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Severe Mental Illness as a risk factor for recorded diagnosis of osteoporosis and fragility fractures in people aged 50 and above: retrospective cohort study using UK primary care data

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ABSTRACT

Background: Severe Mental Illness (SMI) has been associated with reduced bone density and increased risk of fractures, although some studies have shown inconsistent results.

Aim: Examine the association between SMI and recorded diagnosis of osteoporosis (OP) and fragility fracture (FF) in people aged ≥50years.

Design and Setting: Population-based cohort study; UK Primary care.

Method: We used anonymised primary care data (IQVIA Medical Research Database). Patients with a diagnosis of SMI aged 50-99y (2000-2018) were matched to individuals without SMI. We used Cox Proportional Hazards models to estimate Hazard Ratios (HR) and 95% Confidence Intervals (95%CI). We stratified analyses by sex and age, accounting for social deprivation, year, smoking, alcohol, and Body Mass Index (BMI).

Results: In total 444,480 people were included (SMI N=50,006; unexposed N=394,474). In men, diagnosis of SMI increased the likelihood of OP diagnosis, with differences mainly observed amongst the youngest (50-54y:HR=2.12;95%CI 1.61-2.79) and oldest (85-99y:HR=2.15;95%CI 1.05-4.37), and also increased the risk of FF across all ages. In women, SMI increased the risk of OP diagnosis only in those aged 50-54y:HR=1.16;95%CI 1.01-1.34, but increased the risk of FF across all ages. There were more than twice as many men with SMI with FF records than with OP diagnosis: FF:OP=2.10, compared to FF:OP=1.89 in men without SMI. The FF:OP ratio was 1.56 in women with SMI vs. 1.11 in women without SMI.

Conclusion: SMI is associated with increased likelihood of fragility fractures and osteoporosis underdiagnosis. Interventions should be considered to mitigate the increased risk of fractures in people with SMI.

Keywords: electronic health records, fragility fracture, osteoporosis, primary care, severe mental Illness.

HOW THIS FITS IN:

- The physical health of people with Severe Mental Illness (SMI) is often neglected, and this group of patients have higher rates of premature mortality
- Severe Mental Illness has been associated with reduced bone mineral density and increased risk of fractures
- We demonstrated that a diagnosis of SMI is a risk factor for fragility fractures in both men and women, accounting for age, social deprivation, smoking, alcohol, and body mass index
- Our data suggest that osteoporosis is underdiagnosed both in men and women with SMI (with a relatively more pronounced effect in women with SMI compared to non-SMI), as well as in men without SMI

- Interventions should be considered to screen for osteoporosis and mitigate the increased risk of fractures in people with SMI

BACKGROUND

The incidence of fractures has increased substantially in recent decades. Globally, in 2019, there were 178 million new fractures, 455 million prevalent cases of acute or long-term symptoms of a fracture and 25.8 million years lived with disability[1]. A significant proportion of these are fragility fractures (FF), due to osteoporosis (OP). The global prevalence of osteoporosis is estimated at 18.3%, with a significantly higher prevalence in women[2]. The economic burden of FF is significant, costing approximately £4 billion/year in the UK[3]. Hip fractures are associated with the highest mortality and healthcare costs[4].

Previous analysis of UK primary care data has demonstrated large differences in the incidence of FF by sex and age[5]. Our recent analysis of routinely collected primary care data demonstrated high incidence rates of FF in oldest age groups and women, underdiagnosis of osteopenia, and higher incidence of FF in people living in socially deprived areas, with remarkable effects in men[6].

Severe Mental Illness (SMI) represents a spectrum of mental health diagnoses, including schizophrenia, bipolar disorder and 'other psychosis', associated with significant mortality[7,8,9], disability[10,11], and health service costs[12]. People with SMI are at a greater risk of poor physical health and have a higher premature mortality than the general population[13,14], and excess morbidity associated with social deprivation[15].

Schizophrenia has been associated with reduced bone mineral density (BMD)[16,17] and increased risk of fractures[18]. It is not clear whether this association is due to antipsychotic medication, lifestyle factors, or both[19]. Many antipsychotic drugs increase prolactin levels as a side effect, leading to an increase in osteoclast activity not compensated by osteoblast activity[20].

In a 2012 systematic review, 15 of 16 studies reported lower BMD or higher prevalence of osteoporosis in at least one subgroup of schizophrenia patients compared to those without schizophrenia, but results were inconsistent across measured areas; higher fracture risk was associated with schizophrenia in 2/2 studies, and 3/4 studies with antipsychotics[21]. A 2007 UK case-control study using data from General Practice Research Database (GPRD) found that prolactin-raising antipsychotics were independently associated with hip fracture, but schizophrenia was not[22]. On the contrary, a 2008 Canadian population-based study found that, although antipsychotics did not significantly increase the risk of osteoporotic fractures, schizophrenia diagnosis did in a fully adjusted model[23].

