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POPULATION HEALTH

Antipsychotic medication use and fracture: A case-control study

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Objective

It has been reported that antipsychotic use is associated with lower bone mineral density and bone quality. We aimed to determine whether antipsychotic use is associated with fracture risk in a population-based sample of adults living in the Barwon Statistical Division, south-eastern Australia.

Material and Methods

In this case-control study, 1,458 participants (51.8% women) with radiologically confirmed fracture between June 1st 2012 and May 31st 2013 (cases) were compared with 1,795 participants (46.5% women) without fracture (controls) for the same time period. Medication use, medical history and lifestyle factors were documented by self-report. Multivariable binary logistic regression was used to explore associations between antipsychotic use and fracture following adjustment for possible confounders.

Results

In women, antipsychotic use was identified for 20 of 755 (2.6%) cases and 10 of 834 (1.2%) controls (p=0.034) and in men, antipsychotic use was identified for 13 of 703 (1.8%) cases and 5 of 961 (0.5%) controls (p=0.010). Following adjustments, antipsychotic use was associated with a 3.0-fold increased risk of fracture in men and a 2.3-fold increased risk of fracture in women. Patterns persisted after exclusion of participants with non-fragility fractures and self-reported schizophrenia.

Conclusion

These population-based data suggest antipsychotic use is associated with higher fracture risk in women and men. While future research exploring underlying mechanisms is needed, regular monitoring of bone health in antipsychotic users is suggested.

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Associations between sarcopenia and domains of quality of life in older adults

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Background

Sarcopenia is characterised by an accelerated loss of skeletal muscle mass and function. It is associated with numerous adverse health outcomes however studies examining the relationship between sarcopenia and aspects of quality of life (QoL) are scarce.

Methods

This cross-sectional study involved 682 men and women (ages 60–96 years) from the Geelong Osteoporosis Study. Sarcopenia was defined according to the EWGSOP2 algorithm. Appendicular lean mass (ALM) was assessed using dual-energy X-ray absorptiometry. Handgrip strength (HGS) and the timed up-and-go (TUG) test were used to assess muscle function. The WHOQoL-BREF was used to assess QoL. Associations between sarcopenia and WHOQoL-BREF domains (physical, psychological, social relationships and environment) were investigated using multivariable logistic regression while testing for potential confounding.

Results

Fifty-seven participants (8.4%) had probable sarcopenia (low HGS strength), 12 (1.8%) had confirmed sarcopenia (low HGS and low ALM), and two had severe sarcopenia (low HGS, low ALM, and slow TUG). In crude analysis, probable sarcopenia was associated with low QoL across all four WHOQoL-BREF domains. After adjusting for sociodemographic and lifestyle variables probable sarcopenia was associated with poor psychological-related QoL [OR 2.11 (95% CI 1.13-3.92) p = 0.019]. No associations between confirmed sarcopenia and QoL were observed, likely due to a lack of statistical power.

Conclusion

Older adults with low HGS were more likely to have poor psychological-related QoL. Our findings reinforce the importance of muscle function for good QoL. Interventions to prevent or manage sarcopenia among older adults may contribute to better QoL for this population.

Bone mineral density and trabecular bone score values in novel subgroups of adult-onset diabetes

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Background

The group of individuals with diabetes are heterogenous and recently new, more homogenous subgroupings have been proposed (1). These are: mild age-related diabetes (MARD), mild obesity-related diabetes (MOD), severe insulin-resistant diabetes (SIRD), severe insulin-deficient diabetes (SIDD), and severe autoimmune diabetes (SAID). Little is known about how bone health varies between these groups. This study investigated these differences, comparing the subgroups and normoglycaemia.

Methods

Male participants (n=895, 20-97yr) were drawn from the Geelong Osteoporosis Study. Diabetes (n=105) was defined as fasting plasma glucose≥7.0mmol/L, self-report and/or use of antihyperglycaemic medication. Using hierarchical clustering, men with diabetes were categorised into the SAID subgroup (positive glutamic acid decarboxylase antibodies), k-means clustering was used to categorise the remaining men. The dual-energy x-ray absorptiometry was used to measure bone mineral density (BMD), lumbar spine scans were used to assess trabecular bone score (TBS). ANOVA and linear regression were used to identify differences in BMD and TBS. The SAID group was excluded from regression analyses due to low numbers.

