REVIEW PAPER Curr Probl Psychiatry, Vol. 25(2024):226-238

DOI:10.12923/2353-8627/2024-0021

Czasopismo indeksowane na liście MNiSW - 70 pkt.

Insights into risk factors of the Metabolic Dysfunction-Associated Steatotic Liver Disease development among patients with schizophrenia

Jakub Rogalski[1] ABCDEFG, https://orcid.org/0000-0002-7322-4844,
Oliwia Gawlik-Kotelnicka[2] ABDE, https://orcid.org/0000-0003-1398-3117,
Tomasz Tomczak[3] ABDE, https://orcid.org/0000-0002-2455-8725,

[1]University Clinical Hospital No. 2, Medical University of Lodz, Poland
[2]Department of Affective and Psychotic Disorders, Medical University of Lodz, Poland
[3]Central Teaching Hospital, Medical University of Lodz, Poland

Abstract

Introduction: The global burden of the Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) constitutes a significant clinical problem for healthcare systems worldwide. Apparently, a subgroup of patients diagnosed with schizophrenia appears to be particularly vulnerable to the MASLD development. However, exact risk factors in schizophrenia subjects remain unclear to date.

Material and methods: The article is a literature narrative review concentrating on the particular risk factors identification for MASLD development among patients with schizophrenia. Internet scientific bases were searched by three independent investigators throughout February-July 2024 for relevant original and review articles from 2000-2024 using different combinations of MeSH terms: "antipsychotics", "diabetes", "dietary habits", "dyslipidemia", "inflammation", "intestinal permeability", "insulin resistance", "metabolic-associated fatty liver disease", "metabolic dysfunction-associated steatotic liver disease", "metabolic syndrome", "non-alcoholic fatty liver disease", "obesity", "prevention", "socioeconomic status", "treatment". Furthermore, a reference search was conducted to find other important manuscripts. Articles in other language than English were excluded from the search. The Scale for the Assessment of Narrative Review Articles was used to ensure the appropriate quality of this review.

Results: Socioeconomic conditions, improper dietary habits, lack of physical activity, smoking addiction issue, gut microbiota dysfunction or the use of antipsychotics may act as trigger points for the MASLD development among patients with schizophrenia.

Conclusions: The identification of particular risk factors of MASLD development among schizophrenia subjects may help to establish a multidisciplinary healthcare programme primarily aimed at MASLD and its complications prevention, early detection and proper treatment.

Keywords: metabolic syndrome, psychiatry, schizophrenia, risk factors, metabolic dysfunction-associated steatotic liver disease

Streszczenie

Wstęp: Stłuszczeniowa Choroba Wątroby Związana z Dysfunkcją Metaboliczną (Metabolic Dysfunction-Associated Steatotic Liver Disease, MASLD) stanowi istotny klinicznie problem dla systemów opieki zdrowotnej na całym świecie. Wydaje się, że subpopulacja pacjentów ze schizofrenią jest szczególnie narażona na jej rozwój. Jednakże, poszczególne czynniki ryzyka rozwoju MASLD wśród pacjentów ze schizofrenią pozostają niejasne.

Materiał i metody: Artykuł stanowi narracyjny przegląd literatury koncentrujący się na identyfikacji czynników ryzyka rozwoju MASLD wśród pacjentów ze schizofrenią. W okresie luty-lipiec 2024 r. trzech badaczy niezależnie przeszukało internetowe bazy naukowe pod kątem odpowiednich artykułów oryginalnych i przeglądowych z lat 2000-2024, stosując różne kombinacje terminów MeSH: "antipsychotics", "diabetes", "dietary habits", "dyslipidemia", "inflammation", "intestinal permeability", "insulin resistance", "metabolic-associated fatty liver disease", "metabolic dysfunction-associated steatotic liver disease", "metabolic syndrome", "non-alcoholic fatty liver disease", "obesity", "prevention", "socioeconomic status", "treatment". Ponadto dokonano sprawdzenia list referencyjnych poszczególnych artykułów w celu identyfikacji dodatkowych publikacji powiązanych z tematyką niniejszego manuskryptu. Z przeglądu wykluczono artykuły w języku innym niż angielski. Aby

zapewnić odpowiednią jakość publikacji, zastosowano The Scale for the Assessment of Narrative Review Articles.

Dyskusja: Czynniki socjoekonomiczne, nieprawidłowe nawyki żywieniowe, niedostateczna ilość aktywności fizycznej, nikotynizm, dysfunkcja mikrobioty jelitowej oraz stosowanie leków przeciwpsychotycznych mogą przyczyniać się do rozwoju MASLD wśród pacjentów ze schizofrenią.

Wnioski: Identyfikacja poszczególnych czynników ryzyka rozwoju MASLD u chorych na schizofrenię może pomóc w ustaleniu multidyscyplinarnego programu opieki zdrowotnej, którego głównym celem będzie zapobieganie MASLD i jej powikłaniom, wczesne wykrywanie oraz właściwe leczenie.

Słowa kluczowe: psychiatria, schizofrenia, czynniki ryzyka, zespół metaboliczny, stłuszczeniowa choroba wątroby związana z dysfunkcją metaboliczną

1. Introduction

1.1. Disease overview

Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD), formerly known as a Non-alcoholic Fatty Liver Disease (NAFLD) or Metabolic-associated Fatty Liver Disease (MAFLD), is the latest term describing Steatotic Liver Disease (SLD) associated with the presence of metabolic syndrome (MetS) components [1]. It is the most common chronic liver disease worldwide – epidemiological studies conducted so far indicated that even 32.4% of a general population may be affected by this condition. Furthermore, fatty liver disease is associated with numerous hepatic and extra-hepatic complications, resulting in significant premature mortality [2,3]. Therefore, the diagnosis and the management of MASLD has become one of the crucial challenges for clinicians in everyday practice (Table 1).

Table 1. MASLD diagnostic criteria [1].

detection of hepatic steatosis (imaging techniques, liver biopsy)
plus the presence of minimum 1 out of 5 cardiometabolic criteria:
BMI ≥ 25 kg/m2 (23 in Asian population) or WC > 94 cm in males or WC > 80 cm in females or ethnicity adjusted
FSG ≥ 5.6 mmol/L (100 mg/dl) or 2-hour post-load glucose levels ≥ 7.8 mmol/L (≥ 140 mg/dl) or HbA1c ≥ 5.7% (39 mmol/l) or t2DM or the treatment of t2DM
BP ≥ 130/85 mmHg or antihypertensive drug treatment
plasma TGs ≥ 1.70 mmol/L (150 mg/dl) or lipid lowering treatment
plasma HDL-C ≤ 1.00 mmol/L (40 mg/dl) in males or ≤ 1.3 mmol/L (50 mg/dl) in females or lipid lowering treatment

Abbreviations: BMI, body mass index; BP, blood pressure; FSG, fasting serum glucose; HbA1c, haemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; t2DM, type 2 diabetes mellitus; TGs, triglycerides; WC, waist circumference.

In the last few years, emerging data have shown that specific subpopulations of patients are particularly vulnerable to the MASLD development. One of them are subjects with schizophrenia. Several studies revealed that the prevalence of fatty liver disease in this group of patients may even reach 70.8% [4].

Thus, it seems necessary for healthcare professionals to identify particular risk factors, which may contribute to the MASLD development among patients with schizophrenia, to ensure proper diagnostic process and effective forms of treatment.

1.2. Objective of the study

We aimed to perform a comprehensive literature review concentrating on possible risk factors for the MASLD development among patients with schizophrenia (Figure 1).

2. Material and Methods

A narrative literature review, focusing on the possible risk factors of the MASLD occurrence among patients with schizophrenia, was conducted. Internet scientific databases, Google Scholar, Medline, PubMed and Science Direct, were searched by three independent investigators throughout February-July 2024 for relevant original and review articles from 2000-2024 using different combinations of MeSH terms: "antipsychotics", "diabetes", "dietary habits", "dyslipidemia", "inflammation", "intestinal permeability", "insulin resistance", "metabolic-associated fatty liver disease", "metabolic dysfunction-associated steatotic liver disease", "metabolic syndrome", "non-alcoholic fatty liver disease", "obesity", "prevention", "socioeconomic status", "treatment". Furthermore, a reference search was conducted to find other important manuscripts. Articles in other language than English were excluded from the search. The Scale for the Assessment of Narrative Review Articles was used to ensure the appropriate quality of this review [5].