Thus, there remains some discordance across studies regarding the association between FF and SMI. Most studies have focussed on the use of antipsychotic medication and there is little research on the role of other factors. We already know that SMI is associated with physical inactivity[24], poor nutrition[25], smoking[26], alcohol[27], and low vitamin D[28], which can all contribute to lower BMD. Moreover, there is little research on the recording of osteoporosis diagnosis in people with SMI. Given additional barriers that people with SMI commonly face

preventing them from seeking help[29], we hypothesise that BMD measurement and fracture risk assessment in primary care take place less often in people with SMI compared to the general population.

The objectives of the present study were: i) to estimate the incidence of recorded OP diagnosis and FF in people with SMI aged ≥50 years in the UK; ii) to compare the incidence of recorded OP diagnosis and FF between people aged ≥50 years with SMI and those without, accounting for age, sex, social deprivation, smoking, alcohol, and Body Mass Index (BMI).

METHODS

Data source

We used data provided as a part of routine primary care (IQVIA Medical Research Database (IMRD)). Approximately 98% of the UK population is registered with a GP[30]. The IMRD is a primary care database of >20 million patients in the UK, where GPs record medical diagnoses and symptoms using Read codes[31]. All data are fully anonymised and representative of the UK population in terms of age, sex, practice size and geographical distribution[32]. Social deprivation is recorded in IMRD using the Townsend index, stratifying the population in quintiles of deprivation[33].

Design

Longitudinal population-based cohort study.

Study population

We included all patients aged ≥50 years registered with IMRD participating practices between 01/01/2000 and 31/12/2018 who had a minimum of 12 months of follow-up data. We excluded practices that did not meet standards for data recording during the study period, i.e. Acceptable Mortality Reporting (AMR)[34] and Acceptable Computer Usage (ACU)[35]. Study entry was defined as the latest date of patient's registration with the practice, when they turned 50 years old, or 01/01/2000. The start of the follow-up period was 12 months after study entry, thus we excluded individuals who died or left before the start of the follow-up period. The end of follow-up was set as the earliest of the outcome event date, the patient's date of death, the patient's transfer out of the practice or the last date the practice contributed data to IMRD.

Definition of variables

The explanatory variable was SMI, defined by a Read code of schizophrenia, bipolar disorder or other psychosis (based on our previous validation study)[36] (**Appendix 1**). The outcome variables were: a) 1st recorded diagnosis of OP; b) 1st recorded FF, based on Read code (code lists published previously[6]). Prevalent cases of SMI were included (SMI diagnosed before outcome event). The demographic (age, Townsend quintile of deprivation, calendar year) and lifestyle (smoking, alcohol, body mass index (BMI)) covariates were treated as categorical

variables (age: 5-year bands, year: 6-year intervals, definition of lifestyle covariates: **Supplementary Table 1**, alcohol code list: **Appendix 2)**.

Statistical analysis

We used Exposure Density Sampling (EDS) to identify a comparison cohort. This is an approach to dynamic matching with respect to a rare exposure occurring over time. For every exposed individual, unexposed individuals are sampled at the time of exposure from those who are still at risk of an event and not exposed at that point in time. Hence, a sample of individuals (yet unexposed) may be exposed after being sampled[37]. This means that certain individuals served both as unexposed (before they were diagnosed with SMI) and exposed (from their SMI diagnosis onwards) at different time intervals. We used EDS to identify age- and sex-matched individuals (people with no prior SMI) within each GP practice at a 1:8 ratio. We produced two cohorts, one for each outcome (recorded OP/FF). The reason behind this is that it is essential within the design of EDS to consider the event (or outcome) during the sampling process, because *"For every exposed individual, one samples controls at the time of exposure from those individuals who are still at risk for an event and still not exposed at that point in time."*[37]

We estimated crude incidence rates (IR) of recorded OP and FF in people with and without SMI per 10,000 person-years (PY) at risk by adding the number of patients with a first recording of OP or FF, and dividing by the total PY of follow-up. Moreover, we calculated the ratio between FF and OP diagnosis in people with/without SMI.

A fixed effects Poisson model was compared against a mixed effects Poisson model using GP practice as a random intercept. The Akaike's and Bayesian information criterion were very similar with and without the GP cluster effect, therefore the GP practice was not included in the model.

We tested interactions between age/sex, age/exposure, and sex/exposure. We stratified analyses by sex and age and used Cox proportional hazard (PH) regression models to estimate Hazard Ratio (HR) and 95% Confidence Intervals (95%CI). The PH assumption was met using PH test. Age-specific HRs were estimated. We conducted unadjusted and adjusted analyses: model 1 adjusted for Townsend quintile of deprivation and year, model 2 adjusted for above covariates plus smoking, alcohol, and BMI.

