21-5-2018

Predictors of falls and fractures leading to hospitalization in people with schizophrenia spectrum disorder: A large representative cohort study.

Brendon Stubbs
King's College London

Christoph Mueller
King's College London

Fiona Gaughran
King's College London

John Lally
Royal College of Surgeons in Ireland, johnlally@rcsi.ie

Davy Vancampfort
University of Leuven

See next page for additional authors

Citation

Stubbs B, Mueller C, Gaughran F, Lally J, Vancampfort D, Lamb SE, Koyanagi A, Sharma S, Stewart R, Perera G. Predictors of falls and fractures leading to hospitalization in people with schizophrenia spectrum disorder: A large representative cohort study. Schizophrenia Research. 2018; pii: S0920-9964(18)30267-6.

Authors
Brendon Stubbs, Christoph Mueller, Fiona Gaughran, John Lally, Davy Vancampfort, Sarah E. Lamb, Ai Koyanagi, Shalini Sharma, Robert Stewart, and Gayan Perera

Schizophrenia Research xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Predictors of falls and fractures leading to hospitalization in people with schizophrenia spectrum disorder: A large representative cohort study

Brendon Stubbs [a,b,*], Christoph Mueller [a,b], Fiona Gaughran [a,b], John Lally [a,b,c], Davy Vancampfort [d,e], Sarah E. Lamb [f], Ai Koyanagi [g,h], Shalini Sharma [a], Robert Stewart [a,b], Gayan Perera [b]

[a] South London and Maudsley NHS Foundation Trust, Denmark Hill, London SE5 8AZ, United Kingdom
[b] Institute of Psychiatry, Psychology and Neuroscience (IoPPN), King's College London, De Crespigny Park, London, Box SE5 8AF, United Kingdom
[c] Department of Psychiatry, Royal College of Surgeons in Ireland, Beaumont Hospital, Dublin, Ireland
[d] KU Leuven – University of Leuven, Department of Rehabilitation Sciences, Leuven, Belgium
[e] KU Leuven – University of Leuven, University Psychiatric Center KU Leuven, Leuven, Kortenberg, Belgium
[f] Nuffield Department of Orthopedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Windmill Road, Oxford, United Kingdom
[g] Research and Development Unit, Parc Sanitari Sant Joan de Déu, Universitat de Barcelona, Fundació Sant Joan de Déu, Dr. Antoni Pujadas, 42, Sant Boi de Llobregat, Barcelona 08830, Spain
[h] Instituto de Salud Carlos III, Centro de Investigación Biomédica en Red de Salud Mental, CIBERSAM, Monforte de Lemos 3-5 Pabellón 11, Madrid 28029, Spain

ARTICLE INFO

Article history:
Received 24 January 2018
Received in revised form 11 May 2018
Accepted 12 May 2018
Available online xxxx

Keywords:
Falls
Fractures
Schizophrenia
Psychosis
Hospital admission
Osteoporosis

ABSTRACT

Aim: To investigate predictors of falls/fractures leading to hospitalisation in people with schizophrenia-spectrum disorders.
Methods: A historical cohort of people with schizophrenia-spectrum disorders (ICD F20-29) from 01/2006–12/2012 was assembled using data from the South London and Maudsley NHS Biomedical Research Centre Case Register. Falls/fractures were ascertained from a linkage to national hospitalisation data. Separate multivariate Cox regression analyses were employed to identify predictors of falls and fractures.
Results: Of 11,567 people with schizophrenia-spectrum disorders (mean age 42.6 years, 43% female), 579 (incidence rate 12.79 per 1000 person-years) and 528 (11.65 per 1000 person-years) had at least one reported hospital admission due to a fall or fracture respectively and 822 patients had at least either a recorded fall or a fracture during this period (i.e. 7.1% of sample). Overall, 6.69 and 10.74 years of inpatient hospital stay per 1000-person years of follow-up occurred due to a fall and fracture respectively. 14(0.12%) and 28(0.24%) died due to a fall and fracture respectively. In Multivariable analysis, increasing age, white ethnicity, analgesics, cardiovascular disease, hypertension, diseases of the genitourinary system, visual disturbance and syncope were significant risk factor for both falls and fractures. A previous fracture (HR 2.05, 95% CI 1.53–2.73) and osteoporosis (HR 6.79, 95% CI 4.71–9.78) were strong risk factors for consequent fractures.
Conclusion: Comorbid physical health conditions and analgesic medication prescription were associated with higher risk of falls and fractures. Osteoporosis and previous fracture were strong predictors for subsequent fractures. Interventions targeting bone health and falls/fractures need to be developed and evaluated in these populations.

1. Introduction

Falls and fractures are associated with considerable morbidity, reduced quality of life and healthcare expenditure (Johnell & Kanis, 2004). In Europe, fractures account for more disability adjusted life years (DALYs) than all common cancers, with the exception of lung cancer (Johnell & Kanis, 2006). Osteoporosis is a key risk factor that greatly increases an individual's risk of experiencing a fracture (Kanis et al., 2010, 2013). Fractures, particularly of the hip, are associated with substantial morbidity, healthcare costs, deterioration in mobility, reduced social function and admission to long term care facilities (Kanis, 2002a, 2002b, Johnell & Kanis, 2006, Kanis et al., 2010, 2013). Moreover, reduced bone mineral density increases a person's risk of death from a fall (Sanchez-Riera et al., 2014). In recognition of this, improving bone health and preventing fractures are a global public health priority (Kanis, 2002a, 2002b, Johnell & Kanis, 2006).

People with schizophrenia-spectrum disorders have a number of risk factors which increase their risk of lower bone mineral density and osteoporosis (Kishimoto et al., 2012), including high rates of diabetes (Stubbs et al., 2015d), vitamin D deficiency (Lally et al., 2016), sedentary lifestyles (Stubbs et al., 2015b) and poor nutritional intake (Dipasquale et al., 2013). Additionally, raised prolactin, which is associated with some antipsychotic agents, has been suggested to accelerate bone loss (Tseng et al., 2015; De Hert et al., 2016; Gonzalez-Blanco

* Corresponding author at: Physiotherapy Department, South London and Maudsley NHS Foundation Trust, Denmark Hill, London, United Kingdom.
E-mail address: brendon.stubbs@kcl.ac.uk (B. Stubbs).

https://doi.org/10.1016/j.schres.2018.05.010

et al., 2016). A recent meta-analysis found that people with schizophrenia-spectrum disorders (with a mean age of 44 years) were 2.5 times more likely to have osteoporosis than controls (Stubbs et al., 2014b). Another meta-analysis in this clinical population (with a mean age of 33 years) concluded higher likelihood of reduced bone mineral density (BMD) at the femur (standardised mean difference (SMD) −0.5) and lumbar spine (SMD −1.23) compared to matched controls without mental disorders (Gomez et al., 2016). Consistent with this, another recent meta-analysis demonstrated that people with schizophrenia are at a 72% increased risk of experiencing fractures compared to the general population (Stubbs et al., 2015c). However, the authors noted that there was a paucity of information on predictors of fractures in people with schizophrenia-spectrum disorders, which have only been investigated in three representative cohort studies to date (Sorensen et al., 2013; Tsai et al., 2014; Wu et al., 2015). Of these, one largely focussed on antipsychotic medication as an exposure (Wu et al., 2015), two focussed only on hip fractures as an outcome (Sorensen et al., 2013; Wu et al., 2015) and only one provided information on predictors of fractures in Europe (Sorensen et al., 2013). No representative cohort has, to the best of our knowledge, investigated the predictors of falls in people with schizophrenia-spectrum disorders, despite their importance as a precursor to fractures.

Given these limitations, we conducted a representative cohort study investigating predictors of falls and fractures leading to hospitalisation among people with schizophrenia-spectrum disorders (ICD 10 codes F20-29). Secondarily, we investigated length of hospital stay as a result of falls and fractures in this group.

2. Methods

2.1. Study setting and data source

A retrospective observational study was conducted using data from the South London and Maudsley NHS Foundation Trust (SLaM) Biomedical Research Centre (BRC) Case Register. SLaM is one of Europe's largest mental healthcare providers, serving a geographic catchment of four south London boroughs (Lambeth, Lewisham, Southwark, and Croydon) with a population in excess of 1.2 million people. The data for the current study were captured from the Clinical Record Interactive Search (CRIS) application, which generates an anonymised version of SLaM's electronic health record within a robust governance framework (Perera et al., 2016a). The SLaM BRC Case Register has been described in detail (Perera et al., 2016a) and has supported a range of studies (Chang et al., 2010; Hayes et al., 2011; Perera et al., 2014; Sultana et al., 2014; Ward et al., 2015; Perera et al., 2016b). Data are currently archived in CRIS on over 350,000 cases with a range of mental disorders and the database, with associated data linkages, has approval for secondary analysis (Oxford Research Ethics Committee C, reference 08/H0606/71 + 5). Data from CRIS have been supplemented through natural language processing (NLP) applications using Generalised Architecture for Text Engineering (GATE) software, applying information extraction techniques to derive structured information from the extensive text fields held in the mental health record (Perera et al., 2016a).

