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Review article

The prevalence and predictors of obstructive sleep apnea in major depressive disorder, bipolar disorder and schizophrenia: A systematic review and meta-analysis

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ABSTRACT

Background: Obstructive sleep apnea (OSA) is a health hazard since it is associated with neurocognitive dysfunction and cardio-metabolic diseases. The prevalence of OSA among people with serious mental illness (SMI) is unclear.
Method: We searched major electronic databases from inception till 06/2015. Articles were included that reported the prevalence of OSA determined by polysomnography (PSG) or an apnea-hypopnea index (AHI) $\geq$5 events/hr, in people with major depressive disorder (MDD), bipolar disorder (BD) or schizophrenia. A random effects meta-analysis calculating the pooled prevalence of OSA and meta-regression of potential moderators were performed.
Results: Twelve articles were included representing 570,121 participants with SMI (mean age=38.3 years (SD=7.5)), 45.8% male (range=32–80.4) and mean body mass index (BMI) 25.9 (SD=3.7). The prevalence of OSA in SMI in clinical studies was 25.7% (95% CI 13.9 to 42.4%, n=1,535). Higher frequencies of OSA were seen in MDD (36.3%, 19.4–57.4%, n=525) than in BD (24.5%, 95% CI 10.6–47.1, n=681) and schizophrenia (15.4%, 95% CI 5.3–37.1%, n=329). The prevalence of OSA in 568,586 people with SMI from population cohort studies was 10.7% (95% CI 2.4–37.0%) and 19.8% (95% CI 2.5–70.0%) in 358,853 people with MDD. Increasing age (β=0.063, 95% CI 0.0005–0.126, p=0.04, N=10) and BMI predicted increased prevalence of OSA (β=0.1642, 95% CI 0.004–0.3701, p=0.04, N=9).
Conclusion: People with SMI (particularly MDD) have a high prevalence of OSA. Screening for and interventions to manage OSA in SMI including those focused on reducing BMI are warranted.

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1. Introduction

Obstructive sleep apnea (OSA) is an important cause for a number of medical comorbidities and premature mortality (Punjabi, 2008). OSA is characterised by recurrent episodes of pharyngeal obstructions during sleep resulting in a reduction in airflow which can cause derangements in gaseous exchange and disturbed sleep (Punjabi, 2008; Sharafkhaneh et al., 2005, 2004). As a result OSA is associated with a range of adverse outcomes including daytime sleepiness (Johns, 1993) and cognitive dysfunction (Olaithe and Bucks, 2013). It may result in the development of hypertension (Peppard et al., 2000), cardiovascular disease (Peker et al., 2006) and abnormalities in glucose metabolism (Punjabi and Polotsky, 2005). Moreover, OSA often has a deleterious impact on quality of life (Punjabi, 2008) and is associated with symptoms of anxiety and depression (Rezaeitalab et al., 2014).

People with serious mental illness (SMI) (defined as major depressive disorder (MDD), bipolar disorder (BD) and schizophrenia spectrum disorders) have significantly poorer physical health than the general population and are at increased risk of comorbidities (Smith et al., 2013a, 2013b; Stubbs et al., 2014). Of particular concern is the high prevalence of obesity (Mitchell et al., 2013a; Mitchell et al., 2013b) diabetes (Stubbs et al., in press); Vancampfort et al., in press) and metabolic syndrome (Mitchell et al., 2013a, 2013b).

More recently, research has considered the relationship between SMI and respiratory diseases. For instance, in a population cohort study (Partti et al., 2015) demonstrated that schizophrenia is associated with increased odds of having chronic obstructive pulmonary disease (COPD, OR=4.2) and chronic bronchitis (OR=3.8). Furthermore, reduced lung function (Vancampfort et al., 2014) can negatively influence participation in daily life among patients with schizophrenia. One of the most prevalent respiratory disorder is OSA. Key risk factors for OSA include obesity, craniofacial abnormalities (Sutherland et al., 2012), allergic rhinitis (Farabollini et al., 2009) and cardiovascular disease (Young et al., 2004). In addition, lifestyle factors such as smoking and alcohol misuse increase an individual's risk of OSA (Punjabi, 2008). These comorbidities and lifestyle factors are particularly prevalent among people with SMI and therefore it is reasonable to assume that this group may be at increased risk of OSA. As such, the identification and management of OSA in people with SMI may be important in preventing or attenuating cardio-metabolic comorbidities associated with SMI (Punjabi, 2008; Young et al., 2004). The relationship between OSA and cardiovascular disease, stroke, hypertension and altered glucose metabolism is complex and appears to be bidirectional (Punjabi, 2008; Young et al., 2004). Nevertheless, understanding the prevalence of OSA in people with SMI is important.