We performed supplementary subgroup analyses to compare risk of OP/FF by SMI type (schizophrenia, bipolar, other psychosis) adjusted by age, deprivation, and year.

Statistical analyses were conducted using Stata 17 (StataCorp).

Missing data

There were no missing data on age, sex, and Townsend. However only 35% of the cohort had full data on all three smoking/alcohol/BMI, whereas for the remaining 65% one or more of these were missing. People with SMI had fewer missing data compared to those without SMI on smoking (14.7% vs. 26.9%), alcohol (40.9% vs. 61.4%), and BMI (29.2% vs. 42.2%) (**Supplementary Table 2**), but there were no significant differences in missing data between men and women (**Supplementary Table 3**). Further information about missingness on smoking, alcohol and BMI

by sex and age is presented in **Supplementary Tables 4, 5, and 6** respectively. We performed Multiple Imputation (MI)[35] for smoking, alcohol and BMI to obtain estimates under the missing at random assumption (MI details in Appendix 3).

RESULTS

Study cohort

The SMI osteoporosis cohort consisted of a total 444,480 people (50,006 exposed 397,474 age- and sex- matched unexposed individuals, amongst whom 1,437 served in both groups at different time intervals, as explained above) (**Supplementary Table 7**). The SMI fragility fracture cohort consisted of a total 425,364 people (47,851 exposed and 377,513 unexposed, amongst whom 1,351 served in both groups at different time intervals) (**Supplementary Table S8**). The ratio of exposed to unexposed was 1 to 7.9 (with a very small discrepancy to the intended 1:8 due to the complexity of EDS that was used for the matching of individuals).

We found significant interactions between age and sex both for OP (p=0.0190) and for FF (p=<0.0001), between age and exposure for OP (p=0.0001), but not for FF (p=0.3365), and between sex and exposure for OP (p<0.0001) and FF (p<0.0001) (**Supplementary Graphs 1-6**). We performed stratified analyses in view of these interactions.

Incidence rate of recorded Osteoporosis and Fragility fracture in people with vs. without SMI

The incidence rate of OP diagnosis was estimated at 23.0 (20.3-26.0)/10,000PY in men and 76.4 (72.0-80.9)/10,000PY in women with SMI, vs. 15.2 (14.5-16.0)/10,000PY in men and 79.5 (78.1-80.9)/10,000PY in women without SMI. The incidence rate of FF was 48.3 (44.3-52.7)/10,000PY in men and 119.5 (113.9-125.2)/10,000PY in women with SMI vs. 28.70 (27.7-29.7)/10,000PY in men and 88.1 (86.6-89.7)/10,000PY in women without SMI (**Tables 1&2)**. In general, we observed that there were more than twice as many men with SMI with FF record than those diagnosed with OP (FF:OP=2.10). This ratio was slightly smaller in men without SMI (FF:OP=1.89). In women with SMI the FF:OP ratio was 1.56, whereas in women without SMI the ratio was 1.11 (**Tables 1&2**).

Recorded Osteoporosis diagnosis

In men, diagnosis of SMI increased the likelihood of recorded OP diagnosis in specific age groups but not in others. In the fully adjusted model, differences were primarily observed amongst the younger (50-54y: HR=2.12;95%CI 1.61-2.79) and older age groups (85-99y: HR=2.15; 95%CI 1.05-4.37)) (**Table 3**).

In women, age-specific HRs showed only a slightly increased risk of OP diagnosis associated with SMI in those aged 50-54y (HR=1.16;95%CI 1.01-1.34) with no relative differences in other age groups (**Table 4**).

Recorded Fragility Fracture

In men, diagnosis of SMI increased the risk of FF across all age groups, albeit with some small variation. In the fully adjusted model, this risk ranged from HR=1.52(95%CI 1.23-1.88) in men aged 50-54y up to HR=2.29(95%CI 1.78-2.96) in men 65-69y and HR=2.14(95%CI 1.55-2.94) in men 80-84y (**Table 5**).

In women, diagnosis of SMI increased the risk of FF across all age groups, with some small variation of the risk ranging from HR=1.32(95%1.15-1.52) in those aged 70-74y up to HR=1.80(95%CI 1.56-2.08) in the fully adjusted model (**Table 6**).

Overall the HRs show an increased risk of fragility fractures for people with SMI (both men and women). There are small variations in those HRs across age groups, but the results are quite consistent, with little evidence of interaction between age and exposure (as shown above) for the outcome of fragility fracture.

Complete case analysis results are presented in **Supplementary Tables 9&10**. Comparison of these against the imputed results (Tables 3,4,5,6) shows that the HRs were quite similar, but the confidence intervals were narrower for the analyses based on imputed data.

