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Is there a disparity in osteoporosis referral and treatment among people with affective disorders? A ten-year data linkage study

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ABSTRACT

Aims: People with affective disorders (AD) are at increased risk of osteoporosis and fractures. Osteoporosis treatment/referral is thus essential in this population. However, it is unclear whether osteoporosis treatment/referral differs between those with and without AD. This retrospective cohort study compared osteoporosis treatment/referral in people with and without AD across linked primary and mental health care data.

Methods: People with AD (ICD-10 codes F3*) between 1.5.2009–30.11.2019, aged 18+ at first diagnosis, from Lambeth, South London were randomly matched 1:4 to healthy controls based on age band and gender. Outcomes including treatments (prescription of calcium, calcium with vitamin D) and referral (referrals for osteoporosis screening and/or prevention) were analysed using conditional and multivariable logistic regression analyses.

Results: People with AD ($n = 23{,}932$) were more likely than controls ($n = 76{,}593$) to have a recorded prescription of calcium (odds ratio [OR] = 1.64, 95 % confidence interval [CI] 1.40–1.92) and calcium with vitamin D (OR = 2.25, 95 % CI 2.10–2.41), and be referred for osteoporosis screening (OR = 1.87, 95 % CI 1.76–1.99) within 2 years after the date of the first AD diagnosis in adjusted analyses. Older age, female sex, having an ethnic minority background, Class A analgesics use were significant predictors for all osteoporosis management pathways within AD patients.

Conclusion: Findings from the present study suggest that compared to the general population, people with AD are more likely to receive osteoporosis screening/treatments. Whether this increased screening/treatment is sufficient to reduce the burden of osteoporosis and fractures in this population is unclear and warrants further consideration.

1. Introduction

Osteoporosis is a chronic skeletal condition characterised by a low bone mineral density (BMD) and microarchitectural deterioration of the bone tissue [1]. Reduced bone mass characterised by osteoporosis is a well-established risk factor for comorbidities such as diabetes [2], as well as an identified risk factor for premature mortality, regardless of people's age [3]. Osteoporosis is also associated with an increased risk of fractures (particularly hip fracture), leading to increased loss of disability-adjusted life-years, reduced quality of life [1], chronic pain

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and limited ambulation [4]. The prevalence of osteoporosis increases with age, with a global prevalence estimate of 18.3 % [5] and over $25 billion costs for osteoporosis and associated fractures by 2050 [6].

Affective disorders (AD) are chronic mental disorders marked by disruptions in emotions and include conditions such as depression, bipolar disorders (BD), and hypomania [7]. People with AD are at an increased risk of poor physical health, with obesity, metabolic syndrome and cardiovascular diseases being particularly prevalent [8]. Despite this heightened risk of physical health conditions, there is consistent evidence of inferior screening and treatment for major comorbidities among those with AD [9,10].

Compared to the general population, people with AD, including both depression [11,12] and BD 13,14] are at an increased risk of osteoporosis and reduced BMD, as well as increased incidences for falls [15]. For example, Li et al. [13] found an inverse relationship between depressive symptom severity and BMD in both L/R femur. A meta-analysis [15] also reported a reduced hip BMD among older adults with depression. In a case-control study [16], a 4.3 %, 1.6 % and 3.5 % lower BMD was found at the hip, total body and spine, respectively, among individuals with BD under 50 years old, compared to those without BD. Bone quality, measured by three ultrasounds measures, was also found to be lower among those with BD than the controls. Similarly, among a group of drug naive patients with BD, they had a significantly lower BMD level in the regions of total lumbar and left femur than the healthy controls, with a significantly higher prevalence of low bone mass and osteoporosis being reported [13]. Both depression and BD are also associated with increased risk of fractures. A large representative cohort study found approximately 8 % of people with AD were hospitalised with a fall or fracture over a 5-year follow-up period [17]. A 5-year longitudinal study reported a much higher odds for hip fractures among women with depressive symptoms compared to those without, after adjusting for confounders including age, economics, and lifestyle factors [18]. A systematic review also reported a 20–80 % increased risk of fractures but a decreased fracture-free survival time for individuals with BD. Incidence of fracture was 21.4 and 10.8 per 1000 person years among patients with BD and those without, respectively [19].