2.2. Participants and study period

All SLaM patients with schizophrenia-spectrum disorders, defined as schizophrenia, schizotypal and delusional disorder (ICD10 codes F20-F29), with a diagnosis at any point between 1st of January 2007 and 31st March 2013, were included in the current study. SLaM patient records were linked with national Hospital Episode Statistics (HES) which are compiled from all NHS Trusts in England (both acute and mental health services), including statistical abstracts of records of all inpatient episodes, as well as outpatient and emergency care (Perera et al., 2016a). In addition CRIS data were linked to the Office for National Statistics (ONS) mortality records over the same period to investigate mortality due to falls and fractures.

2.3. Primary outcome: falls and fractures

The primary outcome was hospital admission resulting from a fall or fracture extracted from linked HES data and all discharge diagnoses (primary or any secondary diagnosis codes) recorded between January 2007 to March 2013 based on the following ICD 10 codes: i) falls (W00-W19); ii) fractures (M80-M84, M907, S02, S12, S32, S42, S52, S62, S72, S82, S92, S22, T02, T08, T10, T12X, T902, T911, T912, T921). In addition, linked mortality records from the ONS were examined for any instance of fall or fracture ICD codes in any cause of death field on the death certificate to identify the date of death due to a fall or fracture.

2.4. Measurements

A range of additional measurements were obtained from CRIS. All independent variables (covariates) were defined according to the value closest to the date of the first recorded schizophrenia-spectrum diagnosis. Demographic covariates comprised: age at diagnosis, gender, ethnicity (White-European and Non-White) and index of multiple deprivation (IMD 2010) for the neighbourhood of residence (Lower Super Output Area) at the time of diagnosis. The IMD has previously been used in CRIS (Das-Munshi et al., 2017) and takes into account area-level deprivation from Census data across several domains including income, employment, health, education, barriers to housing and services, living environment, and crime (Richardson et al., 2009). Information on cohabiting status (Cohabiting: married/civil partner, married, cohabiting; Non-cohabiting: single, divorced, civil partnership dissolved, widowed, separated) was ascertained at the time of schizophrenia-spectrum diagnosis, supplemented by a binary variable derived using NLP on text mentions of the patient living alone.

The Health of the Nation Outcome Scales (HoNOS) (Wing et al., 1998) are routinely administered measures of illness burden in UK mental health services and are recorded in structured fields on the electronic health record. Individual HoNOS item scores (agitated behaviour, self-injury, problem drinking & drugs, cognitive problems, physical illness, hallucinations, depressed mood, relationship problems, daily living problems, living conditions problems, occupational problems) and dates were obtained within 6 months before or after the index date (date of schizophrenia-spectrum diagnosis), and the closest scores in time to this date were included in analyses. Those scores 2 or over in the Individual HoNOS scores were classified as having a problem on each HoNOS score.

2.5. Mental disorder comorbidity

Diagnoses of affective disorders (ICD10 F30-F39), neurotic, stress-related and somatoform disorders (F40-F48) were ascertained within one year before or after the diagnosis of schizophrenia-spectrum.

2.6. Medication

Medications received by participants were extracted from structured medication fields in the record, supplemented by an NLP applications applied to text fields ascertaining mentions of current medication (Perera et al., 2016a). Presence or not of the following medication groups was ascertained on the basis of information within one year before or after first diagnosis of schizophrenia-spectrum disorders: benzodiazepines, anticholinergics, antihypertensives, antidepressants, antipsychotics, anxiolytics and hypnotics, and analgesics. The total number of medications prescribed was calculated for each participant and used as a continuous variable.

Please cite this article as: Stubbs, B., et al., Predictors of falls and fractures leading to hospitalization in people with schizophrenia spectrum disorder: A large representativ..., Schizophr. Res. (2018), https://doi.org/10.1016/j.schres.2018.05.010

Table 1
Characteristics of those schizophrenia spectrum disorder patients who were admitted to hospital with a fall/fracture after a diagnosis of schizophrenia spectrum disorders (F20* to F29*).

Characteristics of sample	Presence of falls		Presence of fractures	
	No ($n = 10,988$)	Yes ($n = 579$)	No ($n = 11,174$)	Yes ($n = 528$)
Year of first recorded diagnosis				
2006	1826 (91.6)	167 (8.4)	1858 (93.2)	135 (6.8)
2007	2396 (93.9)	157 (6.1)	2399 (94)	154 (6)
2008	1573 (95.0)	83 (5.0)	1570 (94.8)	86 (5.2)
2009	1364 (96.1)	56 (3.9)	1360 (95.8)	60 (4.2)
2010	1403 (95.6)	64 (4.4)	1420 (96.8)	47 (3.2)
2011	1194 (96.8)	40 (3.2)	1204 (97.6)	30 (2.4)
2012	1232 (99.0)	12 (1.0)	1228 (98.7)	16 (1.3)
Age				
18–34	4340 (98.0)	87 (2.0)	4319 (97.6)	108 (2.4)
35–49	3849 (97.6)	96 (2.4)	3822 (96.9)	123 (3.1)
50–64	1637 (92.8)	127 (7.2)	1655 (93.8)	109 (6.2)
65–79	892 (84.2)	167 (15.8)	943 (89.0)	116 (11.0)
80 & over	270 (72.6)	102 (27.4)	300 (80.6)	72 (19.4)
Gender				
Female	4670 (93.9)	305 (6.1)	4711 (94.7)	264 (5.3)
Male	6318 (95.8)	274 (4.2)	6328 (96.0)	264 (4.0)
Ethnicity				
White	5480 (92.7)	434 (7.3)	5529 (93.5)	385 (6.5)
Non-White	5508 (97.4)	145 (2.6)	5510 (97.5)	143 (2.5)
Marital status				
Cohabiting	2356 (95.4)	113 (4.6)	2366 (95.8)	103 (4.2)
Non-cohabiting	8632 (94.9)	466 (5.1)	8673 (95.3)	425 (4.7)
Living status				
Living with someone	8647 (95.6)	402 (4.4)	8678 (95.9)	371 (4.1)
Living alone	2341 (93.0)	177 (7.0)	2361 (93.8)	157 (6.2)
Index of multiple deprivation: IMD 2010 (SD)	29.4 (11.1)	29.3 (11.1)	29.5 (11.1)	28.9 (11.1)
Medication prescription (*within one year before or after diagnosis schizophrenia spectrum disorders*)				
Benzodiazepines	3821 (95.9)	163 (4.1)	3831 (96.2)	153 (3.8)
Anticholinergics	5068 (95.8)	223 (4.2)	5079 (96.0)	212 (4.0)
Antihypertensive	1058 (88.5)	137 (11.5)	1095 (91.6)	100 (8.4)
Antidepressants	3161 (94.3)	192 (5.7)	3191 (95.2)	162 (4.8)
Antipsychotics	7714 (95.4)	371 (4.6)	7744 (95.8)	341 (4.2)
Anxiolytics and hypnotics	3753 (95.8)	166 (4.2)	3765 (96.1)	154 (3.9)
Analgesics	1130 (89.4)	134 (10.6)	1150 (91.0)	114 (9.0)
Number of medications received (*within one year before or after diagnosis of schizophrenia spectrum disorder*)				
0	2198 (94.1)	138 (5.9)	2216 (94.9)	120 (5.1)
1	1733 (95.7)	78 (4.3)	1727 (95.4)	84 (4.6)
2	2163 (96.3)	82 (3.7)	2163 (96.3)	82 (3.7)
3	1476 (95.3)	73 (4.7)	1477 (95.4)	72 (4.6)
4	1800 (95.5)	85 (4.5)	1811 (96.1)	74 (3.9)
5 or more	1618 (92.9)	123 (7.1)	1645 (94.5)	96 (5.5)
Other psychiatric conditions (*within one year before or after diagnosis schizophrenia spectrum disorders*)				
F40–F48 (neurotic, stress-related and somatoform disorders)	1178 (95.4)	57 (4.6)	1180 (95.5)	55 (4.5)
F30–F39 (mood [affective] disorders)	2920 (94.3)	177 (5.7)	2945 (95.1)	152 (4.9)
f30 & F31 (mania and bipolar disorders)	396 (94.1)	25 (5.9)	406 (96.4)	15 (3.6)
Problem HoNOS (*score 2 or over*) (*within six months before or after diagnosis schizophrenia spectrum disorders*)				
Agitated behaviour	1917 (94.2)	118 (5.8)	1929 (94.8)	106 (5.2)
Self-injury	592 (94.3)	36 (5.7)	590 (93.9)	38 (6.1)
Problem drinking drugs	1329 (93.7)	89 (6.3)	1320 (93.1)	98 (6.9)
Cognitive problems	1715 (93.0)	130 (7.0)	1734 (94.0)	111 (6.0)
Physical illness	1856 (87.8)	259 (12.2)	1890 (89.4)	225 (10.6)
Hallucinations	4349 (94.9)	236 (5.1)	4362 (95.1)	223 (4.9)
Depressed mood	2587 (95.6)	120 (4.4)	2590 (95.7)	117 (4.3)
Relationship problems	3209 (94.9)	171 (5.1)	3220 (95.3)	160 (4.7)
Daily living problems	2593 (92.5)	210 (7.5)	2637 (94.1)	166 (5.9)
Living conditions problems score	1934 (94.9)	104 (5.1)	1953 (95.8)	85 (4.2)
Occupational problems	2747 (94.9)	147 (5.1)	2759 (95.3)	135 (4.7)
Mean overall HoNoS score (mean)	11.3 (9.4)	13.0 (10.8)	11.3 (9.5)	12.7 (8.9)
Number of missing HoNoS patients	2087 (96.3)	80 (3.7)	2083 (96.1)	84 (3.9)
Hospital admissions (*within six months before or after diagnosis schizophrenia spectrum disorders*)				
Ischaemia + CHD + IHD	46 (37.4)	77 (62.6)	77 (62.6)	46 (37.4)
Arrhythmia + AF	56 (41.5)	79 (58.5)	75 (55.6)	60 (44.4)
Heart failure	7 (18.9)	30 (81.1)	28 (75.7)	9 (24.3)
Diabetes	68 (52.7)	61 (47.3)	84 (65.1)	45 (34.9)
Hypotension	13 (37.1)	22 (62.9)	20 (57.1)	15 (42.9)

