Sex- and Age-Specific Incidence of Fractures in Mental Illness: A Historical, Population-Based Cohort Study

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Objective: To estimate risks of fracture at any site, and at sites linked with osteoporosis, in mentally ill adults compared with the general population.

Method: We created a community-based cohort by using the U.K. General Practice Research Database, with follow-up from January 1987 through April 2005. We investigated age- and sex-specific fracture risks in psychotic illness (N = 4283), nonpsychotic affective disorder (N = 95,228), and any other psychiatric condition (N = 49,439). Comparison cases were subjects with no psychiatric code (N = 182,851); age-stratified (18–44 years, 45–74 years, ≥ 75 years) relative risks (RRs) were estimated by Poisson regression. Outcomes were incident cases of fracture at any site, at the hip, and at the distal radius.

Results: Among all mentally ill women, highest RRs of fracture at any site were in the youngest age group, whereas the strongest effects in men were with older age. The highest raised risk of any fracture occurred in premenopausal women with psychotic disorders (RR = 2.5, 95% CI = 1.5 to 4.3). Hip fracture rates were raised in elderly women and men with psychiatric illness and were especially high in women (RR = 5.1, 95% CI = 2.7 to 9.6) and men (RR = 6.4, 95% CI = 2.6 to 16.1) with psychotic disorders at ages 45 to 74 years. Data were too sparse to estimate RR of distal radius fracture, although risk was modestly (but significantly) higher among women with any mental illness in each age group than the reference population, i.e., women with no history of psychiatric disorder.

Conclusion: Raised risks of fracture in mental illness are likely to be explained by a range of mechanisms. Further research is needed to elucidate these mechanisms and to inform the development of targeted interventions.

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It is now well recognized that patients with mental illness are less likely to have a physical illness diagnosed[1–3] or medically managed.[3] However, in recent years a growing number of physical problems have been identified in patients with psychiatric illness, including the metabolic syndrome and osteoporosis. This article focuses on general rates of fracture in the mentally ill, including osteoporotic fracture. Although osteoporotic fracture occurs rarely in people before they reach middle age,[4] 3 studies have reported a significant increase in the risk of osteoporotic hip fracture in psychiatric patients.[5–7] There is also growing evidence of an association between reduced bone mineral density in patients with schizophrenia[8–10] and possibly other medicated psychiatric patient groups.[11–15] The postulated mechanism for such associations has been hypogonadism, which may occur as a result of prolactin-raising antipsychotic drugs. As osteoporotic fractures are common in the growing elderly population, a small increase in the risk of fracture could have considerable public health impact.

It is also possible that psychiatric patients are at increased risk of fractures in general, yet only 1 study has examined the risk of any fracture[16]: in that study, a moderately raised risk of any fracture was reported in people in contact with psychiatric health-care services exposed to psychotropic medication rather than in those with a particular diagnosis of mental illness. It is therefore not clear whether patients with psychiatric illness are actually at increased risk of osteoporotic and/or nonosteoporotic fractures.

In the present study, we wished to extend these previous findings and to address the key clinical questions of whether or not people with mental illness are at greater

Table 1. Diagnostic Categories Investigated Using the U.K. General Practice Research Database Dataset

Diagnostic Category[a]	N	Diagnoses Included
Psychotic illness	4,283	Schizophrenia and other psychotic disorders
		Manic and bipolar mood disorders and disturbances
		Disturbances in thinking and perception
Nonpsychotic affective disorder	95,228	Anxiety disorders and symptoms
		Depressed mood disorders and disturbances
		Mood disorders and disturbances NEC
		Suicidal and/or self-injurious behavior
All other psychiatric conditions	49,439	All others

[a]The diagnostic categories are hierarchical and sum to a total of 148,950 exposed patients diagnosed with any psychiatric disorder.
Abbreviation: NEC = not elsewhere classified.