Previously, a number of narrative systematic reviews have considered the prevalence of OSA in schizophrenia (Kalucy et al., 2013), and SMI more generally (Gupta and Simpson, 2015). Whilst not focussing on OSA, another review (Plante and Winkelman, 2008) established the critical relationship between sleep disturbances generally and bipolar disorder. Although these reviews have advanced the field, a number of limitations persist. First, none have attempted to conduct a meta-analysis and the prevalence of OSA was limited to considering individual studies as single entities or calculating arithmetic means or medians of the prevalence of OSA. Meta-analyses enable the pooling of data across studies in order to provide a more accurate effect size than when individual studies are considered separately (Ioannidis, 2009). The recent reviews have also considered differing inclusion criteria when reviewing the literature on OSA. For instance, (Gupta and Simpson, 2015) only considered studies measuring OSA confirmed by polysomnography (PSG) the gold standard recognised by the International Classification of Sleep Disorders 2nd edition (ICSD-2) (Medicine, 2005) criteria. However, (Kalucy et al., 2013) considered 'sleep disordered breathing' including studies that report OSA from screening questionnaires.

We aimed to conduct a meta-analysis investigating the prevalence of OSA in SMI and investigate diagnostic subgroup differences among people with MDD, BD and schizophrenia when determined according to standardised OSA measures. Where possible, we anticipated conducting a comparative meta-analysis comparing the risk of OSA in people with SMI versus the general population. Moreover, we sought to investigate differences reported in clinical and population cohort studies and conduct meta-regression analyses on potential moderator variables (if reported in at least 4 studies).

2. Method

This systematic review was conducted in accordance with the Meta-analysis of Observational Studies in Epidemiology guidelines (Stroup et al., 2000) and reported in accordance with the PRISMA statement (Moher et al., 2009) following a predetermined but unpublished protocol.

2.1. Inclusion and exclusion criteria

We included observational (clinical or population cohort) studies (prospective, retrospective or cross-sectional) that: (a) included people with a diagnosis of MDD, BD or schizophrenia spectrum disorders according to a structured clinical assessment and/ or meeting standardised diagnostic criteria (e.g. DSM-IV (American Psychiatric Association, 2000) or ICD-10 (World Health Organisation, 1993) (b) assessed for OSA in line with the international classification of sleep disorders, 2nd edition diagnostic and coding manual (American Academy of Sleep Medicine, 2005). This includes PSG (single or split-night) or OSA with apnea-hypopnea index (AHI, the number of episodes of apnea or hypopnea per hour during sleep) ≥ 5 events/h or the respiratory disturbance index (RDI) equivalent (American Academy of Sleep Medicine, 2005). We excluded studies that measured OSA with screening instruments alone or studies that identified those with SMI using a screening tool alone. When we encountered studies reporting data from the same sample at different time points, we used the most recent data and/or the largest data set. If necessary, we planned to contact study authors to confirm eligibility and/ or to acquire data, although this was not needed.

2.2. Information sources and searches

Two independent reviewers (B.S. and M.F.) searched Academic Search Premier, MEDLINE, Psychology and Behavioral Sciences Collection, PsycINFO, SPORTDiscus, CINAHL Plus and Pubmed from inception until June 2015. We used the key words 'bipolar disorder' or 'bipolar*' or 'affective disorders' or 'schizophrenia' or 'psychosis' or 'depression' or major depression AND 'sleep' or 'sleep apnea' or 'obstructive sleep apnea'. In addition, the reference lists of all eligible articles and recent narrative systematic reviews on OSA and sleep disorders in people with SMI were reviewed (Gupta and Simpson, 2015; Kalucy et al., 2013). Only articles written in Italian or English were included.

2.3. Study selection

After the removal of duplicates, two independent reviewers screened the titles and abstracts of all potentially eligible articles. Both authors applied the eligibility criteria, and a list of full text articles was developed through consensus. The two reviewers then considered the full texts of these articles and the final list of included articles was reached through consensus.

2.4. Data extraction

Two authors (B.S. and M.F.) independently extracted data and recorded this in a predetermined database. The data collected from each article included: study design, geographical location, details of SMI participants (mean age, percentage of males, diagnosis method, body mass index (BMI), details of medications and chronicity of illness) and details regarding diagnosis. In addition, we sought to extract data on the classification of OSA and number diagnosed with OSA.