(continued on next page)

Please cite this article as: Stubbs, B., et al., Predictors of falls and fractures leading to hospitalization in people with schizophrenia spectrum disorder: A large representativ..., Schizophr. Res. (2018), https://doi.org/10.1016/j.schres.2018.05.010

Table 1 (*continued*)

Characteristics of sample	Presence of falls		Presence of fractures	
	No ($n = 10,988$)	Yes ($n = 579$)	No ($n = 11,174$)	Yes ($n = 528$)
Hypercholesterolemia	46 (46.5)	53 (53.5)	61 (61.6)	38 (38.4)
Hypertension	115 (45.3)	139 (54.7)	149 (58.7)	105 (41.3)
Diseases of genitourinary system including UTI	93 (49.7)	94 (50.3)	109 (58.3)	78 (41.7)
Osteoporosis	64 (68.1)	30 (31.9)	23 (24.5)	71 (75.5)
Visual disturbance and blindness	16 (53.3)	14 (46.7)	20 (66.7)	10 (33.3)
Hearing loss	12 (46.2)	14 (53.8)	14 (53.8)	12 (46.2)
Syncope or collapse	25 (34.7)	47 (65.3)	45 (62.5)	27 (37.5)
Parkinson's disease	43 (61.4)	27 (38.6)	53 (75.7)	17 (24.3)
Falls before diagnosis	414 (77.7)	119 (22.3)	434 (81.4)	99 (18.6)
Fractures before diagnosis	626 (84.4)	116 (15.6)	604 (81.4)	138 (18.6)

2.7. Physical comorbidity

Information on physical comorbidities were ascertained utilising the data linkage between CRIS and national HES records. Information on all ICD-10 diagnoses at discharge (primary or any secondary diagnosis codes) for physical comorbidities was ascertained within 6 months before or after diagnosis of Schizophrenia spectrum disorders and the following binary variables generated: i) Ischaemia (I20, I21, I22) + coronary heart disease (CHD) (I25) + Ischaemic heart disease (IHD); ii) Arrhythmia (I44-I49) + atrial fibrillation (AF) (I48); iii) Heart failure (I50); iv) Diabetes (E08, E09, E10, E11, E12, E13; v) Hypotension (I95-99); vi) Hypercholesterolemia (E78); vii) Hypertension (I10-15); viii) Diseases of genitourinary system including urinary tract infections (UTI) (N39); ix) Osteoporosis (M80-85); x) Visual Disturbance and Blindness (H53-54); xi) Hearing Loss (H90-95); xii) Syncope or Collapse (R50-R69); xiii) Parkinson's Disease (G20).

2.8. Statistical analysis

The study sample was described initially in terms of demographic and clinical variables, followed by unadjusted Cox proportional hazard models to predict the first fall and first fracture after schizophrenia-spectrum diagnosis separately. The predictor variables at baseline used in the first univariate models included sociodemographic information (year of schizophrenia spectrum disorder diagnosis, mean age, gender, ethnicity, marital status, living status), medications (benzodiazepines, antipsychotics, anxiolytics & hypnotics, antidepressants, analgesics, anticholinergics, antihypertensives), comorbid psychiatric diagnosis (F30-39 mood disorders, F40-48 neurotic/stress disorders), HONOS scores (mean total and each individual item) and physical health comorbidities (as indicated above). Factors that were significant ($P < 0.05$) in the univariate models for fall and fracture outcomes were subsequently entered into the multivariable model. A final multivariable Cox proportional hazards model, using stepwise backward elimination technique where those variables not significant (P value < 0.05) were eliminated, with hazard ratios and 95% confidence intervals (CI), was assembled removing all non-significant variables from the model. Correlation matrix of coefficients of cox model was used investigate collinearity among independent variables and found that number of medications received (polypharmacy) was significantly collinear with individual types of medication received and therefore, polypharmacy variable was removed from final predictors. All analyses were conducted utilising STATA, version 13.

3. Results

The analysed cohort comprised 11,174 people with a schizophrenia-spectrum disorder with a mean age of 42.6 years (SD: 16.70) of whom with 43.01% patients were females. During the observation period, 822 of these patients had at least one hospital admission due to a fall or fracture (7.1% of the sample) of whom 579 and 528 were admitted due to a fall and fracture respectively and 285 patients were admitted to both falls and fractures in this cohort. The incidence rate of falls among schizophrenia-spectrum disorder patients was 12.79 per 1000 person years. The incidence rate of fractures among the cohort was 11.65 per 1000 person years. Table 1 summarises characteristics of those who had a fall or fracture compared to those who did not. Overall, 14 (0.12%) and 28 (0.24%) of patients died due to a fall and fracture respectively based on their death certificate.

3.1. Length of hospital stay and mortality

Among the 822 who experienced a fall or fracture, the mean length of hospital stay following a fall ($n = 579$) was 10.83 days (range 0–216) equating to a total of 6270 full days in hospital. The mean length of stay in hospital following a fracture across the sample was 20.20 days (range 0–222) and a total of 10,668 days. This equates to 12.83 years of inpatient hospital stay for 1000-person years of follow-up due to a fall and 23.70 years of inpatient hospital stay for 1000-person years of follow-up due to a fracture.

3.2. Factors associated with falls and fractures

Unadjusted predictors of fall/facture in Cox regression models are summarised in Table 2.

3.3. Multivariate predictors of falls

Multivariate models of factors associated with falls are presented in Table 3. In the final model the following remained independent and significant factors associated with falls leading to hospitalisation: older age (HR per 10-year increment, Hazard ratio (HR) 1.49, 95% CI 1.40, 1.58), non-cohabiting marital status (HR 1.34, 95% CI 1.05, 1.71), physical health problems on the HONOS subscale (HR 1.48, 95% CI 1.21, 1.81), and hospitalisations in which the following was recorded as either primary or one of the secondary discharge diagnoses: ischaemic heart disease (HR 1.72, 95% CI 1.26, 2.35), arrhythmia or atrial fibrillation (HR 1.90, 95% CI 1.4, 2.59), diabetes (HR 1.78, 95% CI 1.27, 2.49), hypotension (HR 1.78, 95% CI 1.1, 2.89), hypertension (HR 2.77, 95% CI 2.02, 3.8), diseases of genitourinary system and UTI (HR 1.74, HR 95% CI 1.28, 2.36), visual disturbance or blindness (HR 5.04, 95% CI 2.76, 9.19), syncope (HR 2.12, 95% CI 1.46, 3.08), Parkinson's disease (HR 2.77, 95% CI 1.79, 4.27). Factors associated with a reduced risk of falls comprised non-white ethnicity (HR 0.50, 95% CI 0.4, 0.61) and antihypertensive medication (HR 0.66, 95% CI 0.51, 0.87). There was no interaction between age and gender with a P-value for Likelihood-ratio test of 0.962.