Effect of SMI subtype

Men 50-54y with schizophrenia (HR=1.68;95%CI 1.03-2.75) and bipolar (HR=2.15;95%CI 1.28-3.62) were more likely to receive an OP diagnosis compared to men without SMI. Men with other psychosis were more likely to be diagnosed with OP aged 50-54y (HR=2.81;95%CI 2.03-3.89) compared to non-SMI, with small differences in some other age groups (60-64y, 65-69y, 70-74y) (**Supplementary Table 11**).

Women with other psychosis in their 50s had a slightly higher chance of being diagnosed with OP compared to women without SMI (50-54y: HR=1.29; 95%CI 1.08-1.55; 55-59y: HR=1.28; 95%CI 1.03-1.59), whereas there were no significant differences for other SMI subtypes or age groups (**Supplementary Table 12**).

Men and women with all subtypes of SMI were at an increased risk of FF across most (but not all) age groups compared to those without SMI, with variation of the observed risk by age (**Supplementary Tables 13&14)**.

DISCUSSION

Summary

Our findings suggest that SMI is an independent risk factor for fragility fractures across all age groups in both men and women, accounting for social deprivation, smoking, alcohol, and BMI. Men with SMI are more likely to be diagnosed with osteoporosis if they are in their early 50s or above 85y. Women with SMI are more likely to be diagnosed with osteoporosis in their early 50s and less likely in their early 80s, with no relative differences in other age groups. Amongst men with SMI there were more than twice as many with a FF record than with OP diagnosis. This ratio was slightly smaller for men without SMI (FF:OP=1.89). For women with SMI the FF:OP ratio was 1.56, whereas for women without SMI the ratio was 1.11. These figures suggest that osteoporosis is underdiagnosed both in men and women with SMI (with a relatively

more pronounced effect in women with SMI compared to non-SMI), as well as in men without SMI.

Strengths and limitations

The main strength of this study is the robust methodology, using nationally representative, real-world data. A limitation is that analyses were based on Read codes as they were recorded by GPs, which can be influenced by various factors[39]. The diagnosis of SMI is traditionally established by a psychiatrist, and the classification is expected to follow current guidelines at the time of diagnosis, some of which may have changed during the study period [40]. We did not have access to dual-energy X-ray absorptiometry (DXA) results, therefore the incidence of osteoporosis is likely to be underestimated. We addressed the high proportion of missing data on smoking, alcohol and BMI through Multiple Imputation which is a reliable method to reduce bias[38]. After adjusting for smoking, alcohol, and BMI, we found an increased risk of fractures in people with SMI. Given the negative impact of antipsychotic medication on BMD mentioned above, this might be due to antipsychotic medication. However, investigating the effect of medication was not undertaken at this time, as it was outside the scope of this project and would require a different study design. Finally, data was not available regarding other lifestyle factors e.g. physical activity, that can also affect BMD.

Comparison with existing literature

The IR of recorded OP in men with SMI in the current study (23.0 (20.3-26.0)/10,000PY) was higher compared to the IR previously reported in the general population of men ≥50y (15.3 (15.1-15.5)/10,000PY)[6]. In contrast, the IR of recorded OP in women with SMI (76.4 (72.0-80.9)/10,000PY) was slightly lower but similar compared to that in the general population of women ≥50y (79.8 (79.3-80.3)/10,000PY)[6]**.** The IRs of FF in people with SMI in the current study were much higher compared to the general population ≥50y (men: 48.3 (44.3-52.7)/10,000PY vs. 28.7 (28.4-29.0)/10,000PY; women: 119.5 (113.9-125.2)/10,000PY vs. 82.0 (81.5-82.5)/10,000PY). The IRs of recorded OP and FF in people without SMI were very similar to those reported in the general population aged ≥50y [6].

Another study using data from South London and Maudsley (SLaM) NHS Biomedical Research Centre Case Register (2006-2012) found that increasing age, white ethnicity, analgesics, cardiovascular disease, hypertension, genitourinary diseases, visual disturbance and syncope were significant risk factors for both falls and fractures in people with schizophrenia-spectrum disorders[41]. A Canadian study showed that antipsychotic medication increased the risk of hip fracture above and beyond risk factors included in FRAX risk assessment, whereas FRAX underestimated the 10-year risk of hip fracture in people taking selective serotonin reuptake inhibitors (SSRI), mood stabilizers, antipsychotics, or benzodiazepines[42]. A population-based cohort study from Taiwan which included a younger population (aged ≥16y) found that people with bipolar disorder had a higher risk of fracture HR 1.33 (95%CI 1.23-1.48) compared to those without. The risk increased by age, although the results were adjusted for but not stratified by sex[43].