Results

The groups analysed were normoglycaemia (n=790, age±SD 57.0±19.4yr) MARD (n=25, 80.2±4.5yr), MOD (n=30, 68.4±3.8yr), SIRD (n=31, 58.2±3.1yr), SIDD (n=16, 45.8±6.0yr), and SAID (n=3, 27.0±11.5yr). Femoral-neck BMD was lowest in the MARD group; this was not significant after adjusting for age. TBS was lower in all subgroups compared to normoglycaemia. The SIDD group remained lower (1.557(1.440-1.675)vs1.672(1.586-1.758),p=0.003) after adjusting for age and weight.

Conclusion

The SIDD group sustained a lower TBS after adjustment. These results may guide diabetes management strategies, focussing interventions on subgroups with poorer bone health.

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Effects of antipsychotics on embryonic bone development

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Background

Antipsychotics are the first line treatment in psychosis, with treatment often continued during pregnancy. To date there is no clear evidence on the effects of antipsychotics on fetal bone development. Therefore, we investigate the effects of antipsychotics on embryonic bone formation *in-vivo* using a zebrafish model.

Methods

The effect of first- (haloperidol; FGA), second- (olanzapine; SGA) and third- (aripiprazole; TGA) generation antipsychotics on zebrafish bone development was measured using alizarin red staining. Osteoblast development marker expression was measured using whole-mount in situ hybridization. Dopamine, serotonin and adrenergic receptor expression profiles were measured along with a marker of apoptosis (*casp3a*).

Results

Each antipsychotic reduced zebrafish bone formation in a dose-dependent manner, where haloperidol was the most potent inhibitor and olanzapine was the least potent inhibitor. Osteoblast genes expression was reduced with 10 μM of haloperidol and aripiprazole, whereas olanzapine reduced bone formation at 30 μM. There was no effect on *casp3a* expression, or dopamine or serotonin receptor expression upon antipsychotic exposure. However, higher concentration of olanzapine increased adrenergic receptor beta-2 expression, while lower concentrations had no effect.

Conclusion

Each antipsychotic reduced embryo bone development, with haloperidol being the most potent inhibitor. Haloperidol- and aripiprazole-induced bone loss was not due to apoptosis nor did antipsychotic exposure effect dopamine, serotonin or adrenergic receptor expression. Although, olanzapine-induced bone loss could be due to increased adrenergic receptor beta-2

expression. Further work into signalling pathways is needed to further understand the mechanisms involved in antipsychotic induced bone loss.

Exploring lifestyle factors as key determinants for joint replacement surgery

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Background

Chronic Osteoarthritis is a debilitating condition that can lead to the necessity of joint replacement surgery. This condition is characterized by severe pain, and, in some cases, loss of mobility. Thus, this study aimed to investigate the role of lifestyle as a key determinant associated with joint replacement.

Methods

Data from males participating in the Geelong Osteoporosis Study was linked with the Barwon Joint Registry (n=1539, 20-94 years). Height and weight were measured, and lifestyle factors were obtained via a questionnaire at baseline (2001-06). A preliminary analysis using Cox proportional hazards models was conducted by following men from baseline until JRS, death, or end of study (December 2022). The analysis was conducted using R statistical package.

Results

Eighty-one men (5.3%) underwent JRS during 15 years of follow-up. Hip replacement surgery was the prevailing procedure (71/81, 87.7%), followed by knee replacement surgery (6/81, 7.4%) and shoulder replacement surgery (4/81, 4.9%). Body mass index (BMI) and daily alcohol consumption were significantly associated with the increased risk of JRS (HR:1.04, CI:1.00, 1.08, HR:1.22, CI:1.07,1.38) after adjusting for smoking, dietary calcium intake and physical activity.

Conclusion

Higher BMI and daily alcohol consumption but not smoking, physical activity or dietary calcium intake appeared to be independently associated with increased risk for joint replacement surgery. Higher BMI and daily alcohol consumption are likely to be associated with the presence of osteoarthritis.