Both mental illness (e.g., AD) and musculoskeletal disorders (e.g., osteoporosis) are two leading causes of years lived due to disability [20], highlighting significant public health concerns. Osteoporosis screening is a crucial preventive measure to reduce risk of osteoporosis and fractures. Previous studies reported a 42 % reduced fracture recurrence in patients with fracture [21], a 28 % reduced hip fracture risk and a 78 % osteoporosis treatment uptake rate in women aged 70–85 years following an osteoporosis screening [22]. However, to the best of our knowledge, no study to date has examined referral and treatment rates of osteoporosis in patients with AD. This 10-year data linkage research therefore aims to investigate osteoporosis treatments, referral for osteoporosis screening and/or prevention among individuals with AD vs. non-AD controls.

2. Methods

2.1. Data source

This study obtained data from electronic health records (EHR) for primary and mental healthcare in a population-based electronic health record database linkage. Primary general practice (point-based numeric) data were retrieved from Lambeth Datanet (LDN), covering 96.8 % of primary care services in the borough of Lambeth in south London, and including over 827,000 registered adults. LDN provides pseudonymised clinical data including sociodemographic information (e.g., age, gender, ethnicity), consultations, service referrals and medications [23]. The borough of Lambeth is the 11th (out of 32) and the 81st (out of 309) most deprived borough in London and England, respectively [24]. Lambeth has a very diverse population, with 43 % identified as an ethnic-minority (Black, Asian or multi-ethnic) and a high proportion (24 %) having a Black, Black British African or British Caribbean background [25].

The primary care data from LDN has been linked to specialist mental healthcare EHR data from the South London and Maudsley NHS Foundation Trust (SLaM) Clinical Record Interactive Search (CRIS) [26]. SLaM is one of the largest secondary and tertiary mental healthcare providers in Europe, serving 4 local authorities (Croydon, Lambeth, Lewisham and Southwark) with an estimated 1.3 million population. De-identified CRIS data from structured fields in the EHR have been extensively supplemented by natural language process (NLP) applications to derive structured information from text fields [26]. CRIS has full approval for secondary analysis (Oxford Research Ethnic Committee C, reference 23/SC/0257), and has been previously described in detail [26,27]. The LDN-CRIS linkage is regularly updated and curated by the SLaM Clinical Data Linkage Service, a local trusted safe haven service [26].

2.2. Study cohort and matched controls

People with AD in CRIS were identified based on an International Classification of Disease, Tenth Revision (ICD-10) diagnosis of mood disorder (ICD-10 codes F3*; [28]). AD in LDN was identified using relevant Read codes for AD [29]. The date of the first AD diagnosis recorded, either in CRIS or LDN, whichever recorded first served as the index date. Eligible patients were those aged 18 years and over at the time of first AD diagnosis and active in both CRIS and LDN for at least 2 years from the index date between 1st May 2010 and 30th November 2019. To avoid the potential impact of COVID-19 on the screening and treatment provision of long-term conditions (LTCs) in the UK, a pre-COVID study period was utilised.

AD patients and randomly selected non-AD controls (also without other mental illness ever identified by Read codes, including severe mental illnesses (SMI), anxiety, learning disabilities, eating disorders and personality disorders) were matched for gender and age band in LDN on a 1:4 ratio. The date of the first GP registration in LDN served as the index date for matched controls. Age was grouped into 5-year bands from 18 to 22 inclusive to 88+ years [30]. Controls were only included if data on all two matching variables were available.

2.3. Measures

Two outcomes served as co-primary outcomes for both cases and controls included prescription of osteoporosis medications and referral for osteoporosis screening, diagnostic tests and prevention/education programmes. All outcomes were recorded within 2 years after the index date and derived from LDN using relevant Read and Dictionary of medicines and devices codes. Whether any recorded prescription of a medication for osteoporosis (i.e., calcium, calcium + vitamin D) was prescribed within 2 years after the index date was created into a binary variable. Bisophosphonate prescription was also extracted but later removed when examining the predictors of outcomes, due to insufficient numbers being prescribed ($n = 84$ within the whole sample). Another binary variable was created to indicate whether osteoporosis screening and/or prevention (e.g., dual energy x-ray photon absorptiometry scan, osteoporosis exercise education) was offered within 2 years after the index date.

