside of Western Australia during their mid-life years at risk of exposure and consequently not have had risk factor exposure documented in Western Australian health records. If the proportion of controls and cases not residing in Western Australia during their "mid-life risk" period differed significantly from one another, the inclusion of match-set-pairs with either one or both members having less than 10 years of look-back may bias odds ratio estimates. To determine whether this was the case a sensitivity analysis that included only those match-set-pairs where both case and control had at least one record before age 65 and a look-back period of at least 10 years was conducted.

Sensitivity Analysis 2: Given the lack of certainty with respect to onset of dementia symptoms based on index dementia record, we conducted a second sensitivity analysis with a period of exposure of at least 20 years prior to reference date for depression, bipolar disorder, schizophrenia, anxiety, alcohol dependence, head injury, ischaemic heart disease, and lipids in case a 10-year exposure may have been insufficient.

Sensitivity Analysis 3: The third sensitivity analyses was conducted on a subset of patients where risk factor exposure was required to be documented at least 20 years prior to reference date in addition to the requirement that both members of each match-set pair must have had at least 20 years of look-back period.

RESULTS

Cohort Characteristics

There were 27,982 individuals with an index dementia record between 2000 and 2009 (mean (SD) age 83.4 (8.0) years, 37.4% male). Of these, 14,460 were aged between 65 and 84 years at index dementia record and eligible for entry into the study (mean age 78.7 (4.7) years, 43.1% male). After excluding 892 dementia cases there remained a study cohort of 13,568 cases. Reasons for excluding cases included, i) the control died in the period immediately prior to their index dementia date (n=76, median days prior to index date =20 days (IQR 12-52 days)), ii) the control had a dementia diagnosis in their linked health records (n=78); iii) based on all the linked health records the difference in the age of a case and their control was greater than three years (n=466) iv) case or control had problem data (e.g. records post-death, death record age inconsistent with index dementia age) (n= 309). The 892 excluded dementia cases had proportionally fewer males than the study cohort of included cases (37.6% versus 43.4%, χ^2 =11.8, 1df, p<0.001). The mean (SD) ages of the excluded dementia cases (78.8 (4.8) years) and study cohort cases (78.7 (4.7) years) did not differ significantly (p=0.37). The study cohort controls were on average 0.4 years younger (paired t test: t=35.5, p<0.001) than the cases.

A total of 327 (2.4%) controls and 610 (4.5%) cases had no hospital inpatient or outpatient records prior to their respective reference date. A small group of electoral roll controls (n=173) had no hospital health records either before or after their reference date. The mean (SD) look-back period was 20.4 (10.4) years and 20.0 (10.3) years for cases and controls respectively. The mean difference in look-back period of 0.4 years was statistically significant (paired t test: t=4.24, p<0.001). This means that data records went back on average 19 weeks further for cases than controls. Details on look-back period categories for cases and control are provided in eAppendix 2.

Depression was the most common mid-life psychiatric disorder examined in this study, with 2.6% of controls and 4.8% of cases having a record of depression diagnosis at least 10 years prior to their reference date. A small number of cases (n= 116; 0.85%) and controls (n=39; 0.28%) had a recorded diagnosis of both unipolar major depression and dysthymia/neurotic depression. The most common documented psychiatric disorder after depression was anxiety, followed by alcohol dependence syndrome, schizophrenia spectrum disorder and, lastly, bipolar disorder. Table **1** provides details on the frequency of these and all non-psychiatric risk factors examined in this study. Of the 2,158 index records for psychiatric conditions 77.3% were sourced from mental health inpatient or mental health outpatient records; a detailed breakdown of source of all index psychiatric diagnostic records is given in eAppendix 2.

Mid-life Associations with Late-life Dementia

The mean (SD) age at first documented record for depression, bipolar disorder, schizophrenia and alcohol dependence syndrome were, respectively, 52.7 (6.9), 53.1 (7.5), 48.6 (7.6) and 51.4 (6.3) years. There were no statistical differences between cases and controls with respect to age at first record for these four psychiatric conditions (unpaired t test p-values all >.05). In univariate analysis all mid-life risk factor categories examined in this study were associated with significantly increased odds of developing dementia (Table **1**). The unadjusted odds ratios ranged in magnitude from 1.19 (95%CI 1.00, 1.42) for hyperlipidaemia up to 6.56 (95%CI 3.25, 13.20) for bipolar disorder.

