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Metabolic dysfunction in severe mental illness: updates on prevalence, aetiology and treatment options

ARTICLE

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SUMMARY

Metabolic dysfunction is an established phenomenon in people with severe mental illness (SMI), and it has a higher prevalence than in the general population. It is associated with increased morbidity and mortality, and effective recognition and management are essential to enable good psychiatric care. Despite widespread awareness of this disparity for several decades, health outcomes continue to worsen, highlighting the need for more effective preventive and treatment measures. This article outlines the risk factors that contribute to metabolic dysfunction in this population, including genetic, environmental and pharmacological factors, and considers underlying metabolic pathophysiological processes as part of SMI itself. To aid discussions with patients, recognition and interpretation of metabolic risk factors are outlined, together with mitigating strategies. Novel areas of uncertainty are discussed, including the use of a ketogenic diet. This article advocates use of the term 'metabolic psychiatry', to increase awareness of the significant overlap between psychiatric illness and metabolic dysfunction.

KEYWORDS

Metabolic; psychiatry; cardiovascular; insulin resistance; ketogenic diet.

LEARNING OBJECTIVES

After reading this article you will be able to:

- summarise cause and effect of metabolic dysfunction in severe mental illness
- assess and evaluate metabolic risk
- apply a broad understanding of management strategies to reduce metabolic risk.

Severe mental illness (SMI) typically encompasses bipolar disorder, schizophrenia and other psychotic illnesses, and often major depressive disorder (MDD). It is chronic in nature and significantly impairs functioning. Health records in England showed a prevalence of 0.7–0.9% for SMI, but the true prevalence is likely to be higher (National Mental Health Intelligence Network 2018), as this figure only includes patients with a diagnosis. People with SMI are significantly more likely to die prematurely than those without, with accumulated evidence summarised in a report by the *Lancet Psychiatry* Commission (Firth 2019). Despite most psychiatrists being aware of this disparity, the trend appears to be static or worsening (Firth 2019), and more needs to be done to address it.

The reasons for increased mortality in SMI are complex and multifactorial, but metabolic dysfunction and cardiovascular disease account for a significant proportion. The *Lancet* commission summarised the findings of meta-analyses reporting the prevalence of cardiometabolic morbidities among people with mental illness. These consistently reported a 1.4–2.0 times higher risk of obesity, diabetes and cardiovascular disease in individuals with mental health disorders compared with those without (Firth 2019).

Metabolic dysfunction is a result of abnormal chemical reactions interfering with the body's normal functioning, and it comprises a wide range of pathophysiological processes, including insulin resistance, hypertriglyceridaemia, low high-density lipoprotein (HDL) cholesterol, hypertension and abdominal obesity. These are often more prevalent in people with SMI, and the modification of any can decrease cardiometabolic risk and improve outcomes. This article will provide updates on our understanding of the aetiology, identification and management of metabolic dysfunction in SMI, including novel risk tools, the use of a ketogenic diet and areas of uncertainty.

Cardiometabolic dysfunction in SMI

Metabolic syndrome is defined in Box 1, and each individual diagnostic criterion increases the risk of

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cardiovascular disease and insulin resistance. A recent cohort study found the prevalence of metabolic syndrome in people with SMI to be almost twice that in the general population, at 48.6%, and cardiometabolic risk did not differ substantially between diagnoses (Noortman 2023). Obesity in SMI has been found to have an overall rate ratio of 1.8, and although prevalence increases with age, health inequalities are most apparent in younger age groups (National Mental Health Intelligence Network 2018). Those aged 15–34 years with SMI are three times more likely to be obese compared with all patients. This factor decreases to 1.6 in the 55- to 74-year-old age group, where there is an increase in obesity in all patients, including those with SMI.