Another study using linked primary (Lambeth DataNet) and secondary care data (SLaM), that included all adults (≥18y), reported that people with SMI were more likely to be prescribed medication for osteoporosis and be referred for osteoporosis screening within 2 years of SMI diagnosis, after adjusting for ethnicity, deprivation, and comorbidities, which was an unexpected finding. The authors hypothesised that the reason behind this might be the higher levels of comorbidity in people with SMI leading to more engagement with primary care[44]. Moreover, other UK studies have found an increased risk of falls requiring hospitalisation amongst adults of working age receiving mental health care (18-64y)[45], and a 2-fold risk of falls and 4-fold risk of hip fracture in people above 60y receiving mental health care[46]. In the above-mentioned studies analyses were stratified by age, but no age- or sex-specific risks were presented, therefore those results cannot be compared with our study. Moreover, to our knowledge previous studies have not investigated osteoporosis diagnosis in people with SMI based on primary care data.

In our study we found some age differences regarding diagnosis of osteoporosis. More specifically, the HR for recorded osteoporosis diagnosis in men is greatest for those aged 50-54y and those aged 85-99y, but lower for the intervening age groups, comparing SMI vs. without. These differences are likely to represent gaps in osteoporosis screening in the youngest and oldest age groups in men without SMI. Physical health checks in middle age (50y) might trigger the identification of risk factors for osteoporosis. Presence of SMI is more likely to be associated with multiple comorbidities in older age, and as a result hospital admissions may also trigger more investigations including for osteoporosis (e.g. risk of falls). We interestingly found that women with SMI aged 80-84y are less likely to be diagnosed with osteoporosis compared to those without. Factors such as social isolation, frailty, and dementia (which are more common in women) might affect osteoporosis screening, although it is not possible to determine these associations with certainty within the current dataset. It may however be that recording of fragility fracture (as a hard outcome) is a more reliable indicator of bone health compared to recorded osteoporosis, which is often not diagnosed until a fracture occurs.

Implications for research and practice

The above findings indicate an increased risk of fragility fractures in people aged ≥50 with a diagnosis of SMI. It is not clear if this difference could be due to antipsychotic medication, an underlying biological mechanism of an association between osteoporosis and SMI, other factors such as lack of exercise or differences in osteoporosis management. Further research is needed to explore inequalities in osteoporosis screening and treatment in the presence of SMI.

Primary care clinicians need to become aware of the increased fracture risk in people with SMI, which could be addressed during/following physical health checks. Fracture risk assessment and appropriate osteoporosis treatment as indicated may need to be included in the annual comprehensive care plan in people with SMI. Advice on diet and resistance training to prevent osteoporosis and fractures should also be evaluated.

CONCLUSION

Severe Mental Illness is associated with increased risk of fragility fractures in both men and women, whereas osteoporosis is underdiagnosed in people with SMI. Osteoporosis screening and management may need to be considered as part of the annual care plan for SMI. Appropriate interventions to prevent fragility fractures in people with SMI are needed.

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Ethical approval

The study protocol was approved by the IQVIA Scientific Review Committee (SRC) (Ref. 21SRC044).

Competing interests

The authors do not have any competing interests to declare.

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Table 1. Incidence rates of recorded Osteoporosis diagnosis and Fragility Fracture in people aged ≥50 with a diagnosis of SMI stratified by sex (2001-2018).