2.5. Methodological quality appraisal

We used the Newcastle Ottawa Scale (NOS; (Wells, Shea., O'Connell, & Peterson)) to assess the methodological quality of all included articles. We included studies without a control group due to the paucity of data and such studies were treated as cross sectional case controlled studies for the purposes of methodological assessment. Naturally it was anticipated these studies to have a low methodological quality rating. The NOS assesses the quality of non-randomised trials and its validity and reliability has been established (Wells et al.) and such criterion is particularly essential when critically appraising studies without a control group. The NOS focuses on three main methodological features: 1) the selection of the groups, 2) the comparability of the groups and 3) the ascertainment of the outcome of interest. The maximum score that any study can achieve on the NOS is 9 points. Studies that score 5 or more are normally considered of satisfactory methodological quality. Due to the paucity of literature we included studies with a score less than this (due to the absence of a control group). The methodological assessment was independently completed by two authors and consensus was reached through discussion.

2.6. Meta- analysis

We pooled individual study data using the DerSimonian-Laird proportion method (DerSimonian and Laird, 1988) which calculates pooled prevalence using inverse-variance weighted random effects meta-analysis with StatsDirect® and Comprehensive Meta-Analysis® software (version 3). Due to anticipated heterogeneity, a random effects meta-analysis was employed. If there were 3 or more studies with relevant data, we planned to calculate subgroup analyses of the prevalence of OSA according to SMI diagnostic classification. We also anticipated completing separate subgroup analyses investigating the pooled prevalence of OSA in clinical and population cohort studies and conducted a comparative relative risk (RR) meta-analysis to establish if OSA is more common in people with SMI versus controls. We assessed publication bias with the visual inspection of a funnel plot (Higgins and Green, 2011) and the Begg (Begg and Mazumdar, 1994) and Egger (Egger et al., 1997) tests. Finally, we conducted several meta-regression analyses (if $N \geq 4$) to investigate potential moderators (age, percentage males and BMI) with Comprehensive Meta-Analysis® (version 3). Despite a lack of consensus on the number of studies required for meta-regression, we chose to only conduct meta regression where data was available from 4 or more studies based on recent recommendations (Fu et al., 2011). We anticipated conducting meta regression analyses to investigate the influence of mean age, methodological quality, percentage of males, psychopathology/ depressive symptoms, the percentage taking psychotropic and antipsychotic medication.

3. Results

3.1. Search results and study selection

The initial search identified 2,215 publications. After removal of duplicates, 221 abstracts and titles were screened (Fig. 1). At the full text review stage, 62 articles were considered and 50 articles were excluded with reasons which are listed in Fig. 1. Thus, 12 articles met the eligibility criteria and were included in the review (Ancoli-Israel et al., 1999; Carney et al., 2006; Deldin et al., 2006; Hattori et al., 2009; Hrubos-Strøm et al., 2012; Kelly et al., 2013; Levine et al., 2001; Mysliwiec et al., 2013; Ong et al., 2009; Sharafkhaneh et al., 2005; Soreca et al., 2012; Winkelman, 2001). Details regarding the search results including reasons for exclusion of articles are summarised in Fig. 1.

3.2. Study and participant characteristics

Across the 12 unique included studies 570,121 unique participants with SMI were included. One study included a substantial percentage of the participants included in our meta-analysis (about 99.7% of the whole sample). The mean age across the studies of participants was 38.3 years (SD=7.5) and 45.8% of the