The multivariate conditional logistic regression models were adjusted for all the non-psychiatric risk factors listed in (Table **1**) although unipolar depression and dysthymia/ neurotic depression were combined into a single category to enable more parsimonious modelling. Several interactions with age and sex remained in the final models for 'all dementia' (Table **2**). Depression, schizophrenia, and alcohol abuse were all significant and independent predictors of dementia with onset between 65-79 years, while bipolar and anxiety disorders were predictive for ages 65-84 years. The associations with depression, schizophrenia and alcohol abuse were increasingly attenuated in older age groups whilst there was no age effect with bipolar and anxiety disorders. The sensitivity analyses demonstrated essentially similar results with respect to the magnitude of the odds ratio estimates. However in the third sensitivity analysis, which analysed data from 4,421 match-set pairs with at least 20 years of look-back, the p-values for the depression X age

Table 1. Frequencies and Unadjusted Relative Odds for Mid-Life Risk Factor Categories in 13,568 Dementia Cases (65-84 years old) and their 1:1 Age- and Sex-Matched Controls, Western Australia, Australia, 2000-2009.

Exposure	Controls		Cases				
	n	%	n	%	OR	LL	UL
Unipolar Major Depression	101	0.7	201	1.5	1.99	1.56	2.53
Dysthymia/Neurotic Depression	287	2.1	571	4.2	2.07	1.79	2.39
Depression	349	2.6	656	4.8	1.95	1.70	2.22
Bipolar Disorder	9	0.1	59	0.4	6.56	3.25	13.20
Schizophrenia Spectrum Disorder	28	0.2	117	0.9	4.42	2.89	6.77
Anxiety Disorder	204	1.5	379	2.8	1.88	1.59	2.24
Alcohol Dependence Syndrome	82	0.6	275	2.0	3.16	2.44	4.10
Head Injury	228	1.7	353	2.6	1.56	1.32	1.85
Diabetes	216	1.6	538	4.0	2.56	2.18	3.01
Ischaemic Heart Disease	830	6.1	1056	7.8	1.31	1.19	1.44
Atrial Fibrillation	136	1.0	231	1.7	1.71	1.38	2.12
Heart Failure	243	1.8	389	2.9	1.61	1.37	1.89
Cerebrovascular Disease	222	1.6	535	3.9	2.50	2.13	2.93
Hypertension	1124	8.3	1451	10.7	1.33	1.23	1.45
Lipids	239	1.8	282	2.1	1.19	1.00	1.42
Past or current smoking	5047	37.2	5626	41.5	1.22	1.16	1.28

OR, odds ratio. LL, lower limit of 95% confidence interval. UL, upper limit of 95% confidence interval. Depression includes dysthymia, neurotic and unipolar major depression. Cerebrovascular disease includes acute ischemic stroke, intra-cerebral and subarachnoid haemorrhage and transient cerebral ischaemic attack. Lipids include hyperlipidaemia and hypercholesterolemia. OR p-values <0.0001 for all risk factors except for hyperlipidaemia (p=0.055). In addition to being present between ages 30 to 65 years, all risk factor exposures (except for atrial fibrillation, heart failure and cerebrovascular diseases) were also required to be documented at least 10 years prior to dementia index reference date to be counted as present. Past or current smoking exposure was unique in that it was based on a combination of both pre and post dementia index/reference health records.

Table 2. Adjusted Odds Ratio Estimates for Mid-Life Risk Factor Exposure in a Matched Case-Control Study of All Dementia in Western Australians Aged 65-84 years, 2000-2009.

		Main Study All Dementia Exposure 10+ years prior to dementia onset No look-back restrictions No record restrictions				Sensitivity Analysis One All Dementia Exposure 10+ years prior to dementia onset Minimum of 10 year look-back Minimum of 1 record before age 65				Sensitivity Analysis Two All Dementia Exposure 20+ years prior to dementia onset No look-back restrictions No record restrictions				Sensitivity Analysis Three All Dementia Exposure 20+ years prior to dementia onset Minimum of 20 year look-back Minimum of 1 record before age 65			
		n= 13568				n=6446				n= 13568				n=4421			
Exposure	Age Group	OR	LL	UL	*p* value	OR	LL	UL	*p* value	OR	LL	UL	p value	OR	LL	UL	P value
Depression	65-69	2.77	1.92	4.00	.0001	2.25	1.48	3.40	.05	2.62	1.71	4.03	.001	2.05	1.23	3.42	
	70-74	2.03	1.61	2.56		1.86	1.44	2.40		1.95	1.49	2.56		1.73	1.25	2.38	.13
	75-79	1.49	1.29	1.72		1.54	1.29	1.84		1.45	1.23	1.71		1.45	1.17	1.80	
	80-84	1.09	0.89	1.34		1.27	0.98	1.66		1.08	0.87	1.34		1.22	0.91	1.64	
Bipolar	65-84	4.71	2.29	9.65	<.0001	6.30	2.44	16.28	.0001	4.69	2.08	10.57	.0002	3.83	1.28	11.43	.02

(Table 2) contd….