Body mass index

Evidence suggests that a higher body mass index (BMI) may be associated with poorer outcomes in SMI. Kemp et al (2010) found that for every unit increase in BMI, the chance of response to any treatment for bipolar disorder was reduced by 7.5% and the likelihood of remission decreased by 7.3%. In first-episode psychosis, a higher baseline BMI predicted faster brain ageing over time, although this was also the case for controls (McWhinney 2021). Strategies to reduce BMI may therefore reduce negative outcomes in SMI. However, it is important to consider that more severe SMI may account for increases in BMI alongside other negative outcomes, and that the direction of association is uncertain (Kemp 2010).

Insulin resistance and diabetes

Insulin resistance and diabetes are significant contributors to metabolic dysfunction, and both are more prevalent in people with SMI. A large meta-analysis found a relative risk (RR) of 2.04 for type 2 diabetes in people with schizophrenia or related psychotic episodes, 1.89 in bipolar disorder and 1.43 in MDD, compared with controls (Vancampfort 2016). HbA1c has been found to be raised in those with schizophrenia and to increase with age in people with severe mental illness (Pearsall 2019). However, as with metabolic syndrome, younger age groups are disproportionately more affected compared with people without SMI, with those aged 15–34 being 3.7 times more likely to have diabetes, and those aged 55–74 being 1.6 times more likely; there are also higher rates in females (National Mental Health Intelligence Network 2018). The prevalence of diabetes in people with SMI was also greater in the most deprived areas (12.2%) than in the least deprived areas (8.0%) when compared with all patients (National Mental Health Intelligence Network 2018). Hispanic and Black and minority ethnic backgrounds in the USA have been shown to be associated with higher levels of insulin resistance (measured using HOMA-IR) in people with schizophrenia as compared to White ethnicity (Soontornniyomkij 2019). Deprivation and ethnicity may be direct or indirect contributing factors. Clinicians should ensure adequate monitoring, including in younger age groups, to enable timely detection and treatment of diabetes in more vulnerable groups.

Insulin resistance has also been associated with poorer psychiatric outcomes in people with SMI, but the direction of causality must again be considered. A cross-sectional study found that people with bipolar disorder and type 2 diabetes or insulin resistance had three times higher odds of a chronic course of illness and rapid cycling, and eight times higher odds of a resistance to lithium treatment (Calkin 2015), and Łojko et al (2019) summarise the evidence of a direct impact on the brain and cognitive functioning. In people with schizophrenia, higher levels of insulin resistance have been associated with worse negative symptoms and poorer global cognitive performance, quality of life and everyday functioning (Soontornniyomkij 2019). Early preventive interventions to reduce metabolic risk may therefore improve SMI outcomes, and routine testing may not detect subclinical dysfunction. Meta-analysis has shown that both pharmacological (including switching antipsychotic medication) and non-pharmacological measures can help reduce fasting glucose levels (Taylor 2017).

The homeostasis model assessment of insulin resistance (HOMA-IR) is a more sensitive measure of the condition than standard clinical measures, and its calculations are based on fasting blood glucose and fasting insulin levels. Using this more

BOX 1 Metabolic syndrome

Diagnosis typically requires the presence of three of the following (Grundy 2005):

- Waist circumference >40 inches (102 cm) in men and >35 inches (88 cm) in women
- Elevated triglycerides: ≥150 mg/dL (1.7 mmol/L) of blood
- Reduced high-density lipoprotein (HDL) cholesterol: ≤40 mg/dL (1.03 mmol/L) in men or ≤50 mg/dL (1.30 mmol/L) in women
- Elevated fasting glucose: ≥l00 mg/dL
- Elevated blood pressure: systolic ≥130 mmHg and/or diastolic ≥85 mmHg

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sensitive measure, insulin resistance was found in around half of a group of people with bipolar disorder ($n = 88$), despite over half of these having a normal fasting blood glucose (Łojko 2019). HOMA-IR levels have also been found to be significantly higher in people with schizophrenia ($n = 145$), compared with a control population (mean 3.73, s.d. = 5.07 *v.* mean 1.74, s.d. = 1.57; $P < 0.001$) (Soontornniyomkij 2019). Although HOMA-IR is not widely available (given that fasting insulin measures are often not available), the fasting triglycerides and glucose index (TyG) has been shown to closely correlate with the HOMA-IR and is calculated from more easily available triglyceride and glucose levels. Its use could be implemented more widely in clinical practice in the future as a more sensitive measure of insulin resistance (Łojko 2019), helping clinicians to identify those with SMI and higher metabolic risk. However, more research is required to identify a clinically relevant cut-off point.

