Symptoms of anxiety or depression and risk of fracture in older people: The Hertfordshire Cohort Study

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Abstract

Background—Use of psychotropic drugs has been linked with an increased risk of fracture in older people, but there are indications that the conditions for which these drugs were prescribed may themselves influence fracture risk.

Aim—To investigate the relation between symptoms of anxiety and depression and risk of fracture in older people.

Design—Prospective cohort study.

Methods—1087 men and 1050 women aged 59-73 years completed the Hospital Anxiety and Depression Scale (HADS). Data on incident fracture during an average follow-up period of 5.6 years was collected through interview and a postal questionnaire.

Results—Compared to men with no or few symptoms of anxiety (score ≤ 7 on the HADS anxiety subscale), men with probable anxiety (score ≥ 11) had an increased risk of fracture: after adjustment for age and potential confounding factors, the odds ratio (OR) (95% confidence interval) was 4.03 (1.55, 10.5). Men with possible anxiety (score 8-10) did not have an increased risk of fracture: multivariate-adjusted OR was 1.04 (0.36, 3.03). There were no associations between levels of anxiety and fracture risk in women. Few men or women had probable depression at baseline (score ≥ 11 on the HADS depression subscale). Among men with possible depression (score 8-10) there was an increased risk of fracture that was of borderline significance: multivariate-adjusted OR 3.57 (0.99, 12.9). There was no association between possible depression and fracture risk in women.

Conclusions—High levels of anxiety in older men may increase their risk of fracture. Future research needs to replicate this finding in other populations and investigate the underlying mechanisms.

Keywords

anxiety; depression; fracture

Introduction

There is considerable evidence to link use of psychotropic drugs, such as antidepressants, antipsychotics, anxiolytics or sedatives, with an increased risk of fracture in older people.[1-6] The underlying mechanisms are unclear. One explanation might be that such drugs affect postural balance leading to a greater likelihood of falls[7] – there is evidence from a randomized controlled trial that withdrawal of psychotropic drugs reduces the risk of falling

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in older people.[8] Another explanation might be that some such drugs have an adverse influence on bone physiology and strength. Recent findings suggest that selective serotonin re-uptake inhibitors may decrease bone mineral density (BMD) in animals[9] and humans.[1]

However, there are indications that the pharmacological properties of psychotropic drugs may be less important in determining fracture risk than the mental disorder or symptoms of psychological distress for which these drugs are being taken. A substantial reduction in the use of benzodiazepines among older people in New York after a statewide policy change on prescribing in its Medicaid program showed no change in the incidence of hip fracture.[10] Consistent with this, a case-control study of fractures in the Danish population found that an increase in fracture risk was present with both current and past use of anxiolytics or sedatives, suggesting that it was the underlying condition for which the drugs were prescribed that was responsible rather than the drugs themselves.[11] Further indications of the importance of the underlying mental disorder in influencing fracture risk came from a study of lithium use and fractures among patients in the UK General Practice Research Database: here, current users of lithium had a decreased risk of fracture – for reasons that remain unclear – but past use of lithium was associated with an increased risk and this rose with length of time since the drug was discontinued.[12]

Studies that have examined whether common mental disorders increase risk of fracture have concentrated on depression. Their findings have been inconsistent. Higher levels of depressive symptoms were linked with increased incidence of hip fractures in people aged 25-74 years in NHANES 1,[13] and with an increased risk of vertebral and non-vertebral fracture[14] or any fracture[15] in two prospective study of older women, but in a cohort of >93,000 postmenopausal women depressive symptoms were not associated with risk of hip, wrist or spine fractures and only weakly linked with an increased likelihood of fractures at 'other' sites,[16] and in a large Canadian cohort of older people there was no indication that those with higher levels of depressive symptoms had an increased risk of fracture.[17] Very little is known about the relation between symptoms of anxiety and fracture risk.

The aim of this study was to examine the associations between symptoms of anxiety and depression and subsequent risk of fracture in a cohort of community-dwelling older men and women, and to explore whether the use of anxiolytics, sedatives or antidepressant drugs affects these associations.

