Targeting Metabolic Abnormalities in Mental Health Prevention Strategies

13

Simone Schimmenti, Francesca Maria Camilla Maselli, and Sarah Tosato

People affected by severe mental disorders (SMI) as schizophrenia (SCZ), bipolar disorder (BD), and major depressive disorder (MDD) experience a two to three times higher mortality rate and have a life expectancy shortened of 10–20 years rate compared to the general population [1–3]. The excess mortality observed in SMI is due to physical comorbidities, predominantly cardiovascular diseases (CVD) and type 2 diabetes (T2D) [4, 5]. Specifically, CVD rate is of 11.8%, 8.4%, and 11.7% in SCZ, BD, and MDD, respectively, with only SCZ found significantly associated with the risk of developing coronary heart disease (OR 1.52), cerebrovascular disease (OR 2.05), and congestive heart failure (OR 1.60) [5]. In MDD, a higher risk of stroke (HR 2.04), congestive heart failure (HR 2.02), and coronary heart disease (HR 1.63) has been found compared to the general population [4, 5].

The scandal of "the avoidable mortality" in SMI [6] has made necessary the identification of those patients at high risk of developing physical comorbidities, and it is a clinical imperative [7]. In order to help clinicians to identify these patients, the concept of metabolic syndrome (MetS) may be useful [8]. MetS is a cluster of risk factors consisting of at least three of the following: central obesity, high blood pressure, low high-density lipoprotein cholesterol (HDL-C), elevated triglycerides, and hyperglycemia [9]. These factors significantly increase the risk of CVD, T2D, and all-cause mortality [10].

Simone Schimmenti and Francesca Maria Camilla Maselli contributed equally.

S. Schimmenti · F. M. C. Maselli · S. Tosato (✉)
Department of Neuroscience, Biomedicine and Movement Sciences, Section of Psychiatry, University of Verona, Verona, Italy
e-mail: simone.schimmenti@univr.it; francescamariacamilla.maselli@univr.it; sarah.tosato@univr.it

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13.1 Metabolic Abnormalities in Psychosis (SCZ and BD)

MetS is highly prevalent in patients with chronic SCZ and BD compared to the general population, with pooled prevalence of 31.7% and 33.4%, respectively [11]. They have almost double probability to develop MetS compared to controls, with body max index (BMI) and age being predictors of MetS [12]. Traditionally, the association between cardio-metabolic abnormalities and psychosis has been attributed to the secondary effects of antipsychotics (APs) [11] or to unhealthy diet or sedentary lifestyle associated with negative symptoms [13]. Interestingly, in the first episode of psychosis (FEP), the overall prevalence rate of MetS and diabetes is 9.8% and 2.1% in drug-naïve patients and 9.9% and 1.3% in medicated ones [14]. Thus, MetS has the same prevalence in FEP patients than in the general population [8].

Waist size, blood pressure, and smoking have been found to be significantly lower in drug-naïve FEP patients compared with those under medication [8], while no differences were found in prevalence of hypertriglyceridemia and HDL-C levels [15]; smoking appears to be elevated early after diagnosis [8, 16]. Indeed, all metabolic components and risk factors are significantly lower in both drug-naïve and medicated FEP patients when compared to those affected by chronic SCZ [8].

A recent meta-review highlights impaired glucose metabolism in drug-naïve FEP patients at the onset compared to controls [17]. Specifically, drug-naïve non-affective FEP patients have higher fasting insulin and insulin resistance levels, while 2-h oral glucose tolerance test (OGTT) results were found to be higher in both affective and non-affective psychosis, compared to controls [18]. Moreover, higher levels of insulin and lower levels of leptin have been found in drug-naïve FEP patients compared to controls and suggest that environmental factors (e.g., unhealthy lifestyle and diet) could explain this association [19].

Total (TC) and LDL cholesterol levels (C-LDL) seem decreased in FEP patients compared to controls, indicating that the hypercholesterolemia found in chronic patients is secondary to unhealthy lifestyle, environmental and genetic factors, and antipsychotics treatment, representing a modifiable risk factor [20]. In contrast, triglycerides are elevated in FEP probably reflecting early glucose dysregulation [20] and insulin resistance [18]. Hypertriglyceridemia is a feature of T2D, conferring about a twofold excess risk for coronary heart disease, stroke, and deaths attributed to other vascular causes [21].

The pooled T2D prevalence is 2.9%, 4.0%, 13.1%, and 9.2% among people with antipsychotic-naïve FEP, FEP, chronic SCZ, and BD, respectively; it is higher in North America (12.5%) than in Europe (7.7%) and in women than in men (RR = 1.43) [22]. The relative risk (RR) of T2D is 2.04 and 1.89 in SCZ and BD, compared to controls [22].

Moreover, obesity and insulin resistance have been associated with non-alcoholic fatty liver disease (NAFLD) that can evolve into non-alcoholic steatohepatitis (NASH), which may lead to liver cirrhosis or hepatocellular carcinoma [23]. Although NAFLD is considered a component of MetS, it has been shown that its presence may itself constitute an independent cardiovascular risk factor [24].

Because of the relationship between cardio-metabolic risk and NAFLD, early detection of NAFLD in clinical practice could be useful in prevention [25].