Health literacy is associated with 10-year risk of cardiovascular events: data from the Geelong Osteoporosis Study (GOS)

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Background

While health literacy has a confirmed association with several cardiovascular risk factors, its role in preventing a cardiovascular event has been largely unexplored. This study aimed to investigate how health literacy associates with 10-year predicted risk of a cardiovascular event.

Methods

Data were utilised from the Geelong Osteoporosis Study (GOS) 15-year follow up for 971 participants aged between 40 and 80 years. The Globorisk algorithm was used to predict 10-year risk of cardiovascular disease, providing a score between zero and 100%. The Health Literacy Questionnaire© (HLQ©) was used to measure participants' health literacy across nine domains. Covariates considered in linear regression models were birth country, employment, education, socio-economic status and living alone.

Results

The median (IQR) Globorisk score was 0.014 (IQR 0.019, 0.070) indicating 4.1% risk of cardiovascular event. In adjusted models, the unit increases in three HLQ© scales were associated with lower predicted CVD risk: Scale 5: "Appraise health information" (mean difference -0.74, 95% CI -1.43, -0.05, p=0.03), Scale 8: "Ability to find good health information" (mean difference -0.95, 95% CI -1.61, -0.29, p=0.005) and Scale 9: "Understanding health information enough to know what to do" (mean difference -1.01, 95% CI -1.68, -0.33, p=0.003).

Conclusion

This study demonstrated an inverse association between three domains of health literacy and 10-year risk of cardiovascular event in a sample of Australian men and women. Future studies could further explore this relationship especially among people who live alone.

In older individuals there is greater variance in low mean BMSi values obtained with the OsteoProbe

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Background

Bone material strength index (BMSi) quantifies bone strength *in vivo* at the mid tibia using impact microindentation (IMI). Anecdotal evidence suggests that within-participant variance in BMSi may be associated with individual level mean BMSi. This study aimed to investigate associations between mean and variance of IMI measures in a population-based study.

Methods

Participants were men (n=419) and women (n=32) from the Geelong Osteoporosis Study who underwent BMSi measurement using the OsteoProbe at recent follow-up phases (men 2016-2022; women 2022-2023). Median age was 63.6yr (IQR 52.5-71.6). BMSi standard deviation was skewed and therefore log transformed (referred to as log-SD). Linear regression models with log-SD as the dependent variable and mean BMSi as the independent variable adjusting for sex, age, height and weight were performed.

Results

In unadjusted models, a trend was observed whereby greater BMSi was associated with lower log-SD (β=-0.01, p=0.073). This association was sustained after adjustment, and an interaction between BMSi and age was observed (p=0.013). In those aged 63.6yr and over (median age), mean BMSi was inversely associated with log-SD (β=-0.01, p=0.010). Sex was not identified as an effect modifier. In younger participants, no BMSi-log-SD association observed (p=0.659).

Conclusion

In older men and women, there is greater variance in low BMSi values. One potential reason for this observation may be the presence of an increased number of resorption pits in the cortical bone of older individuals. These data support a heightened fracture risk for men and women with low BMSi and poorer bone structure.

Mean bone Material Strength Index values for women are lower than those for men: data from a single geographical location

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Background

Routine measurements of bone involve performing scans to determine how much bone is present. However, a relatively new technique called impact microindentation can assess the material properties of bone directly and provide an indication of bone strength. This technique produces a value called Bone Material Strength Index, or BMSi. It is not clear if there are differences in BMSi between men and women, and to date, sex differences have not been compared for individuals from the same population. Therefore, we compared BMSi values for men and women drawn from the same geographical location in Australia.

Methods

Participants (n=220) were from the Geelong Osteoporosis Study. BMSi was measured for participants at recent follow-up phases (women 2022-2023 and men 2016-2022). Women (n=55) were age matched to men (n=165) in a 1:3 ratio. A two-sample t test was used to determine intergroup differences in mean BMSi. Linear regression was also performed, adjusting for weight and height.

Results

Median (IQR) ages for men and women were 67.0 (61.7-71.5) and 67.4 (62.0-71.2) years (p=0.998). Men were heavier (81.0±10.9 vs 71.0±13.9 kg, p<0.001) and taller (173.9±6.4 vs 161.5±7.5 cm, p<0.001) than women.