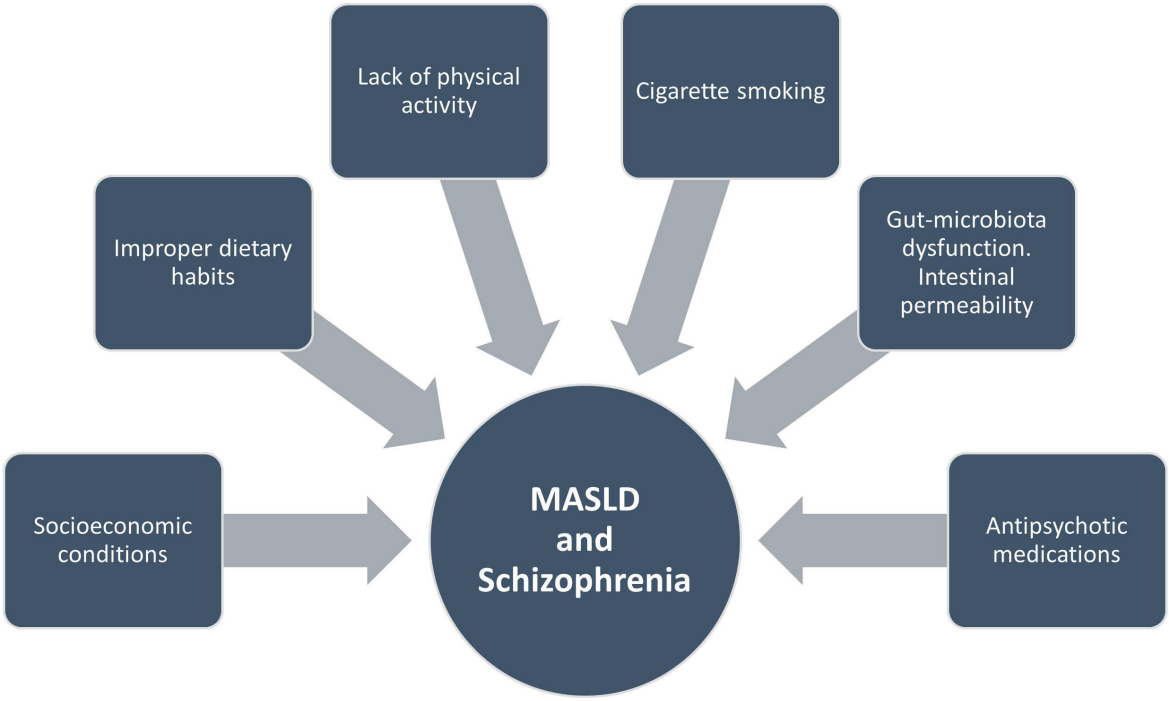

Figure 1. Possible risk factors of the MASLD development among patients with schizophrenia.

3. Possible risk factors of the MASLD development among patients with schizophrenia

3.1. Socioeconomic conditions

Studies suggest that the low socioeconomic status (SES) is a separate risk factor for both schizophrenia and MASLD [6–8]. In this context, particular attention has been paid to the limited healthcare system access and presence of poor dietary habits (described below).

As it has been revealed recently, the issue of improper dietary patterns is the main factor modifying the relationship between the fatty liver disease and SES [9,10]. Schizophrenia subjects often do not follow healthy eating habits or recommendations, and such an attitude may be a consequence of the positive symptoms presence, low cognitive performance, insufficient level of education in this field or lack of financial resources to maintain a healthy diet pattern [11,12]. As a result of this state, numerous metabolic disorders, including MASLD, may occur.

On the other hand, patients with schizophrenia do not receive the proper level of medical care, resulting in the lack or insufficient schizophrenia and other somatic comorbidities management [13]. It may be partially caused by the presence of delusions or cognitive impairment, which limit their social drive. Moreover, a stigma toward mental illness among healthcare professionals may also lead to the avoidance of medical services and less adherence to the treatment regimen [14]. Finally, it should not be forgotten that low wealth index of schizophrenia subjects may potentially limit their access to the private sector healthcare, which plays a complementary role in national health services structures [15]. All in all, these above-mentioned issues may contribute to the delay in the diagnosis and proper treatment of various metabolic comorbidities contributing to the fatty liver disease incidence, as well as the same MASLD.

3.2. Improper dietary habits

As it was mentioned previously, food insecurity is perceived as one of the most important features contributing to the MASLD development. MASLD metabolic risk factors, such as overweight/obesity, insulin resistance, type 2 diabetes mellitus (t2DM) or dyslipidemia, are often linked with Western dietary patterns, including excessive caloric intake and high fructose consumption [16–19]. Besides its contribution to the metabolic abnormalities' occurrence, improper dietary habits (e.g. high intake of sugar-sweetened beverages and processed red meat, as well as low consumption of nuts/seed or milk) have been also found to independently drive the global burden of NAFLD-related liver mortality [20].

In the context of schizophrenia, numerous abnormalities regarding diet composition and appetite-satiety dysregulation have been already observed. In the light of above-mentioned findings, it seems that these factors may make schizophrenia subjects particularly vulnerable to the MASLD development.

3.2.1. Diet composition

A systematic review conducted by Dipasquale et al. revealed that the diet of patients with schizophrenia is mainly characterized by a high intake of saturated fats,

accompanied by a low fibre and fruit consumption [21]. Similar findings were observed by Jakobsen et al. and Firth et al., who additionally indicated that the intake of carbohydrates, sugar, protein, as well as alcohol is higher among schizophrenia subjects in comparison to healthy controls, or even exceed the recommended amounts [22,23]. Moreover, Stefańska et al. revealed that food rations of patients with schizophrenia were characterized by a deficiency in particular microelements (iron and iodine in women), macroelements (potassium, calcium, magnesium in men) and vitamins (B9, C, D and E) [24]. Interestingly, the diet of schizophrenia subjects has been also found to have more pro-inflammatory properties compared to controls [23,25,26].

It is hypothesized that poverty can significantly affect the access to healthy or high-quality food. Therefore, subjects with schizophrenia may have serious problems with healthy diet maintenance. Moreover, the presence of schizophrenia psychopathological symptoms – positive and negative ones, as well as cognitive deficiencies or mood problems – leads to reduced interest in food and struggles with its preparation [27].

3.2.2. Appetite and satiety dysregulation

A systematic review and meta-analysis conducted by Misiak et al. showed a dysregulation of the adipoinsular axis in terms of elevated insulin and decreased leptin levels (both act as anorexigenic hormones), occurring in early stages of psychosis, even before the antipsychotic treatment initiation. It is suspected that this state may predispose patients with schizophrenia to gain weight after the initiation of antipsychotic treatment [28].

Another cause which may contribute to the appetite and satiety dysregulation among subjects with schizophrenia are abovementioned antipsychotic drugs. Nowadays, second-generation antipsychotics (SGAs) and dopamine receptor partial agonists (DRPAs) are the most common medication groups used in the schizophrenia treatment regimen. A large number of scientific evidence has already revealed that hyperphagic effect and lack of satiety during their application is relatively often observed, both in clinical practice, as well as on rodent models [29,30]. Most of antipsychotic drugs, through their antagonism to dopamine receptors, interfere with dopaminergic pathways in specific central nervous system structures such as ventral tegmental area, nucleus accumbens or arcuate nucleus. Therefore, hyperphagic effect in terms of dysregulated hedonic feeding behaviors may occur [29,31,32]. In turn, an antagonism of SGA towards serotonin receptors, especially 5-HT2c, leads to the increase in the expression of Neuropeptide Y (NPY) and Agouti-related Peptide which activate brain hunger centre [33,34]. On the other hand, a postsynaptic H1-receptor antagonism in hypothalamus may also contribute to the appetite stimulation mainly through two processes: (1) causing an increase in AMP-activated protein kinase (AMPK) and NPY pathways activity, (2) decreasing histamine release via presynaptic H3-receptors, with subsequent reduction in serotonergic, cholinergic and noradrenergic transmission [35,36]. Additionally, some antipsychotics, such as olanzapine or clozapine, block muscarinic acetylcholine receptors, particularly M3 receptors (M3R), in hypothalamic regions, which also results in increased food intake and weight gain [37–41]. Moreover, M3R have been pointed out to play a significant role in terms of peripheral hormonal and metabolic dysregulation, probably via the vagus nerve activity regulation [29]. Apart from that, some antipsychotics interfere with endocannabinoid system signalling, resulting in the increased appetite and weight gain [42–44].

Another aspect is a dysregulation of the adipoinsular axis occurring after the antipsychotic treatment initiation. It has been found that during the neuroleptic's treatment, an increase in the concentration of leptin, in terms of leptin resistance, is observed [45]. Albeit there are some inconsistencies in the context of serum leptin levels among schizophrenia patients comparing to the controls [46]. Leptin resistance, despite the anorexigenic properties of the same leptin, contribute to the feeling of hunger with subsequent increased food intake [47]. This state may be caused by the antipsychotics impact on the leptin receptor gene expression or leptin receptor signalling pathways [29].