Cardiovascular disease

Cardiovascular disease is closely linked to metabolic syndrome, and people with SMI are disproportionately affected. A large systematic review and meta-analysis found the prevalence of cardiovascular disease in SMI to be 9.9% (Correll 2017), and a narrative review highlights the significant number of people with SMI who die from cardiovascular disease, particularly those with bipolar disorder and schizophrenia (Nielsen 2021). Compared with the general population, the cross-sectional odds ratio for coronary heart disease was 1.52 higher in schizophrenia and 2.52 higher in MDD (Correll 2017). Longitudinal studies found a hazard ratio for death related to cardiovascular disease of 2.45 in schizophrenia, 1.65 in bipolar disorder and 1.63 in MDD, compared with the general population. For coronary heart disease the hazard ratio was 1.59 in schizophrenia and 1.72 in MDD, with no significant association in bipolar disorder found (Correll 2017). This again highlights the need for timely identification and effective therapeutic interventions in this population.

Contributions of healthcare and environmental factors to cardiometabolic dysfunction

People with SMI frequently receive less than optimal physical healthcare and experience a negative attitude from medical professionals (Nielsen 2021). This disparity may be due to the arbitrary separation of physical and mental healthcare, and unclear responsibility for managing physical ill health. Limited time and resources for mental health services mean that priority may be given to mental health treatment over physical health concerns. Nielsen et al's (2021) review article highlights research demonstrating lower rates of screening for cardiovascular disease in SMI than guidelines recommend.

Physical health checks

Ensuring comprehensive and routine physical healthcare assessments and interventions in psychiatric settings, and seeking specialist advice if needed, is essential. Nielsen et al (2021) summarise the evidence for treating physical health in a psychiatric setting, including the benefits of an established therapeutic relationship. Advocating for patients is crucial, and if psychiatric patients are not receiving optimal care from medical professionals, their psychiatrists need to ensure effective communication and education about their patients. If requesting further investigations or interventions from colleagues the reasons must be clearly stated, including that the patient may have a higher burden of metabolic dysfunction and related disease processes. Positive cross-specialty collaboration, along with clear advocating for psychiatric patients, will help in the fight to reduce stigma and improve poor cardiometabolic health-related outcomes.

Lifestyle and environment

Modifiable lifestyle and environmental factors, such as smoking and social deprivation, have a higher prevalence in SMI, and contribute to poorer cardiometabolic health and consequent increased mortality (Nielsen 2021). A systematic review and meta-analysis found tobacco use disorder or nicotine dependence in 65% of people with schizophrenia, 46.3% of those with bipolar disorder and 33.4% in those with MDD, which is much higher than in the general population (Fornaro 2022). The evidence for individual therapies is of a low quality, but varenicline and bupropion have shown promise in people with schizophrenia (Fornaro 2022). Combined behavioural and pharmacological intervention showed an odds ratio of 1.67 for successful quitting, and an absolute reduction in smoking rate of 5% (Gilbody 2021). This highlights the importance of ensuring that people with SMI are regularly offered support and options for smoking cessation to maximise chances of success and improve longer-term cardiometabolic outcomes.

