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The resting metabolic rate of people with severe mental illness: a systematic review and meta-analysis

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Abstract

People with severe mental illness (SMI), including schizophrenia and related psychoses and bipolar disorder, are at greater risk for obesity compared with people without mental illness. An altered resting metabolic rate (RMR) may be a key driving factor; however, published studies have not been systematically reviewed. This systematic review and meta-analysis aimed to determine whether the RMR of people with SMI assessed by indirect calorimetry differs from (i) controls, (ii) predictive equations and (iii) after administration of antipsychotic medications. Five databases were searched from database inception to March 2022. Thirteen studies providing nineteen relevant datasets were included. Study quality was mixed (62 % considered low quality). In the primary analysis, RMR in people with SMI did not differ from matched controls (n 2, standardised mean difference (SMD) = 0·58, 95 % CI −1·01, 2·16, $P = 0{\cdot}48$, $I^2 = 92$ %). Most predictive equations overestimated RMR. The Mifflin–St. Jeor equation appeared to be most accurate (n 5, SMD = −0·29, 95 % CI −0·73, 0·14, $P = 0{\cdot}19$, $I^2 = 85$ %). There were no significant changes in RMR after antipsychotic administration (n 4, SMD = 0·17, 95 % CI −0·21, 0·55, $P = 0{\cdot}38$, $I^2 = 0$ %). There is little evidence to suggest there is a difference in RMR between people with SMI and people without when matched for age, sex, BMI and body mass, or that commencement of antipsychotic medication alters RMR.

Key words: Basal metabolism: Calorimetry indirect: Mental disorders: Schizophrenia spectrum and other psychotic disorders: Bipolar and related disorders

People living with serious mental illness (SMI) such as schizophrenia, related psychotic disorders, and bipolar affective disorder, develop metabolic syndrome and its components at rates considerably higher than the general population (RR = 1·4 to 2·0)[1]. Physical health comorbidities are the largest contributor to the 13–15-year mortality gap in people with SMI compared with the general population, drive psychotropic medication non-adherence[2] and reduce quality of life[3]. The reasons for this are not fully understood but include medication side-effects[4], characteristics of the mental illness[5], detrimental lifestyle[6–8], stigma and diagnostic overshadowing[9].

People living with SMI frequently experience significant weight gain early in the course of the illness and psychotropic medication exposure, particularly second-generation antipsychotic medications[10]. These medications are often essential for managing psychiatric symptoms; however, appetite and binge eating behaviours may increase[11]. A systematic critical reappraisal showed that without physical health intervention, people with first-episode psychosis commencing antipsychotic medication gain on average 7·1–9·2 kg in weight with olanzapine, 4·0–5·6 kg with risperidone and 2·6–3·8 kg with haloperidol in the first 10–12 weeks of treatment[12]. This weight gain can continue for 10–20 years in those who receive ongoing antipsychotic medication treatment for enduring SMI[13]. However, the higher risk for metabolic syndrome and its elements is not exclusively due to antipsychotic medication, with increased risk for abdominal obesity (OR = 4·43), metabolic syndrome (OR = 2·35) and diabetes (OR = 1·99) being observed

Abbreviations: IC, indirect calorimetry; SMD, standardised mean difference; SMI, severe mental illness.

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in antipsychotic-naïve people with schizophrenia compared with general population controls[14].

A lower resting metabolic rate (RMR) in people with SMI compared with people without mental illness has been suggested as a potential driving factor. A review published in 2013 examined studies that assessed the impact of antipsychotic medications on RMR in healthy volunteers and in people with SMI[11]. This review suggested that antipsychotic medications may impact RMR and questioned the validity of using predictive equations such as the Harris–Benedict and Schofield equations. However, it lacked the comprehensive approach of a systematic review[11]. To the authors' knowledge, a comprehensive systematic review and critical evaluation of the literature on RMR in people living with SMI has not been undertaken.

This study aims to systematically review whether RMR measured via indirect calorimetry (IC) in people with SMI differs: (i) from RMR via IC in controls, (ii) values derived from predictive equations (e.g., Harris–Benedict) and (iii) after administration of antipsychotic medication.

Methods

This systematic review was pre-registered on the PROSPERO database (CRD42022312667) and was reported in line with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (see online Supplementary Table 1 for completed PRISMA checklist)[15].

Search strategy

An online search was undertaken to identify studies published from database inception to March 2022. PubMed, Embase via Ovid, CENTRAL via Ovid, CINAHL via EBSCO*host* and PsychINFO via Ovid were searched using a comprehensive search strategy (online Supplementary Tables 2(a)–(e)). The search strategy was developed by researchers in the fields of nutrition and psychiatry, experienced in systematic review. This was complemented by targeted Google Scholar searches and screening of the reference list of a relevant scoping review. For publications with insufficient or missing information, email contact was attempted with corresponding authors a maximum of two times, 2 weeks apart. Searches were restricted to human studies. There was no language restriction. Google Translate was used for studies published in a language other than English[16].

The following Participant, Intervention/exposure, Comparator, Outcome, Study Design (PICOS) framework was developed to define inclusion and exclusion criteria (Table 1). Studies were included if they provided data on RMR measured by IC for people with SMI, including clinical (Diagnostic and Statistical Manual of Mental Disorders (DSM), e.g., DSM-5[17] or International Classification of Diseases (ICD), e.g., ICD-11[18]) diagnosis of schizophrenia and related psychoses, and/or bipolar affective disorder, and compared this to data to: (i) RMR measured by IC for a control group, (ii) predictive equations and/or (iii) RMR measured by IC for people with SMI post-administration of antipsychotic medication.

Types of articles included were observational studies (cross-sectional, case–control, cohort) and intervention studies (baseline data or pre–post administration of antipsychotic medication). Included article types were full-length original data articles. Excluded study and article types were qualitative studies, case reports, reviews, perspectives, grey literature, conference abstracts, dissertations, editorials and letters to the editor.

Study selection

For the purpose of this review, a 'study' (or 'studies') refers to a publication(s) and a 'dataset' refers to a set of data within a study relevant to a single outcome of interest, so one study may have multiple datasets of interest. Completed searches were exported and combined in Endnote 20 (Clarivate, Philadelphia, 2013) and deduplicated. Two reviewers (SYN and ST) screened all identified records through Covidence (Veritas Health Innovation, Melbourne) in two phases (i) title/abstract screening and (ii) full-text screening. Disagreements on included and excluded studies were resolved through discussion between reviewers. Reasons for exclusion, e.g., 'wrong population', were agreed upon and recorded for all the studies that did not meet the inclusion criteria during full-text screening.

Data extraction

Data were extracted independently by two reviewers (SYN and ST) through Covidence (Veritas Health Innovation, Melbourne), and any disagreements were resolved through discussion. The following data were extracted: reference (author, year, country), study design, study aim, target group and comparator group details (diagnoses/comparator, sample size, gender, age and other reported factors that may impact RMR, e.g., BMI), RMR data such as group mean/median and/or between-group data (e.g., mean biases, p-values) and spread of data values, and other additional information relevant to RMR (e.g., gender differences, adjusting for other factors).