		Main Study All Dementia Exposure 10+ years prior to dementia onset No look-back restrictions No record restrictions				**Sensitivity Analysis One All Dementia Exposure 10+ years prior to dementia onset Minimum of 10 year look-back Minimum of 1 record before age 65**				**Sensitivity Analysis Two All Dementia Exposure 20+ years prior to dementia onset No look-back restrictions No record restrictions**				**Sensitivity Analysis Three All Dementia Exposure 20+ years prior to dementia onset Minimum of 20 year look-back Minimum of 1 record before age 65**			
		n= 13568				**n=6446**				**n= 13568**				**n=4421**			
Exposure	**Age Group**	**OR**	**LL**	**UL**	***p* value**	**OR**	**LL**	**UL**	***p* value**	**OR**	**LL**	**UL**	**p value**	**OR**	**LL**	**UL**	**P value**
Schizophrenia	65-69	12.07	4.04	36.03	.01	14.41	3.98	52.10	.02	20.59	4.88	86.81	.004	14.52	2.96	71.17	
	70-74	6.67	3.33	13.40		7.30	3.23	16.48		8.81	3.51	22.11		6.55	2.39	17.95	.02
	75-79	3.69	2.34	5.82		3.70	2.16	6.32		3.77	2.22	6.41		2.95	1.59	5.49	
	80-84	2.04	1.12	3.72		1.87	0.91	3.87		1.61	0.87	2.98		1.33	0.60	2.94	
Anxiety	65-84	1.37	1.14	1.65	.001	1.61	1.28	2.02	<.0001	1.50	1.21	1.85	.0002	1.69	1.28	2.22	.0002
Alcohol	65-69	4.14	2.25	7.61	.02	4.21	2.13	8.33	.05	3.42	1.64	7.15	.11	3.72	1.38	10.00	.24
	70-74	2.96	2.03	4.32		2.99	1.98	4.54		2.59	1.64	4.09		2.80	1.55	5.09	
	75-79	2.12	1.60	2.80		2.13	1.50	3.02		1.96	1.43	2.69		2.11	1.39	3.21	
	80-84	1.51	0.99	2.31		1.51	0.86	2.65		1.49	0.93	2.37		1.59	0.83	3.08	
Head Injury	65-84	1.26	1.06	1.51	.01	1.35	1.09	1.69	.007	1.30	1.07	1.58	.001	1.19	0.92	1.56	.19
Diabetes	65-69	3.47	2.36	5.12	.006	3.38	2.17	5.29	.03	2.89	1.33	6.30	.28	3.29	1.14	9.53	
	70-74	2.69	2.12	3.41		2.65	2.02	3.48		2.42	1.48	3.96		2.46	1.26	4.82	.10
	75-79	2.09	1.76	2.47		2.08	1.69	2.56		2.03	1.52	2.71		1.84	1.25	2.70	
	80-84	1.62	1.25	2.10		1.63	1.18	2.26		1.70	1.17	2.46		1.37	0.87	2.18	
AF	65-84	1.26	0.99	1.61	.06	1.27	0.95	1.71	.11	1.27	1.00	1.62	.05	1.18	0.82	1.71	.37
HF	65-84	1.15	0.95	1.39	.14	1.20	0.96	1.52	.11	1.21	1.01	1.46	.04	1.30	0.98	1.73	.07
IHD	65-84 M	0.71	0.53	0.96	.003	0.63	0.44	0.92	.003	1.06	0.69	1.63	.70	0.92	0.51	1.65	.68
	65-84 F	0.97	0.85	1.11		0.93	0.79	1.09		1.12	0.94	1.35		1.00	0.78	1.29	
CVD	65-69	4.41	3.02	6.44	<.0001	4.35	2.77	6.84	.0006	5.00	3.45	7.25	<.0001	5.06	2.88	8.87	
	70-74	2.92	2.30	3.70		3.01	2.27	4.00		3.14	2.49	3.97		3.27	2.29	4.66	.0006
	75-79	1.93	1.62	2.29		2.08	1.68	2.58		1.97	1.66	2.34		2.11	1.64	2.71	
	80-84	1.27	1.00	1.63		1.44	1.05	1.98		1.24	0.97	1.59		1.36	0.96	1.94	
Smoking	65-69	1.55	1.34	1.79	<.0001	1.27	1.05	1.54	.32	1.60	1.39	1.84	<.0001	1.50	1.18	1.91	
	70-74	1.36	1.24	1.49		1.22	1.08	1.37		1.39	1.27	1.52		1.36	1.16	1.58	.06
	75-79	1.19	1.13	1.26		1.17	1.08	1.26		1.20	1.14	1.27		1.23	1.12	1.35	
	80-84	1.05	0.98	1.12		1.12	1.01	1.25		1.04	0.98	1.12		1.11	0.99	1.26	
Hypertension	65-84	1.07	0.98	1.17	.14	1.12	1.00	1.25	.06	1.15	1.00	1.32	.04	1.26	1.05	1.50	.01
Lipids	65-84	0.79	0.65	0.97	.02	0.80	0.63	1.02	.07	0.89	0.58	1.36	.59	0.86	0.49	1.52	.61