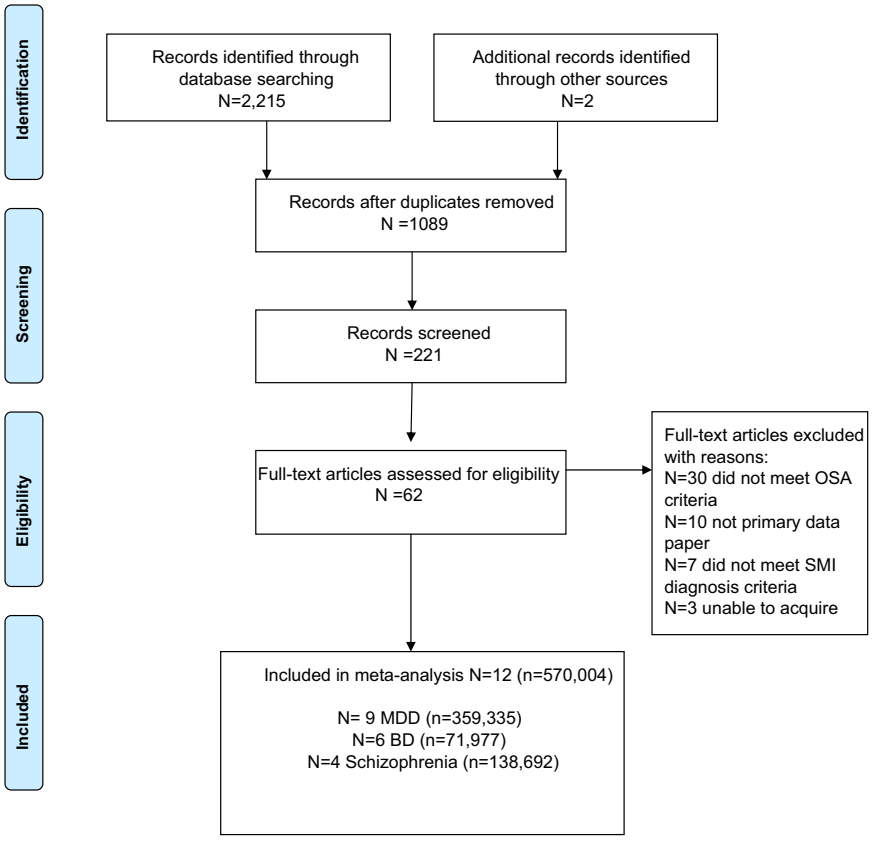

Fig. 1. PRISMA flow diagram.

included participants were male (range=32–80.4%). The mean BMI across 10 studies with complete data was 25.9 (SD=3.7) (overweight). Across the 12 studies, 9 considered OSA in MDD (n=359,378)(Carney et al., 2006; Deldin et al., 2006; Hattori et al., 2009; Hrubos-Strøm et al., 2012; Levine et al., 2001; Mysliwiec et al., 2013; Ong et al., 2009; Sharafkhaneh et al., 2005; Winkelman, 2001). Six studies provided data on 72,043 people with BD (Hattori et al., 2009; Kelly et al., 2013; Levine et al., 2001; Sharafkhaneh et al., 2005; Soreca et al., 2012; Winkelman, 2001) and 4 studies provided data on 138,700 people with schizophrenia spectrum disorders (Ancoli-Israel et al., 1999; Levine et al., 2001; Sharafkhaneh et al., 2005; Winkelman, 2001). Only two of the included studies were population cohort designs (Hrubos-Strøm et al., 2012; Sharafkhaneh et al., 2005) and the remainder included clinical samples. The average NOS was 4.25 (range 4–5). Full details of the included studies according to SMI diagnosis are summarised in Table 1.

4. Meta-analysis of the prevalence of OSA in clinical studies

4.1. Prevalence of OSA among people with SMI

Data were pooled from 1,535 unique participants with SMI resulting in a pooled prevalence of OSA of 25.7% (95% CI 13.9 to 42.4, Q=156 (df=13) $p<0.01$) (Fig. 2). The Begg (−0.9, p=0.59) and Egger tests (−0.45, p=0.79) did not demonstrate any evidence of publication bias in the overall pooled analyses.

4.2. Prevalence of OSA among different diagnostic subgroups

Data was pooled from 6 clinical studies from 522 people with MDD to establish a pooled prevalence of OSA of 36.3% (95% CI 19.4 to 57.4, Q=82.83, (df=6) $p<0.01$). The pooled prevalence of OSA among 681 people with BD was 24.5% (95% CI 10.6 to 47.1, Q=26.55 (df=4) $p<0.01$). The prevalence of OSA among 329 people with schizophrenia was 15.4% (95% CI 5.3 to 37.1, Q=46 (df=3), $p<0.01$). The prevalence of OSA in in each diagnostic subgroup is presented in Fig. 2.

4.3. Sensitivity analyses

Two studies (Carney et al., 2006, Ong et al., 2009) focussing on people with MDD were identified as being potentially biased due to the nature of included participants. Therefore, these were removed in a sensitivity analysis and the pooled prevalence of OSA among 378 people with MDD was recalculated at 25.2% (95% CI 10.2 to 50.2, Q=58, $p<0.01$). The overall pooled prevalence of OSA in SMI established the pooled prevalence of OSA was 25.5% (95% CI 16.6 to 37.6, *Q=199, $p<0.01$, n=1,314*).

4.4. Meta regression of pooled prevalence of OSA in SMI

Meta regression analysis using data from 10 studies established that a higher mean age predicted an increased prevalence of OSA in the SMI participants (β=0.063, 95% CI 0.0005 to 0.126, z=1.97, p=0.04, $R^2=0.34$). Meta-regression with data from 9 studies established that higher BMI predicted increased prevalence of OSA (β=0.1642, 95% CI 0.004 to 0.3701, z=1.56, p=0.04, $R^2=0.23$). No relationship was found with the percentage of males in the studies ($p>0.05$, N=9) or methodological quality according to the NOS ($p>0.05$, N=10).

Table 1
Summary of included studies.