Materials and Methods

In 1998-2004, men and women born in Hertfordshire between 1931 and 1939 and still living in the county were recruited to take part in a cohort study to evaluate interactions between the genome, the intrauterine and early postnatal environment, and adult lifestyle in the aetiology of chronic disorders of later life. A description of the setting up of the Hertfordshire Cohort Study has been published previously.[18]

In total, 7,106 men and women born in the county between 1931-1939 and still living there were traced using the NHS Central Register. Of these, 3225 (45%) people consented to be visited at home. A research nurse administered a structured questionnaire that enquired about medical history, history of fractures since age 45 years, current medications, cigarette smoking, alcohol consumption, and current or last job. A question about history of falls in the last year was included in the home interview part way through the study; falls data were therefore only collected for 2339 people. Information on current or most recent job (in the case of married women, their husband's job) was later used to derive social class categorized in six groups according to the OPCS Occupational Classification scheme. Diet was assessed using a food frequency questionnaire (FFQ) that was based on the EPIC questionnaire.[19]

The FFQ includes 129 foods and food groups and was used to assess an average frequency of consumption of the listed foods over a 3-month period preceding the home interview. Calcium intake was calculated by multiplying the frequency of consumption of a portion of each food by its calcium content according to the UK national food composition database or manufacturers' composition data.[20] Use of calcium supplements over the preceding 3 months was also recorded and calcium intake from dietary supplements was calculated using the frequency and dose reported by the participant and manufacturers' composition data. Physical activity was assessed using a previously validated questionnaire that asked about frequency of gardening, housework, climbing stairs and carrying loads in a typical week.[21] Symptoms of depression and anxiety were assessed using the Hospital Anxiety and Depression Scale (HADS).[22] This scale was designed to identify cases of depression and anxiety using two sub-scales each of seven items. Scores range from 0 to 21, with higher scores indicating more severe symptoms. The authors of the HADS suggest cut-points for scores according to possible (8-10) or probable (11) depression or anxiety. Subsequently, 2997 of those interviewed at home (93%) attended a clinic where handgrip strength was measured three times on each side with a Jamar dynamometer. The highest of these six measurements was used to characterise muscle strength. Participants who were eligible – in this case, not taking drugs known to alter bone metabolism, such as bisphosphonates - were invited to return for bone density measurements. In total, 966 people attended for measurement of BMD (bone mineral density) using dual energy X-ray absorptiometry (DXA) at the lumbar spine and proximal femur using a Hologic QDR 4500 instrument (Vertec Scientific, Reading, UK). Measurement precision error, expressed as coefficient of variation, was 1.55% for lumbar spine BMD, 1.45% for total femur and 1.83% for femoral neck BMD for the Hologic QDR 4500.

Information on fractures that occurred after the initial survey was obtained from two sources. In 2004-5, a subset of participants resident in East Herts took part in a survey of musculoskeletal health during which they were asked "Have you broken any bones since we saw you last?" In 2007, all surviving participants who took part in the initial survey were sent a postal questionnaire in which they were asked the same question. Data from these two sources were then combined into a single variable to indicate the incidence of fracture since the initial survey. In total, 2147 people (67% those who took part in the initial survey) provided information about fractures that had occurred after that date. Compared to people who provided information on incident fractures at follow-up, men and women with missing data had a higher BMI (p=0.01), were less physically active (p<0.001), more likely to be a smoker (p<0.001), and to be depressed (p<0.001). Men who had missing data on incident fracture were more likely to be anxious (p=0.01), but this difference was not present in women (p=0.383). There were no differences in age, history of fracture or falls, or alcohol and calcium intake between those with and without data on incident fracture.

The study had ethical approval from the Bedfordshire & Hertfordshire Local Research Ethics Committee and the West Hertfordshire Local Research Ethics Committee. All participants gave written informed consent.