Covariates including sociodemographic information, comorbidity score, age at index date, ethnicity, 2011-defined lower super output area (LSOA) and medications were included. LSOA are geographic areas of residence (32,8444 in total in England) covering an average of 1500 residence or 650 households [31], and were used to derive a deprivation score, the Index of Multiple Deprivation (IMD15), for both cases and controls based on areas of residence closest to the index date. Ethnicity was categorised into four categories (White, Black, Asian, Mixed and/or other). Defined by Read codes, data on 17 LTCs was derived from LDN, including myocardial infarct, HIV/AIDS, renal failure, respiratory

disease, connective tissue disorders, peptic ulcer disease, heart failure, mild and severe liver disease, stroke, paralytic syndromes (e.g., hemiplegia, paraplegia), dementia, diabetes and associated complications, cancer, peripheral arterial disease and metastases. A revised Charlson Comorbidity Index [32,33] was applied to generate a comorbidity score to quantify comorbidity. Antipsychotics, antidepressants, mood stabilisers, anxiolytics and hypnotics were obtained from both CRIS and LDN. Analgesics (non-opioids and compound prescriptions [Class A], opioids [Class B], analgesics for neuropathic pain [Class C] and antimigraine analgesics [Class D]) and antihypertensives (renin-angiotensin-aldosterone system [Class A], beta blockers [Class B], Calcium antagonists [Class C], diuretics [Class D] and other/combined [Class E]) were also extracted from LDN. Binary variables were created to indicate whether or not these medication groups were prescribed within 1 year before and after the index.

2.4. Statistical analysis

Data were tested for normality using Kolmogorov-Smirnov tests and then characteristic differences between cases and controls were examined using *t*-tests (for continuous variables) and Pearson's Chi-Square tests (for categorical variables). Within the whole sample, using conditional logistic regression, the association between an AD diagnosis and two co-primary outcomes (i.e., osteoporosis treatments and referral for screening and/or prevention) were examined in 3 steps: an unadjusted model (Model 1), an ethnicity-adjusted model (Model 2), a model adjusted for ethnicity, deprivation and comorbidity score (Model 3) and a model additionally adjusted for analgesics and antihypertensives prescribed after the index date (Model 4). Since cases and controls were matched on age band and gender, these variables were not accounted for in our models.

Predictors of osteoporosis treatment and referral within 2 years after the index date was further investigated within cases in logistic regression models. The predictor variables including age at initial diagnosis (cases only), AD diagnoses (cases only), gender, ethnicity, deprivation score, comorbidity score and medications (only analgesics and antihypertensives after index date were included for controls) were entered initially into the univariate models. Mood stabilisers use before index date was removed from the model for calcium prescriptions due to collinearity. Factors that yielded a *p*-value ≤ 0.05 were then simultaneously entered into multivariable models. Odds ratios (ORs) and 95 % confidence intervals (CI) were reported. All analyses were conducted using STATA 18 (do software (Stata Corp LP, College Station, TX).

3. Results

The total sample included 100,525 people, including 23,932 patients with AD (mean age 47.0, SD = 14.7; 58 % female) and 76,593 non-AD controls (mean age 47.1, SD = 14.8; 56 % female). Within the AD cohort, 23,607 (98.64 %) had depressive disorders, and 325 (1.36 %) had a BD or mania or other unspecified AD. Within 2 years after the index date, there were 842, 4877 and 7284 recorded receipts of calcium, calcium + vitamin D and osteoporosis screening and/or prevention, respectively. Table 1 compares the characteristics of AD and non-AD matched controls. The comparison identified that compared to non-AD controls, AD cases had a higher deprivation score and comorbidity

Table 1
Comparison of variables between AD cases and non-AD control.