Risk of bias

Risk of bias assessment was conducted independently by two reviewers (SYN and OAY) using the Joanna Briggs Institute Critical Appraisal Checklists for observational studies (Checklist for Cohort Studies and Checklist for Analytical Cross-sectional Studies)[19] and Cochrane Risk of bias tool for intervention studies[20]. The Joanna Briggs Institute tools evaluated eleven and eight domains for cohort and cross-sectional studies, respectively, and scored as 'yes' (=1), 'no' (=0), 'unclear' (=?) or 'not applicable' (=NA). The Cochrane Risk of bias tool evaluated seven domains: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome data, incomplete data outcome, selective reporting and other sources of bias. Then each domain was evaluated as 'low risk' (=1), 'high risk' (=0) or 'unsure' (=?). For each tool, a final score of $\geq 75\,\%$ was considered 'high quality', while $< 75\,\%$ was considered 'low quality'. In the Joanna Briggs Institute tool, the criteria for

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Table 1. PICOS: inclusion and exclusion criteria of the review

Component	Included	Excluded
Population	• ≥ 75 % of clinical group with a clinical diagnosis (ICD or DSM) of schizophrenia or related psychotic disorders or bipolar affective disorder • With and without prescription of antipsychotic medication • Youth and adults (included participants ≥ 12 years* or mean age ≥ 15 years) • Human studies	• Animal studies
Intervention/ Exposure	• RMR via IC	• RMR not measured by IC such as bioimpedance • Physical energy expenditure • Cerebral metabolic rate via positron emission tomography scan
Comparison	• RMR (via IC) in controls without a mental illness • RMR from predictive equations (e.g., Harris–Benedict equation). • RMR (via IC) post-commencement of antipsychotic medication	
Outcome	• Difference in RMR	
Study Design/ Publication Type	• Observational studies (cross-sectional, cohort, case-control) • Chart audit • Intervention studies (relevant cross-sectional data or pre-post administration of antipsychotic medication) • Original research publications and brief reports	• Qualitative studies • Case reports • Reviews • Perspectives • Grey literature • Conference abstract • Dissertation • Editorial • Letter to the editor
Language	• No language restriction	• Unable to translate into English by a third party (e.g., Google Translate)

IC, indirect calorimetry; ICD, International Classification of Diseases; DSM, Diagnostic and Statistical Manual of Mental Disorders.
* Australian Institute of Health and Welfare defines youth age starts from 12 years.

'were the outcomes measured in a valid and reliable way' was identified as 'not applicable' as it was covered in the criteria for 'was the exposure measured in a valid and reliable exposure way'. Any discrepancies with quality assessment were resolved through discussion between reviewers.

Certainty of evidence

Certainty of the evidence for each outcome was conducted independently by two reviewers (SYN and OAY) using Grades of Recommendation, Assessment, Development and Evaluation (GRADE)[21]. GRADE evaluated five domains: risk of bias, inconsistency, indirectness, imprecision and publication bias. Each domain was then evaluated to rate the certainty of evidence as 'high', 'moderate', 'low' or 'very low'. Publication bias was rated as either 'undetected' or 'strongly suspected'. Overall certainty of evidence for each outcome was then assessed as 'high', 'moderate', 'low' or 'very low'. Any discrepancies with GRADE were resolved through discussion between the reviewers. All outcomes with ≥ 2 datasets were subjected to GRADE assessment.

Inconsistency was downgraded if studies under the same outcome had large variations in point estimates/presence of heterogeneity. Indirectness was downgraded if studies under the same outcome varied in the study population, prognostic factor (SMI) and outcomes. Imprecision was downgraded if sample sizes were too small to detect a significant difference and thus had wide CI. Publication bias was downgraded if there was a small sample size and if there was an unequal distribution presented in the funnel plot.

Data analysis

The group means or between-group difference in RMR between the target population group (SMI) and each comparator group (i) controls, (ii) predictive equations and (iii) after administration of antipsychotic medications were compared for strength (degree of difference and statistical significance) through narrative synthesis.

Outcomes with ≥ 2 datasets were pooled for meta-analysis using comprehensive meta-analysis[22]. For a dataset to be included, there needed to be sufficient information reported, for example, group means, standard deviations (SD's) and sample size, or mean difference, SD and sample size. For comparing RMR between people with SMI and controls, participants needed to be matched for age, sex, BMI and body fat percentage. Due to anticipated heterogeneity, a random effects model was applied. Outcomes were reported as standardised mean difference (SMD) and 95 % CI's. SMD's were considered small at 0·2, medium at 0·5 and large at 0·8[23]. Heterogeneity was assessed using the I^2 statistic. Publication bias was assessed by inspection of funnel plots and the Egger's regression test. Duval and Tweedie's trim and fill analysis was used to correct for publication bias. Statistical significance was set at $P < 0{\cdot}05$ for SMD, heterogeneity and publication bias.

Results

Study selection

The systematic search identified 516 unique titles after the removal of 313 duplicates. A total of forty-three studies were

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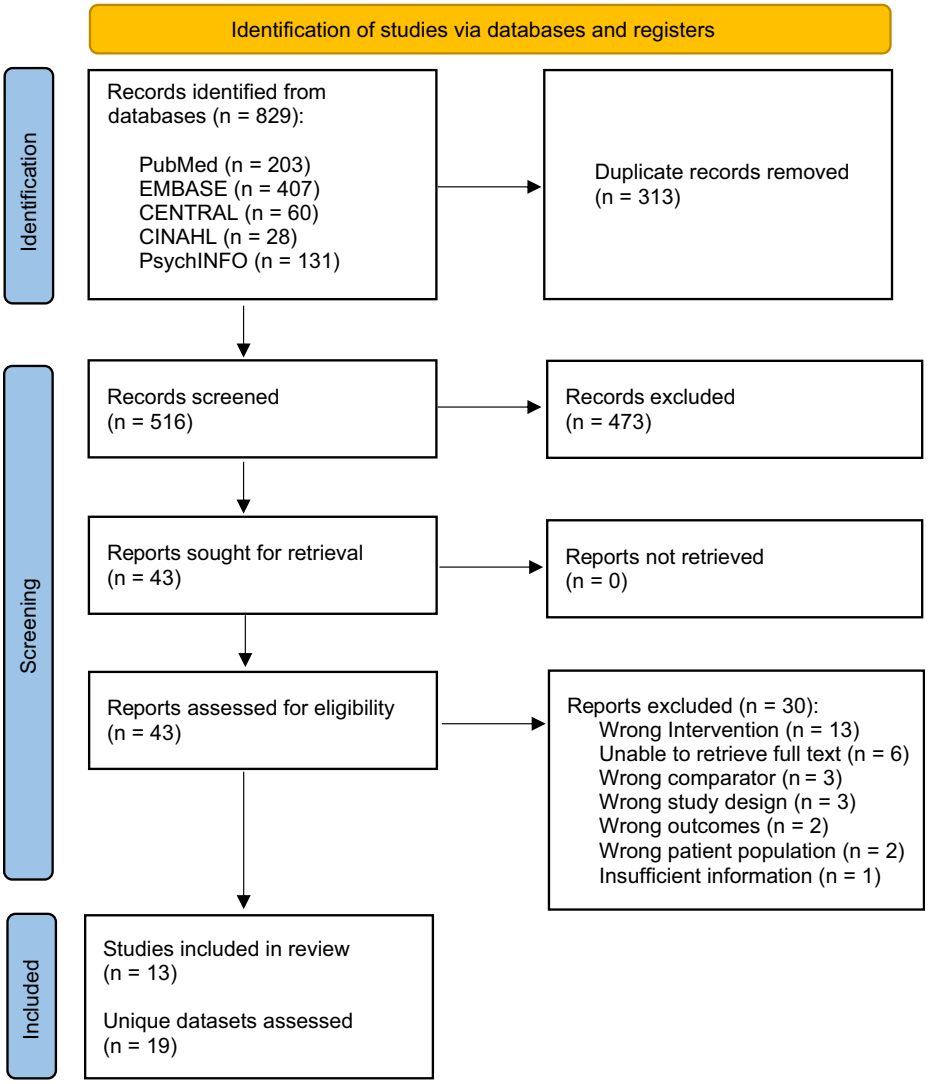

Fig. 1. PRISMA flowchart.

eligible for full-text screening. From this, thirteen studies were included in the final analysis (Fig. 1).