	Men			Women		
	Recorded Osteoporosis diagnosis	**Recorded Fragility fracture**	**Ratio FF:OP diagnosis**	**Recorded Osteoporosis diagnosis**	**Recorded Fragility fracture**	**Ratio FF:OP diagnosis**
Age (years)	**Men – IR per 10,000 PY (95%CI)**	**Men – IR per 10,000 PY (95%CI)**	**Men FF:OP ratio**	**Women – IR per 10,000 PY (95%CI)**	**Women – IR per 10,000 PY (95%CI)**	**Women FF:OP ratio**
All ages	22.99 (20.28-25.97)	48.33 (44.27-52.67)	2.10	76.36 (72.04-80.88)	119.46 (113.94-125.18)	1.56
50-54	13.76 (9.28-19.65)	19.18 (13.70-26.11)	1.39	29.05 (22.47-36.96)	40.81 (32.86-50.10)	1.40
55-59	15.23 (10.73-21.00)	30.56 (23.87-38.55)	2.01	51.11 (42.91-60.42)	53.67 (45.18-63.30)	1.05
60-64	19.25 (13.75-26.21)	34.22 (26.57-43.38)	1.78	58.48 (49.20-69.01)	68.04 (57.90-79.44)	1.16
65-69	28.84 (21.27-38.24)	43.87 (34.20-55.43)	1.52	78.95 (67.43-91.87)	106.54 (92.93-121.59)	1.35
70-74	26.89 (18.39-37.96)	64.85 (50.92-81.41)	2.41	109.45 (94.67-125.90)	137.16 (120.36-155.66)	1.25
75-79	42.18 (29.38-58.67)	89.38 (69.81-112.74)	2.12	137.37 (119.25-157.47)	198.04 (175.71-222.41)	1.44
80-84	37.43 (22.87-57.81)	141.02 (110.34-177.59)	3.77	110.46 (92.42-130.99)	236.49 (208.87-266.75)	2.14
85-99	47.47 (27.65-76.00)	161.05 (121.33-209.64)	3.39	92.58 (76.76-110.70)	315.58 (283.60-350.18)	3.41
Townsend quintile	**Men – IR per 10,000 PY (95%CI)**	**Men – IR per 10,000 PY (95%CI)**	**Men FF:OP ratio**	**Women – IR per 10,000 PY (95%CI)**	**Women – IR per 10,000 PY (95%CI)**	**Women FF:OP ratio**
1 (least deprived)	27.52 (20.36-36.38)	55.88 (45.27-68.24)	2.03	81.93 (71.72-93.18)	126.36 (113.41-140.38)	1.54
2	19.77 (14.19-26.82)	42.07 (33.56-52.09)	2.13	77.33 (67.80-87.83)	123.43 (111.07-136.78)	1.60
3	23.95 (18.04-31.18)	47.23 (38.55-57.29)	1.97	75.24 (66.08-85.32)	119.52 (107.68-132.30)	1.59
4	17.94 (13.13-23.93)	48.86 (40.47-58.46)	2.72	67.79 (59.26-77.20)	119.72 (108.09-132.26)	1.77
5 (most deprived)	26.68 (20.72-33.83)	48.60 (40.26-58.15)	1.82	81.29 (71.01-92.63)	107.59 (95.50-120.78)	1.32
Year	**Men – IR per 10,000 PY (95%CI)**	**Men – IR per 10,000 PY (95%CI)**	**Men FF:OP ratio**	**Women – IR per 10,000 PY (95%CI)**	**Women – IR per 10,000 PY (95%CI)**	**Women FF:OP ratio**
2001-2006	19.69 (14.83-25.63)	41.58 (34.23-50.03)	2.11	75.71 (67.70-84.41)	111.68 (101.70-122.38)	1.48
2007-2012	22.04 (17.93-26.81)	46.18 (40.01-53.02)	2.10	80.37 (73.45-87.76)	125.52 (116.69-134.83)	1.56
2013-2018	26.45 (21.61-32.04)	55.72 (48.41-63.83)	2.11	71.78 (64.38-79.79)	118.55 (108.83-128.90)	1.65

Table 2. Incidence rates of recorded Osteoporosis diagnosis and Fragility fracture in people aged ≥50 with no diagnosis of SMI (unexposed) stratified by sex (2001-2018).