Author	Location, setting	Population	Participant details	OSA measurement	NOS summary score
Clinical samples					
Levine et al. (2001)	US, retrospective study	MDD (n=43), BD (n=66), Schizophrenia (n=140), Schizoaffective (n=91)	MDD 41 years, 65% male BD 42 years, 59% male Schizophrenia 41 years Consecutive psychiatric patients. 80% overall sample taking antipsychotic medication.	Diagnosed by overnight polysomnography and oxyhemoglobin desaturation	4
Winkelman et al., 2001	US, retrospective study	MDD (n=176) BD (n=92) Schizophrenia (n=46)	MDD 39.9 ± 16.6 years, 51.1% male, BMI 27 ± 8.6, 10.8% taking neuroleptics BD 38 ± 15 years, 32.6% male, BMI 27.9 ± 7.6, 21.7% taking psychotropic medicine Schizophrenia 35.3 ± 8.4 years, 80.4% male, BMI 31.5 ± 8.2, 100% taking psychotropic medication. All patients were referred to a sleep disorder consultation service from an inpatient psychiatric hospital	Defined as present if the RDI exceeded 10 (or 20) apnea + hypopnea per hour of sleep	4
Deldin et al., 2005	US, cross sectional	MDD (n=19)	34.47 ± 11.52 years, 21% male, BMI 26.13 ± 7.40, Antidepressants: 37% Sedative hypnotics: 16% Recruited through newspaper advert and part of larger trial on MDD and memory.	Polysomnography, RDI > 5 major events per hour	4
Carney et al. (2006)	US, cross sectional	MDD (n=53)	53.8 ± 9 years, 53% male, BMI 30.1 ± 6.8 Participants all had stable coronary heart disease.	Polysomnography OSAHS (obstructive sleep apnea encompassing hypopnea syndrome) was a priori defined as ≥5 apneic or hypopneic episodes per hour of sleep	5
Hattori et al., 2009	Japan, cross sectional	MDD (n=19) BD (n=13)	Overall 75% sample were male, not possible to determine further participant details.	Overnight PSG plus AHI ≥5, according to the International Classification of Sleep Disorders 2nd edition (ICSD2); alternative criterion was AHI > 10 for secondary analyses	4
Ong et al., 2009	US, baseline RCT data	MDD (n=51)	48.28 ± 12.32 years, 59% male, BMI 27.18 ± 6.39 All participants had comorbid insomnia	Polysomnography; a AHI score ≥15 was considered diagnostic for OSA	4
Mysliwiec et al., 2012	US, retrospective	MDD (n=164)	Overall 93% sample male, not possible to determine further participant details. Cases were recruited among active duty military personnel	PSG using the American Academy of Sleep Medicine alternative scoring method for hypopneas requiring a ≥50% decrease in the nasal pressure signal excursion from baseline lasting 10 sec or more with either a ≥3% desaturation or an arousal. OSA cases were further distinguished in "mild" ones AHI 5–15, or "moderate-to-severe" OSAs if AHI score was > 15.	4
Soreca et al., 2014	US, cross sectional	BD (n=28)	41.7 ± 9.8 years, 32% male, BMI 33.8, all BD I	Objective measurement of AHI > 5	4
Kelly et al., 2013	US, retrospective	BD (n=482)	44.21+17 years, 40% male, BMI 26.7 ± 5.51 BD-I (n=58), BD-II (n=301) or BD-unclear (n=123)	Clinical sleep lab for PSG, using the standard American Academy of Sleep Medicine criteria of an apnea index of at least 15 or at least 5 with daytime hypersomnolence	4
Ancoli-Israel et al. (1999)	US, cross sectional	Schizophrenia (n=52)	59.6 ± 8.9 years, 67.30% male, BMI 28.5 ± 7.4, 84.60% taking antipsychotic medication	The Medilog/Respitrace portable recording system was used in conjunction with portable oxymetry to record sleep, RDI > 10	4
Population cohort studies					
Sharafkhaneh et al. (2005)	US, retrospective cohort	MDD (n= 358,817) BD (n= 71,362) Schizophrenia (n= 138,371)	Overall 90.2% of sample were male. No clear demographic data on diagnostic sub groups Inpatient records of Veteran's Health Administration from 1992–2001	Confirmed medical diagnosis of OSA based on ICD criteria	5
Hrubos-Strom H et al., 2012	Norway, cross sectional	MDD (n=36)	48.8 ± 10.3 years, 65.50% male, BMI 29.1 ± 5.2	PSG and AHI > 5 events h-1 were diagnosed with OSA following an initial screen with the Berlin sleep Screening questionnaire.	5

KEY: US=United States, MDD=Major depressive disorder, BD=bipolar disorder, RDI=respiratory disturbance index, PSG=polysomnography.

5. Prevalence of OSA in population cohort studies

Data were pooled from 4 samples utilising two studies including 359,378 people with MDD, 72,043 with BD and 138,700 people with schizophrenia. As reported in Fig. 3, the pooled prevalence of OSA among a total of 568,586 people with SMI was 10.7% (95% CI 2.4 to 37.0, 1368.3 (df=3), $p < 0.01$). The pooled prevalence of OSA in MDD, calculated from pooled data from two unique studies was 19.8% (95% CI 2.5 to 70.0).