Study characteristics

One RCT[24], ten cross-sectional studies[25–34] and two cohort studies[35,36] were included (Table 2). Five studies targeted schizophrenia and related psychoses[25,26,29,34,36], four targeted bipolar disorder I (BD-I)[27,28,30,31], three targeted both schizophrenia and related psychoses, and bipolar affective disorder[32,33,35] and one targeted first episode psychosis[36]. Sample size of SMI population groups ranged from *n* 9 to *n* 128. Nine studies included both males and females[24,26,27,30,32–36], two studies were limited to only males[25,29] and two studies were limited to only females[28,31]. Selected studies were based in different countries including Australia (*n* 3)[25,29,32], USA (*n* 2)[28,36], Italy (*n* 2)[30,31], Spain (*n* 1)[35], Turkey (*n* 1)[27], Sweden (*n* 1)[26], Greece (*n* 1)[33], South Korea (*n* 1)[24] and Japan (*n* 1)[34]. All were published between the years 2005 and 2015. Individual study details are listed in Table 2.

Quality assessment using the Cochrane Risk of bias tool and Joanna Briggs Institute critical appraisal tools revealed that 5/13 studies were considered as 'High quality'[26–29,35], while 8/13 studies were considered as 'Low quality'[24,25,29–31,33,34,36], (online Supplementary Tables S2–S4).

Within the thirteen studies, there were nineteen primary datasets of interest. Eight studies provided a single dataset of interest[25,27–29,31,33,34,36], three studies provided datasets for two different review questions[26,30,35], one study presented a dataset on men and women individually without an overall analysis[32], one study presented data compared with controls prior to antipsychotic medication exposure and then in a smaller sample at follow up subsequent to weight gain[35] and one RCT presented pre–post antipsychotic data separately for the two antipsychotic medication arms without a combined analysis[24].

Table 2. Characteristics of selected studies

Reference	Study design	Study aim and relevant data	Target group	Comparator group	RMR data	Additional findings	Quality score
Caliyurt, 2009, Turkey	Cross-sectional study	Aim: To assess the REE of BD-I manic episode patients and compare it with that of healthy controls. Relevant data: SMI (IC) *v.* Controls (IC)	Diagnosis: BD-I *n* 42 48 % F, 52 % M Age: mean 34·33 ± 10·56 y BMI: mean 25·33 ± 4·40 kg/m^2	Control: *n* 27 59 % F, 41 % M Age: mean 34·00 ± 9·41 y BMI: Mean 26·19 ± 5·67 kg/m^2	SMI: mean 1638·26 ± 459·65 kcal/d Control: mean 1368·81 ± 463·02 kcal/d Between groups: t = 2·37 *P* = 0·02	Gender had NS impact on RMR between groups (OR = 1·02; 95 % CI: 1·01, 1·03; *P* = 0·002)	6/7
Cuerda, 2011, Spain	Cohort study	Aim: To examine the influence of second-generation antipsychotics on REE and the relationship of REE to weight gain in adolescent patients. Relevant data: 1. SMI (IC) *v.* Predictive equations 2. Pre- *v.* post administration of AP.	Diagnosis: Schizophrenia and related psychoses, bipolar disorder *n* 46 (baseline) *n* 16 (1 y) 28 % F, 72 % M Age: mean 16·3 ± 1·4 y BMI (baseline): mean 20·6 ± 3·1 kg/m^2 BMI (1 y): mean 23·3 ± 2·3 kg/m^2	Predictive equations: HB Pre- and post-administration of: Risperidone, olanzapine or quetiapine for 1 year	SMI: Pre-AP: mean 1494 ± 260 kcal/d Post-AP (1 y): mean 1556 ± 247 kcal/d HB: Baseline: mean 1551 ± 161 kcal/d 1 y: mean 1642 ± 191 kcal/d Between groups: REE over 12 months treatment period: F = 1·93, *P* = 0·118 REE was lower than HB during treatment (12 months, t = –2·53, *P* = 0·02)	Decrease in REE/kg body mass ratio (F = 3; df = 4; *P* = 0·03). Increase in REE/% FFM ratio (F = 3·93; df = 4; *P* = 0·007). REE/% FFM ratio correlated with weight gain (*r* = 0·69, *P* = 0·004). Baseline REE was higher in men (F = 2·7; df = 1, *P* = 0·001). No differences in RMR between drug groups (F = 0·84, df = 6, *P* = 0·55).	7/9
Fleet-Michaliszyn, 2008, USA	Cross sectional study	Aim: To compare insulin resistance in women with BD-I to race-, age- and BMI-matched controls. Relevant data: SMI (IC) *v.* controls (IC)	Diagnosis: BD-I *n* 18 100 % F Age: mean 41·4 ± 2·1 y BMI: mean 29·0 ± 0·9 kg/m^2	Control: *n* 17 100 % F Age: mean 40·9 ± 2·3 y BMI: mean 28·6 ± 1·0 kg/m^2	SMI: mean 1533·9 ± 51·4 kcal/d Control: mean 1459·1 ± 54·7 kcal/d Between groups: NS differences in RMR (after accounting for FFM).	Significant differences in RMR between obese and normal weight women with and without BD-I (*P* < 0·05).	7/7
Graham, 2005, USA	Cohort study	Aim: To investigate causes of weight gain from atypical AP through a cohort of first-episode AP naive subjects to eliminate confounding effects of other medications. Relevant data: Pre- *v.* post-administration of AP	Diagnosis: First-episode psychosis *n* 9 (baseline) *n* 9 (last visit) 33 % F, 66 % M Age: median 21·5 y (range: 20·8–27·3) BMI (baseline): median 24·5 kg/m^2 (IQR 20·8 to 25·9) BMI (12 w): median 24·9 kg/m^2 (IQR 23·6 to 27·2)	Pre- and post-administration of: Olanzapine for 12 w	Pre AP: median 1720 (IQR 1309–2181) kcal/d Post-AP: median 1741 (IQR 1484–2192) kcal/d Change: median 63 kcal/d (IQR –3 to 464), 4·0 % (IQR –0·1–32·0) Between groups: *P* = 0·20	No evidence of lower baseline REE in subjects who gained the most weight.	5/8
Miniati, 2015, Italy	Cross sectional study	Aim: To compare predictive formulae commonly used to calculate REE with IC in a sample of female outpatients with BD-I, stabilised with long-term psychopharmacologic al treatment. Relevant data: SMI (IC) *v.* Predictive equations	Diagnosis: BD-I *n* 17 100 % F Age: mean 37·3 ± 11·4 y BMI: mean 28·9 ± 5·7 kg/m^2	Predictive equation: HB, MIF, LARN	SMI: mean 1122·1 ± 228·6 kcal/d HB: Mean: 1547·8 ± 156·7 kcal/d Bias: 425·6 kcal/d (t = 8·48; *P* < 0·001) MIF:	BMI was significantly correlated to REE measured using HB (rho = 0·77, *P* < 0·001), MIF (rho = 0·69, *P* = 0·002) and LARN (rho = 0·78, *P* < 0·001). Not correlated to measured REE (IC) (rho = 0·08, *P* = 0·747). Measured REE was not significantly	4/7