OR, adjusted odds ratios for cases relative to controls. LL, lower limit of 95% confidence interval. UL, upper limit of 95% confidence interval. Bipolar, bipolar disorder. Schizophrenia, schizophrenia spectrum disorder. Alcohol, alcohol dependence syndrome. AF, atrial fibrillation. HF, heart failure. IHD, ischemic heart disease. CVD, cerebrovascular disease. Smoking, any history of smoking. Lipid, hyperlipidemia or hypercholesterolemia. Age Group, dementia onset age, the presence of significant interactions between six mid-life risk factors and age at dementia index record in logistic modelling has resulted in adjusted odds ratio estimates for these six risk factors being provided for dementia outcomes in four age

categories. Sex, a sex-ischemic heart disease interaction was identified therefore separate odds ratios for males (M) and females (F) are provided for this risk factor. Conditional logistic regression models were constructed using all univariate risk factors together with all significant two-way interactions (p<0.15) between risk factors and i) age and/or ii) sex. Using backward selection all non-significant two-way interaction terms were removed from the model (p stay <0.05). Significant interactions remaining in the 'all dementia' model included: depression × age ($\chi 2$ =14.6; p<.0001), schizophrenia × age ($\chi 2$ =6.2; p= .01), alcohol × age ($\chi 2$ =5.2; p=.02), diabetes x age ($\chi 2$ =7.5; p=.006), cerebrovascular disease × age ($\chi 2$ =22.2; p<.0001), smoking × age ($\chi 2$ =18.5; p<.0001), ischemic heart disease × sex ($\chi 2$ =8.6; p=.003). Hypertension and lipids were kept in the adjusted model since they are both "well established" risk factors. All explanatory variables in the final adjusted model for 'all dementia' in the main body of the study were used in the three Sensitivity Analyses to enable ease of comparison.

(p= 0.13) and alcohol X age (p=0.24) interaction terms had become non-significant, even though the odds ratio estimates continued to reflect a decreasing effect of depression and alcohol in the older age groups. The number of matched case-control pairs in each age group used to estimate the Odds Ratio estimates in Table **2** are i) Main Study and Sensitivity Analysis Two (n=13,568), 846 pairs aged 65-69 years, 1,923 pairs aged 70-74 years, 4,338 pairs aged 75-79 years and 6,461 pairs aged 80-84 years, ii) Sensitivity Analysis One (n=6,446), 533pairs aged 65-69 years, 1,205 aged 70-74 years, 2,334 aged 75-79 years and 2,374 aged 80-84 years; iii) Sensitivity Analysis Three (n=4421), 305 pairs aged 65-69years, 693 aged 70-74 years, 1,439 aged 75-79 years and 1,984 aged 80-84 years.

When dementia sub-types were explored, some variation in association between psychiatric conditions and odds of developing the dementia sub-type were seen (Table **3**). Non-specific dementia had a very similar risk factor profile as 'all dementia'. Alzheimer's disease was associated with depression, schizophrenia and alcohol dependency in the younger age categories but not with bipolar and anxiety disorder. No vascular dementia controls had a history of bipolar disorder or schizophrenia so these factors could not be modelled and the other disorders were non-significant. In a post hoc analysis that allowed for removal of non-significant interactions (while keeping all main effects in the model), depression remained associated with risk of vascular dementia (OR 2.25, 95%CI 1.35, 3.74).