6. Discussion

6.1. General findings

Results our meta-analysis demonstrates in clinical studies that approximately a quarter of people with SMI meet the criteria for OSA. People with MDD appear to have a higher prevalence of OSA compared to people with BD or schizophrenia. However, after the removal of two potentially biased studies the prevalence of OSA in MDD appears similar to BD. When we considered population cohort data only, the pooled prevalence of OSA was lower at 10.7%, although pooled data from the two MDD cohorts suggest that OSA is higher in this population (19.8%). We found that both increasing age and increased BMI predict an elevated prevalence of OSA among people with SMI.

The increased prevalence of OSA in MDD compared to other diagnostic subgroups is of interest and warrants further investigation. It has been previously suggested that sleep fragmentation associated with hypoxaemia and altered serotonergic neurotransmission, as well as common shared risk factors for both MDD and OSA may account for an increased prevalence of OSA in people with MDD (Schroder & O'Hara 2005). Among pathways linking OSA and MDD, low serotonin levels seem to play an important role since serotonin has been involved in both the development of depression (Muñoz, Mayoralas, Barbé, Pericás, & Agusti, 2000) and might also influence upper airway dilator motor neurons particularly through the hypoglossal nucleus (Canessa et al., 2011). In people with MDD, the early identification and treatment of OSA seems to correspond to a better improvement of depressive symptoms (Edwards et al., 2015). OSA and MDD are risk factors for the development of obesity (El-Ad and Lavie, 2005), cardiovascular disease (Vozoris, 2012), and metabolic syndrome (Lett et al., 2004), while there is also an increased risk in both disorders of excessive alcohol consumption (Harris et al., 2009). In addition, given that in the general population OSA is independently associated with metabolic syndrome (Coughlin et al., 2004), cardiovascular disease (Peker et al., 2006) and abnormalities in glucose metabolism (Punjabi, 2008), the identification and management of OSA may prove also a valuable means to prevent cardiovascular disease in people with MDD.

Obtaining the precise prevalence of OSA in the general population is challenging and many cases within the general population are under-recognised (Ravesloot et al., 2012), with previous research suggesting 1–2% and 2–4% of women and men are affected (Gibson, 2005). Others have suggested a higher prevalence in studies conducted in clinical settings with (Young et al., 1993) establishing a prevalence of 24% and 9% in males and females with an AHI $\geq$ 5. Unfortunately, there were insufficient data to enable a comparative meta-analysis to directly compare the prevalence of OSA in people with SMI versus general population controls. Thus, it remains unclear if people with SMI are at increased risk of OSA compared to people in the general population. However, the pooled prevalence of OSA in MDD was 36.3% which is higher than previous estimates in the general population (Young et al., 1993). Studies that have previously investigated sleep disordered breathing in MDD defined according to structured clinical assessment have reported greatly increased rates of OSA, with odds ratios of over 5, thus also supporting our results that people with MDD are particularly at increased risk (Ohayon, 2003). Moreover, a previous narrative systematic review tabulated the median prevalence of OSA in MDD (Gupta and Simpson, 2015) and reported this as 48.1%. Thus, utilising meta-analysis we were able to establish that the prevalence of OSA in MDD in clinical settings appears to be less than that reported previously (Gupta and Simpson, 2015). It was also possible to pool data from 358,853 people with MDD and establish the prevalence of OSA in population cohort studies is almost one in 5 (19.8%). Given the likely bias attributed to the studies conducted in clinical settings, the prevalence in population studies may be a truer reflection of the actual prevalence of OSA.

The pooled prevalence of OSA in BD in clinical settings was 24.5% and is comparable to clinical studies in the general population (Young et al., 1993), yet higher than the arithmetic median reported in a previous narrative review (19.8%) (Gupta and Simpson, 2015). Our pooled analysis of 4 clinical studies in schizophrenia established that 15.4% are affected by OSA, lower than reported in the general population. A previous narrative review suggested people with schizophrenia have a particularly high prevalence of OSA (Kalucy et al., 2013). Our current findings should however be interpreted with caution given the limitations in the available data. Moreover, only one representative study (Sharafkhaneh et al., 2005) adopted a population cohort study approach which reported 4.5% and 6.9% of people with schizophrenia and BD have OSA respectively. Therefore, it is important that future representative research is conducted to attempt to build on the results of our review and establish the true prevalence of OSA in the diagnostic SMI groups.

