The association of anxiety and depression with future dementia diagnosis: a case-control study in primary care

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Background. Depression is identified as a risk factor for dementia. Little research has been carried out on the importance of anxiety, despite strong evidence of co-morbidity with depression.

Objective. To examine the association of anxiety and depression with future dementia diagnosis.

Methods. This case-control study was set in the Consultations in Primary Care Archive. Cases (*n* = 400), were patients aged >65 years old. About 1353 controls were matched to cases by gender, practice, age group and year of case diagnosis. Read codes of risk factors for dementia were searched in patient records. The associations of prior consultations for anxiety and depression, with future diagnosis of dementia were determined using multivariable logistic regression.

Results. A past anxiety diagnosis was associated with a future dementia diagnosis [odds ratio 2.76 (95% confidence interval 2.11–3.62)]. The association of depression with dementia was attenuated by the high prevalence of anxiety within those who have depression. Including an interaction of depression and anxiety showed that having only depression was associated with future dementia diagnosis but a diagnosis of depression alongside anxiety did not increase the likelihood of a dementia diagnosis compared to having just an anxiety diagnosis.

Conclusion. Prior diagnosis of anxiety was strongly associated with dementia diagnosis after adjustment for other risk factors. The independent effect of depression was weaker compared to anxiety. Given the higher prevalence of anxiety primary care physicians should consider anxiety as well as depression as premorbid risk factors of dementia to improve early recognition and facilitate greater access to services.

Keywords. Anxiety, dementia, depression, epidemiology, primary care.

Introduction

The term 'dementia' describes a 'collection of symptoms including a decline in memory, reasoning and communication skills and a gradual loss of skills needed to carry out every day living.'[1] Approximately 700 000 people in the UK suffer from dementia, costing the economy £17 billion a year.[1] Over the next 30 years the number of people with dementia is forecast to double, with costs trebling to over £50 billion a year.[2] The rate of diagnosis of dementia is low and variable in the UK.[3] Estimations suggest that only one-third of people with dementia receive a formal diagnosis leading to a lower level of access to management interventions such as medication and social support that could improve outcome.[1,4] As there is no known cure for dementia the aim of current clinical management is to reduce the risk of developing dementia and minimise

its consequences. This principle underpins the National Dementia Strategy's public health campaign.[3]

Many risk factors have been identified in the literature.[5] One strong risk factor is premorbid depression. Prospective studies show an increase in risk for dementia if the person has or reports they have depression.[6–8] However, contradictory evidence exists on whether the relationship between depression and later dementia is similar in men and women. The PAQUID study found a positive association between dementia and depression in men only.[9] The CHSA (Community Health Status Assessment) however found that depression increased the risk of vascular dementia in both sexes.[10] Less is known about the role of premorbid anxiety despite evidence of close co-morbidity with depression and evidence that anxiety may be a predisposing factor for depression.[11,12] One recent prospective cohort study (Gallacher *et al.*[13])

reported that after adjustment for age, vascular risk factors and premorbid cognitive function, higher anxiety levels were significantly associated with cognitive impairment and non-vascular dementia in a male population. However they did not adjust for possible co-morbid depression and comment that further study is required to distinguish whether the association between anxiety and dementia is independent of the relationship between depression and dementia.

This study aimed to examine relative associations of a prior anxiety diagnosis, or a prior depression diagnosis, with future diagnosis of dementia in primary care. Recognition of predisposing factors for dementia should alert primary care physicians to the increased risk of dementia, in order to facilitate the early recognition and management of this disease.

Methods

Setting
The setting for this study is the Consultations in Primary Care Archive (CiPCA). CiPCA is a high quality, validated database, containing recorded consultation data from 13 general practices in North Staffordshire, UK from 1998. Ethical approval for the use of CiPCA was granted by the North Staffordshire Research Ethics Committee.[14,15] CiPCA contains information on all primary care consultations with these practices. CiPCA practices utilise Read codes to record consultation data, a common method in UK primary care. Read codes are used to record categories of symptoms and diagnoses. They make up a hierarchical 'thesaurus' stored by the computer. Clinical information is stored as data which is retrievable and analysable.[16]

Participants
Cases and controls were identified from the 10 practices which contributed consultation data to CiPCA for the entire study period (2000 to 2008). In 2008, the 10 practices had a registered population of 96 618 patients. Dementia cases were identified by a Read coded (codes available on request) primary care consultation (or documentation from specialist services) in the period 2003–08, with no prior Read code for dementia, from 2000 onwards and were aged 65 years or more at time of first diagnosis. Patients had to be fully registered at least 3 years prior to the date of dementia diagnosis and have consulted a primary care physician in the year preceding their diagnosis. This timeframe was chosen to allow for a 3-year run-in period (2000 to 2003) to ensure that only people with a newly coded diagnosis of dementia were included. Research has shown that patients may wait up to 3 years before consulting a primary care physician after their initial symptoms appear.[3]

Exclusion criteria for cases
The lower age limit of 65 years was chosen to coincide with the International Classification of Disease Version—10 definition of late-onset dementia. Patients with diagnostic Read codes of dementia subtypes including Lewy Body dementia, frontotemporal dementia and HIV associated dementia were also excluded as they have potentially different aetiologies.