Finally, young people at ultra-high risk for psychosis (UHR) have increased rates of cardio-metabolic risk factors when compared with controls: they have lower levels of physical activity and higher rates of smoking (33%, pooled OR 2.3) and alcohol abuse, while no differences are found for BMI or blood pressure [26]. Thus, UHR people display cardio-metabolic risk factors which are largely modifiable and, therefore, a possible target for early intervention [26].

Other relevant metabolic abnormalities in FEP are hyperprolactinemia (HPRL) and an increased risk for osteoporosis [27].

HPRL can occur in about one-third of antipsychotic-naïve FEP patients [28] and in nearly three-fourths of the patients treated with first-generation antipsychotics (FGAs) [29].

Finally, over half of people with SCZ have a low bone mineral density (BMD) equating to an almost threefold increased risk compared to the general population [30]. An increased prevalence of osteoporosis was found in patients with SCZ aged 50 or older compared to healthy age-matched controls, and women have twofold higher evidence of osteopenia or osteoporosis compared with men [31]. People with SCZ have also a longer recovery time in case of hip fracture, compared with controls, and they are at a greater risk of adverse events such as postoperative infection and renal failure [32]. Risk factors related to patients' lifestyle (e.g., smoking, sedentariness, alcohol abuse, vitamin D deficiency, diabetes) as well as use of antipsychotics are likely to be involved [33].

Taken together, these data show that cardio-metabolic alterations are present at the onset of psychosis, are probably related to the disease, interact with each other, and worsen with antipsychotics, especially if they are administered for a long time [34]. Indeed, people with psychosis are more likely than the general population to have unhealthy lifestyle behaviors, such as being sedentary [35], smoking [16], and having diets rich in saturated fats while low in fruit and vegetables [36]. These unhealthy lifestyle behaviors could contribute to the worsening of cardio-metabolic alterations.

13.1.1 Pathophysiology

In recent years, the hypothesis that psychosis involves multiple systems at onset has emerged [37] (Fig. 13.1). In fact, dysfunctions in cardio-metabolic [20], immune [38], and hypothalamic-pituitary-adrenal (HPA) systems have been observed at the onset [39]. A recent meta-review confirmed these data, also reporting brain structure and neurophysiology aberrations [37]. Immune abnormalities are those most supported ones both in antipsychotic-naive and FEP patients [37].

Blood **cortisol** level is significantly increased in FEP individuals compared to controls [40]. Increased levels of pro-inflammatory cytokines have been demonstrated in drug-naïve FEP [38] and could cause insulin-like growth factor-1 (IGF-1) resistance and high concentrations of IGF-1, insulin, and C-peptide independently

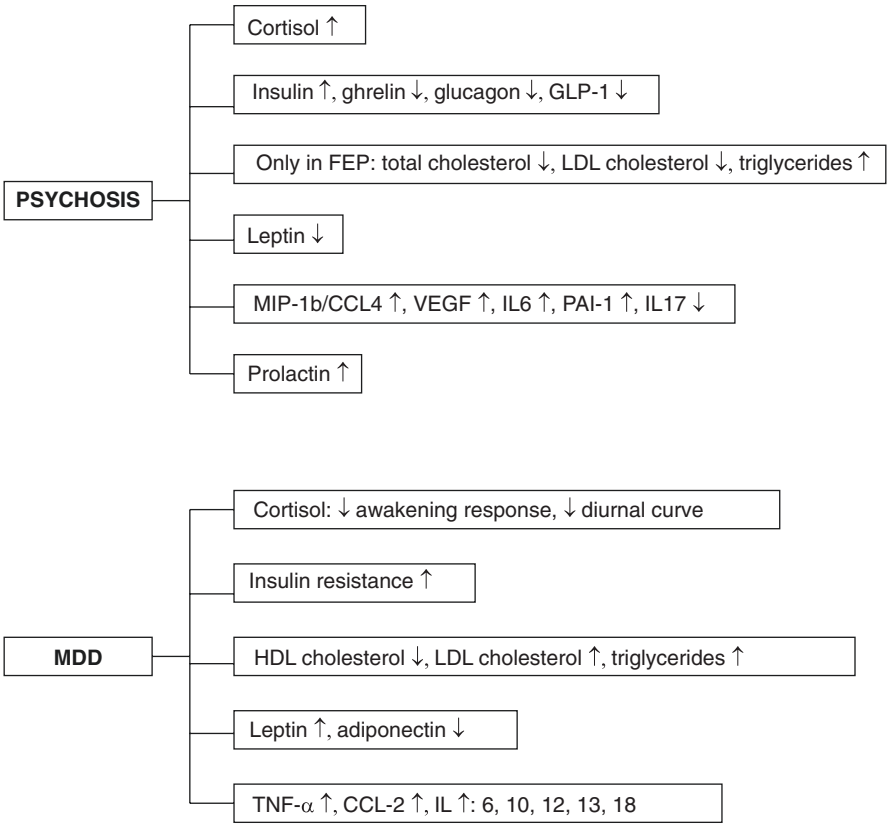

Fig. 13.1 Serum abnormalities in psychosis and major depressive disorders. ↑ increased/increases, ↓ decreased/decreases, *GLP-1* glucagon-like peptide 1, *LDL* low-density lipoprotein, *FEP* first episode of psychosis, *MPI-1b/CCL4* MPI-1b chemokine (C-C motif) ligand 4, *VEGF* vascular endothelial growth factor, *IL* interleukin, *PAI-1* plasminogen activator inhibitor-1, *MDD* major depressive disorder, *HDL* high-density lipoprotein, *TNF-α* tumor necrosis factor-α, *CCL-2* chemokine (C-C motif) ligand 2

of the glucose metabolism and cortisol serum levels. These findings may suggest the presence of insulin resistance in psychosis [41]. These data are in line with analysis of downstream serine-threonine kinases of GSK3β (AKT, mTOR, p70S6K) which revealed lower phosphorylation protein ratios in drug-naive FEP patients, supporting the hypothesis of neuronal insulin resistance which could partially reflect a reduced downstream signal transduction of GABA-R or NMDA-R, D2-R hyperactivity, lower BDNF level, or low-grade inflammation [42].