risk of fractures per se[14] and whether risks are confined to a particular age, sex, or diagnostic group. We chose to compare the age-specific all-site and hip and wrist fracture rates in women and men having any mental disorder with those in healthy population controls. Hip and wrist fractures are typically associated with osteoporosis and increased risks in such fractures are likely to reflect underlying decreases in bone mineral density. We therefore hypothesized that (1) mentally ill women and men would have higher age-specific rates of all-site and hip and wrist fractures than healthy controls, (2) higher age-specific relative risks (RRs) for hip and wrist fracture would be observed in those exposed to prolactin-raising antipsychotic drugs, and (3) age-specific RRs for fracture, all site and site specific, would be especially high among women and men with psychotic disorders.

METHOD

The Study Cohort

Exposed subjects (N = 148,950) were patients older than 18 years and registered with a practice belonging to the U.K. General Practice Research Database (GPRD) from January 1987 through April 2005 with at least 1 psychiatric diagnosis recorded in the dataset; the unexposed group (N = 182,851) were all patients older than 18 years with no such code ever recorded. The exposed group was split into 3 broad diagnostic categories (Table 1): (1) psychotic illness, (2) nonpsychotic affective disorder, and (3) all other psychiatric conditions. These groups were mutually exclusive and hierarchical in that order.

The GPRD was set up in 1987 and contains computerized primary care records of approximately 5% of the U.K. population.[15] Data recorded include prescription details, clinical events, preventive care provided, specialist referrals, and hospital admissions and their major outcomes. The data collected are audited regularly and the participating general practices subjected to a number of quality checks, including internal validation by cross-checking within practices and by comparisons with national statistics.[17] Only practices that comply with this quality control (i.e., are up-to-research standard) are retained within the database. The data are representative of the general population in the United Kingdom (almost all patients are registered with a general practitioner, as this is the only way to be referred to secondary care); however, there is a bias toward larger-group practices.

A validation study has shown that the classification of schizophrenia and nonaffective psychosis is accurate and sensitive.[18] Further validation of psychiatric diagnoses has found that few cases of psychiatric disorder treated in secondary care settings are not recorded by general practitioners (H.H., personal communication).

Subjects were assigned a study entry date according to their registration with a GPRD practice. If patients were registered before the date of their practice's entry into the GPRD reporting system, the latter was applied as their entry date. Entry dates ranged from January 1987 through April 2005. Study exit dates were also assigned according to whichever came first, the date when the patient left the practice or when the practice last reported to the GPRD. These dates ranged from January 1987 to May 2005.

Exposure to prolactin-raising antipsychotic drugs was defined as any record of a patient's prescription for benperidol, chlorpromazine, droperidol, flupenthixol, fluphenazine, haloperidol, methotrimeprazine, pericyazine, perphenazine, pimozide, prochlorperazine, promazine, risperidone, sulpiride, thioridazine, trifluoperazine, or zuclopenthixol.

Fracture Outcomes

Age was stratified as follows: 18 to 44 years, 45 to 74 years, and 75 years and older. Age-/sex-specific fracture rates were calculated for the following sites: (1) all sites, (2) hip (i.e., hip, neck of femur, or pelvis), and (3) distal radius (i.e., Colles' fracture or unspecified radius fracture; hip and radial fractures are associated with osteoporosis). There were insufficient events to enable investigation of risks of vertebral fractures, the other main type of osteoporotic fracture. Many vertebral fractures are asymptomatic and remain undetected, making the definition of vertebral fracture problematic.[17]

Statistical Methods

All analyses were conducted using Stata software (StataCorp, College Station, Tex.). In order to investigate the broad range of outcomes of interest for our research question (i.e., age-, sex-, and site-specific fracture rates in mental illness), we opted for a cohort design rather than a series of case control studies. For each outcome, age-/sex-specific rates were calculated for first fracture episodes coded within patients' observation periods. The

Table 2. Age-Specific Relative Risks of Fracture at All Sites in Patients Diagnosed With Psychiatric Disorders