A systematic review and meta-analysis found that people with SMI had significantly higher dietary energy intake (mean difference 1332 kJ, 95% CI 487–2178 kJ, $P = 0.002$). In addition, they were more sedentary than age- and gender-matched controls, spending on average 8 h of their waking day being sedentary, and were less likely to meet the recommended guidelines for

physical activity. Although people with bipolar disorder were the most physically active, they spent the most time being sedentary (Vancampfort 2017). Clinicians must be aware of these factors to help inform discussions with patients about lifestyle advice to reduce cardiometabolic risk. Social deprivation is also associated with worsened control of cholesterol and blood sugar levels, and lower adherence to physical health medication in SMI (Nielsen 2021).

Cardiometabolic dysfunction and SMI – which comes first?

Cardiometabolic comorbidity has historically been considered a consequence of SMI, secondary to disease-related processes, environmental risk factors and antipsychotic medication use. In this section we will discuss increasing evidence demonstrating the presence of metabolic dysfunction at first presentation of SMI, before antipsychotic use, and as far back as childhood.

Studies have shown that people with schizophrenia, whether treated or untreated, are at increased risk of cardiovascular disease, diabetes and metabolic syndrome (Goh 2022). A systematic review and meta-analysis found that the prevalence of metabolic syndrome in people with first-episode psychosis who were not taking antipsychotic medication was 13.2% worldwide, representing a 2.52-fold increased risk compared with age- and gender-matched populations (Garrido-Torres 2021). This suggests that metabolic dysfunction is not solely a consequence of antipsychotic treatment. However, total cholesterol and low-density lipoprotein (LDL) cholesterol are reduced in people with first-episode psychosis (Pillinger 2017), highlighting the importance of early prevention. Triglyceride levels are increased in this population, which is a feature of type 2 diabetes (Pillinger 2017) and provides further evidence suggesting glucose dysregulation may be a precursor to SMI.

High rates of diabetes have been found to be comorbid with depression, with rates of depression in type 1 diabetes three times higher than in the non-diabetic population and close to twice as high in type 2 diabetes (Roy 2012). Both conditions may have shared underlying biological mechanisms, such as hypothalamic–pituitary–adrenal axis activation and inflammation. Roy & Lloyd (2012) suggest that for those with diabetes who develop depression, the course of depression is more likely to be persistent or to relapse in comparison with those who do not have diabetes. The relationship between depression and diabetes is bidirectional, with a diagnosis of depression increasing the risk of a subsequent diagnosis of diabetes and vice versa.

One cohort study found that persistently high fasting insulin levels from 9 years of age were associated with psychosis but not depression at 24 years, and that an increase in BMI at puberty onset was associated with depression but not psychosis at 24 years (Perry 2021a). In addition, recent evidence suggests a genetic predisposition to cardiovascular disease in people with SMI (Nielsen 2021) and genome-wide association studies have demonstrated shared genetic mechanisms between schizophrenia and type 2 diabetes, with several genes implicated in biological processes in these disorders (Hackinger 2018).

It is therefore too simplistic to suggest that metabolic dysfunction in SMI is secondary to consequences of illness, with evidence demonstrating overlapping comorbidity between SMI and metabolic dysfunction and suggesting a shared aetiology. This complex relationship between metabolic dysfunction and SMI highlights the importance of more widespread use of the term ‘metabolic psychiatry’ to improve recognition, management and further research into this complex and poorly addressed phenomenon.

Psychopharmacology and metabolic dysfunction

Pharmacological therapies are essential tools in the management of SMI to reduce symptoms, achieve remission and prevent relapse. All psychotropic medications have the potential to affect metabolic function, particularly antipsychotics, which are known to increase waist circumference, body weight, dyslipidaemia and hyperglycaemia, and are associated with increased risk of sudden cardiac death and ventricular arrhythmias (Nielsen 2021). However, overall, they are correlated with reduced all-cause and cardiac mortality, and a reduced symptom burden, which may increase the ability to make positive lifestyle choices (Nielsen 2021). This highlights the importance of continuing effective treatments and focusing on other modifiable risk factors in people with SMI.