Variables	Total (n = 100,518)		AD cases (n = 23,932)		Non-AD controls (n = 76,593)			
	Mean (SD) or %	N	Mean (SD) or %	N	Mean (SD) or %	N	Chi-square (df)	*P* value
Age	47.1 (14.81)	100,518	47.0 (14.72)	23,932	47.2 (14.8)	76,586		
Gender								
Male	43.9 %	44,090	41.9 %	10,015	44.5 %	34,075		
Female	56.1 %	56,435	58.1 %	13,917	55.5 %	42,518		
Ethnicity							1.1(3)	**<0.001**
White	52.6 %	52,871	57.6 %	13,772	51.1 %	39,099		
Black	18.0 %	18,078	19.4 %	4640	17.5 %	13,438		
Asian	7.2 %	7248	5.9 %	1417	7.6 %	5831		
Mixed/others	7.1 %	7158	8.3 %	1986	6.8 %	5172		
Deprivation score	28.5 (9.9)	97,263	29.2 (9.8)	23,375	28.2 (9.9)	74,050		**<0.001**
Comorbidity score	0.20 (0.7)	100,525	0.3 (0.9)	23,932	0.1 (0.6)	76,593		**<0.001**
Calcium prescription (Yes)	0.8 %	842	1.4 %	336	0.7 %	506	121.3 (1)	**<0.001**
Calcium with vitamin D prescription (Yes)	4.8 %	4877	9.0 %	2151	3.6 %	2726	1.2 (1)	**<0.001**
Osteoporosis screening and/or prevention (Yes)	7.3 %	7284	11.5 %	2760	5.9 %	4524	857.8 (1)	**<0.001**
Analgesics after index date								
Class A (Yes)	8.0 %	8085	15.4 %	3681	5.8 %	4404	2.3 (1)	**<0.001**
Class B (Yes)	2.1 %	2152	4.7 %	1130	1.3 %	1022	998.7 (1)	**<0.001**
Class C (Yes)	0.6 %	583	1.6 %	385	0.3 %	198	**576.5 (1)**	**<0.001**
Class D (Yes)	0.9 %	944	1.9 %	447	0.7 %	497	291.2 (1)	**<0.001**
Antihypertensives after index date								
Class A (Yes)	5.3 %	5291	7.4 %	1774	4.6 %	3517	291.0 (1)	**<0.001**
Class B (Yes)	2.9 %	2910	6.7 %	1605	1.7 %	1305	1.6 (1)	**<0.001**
Class C (Yes)	0.3 %	283	0.4 %	83	0.3 %	200	4.8 (1)	**0.03**
Class D (Yes)	1.4 %	1373	1.7 %	395	1.3 %	978	18.9 (1)	**<0.001**
Class E (Yes)	0.9 %	940	1.3 %	298	0.8 %	642	32.6 (1)	**<0.001**

Variables with a p-value <0.05 are marked in bold.
Abbreviations
AD: affective disorder.
df: degree of freedom.
SD: standard deviation.

score, more calcium and calcium + vitamin D prescriptions, as well as more recorded osteoporosis screening and/or prevention. Further characteristics of AD patients are summarised in Supplementary Table 1.

3.1. Prescriptions of osteoporosis medications

Within the whole sample, having an AD diagnosis was independently associated with a higher recording of calcium and calcium + vitamin D being prescribed within 2 years after the index date (Table 2). The multivariable model indicates that within the AD cohort (Supplementary Table 2), older age at initial AD diagnosis, female sex, Asian ethnicity, antidepressants use after index, Class A analgesics use before and after index date were associated with a higher recording of calcium within 2 years after the index date. In the multivariable model for the AD

Table 2
Conditional logistic regression between 3 osteoporosis management pathways (AD/control), controlling for covariates.