Statistical analysis

We used the t-test, chi-square test, and Kruskal-Wallis test to examine differences in baseline characteristics between men and women with and without an incident fracture. We used logistic regression to examine the relation between anxiety and depression and risk of fracture, controlling for potentially confounding factors (age, BMI, physical activity, dietary calcium intake, smoking status, alcohol consumption, use of bisphosphonate drugs, and history of previous fracture). As use of antidepressant or anxiolytic/sedative drugs might reduce symptoms, thereby potentially obscuring any association between symptoms of depression or anxiety and fracture, we also carried out analyses in the subsets of people who

were not using antidepressants or anxiolytic/sedative drugs at baseline. The main analyses are based on 2137 people (1087 men and 1050 women) with complete data on incident fracture, anxiety and depression, and the covariates. Finally, we carried out some additional analyses in subsets of participants who had data on BMD, history of falls and grip strength at baseline in order to investigate whether these factors helped explain the association between anxiety and fracture. We present results for men and women separately as preliminary analyses suggested that the relation between probable anxiety and fracture risk was stronger in men than in women (p for interaction term=0.07).

Results

During the follow-up period, 47 men and 116 women experienced an incident fracture. Table 1 shows the baseline characteristics of the men and women in this study according to whether they had an incident fracture. In both sexes, incident fracture occurred more frequently in people with a history of previous fracture. In men, fracture occurred more frequently in those with a history of smoking and in those with higher anxiety scores. There were borderline significant associations in men between younger age and lower BMI and greater frequency of fracture. In women, fracture occurred more frequently in those with a higher BMI, in those with a history of falling in the year prior to the baseline survey, and in those who were taking antidepressant drugs; there was a borderline significant association between older age and greater frequency of fracture. No other characteristics were significantly associated with incident fracture in either sex.

Anxiety

Table 2 shows the odds ratios (95% confidence intervals) for having a fracture in men and women separately according to symptoms of anxiety at baseline. Results are shown adjusted for age and then with further adjustment for BMI, physical activity, alcohol intake, smoking status, bisphosphonate use, and history of previous fracture at baseline. Men who had probable anxiety at baseline, as defined by a score of 11 or more on the HADS anxiety subscale, had a significantly increased risk of having a fracture during the follow-up period compared to those no or few symptoms of anxiety (score of 7 or less): after adjustment for age, the OR (95% CI) was 3.52 (1.40, 8.33). Further adjustment for potential confounding factors strengthened this association: multivariate-adjusted OR (95% CI) 4.03 (1.55, 10.5). Only 18 men were taking anxiolytic drugs at baseline. Use of this drug was not significantly associated with risk of fracture (age-adjusted OR 1.42 (0.18, 11.0), but exclusion of men taking these drugs strengthened the association between symptoms of anxiety and fracture: multivariate-adjusted OR (95% CI) 4.18 (1.60, 10.9). Men whose score on the HADS anxiety subscale indicated possible anxiety (score 8-10) did not have an increased risk of fracture. In women, there was no significant difference in risk of fracture according to levels of anxiety at baseline, though there was a suggestion of higher risk amongst women with probable anxiety at baseline: age-adjusted OR (95% CI) 1.30 (0.71, 2.39). The use of anxiolytic/sedative drugs was not associated with fracture risk in women: age-adjusted OR 1.10 (0.49, 2.50) and the association between symptoms of anxiety and fracture risk changed very little when women taking anxiolytic/sedative drugs at baseline were excluded.

In the subset of people who had reported a history of fracture since age 45 at the baseline interview (141 men, 247 women), we examined whether anxiety was associated with an increased risk of having a second fracture. Out of the 141 men with a past history of fracture, 6 had scores suggestive of probable anxiety at baseline and 2 of these experienced a second fracture during follow-up. Compared to men with no or few symptoms of anxiety at baseline, men with probable anxiety were over 6 times more likely to experience a second fracture: age-adjusted OR (95% CI) 6.55 (1.01, 42.4). In the 247 women with a past history

of fracture, there was no indication that probable anxiety increased the risk of having a second fracture: age-adjusted OR (95% CI) 1.01 (0.35, 2.94).