Table 2. (*Continued*)

Reference	Study design	Study aim and relevant data	Target group	Comparator group	RMR data	Additional findings	Quality score
					Mean: 1485·3 ± 177·9 kcal/d Bias: 363·2 kcal/d (t = 6·29, $P < 0·001$) LARN: Mean: 1559·3 ± 168·7 kcal/d Bias: 437·2 kcal/d (t = 7·34, $P < 0·001$) Between groups: HB: Z = –4·23, $P < 0·001$ MIF: Z = –4·06, $P < 0·001$ LARN: Z = –4·17, $P < 0·001$	correlated with the three equations (HB rho = 0·23, $P = 0·376$; MIF rho = 0·24, $P = 0·360$; LARN rho = 0·17, $P = 0·501$).	
Nilsson, 2006, Sweden	Cross sectional study	Aim: To test the hypothesis that the REE assessed with IC is lower in patients with schizophrenia than in healthy controls. Relevant data: 1. SMI (IC) *v.* Controls (IC) SMI (IC) *v.* Predictive equations	Diagnosis: Schizophrenia, schizophreniform disorder *n* 30 30 % F, 70 % M Age: mean 33·0 ± 8·7 y BMI: mean 25·7 ± 5·3 kg/m^2	Control: *n* 17 29 % F, 71 % M Age: mean 32·3 ± 7·9 y BMI: mean 23·7 ± 2·9 kg/m^2 Predictive equation: FAO/WHO/UNU	SMI: mean 6720 ± 997 kJ Control: mean 6917 ± 1046 kJ FAO/WHO/UNU: 7390 ± 1103 kJ Between groups: SMI *v.* Control: $P = 0·53$ SMI *v.* FAO/WHO/UNU: t = –2·47, df = 58, $P < 0·02$	REE expressed as kJ/kg/d was significantly lower in the patient group (t = –3·05, df = 45, $P < 0·004$).	7/7
Park, 2013, South Korea	RCT	Aim: Compare the effects of 12 w of treatment with ziprasidone or olanzapine on weight, body composition, appetite, REE, substrate oxidation, and metabolic parameters in adults with schizophrenia and or other psychotic disorders. Relevant data: Pre- *v.* post-administration of AP	Diagnosis: Schizophrenia, other psychotic disorders *n* 20 (Ziprasidone *n* 10, Olanzapine *n* 10) 50 % F, 50 % M Ziprasidone age: median 34·50 y (IQR 26·25 to 40·25) Olanzapine age: median 31·50 y (IQR 26·50 to 41·25)	Pre- and post-administration of: Olanzapine or ziprasidone for 12 weeks	Pre-AP (median): Ziprasidone: 1075·20 kcal/d (IQR 1024·78 to 1416·81) Olanzapine: 1630·24 kcal/d (IQR 1079·23 to 1898·10) Post-AP (median): Ziprasidone end: 1132·38 kcal/d (IQR 1006·71 to 1723·06) Olanzapine end: 1255·40 kcal/d (IQR 1069·48 to 1747·83) Change (%): Ziprasidone change: 1·41 (IQR – 11·98 to 61·96) (NS) Olanzapine change: –5·27 (IQR – 33·37 to 10·58) (NS) Between groups: Ziprasidone $P = 0·678$ Olanzapine $P = 0·241$	REE normalised to LBM (kcal/g) significantly increased in ziprasidone ($P = 0·011$), but not with olanzapine ($P = 0·445$).	4/7
Sharpe, 2005, Australia	Cross sectional study	Aim: To measure REE via IC in a group of men taking clozapine and to determine whether REE can be accurately predicted using previously published regression equations for this population. Relevant data: SMI (IC) *v.* Predictive equations	Diagnosis: Schizophrenia *n* 8 100 % M Age: mean 28·0 ± 6·7 y BMI: mean 29·8 ± 6·8 kg/m^2 FFM: mean 66·1 ± 11·5 kg	Predictive equations: HB, SCH, Movahedi, Owen and colleagues, Jensen and colleagues	SMI: mean 1825 ± 408 kcal/d Between groups: HB bias: 284 ± 242 kcal/d SCH bias: 287 ± 262 kcal/d Movahedi bias: 252 ± 535·97 kcal/d Owen and colleagues bias: 60 ± 184 kcal/d Jensen and colleagues bias: 119 ± 203 kcal/d	REE correlated with FFM ($r = 0·95$, $P = 0·001$), BMI ($r = 0·91$, $P = 0·002$), and WC ($r = 0·89$, $P = 0·003$).	4/7

Table 2. (*Continued*)

