Are metabolic disorders part of a severe mental illness? Historical and current perspective

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Abstract

Introduction and purpose: People with severe mental illness (SMI) live shorter lives than general population. The main cause of mortality in this group is not psychiatric tax diseases, but comorbidities, which are mainly classified as diseases associated with metabolic disorders, such as: obesity, metabolic syndrome (MetS), diabetes type 2, CVDs, coronary artery disease (CAD), cerebrovascular disease. The aim of this review was to identify the factor relating to relationship between metabolic disorders and mental illness.

Description of the state of knowledge: People with SMI are characterized by a higher level of adipose tissue in the visceral region (abdominal obesity) compared to the control group, without any mental disorders. Current studies indicate, that persons with SMI have a genetic tendency of to accumulate adipose tissue in the abdominal area. They are also characterized by higher level of body mass index (BMI), overweight or obesity, than general population. This is mostly caused by
lifestyle and specific pharmacological treatment using antipsychotic drug, especially atypical (second generation), which cause weight gain and disturbed carbohydrate metabolism. The fact is, that carbohydrate metabolic disorders were observed in patients with schizophrenia before the first neuroleptic was discovered. Last studies indicated that overweight, obesity may has the same genetic loci as SMI.

**Summary:** SMI seems to be part of a metabolic disorder. This relationship mostly results from the lifestyle, pharmacological treatment, and also the genetic factors. It should be taken into account that the treatment of SMI always requires monitoring of metabolic indicators. Additionally, motivating patients to a healthy lifestyle and physical activity should be the standard of treatment.

**Key words:** metabolic syndrome, diabetes type 2, obesity, severe mental illness

**Introduction purpose**

Mental illness, due to its long-term character, contributes to the decline in the quality of life [1]. People suffering from severe mental illness (SMI) often experience cognitive difficulties such as: weakened range of attention and memory, psychomotor skills, problems with decision making and reasoning [2]. This often makes it difficult for them to function in everyday life as well as at work. It happens that they are forced to give up their professional career. Often the disease is a barrier to acquiring appropriate professional qualifications and thus taking up employment in the open market. Most psychiatric patients experience financial problems [3]. This often affects the quality of family and interpersonal relationships. As a result, they withdraw from the sphere of social life [4].

Somatic factors also affect the deterioration of quality of life of a person with mental illness. Patients who have experienced psychotic disorders (e.g. schizophrenia) and mood disorders (affective disorder, depression), statistically live shorter than the population without
mental disorders [5]. Viron et al. showed that patients with psychotic and mood disorders live an average of 25 years shorter than the rest of population. According to researches the main cause of death in these groups are complications of cardiovascular diseases (CVDs) [6].

The most common somatic disorders and diseases occurring in people suffering from mental disorders include: obesity, metabolic syndrome (MetS), diabetes type 2, CVDs, coronary artery disease (CAD), cerebrovascular disease, viral diseases such as: human immunodeficiency virus (HIV), jaundice, pneumonia, chronic obstructive pulmonary disease (COPD), cancer, dental diseases [7].

The most important factors leading to health deterioration of people with SMI are: difficulty in accessing adequate medical care - due to persistent symptoms of the underlying disease (e.g. positive and negative), unhygienic lifestyle: low physical activity, inadequate diet, nicotine and addiction to psychoactive substances, usage of neuroleptic drugs - adversely affecting, inter alia, lipid and carbohydrate metabolism and weight gain [8].

Another factor contributing to the deterioration of health of the mentioned above group is the fact that they receive a lower standard of primary care. Often, the comorbid somatic disorders of persons with mental illness are not properly treated or not treated at all by general practitioners and specialist doctors [9-10].

The aim of this study is to find an answer to the question of whether metabolic disorders are part of the SMI picture. PubMed/MEDLINE and Google Scholar data bases were searched for publications describing relationship between metabolic disorders (overweight, obesity, dyslipidemia, carbohydrate metabolism disorders and diabetes) and SMI (schizophrenia and schizoaffective disorder, major depression and bipolar disorder).

**Description of the state of knowledge**

**Metabolic disorders and SMI**

**Overweight and obesity**

Numerous clinical studies have shown that people suffering from mental disorders are more prone to overweight and obesity, as well as diseases resulting from them, such as: type 2 diabetes, cardiovascular diseases, metabolic syndrome [11], [12]. The first scientific reports in
this regard came from studies conducted on a group of people suffering from schizophrenia. Already at the beginning of the 20th century, long before the appearance of the first neuroleptics, it was observed that people suffering from schizophrenia exhibit more metabolic disorders than people without mental disorders. At the end of the 20th century, a number of studies were carried out in which metabolic disorders in mentally ill people were mainly associated with the effects of neuroleptics [13].

For example, Allison et al. used the data form National Health Interview Survey (NHIS), (N = 80,130 nonschizophrenic and 150 schizophrenic individuals) showed that overweight and obesity as measured by the body mass index (BMI) occurred more often in people with schizophrenia than in the general population, especially in women. The gains in body weight were primarily related [14].

Current research indicates that not only antipsychotic drugs cause metabolic disorders in person with mental illness [15]. Metallize of 136 study, showed that drug naïve patients of schizophrenia have a higher level of adipose tissue in the visceral region (abdominal obesity) compared to the control group, without any mental disorders [16]. This indicates the genetic tendency of people suffering from schizophrenia to accumulate adipose tissue in the abdominal area. Currently, it is assumed that metabolic disorders are a part of the picture of schizophrenia [17].

The tendency to increase body weight also occurs in the group of people suffering from mood disorders. Research by Maina et al. conducted in a group of 76 patients with bipolar disorder who had not been treated pharmacologically so far, showed that compared to a control group of people suffering from obsessive-compulsive disorder (also untreated), patients with bipolar disorders are more likely to be overweight and obese. Interestingly, the depressive episode was much more common in overweight people than in non-overweight people [18].