Antipsychotics and weight gain

Most antipsychotics are known to contribute to weight gain, with implications for metabolic health and morbidity, but there is wide variation between them and the evidence is mainly based on short-term studies. Clozapine and olanzapine are associated with the highest risk of weight gain and the highest mean weight gain; quetiapine, paliperidone, risperidone, zuclopenthixol, flupentixol and chlorpromazine are associated with moderate risk of weight gain; haloperidol, amisulpride and sulpiride are associated with low risk of weight gain and

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aripiprazole and lurasidone with very low risk (Taylor 2021: pp. 41 and 123). Higher vigilance for screening (see next section) and weight interventions is required for antipsychotics conferring the highest risk.

Antipsychotics are thought to cause weight gain by increasing food intake and through the action of these drugs on receptors, rather than via a direct metabolic effect. Antagonism of the serotonin 5-HT_{2C} and histamine H_1 receptors interferes with the hypothalamic mechanisms controlling food intake, and alpha adrenoreceptors and dopamine D_2 receptors are involved in appetite and reward. Aripiprazole's partial agonism of dopamine D_2 receptors may be part of the explanation for its low-risk status (Cooper 2016; Taylor 2021: p. 123). There is an increased risk of weight gain in people who are antipsychotic naive, and possibly in women, and it is worth noting that there is considerable and unpredictable individual variation, with some people losing weight after commencing antipsychotics (Taylor 2021). Early and rapid weight gain of >5% in the first month is a predictor for longer-term weight gain and should increase consideration of intervention (Taylor 2021).

Management of antipsychotic-related weight gain

The first-line management of antipsychotic-associated weight gain is lifestyle changes, for example improving diet and increasing physical activity. If weight gain remains an issue, switching to or augmenting treatment with a partial agonist antipsychotic such as aripiprazole can be considered. A meta-analysis found that switching to aripiprazole compared with staying on the same antipsychotic was associated with decreased weight and improved fasting glucose, but no similar effect was seen when switching to any other antipsychotic (Siskind 2021). Switching to olanzapine compared with remaining on the same antipsychotic was associated with significantly increased weight (Siskind 2021). Clinicians must balance potential benefits of weight loss with the risk of relapse associated with switching antipsychotics, as staying well is also protective of metabolic health.

Metformin is the first-line pharmacological treatment for antipsychotic-related weight gain and has evidence from meta-analyses for reducing blood sugar and lipid levels (Cooper 2016; Nielsen 2021; Taylor 2021: pp. 125–7). Studies have shown a reduction in weight of around 3 kg in people taking metformin as an adjunct to antipsychotic medication for schizophrenia and schizoaffective disorder (de Silva 2016). Owing to risks associated with metformin, monitoring of renal function and vitamin B_{12} levels is required (Cooper 2016). We will return to metformin below.

Studies have shown elevation in total cholesterol and triglycerides, as well as increasing levels of the hormone leptin in people taking antipsychotic medication (Zhang 2004). The increase in diabetic risk appears not to be solely due to weight gain, as some develop diabetes in the absence of weight gain. Postulated mechanisms for increased diabetic risk include changes in glucose regulation, increased insulin resistance and interference with the normal secretion of insulin (Cooper 2016). Essential monitoring for people taking antipsychotics (detailed in the next section) allows these abnormalities to be identified and managed appropriately.

Screening for metabolic dysfunction

Despite clear guidelines on monitoring for metabolic dysfunction in SMI, this is frequently not completed. Younger age groups are twice as likely

TABLE 1 **Antipsychotic monitoring recommendations**

Parameter/test	Frequency
Urea and electrolytes	Baseline and yearly
Full blood count	Baseline and yearly
Blood lipids	Baseline, 3 months after drug commencement and yearly thereafter
Weight	Baseline, every 1–2 weeks for the first 6 months and yearly thereafter
Plasma glucose (preferably fasting)	Baseline, every 4–6 months for the first year and yearly thereafter
Electrocardiogram	Baseline, at target dose, on admission to hospital, before hospital discharge if medication regimen changed, and ideally at least yearly
Blood pressure	Baseline, and frequently during dose titration and dosage changes
Prolactin	Baseline, then at 6 months, then yearly
Liver function tests	Basline, then yearly
Creatine phosphokinase	Baseline, then if NMS suspected