Reference	Study design	Study aim and relevant data	Target group	Comparator group	RMR data	Additional findings	Quality score
			WC: mean 108·1 ± 19·3 cm				
Sharpe, 2009, Australia	Cross sectional study	Aim: To clarify whether there are any differences in energy metabolism specifically REE and substrate utilisation at rest between people with schizophrenia who take AP medications and healthy controls of the same age and body size. Relevant data: SMI (IC) *v.* Controls (IC)	Diagnosis: Schizophrenia *n* 31 100 % M Age: mean 34·2 ± 10·1 y BMI: mean 30·2 ± 5·7 kg/m^2	Control: *n* 31 100 % M Age: mean 34·6 ± 10·1 y BMI: mean 30·1 ± 6·0 kg/m^2	SMI: mean 1843 ± 287 kcal/d Control: 1933 ± 329 kcal/d Between groups: $P < 0·05$	NS difference in REE between groups when adjusting for FFM (1870 ± 172 kcal/d *v.* 1906 ± 172 kcal/d, F = 0·69, $P = 0·41$, 95 % CI difference 124 to 54 kcal/d).	7/7
Sharpe, 2010, Australia	Cross sectional study	Aim: To determine whether the regression equations published by MIF are suitable for the prediction of RMR in people taking weight inducing AP medications. Relevant data: SMI (IC) *v.* Predictive equations	Diagnosis: Schizophrenia (81 %), bipolar disorder, nonspecific psychotic disorder and schizoaffective disorder *n* 45 (table) *error in text reporting *n* 47* 24 % F, 76 % M Age (M): mean 36·3 ± 11·2 y Age (F): mean 37·4 ± 10·5 y BMI (M): mean 30·2 ± 5·7 kg/m^2 BMI (F): mean 31·9 ± 8·4 kg/m^2	Predictive equation: HB, SCH, MIF	SMI group (mean): M: 7632 ± 1267 kcal/d F: 6679 ± 1087 kcal/d Comparator males (mean): HB: 8418 ± 1326 kcal/d HB: bias 786 ± 715 kcal/d ($P < 0·001$) SCH: 8535 ± 1234 kcal/d SCH bias 899 ± 803 kcal/d ($P < 0·001$) MIF: 7866 ± 1004 kcal/d MIF bias 234 ± 699 kcal/d ($P < 0·001$) Comparator female (mean): HB: 6917 ± 1117 kcal/d HB bias 79 ± 259 kcal/d (NS) SCH: 7076 ± 1397 kcal/d SCH bias 401 ± 807 kcal/d (NS) MIF: 6666 ± 1246 kcal/d MIF bias −13 ± 506 kcal/d (NS)	RMR differences between independent genders and predictive equations: Male IC *v.* HB $P < 0·001$ IC v. SCH $P < 0·001$ IC *v.* MIF $P < 0·05$ Female IC *v.* HB = NS IC *v.* SCH = NS IC *v.* MIF = NS	4/7
Skouroliakou, 2009, Greece	Cross sectional study	Aim: To compare the validity of four RMR equations on patients with SMIs taking olanzapine. Relevant data: SMI (IC) *v.* Predictive equations	Diagnosis: SMI *n* 128 68 % F, 32 % M Age: mean 41·19 ± 11·22 y BMI: mean 34·07 ± 6·47 kg/m^2 FFM: mean 52·56 ± 11·99	Predictive equation: HB ABW, HB CBW, SCH, MIF	SMI (mean): 1595·35 ± 475·86 kcal/d Comparator (mean): HB ABW: 1676·10 ± 329·6 kcal/d Bias: 80·75 ± 16·40 kcal/d ($P < 0·01$) HB CBW: 1762·20 ± 343·83 kcal/d Bias: 166·85 ± 395·51 kcal/d ($P < 0·01$) SCH: 1737·01 ± 340·27 kcal/d Bias: 141·66 ± 387·35 kcal/d ($P < 0·01$) MIF: 1648·28 ± 302·54 kcal/d Bias: 52·93 ± 385·934 kcal/d (NS) Between groups: HB ABW: $r = 0·502$, $P = 0·001$ HB CBW: $r = 0·697$, $P = 0·001$	RMR correlated with FFM ($r = 0·65$, $P < 0·01$) and body weight ($r = 0·51$, $P < 0·01$), but NS differences between genders.	5/7

Table 2. (*Continued*)

Reference	Study design	Study aim and relevant data	Target group	Comparator group	RMR data	Additional findings	Quality score
					Sch: $r = 0{\cdot}678$, $P = 0{\cdot}001$ Mifflin: $r = 0{\cdot}712$, $P = 0{\cdot}001$		
Soreca, 2007, Italy	Cross sectional study	Aim: To measure REE by means of IC in bipolar patients on maintenance treatment and in controls, and to estimate the agreement between measured and predicted REE in both groups. Relevant data: 1. SMI (IC) *v.* Controls (IC) SMI (IC) *v.* Predictive equations	Diagnosis: BD-I *n* 15 73 % F, 27 % M Age: mean 37·13 y (range 21–51) BMI: mean 28·18 kg/m^2 (range 21·45–37·19)	Control: *n* 17 65 % F, 35 % M Age: mean 35·59 y (range 21–53) BMI: mean 23·42 (range 18·00–43·43) Predictive equation: HB, SCH, LARN, OUR	SMI: NR Control: NR Between groups: BD-I *v.* control: NS HB: mean bias 483·38 ± 255·63 kcal/d (38 % overestimation) ($t = 7{\cdot}23$, $P < 0{\cdot}001$) SCH: mean bias 397·08 ± 192·38 kcal/d (31·9 % overestimation) ($t = 7{\cdot}994$, $P < 0{\cdot}001$) LARN: mean bias 423·3 ± 191·52 kcal/d (34·0 % overestimation) ($t = 8{\cdot}56$, $P < 0{\cdot}001$) OUR: mean bias 292·47 ± 427·38 kcal (23·5 % overestimation) ($t = 4{\cdot}53$, $P < 0{\cdot}001$)	NS difference in RMR between patients and controls. NS differences in RMR between controls and predictive equations. NS in controls for REE measured via HB, SCH, LARN, OUR and measured REE ($t = 1{\cdot}48$, $P = 0{\cdot}158$; $t = 1{\cdot}53$, $P = 0{\cdot}145$; $t = 1{\cdot}71$, $P = 0{\cdot}106$; $t = 0{\cdot}36$, $P = 0{\cdot}726$, respectively). HB for males showed the lowest mean bias (17·0 % overestimation).	4/7
Sugawara, 2014, Japan	Cross-sectional study	Aim: To compare the validity of four REE equations for patients with schizophrenia taking AP. Relevant data: SMI (IC) *v.* Predictive equations	Diagnosis: Schizophrenia or schizoaffective disorder *n* 110 37 % F, 63 % M Age: mean 45·9 ± 13·2 y BMI: mean 24·7 ± 4·5 kg/m^2	Predictive equation: HB, MIF, SCH, FAO/WHO/UNU	SMI: Mean 1442 ± 358 kcal/d Comparator: HB: mean 1440 ± 230 kcal/d Mean bias: −1·7 ± 282·3 kcal/d (NS) MIF: mean 1395 ± 224 kcal/d Mean bias: 46·7 ± 290·3 kcal/d (NS) SCH: mean 1506 ± 226 kcal/d Mean bias: 64·7 ± 301·8 kcal/d ($P < 0{\cdot}001$) FAO/WHO/UNU: mean 1530 ± 235 kcal/d Mean bias: 88·7 ± 305·5 kcal/d ($P < 0{\cdot}001$)	HB was the most accurate equation (RMSE = 283·41, $r = 0{\cdot}617$, $P < 0{\cdot}001$), followed by MIF (RMSE = 291·31, $r = 0{\cdot}588$, $P < 0{\cdot}001$), SCH (RMSE = 301·70, $r = 0{\cdot}546$, $P < 0{\cdot}001$), FAO/WHO/UNU (RMSE = 303·93, $r = 0{\cdot}536$, $P < 0{\cdot}001$). In males, NS mean biases with HB and MIF, However, FAO/WHO/UNU and SCH showed significant mean biases. In females, NS mean biases HB, SCH and FAO/WHO/UNU. MIF showed significant mean bias.	5/7

ABW, actual body weight; AP, antipsychotic(s); BD-I, bipolar disorder I; CBW, current body weight; d, day; F, female; FAO/WHO/UNU, Food & Agriculture Organisation/World Health Organisation/United Nations University; FFM, fat-free mass; HB, Harris Benedict; LARN, Recommended Nutrients Assumption Levels; LBM, lean body mass; M, male;, MIF, Mifflin–St. Jeor; REE, resting energy expenditure, SCH, Schofield; SMI, serious mental illness; w, week; wc, waist circumference; y, year.

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Table 3. Standardised mean difference of RMR measured by indirect calorimetry compared with controls, predictive equations and pre–post commencement of antipsychotic medication

Outcome	Number of datasets	SMD	Lower limit	Upper limit	*P*-value	I^2	*P*-value
SMI compared with control	2	0.58	−1.01	2.16	0·48	92 %	<0·001
SMI compared with predictive equation							
Harris–Benedict	9	−0·67	−1·05	−0·30	< 0·001	84 %	< 0·001
Schofield	6	−0·64	−1·03	−0·26	0·001	74 %	0·002
Mifflin–St. Jeor	5	−0·29	−0·73	0·14	0·19	85 %	< 0·001
LARN	2	−2·19	−2·81	−1·57	< 0·001	0 %	0·887
FAO/WHO/UNU	2	−0·39	−0·70	−0·08	0·01	0 %	0·347
Pre/post-antipsychotic medication commencement	4	0·17	−0·21	0·55	0·38	0 %	0·408

LARN, recommended nutrients assumption levels, FAO/WHO/UNU, Food & Agriculture Organisation/World Health Organisation/United Nations University; SMD, standardised mean difference; SMI, severe mental illness.