	Men			Women		
	Recorded Osteoporosis diagnosis	Recorded Fragility fracture	Ratio FF:OP diagnosis	Recorded Osteoporosis diagnosis	Recorded Fragility fracture	Ratio FF:OP diagnosis
Age (years)	**Men – IR per 10,000 PY (95%CI)**	**Men – IR per 10,000 PY (95%CI)**	**Men FF:OP ratio**	**Women – IR per 10,000 PY (95%CI)**	**Women – IR per 10,000 PY (95%CI)**	**Women FF:OP ratio**
All ages	15.21 (14.50-15.95)	28.70 (27.69-29.73)	1.89	79.48 (78.07-80.92)	88.12 (86.60-89.65)	1.11
50-54	3.82 (2.98-4.83)	12.80 (11.18-14.60)	3.35	23.99 (21.82-26.32)	24.35 (22.14-26.71)	1.02
55-59	6.99 (5.93-8.19)	15.42 (13.79-17.20)	2.21	38.39 (35.92-40.99)	37.09 (34.65-39.66)	0.97
60-64	9.99 (8.65-11.48)	17.14 (15.32-19.10)	1.72	58.48 (55.31-61.80)	46.51 (43.67-49.49)	0.80
65-69	16.93 (15.00-19.04)	22.56 (20.28-25.03)	1.33	79.98 (76.08-84.03)	66.22 (62.66-69.92)	0.83
70-74	19.06 (16.73-21.62)	29.46 (26.48-32.68)	1.55	105.36 (100.60-110.29)	86.31 (82.00-90.80)	0.82
75-79	26.63 (23.51-30.04)	44.24 (40.11-48.69)	1.66	126.28 (120.82-131.93)	128.92 (123.36-134.67)	1.02
80-84	37.59 (33.22-42.37)	67.50 (61.46-73.99)	1.80	136.36 (130.37-142.55)	169.31 (162.46-176.37)	1.24
85-99	39.13 (34.28-44.48)	109.61 (101.12-118.63)	2.80	101.70 (97.29-106.27)	202.65 (195.96-209.51)	1.99
Townsend quintile	**Men – IR per 10,000 PY (95%CI)**	**Men – IR per 10,000 PY (95%CI)**	**Men FF:OP ratio**	**Women – IR per 10,000 PY (95%CI)**	**Women – IR per 10,000 PY (95%CI)**	**Women FF:OP ratio**
1 (least deprived)	13.62 (12.28-15.06)	25.12 (23.25-27.09)	1.84	75.88 (73.13-78.71)	81.16 (78.28-84.12)	1.07
2	13.10 (11.75-14.56)	26.58 (24.60-28.68)	2.03	73.37 (70.57-76.25)	85.93 (82.87-89.08)	1.17
3	16.64 (15.03-18.38)	29.15 (26.96-31.47)	1.75	80.30 (77.24-83.44)	88.38 (85.10-91.75)	1.10
4	15.71 (14.03-17.55)	30.98 (28.53-33.59)	1.97	82.18 (78.81-85.67)	92.57 (88.94-96.31)	1.13
5 (most deprived)	18.99 (16.83-21.35)	35.45 (32.41-38.69)	1.87	93.59 (89.17-98.18)	99.99 (95.34-104.81)	1.07
Year	**Men – IR per 10,000 PY (95%CI)**	**Men – IR per 10,000 PY (95%CI)**	**Men FF:OP ratio**	**Women – IR per 10,000 PY (95%CI)**	**Women – IR per 10,000 PY (95%CI)**	**Women FF:OP ratio**
2001-2006	12.64 (11.28-14.12)	24.17 (22.23-26.24)	1.91	84.29 (81.39-87.27)	72.99 (70.24-75.83)	0.87
2007-2012	13.96 (12.91-15.08)	27.04 (25.53-28.62)	1.94	79.97 (77.77-82.22)	94.74 (92.30-97.22)	1.18

2013-2018	18.12 (16.85-19.46)	33.27 (31.49-35.12)	1.84	75.28 (72.91-77.71)	91.10 (88.45-93.81)	1.21

Table 3. Association between diagnosis of SMI and recorded Osteoporosis diagnosis in Men.

Outcome: Osteoporosis			Men					
Exposure: SMI			Unadjusted		Adjusted Model 1*		Adjusted Model 2**	
Age-specific HRs	**Age (years)**	**N**	**Hazard Ratio (HR)**	**95%CI**	**Hazard Ratio (HR)**	**95%CI**	**Hazard Ratio (HR)**	**95%CI**
SMI vs. Non-SMI	50-54	78,942	2.52	1.95-3.25	2.34	1.81-3.03	2.12	1.61-2.79
SMI vs. Non-SMI	55-59	29,596	1.45	1.04-2.03	1.39	1.00-1.94	1.16	0.82-1.65
SMI vs. Non-SMI	60-64	22,874	1.77	1.27-2.48	1.67	1.19-2.35	1.44	1.01-2.05
SMI vs. Non-SMI	65-69	18,485	1.67	1.17-2.40	1.59	1.10-2.28	1.50	1.03-2.18
SMI vs. Non-SMI	70-74	14,507	1.40	0.94-2.11	1.39	0.92-2.08	1.25	0.82-1.90
SMI vs. Non-SMI	75-79	12,694	1.41	0.94-2.11	1.38	0.92-2.07	1.29	0.85-1.96
SMI vs. Non-SMI	80-84	8,529	0.81	0.40-1.66	0.81	0.40-1.66	0.80	0.39-1.65
SMI vs. Non-SMI	85-99	5,249	2.22	1.13-4.37	2.27	1.15-4.47	2.15	1.05-4.37

* Adjusted for Townsend and calendar year (6-year intervals)

**Adjusted for Townsend, calendar year (6-year intervals), smoking, alcohol and body mass index

**Missing data on smoking, alcohol and body mass index were handled with multiple imputation for bias correction

Table 4. Association between diagnosis of SMI and recorded Osteoporosis diagnosis in Women.