Source: Taylor et al (2021): pp. 38–39. NMS, neuroleptic malignant syndrome.

not to have a clinical record of routine blood monitoring, and lipid and glycosylated haemoglobin tests have the poorest completion rates (Pearsall 2019). One study found that only 7.6% of patients had screening for all five metabolic syndrome criteria (Noortman 2023).

Monitoring is strongly recommended for those taking antipsychotic medication, and is substandard in many countries (Taylor 2021: pp. 38 and 125). Table 1 outlines the current recommendations from the Maudsley Prescribing Guidelines in Psychiatry (Taylor 2021), where more detail can be found about the additional implications for individual antipsychotics. Evidence suggests that staff education on the rationale and guidelines for treatment, and paper or electronic reminders when patients are due monitoring increases monitoring rates (Soda 2021). Clinicians should think about how to incorporate these measures into their own healthcare environments.

Recent guidance from National Health Service (NHS) England recommends that all people with SMI have a yearly health check, regardless of medication use. The recommended core and more comprehensive elements are listed in Box 2 (NHS England 2024). Many aspects of these physical health checks are directly relevant to cardiometabolic health, and should aid in the identification and management of cardiometabolic disorders as part of an improvement in holistic physical healthcare in this population.

Metformin in SMI

Metabolic dysfunction in SMI may help to explain the emerging and established evidence of metabolic therapies benefiting symptoms in this population. These include use of a ketogenic diet, a metabolic therapy used in the treatment of epilepsy, and of metformin, a diabetes medication. Metformin is a biguanide, an oral anti-hyperglycaemic medication, which acts to lower blood glucose and is mainly used to manage type 2 diabetes. It is thought to inhibit hepatic gluconeogenesis by targeting hepatic mitochondria and interfering with adenosine triphosphate (ATP) synthesis, and it improves insulin sensitivity through various mechanisms.

Metformin is effective as a treatment for weight gain in people taking antipsychotic medication, but also improves fasting glucose in people with SMI (Taylor 2017). There is emerging evidence that it may reduce the symptoms of mental illness itself, which could be a consequence of improved metabolic health or independent of this. Calkin et al (2022) showed significant improvement in

BOX 2 NHS England's recommended physical health checks for people with severe mental illness (SMI)

NHS England strongly recommends that all people with SMI have at least a 'core' annual health check, but as best practice it recommends a more comprehensive annual check

Core annual check

- Alcohol consumption status
- Blood glucose or glycated haemoglobin (HbA1c) test (as clinically appropriate)
- Blood pressure
- Body mass index
- Lipid profile
- Smoking status

Comprehensive annual check

- Medical and family history
- Blood-borne virus and liver function screening
- Cardiovascular risk assessment (including QRisk)
- Relevant national immunisation programmes
- Support to access relevant national screening programmes, including cancer screening
- Oral health and brief interventions
- Assessment of physical activity levels
- Sexual and reproductive health assessment and advice
- Substance misuse assessment
- Medicines reconciliation and monitoring

(Source: NHS England, 2024)

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depression and anxiety scale scores at 14 and 26 weeks in people with treatment-resistant bipolar depression randomised to metformin as compared with placebo.