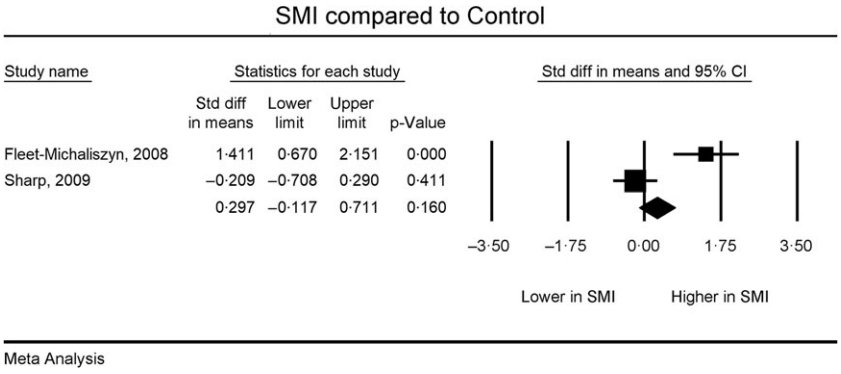

Fig. 2. RMR of people with severe mental illness measured by indirect calorimetry compared with controls.

Five datasets investigated RMR between people with SMI and controls[26–30]. Ten datasets investigated RMR between people with SMI and predictive equations[25,26,29–31,33–35]. Predictive equations that were reported included: Harris–Benedict (*n* 9)[25,29–31,33–35], Schofield (*n* 6)[25,30,32–34], Mifflin–St. Jeor (*n* 5)[31–34], FAO/WHO/UNU (*n* 2)[26,34], LARN (*n* 2)[30,31], OUR (*n* 1)[30], Movahedi (*n* 1)[25], Owen and colleagues (*n* 1)[25] and Jensen and colleagues (*n* 1)[25]. Four datasets investigated RMR pre and post-administration of antipsychotic medication[24,35,36]. Antipsychotic medications that were reported included: olanzapine (*n* 3)[24,35,36], ziprasidone (*n* 1)[24], risperidone (*n* 1)[35] and quetiapine (*n* 1)[35].

Study results

RMR of people with SMI compared with controls. Two of five datasets (40 %) appropriately matched people with SMI and controls for age, sex, BMI and body fat percentage[28,29]. Sharpe *et al.*[29] found that males with schizophrenia had a significantly lower RMR compared with controls ($P < 0·05$). However, when fat-free mass was controlled for, there was no difference between groups ($F = 0·69$, $P = 0·41$)[29]. Fleet-Michaliszyn *et al.*[28] found no significant difference in RMR for women with bipolar compared with controls after accounting for body composition; however, people with SMI oxidised 13 % less fat at rest compared with controls. When pooled together, there was no significant difference in RMR between SMI and control (*n* 2, SMD = 0·58, 95 % CI −1·01, 2·16, $P = 0·48$, $I^2 = 92$ %) (Table 3 and Fig. 2).

Three datasets included groups that were not adequately matched. Caliyurt *et al.*[27] found that people with BD-I had significantly higher RMR compared with controls ($t = 2·37$, $P = 0·02$). In this study, there was a higher number of females in the control group compared with males (59 % compared with 48 %), and authors did not report on matching groups for body composition. Nilsson *et al.*[26] found no difference between people with SMI and controls ($P = 0·53$); however, when RMR was expressed by kg, RMR was significantly lower in the SMI group compared with control group ($t = −3·05$, $df = 45$, $P < 0·004$). In this study, BMI and body fat percentages were lower in the control group. Soreca *et al.*[30] did not provide RMR data but stated no significant difference between the SMI and control groups. In this study, BMI was significantly lower in the control group, and no data were provided on body composition.

RMR of people with SMI compared with predictive equations. Seven out of nine datasets (78 %) revealed that the Harris–Benedict equation significantly overestimated RMR in people with SMI, with discrepancies ranging from 339 to 3,289 kJ/d[25,30–35]. In the two datasets that did not find a significant between-group difference, Sharpe *et al.*[32] found that the Harris–Benedict equation did not show any significant mean