DISCUSSION

The major finding of this study was that after adjustment for several known medical risk factors five psychiatric conditions, depression, anxiety disorders, bipolar disorder, schizophrenia and alcohol dependency syndrome in mid-life were associated with dementia at ages 65-79. We employed a case-control study design to explore the impact of a range of psychiatric and medical disorders experienced during and before middle age on incident dementia in the state of Western Australia. In addition to a long duration of follow-up, steps were taken to ensure an adequate time gap between initial exposure to the chosen risk factors and the development of dementia. These data suggest that these five psychiatric conditions need to be added to the list of risk factors for dementia. This would increase the proportion of the population at risk for dementia from identifiable causes and increases the number possible targets of dementia prevention strategies [47].

Whilst the present findings can be considered to support previous research findings [3, 5, 18, 20, 25, 40], the strength of the evidence base varies considerably for each psychiatric condition and, to our knowledge, this is the first study to consider them together in the same population. The temporal sequence, the long follow-up and the substantial time gap between exposure and dementia provide strong evidence that each of these disorders may be on the causal pathway for dementia. There were differences in psychiatric risk factors when we explored dementia subtypes but the significance of these analyses is uncertain given that dementia diagnoses were based on clinical records from such a wide source and the consequently large number of cases classified as non-specific dementia and the considerable loss of power with less common psychiatric disorders. Nevertheless, depression was associated with both Alzheimer's disease and vascular dementia and schizophrenia with Alzheimer's disease.

Depression is known to be associated with cardiovascular risk factors mediated by poor self-care behaviours including reduced physical activity, obesity and smoking [48-50]. We adjusted for smoking in our analyses but were unable to correct for obesity or physical activity. This leads us to speculate as to whether depression increased dementia risk by a vascular mechanism which would be consistent with the vascular-depression-dementia hypothesis posited by Alexopoulos [51]. A similar explanation may operate in bipolar disorder, schizophrenia and anxiety disorders that are also associated with smoking, cardiovascular risk factors and associated medical conditions [49, 50, 52]. We were struck by the age pattern with depression, schizophrenia and alcohol abuse and how the pattern mirrors the relationship with diabetes, smoking, cerebrovascular disease and dementia. Whilst the psychiatric findings are independent of the medical conditions in these analyses, it may be that the pattern seen with all these disorders is consistent with a single aetiology possibly based on a vascular mechanism. Anxiety disorders frequently co-exist with depressive disorders and anxiety is known to render the management of depression and bipolar disorder more difficult [53] hence there could be an indirect impact on dementia risk. Bipolar disorder, schizophrenia and alcohol dependence substantially increased the risk of dementia although the numbers in the sample were small and the confidence intervals consequently large. There may be different additional mechanisms for dementia for each of these entities; the toxic nature of alcohol on the brain is well understood for example, and neurodegenerative mechanisms have been postulated for bipolar disorder and schizophrenia [54-57].

An alternative explanation is that psychiatric disorders and dementia are associated through shared risk factors. For example it has been shown that inflammation and immune activation can be a characteristic of depression [58] and increased levels of peripheral inflammatory markers are associated with increased risk for all-cause dementia [59]. Both disorders have been associated with insulin resistance [60] which has been associated with reduced hippocampal volume which may lead to increased vulnerability to dementia [61].

Table 3. Dementia Sub-Type Adjusted Odds Ratio Estimates for Mid-Life Risk Factor Exposure in a Matched Case-Control Study of Dementia in Western Australians aged 65-84 years, 2000-2009.