Outcome: Osteoporosis			Women					
Exposure: SMI			Unadjusted		Adjusted Model 1*		Adjusted Model 2**	
Age-specific HRs	**Age (years)**	**N**	**Hazard Ratio (HR)**	**95%CI**	**Hazard Ratio (HR)**	**95%CI**	**Hazard Ratio (HR)**	**95%CI**
SMI vs. Non-SMI	50-54	80,139	1.19	1.03-1.37	1.17	1.02-1.35	1.16	1.01-1.34
SMI vs. Non-SMI	55-59	31,052	1.16	0.98-1.36	1.13	0.96-1.34	1.11	0.93-1.31
SMI vs. Non-SMI	60-64	26,391	0.96	0.81-1.13	0.95	0.80-1.12	0.95	0.80-1.12
SMI vs. Non-SMI	65-69	24,576	1.01	0.87-1.18	1.00	0.86-1.16	0.97	0.83-1.14
SMI vs. Non-SMI	70-74	22,968	1.04	0.89-1.21	1.02	0.88-1.20	1.01	0.86-1.18
SMI vs. Non-SMI	75-79	22,823	0.88	0.74-1.06	0.88	0.73-1.05	0.87	0.72-1.04
SMI vs. Non-SMI	80-84	21,481	0.75	0.59-0.94	0.75	0.59-0.94	0.74	0.59-0.93
SMI vs. Non-SMI	85-99	24,174	1.05	0.82-1.35	1.04	0.81-1.34	1.00	0.78-1.29

*Adjusted for Townsend and calendar year (6-year intervals)

**Adjusted for Townsend, calendar year (6-year intervals), smoking, alcohol and body mass index

**Missing data on smoking, alcohol and body mass index were handled with multiple imputation for bias correction

Table 5. Association between diagnosis of SMI and recorded Fragility fracture in Men.

Outcome: Fragility fracture			Men					
Exposure: SMI			Unadjusted		Adjusted Model 1*		Adjusted Model 2**	
Age-specific HRs	**Age (years)**	**N**	**Hazard Ratio (HR)**	**95%CI**	**Hazard Ratio (HR)**	**95%CI**	**Hazard Ratio (HR)**	**95%CI**
SMI vs. Non-SMI	50-54	75,610	1.71	1.40-2.09	1.59	1.30-1.94	1.52	1.23-1.88
SMI vs. Non-SMI	55-59	28,317	1.78	1.38-2.30	1.64	1.27-2.11	1.56	1.19-2.05
SMI vs. Non-SMI	60-64	22,108	2.14	1.65-2.78	2.03	1.56-2.64	1.95	1.48-2.58
SMI vs. Non-SMI	65-69	17,627	2.44	1.91-3.11	2.36	1.85-3.01	2.29	1.78-2.96
SMI vs. Non-SMI	70-74	13,897	1.91	1.46-2.50	1.90	1.45-2.49	1.92	1.45-2.55
SMI vs. Non-SMI	75-79	12,164	1.77	1.34-2.34	1.77	1.33-2.34	1.72	1.29-2.30
SMI vs. Non-SMI	80-84	8,025	2.10	1.55-2.84	2.08	1.53-2.83	2.14	1.55-2.94
SMI vs. Non-SMI	85-99	4,815	1.97	1.26-3.06	1.96	1.26-3.06	1.81	1.15-2.85

*Adjusted for Townsend and calendar year (6-year intervals)

**Adjusted for Townsend, calendar year (6-year intervals), smoking, alcohol and body mass index

**Missing data on smoking, alcohol and body mass index were handled with multiple imputation for bias correction

Table 6. Association between diagnosis of SMI and recorded Fragility fracture in Women.

Outcome: Fragility fracture			Women					
Exposure: SMI			Unadjusted		Adjusted Model 1*		Adjusted Model 2**	
Age-specific HRs	**Age (years)**	**N**	**Hazard Ratio (HR)**	**95%CI**	**Hazard Ratio (HR)**	**95%CI**	**Hazard Ratio (HR)**	**95%CI**
SMI vs. Non-SMI	50-54	78,593	1.40	1.23-1.60	1.36	1.19-1.55	1.35	1.18-1.56
SMI vs. Non-SMI	55-59	30,515	1.77	1.53-2.05	1.77	1.53-2.05	1.73	1.49-2.02
SMI vs. Non-SMI	60-64	25,978	1.52	1.30-1.76	1.50	1.29-1.74	1.48	1.26-1.73
SMI vs. Non-SMI	65-69	24,116	1.52	1.32-1.74	1.52	1.32-1.75	1.49	1.29-1.71
SMI vs. Non-SMI	70-74	22,338	1.37	1.20-1.57	1.36	1.18-1.55	1.32	1.15-1.52
SMI vs. Non-SMI	75-79	21,517	1.43	1.24-1.64	1.43	1.24-1.64	1.41	1.23-1.62
SMI vs. Non-SMI	80-84	19,587	1.81	1.57-2.08	1.82	1.58-2.09	1.80	1.56-2.08
SMI vs. Non-SMI	85-99	20,157	1.64	1.41-1.91	1.63	1.40-1.90	1.61	1.38-1.88

*Adjusted for Townsend and calendar year (6-year intervals)

**Adjusted for Townsend, calendar year (6-year intervals), smoking, alcohol and body mass index

**Missing data on smoking, alcohol and body mass index were handled with multiple imputation for bias correction