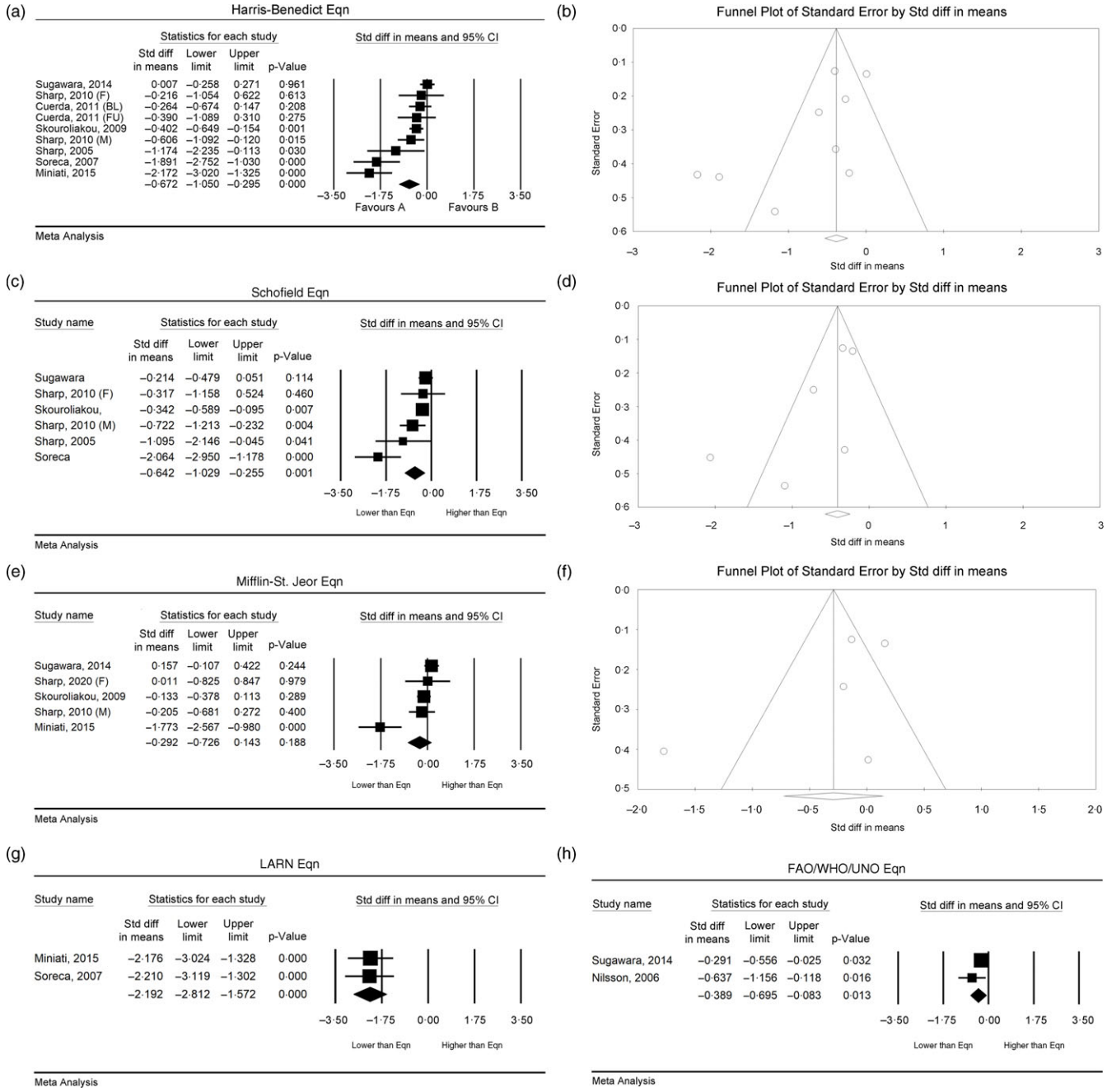

Fig. 3. RMR of people with severe mental illness measured by indirect calorimetry compared with predictive equations. Harris–Benedict equation: (a) forest plot of standardised mean difference, (b) funnel plot assessing publication bias; Schofield equation: (c) forest plot of standardised mean difference, (d) funnel plot assessing publication bias; Mifflin–St. Jeor equation: (e) forest plot of standardised mean difference, (f) funnel plot assessing publication bias; LARN equation: (g) forest plot of standardised mean difference; FAO/WHO/UNU equation: (h) forest plot of standardised mean difference. FAO, Food and Agriculture Organisation; LARN: SMD, standardised mean difference; UNU, United Nations University.

biases in females with schizophrenia or schizoaffective disorder, and Sugawara *et al.*[34] found the Harris–Benedict equation to be the most accurate predictive equation for people with schizophrenia, when compared with Schofield, Mifflin–St-Jeor and FAO/WHO/UNU equations. Pooled effects found a significant overestimation for the Harris–Benedict Equation (n 9, SMD = −0·67, 95 % CI −1·05, −0·30, $P < 0·001$, $I^2 = 84$ %) (Table 3; Fig. 3(a)). Publication bias was identified (Fig. 3(b); Egger's regression: $P = 0·04$); however, trim and fill analysis did not alter the pooled effects.

Five out of six datasets (83 %) that compared RMR in SMI to the Schofield equation found that there was a significant overestimation of RMR, with a bias ranging from 272 to 3,761 kJ/d[25,30,32–34]. In the dataset that did not find a between-group

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difference, Sharpe *et al.*[32] found that the Schofield equation did not show any significant mean biases in females with schizophrenia or schizoaffective disorder. Pooled effects found significant overestimation when using the Schofield equation (n 6, SMD = –0·64, 95 % CI –1·03, –0·26, P = 0·001, I^2 = 74 %) (Table 3, Fig. 3(c)), with no indication of publication bias (Fig. 3(d); Egger's regression: P = 0·09).

One out of five datasets (20 %) found the Mifflin–St-Jeor equation to significantly differ from the RMR of people with SMI. In the one dataset that found a statistical difference, Sharpe *et al.*[32] found significant mean bias in males by 979 kJ/d (P < 0·001). In a subgroup analysis, Miniati *et al.*[31] reported that the Mifflin–St. Jeor equation significantly overestimated RMR in females with BD-I by 1,519 kJ/d (t = 6·29, P < 0·001). Skouroliakou *et al.*[33], Sugawara *et al.*[34] and the female analysis dataset within Sharpe *et al.*[32] revealed no significant mean bias. Pooled effects found no significant bias when using the Mifflin–St-Jeor equation (n 5, SMD = −0·29, 95 % CI −0·73, 0·14, P = 0·19, I^2 = 85 %) (Table 3; Fig. 3(e)); however, heterogeneity was significant. There was no indication of publication bias (Fig. 3(f); Egger's regression: P = 0·28).

Two datasets out of two found that the LARN equation significantly overestimates RMR in people with BD-I by 1,770 to 1,828 kJ/d ($P \leq$ 0·001) [30,31]. Pooled effects found significant overestimation when using the LARN equation (n 2, SMD = −0·39, 95 % CI −0·70, −0·08, P = 0·01, I^2 = 0 %) (Table 3; Fig. 3(g)).

Two of two datasets (100 %) found that the FAO/WHO/UNU equation showed significant mean biases and overestimation of RMR[26,34]. Sugawara *et al.*[34] found a significant overestimation by 372 kJ/d (P < 0·02) in people with schizophrenia or schizoaffective disorder. However, when adjusting for gender, there was no significant difference in RMR for females with schizophrenia or schizoaffective disorder.[34] Pooled effects found significant overestimation when using the FAO/WHO/UNU equation (n 2, SMD = –0·39, 95 % CI –0·70, –0·08, P = 0·01, I^2 = 0 %) (Table 3; Fig. 3(h)).

The OUR[30], Movahedi[25] and Jensen and colleagues[25] equations were found to overestimate RMR in people with SMI by 1,222 kJ/d, 1,054 kJ/d and 498 kJ/d, respectively, while the Owen and colleagues equation underestimated RMR by 251 kJ/d[25].

RMR of people with SMI pre- and post-antipsychotic medication exposure. All datasets (n 4) assessing RMR difference pre- and post-administration of antipsychotic medications revealed no significant changes[22,31,32]. Changes in RMR ranged from −5·27 % to 4 %[30,31]. When pooled for meta-analysis, there was no difference between pre- and post-data (n 4, SMD = 0·17, 95 % CI −0·21, 0·55, P = 0·38, I^2 = 0 %) (Table 3, Fig. 4(a)) with no indication of publication bias (Fig. 4(b); Egger's regression: P = 0·64). When adjusted to lean body mass, Park *et al.*[22] found a significant increase in RMR at follow-up in the ziprasidone group (P = 0·011) but not in the olanzapine group (P = 0·445). Cuerda *et al.*[31] provided a subgroup investigation on three antipsychotic medications (olanzapine, risperidone and quetiapine) and revealed no differences in RMR between the antipsychotic groups (F = 0·84, df = 6, P = 0·55).

Certainty of evidence

Certainty of the evidence is summarised in Table 4. The certainty of evidence for comparing RMR between SMI and controls was very low predominantly due to indirectness, imprecision and publication bias. The certainty of evidence in relation to predictive equations ranged from low (LARN and FAO/WHO/UNU) to moderate (Harris–Benedict, Schofield and Mifflin–St-Jeor). The certainty of evidence for pre–post administration of APM was low due to risk of bias, indirectness, imprecision and publication bias.

Discussion

This review found that (i) there is limited evidence for a difference in RMR between people with SMI and people without an SMI when matched for covariates, (ii) most predictive equations significantly overestimate RMR in people with SMI and (iii) antipsychotic medications do not appear to significantly affect RMR.