A ketogenic diet and its use in SMI

A ketogenic diet is high in fat and low in carbohydrate, with an adequate protein intake, and in this section we will discuss what is known about its use in people with SMI. When referring to a clinical ketogenic diet in this article, we assume that at least 60–80% of total energy intake comes from fat and <10% from carbohydrate. Initiating a ketogenic diet triggers a significant shift in metabolism, causing the body to transition from using glucose as the main source of energy to using ketones. A ketogenic diet has been used as an established evidence-based treatment for childhood epilepsy for more than a century (Martin-McGill 2018), with National Health Service (NHS) ketogenic diet services running across the UK for this purpose. It has also been trialled in people with brain tumours, migraine and type 2 diabetes, and research into its use in a variety of medical conditions is expanding.

Recently, it has been proposed that a ketogenic diet may be useful as an adjunctive therapy for schizophrenia and bipolar disorder (Sethi 2022). Some people with SMI are already following this diet, and some psychiatrists are recommending its use. It is therefore important for psychiatrists to understand the evidence and clinical implications of this intervention. Case reports suggest beneficial effects, including improved depression rating scale scores and metabolic health measures, in refractory MDD, bipolar disorder and schizoaffective disorder (Danan 2022). Feasibility of maintaining ketosis and acceptability of a ketogenic diet have been demonstrated in people with bipolar disorder (Needham 2023), but no randomised controlled trials have been performed.

Mechanism of action

The exact mechanism by which a ketogenic diet alleviates epileptic seizures is not yet fully understood and is likely to be multifactorial. As glucose is crucial for seizure induction, it has been suggested that when the brain shifts to using ketone bodies, seizure frequency is reduced. The anti-seizure effects of ketogenic diets are sustained during chronic ketosis while stabilising and reducing synaptic excitability. Other theories suggest the role of changes in neurotransmitter functions, gut microbiota, inflammatory cytokines or epigenetics (D'Andrea Meira 2019). Ketone bodies are suggested to have beneficial anti-inflammatory, antioxidant and metabolic (improved mitochondrial function and neurotransmitter systems) effects (Zhu 2022). There are several clinical similarities between epilepsy and SMI, including the overlap of some pharmacological interventions, so exploration of its use in SMI is worth pursuing.

The clinical use of a ketogenic diet

For the best chances of success, a ketogenic diet needs to be individualised (Cervenka 2021), and this is why we recommend initiation only by a dietitian or clinician with extensive experience in this area and the capacity to provide regular follow-up. While we await more robust evidence on its efficacy, it should be considered only in treatment-resistant SMI to manage psychiatric symptoms, although it is known to have wider independent benefits for metabolic dysfunction and may be used for this purpose. For patients who are already following a ketogenic diet of their own accord, it is important to understand the safety considerations, and Boxes 3 and 4 detail clinical recommendations and absolute contraindications. Preliminary recommendations for the management of adults treated with ketogenic diet therapies have been synthesised from the results of an international survey of neurologists and dietitians (Cervenka 2021). Containing much detail on these therapies and their relative contraindications, this is a useful resource for clinicians.

Possible side-effects when initiating a ketogenic diet include fatigue, thirst, irritability and constipation, which can all be managed with simple strategies (Cervenka 2021). Additional common side-

BOX 3 Recommendations for people following a ketogenic diet

- Supplementation with a multivitamin and mineral and additional calcium and vitamin D
- Increased fluid intake
- Education on managing hypoglycaemia and hyperketosis
- Serial bone density scans within 5 years if other risk factors are present
- Full blood count, metabolic panel, fasting lipid profile and vitamin D levels every 6–12 months

(Cervenka et al, 2021)

BOX 4 Absolute contraindications to ketogenic diet therapies

- Disorders of fatty acid transport and oxidation, organic acidurias and inborn errors of metabolism, including carnitine deficiencies and pyruvate carboxylase deficiencies
- Current pregnancy
- Acute pancreatitis (breakdown of fat is compromised)
- Liver failure
- Type 1 diabetes without endocrinology supervision
- Porphyria

(Cervenka et al, 2021)

effects once established on the diet include weight loss, nausea, hyperlipidaemia, leg cramps and, rarely, gallstones, orthostatic hypotension, osteopenia/osteoporosis and nephrolithiasis. Evidence about longer-term side-effects is still limited, and patients should be informed of this.

