THE NEGLECTED ASSOCIATION BETWEEN SCHIZOPHRENIA AND BONE FRAGILITY: A SYSTEMATIC REVIEW AND META-ANALYSES

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Introduction

Osteoporosis is a pressing public health concern (Riggs, 1995, Bone); and it is often not detected until a fracture occurs (Garnero, 2004, J Musculoskelet Neuronal Interact). Fracture can result in reduced quality of life, short-term morbidity, higher disability rate and related hospital admissions (Pasco, 2017, J Cachexia Sarcopenia Muscle & Otmar, 2013, J Men's Health) as well as heavy financial burden (2021, Lancet Healthy Longev). Thus, identifying subgroups of the population who may have an increased risk of bone fragility is imperative for prevention and anticipating health care needs.

Schizophrenia, a severe mental disorder, is associated with increased risk of medical comorbidity (Janssen, 2015, Gen Hosp Psychiatry), possibly including osteoporosis (Kishimoto, 2012, Curr Opin Psychiatry). Thus, we aimed to determine whether schizophrenia is associated with bone fragility.

Methods

The research question and inclusion/exclusion criteria were developed using a PECO structure:

Population: Adult populations aged 18 years or older

Exposure: Schizophrenia recorded in medical records, DSM-IV/5 or the ICD

Comparison: Only studies with an appropriate comparison group

Outcome: Bone fragility assessed by (I) **BMD,** (II) **Bone quality,** (III) **Fracture**, (IV) **Bone turnover markers**

Full-text published observational studies (cohort, cross-sectional and/or case-control) were eligible for inclusion in this study. Eligible studies were not restricted based on the sex or nationality of the sample, publication year or language.

A search strategy was developed and implemented for the electronic databases.

Two reviewers independently determined the eligibility of studies according to pre-determined criteria, and assessed the methodological quality using the National Institute of Health (NIH). We used the 14-item checklist for observational cohort and cross-sectional studies, and the 12-item checklist for case-control studies in this systematic review, respectively.

Due to the dearth of available studies and heterogeneity, regarding the bone quality and bone turnover markers outcomes, only studies that examined BMD and fracture were selected for the meta-analyses. As potential heterogeneity was anticipated, all analyses were conducted in Stata 17 using a restricted maximum likelihood random-effects model. Hedge's g was considered the main effect size for the meta-analyses for continuous variable (BMD) with the odds ratio (OR) being considered the main effect size for the binary outcome (fracture-yes).

The protocol for this review has been registered with PROSPERO (CRD42020171959).

Heterogeneity was assessed by calculating I^2 and H^2 values. An I^2 score of 25% was considered as low, 50% as medium and 75% as high heterogeneity. Heterogeneity was further explored via subgroup analyses, including sample size, year of publication, methodological quality, and site (for fracture only). Small-study effects were assessed using funnel plots and regression-based Egger and Begg tests. When publication bias was suspected, contour-enhanced funnel plots were generated, a trim-and-fill analysis by Duval and Tweedie was performed and adjusted results with the trim-and-fill method were reported.

Results

Figure 1: Flow diagram for included studies and reasons for full-text screening study selection