In turn, adiponectin and ghrelin also seem to play a significant role in the feeding behaviors disorders occurrence. However, results of already conducted studies are inconclusive. It is suspected that antipsychotics can affect their serum concentrations in time-dependent, biphasic manner [48,49]. Therefore, the assessment of serum concentrations of these hormones and their role in the appetite increase and weight gain associated with neuroleptics use remains controversial.

3.3. Sleep disorders

Sleep disorders are relatively quite often observed among patients with schizophrenia, probably due to the increased dopamine release and sensitivity, impaired melatonin secretion, as well hypothalamic-pituitary-adrenal axis function disturbances [50,51]. Numerous studies conducted so far revealed that insomnia, eveningness chronotype or impaired sleep quality are associated with the higher risk of the obesity and Metabolic Syndrome occurrence [52,53]. Although the exact mechanisms conditioning this relationship remain unclear to date, it is suspected that obstructive

sleep apnea may be an interplaying factor mediating systemic metabolic alternations, as well as some of sleep disturbances [54]. Moreover, it is perceived that disturbed circadian host rhythms may affect the timing of meal consumption, as well as the quality of the dietary regimen [27,55]. Additionally, receptor binding profiles of particular antipsychotic drugs (e.g. quetiapine) also lead to sleep-related eating disorder, a specific form of parasomnia, with recurrent, involuntary, amnestic eating episodes during sleep [56].

3.4. Lack of physical activity

Stubbs et al. revealed that people with schizophrenia engage in significantly less moderate and vigorous physical activity (PA) in comparison to healthy controls [57]. Similar findings were observed by Andersen et al. who additionally indicated that cardiorespiratory fitness level among patients with schizophrenia is poorer compared with the general population [58]. In turn, Lee et al. observed that only 26% of schizophrenia subjects meets the World Health Organization recommendations guidelines on PA [59]. In this context, the presence of depressive and negative symptoms or extrapyramidal side effects associated with neuroleptics use were identified as risk factors of low PA level [57,59–61].

Lack of PA is a well-documented risk factor for the numerous cardiometabolic diseases occurrence. On the one hand, it leads to disturbances of the body's energy homeostasis in terms of insufficient expenditure of food energy supply, resulting in fat accumulation or insulin resistance development [62]. Additionally, sedentary lifestyle is associated with various immune cells activation, pro-inflammatory cytokines production and reactive oxygen species accumulation, which promote the occurrence of abnormal inflammatory and metabolic changes in various tissues [63]. Therefore, lack of PA may contribute to the obesity, dyslipidemia, hypertension, type 2 diabetes mellitus, as well as MASLD development [64–68]. On the contrary, vigorous PA appears as a possible protective factor for noncommunicable civilization diseases, including NAFLD [69,70]. Moreover, exercising has been pointed out as a one of possible non-pharmacological methods of fatty liver disease treatment [71].

3.5. Cigarette smoking

A significant association between the fatty liver disease development and smoking (both active and passive) was confirmed in the plethora of studies [72]. Moreover, smoking has been pointed out as an independent risk factor for the liver fibrosis occurrence among subjects already diagnosed with NAFLD [73]. Nevertheless, exact pathogenetic pathways linking smoking cigarettes with NAFLD have not been fully revealed yet. Firstly, it is postulated that tobacco smoking disturbs carbohydrate-lipid metabolism (Table 2.)

In addition, smoking contributes to the hypertension development through sympathetic nervous system stimulation, intima media thickening and atherogenesis, as well as kidneys function impairment [82,83]. The role of low-grade inflammation and circulating ROS is also emphasized. Furthermore, metabolic repercussions in terms of dysregulated carbohydrate-lipid metabolism also contribute to the arterial stiffness occurrence [84].

Moreover, sidestream whole smoke was found to induce lipid accumulation within hepatic tissue through 5′-AMP-activated protein kinase (AMPK) and sterol response element binding protein-1 (SREBP-1) activity modulation [85]. Other studies indicate that nicotine (similarly as other cytotoxic chemicals present is cigarette smoke) is responsible for hepatocytes injury, in this case through nicotinic acetylocholine receptors (nAChR) activation, with the subsequent Transforming Growth Factor β production and hepatic stellate cells differentiation into myofibroblasts, which produce fibrillar collagens [86,87]. It is also believed that smoking contributes to the gut dysbiosis development with intestinal bacteria translocation through portal vein, enhancing reactive inflammatory and fibrosis processes within liver tissue [86]. Additionally, cigarettes smoking may disturb the organism's oxidant and antioxidant balance, reducing total antioxidant capacity, as well as promote systemic inflammation state [88,89]. Thus, all these abovementioned processes may contribute to the non-alcoholic steatohepatitis occurrence, with the consecutive liver fibrosis [90].

Interestingly, tobacco smoking constitutes a significant clinical problem among patients with schizophrenia. It is estimated that 60% of them is reported to be current smokers – these rates are higher in comparison to the healthy controls [91]. Several complementary hypotheses have been formulated to explain the phenomenon of simultaneous coexistence of both states. It is suspected that nicotine may interplay with midbrain dopaminergic pathways as well as compensate central nAChRs hypofunction observed in the course of schizophrenia [92]. A shared genetic propensity in terms of both tobacco smoking addiction and schizophrenia development is also emphasized as an explanation for their co-occurrence [93]. Moreover, there is some evidence that tobacco smoking may even contribute to the development of schizophrenia [94,95].

All in all, considering abovementioned findings, it seems that patients with schizophrenia may be particularly vulnerable to the MASLD development with subsequent liver fibrosis, at least partially due to smoking.

Table 2. Impact of tobacco smoking on carbohydrate-lipid metabolism.

Type of the metabolic disorder	Examples of metabolic abnormalities	Possible mechanisms leading to the metabolic disorders occurrence	References
Insulin resistance, Diabetes Mellitus	- IFG - IGT - t2DM	- smoking-induced central obesity development - nicotine-mediated pancreatic β cells apoptosis through oxidative stress exacerbation - direct cytotoxic effect of chemicals present in tobacco smoke on pancreatic β cells - systemic inflammation state mediation with subsequent chronic pancreatitis and its exo- and endocrine functions impairment - decreased insulin sensitivity through increased saturation of intramyocellular triglyceride and diacylglycerol as well as increased serine-phosphorylation of the insulin-receptor substrate-1 - increased skeletal muscle FFAs generation - decreased peripheral glucose metabolism - impaired gluconeogenesis - an increase in insulin antagonistic hormones levels - shared genetic propensity to both smoking and schizophrenia - DNA methylation changes	[74–77]
Dyslipidemia	- ↑ TC - ↑ VLDL, LDL-C - ↑ TGs - ↑ ApoB - ↓ HDL-C	- increased lipolysis - Lipoprotein Lipase activity reduction - an increase in Sterol Regulating Element Binding Protein activity - an increase in 3-hydroxy-3-methylglutaryl-CoA Reductase activity - an increase in Glucose-6-phosphatase Dehydrogenase activity - hyperinsulinemia, IR	[74,75,78–81]

Symbols: ↑, an increase; ↓, a decrease.

Abbreviations: ApoB, apolipoprotein B-100; CoA, coenzyme A; FFAs, free fatty acids; HDL-C, high-density lipoprotein cholesterol; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; IR, insulin resistance; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; t2DM, type 2 diabetes mellitus; TGs, triglycerides; VLDL, very-low-density lipoprotein.

What is more, drug resistance in schizophrenia may result from cigarette smoking – substances contained in cigarette smoke (especially polycyclic aromatic hydrocarbons) act as enzymatic inducers of various cytochrome P450 isoenzymes [96]. Thus, therapeutic serum concentrations of neuroleptics, such as haloperidol, clozapine or olanzapine, may be reduced by up to even 50%. This condition often requires increasing the doses of applied antipsychotic drugs or using several neuroleptics at the same time [97]. Subsequently, it contributes to the metabolic repercussions (obesity, dyslipidemia, impaired fasting-glucose levels etc.) aggravation [98–100]. Therefore, the risk of the MASLD development increases.

3.6. Gut microbiota dysfunction. Intestinal permeability.

In recent years, particular attention has been paid to the gut dysbiosis and intestinal permeability issue in the development and clinical course of various diseases, including neuropsychiatric and gastrointestinal ones.