	Female				Male			
Diagnostic Category	N	Rate[a]	Relative Risk[b]	95% CI	N	Rate[a]	Relative Risk[b]	95% CI
Any psychiatric diagnosis								
18–44 y	756	4.1	1.59	1.43 to 1.76	716	7.2	1.32	1.21 to 1.44
45–74 y	1789	9.3	1.39	1.30 to 1.49	733	5.9	1.40	1.27 to 1.53
≥ 75 y	1482	25.2	1.39	1.28 to 1.51	309	10.9	1.77	1.48 to 2.12
Psychotic illness								
18–44 y	14	6.3	2.53	1.49 to 4.32	23	6.2	1.18	0.78 to 1.78
45–74 y	58	12.6	1.87	1.44 to 2.44	27	7.4	1.91	1.30 to 2.79
≥ 75 y	52	22.4	1.41	1.06 to 1.88	9	11.1	1.90	0.96 to 3.74
Affective disorder								
18–44 y	577	4.3	1.56	1.39 to 1.74	438	7.6	1.37	1.23 to 1.52
45–74 y	1262	9.1	1.41	1.31 to 1.52	426	6.0	1.41	1.26 to 1.58
≥ 75 y	784	27.2	1.49	1.35 to 1.65	129	12.7	2.12	1.68 to 2.67
Other psychiatric conditions								
18–44 y	111	3.3	1.45	1.18 to 1.79	211	6.6	1.30	1.13 to 1.50
45–74 y	378	9.6	1.35	1.20 to 1.51	246	5.6	1.36	1.18 to 1.56
≥ 75 y	525	22.8	1.30	1.16 to 1.46	152	10.0	1.63	1.30 to 2.03

[a]First-episode fracture rates per 1000 person-years at risk in exposed subjects.
[b]Relative risks estimated by Poisson regression adjusted for calendar year period and finer subdivisions within reported age strata.

total time between study entry and exit dates was calculated for each patient. If applicable, this person-years denominator was truncated at date of first fracture (at all sites or at specific sites, depending on the outcome of interest). Time-dependent exposure variables were created, with exposure commencing on date of first coding for any psychiatric disorder or specific diagnostic category.[19,20] Age- and sex-specific RRs of fracture were estimated using Poisson regression of aggregated person-years data, with no significant evidence of overdispersion.[21] All RRs were adjusted by 5-year age bands and time period (1987–1994 vs. 1995–2005). Further analyses were conducted to adjust for practice; the RRs and their CIs were not materially changed in these models, inferring that practice was not a confounder in this study as in other GPRD studies. We could not adjust for other important confounders because they were unmeasured, or levels of missing data were high. For example, alcohol and smoking data were only available for 70.5% and 78.5% of all subjects, respectively; quantity of consumption was not recorded, and these data were usually only recorded on registration.

RESULTS

Table 2 shows the age- and sex-specific RRs of fracture at all sites in adult patients previously diagnosed with psychiatric disorders. The RRs were significantly elevated across all age/sex strata and diagnostic categories, except for men with psychotic disorders at ages 18 to 44 years and 75 years and older (the lack of significant effects in these strata may be due to low statistical power). The effect sizes were modest, with RRs being mostly less than 2. Among mentally ill women, the greatest RRs were in the youngest age stratum, whereas in mentally ill men, the strongest effects were seen in the oldest group. These patterns in age-specific effects by sex were generally consistent across psychiatric diagnostic categories.

Compared with the other diagnostic categories, higher RRs were observed in women aged younger than 75 years and diagnosed with psychotic disorders. Women with psychotic disorder in the youngest age group (18–44 years) had the highest RR (N = 14, RR = 2.5, 95% CI = 1.5 to 4.3) of fracture at any site. The all-site fracture rates in younger women and men with psychotic disorders were similar (around 6 per 1000), whereas in the healthy group, younger men had considerably higher rates than younger women (5 per 1000 vs. 2 per 1000).