Other line of evidence suggests specific immune and metabolic signature in FEP: there are reports of an increase of MIP-1b/CCL4, VEGF, IL-6, and PAI-1 in patients compared to controls, while IL-17, ghrelin, glucagon, and GLP-1 have been found decreased [43]. Among these parameters, MIP-1b/CCL4 serum level appears to be the marker that best characterizes FEP. Since MIP-1b/CCL4 is a chemokine linked

to neuro-inflammatory processes, it may contribute to the pathogenesis of psychosis [44]. A potential correlation of FEP polygenic risk score [45] with the CCL4 and ghrelin serum concentration was observed, supporting the idea that a genetic liability to inflammatory and metabolic alterations characterizes psychosis onset [46].

Regarding the environmental risk factors of psychosis, it has been demonstrated that FEP patients with a history of childhood trauma (CT) show higher C-peptide and insulin serum concentrations than those without CT, pointing out that hyperinsulinemia could be also the result of environmental exposure [47]. Specifically, patients who had experienced childhood sexual abuse had a higher BMI and C-reactive protein (CRP) compared not only to controls but also to the those without childhood sexual abuse [48]. It is plausible that CT could lead to the development of glucose metabolism dysfunction through HPA axis and the increment of CRP [49], facilitating the progression to TD2 and MetS [50].

Finally, a very important issue to take into account is the regular cannabis use present in one-third of FEP patients [51] that might be crucial in FEP-related metabolic abnormalities. Patients treated with antipsychotics who do not use cannabis show higher serum levels of glucose and triglycerides, lower C-HDL level, and an elevated waist circumference, while cannabis users show no significant changes in metabolic parameters after 1 year of medications [52]. It may be that chronic cannabis use directly suppresses appetite [53], although dietary neglect [54], polysubstance use and smoking [55], and the composition of cannabis [56] could also contribute to these findings. Finally, cannabis consumption may likewise produce a protective effect against liver steatosis in FEP treated patients, probably through the modulation of antipsychotic-induced weight gain [57].

13.1.2 Antipsychotic Treatment

APs play a remarkable role in metabolic abnormalities in FEP, chronic SCZ, and BD [58]. It has been found that after 3 years of APs, 25.1% of FEP individuals show an increase of more than 7% of BMI, increased triglyceride and decreased HDL-C levels, hypertension, increased waist circumference, hyperinsulinemia, and a higher prevalence of MetS [59].

There are marked differences between APs in terms of effects on metabolic parameters (weight, BMI, total cholesterol, C-LDL, triglycerides, and glucose serum levels) in a median treatment duration of 6 weeks: olanzapine and clozapine exhibit the worst profiles, while aripiprazole, brexpiprazole, cariprazine, lurasidone, and ziprasidone show the most benign profiles [60]. Specifically, a weight gain $\geq$7% compared to baseline was significantly more likely with olanzapine (RR = 3.31) and risperidone (RR = 1.61) than haloperidol and with second-generation antipsychotics (SGAs) than FGAs (RR = 1.45) after 6 months [61]. Interestingly, SGA-FGA effect size differences for weight and lipid outcomes declined with longer follow-up ($\geq$6 months), suggesting that non-medication effects, such as unhealthy lifestyle, the underlying illness, environment, and genetic factors, play a role [62]. Increased baseline weight, male sex, and non-white ethnicity are predictors of susceptibility to AP-induced metabolic change [60].

Antipsychotic-naïve or FEP patients are more vulnerable to weight gain when they start treatment [63]. Generally, weight gain is rapid; then, it slows gradually and often reaches a plateau within 1 year [64]: the first year of AP treatment is a critical period for weight gain and metabolic abnormalities [65], as initial rapid weight gain is a good indicator for long-term obesity [64].

The weight gain risk increases about two times in FEP patients treated with APs compared with placebo, and it is associated with duration of treatment [66]. Except perhaps for ziprasidone, most APs are associated with weight gain and BMI increase. More specifically, over the course of 1 year, increase in BMI ≥1 unit occurs with a higher frequency in olanzapine-treated FEP patients compared to those treated with quetiapine or risperidone [67]. An early indicator of an increased risk of weight gain at 1 year during olanzapine therapy may be ≥7% weight gain during the first 6 weeks of treatment [68]. There are marked individual variations in weight gain, independently of prescribed AP [69], and this suggests that genetic factors play a role [70]. Specifically, it has been found an association between antipsychotic-induced weight gain [71] and single-nucleotide polymorphisms (SNPs) in HTR2C, the most studied serotonin receptor gene, in FEP patients [61, 72], but not in chronic ones [73].

The mean time to the development of MetS is nearly 12 weeks, and after 1 year of treatment, MetS rate is three times higher compared to baseline and occurs more frequently with olanzapine [67].