3.4. Multivariate predictors of fractures

Full details of the multivariate predictors of fractures are displayed in Table 4. In the final model, the following factors remained independent and significantly associated with hospitalisation due to fractures:

Please cite this article as: Stubbs, B., et al., Predictors of falls and fractures leading to hospitalization in people with schizophrenia spectrum disorder: A large representativ..., Schizophr. Res. (2018), https://doi.org/10.1016/j.schres.2018.05.010

analgesics (HR: 1.47, 95% CI 1.17, 1.86) and hospitalisations in the primary/secondary discharge diagnoses: hypertension (HR: 2.36, 95% CI 1.65, 3.38), diseases of the genitourinary system and UTIs (HR 1.83, 95% CI 1.29, 2.57), osteoporosis (HR: 6.79, 95% CI 4.71, 9.78), Arrhythmia and atrial fibrillation (HR 1.69, 95% CI 1.19, 2.39), Visual Disturbance and Blindness (HR: 3.10, 95% CI 1.55, 6.21), and previous fracture before psychosis (HR: 2.05, 95% CI 1.53, 2.73). Factors associated with a reduced risk of hospital admission due to fractures included Hypercholesterolemia (HR: 0.63, 95% CI 0.41, 0.96) and non-white ethnicity (HR 0.60, 95% CI 0.48, 0.74).

4. Discussion

The study found that over a 6-year period, approximately 7.1% of people receiving care for schizophrenia-spectrum disorders were admitted to an acute hospital setting due to a fall/fracture, equating to an incidence rate 12.79 per falls 1000 person years and 11.65 fractures per 1000 person years. Of concern, our data indicated that cohort members who had a fall ($n = 579$) spent a total of 6270 days in hospital, whilst those who had a fracture spent ($n = 528$) a total of 10,668 days in hospital. Multivariate models indicated increasing age,

Table 2
Univariate Cox proportional hazard model (95% CI) showing factors affecting time to first fall/fracture hospital admission since diagnosis of schizophrenia spectrum disorders.

Characteristics	Outcome falls		Outcome fractures	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Year of first recorded diagnosis				
2006	Ref.		Ref.	
2007	0.81 (0.65, 1.01)	0.059	1.04 (0.82, 1.32)	0.747
2008	0.77 (0.59, 1.01)	0.059	1.1 (0.83, 1.46)	0.519
2009	0.75 (0.55, 1.02)	0.070	1.1 (0.80, 1.51)	0.565
2010	1.07 (0.79, 1.45)	0.653	1.06 (0.75, 1.5)	0.747
2011	1.25 (0.87, 1.8)	0.236	1.19 (0.78, 1.8)	0.425
2012	0.83 (0.45, 1.53)	0.550	1.25 (0.72, 2.16)	0.423
10-year increase in age	1.79 (1.72, 1.87)	<0.001	1.54 (1.47, 1.61)	<0.001
Female gender	1.5 (1.28, 1.77)	<0.001	1.34 (1.13, 1.59)	<0.001
Non-white ethnicity	0.34 (0.28, 0.41)	<0.001	0.38 (0.31, 0.46)	<0.001
Non-cohabiting marital status	1.13 (0.92, 1.39)	0.242	1.13 (0.91, 1.40)	0.277
Living alone	1.61 (1.35, 1.92)	<0.001	1.55 (1.28, 1.86)	<0.001
Ten units increase in IMD score	0.98 (0.91, 1.06)	0.632	0.94 (0.87, 1.02)	0.152
Medication prescribed (*within one year before or after diagnosis of schizophrenia spectrum disorders*)				
Benzodiazepines received	0.82 (0.68, 0.98)	0.029	0.85 (0.71, 1.03)	0.099
Anticholinergics received	0.76 (0.64, 0.89)	<0.001	0.81 (0.68, 0.96)	0.016
Antihypertensive received	2.86 (2.29, 3.57)	<0.001	2.03 (1.57, 2.64)	<0.001
Antidepressants received	1.21 (1.02, 1.44)	0.027	1.08 (0.90, 1.3)	0.413
Antipsychotics received	0.75 (0.63, 0.89)	0.001	0.76 (0.64, 0.91)	0.003
Anxiolytics and hypnotics received	0.85 (0.71, 1.01)	0.069	0.87 (0.72, 1.05)	0.146
Analgesics received	2.65 (2.18, 3.21)	<0.001	2.42 (1.97, 2.98)	<0.001
Increase in one type of polypharmacy	1.05 (1.00, 1.1)	0.037	1.03 (0.99, 1.08)	0.154
Presence of other psychiatric conditions (*within one year before or after schizophrenia spectrum diagnosis*)				
F40–F48 (neurotic, stress-related and somatoform disorders) present	0.88 (0.67, 1.15)	0.354	0.94 (0.71, 1.24)	0.655
F30–F39 (mood [affective] disorders) present	1.13 (0.94, 1.34)	0.192	1.03 (0.85, 1.24)	0.758
f30 & F31 (mania and bipolar disorders)	1.11 (0.74, 1.66)	0.614	0.70 (0.42, 1.18)	0.180
Problem HoNOS present (*within 6 months before or after schizophrenia spectrum diagnosis*)				
Agitated behaviour	1.20 (0.98, 1.48)	0.077	1.22 (0.98, 1.52)	0.070
Self-injury	1.15 (0.82, 1.61)	0.432	1.39 (1, 1.94)	0.051
Problem drinking drugs	1.21 (0.96, 1.52)	0.110	1.59 (1.27, 1.99)	<0.001
Cognitive problems	1.50 (1.23, 1.84)	<0.001	1.41 (1.14, 1.75)	0.002
Physical illness	4.04 (3.39, 4.82)	<0.001	3.79 (3.14, 4.56)	<0.001
Hallucinations	1.00 (0.84, 1.2)	0.959	1.13 (0.94, 1.36)	0.191
Depressed mood	0.79 (0.65, 0.97)	0.026	0.90 (0.73, 1.11)	0.326
Relationship problems	0.92 (0.77, 1.11)	0.392	0.99 (0.82, 1.2)	0.919
Daily living problems	1.73 (1.45, 2.07)	<0.001	1.38 (1.14, 1.67)	0.001
Living conditions problems	0.97 (0.78, 1.2)	0.781	0.86 (0.68, 1.09)	0.219
Occupational problems	0.95 (0.78, 1.16)	0.623	1.00 (0.81, 1.22)	0.986
Overall increase in one unit of HoNoS	1.02 (1.01, 1.02)	<0.001	1.01 (1.01, 1.02)	<0.001
Admitted to general hospital (*within 6 months before or after schizophrenia spectrum diagnosis*)				
Ischaemia + CHD + IHD	25.04 (19.63, 31.93)	<0.001	12.35 (9.11, 16.73)	<0.001
Arrhythmia + AF	21.00 (16.54, 26.66)	<0.001	15.09 (11.52, 19.76)	<0.001
Heart failure	25.47 (17.62, 36.82)	<0.001	6.31 (3.27, 12.21)	<0.001
Diabetes	18.38 (14.07, 24.02)	<0.001	13.23 (9.73, 17.98)	<0.001
Hypotension	25.19 (16.43, 38.62)	<0.001	14.81 (8.86, 24.78)	<0.001
Hypercholesterolemia	18.04 (13.58, 23.95)	<0.001	12.30 (8.84, 17.12)	<0.001
Hypertension	24.83 (20.46, 30.12)	<0.001	17.13 (13.81, 21.26)	<0.001
Diseases of genitourinary system including UTI	22.41 (17.92, 28.03)	<0.001	18.55 (14.55, 23.64)	<0.001
Osteoporosis	10.01 (6.93, 14.47)	<0.001	54.27 (42.04, 70.07)	<0.001
Visual disturbance and blindness	18.82 (11.06, 32.02)	<0.001	11.01 (5.89, 20.6)	<0.001
Hearing loss	26.12 (15.33, 44.49)	<0.001	17.97 (10.12, 31.89)	<0.001
Syncope or collapse	23.16 (17.16, 31.25)	<0.001	11.92 (8.09, 17.57)	<0.001
Parkinson's disease	13.68 (9.29, 20.16)	<0.001	7.92 (4.88, 12.85)	<0.001
Falls before schizophrenia spectrum disorder diagnosis	7.06 (5.77, 8.64)	<0.001	6.17 (4.95, 7.68)	<0.001
Fractures before schizophrenia spectrum disorder diagnosis	4.19 (3.42, 5.14)	<0.001	6.12 (5.04, 7.44)	<0.001

Please cite this article as: Stubbs, B., et al., Predictors of falls and fractures leading to hospitalization in people with schizophrenia spectrum disorder: A large representativ..., Schizophr. Res. (2018), https://doi.org/10.1016/j.schres.2018.05.010

Table 3
Two models showing predictors of first fall hospital admission among schizophrenia spectrum disorders (used stepwise removal of factors that were not significant at 0.05 *P* value).