Relative risks of hip fracture are shown in Table 3. In the youngest age group, these events were rare; these effects were not estimable for people aged younger than 45 years and diagnosed with psychoses. In patients with any psychiatric disorder, the risks of hip fracture were significantly elevated in women aged 45 to 74 years and 75 years and older and men aged 75 years and older. Although event numbers were small, RRs greater than 5 were observed in men and women aged 45 to 74 years and diagnosed with a psychotic disorder (women: N = 11, RR = 5.1, 95% CI = 2.7 to 9.6; men: N = 5, RR = 6.4, 95% CI = 2.6 to 16.1). The effect sizes were smaller in elderly women and in men with psychotic disorders.

Distal radius fracture was also investigated as an osteoporotic fracture outcome (Table 4). Risks of fracture at this site were significantly elevated in all age groups among all mentally ill women. This was not the case for men with any mental disorder, although the number of events in this group was much smaller in men than in women. With such small numbers of events, we were unable to assess evidence of higher fracture rates at this site in women or men diagnosed with psychotic disorders.

Table 3. Age-Specific Relative Risks of Hip Fracture in Patients Diagnosed With Psychiatric Disorders

	Female				Male			
Diagnostic Category	N	Rate[a]	Relative Risk[b]	95% CI	N	Rate[a]	Relative Risk[b]	95% CI
Any psychiatric diagnosis								
18–44 y	9	0.0	1.40	0.56 to 3.48	5	0.0	0.81	0.31 to 2.16
45–74 y	161	0.8	1.90	1.49 to 2.42	39	0.3	1.40	0.93 to 2.08
≥ 75 y	542	8.6	1.61	1.38 to 1.87	108	3.7	2.13	1.54 to 2.95
Psychotic illness								
18–44 y	1	0.4	…	…	0	…	…	…
45–74 y	11	2.3	5.12	2.73 to 9.63	5	1.3	6.41	2.55 to 16.11
≥ 75 y	19	8.1	1.50	0.93 to 2.42	3	3.6	2.17	0.67 to 7.07

[a]First-episode fracture rates per 1000 person-years at risk in exposed subjects.
[b]Relative risks estimated by Poisson regression adjusted for calendar year period and finer subdivisions within reported age strata.

Table 4. Age-Specific Relative Risks of Distal Radius Fracture in Patients Diagnosed With Psychiatric Disorders

	Female				Male			
Diagnostic Category	N	Rate[a]	Relative Risk[b]	95% CI	N	Rate[a]	Relative Risk[b]	95% CI
Any psychiatric diagnosis								
18–44 y	71	0.4	1.63	1.17 to 2.27	29	0.3	1.15	0.76 to 1.76
45–74 y	340	1.7	1.15	1.00 to 1.33	48	0.4	1.25	0.88 to 1.78
≥ 75 y	262	4.2	1.21	1.00 to 1.46	15	0.5	1.19	0.59 to 2.41
Psychotic illness								
18–44 y	1	0.4	…	…	1	0.3	…	…
45–74 y	7	1.5	0.90	0.43 to 1.91	2	0.5	1.85	0.45 to 7.53
≥ 75 y	8	3.4	1.11	0.54 to 2.27	0	0.0	…	…

[a]First-episode fracture rates per 1000 person-years at risk in exposed subjects.
[b]Relative risks estimated by Poisson regression adjusted for calendar year period and finer subdivisions within reported age strata.

Table 5. Age-Specific Relative Risks of Fracture at All Sites in Patients Diagnosed With Psychotic Disorders and Treated With Prolactin-Raising Antipsychotic Medications[a]

Variable	N	Rate[b]	Relative Risk[c]	95% CI
Female				
18–44 y	11	6.7	2.74	1.50 to 4.98
45–74 y	46	13.1	1.94	1.44 to 2.60
≥ 75 y	40	25.1	1.49	1.08 to 2.05
Male				
18–44 y	15	5.8	1.09	0.66 to 1.81
45–74 y	18	7.4	1.92	1.20 to 3.06
≥ 75 y	9	17.3	3.02	1.54 to 5.95

[a]N = 2874.
[b]First-episode fracture rates per 1000 person-years at risk in exposed subjects.
[c]Relative risks estimated by Poisson regression adjusted for calendar year period and finer subdivisions within reported age strata.