Depression

Table 3 shows the odds ratios (95% confidence intervals) for having a fracture in men and women separately according to symptoms of depression at baseline. Numbers of men or women with probable depression were very small and there were too few cases of incident fracture among them for separate analysis. In men, there was a borderline association between having possible depression at baseline (scores on the HADS depression subscale 8-10) and risk of fracture: age-adjusted OR (95% CI) 3.19 (0.90, 11.1). This was strengthened by adjustment for potential confounding factors: multivariate-adjusted OR (95% CI) 3.57 (0.99, 12.9). There were too few men taking antidepressants drugs at baseline to allow calculation of the risk of fracture associated with use of these drugs, but exclusion of these men slightly strengthened the association between possible depression and risk of fracture: multivariate-adjusted OR (95% CI) 3.74 (1.03, 13.6). In women, there was no significant association between having possible depression at baseline and risk of fracture: age-adjusted OR (95% CI) 1.35 (0.56, 3.28). There was a significant association in age-adjusted analysis between use of antidepressant drugs and risk of fracture in women (OR 2.30 (1.11, 4.77) but this was no longer significant after multivariate adjustment OR 2.03 (0.95, 4.35). The relation between possible depression and risk of fracture changed very little when women who were taking antidepressants at baseline were excluded.

Potential mechanisms

In subsets of men who had data on BMD, grip strength or history of falls at baseline, we investigated potential mechanisms that might explain why men with higher levels of anxiety had an increased risk of subsequent fracture. In age-adjusted regression analysis based on 347 men who had DXA scans, there was no significant linear trend between levels of anxiety and total femoral BMD (p for trend = 0.26) or lumbar spine BMD (p for trend = 0.78). There was a weak linear association between levels of anxiety and grip strength in age-adjusted analysis (p for trend = 0.04), such that men with higher anxiety levels had poorer grip strength. There was a stronger association between anxiety and falls. Likelihood of having fallen in the past year rose with increasing symptoms of anxiety: in a subset of 939 men with these data, compared to men with no or few symptoms of anxiety, the age-adjusted OR (95% CI) for having a history of falls was 1.34 (0.76, 2.35) in men with possible anxiety and 2.10 (1.06, 4.17) in men with probable anxiety. Adjustment for history of falls did not attenuate the association between probable anxiety and incident fracture, but we may have had too few cases for accurate assessment of this inter-relationship: in the subset of 624 men with information on all three factors, there were only 23 cases of incident fracture and none of these occurred among the 6 men who had probable anxiety and a positive history of falls at baseline.

Discussion

In this prospective study of people aged 59 to 73 years, men who had probable anxiety at baseline, as defined by a score of 11 or more on the HADS anxiety subscale, were over four times more likely to experience a fracture during the follow-up period than those who had few or no symptoms of anxiety, after adjusting for potential confounding factors. This association was strengthened by the exclusion of men taking anxiolytic or sedative drugs at baseline. Men with possible anxiety (score 8-10 on the HADS anxiety subscale) did not have an increased risk of fracture. There was no significant association between levels of anxiety and risk of fracture in women. There were too few people with probable depression at baseline for separate analysis, but possible depression (score 8-10 on the HADS depression

subscale) was associated with an increased risk of fracture in men that was of borderline statistical significance. There was no such association in women.

We were unable to identify any previous studies that had examined the relation between anxiety *per se* and subsequent risk of fracture. Existing evidence from prospective studies of common mental disorders and fracture risk is almost exclusively about depression. This evidence is inconsistent, with three large studies finding that risk of fracture was increased in people with higher levels of depressive symptoms,[13-15] but two other studies - equally large - finding no such association.[16, 17] One study of over 18,000 older women found that those who gained high scores on an index of mental distress – a measure that included items on symptoms of anxiety and depression – had an increased risk of subsequent fracture compared to those with low scores.[23] One mechanism that could plausibly underlie any link between anxiety or depression and subsequent fracture is bone loss. There is now a considerable body of evidence that people with depression show dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis.[24] There has been less research on the relation between anxiety and the HPA axis, but some studies have found higher salivary cortisol levels in people with anxiety disorders compared to those without such symptoms.[24, 25] This dysregulation of the HPA axis may have implications for osteoporosis: in small samples of older people, higher plasma cortisol was associated with lower baseline BMD and greater rate of bone loss over a four-year period.[26, 27] In the present study, we examined whether lower BMD might account for the association between probable anxiety and fracture in men, but we found no evidence of a trend between increasing symptoms of anxiety and lower BMD.