Characteristics	Model 1 ($n = 9236$)		Model 2 ($n = 9366$)	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
10-year increase in age	1.50 (1.40, 1.60)	<0.001	1.49 (1.40, 1.58)	<0.001
Female gender	0.97 (0.80, 1.18)	0.797		
Non-white ethnicity	0.48 (0.39, 0.60)	<0.001	0.50 (0.4, 0.61)	<0.001
Non-cohabiting marital status	1.29 (1.00, 1.66)	0.05	1.34 (1.05, 1.71)	0.025
Living alone	1.10 (0.90, 1.35)	0.355		
Medication prescribed (*within one year before or after diagnosis of schizophrenia spectrum disorder*)				
Anticholinergics received	1.21 (0.98, 1.50)	0.078		
Antihypertensive received	0.61 (0.46, 0.81)	<0.001	0.66 (0.51, 0.87)	0.026
Antidepressants received	1.12 (0.91, 1.37)	0.289		
Antipsychotics received	0.79 (0.63, 0.99)	0.043	0.88 (0.73, 1.07)	0.183
Analgesics received	1.43 (01.14, 1.80)	0.002	1.48 (1.19, 1.85)	0.001
Problem HoNOS present (*within 6 months before or after schizophrenia spectrum diagnosis*)				
Cognitive problems	1.23 (0.98, 1.53)	0.073		
Physical illness	1.44 (1.17, 1.78)	<0.001	1.48 (1.21, 1.81)	<0.001
Depressed mood	0.91 (0.73, 1.14)	0.415		
Daily living problems	0.95 (0.77, 1.17)	0.645		
Admitted to general hospital (*within one year before or after diagnosis of schizophrenia spectrum disorder*)				
Ischaemia + CHD + IHD	1.80 (1.28, 2.55)	<0.001	1.72 (1.26, 2.35)	<0.001
Arrhythmia + AF	1.91 (1.39, 2.63)	<0.001	1.90 (1.4, 2.59)	<0.001
Heart failure	1.29 (0.79, 2.08)	0.307		
Diabetes	1.77 (1.24, 2.51)	<0.001	1.78 (1.27, 2.49)	<0.001
Hypotension	1.92 (1.17, 3.14)	0.010	1.78 (1.1, 2.89)	0.007
Hypercholesterolemia	0.88 (0.60, 1.28)	0.508		
Hypertension	2.79 (1.98, 3.95)	<0.001	2.77 (2.02, 3.8)	<0.001
Diseases of genitourinary system including UTI	1.79 (1.30, 2.47)	<0.001	1.74 (1.28, 2.36)	<0.001
Osteoporosis	1.05 (0.68, 1.62)	0.820		
Visual disturbance and blindness	5.01 (2.66, 9.43)	<0.001	5.04 (2.76, 9.19)	<0.001
Hearing loss	1.25 (0.70, 2.23)	0.459		
Syncope or collapse	2.01 (1.37, 2.96)	<0.001	2.12 (1.46, 3.08)	<0.001
Parkinson's disease	2.71 (1.72, 4.26)	<0.001	2.77 (1.79, 4.27)	<0.001
Falls before schizophrenia spectrum disorder diagnosis	0.85 (0.62, 1.16)	0.306		
Fractures before schizophrenia spectrum disorder diagnosis	1.10 (0.82, 1.50)	0.515		

Model 1 includes all significant univariable predictors of falls, whilst model 2 is the final model and includes only significant predictors of falls after removal of non-significant (at $P < 0.05$ level) predictors.

a history of co-morbid physical illnesses (in particular cardiovascular and metabolic diseases), analgesic use were associated with an increased hazard of hospital admission due to falls and fractures, whilst receipt of antihypertensive medication, and being non-white ethnicity were all associated with a reduced risk. We found no relationship between antipsychotic medication and falls or fractures in the fully adjusted models. Of note, a previous fracture and osteoporosis were strong risk factors for future fractures in the cohort, which is a concern given that a previous meta-analysis found that half of people with schizophrenia-spectrum disorders had osteoporosis or osteopenia (Stubbs et al., 2014b). Given that the falls recorded were those that required hospitalisation (i.e. the most severe), the true incidence of actual falls is likely to be much higher.

Our data shed new light on the hospital length of stay burden from people with schizophrenia who experience a fall of fracture. The rate of inpatient hospital stay of 12.79 and 11.65 years per 1000-person years of follow-up due to a fall and fracture respectively is of concern. Little previous information is available on the length and duration of hospital admission due to falls and fractures in schizophrenia spectrum disorders. A previous study considering over 10 million hip fractures in a range of psychiatric conditions (Menendez et al., 2013), established that patients with schizophrenia (0.6% of the sample) spent more time in hospital than (11 days) than any other patient group, including those with dementia, where there has been an increasing body of research attempting to prevent falls and fractures (Bunn et al., 2014; Chan et al., 2015). The authors (Menendez et al., 2013) found that lengthened stay was attributed to the greatly increased number of adverse events such as pneumonia, acute renal failure and deep venous thrombosis compared to those without mental illness.

There is considerable recognition from the general medical literature that the development and prediction of fractures is complex and multifactorial (Kanis, 2002a, 2002b; Kanis et al., 2010, 2013). The risk factors for falls and fractures in people with schizophrenia-spectrum disorders are perhaps even more complex/multifactorial and our data attempts to disentangle some of the key risk factors. Specifically, our data suggest that pre-existing comorbid physical health conditions, particularly cardiovascular, metabolic and osteoporosis are associated with future hospital admissions due to falls. An extensive evidence base has demonstrated that people with schizophrenia-spectrum have considerably worse physical health compared to the general population (De Hert et al., 2011a, 2011b; Correll et al., 2015) including diabetes and cardiometabolic abnormalities (Vancampfort et al., 2015, 2016; Correll et al., 2017) which are known to be key risk factors for fractures (Abdulameer et al., 2012). Despite the poor physical health of people with schizophrenia spectrum, few studies have considered comorbid physical illnesses and falls. To our knowledge, only one study (Tsai et al., 2014) has previously established that diabetes (HR 1.55) and hypertension (HR 1.24) were associated with hip fractures in people with schizophrenia. Our data suggest that arrhythmia and atrial fibrillation, hypertension, genitourinary disease and UTIs, visual disturbance and blindness, and syncope or collapse are associated with an increased longer-term risk of both falls and fractures whilst diabetes, hypotension, Parkinson's disease were associated with falls only. Osteoporosis was a significant risk factor for fractures only. It should clearly be noted that these diagnoses were extracted from those associated with previous hospitalisations (although not necessarily the primary cause of the hospitalisation), and will represent an underestimation. Perhaps unsurprisingly, osteoporosis, a common condition in schizophrenia at a much

Please cite this article as: Stubbs, B., et al., Predictors of falls and fractures leading to hospitalization in people with schizophrenia spectrum disorder: A large representativ..., Schizophr. Res. (2018), https://doi.org/10.1016/j.schres.2018.05.010

Table 4
Two models showing predictors of first fracture hospital admission among schizophrenia spectrum disorder patients.