Table 6. Age-Specific Relative Risks of Hip Fracture in Patients Diagnosed With Psychotic Disorders and Treated With Prolactin-Raising Antipsychotic Medications[a]

Variable	N	Rate[b]	Relative Risk[c]	95% CI
Female				
18–44 y	1	0.6	…	…
45–74 y	10	2.7	6.19	3.21 to 11.97
≥ 75 y	15	8.6	1.64	0.96 to 2.79
Male				
18–44 y	0	0.0	…	…
45–74 y	2	0.8	4.12	1.00 to 16.96
≥ 75 y	3	5.6	3.57	1.10 to 11.63

[a]N = 2874.
[b]First-episode fracture rates per 1000 person-years at risk in exposed subjects.
[c]Relative risks estimated by Poisson regression adjusted for calendar year period and finer subdivisions within reported age strata.

Tables 5 and 6 show fracture rates and RRs among patients treated with prolactin-raising antipsychotic medication (N = 2874). For fractures at all sites (Table 5), the RRs were somewhat higher in this subgroup than in all patients with psychotic disorder (Table 2). Events were rather sparse for assessing risks of hip fracture in this group; even so, the RRs in women and in men were again highest at 45 to 74 years.

DISCUSSION

This is the first study of a large population-based community sample to report that having a mental illness increases the risk of sustaining any fracture compared to the healthy general population. The highest increased risk of any fracture occurred in young (premenopausal) women with psychotic disorders, and this risk appeared somewhat greater if these women had been treated with prolactin-raising antipsychotic medication. Numbers were too few to assess whether premenopausal young women with psychotic disorders treated with prolactin-raising antipsychotics have more osteoporotic fractures. Among mentally ill women, the highest RRs for any fracture were in the youngest group, whereas the strongest effects for men were seen in the oldest group. These age- and sex-specific patterns were generally consistent across psychiatric diag-

noses. Our main finding of moderately raised risk of any fracture in the mentally ill is consistent with the only comparable population-based study,[16] although the sample in that study consisted of psychiatric hospital contacts rather than a broader community sample as was the case in our dataset.

Women diagnosed with any mental illness also showed higher overall rates of site-specific osteoporotic fracture than well women. Consistent with the general population, rates of osteoporotic fracture were too rare in women with psychotic disorder younger than 45 years to generate RR estimates. Hip fractures were elevated in women older than 45 years with any mental illness, whereas men with mental illness had more hip fracture only after the age of 75 years. Women (RR = 5.1) and men (RR = 6.4) with psychotic disorder appeared to have a greatly elevated risk of hip fractures between ages 45 and 75 years, although the absolute number of events was small; wrist fracture was too rare to estimate in psychotic disorder. These findings are consistent with Howard et al.,[7] who found higher increased risk of osteoporotic hip fractures in men with psychotic disorders and in those treated with prolactin-raising antipsychotics. Our data support the view that being diagnosed with psychotic disorder and receiving treatment with a prolactin-raising antipsychotic elevate risk of a fracture at any site, especially in young women and older (≥ 75 years) men. This elevated risk may be due to hypogonadism induced by prolactin-raising antipsychotics, which would be particularly apparent in young ill women compared with female controls but then, as exposure continues, would have a greater impact on older male patients than older women, as female controls would also be hypogonadal and male controls less so.