		Alzheimer's Dementia				Vascular Dementia				Non-specific Dementia			
		n=5565				n=1280				n=6043			
Exposure	**Age Group**	**OR**	**LL**	**UL**	***p* value**	**OR**	**LL**	**UL**	***p* value**	**OR**	**LL**	**UL**	***p* value**
Depression	65-69	2.03	1.19	3.45	.06	2.85	0.85	9.62	.67	2.86	1.56	5.25	.01
	70-74	1.62	1.16	2.25		2.54	1.18	5.44		2.04	1.40	2.99	
	75-79	1.29	1.03	1.61		2.26	1.35	3.76		1.46	1.16	1.84	
	80-84	1.02	0.74	1.41		2.01	0.98	4.12		1.04	0.77	1.41	
Bipolar	65-84	2.03	0.70	5.88	.19	-	-	-		6.25	2.13	18.36	.0009
Schizophrenia	65-69	6.60	1.36	32.16	.09	-	-	-		12.95	2.86	58.59	.06
	70-74	3.62	1.29	10.21		-	-	-		7.13	2.74	18.61	
	75-79	1.99	0.90	4.37		-	-	-		3.93	2.17	7.12	
	80-84	1.09	0.37	3.19		-	-	-		2.17	1.01	4.64	
Anxiety	65-84	1.08	0.81	1.45	.59	1.76	0.94	3.30	.08	1.60	1.20	2.14	.001
Alcohol	65-69	2.82	1.02	7.77	.22	1.60	0.31	8.25	.89	6.98	2.68	18.19	.04
	70-74	2.07	1.12	3.81		1.71	0.62	4.68		4.46	2.43	8.17	
	75-79	1.52	0.95	2.41		1.82	0.74	4.50		2.85	1.89	4.31	
	80-84	1.11	0.53	2.35		1.94	0.46	8.26		1.82	1.03	3.24	
Head Injury	65-84	1.16	0.87	1.55	.32	1.15	0.63	2.11	.65	1.41	1.08	1.84	.01
Diabetes	65-69	3.45	1.82	6.54	.09	3.23	1.25	8.32	.38	3.45	1.88	6.32	.07
	70-74	2.67	1.80	3.96		2.57	1.44	4.60		2.66	1.83	3.85	
	75-79	2.06	1.55	2.73		2.04	1.18	3.54		2.05	1.59	2.63	
	80-84	1.59	1.04	2.44		1.63	0.67	3.94		1.58	1.08	2.30	
AF	65-84	1.33	0.89	1.98	.16	1.33	0.62	2.86	.46	1.23	0.85	1.78	.28
HF	65-84	0.84	0.62	1.14	.26	1.49	0.81	2.74	.20	1.41	1.06	1.88	.02
IHD	65-84 M	0.90	0.56	1.47	.41	0.66	0.23	1.86	.31	0.51	0.32	0.80	.0005
	65-84 F	1.03	0.83	1.29		0.99	0.65	1.49		0.89	0.73	1.09	
CVD	65-69	1.50	0.80	2.81	.35	11.32	3.94	32.56	.009	6.26	3.26	12.02	.0007
	70-74	1.31	0.88	1.94		5.86	2.96	11.58		3.84	2.55	5.80	
	75-79	1.14	0.86	1.53		3.03	1.75	5.25		2.36	1.81	3.09	
	80-84	1.00	0.65	1.52		1.57	0.71	3.46		1.45	1.01	2.09	
Smoking	65-69	0.97	0.78	1.21	.65	3.25	2.08	5.08	.003	2.15	1.69	2.73	<.0001
	70-74	0.95	0.83	1.09		2.43	1.83	3.21		1.74	1.50	2.03	
	75-79	0.93	0.86	1.01		1.81	1.51	2.17		1.41	1.30	1.54	
	80-84	0.91	0.82	1.02		1.35	1.06	1.73		1.15	1.04	1.27	

(Table 3) contd….

		Alzheimer's Dementia				Vascular Dementia				Non-specific Dementia			
		n=5565				n=1280				n=6043			
Exposure	**Age Group**	**OR**	**LL**	**UL**	***p* value**	**OR**	**LL**	**UL**	***p* value**	**OR**	**LL**	**UL**	***p* value**
Hypertension	65-84	0.81	0.70	0.93	.004	1.57	1.17	2.12	.003	1.24	1.08	1.43	.003
Lipids	65-84	1.00	0.74	1.39	.95	0.66	0.35	1.24	.20	0.70	0.51	0.95	.02

OR, adjusted odds ratios for cases relative to controls. LL, lower limit of 95% confidence interval. UL, upper limit of 95% confidence interval. Bipolar, bipolar disorder. Schizophrenia, schizophrenia spectrum disorder. Alcohol, alcohol dependence syndrome. AF, atrial fibrillation. HF, heart failure. IHD, ischemic heart disease. CVD, cerebrovascular disease. Smoking, any history of smoking. Lipid, hyperlipidemia or hypercholesterolemia. The Alzheimer's and non-specific dementia conditional logistic regression models used the same model exposure variables and interactions as used in the 'All Dementia' model for the primary analysis given in Table 4. The vascular dementia model excluded bipolar and schizophrenia disorders as no controls in this subgroup had such an exposure. Depression, bipolar, schizophrenia, anxiety, alcohol, head injury, diabetes, ischaemic heart disease, hypertension and lipid exposures were considered to be present in either case or control subject if documented in linked health records before age 65 and at least 10 years prior to the reference date.