3.6.1. Gut microbiota dysfunction.

Gut microbiome dysfunction, in terms of reduced bacterial diversity with less abundant short-chain fatty acids (SCFAs) releasing bacteria, has been already observed among patients with schizophrenia [101,102]. Nevertheless, it is still unknown, whether these alternations contribute to the development and clinical course of schizophrenia, or rather are a consequence of other somatic comorbidities, poor dietary habits and applied therapies [103].

In the context of the MASLD development, intestinal dysbiosis may significantly alter the bile acid metabolism

pathway and disrupts the balance between the primary and secondary bile acids, leading to the increased hepatic lipogenesis and gluconeogenesis [104,105].

In turn, a decrease in SCFAs-releasing bacteria may also promote lipid accumulation within the liver tissue in terms of insufficient inhibition of carbohydrate-responsive element-binding protein (ChREBP) and SREBP-1, down-regulation of the expression of glucagon-like peptide 1 (GLP-1) and peptide YY (PYY), as well as gluconeogenesis and adipogenesis stimulation [106–109]. In addition, lack of SCFAs may lead to disrupted feeding behaviours, interfering with particular hormones release and the activity of hypothalamic regions responsible for the appetite regulation. Propionate acid has been found to modulate the release of PYY and GLP-1, which affect the food intake and satiety-hunger feeling [108, 110–112]. Similar findings have been also revealed in terms of cholecystokinin, as the lack of SCFAs may contribute to its insufficient secretion, which activates afferent vagus nerve fibers and provides the feeling of fullness after the meal [113].

Moreover, there is emerging data suggesting that intestinal dysbiosis may contribute to the t2DM, dyslipidemia or hypertension development, which act as risk factors for the MASLD occurrence [114–116]. It is postulated that products of bacterial metabolism may, at least partially, contribute to the development and progression of plethora of cardiometabolic diseases. For example, choline metabolites (trimethylamine, trimethylamine N-oxide) may be transferred through the portal vein to the liver, initiating or aggravating lipid's accumulation within the liver tissue, as well as atherosclerotic changes development through low-grade inflammation burnout, cholesterol accumulation in macrophages and foam cell formation [117,118]. There are also some studies indicating that other gut microbiota-derived metabolites, branched-chain amino acids or indole derivatives, may increase the cardiovascular/cardiometabolic risk [119]. Branched-chain amino acids may mediate hepatic lipogenesis, skeletal muscle lipid accumulation and cardiac dysfunction, interfering with various molecular and metabolic pathways [120,121]. In turn, indole is transformed in the liver to the indoxyl sulfate, which has been found to impair the function of endothelium with an increase in vascular calcification and stiffness [122]. Nevertheless, exact pathogenic pathways linking bacterial metabolism derivatives with cardiometabolic diseases, including MASLD, remain unclear to date.

3.6.2. Intestinal permeability

On the other hand, an intestinal permeability, a state in which a disruption of the integrity of the gut epithelial barrier with subsequent bacterial endotoxemia occur, has been also found to be significantly more often observed among patients with schizophrenia in comparison to healthy controls. It is suspected that the dysfunction of the immune system, abovementioned gut microbiome dysbiosis or poor dietary habits may lay at the core of this state [123,124]. Interestingly, a "leaky" gut syndrome has been described as an important component in the pathogenesis of NASH and liver cirrhosis [125]. It is postulated that circulating through portal vein bacterial components or metabolites may trigger the low-grade inflammation and exacerbate oxidative stress within the hepatic tissue, thus, contributing to the lipid accumulation, NASH and liver fibrosis occurrence [126].

3.7. Applied psychopharmacotherapy

Antipsychotic medications stand at the core of the schizophrenia treatment regimen. As it was mentioned above, neuroleptics may contribute to the MASLD occurrence through affecting hunger-satiety balance – it is suggested that hyperphagia, as a consequence of antipsychotic medications use, is the main stimulus contributing to the weight gain, adipose tissue and insulin resistance development [29]. Additionally, an antagonism towards particular receptors (D2/3, α1, H1, 5-HT2c and M3) in peripheral tissues may mediate hepatic steatosis, NASH and liver fibrosis occurrence via various immunometabolic effects, including the autonomic nervous system dysfunction, hepatic insulin resistance or systemic low-grade inflammation state initiation/aggravation [127]. Furthermore, sedation and extrapyramidal symptoms as side effects of applied psychopharmacotherapy are also pointed out to limit energy expenditure. Moreover, their role in the carbohydrate and lipid metabolism disruption is unquestionable (reviewed in [128]). Thus, they have a potential to cause overweight/obesity, insulin-resistance, t2DM, dyslipidemia and other cardiometabolic diseases, which presence is linked with the MASLD occurrence. In this context, the risk of MASLD development during the antipsychotic treatment should be stratified via the potential effect of particular neuroleptics to cause these metabolic alternations (Figure 2.).

Two atypical antipsychotics, quetiapine and clozapine, have been found to stimulate glucagon secretion and inhibit GLP-1 synthesis, thus, contributing to glucose homeostasis disturbances [130,131]. Moreover, some antipsychotics impair cellular glucose uptake and affect the expression of glucose transporters (GLUT), resulting in systemic glucotoxicity [132].

In addition, clozapine, olanzapine and risperidone activate SREBPs, leading to the increased lipogenesis in hepatocytes [133]. A decreased level of lipolysis was

The risk of metabolic alternations occurrence	Weight gain	Glucose level	Total cholesterole level	TGs level
↓	Haloperidol	Lurasidone	Cariprazine	Brexipiprazole
	Ziprasidone	Amisulpride	Iloperidone	Lurasidone
	Aripiprazole	Asenapine	Ziprasidone	Cariprazine
	Lurasidone	Ziprasidone	Sertindole	Sertindole
	Cariprazine	Risperidone, Paliperidone	Lurasidone	Ziprasidone, Aripiprazole
	Amisulpride	Quetiapine	Aripiprazole	Risperidone, Paliperidone
	Brexipiprazole	Aripiprazole	Brexipiprazole	Amisulpride
	Flupenthixol	Haloperidol	Risperidone, Paliperidone	Brexipiprazole
	Asenapine	Olanzapine	Haloperidol	Haloperidol, Iloperidone
	Risperidone, Paliperidone	Cariprazine	Amisulpride	Quetiapine
	Quetiapine	Iloperidone	Quetiapine	Olanzapine
	Iloperidone	Zotepine	Olanzapine	Zotepine
	Sertindole	Clozapine	Clozapine	Clozapine
	Zotepine			
	Clozapine			
	Olanzapine			

Figure 2. The risk of metabolic alternations during the neuroleptics use [129]. The direction of arrow represents the higher risk of the metabolic repercussions occurrence.

also observed [134]. In turn, the use of olanzapine was associated with the overgrowth of adipocytes, probably also through lipogenesis enhancing [135]. Moreover, particular second-generation antipsychotics have been linked with mitochondrial dysfunction and ROS generation, which may have a role in glucose and lipid homeostasis disruption, as well as in NASH and liver fibrosis development [136,137]. There is also increasing evidence that neuroleptics may disturb body's iron homeostasis, contributing to the iron overload with possible ferroptosis of hepatocytes, hepatic steatosis aggravation and liver fibrosis occurrence [138,139].

4. Conclusions

Various factors, including socioeconomic conditions, improper dietary habits, lack of physical activity, smoking addiction issue, gut microbiota dysfunction or the use of antipsychotic medications, may act as trigger points for the MASLD development among patients with schizophrenia. Better understanding of this phenomenon and particular risk factors among mentally ill patients may help to establish a multidisciplinary healthcare programme primarily aimed at MASLD and its complications prevention, early detection and proper treatment (Figure 3.). Furthermore, next empirical studies in this field would enrich the current knowledge of the MASLD issue among mentally ill population, especially among those diagnosed with schizophrenia.

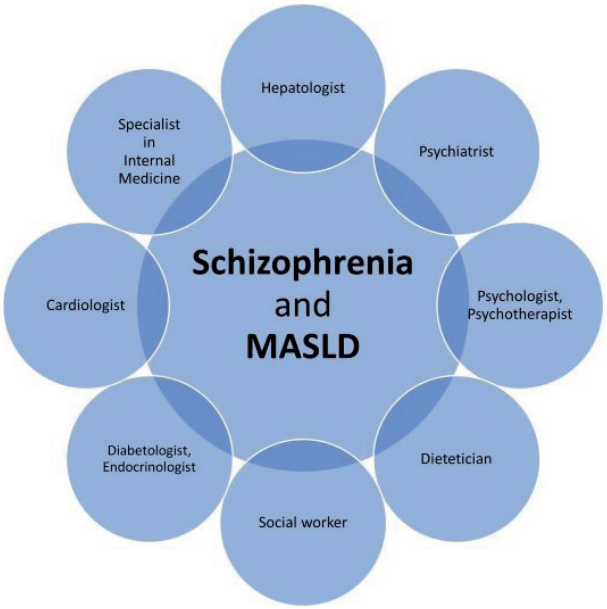

Figure 3. A proposal for the multidisciplinary healthcare programme aimed at prevention, early diagnosis and proper treatment of MASLD among patients with schizophrenia.