The finding that increasing BMI is a significant predictor of increased prevalence of OSA is of interest. Many people with SMI experience increased levels of BMI and in particular central adiposity (De Hert et al., 2011; Gardner-Sood et al., 2015) which is known to increase the risk of OSA in the general population (El-Ad and Lavie, 2005). Reasons for high BMI values in people with SMI could be the high prevalence of sedentary lifestyle (Stubbs et al., in press) and the use of antipsychotic medications that could contribute to obesity in this population. Given this finding, there is further need to develop preventive lifestyle interventions to reduce weight gain in people with mental illness. Future work is needed to investigate the impact of medication on OSA risk in people with SMI. Moreover, other sedative medications commonly prescribed to people with SMI such as benzodiazepines may also increase the risk of OSA (Gupta and Simpson, 2015). Research in the general population has established that men are at particularly increased risk of OSA (Gibson, 2005; Young et al., 1993). However, we were unable to elucidate any gender effects in our meta-regression analyses.

There are a number of reasons why identifying and managing OSA is clinically important among people with SMI. First, OSA can result in neurocognitive and mood deterioration among people with mental health problems through intermittent hypoxia and disrupted sleep (Bucks et al., 2015). Clearly, this is an unwanted potential consequence among people who already experience compromised cognition and mood instability (Gupta and Simpson, 2015). Second, if left untreated there are considerable concerns that OSA may increase the risk of cardiovascular disease, impair glucose regulation and increase the risk of metabolic syndrome. Previous work from our group has extensively documented that people with SMI are at risk of metabolic syndrome (Gardner-Sood et al., in press; Mitchell et al., 2013a, 2013b; Vancampfort et al., 2013) and diabetes (Stubbs et al., in press; Vancampfort et al., in press). Emerging evidence has demonstrated a number of

Group by Subgroup within study	Study name	Subgroup within study	Event rate	Lower limit	Upper limit
1 MDD	Carney RM et al., 2006	1 MDD	0.660	0.524	0.774
1 MDD	Ong JC et al., 2009	1 MDD	0.588	0.450	0.714
1 MDD	Hattori M. et al., 2009	1 MDD	0.526	0.311	0.732
1 MDD	Mysliwiec V. et al., 2012	1 MDD	0.494	0.418	0.570
1 MDD	Deldin PJ et al., 2005	1 MDD	0.263	0.114	0.498
1 MDD	Winkelman JW., 2001	1 MDD	0.125	0.084	0.183
1 MDD	Levine J et al., 2001	1 MDD	0.011	0.001	0.157
1 MDD			0.363	0.194	0.574
2 BD	Hattori M. et al., 2009	2 BD	0.692	0.409	0.880
2 BD	Soreca I et al., 2014	2 BD	0.393	0.233	0.580
2 BD	Kelly T. et al., 2013	2 BD	0.210	0.176	0.248
2 BD	Winkelman J.W. et al. 2001	2 BD	0.196	0.127	0.289
2 BD	Levine J. et al., 2001	2 BD	0.030	0.008	0.113
2 BD			0.245	0.106	0.471
3 Schizophrenia	Winkelman JW. 2001	3 Schizophrenia	0.478	0.340	0.620
3 Schizophrenia	Ancoli-Israel S. et al., 1999	3 Schizophrenia	0.477	0.336	0.623
3 Schizophrenia	Levine J. et al., 2001 (Schizoaffective)	3 Schizophrenia	0.033	0.011	0.097
3 Schizophrenia	Levine J. et al., 2001 (Schizophrenia)	3 Schizophrenia	0.007	0.001	0.049
3 Schizophrenia			0.154	0.053	0.371
Overall			0.257	0.139	0.424

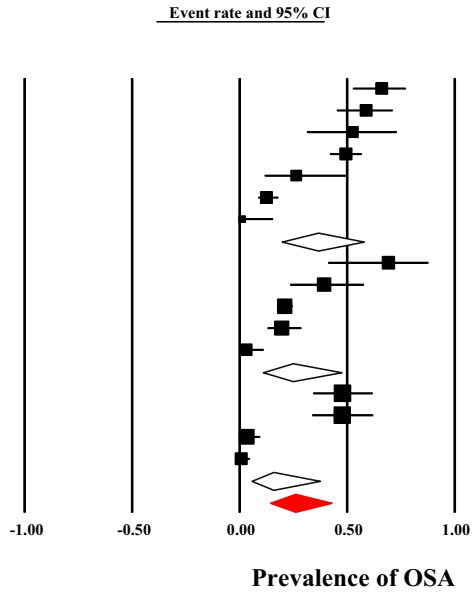

Fig. 2. Prevalence of OSA clinical studies in each SMI diagnostic subgroup.