Variables	Calcium prescriptions		Calcium + vitamin D prescriptions		Osteoporosis screening and/or prevention programmes	
	OR (95 %CI)	P value	OR (95 % CI)	P value	OR (95 % CI)	P value
Group						
Non-AD control	Reference		Reference		Reference	
AD cases	1.64 (1.40, 1.92)	**<0.001**	2.25 (2.10, 2.41)	**<0.001**	1.87 (1.76, 1.99)	**<0.001**
Ethnicity						
White	Reference		Reference		Reference	
Black	1.32 (1.06, 1.63)	**0.01**	1.79 (1.63, 1.98)	**<0.001**	0.73 (0.67, 0.79)	**<0.001**
Asian	1.66 (1.25, 2.21)	**<0.001**	2.77 (2.42, 3.17)	**<0.001**	0.73 (0.67, 0.86)	**<0.001**
Mixed/others	0.89 (0.61, 1.29)	0.53	1.36 (1.17, 1.59)	**<0.001**	0.81 (0.71, 0.92)	**0.002**
Deprivation score	1.00 (1.00, 1.01)	0.85	1.01 (1.00, 1.01)	**<0.001**	1.00 (0.99, 1.00)	**0.01**
Comorbidity score	1.18 (1.09, 1.26)	**<0.001**	1.21 (1.16, 1.26)	**<0.001**	1.19 (1.15, 1.23)	**<0.001**
Analgesics after index date						
Class A						
No	Reference		Reference		Reference	
Yes	1.92 (1.55, 2.37)	**<0.001**	2.62 (2.36, 2.90)	**<0.001**	1.68 (1.53, 1.84)	**<0.001**
Class B						
No	Reference		Reference		Reference	
Yes	1.30 (0.93, 1.81)	0.13	1.47 (1.23, 1.75)	**<0.001**	1.53 (1.31, 1,79)	**<0.001**
Class C						
No	Reference		Reference		Reference	
Yes	1.30 (0.75, 2.23)	0.35	1.51 (1.11, 2.06)	**0.01**	1.51 (1.15, 2.00)	**0.003**
Class D						
No	Reference		Reference		Reference	
Yes	1.92 (0.94, 3.92)	0.07	1.77 (1.31, 2.40)	**<0.001**	1.50 (1.13, 1.99)	**0.01**
Antihypertensives after index date						
Class A						
No	Reference		Reference		Reference	
Yes	1.22 (0.96, 1.56)	0.10	1.18 (1.03, 1.34)	**0.01**	1.20 (1.08, 1.34)	**0.001**
Class B						
No	Reference		Reference		Reference	
Yes	1.26 (0.92, 1.72)	0.15	1.53 (1.30, 1.81)	**<0.001**	1.09 (0.95, 1.26)	0.22
Class C						
No	Reference		Reference		Reference	
Yes	1.26 (0.62, 2.59)	0.52	1.49 (0.99, 2.23)	0.05	1.40 (0.98, 2.02)	0.07
Class D						
No	Reference		Reference		Reference	
Yes	0.95 (0.66, 1.38)	0.80	1.14 (0.93, 1.39)	0.20	1.05 (0.89, 1.25)	0.54
Class E						
No	Reference		Reference		Reference	
Yes	0.71 (0.45, 1.12)	0.14	0.77 (0.60, 0.98)	**0.04**	1.10 (0.90, 1.36)	0.35

Note: Conditional logistic regression model examined the association between an affective disorder diagnosis and calcium, calcium + vitamin D prescriptions, as well as referrals for osteoporosis screening and/or prevention programmes, after controlling for covariates including ethnicity, deprivation, comorbidity score, analgesics (Class A, B, C and D) and antihypertensives use (Class A, B, C, D and E) after index date.
Variables with a p-value <0.05 are marked in bold.
Abbreviations
AD: affective disorder.
CI: confidence interval.
OR: odds ratio.

cohort (Supplementary Table 3), older age at initial AD diagnosis, female sex, having an ethnic minority background, a higher deprivation score, a higher comorbidity score, mood stabilisers and antidepressants use before index, Class A and B analgesics use before index, antipsychotics and antidepressants use after index, Class A and D analgesics use after index, and Class B antihypertensives use after index were associated with a higher recording of calcium + vitamin D prescriptions within 2 years after index date.

3.2. Osteoporosis screening and/or prevention

Within the whole sample, having an AD diagnosis was independently associated with a higher recording of osteoporosis screening and/or prevention within 2 years after the index date (Table 2). In the multivariable model for AD cases (Supplementary Table 4), older age at initial AD diagnosis, female sex, a higher comorbidity score, Class A analgesics use before and after index, Class A antihypertensives use before index and Class B analgesics use after index were associated with a higher recording of osteoporosis screening and/or prevention within 2 years after the index date. Having an ethnic minority background was instead associated with a lower recording within AD patients.

4. Discussion

The current study is among the first representative primary and mental health care data linkage project investigating osteoporosis medication prescriptions and referrals for screening and/or prevention in patients with AD. Results of this study indicate that AD cases in our sample were more likely to have a recorded prescription for osteoporosis treatment including calcium and calcium + vitamin D, as well as referrals for osteoporosis screening and prevention than their matched non-AD controls. Older age at initial AD diagnosis, female sex and Class A analgesic use before and after index date were associated with all three osteoporosis management pathways (i.e., calcium, calcium + vitamin D prescriptions, referrals for osteoporosis screening and/or preventive programmes) among AD patients. However, it is also important to acknowledge that our sample was derived from one borough of London, and Lambeth is characterised by a high deprivation level and an extremely diverse population with a large number of people from an ethnic minority background. The generalisability of our results to the wider AD population in other parts of London and England is therefore limited. Further research is thus now required in other areas of England.