Mean (±SD) BMSi for women (75.7±7.4) was lower than for men (82.8±6.8) (p<0.001). The difference persisted after adjustment for weight and height (mean±SE: 76.5±1.1 vs 82.5±0.6, p<0.001).

Conclusion

BMSi was lower for women than men derived from the same population. This information is consistent with poorer bone health in women, and provides a baseline to perform longitudinal studies in the future.

Moderate alcohol consumption and late life depression: A causal Inference

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Background

Alcohol intake is a potentially modifiable risk factor for depression. There are data suggesting that light to moderate consumption may be associated with a lower risk for depressive symptoms when compared with abstinence, with risk increasing again for heavier drinkers, resulting in a J-shaped relationship. However, the extent to which these protective effects are genuine causal relationships, as opposed to biased associations driven by methodological limitations, has not been established. We employed a marginal structural model (MSM) approach to investigate the J-shaped relationship between alcohol consumption and depression.

Methods

Community-dwelling, initially healthy individuals aged 70+ years (N = 19,114), were recruited from 2010 to 2014 through general practitioners (Australia) and clinic-based mailing lists (United States) and followed until June 2017 (median 4.7 years follow-up). The 10-item Center for Epidemiologic Studies Depression scale (CES-D10) was used to detect depressive symptoms. Alcohol drinking was stratified into abstinence, occasional consumption, moderate consumption, and above-guideline consumption according to current U.S. guidelines by incorporating frequency, volume, and heavy episodic drinking. Age, sex, race, ethnicity, education, smoking status, residential type, living arrangement, BMI, morbidities, or chronic conditions were considered as potential confounders. Subgroup analyses for men and women were performed.

MSMs were used to fully adjust for measured confounders through a "marginal" approach and balance confounders and withdrawals across different levels of alcohol consumption.

Results

The model confirmed J-shaped relationship between alcohol and depression symptoms. Moderate drinkers had the lowest depression rate followed by occasional drinkers (OR:1.11; 95% CI [1.03-1.20]), and above the guideline drinkers (1.15; [1.06-1.24]), and abstinence from alcohol group had the highest rate of depression (1.19; [1.10-1.29].

Conclusion

Our findings contribute preliminary evidence that associations between moderate alcohol consumption and reduced risk for depression may reflect a causal linked. Further adjustment by considering the effect of healthier lifestyles known to be associated with light alcohol consumption including diet, physical activity, socioeconomic status, social networking, and social isolation on Australian sample (n=17,320) will be discussed. The collinearity of these factors has long been a pitfall for epidemiologic studies of the possible benefits of alcohol drinking.

Paternal exposures and offspring musculoskeletal health and growth; A systematic review protocol and preliminary findings

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Background

There have been an abundance of studies reporting on maternal lifestyle during pregnancy and offspring health, with growing evidence examining the paternal origins of health and disease. This review aimed to systematically search extant literature regarding the relationship between paternal lifestyle and health exposures during early life, conception and pregnancy and offspring musculoskeletal, body composition and growth measures. This abstract focuses on offspring bone outcomes.

Methods

A systematic search of the research databases MEDLINE, Embase, CINAHL and Cochrane Library was conducted and identified papers were reviewed for their eligibility by two independent reviewers. Searches were run from database inception until 1 March 2022. Findings were summarised descriptively.

Results

In total, 241 papers met inclusion for the review. There were 27,840 children reported in eight papers examining offspring bone health outcomes including bone mineral density (BMD), content (BMC) and area (BA). Seven were cohort studies and one was a cross-sectional study. There were nine paternal exposures examined and findings were mixed (Body mass index: no association with BMD, BMC or BA in full cohort, ↑ BMD in females. Age: mixed findings from two studies. Height: mixed findings from two studies. Bone measures: BA, BMC and BMD correlated with ↑ BA and BMC. BMD correlated with ↑ BMD. Education: ↓ BMD, BMC and BA. Smoking: mixed findings from two studies.)

Conclusion

Few studies report paternal determinants of offspring bone health, and existing papers provide conflicting evidence. More studies looking at associations such as paternal health behaviours are required.