A ketogenic diet is widely accepted to have positive effects on metabolic health, and research suggests positive cardiometabolic outcomes, including reduced total cholesterol, increased HDL cholesterol and reduced triglyceride levels (Zhu 2022), and decreased weight, waist and hip circumference and percentage of body fat (McDonald 2018). However, evidence also suggests increased LDL cholesterol, albeit with no impact on carotid plaque presence (McDonald 2018). Hypercholesterolaemia occurs in approximately one-third of adults treated with a ketogenic diet (Cervenka 2021), but typically returns to baseline within a year (Cervenka 2016; McDonald 2018). Further research into the longer-term effects of a ketogenic diet is needed, and anyone with SMI following such a diet should be supported to ensure relevant recommendations are followed.

Metabolic risk prediction and risk calculators in SMI

Cardiometabolic risk scores are algorithms, usually based on age, gender, smoking status, hypertension, blood lipid profile and medical history, used to predict an individual's risk of specific cardiometabolic adverse outcomes. NHS England (2024) now recommends that people with SMI receive a yearly cardiometabolic risk assessment including the QRisk® tool.

Risk scores may over- or underestimate the risk in specific populations, including those with SMI. Nielsen et al (2021) discuss the PRIMROSE (prediction and management of cardiovascular risk for people with severe mental illnesses) risk score models, which were developed specifically for SMI populations in the UK. They highlight improved validation in comparison with conventional tools, but note that PRIMROSE models have shown mixed results for longer-term outcomes and call for more accurate estimation and for validation in populations outside of the UK. More specific and relevant tools are being developed, particularly for populations in which current tools are not accurate. For example Perry et al (2021b) have developed the Psychosis Metabolic Risk Calculator (PsyMetRiC) to predict the risk of metabolic syndrome in people with psychosis aged 16–35 years.

Conclusions

People with SMI have increased mortality, a large proportion of which is secondary to cardiometabolic dysfunction. Although this is well-known, there has been little improvement in management or outcomes over the past few decades. Research into metabolic dysfunction in SMI is increasing, helping us to understand the complex and likely interlinked relationship between the two, including independent and overlapping risk factors. Despite guidelines and recommendations, current management of metabolic burden in people with SMI is inadequate. Clinicians must ensure that poor metabolic health in people with SMI is screened for, recognised early and managed appropriately. Use of the term metabolic psychiatry may help increase awareness and improve metabolic outcomes.

Data availability

Data availability is not applicable to this article as no new data were created or analysed in this study.

Author contributions

N.N. was responsible for conceptualising this article. All authors were responsible for drafting the article and subsequent revisions, and agree to be accountable for all aspects of the work.

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MCQ answers
1 d 2 c 3 a 4 e 5 b

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MCQs

Select the single best option for each question stem

1 As regards the relationship between SMI and metabolic dysfunction:
- a severe mental illness causes metabolic dysfunction
- b metabolic dysfunction causes severe mental illness
- c there is no relationship between the two
- d the relationship is bidirectional
- e the relationship is unknown.

2 The estimated prevalence of metabolic syndrome in people with first-episode psychosis not taking antipsychotic medication is approximately:
- a 2%
- b 7%
- c 13%
- d 20%
- e 40%.

3 A ketogenic diet has established evidence for the treatment of:
- a epilepsy
- b bipolar disorder
- c multiple sclerosis
- d schizophrenia
- e asthma.

4 During dose titration and dose changes for people taking antipsychotics, clinicians should carry out baseline and subsequent frequent measurement of:
- a prolactin
- b heart rate
- c liver function
- d C-reactive protein
- e blood pressure.

5 Commencing a ketogenic diet is contraindicated in someone with:
- a raised cholesterol
- b liver failure
- c type 2 diabetes
- d no social support
- e a previous pregnancy.