Conflict of interest

The authors have declared no conflict of interest.

References

1. Rinella ME, Lazarus JV, Ratziu V, Francque SM, Sanyal AJ, Kanwal F, et al. A multisociety Delphi consensus statement on new fatty liver disease nomenclature. Hepatology. 2023; 78(6): 1966-1986.
2. Riazi K, Azhari H, Charette JH, Underwood FE, King JA, Afshar EE, et al. The prevalence and incidence of NAFLD worldwide:

a systematic review and meta-analysis. Lancet Gastroenterol Hepatol. 2022; 7(9): 851-861.
3. Chan WK, Chuah KH, Rajaram RB, Lim LL, Ratnasingam J, Vethakkan SR. Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD): A State-of-the-Art Review. J Obes Metab Syndr. 2023; 32(3): 197-213.
4. Grant RK, Brindle WM, Donnelly MC, McConville PM, Stroud TG, Bandieri L, et al. Gastrointestinal and liver disease in patients with schizophrenia: A narrative review. World J Gastroenterol. 2022; 28(38): 5515-5529.
5. Baethge C, Goldbeck-Wood S, Mertens S. SANRA-a scale for the quality assessment of narrative review articles. Res Integr Peer Rev. 2019; 4: 5.
6. Cho J, Lee I, Park DH, Kwak HB, Min K. Relationships between Socioeconomic Status, Handgrip Strength, and Non-Alcoholic Fatty Liver Disease in Middle-Aged Adults. Int J Environ Res Public Health. 2021; 18(4): 1892.
7. Hakulinen C, Webb RT, Pedersen CB, Agerbo E, Mok PLH. Association Between Parental Income During Childhood and Risk of Schizophrenia Later in Life. JAMA Psychiatry. 2020; 77(1): 17-24.
8. Xu Q, Cai M, Ji Y, Ma J, Liu J, Zhao Q, et al. Identifying the mediating role of socioeconomic status on the relationship between schizophrenia and major depressive disorder: a Mendelian randomisation analysis. Schizophrenia (Heidelb). 2023; 9(1): 53.
9. Tutunchi H, Saghafi-Asl M, Ebrahimi-Mameghani M, Ostadrahimi A. Food Insecurity and Lipid Profile Abnormalities Are Associated with an Increased Risk of Nonalcoholic Fatty Liver Disease (NAFLD): A Case-Control Study. Ecol Food Nutr. 2021; 60(4): 508-524.
10. Golovaty I, Tien PC, Price JC, Sheira L, Seligman H, Weiser SD. Food Insecurity May Be an Independent Risk Factor Associated with Nonalcoholic Fatty Liver Disease among Low-Income Adults in the United States. J Nutr. 2020; 150(1): 91-98.
11. Adamowicz K, Kucharska-Mazur J. Dietary Behaviors and Metabolic Syndrome in Schizophrenia Patients. J Clin Med. 2020; 9(2): 537.
12. Smith J, Stevens H, Lake AA, Teasdale S, Giles EL. Food insecurity in adults with severe mental illness: A systematic review with meta-analysis. J Psychiatr Ment Health Nurs. 2024; 31(2): 133-151.
13. Lawrence D, Kisely S. Inequalities in healthcare provision for people with severe mental illness. J Psychopharmacol. 2010; 24(4 Suppl): 61-68.
14. Peritogiannis V, Ninou A, Samakouri M. Mortality in Schizophrenia-Spectrum Disorders: Recent Advances in Understanding and Management. Healthcare (Basel). 2022; 10(12): 2366.
15. Sadeghianpour Z, Cheraghian B, Farshchi HR, Asadi-Lari M. Non-alcoholic fatty liver disease and socioeconomic determinants in an Iranian cohort study. BMC Gastroenterol. 2023; 23(1): 350.
16. Marchesini G, Brizi M, Blanchi G, Tomassetti S, Bugianesi E, Lenzi M, et al. Nonalcoholic fatty liver disease: a feature of the metabolic syndrome. Diabetes. 2001; 50(8): 1844-1850.
17. Byrne CD, Targher G. NAFLD: a multisystem disease. J Hepatol. 2015; 62(1 Suppl): S47-S64.
18. Dongiovanni P, Valenti L. A Nutrigenomic Approach to Non-Alcoholic Fatty Liver Disease. Int J Mol Sci. 2017; 18(7): 1534.
19. Chaturvedi S, Tripathi D, Vikram NK, Madhusudhan KS, Pandey RM, Bhatia N. Dietary pattern associated with non-alcoholic fatty liver disease (NAFLD) in non-diabetic adult patients: A case control study. Clin Nutr ESPEN. 2024; 60: 247-253.
20. Paik JM, Mir S, Alqahtani SA, Younossi Y, Ong JP, Younossi ZM. Dietary Risks for Liver Mortality in NAFLD: Global Burden of Disease Data. Hepatol Commun. 2022; 6(1): 90-100.
21. Dipasquale S, Pariante CM, Dazzan P, Aguglia E, McGuire P, Mondelli V. The dietary pattern of patients with schizophrenia: a systematic review. J Psychiatr Res. 2013; 47(2): 197-207.
22. Jakobsen AS, Speyer H, Nørgaard HCB, Karlsen M, Hjorthøj C, Krogh J, et al. Dietary patterns and physical activity in people with schizophrenia and increased waist circumference. Schizophr Res. 2018; 199: 109-115.
23. Firth J, Stubbs B, Teasdale SB, Ward PB, Veronese N, Shivappa N, et al. Diet as a hot topic in psychiatry: a population-scale study of nutritional intake and inflammatory potential in severe mental illness. World Psychiatry. 2018; 17(3): 365-367.
24. Stefańska E, Wendołowicz A, Lech M, Konarzewska B, Zapolska J, Waszkiewicz N et al. Does the usual dietary intake of schizophrenia patients require supplementation with vitamins and minerals?. Psychiatria Polska. 2019; 53(3): 599-612.
25. Jahrami H, Faris MA, Ghazzawi HA, Saif Z, Habib L, Shivappa N, et al. Increased Dietary Inflammatory Index Is Associated with Schizophrenia: Results of a Case-Control Study from Bahrain. Nutrients. 2019; 11(8): 1867.
26. Cha HY, Yang SJ, Kim SW. Higher Dietary Inflammation in Patients with Schizophrenia: A Case-Control Study in Korea. Nutrients. 2021; 13(6): 2033.
27. Seeman MV. Women with Schizophrenia Have Difficulty Maintaining Healthy Diets for Themselves and Their Children: A Narrative Review. Behav Sci (Basel). 2023; 13(12): 967.
28. Misiak B, Bartoli F, Stramecki F, Samochowiec J, Lis M, Kasznia J, et al. Appetite regulating hormones in first-episode psychosis: A systematic review and meta-analysis. Neurosci Biobehav Rev. 2019; 102: 362-370.
29. Mukherjee S, Skrede S, Milbank E, Andriantsitohaina R, López M, Fernø J. Understanding the Effects of Antipsychotics on Appetite Control. Front Nutr. 2022; 8: 815456.
30. Benarroch L, Kowalchuk C, Wilson V, Teo C, Guenette M, Chintoh A, et al. Atypical antipsychotics and effects on feeding: from mice to men. Psychopharmacology (Berl). 2016; 233(14): 2629-2653.
31. Romanova IV, Derkach KV, Mikhrina AL, Sukhov IB, Mikhailova EV, Shpakov AO. The Leptin, Dopamine and Serotonin Receptors in Hypothalamic POMC-Neurons of Normal and Obese Rodents. Neurochem Res. 2018; 43(4): 821-837.
32. Rezitis J, Herzog H, Ip CK. Neuropeptide Y interaction with dopaminergic and serotonergic pathways: interlinked neurocircuits modulating hedonic eating behaviours. Prog Neuropsychopharmacol Biol Psychiatry. 2022; 113: 110449.
33. Wan XQ, Zeng F, Huang XF, Yang HQ, Wang L, Shi YC, et al. Risperidone stimulates food intake and induces body weight gain via the hypothalamic arcuate nucleus 5-HT2c receptor-NPY pathway. CNS Neurosci Ther. 2020; 26(5): 558-566.
34. Bonn M, Schmitt A, Lesch KP, Van Bockstaele EJ, Asan E. Serotonergic innervation and serotonin receptor expression of NPY-producing neurons in the rat lateral and basolateral amygdaloid nuclei. Brain Struct Funct. 2013; 218(2): 421-435.
35. Deng C, Weston-Green K, Huang XF. The role of histaminergic H1 and H3 receptors in food intake: a mechanism for atypical antipsychotic-induced weight gain?. Prog Neuropsychopharmacol Biol Psychiatry. 2010; 34(1): 1-4.
36. Khouma A, Moeini MM, Plamondon J, Richard D, Caron A, Michael NJ. Histaminergic regulation of food intake. Front Endocrinol (Lausanne). 2023; 14: 1202089.
37. Zendehdel M, Lankarani Mohajer L, Hassanpour S. Central muscarinic receptor subtypes (M1 and M3) involved in carbacol-induced hypophagia in neonatal broiler chicken. Int J Neurosci.