The prevalence of diabetes increases rapidly after starting AP [74], and higher AP doses are associated with a higher risk of TD2 [75]. The risk to develop TD2 is higher in FEP patients treated with olanzapine (HR 1.41) and with FGAs (HR 1.60) compared with drug-naïve ones; during longer-term treatment, TD2 risk appears associated with FGAs (OR 1.45), olanzapine (OR 1.57), and clozapine (OR 2.31) [76]. The cumulative risk for TD2 appears to be higher in adolescents and young adults using AP for many different psychiatric disorders when compared with healthy controls (OR 2.58) and with controls affected by psychiatric disorders not treated with AP (OR 2.09) [77]. In addition, TD2 risk is higher in male sex [77].

Finally, olanzapine treatment is associated with higher insulin resistance levels than aripiprazole, ziprasidone, or risperidone [76]. For these reasons, olanzapine should be avoided in FEP [78].

A recent meta-review has investigated metabolic abnormalities in children and adolescents affected by psychiatric disorders treated with APs, finding that lurasidone has the safest profile and olanzapine the worst [79].

Regarding HPRL, it has been established that SGAs cause a minor elevation of the PRL plasma levels than the FGAs [80]. The notable exceptions in this regard are amisulpride, risperidone, and paliperidone [81]. Amisulpride is one of the most pronounced "PRL-raising" AP [58], independently of dosage and duration of administration [82], followed by risperidone and its metabolite paliperidone [83]. On the contrary, aripiprazole, cariprazine, quetiapine, and brexpiprazole have the most favorable profile with respect to PRL elevation toward placebo [58], and aripiprazole at low dose in combination with risperidone or olanzapine significantly reduces the PRL levels induced by these APs [84] probably for its D2R partial agonism [85].

Identifying carriers of the relevant genetic risk factors leading to the greatest increases in PRL levels after AP treatment may help to guide AP choices in FEP patients to avoid adverse effects such as sexual dysfunction and osteoporosis, which are among the most burdensome for patients with psychotic disorders and can compromise the adherence to treatment [86]. To this regard, pharmacogenetic studies have been conducted in FEP patients, showing polymorphisms in NTRK2, DRD2, and ACE genes associated with PRL concentration [87].

Compared with SGAs, a higher fracture risk, in particular of the hip, was found for FGAs in some studies [88, 89], possibly due to extrapyramidal symptoms causing gait disturbances and impairing balance, which are risk factors for falls in older adults [90]. However, other studies found no differences between FGAs and SGAs [91]. No significant differences in BMD between FEP patients and controls before treatment have been found [92]. On the contrary, after 12 months of APs, the decrease in BMD correlated with longer duration of treatment with FGAs, rather than with PRL levels, suggesting that the duration of HPRL may have a greater impact than PRL levels themselves [92].

In conclusion, the choice of AP should be made on an individual basis, considering the clinical circumstances and preferences of patients [60], taking into account that weight gain and HPRL negatively affect adherence rates, especially in younger patients [93] (Fig. 13.2).

13.2 Metabolic Abnormalities in MDD

Patients suffering from MDD are subject to socioeconomic and lifestyle conditions that may influence the development of CVD and MetS [94]. These include poor receipt of physical health care [95], reduced compliance with medical recommendations [96], and adverse medication treatment effects [34], along with modifiable risk factors, such as smoking and physical inactivity [35]. Among medications, APs are the main contributors to increase of MetS risk in MDD compared to controls [7]. A higher BMI is significantly related with lower education, no tobacco use, and male sex [97]. An umbrella review of meta-analyses of cohort studies and randomized controlled trials found that the only risk factor with convincing evidence for obesity in adults is depression [98].

Compared with age- and gender-matched controls, nearly 30% of depressed patients are affected by MetS (RR 1.57), and they also have a heightened risk of hyperglycemia and hypertriglyceridemia [7, 11].

There is a bidirectional relationship between obesity and depression, where the direction depression leading to obesity is stronger than the reverse direction [99]. Adults who were depressed at baseline demonstrated a 37% increase in risk of obesity at follow-up compared with adults who did not experience depression [99]. Conversely, obese adults had an 18% increase in the risk of being depressed over a long-term follow-up [99].

The relationship between MDD and T2D appears also bidirectional [100]. T2D is more common in people with MDD than in age- and gender-matched controls