Characteristics	Model 1 ($n = 9176$)		Model 2 ($n = 9203$)	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
10-year increase in age	1.27 (1.19, 1.36)	<0.001	1.27 (1.19, 1.35)	<0.001
Female gender	0.97 (0.79, 1.2)	0.776		
Non-white ethnicity	0.60 (0.48, 0.75)	<0.001	0.60 (0.48, 0.74)	<0.001
Living alone	1.17 (0.95, 1.44)	0.147		
Medication prescribed (*within one year before or after diagnosis of schizophrenia spectrum disorder*)				
Anticholinergics received	1.03 (0.82, 1.28)	0.817		
Antihypertensive received	0.79 (0.58, 1.09)	0.156		
Antipsychotics received	0.91 (0.72, 1.16)	0.456		
Analgesics received	1.51 (1.18, 1.93)	<0.001	1.47 (1.17, 1.86)	<0.001
Problem HoNOS present (*within 6 months before or after schizophrenia spectrum diagnosis*)				
Self-injury	1.16 (0.8, 1.67)	0.432		
Problem drinking drugs	2.00 (1.56, 2.58)	<0.001	2.17 (1.7, 2.77)	<0.001
Cognitive problems	1.16 (0.91, 1.46)	0.224		
Physical illness	1.72 (1.38, 2.15)	<0.001	1.72 (1.38, 2.15)	<0.001
Daily living problems	0.72 (0.58, 0.9)	0.004	0.77 (0.62, 0.94)	0.013
Admitted to general hospital (*within one year before or after diagnosis of schizophrenia spectrum disorder*)				
Ischaemia + CHD + IHD	1.31 (0.88, 1.95)	0.186		
Arrhythmia + AF	1.67 (1.16, 2.41)	0.005	1.69 (1.19, 2.39)	0.003
Heart failure	0.56 (0.27, 1.17)	0.124		
Diabetes	1.54 (1.03, 2.32)	0.036	1.37 (0.92, 2.05)	0.117
Hypotension	1.34 (0.75, 2.38)	0.321		
Hypercholesterolemia	0.59 (0.38, 0.92)	0.021	0.63 (0.41, 0.96)	0.031
Hypertension	2.38 (1.64, 3.45)	<0.001	2.36 (1.65, 3.38)	<0.001
Diseases of genitourinary system including UTI	1.93 (1.36, 2.75)	<0.001	1.83 (1.29, 2.57)	<0.001
Osteoporosis	6.92 (4.76, 10.06)	<0.001	6.79 (4.71, 9.78)	<0.001
Visual disturbance and blindness	3.13 (1.53, 6.43)	0.002	3.10 (1.55, 6.21)	<0.001
Hearing loss	1.62 (0.86, 3.07)	0.136		
Syncope or collapse	2.25 (1.39, 3.63)	0.001	2.30 (1.45, 3.67)	<0.001
Parkinson's disease	1.20 (0.67, 2.16)	0.538		
Falls before schizophrenia spectrum disorder diagnosis	0.69 (0.49, 0.97)	0.034	0.80 (0.58, 1.1)	0.164
Fractures before schizophrenia spectrum disorder diagnosis	1.96 (1.46, 2.64)	<0.001	2.05 (1.53, 2.73)	<0.001

Model 1 includes all significant univariable predictors of fractures, whilst model 2 is the final model and includes only significant predictors of fractures after removal of non-significant (at $P < 0.05$ level) predictors.

younger age than the general population (Stubbs et al., 2014b), was strongly (HR: 6.79) associated with hospital admission due to fractures. Moreover, a previous fracture was also associated with a future fracture. Despite this, there are, to the best of our knowledge, no interventions that have specifically sought to prevent or manage osteoporosis or fractures in people with schizophrenia-spectrum disorders. This is a point of major inequity, especially given that a recent meta-analysis demonstrated that 50% of people with schizophrenia spectrum with a mean age of 44 years had low bone mass (i.e. osteopenia or osteoporosis) according to DEXA scans (Stubbs et al., 2014c).

Interestingly, we found no relationship between antipsychotic medication and falls or fractures in the full adjusted models. The literature to date considering the impact of antipsychotic medication on both bone mineral density and fractures has lacked clarity and has been compounded by failure to consider other important confounders (De Hert et al., 2016). A previous review (Kishimoto et al., 2012) found that whilst 60% of studies suggested that antipsychotic medication, and in particular prolactin-raising medication, was associated with lower bone mineral density, there were inadequacies in the consideration of other risk factors and the studies were hampered by small sample sizes. When considering fractures, some studies have not found that antipsychotic medication is associated with fractures (Bolton et al., 2008) whilst other studies have (Sorensen et al., 2013; Tsai et al., 2014; Wu et al., 2015). A recent study in Canada found that antipsychotic medication (across several psychiatric diagnoses) was an independent predictor of hip fracture above and beyond traditional risk factors considered in the FRAX fracture risk assessment tool (Bolton et al., 2017). The reasons for the inconsistencies are not clear but warrent further investigation. Also of surprise is that in the univariate analysis benzodiapines were not associated with falls and the precise reasons for this are unclear. In addition, the univariable models suggested that anticholinergic medication appeared protective of falls, although this disappeared in the multivariable models, suggesting other factors highlighted above are more important. Our data also suggests that analgesics agents may be associated with falls and fractures. In the general population, research has demonstrated that analgesic use (Leveille et al., 2002) and pain (Stubbs et al., 2014a) are associated with falls. A previous meta-analysis demonstrated that a third of people with schizophrenia spectrum had clinical pain (Stubbs et al. (2014d)). The underlying relationship between analgesics and increased falls, may in fact be attributed to underlying physical comorbidities, although clearly more work is required to understand these relationships. However, our data was also suggest that antihypertensive medication was associated with reduced falls but not fractures. Finally, non-white ethnicity was associated with a protective effect of falls and fractures in the sample. The reasons for this are unclear and warrant investigation.

The current study adds to the limited data on hospital admission due to falls, which are often a precursor to fractures. A number of physical comorbidities recorded were associated with both falls and fractures, which is in line with the general falls/fracture literature. Much in line with the absence of efforts to improve the bone health and prevent fractures in people with schizophrenia spectrum, there is to the best of our knowledge no interventions that have sought to understand or prevent falls in this population. Given the remarkably poor bone health at young age (50% with low bone mass at 44 years) (Stubbs et al., 2014b), increased fracture and falls risk and the increased adverse consequences which appear more marked than other at risk populations (Menendez et al., 2013), the absence of research attempting to improve bone health and prevent falls and fractures strikes as a major inequity.

Our data have potentially important implications for clinicians and policy makers. The key message is that people with schizophrenia-spectrum disorders should be screened for falls risk, particularly those

Please cite this article as: Stubbs, B., et al., Predictors of falls and fractures leading to hospitalization in people with schizophrenia spectrum disorder: A large representativ..., Schizophr. Res. (2018), https://doi.org/10.1016/j.schres.2018.05.010

who are older, or who have comorbid medical comorbidities (particularly cardiovascular disease). In addition to screening for traditional falls risk factors such as the assessment of gait, balance and mobility, muscle weakness and visual impairments, such an assessment should also include an evaluation of the risk for osteoporosis, a cardiovascular and metabolic examination, a medication review in order to identify people at high risk. Given the reduced bone mineral density among people with schizophrenia-spectrum (De Hert et al., 2016) it is imperative that any falls screening interventions seek to also target improvements in bone health. If a person is identified as being a high risk of falls, multifactorial interventions should include an exercise component under supervision of a physiotherapist, given that exercise was identified as the most consistently effective intervention to prevent falls in older adults (Stubbs et al., 2015a), although clearly research specifically among people with schizophrenia-spectrum is required to establish the best evidence.

Whilst the current data are novel, some important limitations should be noted. First, it was not possible to collect information on pre-fall/fracture mobility, balance and physical performance levels, which are key risk factors for falls (Deandrea et al., 2010). Additional research is required to understand mobility limitations for people with psychosis and specifically if interventions can be developed to reduce these pertinent risk factors. Second, it was not possible to decipher the different types of fracture that occurred during the study. Future research is required to explore this, with a particular emphasis on hip fractures which are associated with particular deleterious outcomes (Menendez et al., 2013). Third, the study relied only on falls and fractures leading a hospital admission, thus it is likely that the figures and predictors for falls in particular may differ and require investigation. Fourth, it was not possible to decipher the potential differential effects of individual antipsychotic agents and their relationship with falls and fractures. Fifth, schizophrenia spectrum is recognised as being heterogeneous and future research should consider how the risk and predictors of falls and fractures may differ on this diagnostic continuum. Finally, we did not have a healthy control group to compare the outcomes and predictors of the study.

5. Conclusion

Our data found that over a 6 year period, 7% of a large cohort with schizophrenia spectrum were admitted to hospital due to a fall or fracture. Much in line with the general population, older age, comorbid physical health disorders and some physical health medications are predictors of falls and fractures in people with schizophrenia spectrum disorders. Of note, osteoporosis and a previous fracture were strongly associated with a subsequent fracture. The mean and total length of stay following falls and fractures for people with schizophrenia-spectrum are considerable. Our study investigated falls requiring hospitilisation (i.e. the most severe end of the spectrum) and falls of a less severe nature are almost certainly more common and future research is required to understand this issue. Future bone health promotion interventions targeting reducing falls and fractures are indicated among people with schizophrenia spectrum.