2020; 130(2): 204-211.
38. Mlambo R, Liu J, Wang Q, Tan S, Chen C. Receptors Involved in Mental Disorders and the Use of Clozapine, Chlorpromazine, Olanzapine, and Aripiprazole to Treat Mental Disorders. Pharmaceuticals (Basel). 2023; 16(4): 603.
39. Han M, Lian J, Su Y, Deng C. Cevimeline co-treatment attenuates olanzapine-induced metabolic disorders via modulating hepatic M3 muscarinic receptor: AMPKα signalling pathway in female rats. J Psychopharmacol. 2022; 36(2): 202-213.
40. Lebois EP, Thorn C, Edgerton JR, Popiolek M, Xi S. Muscarinic receptor subtype distribution in the central nervous system and relevance to aging and Alzheimer's disease. Neuropharmacology. 2018; 136(Pt C): 362-373.
41. Jeong JH, Lee DK, Jo YH. Cholinergic neurons in the dorsomedial hypothalamus regulate food intake. Mol Metab. 2017; 6(3): 306-312.
42. Zou S, Kumar U. Cannabinoid Receptors and the Endocannabinoid System: Signaling and Function in the Central Nervous System. Int J Mol Sci. 2018; 19(3): 833.
43. Lian J, Deng C. The effects of antipsychotics on the density of cannabinoid receptors in selected brain regions of male and female adolescent juvenile rats. Psychiatry Res. 2018; 266: 317-322.
44. Weston-Green K, Huang XF, Han M, Deng C. The effects of antipsychotics on the density of cannabinoid receptors in the dorsal vagal complex of rats: implications for olanzapine-induced weight gain. Int J Neuropsychopharmacol. 2008; 11(6): 827-835.
45. Zhao S, Lin Q, Xiong W, et al. Hyperleptinemia contributes to antipsychotic drug-associated obesity and metabolic disorders. Sci Transl Med. 2023; 15(723): eade8460.
46. Wysokiński A, Dietrich-Muszalska A. Leptin resistance in patients with chronic schizophrenia. Psychiatr i Psychol Klin - J Psychiatry Clin Psychol. 2019; 19(2): 143-148.
47. Mendoza-Herrera K, Florio AA, Moore M, Marrero A, Tamez M, Bhupathiraju SN, et al. The Leptin System and Diet: A Mini Review of the Current Evidence. Front Endocrinol (Lausanne). 2021; 12: 749050.
48. Chen CY, Goh KK, Chen CH, Lu ML. The Role of Adiponectin in the Pathogenesis of Metabolic Disturbances in Patients With Schizophrenia. Front Psychiatry. 2021; 11: 605124.
49. Zhang Q, Deng C, Huang XF. The role of ghrelin signalling in second-generation antipsychotic-induced weight gain. Psychoneuroendocrinology. 2013; 38(11): 2423-2438.
50. Yates NJ. Schizophrenia: the role of sleep and circadian rhythms in regulating dopamine and psychosis. Rev Neurosci. 2016; 27(7): 669-687.
51. Kirlioglu SS, Balcioglu YH. Chronobiology Revisited in Psychiatric Disorders: From a Translational Perspective. Psychiatry Investig. 2020; 17(8): 725-743.
52. Suttajit S, Pilakanta S. Prevalence of metabolic syndrome and its association with depression in patients with schizophrenia. Neuropsychiatr Dis Treat. 2013; 9: 941-946
53. Balcioglu SSK, Balcioglu YH, Devrim Balaban O. The association between chronotype and sleep quality, and cardiometabolic markers in patients with schizophrenia. Chronobiol Int. 2022; 39(1): 77-88.
54. Kim DH, Kim B, Han K, Kim SW. The relationship between metabolic syndrome and obstructive sleep apnea syndrome: a nationwide population-based study. Sci Rep. 2021; 11(1): 8751.
55. Ng CM, Kaur S. Environmental light exposure and mealtime regularity: Implications for human health. Chronobiol Int. 2022; 39(9): 1183-1194.
56. Merino D, Gérard AO, Van Obberghen EK, Ben Othman N, Ettore E, Giordana B, et al. Medications as a Trigger of Sleep-Related Eating Disorder: A Disproportionality Analysis. J Clin Med. 2022; 11(13): 3890.
57. Stubbs B, Firth J, Berry A, Schuch FB, Rosenbaum S, Gaughran F, et al. How much physical activity do people with schizophrenia engage in? A systematic review, comparative meta-analysis and meta-regression. Schizophr Res. 2016; 176(2-3): 431-440.
58. Andersen E, Holmen TL, Egeland J, Martinsen EW, Bigseth TT, Bang-Kittilsen G, et al. Physical activity pattern and cardiorespiratory fitness in individuals with schizophrenia compared with a population-based sample. Schizophr Res. 2018; 201: 98-104.
59. Lee SH, Kim G, Kim CE, Ryu S. Physical Activity of Patients with Chronic Schizophrenia and Related Clinical Factors. Psychiatry Investig. 2018; 15(8): 811-817.
60. Vancampfort D, De Hert M, Stubbs B, Ward PB, Rosenbaum S, Soundy A, et al. Negative symptoms are associated with lower autonomous motivation towards physical activity in people with schizophrenia. Compr Psychiatry. 2015; 56: 128-132.
61. Vancampfort D, De Hert M, Vansteenkiste M, De Herdt A, Scheewe TW, Soundy A, et al. The importance of self-determined motivation towards physical activity in patients with schizophrenia. Psychiatry Res. 2013; 210(3): 812-818.
62. Bosy-Westphal A, Hägele FA, Müller MJ. What Is the Impact of Energy Expenditure on Energy Intake?. Nutrients. 2021; 13(10): 3508.
63. Krüger K, Tirekoglou P, Weyh C. Immunological mechanisms of exercise therapy in dyslipidemia. Front Physiol. 2022; 13: 903713.
64. Linder S, Abu-Omar K, Geidl W, Messing S, Sarshar M, Reimers AK, et al. Physical inactivity in healthy, obese, and diabetic adults in Germany: An analysis of related socio-demographic variables. PLoS One. 2021; 16(2): e0246634.
65. Perrone MA, Feola A, Pieri M, Donatucci B, Salimei C, Lombardo M, et al. The Effects of Reduced Physical Activity on the Lipid Profile in Patients with High Cardiovascular Risk during COVID-19 Lockdown. Int J Environ Res Public Health. 2021; 18(16): 8858.
66. Denche-Zamorano Á, Mendoza-Muñoz DM, Barrios-Fernandez S, Perez-Corraliza C, Franco-García JM, Carlos-Vivas J, et al. Physical Activity Reduces the Risk of Developing Diabetes and Diabetes Medication Use. Healthcare (Basel). 2022; 10(12): 2479.
67. Gamage AU, Seneviratne RA. Physical inactivity, and its association with hypertension among employees in the district of Colombo. BMC Public Health. 2021; 21(1): 2186.
68. Stine JG, Soriano C, Schreibman I, Rivas G, Hummer B, Yoo E, et al. Breaking Down Barriers to Physical Activity in Patients with Nonalcoholic Fatty Liver Disease. Dig Dis Sci. 2021; 66(10): 3604-3611.
69. Zhang X, Chen K, Yin S, Qian M, Liu C. Association of leisure sedentary behavior and physical activity with the risk of nonalcoholic fatty liver disease: a two-sample Mendelian randomization study. Front Nutr. 2023; 10: 1158810.
70. Saqib ZA, Dai J, Menhas R, Mahmood S, Karim M, Sang X, et al. Physical Activity is a Medicine for Non-Communicable Diseases: A Survey Study Regarding the Perception of Physical Activity Impact on Health Wellbeing. Risk Manag Healthc Policy. 2020; 13: 2949-2962.
71. Barrón-Cabrera E, Soria-Rodríguez R, Amador-Lara F, Martínez-López E. Physical Activity Protocols in Non-Alcoholic Fatty Liver Disease Management: A Systematic Review of Randomized Clinical Trials and Animal Models. Healthcare (Basel). 2023; 11(14): 1992.