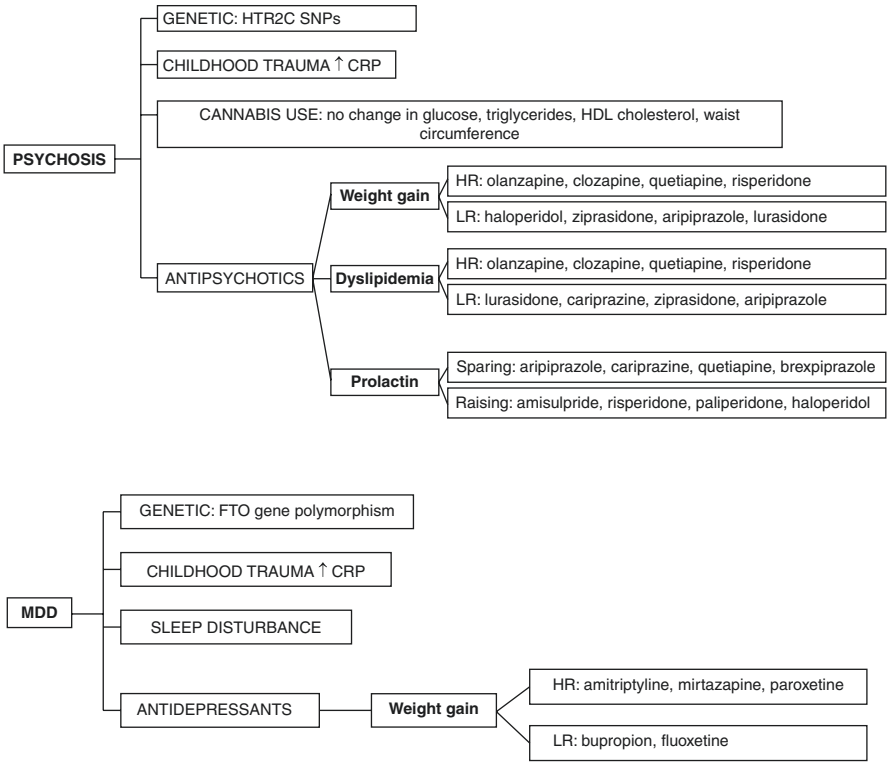

Fig. 13.2 Predictors of obesity in psychosis and major depressive disorder. *HTR2C* 5-hydroxytryptamine receptor 2C, *SNPs* single-nucleotide polymorphisms, ↑ increased/increases, *CRP* C-reactive protein, *HDL* high-density lipoprotein, *MDD* major depressive disorder, *HR* high risk, *LR* low risk, *FTO* FTO alpha-ketoglutarate-dependent dioxygenase

(RR 1.36), whereas there is modest evidence that diabetes is a risk factor for MDD [22, 101]. Treatment duration, antidepressant, and lithium use were significant mediators of T2D prevalence in this population [22].

MDD affects up to 20–25% of adults with T2D [100] and is associated with a nearly twofold risk of all-cause mortality [102]. When combined, depression and diabetes exert an additive effect on all-cause mortality compared with controls without diabetes or MDD (HR 4.59) [103]. Besides, MDD increases the risk of adverse glycemic control: thus, through earlier identification and treatment of long-standing depression, the risk for health complications may be reduced [104].

Depression is prospectively associated with a significant increase in the risk of fracture and bone loss [105]. Hypercortisolemia appears to have a role in decreased bone formation [106]. Higher levels of inflammatory cytokines, such as IL-1β, IL-2, and IL-6, are linked to decreased BMD [107]. Many poor health behaviors associated with MDD, such as smoking, alcohol use, and decreased physical activity, have been found to impact bone metabolism [108]. Specifically, depression has been associated with 39% increase in fracture risk (RR = 1.39) [105]. Due to the high

prevalence of MDD and osteoporosis worldwide, the observed relationship has important implications for public health, especially with increased aging of the population worldwide; thus, prevention and treatment of depression might decrease the risk of osteoporotic fracture [105].

Several studies suggest that antidepressants, particularly SSRIs, are associated with decreased BMD and increased fracture risk (RR 1.72), especially in elderly [109]. The risk is higher during the early stages of treatment, reaching a peak within 1 month for tricyclics and 8 months for SSRIs [110].

In summary, these data support the Canadian Network for Mood And Anxiety Treatments (CANMAT) recommendations stating that individuals with MDD, and in particular those taking APs, must be considered a vulnerable group that should be screened proactively for MetS and CVD risk factors [111]. Therefore, psychiatrists and other mental professionals should help individuals with MDD to improve their lifestyle, through smoking cessation, dietary measures, and exercise; if lifestyle interventions do not succeed, preferential use of lower-risk medication should be considered [112].

13.2.1 Pathophysiology

People suffering from MDD have been shown to be at an increased risk for MetS and T2D [7]. Moreover, MetS comorbidity in mood disorders is associated with a more complex affective presentation, lower probability of recovery, more frequent episodes, and suicide attempts [113].

The biological association between MDD and T2D is hypothesized to be due to a dysregulated HPA axis, a shift in sympathetic nervous system tone toward enhanced sympathetic activity, and a proinflammatory state [114]. Depression is associated with a blunted cortisol awakening response and flattening of the diurnal cortisol curve, which is also associated with insulin resistance and T2D [115]. In particular, in melancholic depression hypercortisolemic condition was found, increasing food intake and obesity [116] according to other studies showing that a relatively hyperactive HPA axis leads to melancholy and that a hypoactive stress response leads to atypical depression [117].

Multiple interacting pathways contribute to the comorbidity between MDD and MetS, such as increased levels of pro-inflammatory cytokines and acute-phase proteins, increased lipid peroxidation and oxidized C-LDL, hypernitrosylation, lowered levels of antioxidants, increased atherogenic index of plasma, and reduced levels of C-HDL [118]. Thus, mood disorders are associated with increased atherogenicity, but not with insulin resistance [119].

Patients during acute depressive episodes have higher activity levels of antioxidant enzymes, such as superoxide dismutase and catalase, compared to controls [120]. Immune-oxidative (IO) and nitrosative stress (NS) pathways are activated in people with a sedentary lifestyle, possibly increasing the risk to develop MDD [121]. Oxidative processes, occurring in MetS and MDD, may modify C-LDL and phospholipids leading to a higher risk for atherosclerosis and myocardial infarction [122]. The formation of oxidized LDL and oxidized phospholipids may

consequently activate the toll-like receptor 4 (TLR4) complex, a phenomenon described as the TLR radical cycle which may cause chronic inflammation and especially chronic IO and NS, which may further aggravate the immune pathophysiology of mood disorders and MetS [123].