Acknowledgements

BS is supported by Health Education England and the National Institute for Health Research HEE/NIHR ICA Programme Clinical Lectureship (ICA-CL-2017-03-001). BS and FG are part supported by the Maudsley Charity and the National Institute for Health Research (NIHR) Collaboration for Leadership in Applied Health Research and Care South London at King's College Hospital NHS Foundation Trust.

The Clinical Records Interactive Search (CRIS) system was funded and developed by the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London, and by a joint infrastructure grant from Guy's and St Thomas' Charity and the Maudsley Charity.

BS, FG, CM., GP, RS are part funded by the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

The views expressed in this article are those of the author(s) and not necessarily those of the NHS, the NIHR, or the Department of Health and Social Care. SEL is supported by the National Institute of Health Research (NIHR) Oxford CLAHRC at Oxford Health NHS Trust, and by the Oxford NIHR Biomedical Research Centre at the Oxford University Health NHS Trust.

AK's work was supported by the Miguel Servet contract financed by the CP13/00150 and PI15/00862 projects, integrated into the National R + D + I and funded by the ISCIII - General Branch Evaluation and Promotion of Health Research - and the European Regional Development Fund (ERDF-FEDER).

Conflict of interest

BS, CM, GP, SS, SEL, DV, JL, SS, AK declares no conflict of interest. RS has received research funding from Roche, Pfizer, Janssen, Lundbeck and GSK outside the submitted work. Outside the submitted work, FG has received honoraria for advisory work and lectures or CME activity support from Roche, BMS, Lundbeck, Otsuka, Janssen and Sunovion, is a collaborator on a NHS Innovations project co-funded by Janssen and has a family member with professional links to Lilly and GSK, including shares.

Contributors

BS, RS, CM, GP designed the study, acquired the data and conducted the analysis with input from all co-authors. BS wrote the first draft of the manuscript with critical comments from all authors. All authors approved the final version.

Role of funding source

The funders had no role in the research at any stage or in the write up or the decision to publish.

References

Abdulameer, S.A., Sulaiman, S.A., Hassali, M.A., Subramaniam, K., Sahib, M.N., 2012. Osteoporosis and type 2 diabetes mellitus: what do we know, and what we can do? Patient Prefer. Adherence 6, 435–448.

Bolton, J.M., Metge, C., Lix, L., Prior, H., Sareen, J., Leslie, W.D., 2008. Fracture risk from psychotropic medications: a population-based analysis. J. Clin. Psychopharmacol. 28 (4), 384–391.

Bolton, J.M., Morin, S.N., Majumdar, S.R., Sareen, J., Lix, L.M., Johansson, H., Oden, A., McCloskey, E.V., Kanis, J.A., Leslie, W.D., 2017. Association of mental disorders and related medication use with risk for major osteoporotic fractures. JAMA Psychiatry 74 (6), 641–648.

Bunn, F., Burn, A.M., Goodman, C., Rait, G., Norton, S., Robinson, L., Schoeman, J., Brayne, C., 2014. Comorbidity and dementia: a scoping review of the literature. BMC Med. 12, 192.

Chan, W.C., Yeung, J.W., Wong, C.S., Lam, L.C., Chung, K.F., Luk, J.K., Lee, J.S., Law, A.C., 2015. Efficacy of physical exercise in preventing falls in older adults with cognitive impairment: a systematic review and meta-analysis. J. Am. Med. Dir. Assoc. 16 (2), 149–154.

Chang, C.K., Hayes, R.D., Broadbent, M., Fernandes, A.C., Lee, W., Hotopf, M., Stewart, R., 2010. All-cause mortality among people with serious mental illness (SMI), substance use disorders, and depressive disorders in southeast London: a cohort study. BMC Psychiatry 10, 77.

Correll, C.U., Detraux, J., De Lepeleire, J., De Hert, M., 2015. Effects of antipsychotics, antidepressants and mood stabilizers on risk for physical diseases in people with schizophrenia, depression and bipolar disorder. World Psychiatry: Off. J. World Psychiatric Assoc. (WPA) 14 (2), 119–136.

Correll, C.U., Solmi, M., Veronese, N., Bortolato, B., Rosson, S., Santonastaso, P., Thapa-Chhetri, N., Fornaro, M., Gallicchio, D., Collantoni, E., Pigato, G., Favaro, A., Monaco, F., Kohler, C., Vancampfort, D., Ward, P.B., Gaughran, F., Carvalho, A.F., Stubbs, B., 2017. Prevalence, incidence and mortality from cardiovascular disease in patients with pooled and specific severe mental illness: a large-scale meta-analysis of 3,211,768 patients and 113,383,368 controls. World Psychiatry 16 (2), 163–180.

Das-Munshi, J., Chang, C.K., Dutta, R., Morgan, C., Nazroo, J., Stewart, R., Prince, M.J., 2017. Ethnicity and excess mortality in severe mental illness: a cohort study. Lancet Psychiatry 4 (5), 389–399.

De Hert, M., Cohen, D., Bobes, J., Cetkovich-Bakmas, M., Leucht, S., Ndetei, D.M., Newcomer, J.W., Uwakwe, R., Asai, I., Möller, H.-J., Gautam, S., Detraux, J., Correll, C.U., 2011a. Physical illness in patients with severe mental disorders. II. Barriers to care, monitoring and treatment guidelines, plus recommendations at the system and individual level. World Psychiatry: Off. J. World Psychiatric Assoc. (WPA) 10 (2), 138–151.

De Hert, M., Correll, C.U., Bobes, J., Cetkovich-Bakmas, M., Cohen, D., Asai, I., Detraux, J., Gautam, S., Möller, H.-J., Ndetei, D.M., Newcomer, J.W., Uwakwe, R., Leucht, S., 2011b. Physical illness in patients with severe mental disorders. I. Prevalence, impact of medications and disparities in health care. World Psychiatry: Off. J. World Psychiatric Assoc. (WPA) 10 (1), 52–77.

De Hert, M., Detraux, J., Stubbs, B., 2016. Relationship between antipsychotic medication, serum prolactin levels and osteoporosis/osteoporotic fractures in patients with schizophrenia: a critical literature review. Expert Opin. Drug Saf. 1–15.

Deandrea, S., Lucenteforte, E., Bravi, F., Foschi, R., La Vecchia, C., Negri, E., 2010. Risk factors for falls in community-dwelling older people: a systematic review and meta-analysis. Epidemiology (Cambridge, Mass.) 21 (5), 658–668.

Dipasquale, S., Pariante, C.M., Dazzan, P., Aguglia, E., McGuire, P., Mondelli, V., 2013. The dietary pattern of patients with schizophrenia: a systematic review. J. Psychiatr. Res. 47 (2), 197–207.