It has been widely established that people with BD and depression are less likely to be screened and receive proper care for their physical health problems [9,10], such as diabetes, cardiovascular disease [34], hypertension [35], bowel and breast cancer [36]. Surprisingly, this study found the opposite and suggests that patients with AD were more likely to receive osteoporosis medications and screening and/or prevention than their matched non-AD controls. There are a few reasons that could explain this finding. Firstly, some evidence suggests a higher likelihood of physical health monitoring in patients with recurrent depressive disorders than BD [10]. Given the majority of our sample are patients with a depressive disorder (99 %), this distribution could have skewed our results. Secondly, AD cases in our study had a higher comorbidity score than their matched non-AD controls. For the first time, an increased odds of being prescribed with osteoporosis medication and being referred for screening/prevention was found among those with a higher comorbidity score. Given their greater medical needs, AD patients with a higher comorbidity score may have engaged more regularly with their GP services, leading to more patient visits. This increased healthcare engagement may have contributed to a higher likelihood of osteoporosis screening and treatment during their GP visits. Additionally, there has been an increased awareness of the link between AD and osteoporosis which subsequently contributed to the dissemination of clinical guidelines emphasising osteoporosis screening for this vulnerable population, and this might have resulted in the changes observed in routine GP care [37]. Lastly and most importantly, primary osteoporosis is most commonly seen in post-menopausal women and the general population age 70+ due to aging [38], and the offer of osteoporosis monitoring in the UK for those with a diagnosis of osteoporosis does not occur till age 50+. Our study includes a relatively young cohort (mean age 47); therefore, it is not surprising that non-AD controls included in our sample were less likely to be treated or referred for osteoporosis. This result also suggests that AD patients experience osteoporosis at a much younger age than the general population.

Within our AD cohort, older age at initial AD diagnosis and female sex were associated with higher odds for osteoporosis medication prescriptions and referrals for screening/prevention. This is not surprising, as both aging [39] and being a female [40] are two well-established and independent factors of osteoporosis, and their needs for osteoporosis prevention and treatment are well acknowledged in primary care. In our study, Class A analgesics use was a significant factor associated with increased odds for all osteoporosis management pathways. Long-term use of analgesics has been recognised as detrimental for skeletal health, subsequently increase the risk of falls, fractures and osteoporosis [41,42], especially among people with SMI [43] and mood disorders [17]. Antidepressants use after index date was also associated with an increased odds of being prescribed with calcium and calcium + vitamin D among AD cases. It is widely acknowledged that antidepressants such as serotonin reuptake inhibitors, which are the first line treatment for depressive disorder, have an adverse effect on BMD and increase fracture risk [44,45], even with the first 14 days of use [46]. GPs in Lambeth are likely aware of the negative impact of antidepressant use on the bone fragility and osteoporosis. As a result, calcium and calcium + vitamin D are frequently prescribed to patients with AD as a preventive measure for reduced BMD and subsequent osteoporosis. In the current study, mood stabilisers had inconsistent effect on the record of osteoporosis medications and referrals for screening and/or prevention. This could be due to a small number of BD participants included in our study and a small amount of mood stabilisers being prescribed. Recent studies suggest a bone-protective effect of mood stabilisers like lithium [44], including decreased risks for falls, fractures and osteoporosis [47], as well as improved BMD and bone formation [48]. However, the exact mechanisms by which lithium has on bone health is not clear and contradicting findings have been reported [49]. Our study further illustrates the need to further understand the exact relationship between mood stabilisers and osteoporosis-related outcomes.

Despite higher odds of recorded osteoporosis medications, referrals for screening and/or prevention being found among our AD participants than the non-AD controls, current screening and treatment rates still may not be sufficient to adequately address the health inequalities in osteoporosis and its related falls and fracture outcomes experienced by people with AD. Previous studies recognised that people with SMI, including BD and major depressive disorders, were 2.5 times more likely to develop osteoporosis or osteopenia than the general population, as early as early 40's [50]. Similarly, the current study identified a young cohort of AD patients (mean age 47) being screened and treated for osteoporosis. These findings emphasise that there is an imperative need to take proactive actions to identify young AD patients who are at a higher risk for poor bone health, regardless of their age. Approaches that may prevent the development of osteopenia and osteoporosis, such as offering annual health review and including vitamin D blood test at a younger age and improving routine screening for fall risk and BMD level, are therefore recommended for people with AD. Additionally, previous studies reported reduced risks for fractures in the general population who were screened for osteoporosis [21,22], yet such study does not exist in vulnerable populations like AD and therefore could be further explored in future studies.