An important consideration for the interpretation of these results is that the psychiatric diagnoses were largely obtained from specialist psychiatric services and not from primary care sources. In Australia, most psychiatric conditions are managed within a primary care setting (possibly excepting psychoses) and referral to specialist psychiatric services is reserved for more severe or complex conditions, for example, only one in a thousand general practice contacts for depression are referred to hospital [62]. Consequently, the present data could be relevant solely for severe psychiatric conditions or, alternatively, they may underestimate the associated risks with dementia. We suspect that our study under-ascertained bipolar disorder as the reported life-time risk has been estimated at between 4.0 and 65.0 per 1000 population [63, 64] and the prevalence in our sample was lower (controls: 0.6 per 1000; cases: 4.3 per 1000). In contrast, we probably identified the majority of individuals with schizophrenia as our prevalence estimate (5.3 per 1000 individuals) was closer to published lifetime risk estimates (7.2 per 1000) [65]. For similar reasons, the true associated risk estimates of anxiety and alcohol dependence disorders could be substantially greater. These considerations and the reliance on hospital acquired data are also likely to be relevant on the estimates of the medical conditions and risk factors such as smoking. Many cases of diabetes and head injury would be expected to be managed in primary care whereas cardiovascular and cerebrovascular conditions are more likely to be managed in hospital.

The strengths of the present study include the population-based sample, the use of the Western Australian Data Linkage system that has been demonstrated to provide accurate hospital and mental health clinic data within known limitations for case ascertainment and the study design that permitted separation between risk factor exposure and dementia. The study does not rely on self-report and is therefore not subject to recall bias. The random selection of electoral roll controls was designed to reduce selection bias. The main limitations of the study include the use of health administrative datasets that relied on diagnoses made by a wide range of doctors of varying seniority and from a range of specialties that could not be verified. Previous studies have indicated that hospital registers have reasonable accuracy in detecting dementia cases [66, 67]. In addition, the accuracy of the recording of dementia subtype is uncertain as reflected by non-specific dementia being the most commonly recorded dementia type. Nevertheless, exploring dementia sub-types provided some insights into the potential pathophysiological basis for some of the associations if it is assumed that the cases given the vascular dementia or Alzheimer's diagnoses by attending medical staff were more or less likely to have evidence for a vascular etiology respectively. A problem with medical-record based case-control studies relates to incomplete documentation in medical records. Because we only used risk factor information recorded prior to the diagnosis of dementia or the corresponding reference date for the control, misclassification due to failure to document the existence of risk factors should be non-differential with respect to the risk factors under study. This would tend to bias any of the risk estimates toward unity. We were also unable to control for a range of potential confounders including low educational status, obesity, physical activity and Apo E associated with dementia. We have, however, considered the possibility that some subjects were not living in Western Australia during their mid-life years thereby potentially introducing biased estimates.The inclusion of all 13,568 case-control pairs regardless of look-back period may have led to biased odds ratio estimates. However, the results from the sensitivity analysis that included only 4,421 match-set pairs with at least 20 years of look-back demonstrated essentially similar results with respect to the magnitude of the estimates, although the increased risk due to depression and alcohol dependency became non-significant. This lack of statistical significance is probably due to the greatly reduced sample size. Nevertheless, the magnitude of the estimates from the sensitivity analysis tend to suggest that if the bias did exist due to including pairs regardless of look-back period, then its impact on risk estimates for the five common psychiatric conditions examined in this study are likely to be negligible.

In summary, severe mid-life depression, anxiety disorder, bipolar disorder, schizophrenia and alcoholic dependency disorder were found to be risk factors for late-life dementia. These psychiatric conditions need to be added to the list of potential risk factors in future studies of the pathophysiology and impact of dementia.

ABBREVIATIONS

AD = Alzheimer's disease

CI = Confidence interval

EDDC = Emergency Department Data Collection
HMDC = Hospital Morbidity Data Collection
ICD = International Classification of Disease
MHIS = Mental Health Information System
OR = Odds ratios

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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eAppendix 1. International Classification of Disease (ICD) Codes Used to Identify the Presence of Potential Risk Factors for Dementia in Western Australian Data Records for Calendar Period 1966 to 2009.