Gomez, L., Stubbs, B., Shirazi, A., Vancampfort, D., Gaughran, F., Lally, J., 2016. Lower bone mineral density at the hip and lumbar spine in people with psychosis versus controls: a comprehensive review and skeletal site-specific meta-analysis. Curr. Osteoporos. Rep. 14 (6), 249–259.
Gonzalez-Blanco, L., Greenhalgh, A.M.D., Garcia-Rizo, C., Fernandez-Egea, E., Miller, B.J., Kirkpatrick, B., 2016. Prolactin concentrations in antipsychotic-naive patients with schizophrenia and related disorders: a meta-analysis. Schizophr. Res. 174 (1–3), 156–160.
Hayes, R.D., Chang, C.K., Fernandes, A., Broadbent, M., Lee, W., Hotopf, M., Stewart, R., 2011. Associations between substance use disorder sub-groups, life expectancy and all-cause mortality in a large British specialist mental healthcare service. Drug Alcohol Depend. 118 (1), 56–61.
Johnell, O., Kanis, J.A., 2004. An estimate of the worldwide prevalence, mortality and disability associated with hip fracture. Osteoporos. Int. 15 (11), 897–902.
Johnell, O., Kanis, J.A., 2006. An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. Osteoporos. Int. 17 (12), 1726–1733.
Kanis, J.A., 2002a. Diagnosis of osteoporosis and assessment of fracture risk. Lancet 359 (9321), 1929.
Kanis, J.A., 2002b. Osteoporosis III: diagnosis of osteoporosis and assessment of fracture risk. Lancet 359 (9321), 1929–1936.
Kanis, J.A., McCloskey, E.V., Johansson, H., Oden, A., Ström, O., Borgström, F., 2010. Development and use of FRAX in osteoporosis. Osteoporos. Int. J. Result Cooperation Eur. Found. Osteoporos. Natl. Osteoporos. Found. U. S. A. 21 (Suppl. 2), S407–S413.
Kanis, J.A., McCloskey, E., Johansson, H., Cooper, C., Rizzoli, R., Reginster, J.Y., 2013. European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporos. Int. 24 (1), 23–57.
Kishimoto, T., De Hert, M., Carlson, H.E., Manu, P., Correll, C.U., 2012. Osteoporosis and fracture risk in people with schizophrenia. Curr. Opin. Psychiatry 25 (5), 415–429.
Lally, J., Gardner-Sood, P., Firdosi, M., Iyegbe, C., Stubbs, B., Greenwood, K., Murray, R., Smith, S., Howes, O., Gaughran, F., 2016. Clinical correlates of vitamin D deficiency in established psychosis. BMC Psychiatry 16 (1), 76.
Leveille, S.G., Bean, J., Bandeen-Roche, K., Jones, R., Hochberg, M., Guralnik, J.M., 2002. Musculoskeletal pain and risk for falls in older disabled women living in the community. J. Am. Geriatr. Soc. 50 (4), 671–678.
Menendez, M.E., Neuhaus, V., Bot, A.G., Vrahas, M.S., Ring, D., 2013. Do psychiatric comorbidities influence inpatient death, adverse events, and discharge after lower extremity fractures? Clin. Orthop. Relat. Res. 471 (10), 3336–3348.
Perera, G., Khondoker, M., Broadbent, M., Breen, G., Stewart, R., 2014. Factors associated with response to acetylcholinesterase inhibition in dementia: a cohort study from a secondary mental health care case register in London. PLoS One 9 (11), e109484.
Perera, G., Broadbent, M., Callard, F., Chang, C.K., Downs, J., Dutta, R., Fernandes, A., Hayes, R.D., Henderson, M., Jackson, R., Jewell, A., Kadra, G., Little, R., Pritchard, M., Shetty, H., Tulloch, A., Stewart, R., 2016a. Cohort profile of the South London and Maudsley NHS Foundation Trust Biomedical Research Centre (SLaM BRC) case register: current status and recent enhancement of an electronic mental health record-derived data resource. BMJ Open 6 (3), e008721.
Perera, G., Stewart, R., Higginson, I.J., Sleeman, K.E., 2016b. Reporting of clinically diagnosed dementia on death certificates: retrospective cohort study. Age Ageing 45 (5), 668–673.
Richardson, E.A., Mitchell, R.J., Shortt, N.K., Pearce, J., Dawson, T.P., 2009. Evidence-based selection of environmental factors and datasets for measuring multiple environmental deprivation in epidemiological research. Environ. Health 8 (Suppl. 1), S18.
Sanchez-Riera, L., Carnahan, E., Vos, T., Veerman, L., Norman, R., Lim, S.S., Hoy, D., Smith, E., Wilson, N., Nolla, J.M., Chen, J.S., Macara, M., Kamalaraj, N., Li, Y., Kok, C., Santos-Hernandez, C., March, L., 2014. The global burden attributable to low bone mineral density. Ann. Rheum. Dis. 73 (9), 1635–1645.
Sorensen, H.J., Jensen, S.O., Nielsen, J., 2013. Schizophrenia, antipsychotics and risk of hip fracture: a population-based analysis. Eur. Neuropsychopharmacol. 23 (8), 872–878.
Stubbs, B., Binnekade, T., Eggermont, L., Sepehry, A.A., Patchay, S., Schofield, P., 2014a. Pain and the risk for falls in community-dwelling older adults: systematic review and meta-analysis. Arch. Phys. Med. Rehab. 95 (1), 175–187 (e179).
Stubbs, B., De Hert, M., Sepehry, A.A., Correll, C.U., Mitchell, A.J., Soundy, A., Detraux, J., Vancampfort, D., 2014b. A meta-analysis of prevalence estimates and moderators of low bone mass in people with schizophrenia. Acta Psychiatr. Scand. 130 (6), 470–486.
Stubbs, B., Mitchell, A.J., De Hert, M., Correll, C.U., Soundy, A., Stroobants, M., Vancampfort, D., 2014c. The prevalence and moderators of clinical pain in people with schizophrenia: a systematic review and large scale meta-analysis. Schizophr. Res. 160 (1–3), 1–8.
Stubbs, B., Mitchell, A.J., De Hert, M., Correll, C.U., Soundy, A., Stroobants, M., Vancampfort, D., 2014d. The prevalance and moderators of clinical pain in people with schizophrenia: a systematic review and large scale meta-analysis. Schizophr. Res. 160 (1–3), 1–8.
Stubbs, B., Brefka, S., Denkinger, M., 2015a. What works to prevent falls in community dwelling older adults? An umbrella review of meta-analyses of randomised controlled trials. Phys. Ther. 95 (8), 1095–1110.
Stubbs, B., Gardner-Sood, P., Smith, S., Ismail, K., Greenwood, K., Farmer, R., Gaughran, F., 2015b. Sedentary behaviour is associated with elevated C-reactive protein levels in people with psychosis. Schizophr. Res. 168 (1-2), 461–464.
Stubbs, B., Gaughran, F., Mitchell, A.J., De Hert, M., Farmer, R., Soundy, A., Rosenbaum, S., Vancampfort, D., 2015c. Schizophrenia and the risk of fractures: a systematic review and comparative meta-analysis. Gen. Hosp. Psychiatry 37 (2), 126–133.
Stubbs, B., Vancampfort, D., De Hert, M., Mitchell, A.J., 2015d. The prevalence and predictors of type two diabetes mellitus in people with schizophrenia: a systematic review and comparative meta-analysis. Acta Psychiatr. Scand. 132 (2), 144–157.
Sultana, J., Chang, C.K., Hayes, R.D., Broadbent, M., Stewart, R., Corbett, A., Ballard, C., 2014. Associations between risk of mortality and atypical antipsychotic use in vascular dementia: a clinical cohort study. Int. J. Geriatr. Psychiatry 29 (12), 1249–1254.
Tsai, K.Y., Lee, C.C., Chou, Y.M., Shen, S.P., Su, C.Y., Wu, H.C., Huang, M.W., Shie, J.P., Chou, F.H., 2014. The risks of major osteoporotic fractures in patients with schizophrenia: a population-based 10-year follow-up study. Schizophr. Res. 159 (2–3), 322–328.
Tseng, P.T., Chen, Y.W., Yeh, P.Y., Tu, K.Y., Cheng, Y.S., Wu, C.K., 2015. Bone mineral density in schizophrenia: an update of current meta-analysis and literature review under guideline of PRISMA. Medicine (Baltimore) 94 (47), e1967.
Vancampfort, D., Stubbs, B., Mitchell, A.J., De Hert, M., Wampers, M., Ward, P.B., Rosenbaum, S., Correll, C.U., 2015. Risk of metabolic syndrome and its components in people with schizophrenia and related psychotic disorders, bipolar disorder and major depressive disorder: a systematic review and meta-analysis. World Psychiatry: Off. J. World Psychiatric Assoc. (WPA) 14 (3), 339–347.
Vancampfort, D., Correll, C.U., Galling, B., Probst, M., De Hert, M., Ward, P.B., Rosenbaum, S., Gaughran, F., Lally, J., Stubbs, B., 2016. Diabetes mellitus in people with schizophrenia, bipolar disorder and major depressive disorder: a systematic review and large scale meta-analysis. World Psychiatry 15 (2), 166–174.
Ward, G., Perera, G., Stewart, R., 2015. Predictors of mortality for people aged over 65 years receiving mental health care for delirium in a South London Mental Health Trust, UK: a retrospective survival analysis. Int. J. Geriatr. Psychiatry 30 (6), 639–646.
Wing, J.K., Beevor, A.S., Curtis, R.H., Park, S.B., Hadden, S., Burns, A., 1998. Health of the Nation Outcome Scales (HoNOS). Research and development. Br. J. Psychiatry 172, 11–18.
Wu, C.S., Chang, C.M., Tsai, Y.T., Huang, Y.W., Tsai, H.J., 2015. Antipsychotic treatment and the risk of hip fracture in subjects with schizophrenia: a 10-year population-based case-control study. J. Clin. Psychiatry 76 (9), 1216–1223.

Please cite this article as: Stubbs, B., et al., Predictors of falls and fractures leading to hospitalization in people with schizophrenia spectrum disorder: A large representativ..., Schizophr. Res. (2018), https://doi.org/10.1016/j.schres.2018.05.010