Another mechanism that could potentially help to explain associations between anxiety or depression and risk of fracture in older people is a propensity to fall. In prospective studies of patients with dementia and of older people in general, high levels of anxiety or depression have been linked with an increased risk of falling [28-31] We found that men with high levels of anxiety were over twice as likely to report a history of falling in the past year as those with few or no symptoms of anxiety. It is impossible to be certain about the direction of effect in this cross-sectional analysis: the anxiety might be a consequence rather than a cause of the fall. Nevertheless, previous evidence that anxiety can predict falls, plus the observation in this study that muscle strength tended to be poorer in the men with higher anxiety, suggests that susceptibility to falling may be the main explanation for our finding that men with high levels of anxiety has an increased risk of fracture.

The fact that we found a strong association between probable anxiety and fracture in men but not in women is surprising. The epidemiology of non-vertebral fractures in men is still poorly understood,[32] so the extent to which risk factors are common to both sexes remains unclear.[33] Men are more likely than women to die after hip fracture,[34] suggesting greater physical frailty at the time of fracture. It may be that differences in frailty between men and women in our study play some part in our findings. It is also possible that sex differences in behavioural responses to anxiety might play a part. Further studies of the role of anxiety in fracture risk in other populations of older men and women are needed to determine whether the sex difference found here is real. Given the small size of our sample, it could be a chance finding.

Our study has a number of limitations. Firstly, the fractures were self-reported and have not been validated. Self reports are subject to errors of recall. However, in a large study that assessed the validity of self-reported non-spine fracture using medical records, in men and women aged over 60 only 8% of self-reported fractures proved to be false-positives and an even smaller proportion turned out to be false-negatives.[35] Secondly, our sample size is small. At the baseline survey, only a small number of participants had symptoms suggestive

of probable depression so we unable to examine whether these were linked with subsequent risk of fracture. Furthermore, numbers with fracture during the follow-up period were small, particularly among men. This resulted in wide confidence intervals around some of our estimates of the relation between anxiety levels and fracture risk and made it impossible for us to establish with certainty whether susceptibility to falls or osteoporosis was the main underlying mechanism. Thirdly, we had no information on the date of fractures so we were unable to draw any inferences on the timing of fracture. Finally, our study is based on older people with an average age of 66 years; whether our findings apply to younger populations is uncertain.

In summary, we have shown that older men, but not women, with probable anxiety have a greater than four-fold risk of experiencing a fracture that was not explained by use of anxiolytic or sedative drugs. The reasons for this link are unclear but it seem likely that falls, and perhaps the neuromuscular ability to protect against falls,[36] play a major part. Future research will need to replicate this finding in other populations of older men and women and establish the underlying mechanisms.

Acknowledgments

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Table 1

Baseline characteristics of the men and women in the study according to incident fracture during follow-up