mechanisms which underlie the relationship between OSA and metabolic dysregulation including sympathetic activation, oxidative stress and related inflammation (JC and SM, 2012). Given that cardiovascular disease is a major cause of premature mortality in people with SMI (Walker et al., 2015), the increased prevalence of OSA is a concern. OSA has been identified as a cause of sudden death in the community (Gami et al., 2013) and among psychiatric patients (Manu, Kane, & Correll, 2011).The magnitude of the risk is predicted by the presence and severity of nocturnal hypoxemia (Gami et al., 2013), an issue of particular concern in psychiatric patients who refuse continuous positive airway pressure (CPAP) or Bilevel Positive Airway Pressure treatment and/or are treated with benzodiazepines or other CNS-depressant psychotropic drugs (Seda et al., 2014). A previous Cochrane review (Giles et al., 2006) suggests that CPAP may be effective in managing OSA, however there are no rigorous trials investigating this in people with SMI (Kalucy et al., 2013).

6.2. Limitations

Although this meta-analysis provides novel findings, there are a number of limitations that must be considered, particularly in light of the data available from the included studies. First, there was some heterogeneity encountered within the study design and participants. We attempted to negate this by conducting subgroup analyses and meta-regressions. Second, the pooled analyses on clinical studies of OSA may not be representative of the wider SMI populations. The meta-analyses results drawn from population cohort studies were sparse but may be a more accurate reflection of the prevalence of OSA. However, these should be interpreted in light of the caveats mentioned above (i.e. clinical setting and overshadowing of co-morbid medical conditions in patients with SMI), indicating the frequencies reported may be underestimates. In this sense, one study (Sharafkhaneh et al., 2005), which accounted for the overwhelming majority of participants in or meta-analysis reported a lower prevalence of OSA than the other studies included in our analyses. Third, there was inadequate comparative data of healthy controls to conduct a meta-analysis to understand if people with SMI are at increased risk of OSA. Representative research is required to understand this further. Fourth, there was inadequate data on important moderators such as antipsychotic medication which may influence OSA. Future research is clearly required to better understand these relationships. Finally, our meta regression considered the SMI

Group by Subgroup within study	Study name	Subgroup within study	Event rate	Lower limit	Upper limit
1 MDD	Sharafkhaneh A. et al., 2005 1 MDD		0.074	0.073	0.075
1 MDD	Hrubos-Strom H et al., 2012 1 MDD		0.444	0.293	0.607
1 MDD			0.198	0.025	0.702
2 BD	Sharafkhaneh A. et al., 2005 2 BD		0.069	0.068	0.071
2 BD			0.069	0.003	0.637
3 Schizophrenia	Sharafkhaneh A. et al., 2005 3 Schizophrenia		0.045	0.044	0.046
3 Schizophrenia			0.045	0.002	0.527
Overall			0.107	0.024	0.370

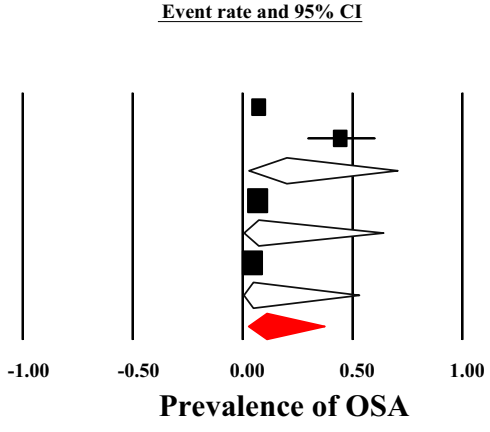

Fig. 3. Prevalence of OSA in SMI diagnostic subgroups in population cohort studies.

group as a whole since there was insufficient data to consider each diagnostic group separately. However, this might have resulted in potentially spurious results, which should be clarified in larger representative studies within each diagnostic group. Nevertheless, allowing for these caveats our meta-analysis provides the most systematic quantitative analysis of the prevalence and predictors of the OSA in people with SMI.

7. Conclusion

Our meta-analysis established that 25.7% of people with SMI have OSA. Higher frequencies were found in MDD (36.3%) compared to BD (24.5%) and schizophrenia (15.4%) although for BD and schizophrenia our findings are unclear due to the small number of the studies included for these conditions. Clearly people with SMI are at risk of OSA and this may negatively impact a range of health outcomes and therefore warrants closer attention in clinical practice. Moreover, future representative research is required to better understand the incidence and prevalence of OSA across all people with SMI with a view to developing effective interventions.

Conflict of interest

BS, SR, PM, DV and MF declare no conflict of interest.

FG has received honoraria for advisory work and lectures from Roche, BMS, Lundbeck, and Sunovion and has a family member with professional links to Lilly and GSK.

Dr De Hert reported being a paid consultant for, receiving grant or research support and honoraria from, and serving on the speakers' bureaus or advisory boards of Janssen-Cilag, Lundbeck, and Takeda.

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