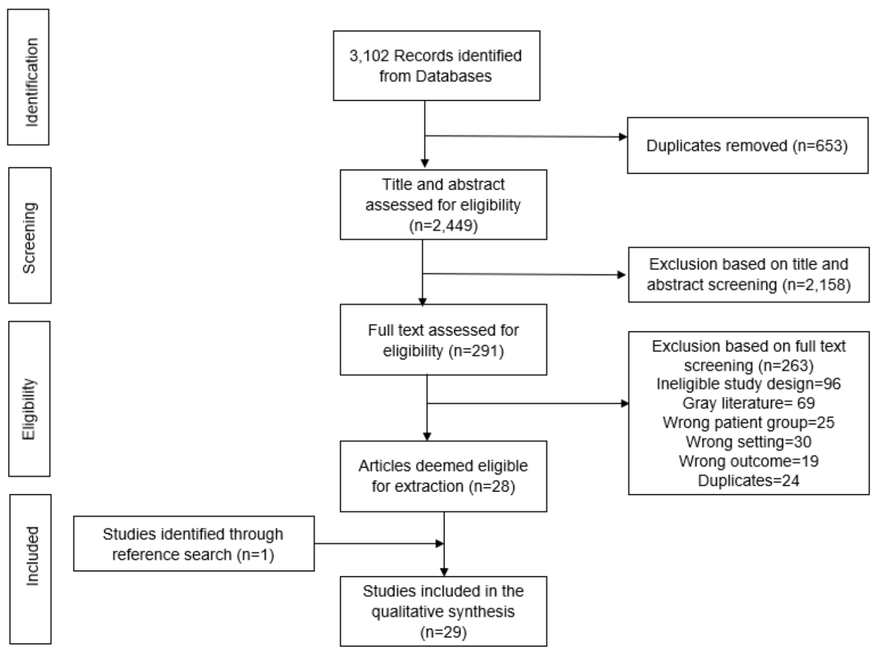


Figure 2: Forest plot and funnel plot for BMD at the femoral neck

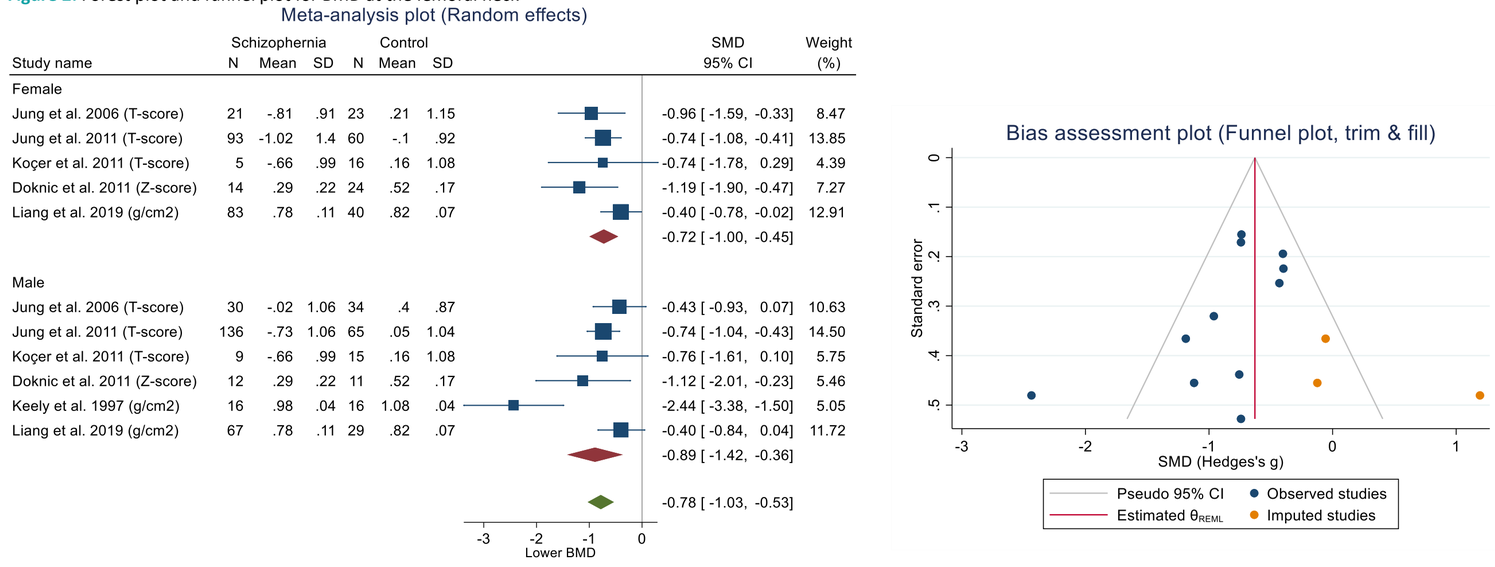


Figure 3: Forest plot and funnel plot for BMD at the lumbar spine

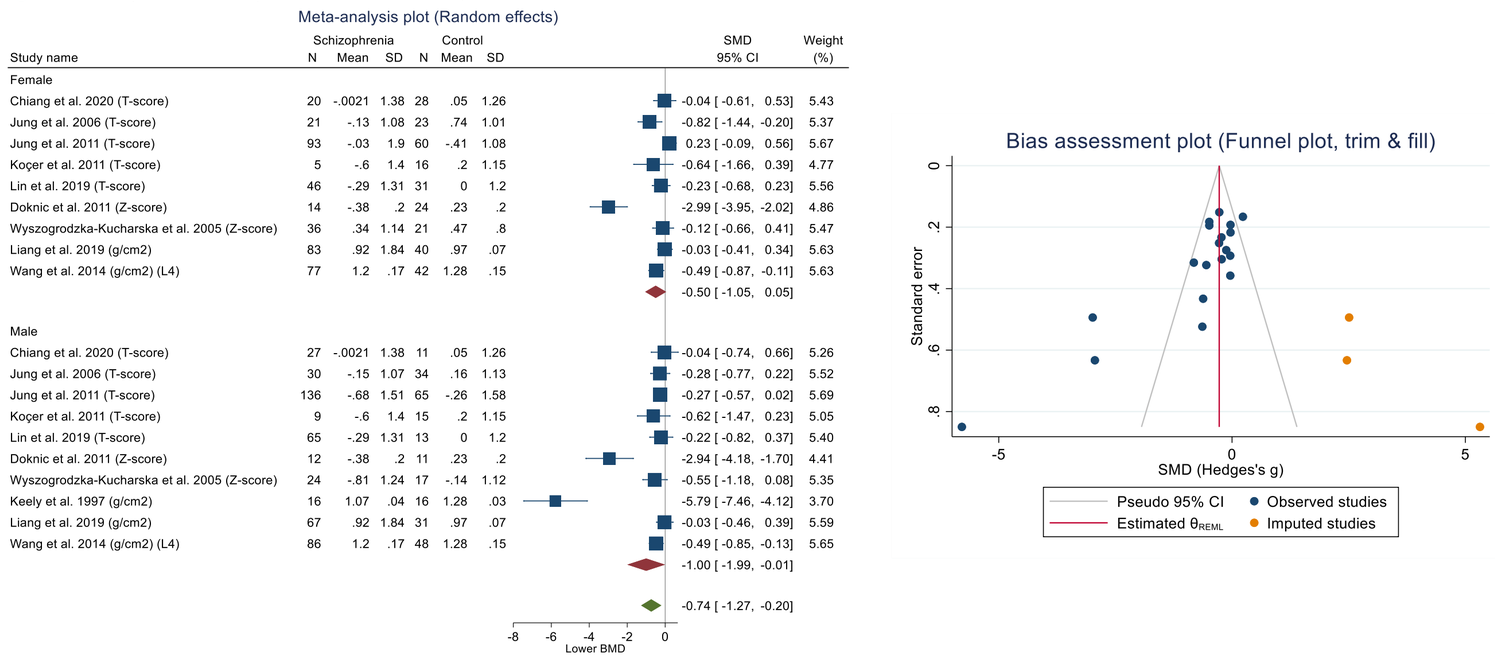
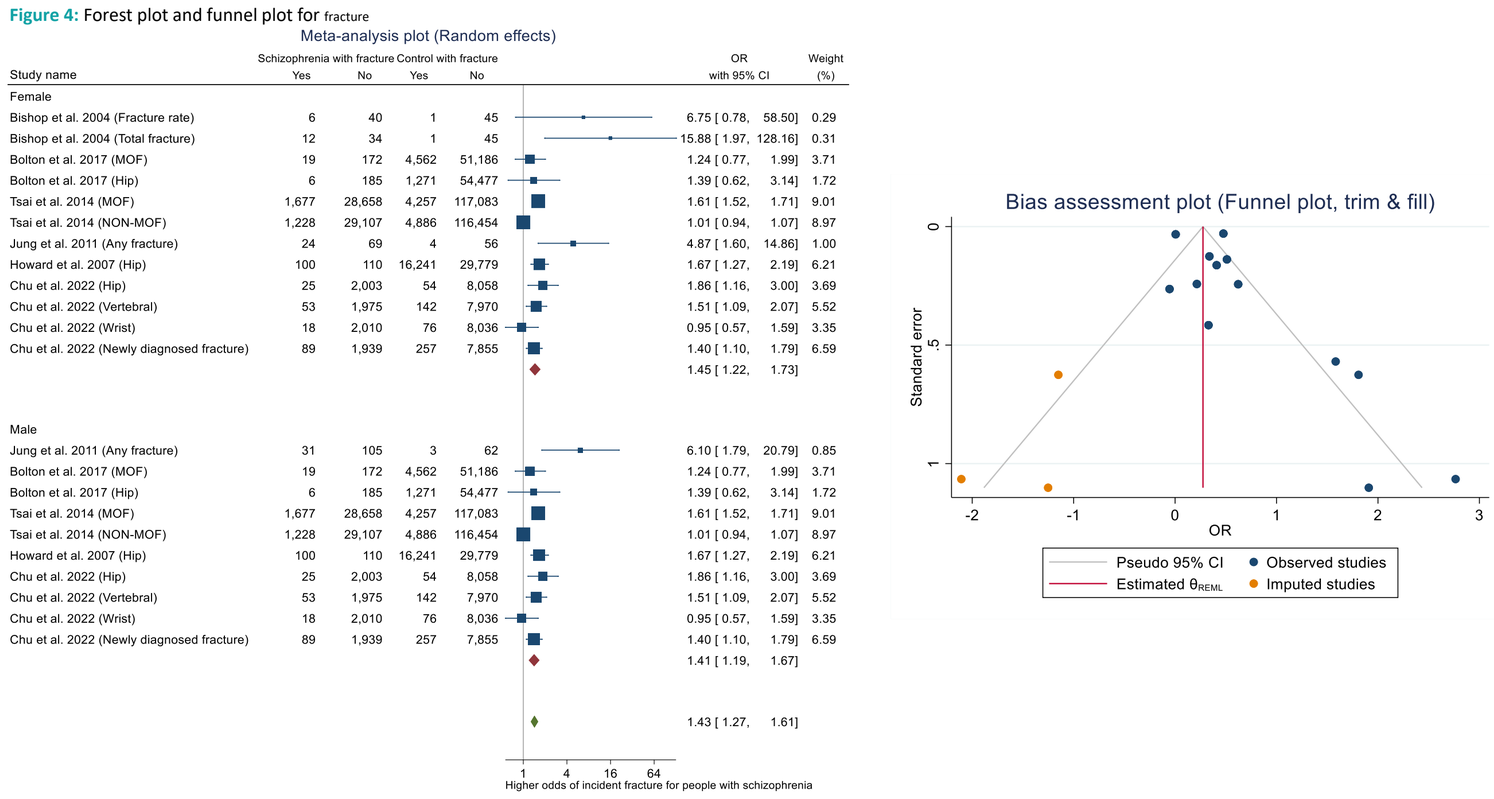


Figure 4: Forest plot and funnel plot for fracture



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.

Discussion and Conclusion

This systematic review comprised 52,246 individuals with schizophrenia aged between 18-90 years and 4,001,143 controls aged between 18-83 years. In aggregate, our results indicate that people with schizophrenia have lower BMD, poorer bone quality and higher rates of bone turnover and fracture than individuals without schizophrenia.

Significantly increased risk of bone fragility was observed in people with schizophrenia. This association was independent of sex, participant number, methodological quality and year of publication. Specifically, people with schizophrenia have lower BMD, particularly at the femoral neck, a higher risk of fracture, poorer bone quality and increased bone turnover. Since osteoporosis is often indetectable before fracture and is associated with multiple detrimental consequences, identifying those at risk of bone fragility is a priority. Further research is needed to evaluate the aetiology of bone fragility in this population and recognise modifiable risk factors such as lifestyle or medications to reduce the potential risk for this patient group. Importantly, there is a need to develop guidelines for preventing risk factors and predicting fracture in people with schizophrenia.

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