Controls
Patients in the control group were randomly selected via The Statistical Package for Social Sciences (random number generation command, version 20, SPSS Inc., Chicago, IL). A ratio of between three and four controls to one case were frequency matched by age group at diagnosis, gender, practice and consultation in the same year as the case's first dementia diagnosis. The controls had no dementia diagnosis for the entire time period 2000–08, had to have registration at the practice for at least 3 years prior to the year of diagnosis of their matched case and had a recorded consultation in the year of diagnosis of the matched case. Matching factors were age and gender, due to the differences in the risk factors for dementia by gender and the rising incidence of dementia associated with age, and GP practice, due to possible differences between practices in socio-economic status and diagnosis or recording practice.

Risk factors
A review of the literature on risk factors for dementia was completed by the first author (CB). Two practicing primary care physicians (first author and last author) independently reviewed the risk factors to identify those factors accessible within routinely collected primary care records. The two reviewers then discussed the inclusion of the risk factors at a final consensus meeting. Read codes for each risk factor (available on request) were identified using the UKTC (UK Terminology centre) Clinical Terminology Browser. The Database of Raw Read codes was also hand searched for relevant Read codes to ensure that categories of codes were not missed. The risk factors identified using the above methods were alcohol misuse,[17–19] smoking,[20] obesity,[21,22] hypertension,[23] ischemic heart disease,[8] cerebrovascular disease,[24,25] hypotension,[5,26] dyslipidaemia,[27] diabetes,[8,28–30] anxiety[13] and depression.[7,9–11] The 'lifestyle' variables including alcohol misuse, smoking and obesity were found to be poorly coded (e.g. only 4 people had a Read code for smoking) and were not included in further analyses. Risk factor information was extracted from the primary care records for each case and control from 1 January 2000 up to the date of diagnosis for the cases.

Analyses
Unconditional logistic regression was used to assess both the unadjusted and adjusted association of each risk factor with dementia after controlling for the matched criteria, with odds ratios and 95% confidence

intervals reported. All risk factor variables were then entered in the fully adjusted analysis. Finally an interaction term of anxiety with depression was included in the adjusted model due to evidence that anxiety and depression often coexist clinically.[11,12] Multivariable analyses were also stratified by gender to assess whether any association between anxiety and depression with dementia was consistent between genders. The analyses were conducted using SPSS version 20.

Results

Four hundred cases of patients with a new dementia diagnosis were identified with 1353 controls. All cases were frequency matched with at least three controls (mean number of controls per case was 3.38); this number varied due to differences in number of eligible controls between practices particularly for the 92+ year group. The mean ages were 80.87 (SD 6.19) for controls and 81.40 (SD 6.5) for cases, 63% of the controls and 62% of the cases were female.

One hundred and twenty two (31%) of cases had a prior diagnosis of anxiety compared to 14% of controls. Prior diagnosis of depression was also higher in some cases (10% versus 5%). Half of those with a depression diagnosis also had a recorded diagnosis of anxiety. Unadjusted analysis showed the presence of a prior Read code for anxiety [OR 2.76 (95% CI 2.11–3.62)], depression [OR 2.19 (95% CI 1.44–3.31)] and cerebrovascular disease [OR 1.97 (95% CI 1.42–2.73)] and increased the odds of a later dementia diagnosis. An anxiety diagnosis remained significantly associated with future dementia [OR 2.67 (95% CI 2.01–3.54)] after adjustment, but depression was not significantly associated [OR1.54 (95% CI 0.99–2.39)], (Table 1). However examination of the interaction analysis showed that having a depression diagnosis alone was significantly associated with dementia [OR 2.54 (95% CI 1.39–4.63)] compared to those with neither anxiety or depression but that this association was less strong than the effect of having depression with anxiety [OR 2.85 (95% CI 1.60–5.07)] or having only anxiety [OR 2.97 (95% CI 2.21–4.00)], (Table 2).

Of the other risk factors, a previous diagnosis of cerebrovascular disease [OR 2.18 (95% CI 1.55–3.07)] increased the odds of dementia but a previous diagnosis of hypertension or dyslipidaemia decreased the odds of dementia [adjusted OR 0.69 (95% CI 0.54–0.87)] and [adjusted OR 0.68 (95% CI 0.46–0.99)] respectively.