Circulating levels of leptin and TNF-α are elevated both in obesity and MDD [124]. Raised levels of leptin can lead to its resistance, which is evident in MDD with atypical features [125]. By contrast, adiponectin levels, which have anti-inflammatory effect, may be reduced in obesity and MDD [126]. However, controversial findings are reported on this topic in literature: a recent meta-review found no differences in leptin levels in MDD toward healthy controls, apart from subgroup samples with BMI ≥ 25 or age ≥ 40, in which leptin was found increased [127]. In addition, depressed patients with BMI ≥ 25 had lower adiponectin levels compared to controls [127], playing a key role in obesity-related diseases, such as T2D.

Besides the well-known leptin and ghrelin, other biomarkers such as orexin and nesfatin-1 seem to be involved in neurovegetative changes, like sleep and appetite regulation [128]. Sleep disturbance appears a stronger mediator of the relationship between MDD and obesity, compared to stress eating [129]. It is thought that the presence of increased leptin concentrations, despite decreased food intake, could contribute to appetite loss, which is a symptom of typical MDD; on the contrary, in atypical depression higher leptin levels would lead to increased fat body mass [128].

Adiposity-driven inflammation, smoking, and unhealthy lifestyle may contribute to the immune activation in MDD and thus to its relationship with MetS [130]. Levels of IL-6, TNF-α, IL-10, CCL-2, IL-13, IL-18, and IL-12 are significantly elevated in individuals with MDD compared to controls [131].

Regarding genetics, it has been shown that depression enhances the effect of FTO polymorphism on BMI: on average, subjects with MDD carrying the risk allele have a 2.2% higher BMI for each risk allele compared with controls [132]. In addition, cardio-metabolic disease risk genes, associated with mood disorders, have been identified [133]. These risk genes are more than 20 potential pleiotropic genes, and they are implicated in significant pathways: corticotrophin-releasing hormone, AMPK, cAMP-mediated or G-protein coupled receptor, axonal guidance, serotonin or dopamine receptors, circadian rhythm, and leptin signaling [133].

Regarding environmental factors, childhood sexual abuse has been associated with MDD (OR 2.7) and obesity (OR 1.4) in adulthood [134], as previously suggested [135]. Depressed patients with a history of CT show significant elevation in inflammation markers (hsRCP) and are more likely to smoke than those only depressed [136]. Therefore, individuals with CT and MDD are at a greater risk of CVD compared with depressed-only ones [136].

13.2.2 Role of Antidepressants

Antidepressants (ADs) may also be associated with weight gain [137], due to their affinity to H1, M1, and 5-HT2C receptors [138].

AD use is greater in patients with comorbidity, particularly with diagnoses of stroke and diabetes, and co-prescriptions of APs, than in those without [139]. The

rate ratio (RR) for weight increase according to AD use is 1.21, indicating that a risk of ≥5% weight gain is 21% higher during AD treatment than during other times [139]. Participants with >1 year of treatment showed an increased risk of weight gain that was maintained at 6 years: RRs were 1.46 at 2 years and 1.48 at 3 years, and then declined, and from year 7 onward, there was no evidence for an increased risk of weight gain [139]. Thus, initiation of AD shows a strong temporal association with weight gain, which is greatest during the second and third years of treatment. During the second year of treatment, the risk of ≥5% weight gain is 46.3%, higher than in the general population (190). In addition, in people who were initially of normal weight, the RR for transition to overweight or obesity was 1.29 [139].

Regarding ADs, amitriptyline, mirtazapine, and paroxetine have been found associated with the greatest risk of weight gain [140]. Interestingly, amitriptyline and mirtazapine were associated with weight gain over both acute (4–12 weeks) and maintenance periods (≥4 months), while paroxetine was associated with weight gain over the medium-long-term period [139]. In contrast, some weight loss occurs with fluoxetine and bupropion, although the effect of fluoxetine appears to be limited to the acute phase of treatment, differently from bupropion [139]. Other ADs have no transient or negligible effect on body weight in the short term; however, the effect of each AD may vary greatly depending on an individual's characteristics and generally became more evident in the long term [139].

Interestingly, lower education status, lower BMI at the onset of AD use, and family history of obesity are independent predictors of weight gain ≥7% compared to the baseline [141].

Noteworthy, an association between ADs and T2D (RR 1.27) has been found, although this finding is still inconclusive [142].

13.3 Treatment and Prevention

Since a range of psychiatric conditions (SCZ, BP, MDD, anxiety, and stress-related disorders) are associated with increased cardio-metabolic disease risk [22] and lower physical fitness [11], the improvement of physical health is both an ethical and clinical priority [6, 143]. The European Psychiatric Association (EPA) stated that maintaining a healthy body weight and shape by healthy eating and regular physical activity is a key component in order to prevent and reduce the risk of developing physical comorbidities, including CVD, and to improve the overall health and well-being of patients [112]. Thus, it is of supreme importance to set up and implement strategies which can prevent and address the problem of physical comorbidity in mental disorders, and it is also crucial to raise the awareness of health professionals regarding these insidious and life-threatening conditions [144]. Two types of interventions can be implemented, pharmacological and non-pharmacological ones, and they can be applied to prevent the onset of cardio-metabolic diseases or to reduce their effects in patients who have already manifested some alterations.