To the best of our knowledge, this is the first study providing novel evidence in relation to the rate of osteoporosis treatment, osteoporosis screening and/or treatment among patients with AD versus the general population. This study utilised an innovative data linkage approach and

included a large sample size, AD patients included were known to both primary GP and secondary mental health services, therefore improve the accuracy of our results. However, routine clinical data has inevitable limitations. First, the current study excluded patients with anxiety disorder. Given the high comorbidity of anxiety and depression [51] and the likelihood that many of these patients were only coded with 'anxiety disorder', these patients may have been missed. Second, although the current study controlled for a large number of covariates, many covariates could not be included, for example, sociodemographic information including education level and marital status, clinical characteristics including mental health and osteoporosis symptom severity. Similarly, the cases and controls of this study were only matched based on age and gender. Techniques like propensity score matching are often used to improve covariates balance between groups. However, due to the nature of the data linkage, access to raw individual-level data was not feasible. To mitigate this limitation, we employed stepwise logistical regressions while accounting for potential confounding. Third, despite bisphosphonates are commonly used to treat osteoporosis [52], only a small number was recorded in our study. This could be because improving calcium and vitamin D deficiency is the first-line priority [53], our relatively young sample was still at the baseline minoring stage before the administration of bisphosphonates. Comparing the bisphosphonates prescription rate between an older AD population with more severe osteoporosis and a matched non-AD sample is therefore recommended for future research. Recent research reported a greater risk of depression in patients taking common bisphosphonates such as alendronate [54]. Therefore, while our study could not explore the use of bisphosphonates in our AD sample, future studies including a large sample taking bisphosphonates should explore how bisphosphonates should be administrated and monitored in patients with AD. Specifically, studies providing further insights into whether patients with pre-existing AD may experience risks associated with bisphosphonate use would be of high importance. Additionally, other second-line osteoporosis medications (e.g., denosumab and teriparatide) that are usually prescribed by specialists when an oral bisphosphonate is not tolerated were not explored in this study. Future studies may further explore the prescription of these medications and differentiate the prescriptions of oral and IV bisphosphonates among AD patients vs. the general population. Forth, as this study only included patients who were known to both CRIS and LDN, AD patients who were not in contact with these services may have been neglected. Lastly, this study did not include GP consultation data. It is possible that the higher referral rates observed among patients with AD could be explained by a higher number of comorbidities and, consequently, more frequent patient visits, rather than the AD diagnosis itself. Future studies may further explore GP consultation rate as a key contributing factor to recorded osteoporosis referral and treatment rates.

5. Conclusion

The current study shows that patients with AD were more likely to receive osteoporosis medications, including calcium and calcium + vitamin D, and being referred to osteoporosis screening and/or prevention programmes than matched non-AD controls. Factors including older age, female sex, having an ethic minority background and Class A analgesics use before and after the index date were significant predictors for all osteoporosis management pathways within AD cases. Despite these higher recording of osteoporosis management strategies, AD patients are still at an elevated risk for poor bone health in general despite at a relatively young age, including reduced BMD and increased risks for osteoporosis, falls and fracturs. Proactive strategies to screen, diagnose and treat osteoporosis are therefore recommended for young AD patients. Increased awareness of factors that may increase the risk of osteoporosis and associated consequences, such as use of antidepressants, opioid and non-opioid analgesics, should also be improved.

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CRediT authorship contribution statement

Ruimin Ma: Writing – review & editing, Writing – original draft, Project administration, Methodology, Formal analysis, Data curation. **Eugenia Romano:** Writing – review & editing. **Mark Ashworth:** Writing – review & editing. **Davy Vancampfort:** Writing – review & editing, Conceptualization. **Marco Solmi:** Writing – review & editing. **Lee Smith:** Writing – review & editing. **Nicola Veronese:** Writing – review & editing. **Christoph Mueller:** Writing – review & editing. **Robert Stewart:** Writing – review & editing, Supervision. **Brendon Stubbs:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

BS is on the Editorial Board of Aging Research Reviews, Mental Health and Physical Activity, The Journal of Evidence Based Medicine, and The Brazilian Journal of Psychiatry. Brendon has received honorarium from a co-edited book on exercise and mental illness (Elsevier), and unrelated advisory work from ASICS and FitXR LTD.

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Appendix A. Supplementary data

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