However, our study also found an increased risk of all-site fractures; these are unlikely to be osteoporotic. Possible mechanisms leading to these fractures may include exposure to other drugs, such as tricyclic antidepressants (which can lead to postural hypotension), benzodiazepines, and other psychotropic medicines causing sedation. Strikingly, young women with psychotic disorder had comparable rates of all-site (as opposed to osteoporotic) fracture to men with psychosis of the same age (around 6 per 1000) and to healthy young men, and they had 3 times the rate seen in healthy young women (2 per 1000). It could be that young women with psychotic disorder are similarly exposed to violence or assault or to intoxication or risk-taking behavior as (healthy) young men. This possibility is supported by the fact that some female psychiatric populations are at particularly high risk of homicide.[22]

Limitations

Although the overall sample size in our study is large, some of the subgroup analyses lacked statistical power. Misclassification of diagnosis is possible, though validation studies, e.g., Nazareth et al.,[18] suggest this is not a major problem in the GPRD. There are a number of other known risk factors for fractures among patients with mental illness that may be acting as confounders, including inadequate exercise and exposure to sunshine, poor nutrition, cigarette smoking, and polydipsia. These risk factors occur in patients with chronic mental disorders, particularly psychotic disorders, and are associated with low bone mineral density.[5–7] Other mechanisms may also be relevant in causing fracture; for example, neuroleptic medications are known to cause sedation, orthostatic hypotension, and extrapyramidal side effects, which may predispose some patients to falls.[7] We were unable to look at duration of treatment, duration of illness, or severity of illness, which may have an important impact on fracture risk behavior in some groups. We were also unable to examine other possible confounders, either because of the high prevalence of missing data (body mass index, alcohol, smoking data) or because relevant data are not available, e.g., levels of exercise, sunlight exposure, vitamin D levels, and assaults or major trauma. In addition, medication may be prescribed in secondary care (psychiatric services), particularly initially, and we were therefore unable to examine whether fractures were more likely in the initial phase of treatment (when hypotension may be of relevance). Underrecording is likely, as there was a lower prevalence of antipsychotic drugs prescribed in this population than one might expect. Finally, some patients may have been prescribed non–prolactin-raising antipsychotic medication because of a previous history of high prolactin levels on antipsychotic medication or because of a medical cause of hyperprolactinemia. Any such bias should reduce the likelihood of a significantly increased RR in the analysis examining patients taking prolactin-raising antipsychotics; we found an increased RR. If there is a selection bias, therefore, this is likely to lead to an underestimation of the size of the increased risk. In addition, in our view, it is unlikely that any selection bias would be large because the sample spans a very long time period.

Clinical Implications

We have found evidence of high risk of any fracture in young mentally ill women, and of osteoporotic hip fracture in all mentally ill women, and men aged 45 to 74 years; and these risks may be especially elevated in those treated with prolactin-raising antipsychotics. Our data, and those of Vestergaard et al.,[16] suggest that fractures in the mentally ill, or those exposed to a broad range of psychoactive medication, are likely to be associated with mechanisms that include hyperprolactinemia, sedation, hypotension, intoxication from alcohol/drugs, and possible increased likelihood of exposure to violence and trauma. A recently conducted U.S. study suggests that rates of detection and treatment of osteoporosis are lower in women with schizophrenia aged 45 years and older than in women of the same age in the general

population.[23] In the general population, most cases of osteoporosis are asymptomatic, and, as routine screening does not occur, fractures are the clinical marker of this disease. Our data suggest that management of all mentally ill individuals (not just those with psychotic disorder) should include longitudinal assessment of gonadal function, bone mineral density, and screening for osteoporosis as well as ongoing advice about the importance of nutrition and exercise. In the oldest and youngest age groups, exposure to violence, risk of falls, effects of sedation, and the cumulative effects of lifestyle choices and poor nutrition may put those with mental illness at particular morbid risk compared to the well population.

Future Research

We have highlighted age- and sex-specific all-site fracture risks in mentally ill populations. Future research should examine preventive measures in the highest risk groups and attempt to examine mechanisms of risk.

Drug names: chlorpromazine (Thorazine, Sonazine, and others), droperidol (Inapsine and others), haloperidol (Haldol and others), pimozide (Orap), prochlorperazine (Compro and others), risperidone (Risperdal), trifluoperazine (Stelazine and others).

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