13.3.1 Non-pharmacological Interventions

In the general population, there is consistent evidence that physical activity (PA) and exercise can decrease the risk of developing cardio-metabolic diseases [145, 146] and reduce inflammatory parameters, such as CRP, IL-6, and IL-8 [147, 148], which are commonly raised in SMI. Moreover, there is evidence that PA is equally effective as frontline pharmacological interventions, such as statins and beta-blockers, in preventing CVD mortality [149]. Conversely, high levels of sedentary behavior (SB), which are common in SMI [107], are independently associated with an increased risk of CVD, T2D, and premature mortality [150]. Thus, as increasing PA is a cornerstone of cardio-metabolic prevention in the general population, there is considerable empirical evidence that the same intervention may result useful in several psychiatric disorders. To date, it has been found that the majority of the lifestyle and behavioral interventions produces an increase in PA in SMI [151]. Particularly, it has been recently highlighted that the use of aerobic exercise of moderate-vigorous intensity at a frequency of two to three times a week, ideally supervised by qualified professionals and achieving 150 min of moderate-to-vigorous physical activity (MVPA) per week, could consistently reduce CVD risk markers in people with MDD and SCZ [152]. Moreover, the same PA program is also recommended for reducing the risk of MDD (including postnatal depression) [153]. Similar results seem to be also achieved with a combination of aerobic and resistance training [152]. In order to improve the efficacy of aerobic exercise, higher-intensity training, such as high-intensity interval training (HIIT), has been used in SMI people with cardio-metabolic risk factors and obesity finding that HIIT could significantly improve metabolic parameters, in particular waist circumference, body mass, fasting glucose, HDL-C, and blood pressure [154]. Some studies have found that HIIT intervention has the potentiality to improve parameters of MetS (particularly BMI, body weight, waist circumference, and heart rate), although more research is needed to validate this preliminary data [155, 156].

The EPA guidelines on physical activity [157] state that evidence is sufficient to recommend PA as an effective first-line treatment option for moderate depression and as an adjunctive intervention for improving psychiatric symptoms, cognition, and cardiorespiratory fitness in SMI.

Although to date existing guidelines focus on PA in SCZ and MDD [158], only few interventions have been designed to address the problem of sedentary behavior, with ambiguities on their efficacy [151]. Current findings indicate that isolated exercise interventions are unlikely to induce weight loss in SMI, while adding behavioral interventions or nutritional therapy to exercise programs seems to be a promising approach to reduce body weight [155]. Particularly, the support of qualified professionals who develop motivation results holds great importance in promoting engagement and adherence to PA [159]. The nature of many mental diseases, in particular psychosis, may contribute to physical inactivity due to symptoms such as avolition, blunted affect, and social withdrawal, which could be overcome by implementing exercise routines with support, educational meetings, and motivational counseling [159, 160].

Several studies have evaluated different behavioral interventions (BI) aimed at raising awareness toward healthy behaviors, informing patients about unhealthy lifestyle risk (e.g., smoking) and promoting healthy habits through psychoeducational interventions [161–163]. It has been found that lifestyle counseling is the most effective intervention for body weight and BMI followed by exercise, psychoeducation, and CBT in SCZ [164]. Several psychoeducational approaches have been developed, as far as the format (individual versus group) and the professional characteristics of the staff performing the intervention (psychiatrists versus nurses versus psychologists) are concerned [161]. However, it is still unclear which setup leads to the best result [161]. Particularly, the individual format allows personal advice, to tailor the plan of intervention to the patient's needs and increase motivation to change [161, 165]; on the other hand, the group format gives the possibility to share opinions and reciprocal support and to have imitative behavior [161, 166]. Nevertheless, when the intervention is provided by a multidisciplinary team, its impact on patients' lifestyle behaviors is more effective compared to the ones led by nurses or psychologists alone [161]. Moreover, it has been suggested that medical personnel are important in setting a good example of a healthy lifestyle, which is fundamental for "modeling" the lifestyle of patients [160, 167].

Regarding nutritional therapy (NT), several studies have highlighted that caloric restrictions and healthy diet educational interventions developed by qualified professionals could prevent and reduce weight gain in SMI [160]. Moreover, NT has shown beneficial effects on anthropometric measurements and biochemical variables among patients, with a significant decrease in BMI, body fat percentage, and waist circumference and a slightly improvement in metabolic profiles of fasting blood glucose, triglyceride, and HDL and LDL-C [168]. These beneficial effects have been shown to be achieved even in patients using SGAs such as clozapine and olanzapine, which are known to cause the most significant amount of weight gain and metabolic abnormalities, suggesting that the adverse effects of these medication could be mitigated adopting an adequate NT [160, 169]. However, in SCZ dietary interventions showed a small glucose level reduction and no effect on insulin [164]. Finally, given the paucity of studies, the data do not allow to determine which type of diet (e.g., Mediterranean diet, ketogenic diet) is the more valid to improve cardiometabolic risk [170].

In conclusion, it can be stated that comprehensive weight and health management programs, including PA, NT, and lifestyle psychoeducation, can be considered more effective than a single-mode approach in preventing and treating cardio-metabolic diseases in SMI [144, 155, 169, 171]. A critical issue is the optimal duration of the intervention. In literature, studies' extent ranges from 3 months to 1–2 years [161]. Although studies do not yet provide clear evidence concerning the optimum length of engagement in these programs [161, 171], experience in the general population suggests that lifestyle change needs to be permanent [172]. Thus, intervention programs should last at least 20 weeks and should provide follow-ups consisting of booster sessions for behavioral, NT, and PA control [171].