It has been proposed that an increased RMR in people with bipolar disorder may be driven by a state of mania[27], characterised by a state of intense activity and energy. Conversely, in people with schizophrenia spectrum disorders, it has been hypothesised that RMR is lower than people without a mental illness due to a decrease in oxidative processes, independent of medication status[26]. Our review found that inconsistent results between studies are likely due to covariates that have not been accounted for, for example, a lacking of matching for BMI and body composition[26,30]. Both studies that were adequately matched/adjusted for age, sex, BMI body composition (e.g., body fat mass) found no significant difference between people with and without SMI. Future studies exploring RMR in people with SMI compared with other population groups should ensure that covariates are adequately matched/adjusted for.

Despite low to very low certainty in evidence for comparing RMR in SMI to people without mental illness and pre- and post-antipsychotic medication administration, there is little to suggest that an altered RMR is significantly contributing to the high rates of obesity in people with SMI[37]. There is a greater evidence base for excessive and unhealthy dietary intake[6], driven by factors including antipsychotic medications, which can increase appetite and reduce satiety[38], and a blunted reward system[39], combined with high levels of sedentary behaviour[40], driven by factors such as fatigue and low energy which can be a result of negative symptoms of the illness and sedative effects of medications[41].

Most predictive equations significantly overestimated RMR in people with SMI, including those commonly used in clinical practice (e.g., Harris–Benedict and. Schofield equation). An avenue requiring further exploration is the use of adjusted body weight measurement when a person is overweight/obese compared with using actual body weight in the equation. The use of actual body weight for the Harris–Benedict equation may make it a viable option, though at present, the Mifflin–St. Jeor equation appears to be the most accurate for people with SMI. However, caution is required given the observed heterogeneity

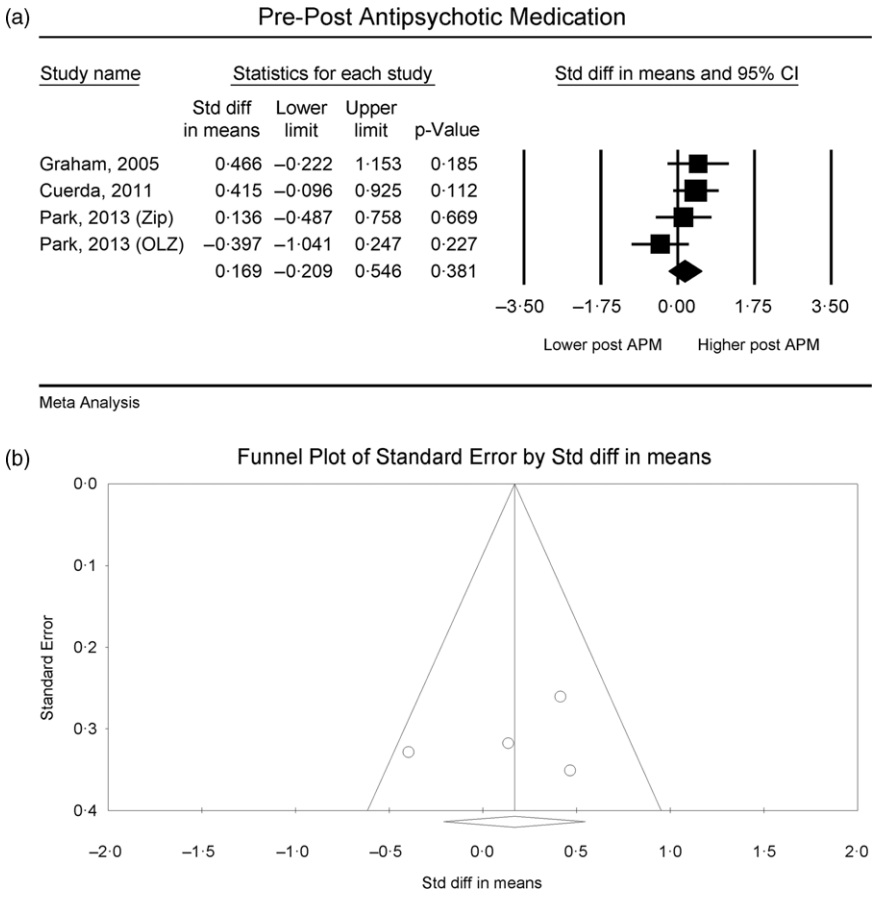

Fig. 4. RMR of people with severe mental illness measured by indirect calorimetry pre- and post-commencement of antipsychotic medication, (a) forest plot of standardised mean difference, (b) funnel plot assessing publication bias.

Table 4. Assessment of quality and certainty using GRADE

Outcome	Risk of bias	Inconsistency*	Indirectness	Imprecision	Publication bias	GRADE
SMI (IC) compared with control (IC)	High certainty	Low certainty	Very low certainty	Very low certainty	Strongly suspected	Very low
IC (SMI) compared with predictive equations						
Harris-Benedict	Very low certainty	Moderate certainty	Moderate certainty	Moderate certainty	Strongly suspected	Moderate
Schofield	Very low certainty	High certainty	Moderate certainty	Moderate certainty	Undetected	Moderate
Mifflin–St. Jeor	Very low certainty	Low certainty	Moderate certainty	Moderate certainty	Undetected	Moderate
LARN	Very low certainty	High certainty	Low certainty	Very low certainty	Strongly suspected	Low
FAO/WHO/UNU	Low certainty	High certainty	Low certainty	Low certainty	Strongly suspected	Low
Pre–post administration of APM						
Overall	Very low certainty	High certainty	Low certainty	Very low certainty	Undetected	Low
Olanzapine	Very low certainty	High certainty	Low certainty	Very low certainty	Strongly suspected	Very low

APM, antipsychotic medication; IC, indirect calorimetry; SMI, severe mental illness.
* n/a: Inconsistency could not be assessed for those with single datasets.

and moderate certainty of evidence. Interestingly Sugawara *et al.* (2014) concluded that the Harris–Benedict equation was the most predictive equation in a sample of people with schizophrenia spectrum disorders in Japan[34]. The lower mean body weight in this sample compared with many other studies conducted in Western countries (and with the use of actual body weight rather than ideal body weight) may explain this. However, ethnicity may be contributing factor, given the development of equations tended to be based on measurements from Caucasian populations.

Authors acknowledge the following limitations. First, the IC machines used differed across studies, increasing the potential for imprecision. Second, despite high consistency in direction of effect (i.e., SMI by subgroup compared with control and IC compared with predictive equations), there was significant heterogeneity. This may be explained, at least in part, by the

difference in machines used to assess RMR by IC across studies. Third, many studies included a mix of different diagnoses under the SMI umbrella term, limiting the ability to explore diagnosis effects.

There is little evidence to suggest that the RMR is different between people with SMI and people without, when accounting for covariates such body mass and body composition. Additional studies accounting for covariates are required. Future studies should also test for differences in rates of fat oxidation. Further, the administration of antipsychotic medication does not appear to significantly impact RMR. Overall, there is limited evidence to support a disruption to RMR as a driving factor for weight gain in people with SMI. More established contributing factors are excess caloric intake and high levels of sedentary behaviour.

Supplementary material

For supplementary material/s referred to in this article, please visit https://doi.org/10.1017/S0007114523001162

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Study conception:

S. T.; study design: all authors; search and screening: S. Y. N. and S. T.; data extraction: S. Y. N. and S. T.; quality assessment: S. Y. N. and O. A. Y., meta-analysis: S. T., GRADE: S. Y. N. and O. A. Y. Manuscript development: S. Y. N. and S. T., manuscript review: all coauthors

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