72. Akhavan Rezayat A, Dadgar Moghadam M, Ghasemi Nour M, et al. Association between smoking and non-alcoholic fatty liver disease: A systematic review and meta-analysis. SAGE Open Med. 2018; 6: 2050312117745223.
73. Ou H, Fu Y, Liao W, Zheng C, Wu X. Association between Smoking and Liver Fibrosis among Patients with Nonalcoholic Fatty Liver Disease. Can J Gastroenterol Hepatol. 2019; 2019: 6028952.
74. Deng X, Wang P, Yuan H. Epidemiology, risk factors across the spectrum of age-related metabolic diseases. J Trace Elem Med Biol. 2020; 61: 126497.
75. Śliwińska-Mossoń M, Milnerowicz H. The impact of smoking on the development of diabetes and its complications. Diab Vasc Dis Res. 2017; 14(4): 265-276.
76. Song W, Lin GN, Yu S, Zhao M. Genome-wide identification of the shared genetic basis of cannabis and cigarette smoking and schizophrenia implicates NCAM1 and neuronal abnormality. Psychiatry Res. 2022; 310: 114453.
77. Rødevand L, Rahman Z, Hindley GFL, Smeland OB, Frei O, Tekin TF, et al. Characterizing the Shared Genetic Underpinnings of Schizophrenia and Cardiovascular Disease Risk Factors. Am J Psychiatry. 2023; 180(11): 815-826.
78. van der Plas A, Antunes M, Pouly S, de La Bourdonnaye G, Hankins M, Heremans A. Meta-analysis of the effects of smoking and smoking cessation on triglyceride levels. Toxicol Rep. 2023; 10: 367-375.
79. Moradinazar M, Pasdar Y, Najafi F, Shahsavari S, Shakiba E, Hamzeh B, et al. Association between dyslipidemia and blood lipids concentration with smoking habits in the Kurdish population of Iran. BMC Public Health. 2020; 20(1): 673.
80. Kumar N, Shaikh SN, Iqbal A, Memon FR, Hussain T, Rafique S. Correlation between Smoking and Dyslipidemia in Elderly Males: An Analytical Cross-Sectional Study. Pakistan J Med Heal Sci. 2022; 16(7): 745–747.
81. Hussein Ali E, Hussein Abod Al-Khafaji K, Hassan Abood A. Effect of Smoking on Low-Density Lipoproteins Level in Human. Arch Razi Inst. 2022; 77(5): 1971-1974.
82. Wagai GA, Jeelani U, Beg MA, Romshoo GJ. Relationship between hypertension and smoking: A preliminary study in South Kashmiri population of J&K. J Family Med Prim Care. 2023; 12(5): 958-961.
83. Drummond CA, Brewster PS, He W, Ren K, Xie Y, Tuttle KR, et al. Cigarette smoking and cardio-renal events in patients with atherosclerotic renal artery stenosis. PLoS One. 2017; 12(3): e0173562.
84. Doonan RJ, Hausvater A, Scallan C, Mikhailidis DP, Pilote L, Daskalopoulou SS. The effect of smoking on arterial stiffness. Hypertens Res. 2010; 33(5): 398-410.
85. Yuan H, Shyy JY, Martins-Green M. Second-hand smoke stimulates lipid accumulation in the liver by modulating AMPK and SREBP-1. J Hepatol. 2009; 51(3): 535-547.
86. Mumtaz H, Hameed M, Sangah AB, Zubair A, Hasan M. Association between smoking and non-alcoholic fatty liver disease in Southeast Asia. Front Public Health. 2022; 10: 1008878.
87. Soeda J, Morgan M, McKee C, Mouralidarane A, Lin C, Roskams T, et al. Nicotine induces fibrogenic changes in human liver via nicotinic acetylcholine receptors expressed on hepatic stellate cells. Biochem Biophys Res Commun. 2012; 417(1): 17-22.
88. Ahmadkhaniha R, Yousefian F, Rastkari N. Impact of smoking on oxidant/antioxidant status and oxidative stress index levels in serum of the university students. J Environ Health Sci Eng. 2021; 19(1): 1043-1046.
89. Elisia I, Lam V, Cho B, Hay M, Li MY, Yeung M, et al. The effect of smoking on chronic inflammation, immune function and blood cell composition. Sci Rep. 2020; 10(1): 19480.
90. Fouda S, Khan A, Chan SMH, Mahzari A, Zhou X, Qin CX, et al. Exposure to cigarette smoke precipitates simple hepatosteatosis to NASH in high-fat diet fed mice by inducing oxidative stress. Clin Sci (Lond). 2021; 135(17): 2103-2119.
91. Dickerson F, Schroeder J, Katsafanas E, Khushalani S, Origoni AE, Savage C, et al. Cigarette Smoking by Patients With Serious Mental Illness, 1999-2016: An Increasing Disparity. Psychiatr Serv. 2018; 69(2): 147-153.
92. Ding JB, Hu K. Cigarette Smoking and Schizophrenia: Etiology, Clinical, Pharmacological, and Treatment Implications. Schizophr Res Treatment. 2021; 2021: 7698030.
93. Ward HB, Lawson MT, Addington J, Bearden CE, Cadenhead KS, Cannon TD, et al. Tobacco use and psychosis risk in persons at clinical high risk. Early Interv Psychiatry. 2019; 13(5): 1173-1181.
94. Scott JG, Matuschka L, Niemelä S, Miettunen J, Emmerson B, Mustonen A. Evidence of a Causal Relationship Between Smoking Tobacco and Schizophrenia Spectrum Disorders. Front Psychiatry. 2018; 9: 607.
95. Kendler KS, Lönn SL, Sundquist J, Sundquist K. Smoking and schizophrenia in population cohorts of Swedish women and men: a prospective co-relative control study. Am J Psychiatry. 2015; 172(11): 1092-1100.
96. Maideen NMP. Tobacco smoking and its drug interactions with comedications involving CYP and UGT enzymes and nicotine. World J Pharmacol. 2019; 8(2): 14-25.
97. Wysokiński A. Możliwości leczenia schizofrenii lekoopornej z objawami pozytywnymi. Psychiatria po Dyplomie. 2022; 13(2): 28-32.
98. Carli M, Kolachalam S, Longoni B, Pintaudi A, Baldini M, Aringhieri S, et al. Atypical Antipsychotics and Metabolic Syndrome: From Molecular Mechanisms to Clinical Differences. Pharmaceuticals (Basel). 2021; 14(3): 238.
99. Alonso Y, Miralles C, Algora MJ, Valiente-Pallejà A, Sánchez-Gistau V, Muntané G, et al. Risk factors for metabolic syndrome in individuals with recent-onset psychosis at disease onset and after 1-year follow-up. Sci Rep. 2022; 12(1): 11386.
100. Wichniak A, Dudek D, Heitzman J, Kapłon-Cieślicka A, Mamcarz A, Samochowiec J, et al. Metabolic risk reduction in patients with schizophrenia treated with antipsychotics: recommendations of the Polish Psychiatric Association. Redukcja ryzyka metabolicznego u chorych na schizofrenię przyjmujących leki przeciwpsychotyczne – zalecenia Polskiego Towarzystwa Psychiatrycznego. Psychiatr Pol. 2019; 53(6): 1191-1218.
101. Li Z, Qing Y, Cui G, Li M, Liu T, Zeng Y, et al. Shotgun metagenomics reveals abnormal short-chain fatty acid-producing bacteria and glucose and lipid metabolism of the gut microbiota in patients with schizophrenia. Schizophr Res. 2023; 255: 59-66.
102. Li Z, Tao X, Wang D, Pu J, Liu Y, Gui S, et al. Alterations of the gut microbiota in patients with schizophrenia. Front Psychiatry. 2024; 15: 1366311.
103. Szeligowski T, Yun AL, Lennox BR, Burnet PWJ. The Gut Microbiome and Schizophrenia: The Current State of the Field and Clinical Applications. Front Psychiatry. 2020; 11: 156.
104. Maczewsky J, Kaiser J, Gresch A, Gerst F, Düfer M, Krippeit-Drews P, et al. GR5 Activation Promotes Stimulus-Secretion Coupling of Pancreatic β-Cells via a PKA-Dependent Pathway. Diabetes. 2019; 68(2): 324-336.
105. Han X, Cui ZY, Song J, Piao HQ, Lian LH, Hou LS, et al. Acanthoic acid modulates lipogenesis in nonalcoholic fatty liver disease via FXR/LXRs-dependent manner. Chem Biol Interact. 2019; 311: 108794.
106. Xiong RG, Zhou DD, Wu SX, Huang SY, Saimaiti A, Yang ZJ,