	Men (n=1087)			Women (n=1050)		
	Incident fracture (n=47)	No fracture (n=1040)	P value	Incident fracture (n=116)	No fracture (n=934)	P value
Age (yrs), mean (SD)	64.9 (2.66)	65.7 (2.91)	0.081	66.9 (2.60)	66.4 (2.72)	0.065
BMI (kg/m^2), median (IQR)	25.5 (23.8, 28.5)	26.7 (24.6, 29.2)	0.091	27.8 (24.5, 31.9)	26.8 (23.8, 29.9)	0.039
Habitual physical activity[1], mean (SD)	61.2 (16.3)	61.5 (15.0)	0.926	59.4 (16.4)	59.7 (15.0)	0.838
Alcohol intake (units/wk), median (IQR)	10.5 (3.25, 23)	9.05 (3, 19.9)	0.519	3 (0.51, 7.32)	2.76 (0.5, 7)	0.382
Calcium intake (mg/wk), median (IQR)	8134 (6664, 10014)	8323 (6952, 9941)	0.809	7999 (6579, 9958)	7860 (6709, 9446)	0.739
Smoking status, no (%)						
Never	8 (17.0)	398 (38.3)	0.002	70 (60.3)	592 (63.4)	0.402
Ex	35 (74.5)	508 (48.9)		38 (32.8)	256 (27.4)	
Current	4 (8.51)	134 (12.9)		8 (6.90)	86 (9.21)	
Had fracture since age 45, no (%)	13 (27.7)	128 (12.3)	0.002	52 (44.8)	175 (18.7)	<0.001
Had fall in the last year, no (%)	3 (13.0)	88 (14.6)	0.826	38 (34.9)	171 (20.3)	0.001
HADS depression score, no (%)			0.185			
0-7	44 (93.6)	1009 (97.0)		109 (9.3.4)	886 (94.9)	0.739
8-10 (possible depression)	3 (6.38)	24 (2.31)		6 (5.17)	36 (3.85)	
11 (probable depression)	0	7 (0.67)		1 (0.86)	12 (1.28)	
HADS anxiety score, no (%)						
0-7	37 (78.7)	908 (87.3)	0.014	85 (73.3)	712 (76.2)	0.667
8-10 (possible anxiety)	4 (8.51)	91 (8.75)		17 (14.7)	133 (14.2)	
11 (probable anxiety)	6 (12.8)	41 (3.94)		14 (12.1)	89 (9.53)	
Taking antidepressants, no (%)	0	18 (1.73)	0.363	10 (8.62)	37 (3.96)	0.022
Taking anxiolytics/sedatives/, no (%)	1 (2.13)	17 (1.63)	0.796	7 (6.03)	50 (5.35)	0.760
Taking bisphosphonate drugs, no (%)	0	3 (0.29)	0.712	2 (1.72)	28 (3.00)	0.437)

[1] Standardised score ranging from 0 to 100 derived from frequency of gardening, housework, climbing stairs and carrying loads in a typical week. Higher scores indicate greater level of activity

[2] Data on history of falls were collected part way through the study so are available for a subset only; percentages with a history of falls are based on the following numbers: men with no fracture n=599, men with fracture=23; women with no fracture=842, women with fracture=108)

Table 2

Odds ratios (95% confidence intervals) for risk of fracture during follow-up according to symptoms of anxiety at baseline in men and women

HADS Anxiety score	Men (n=1087)			Women (n=1050)		
	No of cases/ No at risk	OR (95% CI), age-adjusted	OR (95% CI), fully-adjusted[1]	No of cases/ No at risk	OR (95% CI), age-adjusted	OR (95% CI), fully-adjusted[1]
0-7	37/945	1.0	1.0	85/797	1.0	1.0
8-10, possible anxiety	4/95	1.06 (0.37, 3.04)	1.04 (0.36, 3.03)	17/150	1.09 (0.63, 1.90)	1.06 (0.60, 1.87)
11, probable anxiety	6/47	3.52 (1.40, 8.33)	4.03 (1.55, 10.5)	14/103	1.30 (0.71, 2.39)	1.38 (0.73, 2.59)

[1] Adjusted for age, BMI, physical activity, alcohol intake, smoking status, calcium intake, use of bisphosphonate drugs, and history of fracture at baseline.

Table 3

Odds ratios (95% confidence intervals) for risk of fracture during follow-up according to symptoms of depression at baseline in men and women

HADS Depression score	Men (n=1087)			Women (n=1050)		
	No of cases/ No at risk	OR (95% CI), age-adjusted	OR (95% CI), fully-adjusted[1]	No of cases/ No at risk	OR (95% CI), age-adjusted	OR (95% CI), fully-adjusted[1]
0-7	44/1053	1.0	1.0	109/995	1.0	1.0
8-10, possible depression	3/27	3.19 (0.9, 11.1)	3.57 (0.99, 12.9)	6/42	1.35 (0.56,3.28)	1.42 (0.56, 3.59)
11, probable depression	0/7	-	-	1/13	-	-

[1] Adjusted for age, BMI, physical activity, alcohol intake, smoking status, calcium intake, use of bisphosphonate drugs, and history of fracture at baseline