Stratification by gender (Table 3) indicated that the association of depression only with dementia was higher in males than females. There was less of a difference between genders on the association of anxiety only and both depression and anxiety with future dementia.

TABLE 1   *Unadjusted and adjusted associations of risk factors with future diagnosis of dementia*

Risk factor	Cases with risk factor present n (%)	Controls with risk factor present n (%)	Odds ratio (95% confidence interval)*	Multivariable analysis. Odds ratio (95% CI)[a]
Anxiety	122 (30.5)	192 (14.2)	2.76 (2.11–3.62)	2.67 (2.01–3.54)
Depression	41 (10.3)	67 (5.0)	2.19 (1.44–3.31)	1.54 (0.99–2.39)
Cerebrovascular Disease	66 (16.5)	127 (9.4)	1.97 (1.42–2.73)	2.18 (1.55–3.07)
Diabetes	51 (12.8)	162 (12.0)	1.08 (0.77–1.52)	1.20 (0.84–1.71)
Dyslipidaemia	43 (10.8)	200 (14.8)	0.69 (0.48–0.99)	0.68 (0.46–0.99)
Hypertension	174 (43.5)	720 (53.2)	0.68 (0.54–0.85)	0.69 (0.54–0.87)
Hypotension	10 (2.5)	31 (2.3)	1.04 (0.50–2.17)	0.87 (0.40–1.88)
Ischemic heart Disease	68 (17)	249 (18.4)	0.93 (0.69–1.26)	0.89 (0.65–1.22)

*Controlling for age, gender, practice and year of case diagnosis of dementia.
[a]Controlling for all variables presented.

TABLE 2   *Association of having diagnosis of both depression and anxiety on future diagnosis of dementia*

Risk factor	Case n (%)	Control n (%)	Multivariable analysis. Odds ratio (95% CI)[a]
No anxiety or depression	258 (64.4)	1129 (93.4)	1.00
Anxiety alone	101 (25.3)	157 (11.6)	2.97 (2.21–4.00)
Depression alone	20 (5.0)	32 (2.4)	2.54 (1.39–4.63)
Anxiety and depression	21 (5.3)	35 (2.6)	2.85 (1.60–5.07)

[a]Multivariable model controlling for age, gender, practice, year of case diagnosis of dementia and all risk factors and including interaction of anxiety with depression.

TABLE 3   *Association of depression and anxiety with diagnosis of dementia by gender*

Risk factor	Case *n* (%)	Control *n* (%)	Multivariable analysis. Odds ratio (95% CI)[a]
Female			
No anxiety or depression	152 (60.6)	666 (79.9)	1
Anxiety alone	73 (29.1)	115 (13.8)	1.71 (0.79–3.70)
Depression alone	11 (4.4)	26 (3.1)	2.95 (2.07–4.22)
Anxiety and depression	15 (6.0)	27 (3.2)	2.65 (1.35–5.23)
Male			
No anxiety or depression	106 (71.1)	463 (89.2)	1
Anxiety alone	28 (18.8)	42 (8.1)	3.12 (1.78–5.47)
Depression alone	9 (6.0)	6 (1.2)	5.91 (1.98–17.6)
Anxiety and depression	6 (4.0)	8 (1.5)	3.90 (1.21–12.57)

[a]Multivariable model controlling for age, gender, practice, year of case diagnosis of dementia, and all risk factors and including interaction of anxiety with depression.

Discussion

This study considered the association of diagnoses of anxiety and depression with the future outcome of a dementia diagnosis. A history of anxiety independently increased the odds of being diagnosed with dementia in a primary care setting. Having depression without anxiety was also significantly associated with being diagnosed with dementia, however, having a diagnosis of depression alongside anxiety did not increase the likelihood of a dementia diagnosis compared to having just an anxiety diagnosis.

Interpretation
Anxiety was independently associated with a future dementia diagnosis and was more prevalent within the cohort compared to depression. Half of those with depression also had anxiety diagnoses. This is suggestive that anxiety represents a more important risk factor for dementia than had been previously thought, and along with depression represents an affective risk component that could be screened for within primary care.

One potential explanatory factor is that anxiety was being diagnosed by primary care physicians in patients experiencing mild cognitive impairment (MCI), preceding a later diagnosis of dementia. This concurs with previous work, which suggested that anxiety in patients with MCI does strongly predispose to progression to a dementia diagnosis.[31] Gallacher *et al*. also showed that high trait anxiety was an independent risk factor for developing cognitive impairment and non-vascular dementia.[13] In contrast a study by Bierman *et al*., did not find a long-term effect for cognitive decline in patients with anxiety.[32] They measured self-reported symptoms of anxiety using HADS-A (The Hospital Anxiety and Depression Scale—Anxiety). However their analysis used the scale score of the HADS-A which may not be reflective of the clinically relevant levels of anxiety that may incur a Read code from a primary care physician.