et al. Health Benefits and Side Effects of Short-Chain Fatty Acids. Foods. 2022; 11(18): 2863.
107. Park JH, Kotani T, Konno T, Setiawan J, Kitamura Y, Imada S, et al. Promotion of Intestinal Epithelial Cell Turnover by Commensal Bacteria: Role of Short-Chain Fatty Acids. PLoS One. 2016; 11(5): e0156334.
108. Zhang JM, Sun YS, Zhao LQ, Chen TT, Fan MN, Jiao HC, et al. SCFAs-Induced GLP-1 Secretion Links the Regulation of Gut Microbiome on Hepatic Lipogenesis in Chickens. Front Microbiol. 2019; 10: 2176.
109. Fang J, Yu CH, Li XJ, Yao JM, Fang ZY, Yoon SH, et al. Gut dysbiosis in nonalcoholic fatty liver disease: pathogenesis, diagnosis, and therapeutic implications. Front Cell Infect Microbiol. 2022; 12: 997018.
110. Psichas A, Sleeth ML, Murphy KG, Brooks L, Bewick GA, Hanyaloglu AC, et al. The short chain fatty acid propionate stimulates GLP-1 and PYY secretion via free fatty acid receptor 2 in rodents. Int J Obes (Lond). 2015; 39(3): 424-429.
111. Astrup A. Reflections on the discovery GLP-1 as a satiety hormone: Implications for obesity therapy and future directions. Eur J Clin Nutr. 2024; 78(7): 551-556.
112. Batterham RL, Bloom SR. The gut hormone peptide YY regulates appetite. Ann N Y Acad Sci. 2003;994:162-168.
113. Mansuy-Aubert V, Ravussin Y. Short chain fatty acids: the messengers from down below. Front Neurosci. 2023; 17: 1197759.
114. Iatcu CO, Steen A, Covasa M. Gut Microbiota and Complications of Type-2 Diabetes. Nutrients. 2021; 14(1): 166.
115. Yang Z, Wang Q, Liu Y, Wang L, Ge Z, Li Z, et al. Gut microbiota and hypertension: association, mechanisms and treatment. Clin Exp Hypertens. 2023; 45(1): 2195135.
116. Lei L, Zhao N, Zhang L, Chen J, Liu X, Piao S. Gut microbiota is a potential goalkeeper of dyslipidemia. Front Endocrinol (Lausanne). 2022; 13: 950826.
117. Kasahara K, Rey FE. The emerging role of gut microbial metabolism on cardiovascular disease. Curr Opin Microbiol. 2019; 50: 64-70.
118. Wang Z, Klipfell E, Bennett BJ, Koeth R, Levison BS, Dugar B, et al. Gut flora metabolism of phosphatidylcholine promotes cardiovascular disease. Nature. 2011; 472(7341): 57-63.
119. Sanchez-Gimenez R, Ahmed-Khodja W, Molina Y, Peiró OM, Bonet G, Carrasquer A, et al. Gut Microbiota-Derived Metabolites and Cardiovascular Disease Risk: A Systematic Review of Prospective Cohort Studies. Nutrients. 2022; 14(13): 2654.
120. de la O V, Zazpe I, Ruiz-Canela M. Effect of branched-chain amino acid supplementation, dietary intake and circulating levels in cardiometabolic diseases: an updated review. Curr Opin Clin Nutr Metab Care. 2020; 23(1): 35-50.
121. White PJ, Newgard CB. Branched-chain amino acids in disease. Science. 2019; 363(6427): 582-583.
122. Lano G, Burtey S, Sallée M. Indoxyl Sulfate, a Uremic Endotheliotoxin. Toxins (Basel). 2020; 12(4): 229.
123. Gokulakrishnan K, Nikhil J, VS S, Holla B, Thirumoorthy C, Sandhya N, et al. Altered Intestinal Permeability Biomarkers in Schizophrenia: A Possible Link with Subclinical Inflammation. Ann Neurosci. 2022; 29(2-3): 151-158.
124. Ishida I, Ogura J, Aizawa E, Ota M, Hidese S, Yomogida Y, et al. Gut permeability and its clinical relevance in schizophrenia. Neuropsychopharmacol Rep. 2022; 42(1): 70-76.
125. Fukui H. Increased Intestinal Permeability and Decreased Barrier Function: Does It Really Influence the Risk of Inflammation?. Inflamm Intest Dis. 2016; 1(3): 135-145.
126. Kessoku T, Kobayashi T, Tanaka K, Yamamoto A, Takahashi K, Iwaki M, et al. The Role of Leaky Gut in Nonalcoholic Fatty Liver Disease: A Novel Therapeutic Target. Int J Mol Sci. 2021; 22(15): 8161
127. Gangopadhyay A, Ibrahim R, Theberge K, May M, Houseknecht KL. Non-alcoholic fatty liver disease (NAFLD) and mental illness: Mechanisms linking mood, metabolism and medicines. Front Neurosci. 2022; 16: 1042442.
128. Rogalski JK, Subdys A, Gawlik-Kotelnicka OE. The development of the Metabolic-associated Fatty Liver Disease during pharmacotherapy of mental disorders - a review. Curr Probl Psychiatry. 2022; 23(3): 128-143.
129. Pillinger T, McCutcheon RA, Vano L, Mizuno Y, Arumuham A, Hindley G, et al. Comparative effects of 18 antipsychotics on metabolic function in patients with schizophrenia, predictors of metabolic dysregulation, and association with psychopathology: a systematic review and network meta-analysis. Lancet Psychiatry. 2020; 7(1): 64-77.
130. Carli M, Kolachalam S, Longoni B, Pintaudi A, Baldini M, Aringhieri S, et al. Atypical Antipsychotics and Metabolic Syndrome: From Molecular Mechanisms to Clinical Differences. Pharmaceuticals (Basel). 2021; 14(3) :238.
131. Smith GC, Vickers MH, Cognard E, Shepherd PR. Clozapine and quetiapine acutely reduce glucagon-like peptide-1 production and increase glucagon release in obese rats: implications for glucose metabolism and food choice behaviour. Schizophr Res. 2009; 115(1): 30-40.
132. Babkin P, George Thompson AM, Iancu CV, Walters DE, Choe JY. Antipsychotics inhibit glucose transport: Determination of olanzapine binding site in Staphylococcus epidermidis glucose/H(+) symporter. FEBS Open Bio. 2015; 5: 335-340.
133. Cai HL, Tan QY, Jiang P, Dang RL, Xue Y, Tang MM, et al. A potential mechanism underlying atypical antipsychotics-induced lipid disturbances. Transl Psychiatry. 2015; 5(10): e661.
134. Sarsenbayeva A, Marques-Santos CM, Thombare K, Di Nunzio G, Almby KE, Lundqvist M, et al. Effects of second-generation antipsychotics on human subcutaneous adipose tissue metabolism. Psychoneuroendocrinology. 2019; 110: 104445.
135. Matsuo T, Omori Y, Tomita T, Sadzuka Y. Olanzapine enhances adipogenesis and suppresses lipolysis in 3T3L1 adipocytes under lowglucose and weak differentiation/maturation conditions. Exp Ther Med. 2022; 24(5): 647.
136. Todorović Vukotić N, Đorđević J, Pejić S, Đorđević N, Pajović SB. Antidepressants- and antipsychotics-induced hepatotoxicity. Arch Toxicol. 2021; 95(3): 767-789.
137. Ramanathan R, Ali AH, Ibdah JA. Mitochondrial Dysfunction Plays Central Role in Nonalcoholic Fatty Liver Disease. Int J Mol Sci. 2022; 23(13): 7280.
138. May M, Barlow D, Ibrahim R, Houseknecht KL. Mechanisms Underlying Antipsychotic-Induced NAFLD and Iron Dysregulation: A Multi-Omic Approach. Biomedicines. 2022; 10(6): 1225.
139. Cheng Z, Chu H, Zhu Q, Yang L. Ferroptosis in non-alcoholic liver disease: Molecular mechanisms and therapeutic implications. Front Nutr. 2023; 10: 1090338.

Corresponding author

Jakub Rogalski
e-mail: jakub.rogalski1@stud.umed.lodz.pl
University Clinical Hospital No. 2, Medical University of Lodz, Poland

Otrzymano: 23.07.2024
Zrecenzowano: 25.09.2024
Przyjęto do publikacji: 28.11.2024