13.3.2 Pharmacological Interventions

Psychotropic medications, particularly APs, TCA, and several SSRIs, can cause side effects, including weight gain and metabolic derangements that are often difficult to manage [173]. In this regard, several guidelines have been developed and provide recommendations regarding the monitoring and management for cardio-metabolic risk factors in psychosis [174]. The guidelines recommend several measurements (e.g., weight, glucose, HbA1c, cholesterol/HDL ratio, blood pressure) before starting an antipsychotic and then at the intervals indicated. Tobacco smoking should be inquired, and its cessation should be delivered as part of an overall smoking cessation program [174].

To manage the risk of weight gain and cardio-metabolic disorders associated to APs, some studies have shown that switching antipsychotics to relatively metabolic-neutral agents could lead to an improvement in patients' cardio-metabolic parameters, even if this option is not always feasible (e.g., treatment-resistant patients receiving clozapine) [175]. When non-pharmacological strategies alone are insufficient and switching is not suitable, using concomitant medications to counteract these adversities may be a rational option, although the data concerning this topic are still limited [173]. There is evidence supporting the use of concomitant metformin to mitigate antipsychotic-induced weight gain and other metabolic adversities in SCZ [173, 176]. The use of adjunctive metformin has shown to have a positive effect on different parameters such as body weight, waist circumference, insulin resistance, and serum lipids [173, 176]. Similar but less significant results have also been found for topiramate, sibutramine, and reboxetine [173, 176]. Specifically, topiramate has been found effective in reduction of LDL-C and triglyceride levels, BMI, and weight in SCZ [164]. Pharmacological interventions have shown to be effective in patients affected by psychosis, and FEP patients may derive the most benefit [173]. In fact, FEP patients receiving metformin are less likely to experience clinically relevant weight gain in prevention trials and more likely to achieve clinically relevant weight loss in treatment trials [173, 176]. Specifically, FEP individuals in early treatment lost three times the weight compared with older, more chronic patients [176]. However, given the paucity of studies and the possible onset of side effects related to medications such as metformin, the current evidence is too limited to support the regular clinical use of adjunctive pharmacological treatments, and healthy lifestyle and nutritional interventions should be preferred in the prevention and early treatment of cardio-metabolic alterations [176]. Finally, due to the increased morbidity and mortality among people with SCZ experiencing a fracture, there is a need to develop preventative interventions like more frequent monitoring of serum PRL levels and DEXA scan use in patients with SCZ at high risk of fractures [30, 31]. Importantly, the relatively high prevalence of hypertension, diabetes, smoking, and dyslipidemia is in stark contrast to the lack of related treatment for medical comorbidities in the most patients [95, 177, 178] (Fig. 13.3).

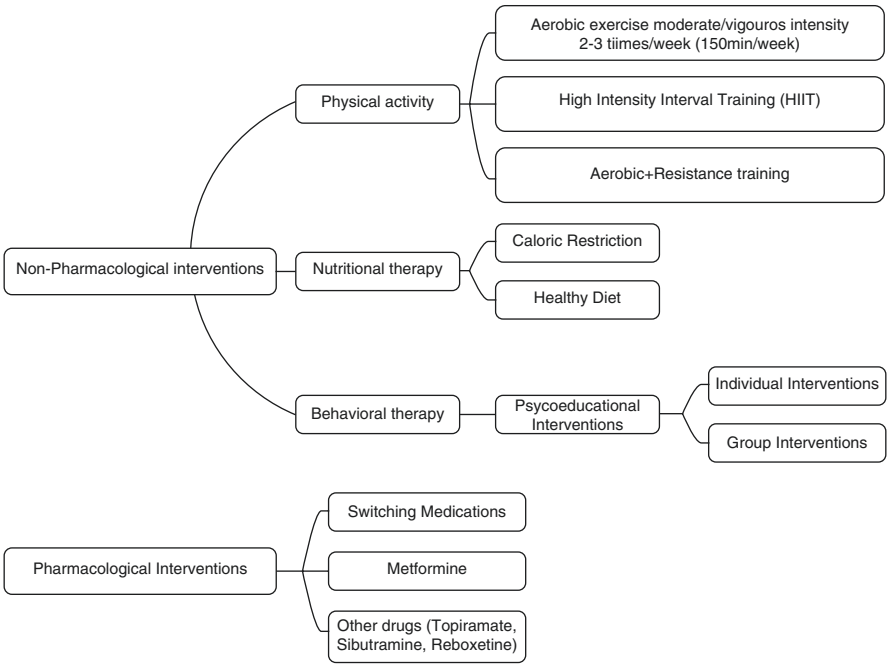

Fig. 13.3 Pharmacological and non-pharmacological interventions to prevent and reduce the risk of developing physical comorbidities in SMI

13.4 Conclusions

Evidence has demonstrated the efficacy of physical activity interventions on cardiometabolic health and other outcomes as well as psychiatric symptoms in people with SMI [157, 179]. The guidelines have made available to clinicians the adequate tools to monitor metabolic parameters. Despite this and several editorials calling for action [180, 181], "lifestyle interventions" are still limitedly available in clinical routine care [182]. Thus, it is imperative to identify the barriers that make such interventions unavailable in clinical practice, educate professionals to implement them, and monitor their effects.

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