One physiological explanation why chronic anxiety may contribute to cognitive decline is Sapolsky's glucocorticoid cascade hypothesis. This hypothesis suggests that high levels of glucocorticoids, brought about by prolonged stress from anxiety and depression, can lead to neurotoxicity and atrophy within the hippocampus which is associated with memory processes.[33] It seems clinically reasonable to postulate that, in a similar way to depression, patients may experience and present with anxiety symptoms as a direct cause of the insight they have into their early experiences of MCI. Gallacher *et al*. however felt that the long run-in period of their study meant that their results were unlikely to be explained by this hypothesis and prefer an explanation including a common biological pathway linking anxiety, depression and dementia (possibly serotonergic).[13]

This study demonstrated differences in the association of dementia and depression between male and females. Prevalence of depression in the male control group was lower than in the female controls. Lower consultation rates and later presentation of depression in men may be a confounding factor, as the severity of depression in females and males may differ. A male patient presenting with depression may therefore be a 'red flag' when considering a possible diagnosis of dementia. 'Vascular depression' has been postulated as an accelerant of dementia and cardiovascular disease being more common in men may explain this study's finding. As depression in women is more common and the cause of their depression more heterogeneous, such an association in this group would be masked.[9] Cerebrovascular disease was a significant risk factor for dementia as would be expected from previous studies.[24,25] Hypertension and dyslipidaemia appeared to decrease the odds for developing dementia, an unexpected result although the results were close to non-significance. It is likely that the patients identified had controlled disease (unlike in population studies) and were on medication that may represent a confounding factor.[34–38] As expected,

ischemic heart disease was not a significant risk factor.[8] The results for diabetes (a well recognised independent risk factor)[8,30] were also unexpectedly non-significant.

Strengths and limitations
By setting the study in the consulting primary care population, using routinely recorded data, the findings are applicable to the primary care population. The sample size was large however, it did not include patients who do not use primary care services. This study is based on anxiety and depression presented by patients rather than self-reported. It is possible that some diagnoses were not coded or mis-coded, although the quality control measures in place around the database should decrease this risk. Due to the nature of the Read code system and the anonymised dataset we were unable to obtain information on the severity of dementia or risk factors such as lifestyle variables, as well as background information such as socio-economic status.

The selection criteria for the study subjects were specific to ensure only patients with late-onset dementia were included; however it was not possible to differentiate between dementia subtypes. To reduce the chance of risk factor variables not being identified in the premorbid time frame, the cases had to have at least 3 years registration prior to the date of dementia diagnosis and had to have consulted in the year preceding the dementia diagnosis, as did the matched controls. A total of 662 people with a dementia code had to be excluded from the cohort as they lacked 3 years continuous registration prior to their diagnosis. This loss of potential cases decreased the sample size but increased the internal validity of the study as only people with a theoretically 'new' diagnosis of dementia were included. The majority of these 662 would likely have a prior history of dementia. This patient movement is likely to represent the migratory nature of patients with dementia and reflect the findings of Rait *et al*. where more than twice the number of people with dementia than without dementia moved between practices.[39] It is possible that the study could have excluded patients with the more severe and advanced cases of dementia (i.e. those not able to function in their own homes and needing to move into residential or nursing care) and hence not be entirely representative of the true community sample of people with dementia.

This study also only looked at co-morbidities in the recent past (up to 8 years) before dementia was diagnosed, meaning it could not look at long-term effects of disease. It was also not possible to analyse all recognised risk factors due to lack of Read coded data found in primary care records, such as Apolipoprotein $_E$4 status. Furthermore even though this study used at least a 3-year exposure timescale before diagnosis, we cannot be completely certain of the temporal relationship between exposure and disease outcome using a case-control design because of the insidious and latent aspects of dementia.[22] Further prospective studies are needed to investigate the influence of prior depression and anxiety as a cause for dementia. The findings presented are based on the frequency matching of cases and controls rather than perfect matching for two reasons. First, the frequency matching selection increased the power and efficiency of the study. Second, previous studies[40,41] found that unconditional logistic regression with adjustments of match variables can derive similar estimates with the conditional logistic regression where perfect matching of cases and controls were required.

Conclusions

This study supports observations that anxiety independently increases the likelihood of later being diagnosed with dementia. In order to support current national guidelines and strategies to improve the rate of earlier diagnosis of dementia and hence access to holistic management, clinicians should be vigilant to symptoms of cognitive impairment especially in older patients with a past history of anxiety, depression and cerebrovascular disease.

Acknowledgements

Declaration

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