Predicting depression in the older Australian population

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Background

Depression among seniors is widespread yet inadequately addressed. Though previous studies have identified depression risk factors, intricate interplay between lifestyle and mental health complicates the identification of those most vulnerable. We compare modern machine learning techniques to model depression outcomes.

Methods

A literature review was conducted to identify health and lifestyle indicative risk factors of depression. Data available from ASPREE (ASPirin in Reducing Events in the Elderly) a large-scale cohort study with outcome of clinical depression was considered. Six popular machine learning algorithms including logistic regression, k-nearest neighbours (k-NN), random forest, gradient-boosted decision trees (GBDT), support vector machine and multi-layer perceptron neural networks were fit to classify depression outcome after three years. A grid search optimized hyperparameters via five-fold cross-validation. Best models were identified based on mean area-under-receiver-operator-curve (AUROC). Feature importance was evaluated. Least important features were gradually pruned while measuring performance to create a compact practical model.

Results

Individuals with 147 predictors of late-life depression were selected (n=12897; 54% female; 41% depressed after 3-years); preprocessing yielded 166 features. GBDT outperformed (AUROC 0.79; accuracy 0.73; precision 0.68; F1-score 0.68). Other models except kNN performed similarly. Compact GBDT matched performance (AUROC 0.78; accuracy 0.71; precision 0.65; F1-score 0.67) with 11 features.

Conclusion

Despite considering several depression predictors from the literature, few were found strongly indicative of depression. A compact machine learning model with only these important features performed similarly. This is valuable in creating

Prognostics factors for regression from prediabetes to normoglycaemia: Individual participant data meta-analysis

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Background

Prediabetes, a subclinical precursor to diabetes that currently affects approximately 374 million adults worldwide, is a risk factor for the development of cardiovascular disease and

stroke in addition to diabetes (1). Prediabetes can be reversed to normoglycaemia (2); hence, we aimed to quantify the role of the metabolic risk factors on prediabetes regression to normoglycaemia.

Methods

We used the Obesity, Diabetes, and Cardiovascular Disease Collaboration database for our individual participant data meta-analysis. This database includes 19 prospective cohort studies involving 113,296 adults across various ethnicities and age groups. We included individuals with prediabetes with at least one follow-up in the analysis. We utilized Discrete-Time Hidden Markov Models to estimate hazard ratios for prognostic factors of prediabetes regression in each cohort study. These estimations were then pooled in the random-effects meta-analysis model.

Results

We included 19,255 participants with prediabetes at baseline; median follow-up 9.8-year (IQR 5.8–12.3); 53% were women, mean age of 51 years for both sexes. Former smoking (hazard ratio 0.98, 95%CI 0.89-1.06), higher waist-to-hip ratio (0.86, 0.79-0.93), higher waist-to-height ratio (0.83, 075-0.92), higher value of waist-circumferences (0.87, 0.71-1.06), overweight (0.88, 0.81-0.96) and obesity (0.86, 0.71-1.04), high diastolic (0.93, 0.87-0.99) and systolic (0.96, 0.91-1.01) blood pressure, low serum HDL-cholesterol (0.87, 0.81-0.92) and high serum triglycerides (0.88, 0.81-0.96), were associated with the lower likelihood of an individuals with prediabetes achieve normoglycaemia.

Conclusions

The role of metabolic risk factors in prediabetes regression underscores the importance of lifestyle modification in the prediabetes state, not only to reduce T2DM development but also to attain normoglycaemia.

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Serotonin and bone metabolism

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Background

Osteoporosis, a rapidly intensifying global health challenge, is intertwined with serotonin, a neurotransmitter influencing mood, appetite, and sleep. A deeper understanding of their relationship can offer insights into osteoporosis's pathophysiology and preventative strategies.

Method

Comprehensive PhD research investigated serotonin's relation to bone metabolism through a mixed-methods approach. Focusing on serotonin's association with bone metabolism influenced by diet, gut health, and psychopathology. Through the Geelong Osteoporosis Study (GOS) and a case-control study (PROFRAC), various aspects such as dietary tryptophan intake, serum lipopolysaccharide-binding protein (LBP) levels, anxiety, depressive symptoms, and antidepressant usage were analysed in relation to bone health indicators. Additionally, *in vitro* studies examined serotonin's impact on osteoclast formation and function.