Risk Factors	ICD-8 Before 1978	ICD-9 1979-1987	ICD-9-CM 1988-June 1999	ICD-10-AM After July 1999
Psychiatric Disorders				
Unipolar (major) depression	296.0, 296.2, 296.9	296.1, 296.6, 296.8, 296.9	296.2x, 296.80, 296.82, 296.3x, 296.89, 296.90	F32-F32.8, F33
Dysthymia/ neurotic depression	300.4	300.4, 311	300.4, 311	F34.1, F32.9
Bipolar disorder	296.1, 296.3	296.2-5	296.4-7	F31
Schizophrenia spectrum disorder	295.x	295.x	295.x	F20, F21, F22, F25
Anxiety disorder	300.0	300.0	300.00 -300.09	F41
Alcohol dependence syndrome	303	303	303.x	F10.x
Heart Disease				
Ischaemic heart disease	410-414	410-414	410-414	I20-I25.x
Atrial Fibrillation	427.9	427.4	427.3x	I48
Heart Failure	427, 428, 402, 425, 429	428, 402, 425, 429	428.x, 402.x, 425.x, 429.x	I50, I11, I42, I43, I51
Cerebrovascular Disease				
Acute ischaemic stroke	432, 433, 436	362.3, 433.x, 434.x, 436	362.3, 433.x1, 434.x1, 436	H34.1, I63.x, I64.x
Intra-cerebral haemorrhage	431	431	431.x	I61.x
Sub-arachnoid haemorrhage	430	430	430.x	I60.x
Transient Ischaemic Attack	435	435	435.x	G45.x
Other				
Diabetes	250	250.x	250.xx	E10-E14
Essential Hypertension	401	401	401.x	I10
Past or current Smoking	-	305.1	V15.82, 305.1	Z72.0,Z86.43,F17
Elevated Lipids/cholesterol	-	272.0, 272.2, 272.4	272.0, 272.2, 272.4	E78.0, E78.2, E78.5
Head Injury	850 – 854, 800-803	850-854.x, 800-803.x	850-854.x, 800-803.x	S06.xx, S02.xx

eAppendix 2. Characteristics of 13,568 dementia cases and their 1:1 sex- and age-matched controls, Western Australia, Australia, 2000-2009.

		Cases		Controls	
		n	%	n	%
Sex	Males	5894	43.4	5894	43.4
	Females	7674	56.6	7674	56.6
Age (years)	62-64	-	-	104	0.8
	65-69	846	6.2	875	6.5
	70-74	1923	14.2	2112	15.6
	75-79	4338	32.0	4693	34.6
	80-84	6461	47.6	5363	39.5
	85-87	-	-	421	3.1
Dementia Type	Non-specific	6043	44.5	-	-
	Alzheimer's	5565	41.0	-	-
	Vascular	1280	9.4	-	-
	Mixed	680	5.0	-	-
Index Dementia Record	General Inpatient	8911	65.7	-	-
	Mental Health Inpatient	2063	15.2	-	-
	Mental Health Outpatient	1816	13.4	-	-
	Emergency Department	497	3.7	-	-
	Death record	281	2.1	-	-
First Depression Record	General Inpatient	110	16.8	54	15.5
	Mental Health Inpatient	346	52.7	160	45.9
	Mental Health Outpatient	200	30.5	135	38.7
First Bipolar Record	General Inpatient	4	6.7	0	0.0
	Mental Health Inpatient	28	47.5	4	44.4
	Mental Health Outpatient	27	45.8	5	55.6
First Schizophrenia Record	General Inpatient	5	4.3	0	0.0
	Mental Health Inpatient	36	30.1	8	28.6
	Mental Health Outpatient	76	65.0	20	71.4
First Anxiety Record	General Inpatient	102	26.9	59	28.9
	Mental Health Inpatient	201	53.0	77	37.8
	Mental Health Outpatient	76	20.1	68	33.3
First Alcohol Record	General Inpatient	98	40.7	29	36.7
	Mental Health Inpatient	128	53.1	43	54.4
	Mental Health Outpatient	15	6.2	7	8.9
Look-back Period (years)	No records available	327	2.4	610	4.5
	0 - 4	1161	8.6	942	6.9
	5-14	2644	19.5	2751	20.3
	15-29	6748	49.7	6761	49.8
	30-40	2688	19.8	2504	18.5

Age is age at time of index dementia record for cases and the age at the equivalent reference date for each matched control. Mixed dementia included cases with both an Alzheimer's dementia and a vascular dementia diagnostic code documented in health records. Look-back period is the number of years between each subject's first linked health record and their reference date.

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