Results

The GOS revealed that in a population-based sample, high dietary tryptophan intake was linked to a more substantial bone mineral density (BMD) at the hip, although this association was attenuated by age. Another chapter found a connection between LBP and reduced mid-forearm BMD in heavier participants. The PROFRAC study underscored that depressive symptoms and antidepressant usage heightened fracture risk, especially in women. *In vitro* investigations denoted that serotonin promoted osteoclast resorption, and its synthesis impediment led to fusion and resorption alterations, indicating serotonin's significant role in osteoclast functions.

Conclusion

The studies collectively illuminate the multifaceted relationship between serotonin and bone health, providing a foundation for potential interventions in osteoporosis management and its prevention.

The practicality of using bone impact microindentation in a population-based study of women at risk of osteoporosis

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Background

Impact microindentation (IMI) is a minimally invasive indentation technique that allows the assessment of bone material strength index (BMSi) *in vivo*, by measuring the depth of a micron-sized, spherical tip into cortical bone that is then indexed to the depth of the tip into a reference material. In this study, we aimed to assess the practicality of its application in women from the Geelong Osteoporosis Study.

Methods

Participants were 58 women aged 49-78yr from the Geelong Osteoporosis Study. Impact microindentation was performed in the mid-shaft of the right tibia using the OsteoProbe. Immediately following measurement, each participant was requested to rate on a Visual Analogue Scale [0-10] the level of discomfort anticipated and experienced, any initial reluctance towards the measurement and whether they were willing to repeat the measurement.

Results

Of 58 potential participants who attended this assessment phase, 32 underwent IMI measurement. Reasons for non-measurement in 26 women were existing skin conditions (n=6), excessive soft tissue around mid-tibial region (n=16); four participants did not provide any reasons for declining. For 32 participants who had IMI performed, the expectation for pain when briefed about the procedure was low (2.07 ± 2.39), as was pain experienced during the measurement (0.91 ± 1.17). Participants were not reluctant to undergo the measurement (0.49 ± 1.17), and all indicated a willingness to repeat the measurement.

Conclusion

Results in this study quell such concerns that the minimally-invasive procedure might limit participant and patient involvement in research and/or clinical settings.

The neglected association between schizophrenia and bone fragility: A systematic review and meta-analyses

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Objective

Schizophrenia is associated with increased risk of medical comorbidity, possibly including osteoporosis, which is a public health concern due to its significant social and health consequences. In this systematic review and meta-analysis, we aimed to determine whether schizophrenia is associated with bone fragility.

Material and Methods

The research question and inclusion/exclusion criteria were developed and presented according to the PECO (Population, Exposure, Comparison, Outcome) framework. Schizophrenia was identified from medical records, DSM-IV/5 or the ICD. The outcomes for this review were bone fragility [i.e., bone mineral density (BMD), fracture, bone turnover markers, bone quality]. A search strategy was developed and implemented for the electronic databases. A narrative synthesis was undertaken for all included studies; the results from eligible studies reporting on BMD and fracture were pooled using a random effects model to complete a meta-analysis. The conduct of the review and reporting of results adhered to PRISMA guidelines.

Results

Our search yielded 3,103 studies, of which 29 met the predetermined eligibility criteria. Thirty-seven reports from 29 studies constituted 17 studies investigating BMD, eight investigating fracture, three investigating bone quality and nine investigating bone turnover markers. The meta-analyses revealed that people with schizophrenia had lower BMD at the lumbar spine [standardised mean difference (SMD) -0.74, 95% CI -1.27, -0.20; Z=-2.71, p=0.01] and at the femoral neck (SMD -0.78, 95% CI -1.03, -0.53; Z=-6.18, p≤0.001). Also observed was a higher risk of fracture (OR 1.43, 95% CI 1.27, 1.61; Z=5.88, p≤0.001). Following adjustment for publication bias, the association between schizophrenia and femoral neck BMD (SMD -0.63, 95% CI -0.97, -0.29) and fracture (OR 1.32, 95% CI 1.28, 1.35) remained.

Conclusion

This systematic review and meta-analysis provides evidence in support of bone fragility in people with schizophrenia. Further research is needed to evaluate the aetiology of bone fragility in this population.

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