The above conclusions imply the relationship between overweight and obesity and depressive disorders. In the research of Lin et al. from 2014, a positive correlation was found between obesity and depression. This means that symptoms of depression increase with increasing body weight [19]. Similar relationships were shown earlier. Roberts et al. study conducted in a group of 2,123 people over 50 years of age showed, that after 5 years of obesity, the risk of developing depressive disorders increased. It has been noted that obesity may contribute to depression, but depression does not increase the risk of obesity [20].
A slightly different picture emerges from the long-term studies by Marmorstein et al. from 2014, conducted in a group of teenagers from early youth to late adolescence. It has been shown that young women who experienced a depressive episode in early adolescence were prone to obesity in late adolescence. As the researchers themselves say, the relationship between depression and obesity requires further detailed research [21].

Undoubtedly, the prevalence of overweight and obesity is greater in the group of people suffering from psychotic and mood disorders, especially in SMI. The following factors are associated with the development of overweight and obesity in this group of people with SMI: unhygienic and inactive lifestyle, antipsychotic drugs play a large role, the effects of which will be discussed in detail later [22].

Recent studies show that genetic factors play an important role in the development of overweight and obesity in the group of people with SMI [23]. Tyrrell et al. using data from the UK Biobank, tested 48,791 individuals with depression and 291,995 controls looking for links between BMI and depression. The responses have been explored as to whether the relationship between BMI and depression is a result of the metabolic consequences of obesity. They showed that obesity increased the incidence of depression, especially in women, and it was not due to the metabolic consequences of an increased BMI. According to researchers, genetic predisposition seems to be important in this respect [24].

Dyslipidemia

Lipid metabolism disorders, also known as dyslipidemia, are manifested by an increased concentration of lipids and lipoproteins in plasma. In clinical practice, its two forms are most often diagnosed: hypercholesterolaemia and atherogenic dyslipidemia. Hypercholesterolemia is diagnosed when the concentration of LDL cholesterol in the blood exceeds 115 mg / dl or the total cholesterol (TC) exceeds 190 mg / dl. In contrast, atherogenic dyslipidemia, otherwise known as the lipid triad, is related with coexistence of increased triglycerides (TG > 150mg / dl), low HDL levels (HDL <40mg / dl in men and 45mg / dl in women) and abnormal LDL cholesterol levels [25-26].

It is known that the increase in lipids is associated with excess body weight and is one of the main factors in the development of cardiovascular diseases. These conditions are the leading
cause of death for sufferers for mental disorders. In psychiatrically treated patients, the increase in serum lipids is a consequence of both lifestyle and a tendency to overweight and obesity as well as a consequence of long-term usage of antipsychotic drugs [27].

Wirshing et al. Long-term studies carried out in a group of 215 psychiatric patients before and after the initiation of treatment with antipsychotic drugs, i.e. olanzapine, clozapine, risperidone and haloperidol, showed statistically significant differences between the effects of individual drugs on the lipid profile of patients. The highest increase in triglyceride levels was noted after the use of olanzapine and clozapine [28].

However, it is disturbing that psychiatric patients are often untreated due to dyslipidemia. It has been shown that only 12% of adults with SMI and diagnosed dyslipidemia received treatment in this area [29-30].

**Carbohydrate metabolism disorders**

People with SMI tend to be overweight and obese. These diseases contribute to the formation of disturbances in carbohydrate metabolism, which in turn leads to the formation of insulin resistance and, as a result, type 2 diabetes. Many researchers indicate that the prevalence of diabetes in the group of people with mental disorders is higher than in the general population [31].

Irregularities in carbohydrate metabolism are observed three times more often in SMI patients than in the general population [32]. The relationship between schizophrenia and hyperglycemia was observed at the beginning of the 20th century. The first publication by Kooy appeared in 1919, much earlier than the first neuroleptics were used [33]. Subsequent publications from 1921 (Drury and Farron-Ridge), 1922 (Lorenz), 1924 (Barrett & Serre), 1926 (Kasanin), 1944 (Freeman et al), 1945 (Braceland et al) also indicated the relationship between mental disorders and impaired glucose tolerance [34].

This phenomenon was increasingly observed with the use of the first neuroleptics in 1952. It was then that the effect of chlorpromazine administered to 38 patients with psychotic diseases was described for the first time [35]. This has radically changed the effectiveness of the treatment of mental disorders. However, it was quickly noticed that, in addition to significantly improving
the quality of life, neuroleptics led to adverse metabolic changes. As early as in 1954, Dobkin et al. published the results of an experiment in which 7 healthy volunteers were administered chlorpromazine. It was noticed that in these people the level of glucose in blood significantly increased [36]. It is now known that some antipsychotic drugs disturb the carbohydrate metabolism, which in turn contributes to the development of type 2 diabetes. [37].

Both diabetes type 2 and schizophrenia are disorders with a complex, multi-gene and multi-factor inheritance model. Glucose intolerance was noted in patients with the first episode of the disease who had not yet started pharmacological treatment. Abnormal glucose values were noted in family members of patients, it is possible that the same genetic loci are responsible for the tendency to manifest these diseases [38].

Suvisaari et al. conducted research among 8,028 people suffering from schizophrenia and other psychotic and non-psychotic diseases. Researchers point out that type 2 diabetes is one of the main health problems of people suffering from psychotic disorders, and the fact of taking antipsychotic drugs increases the risk of developing type 2 diabetes. The prevalence rate of type 2 diabetes was as follows: 22% among people with schizophrenia, 13.4 % among people with psychoses without affective disorders, 3.4% with psychotic disorders of an affective nature, 6.1% in the group of people without psychotic disorders [39]. Hackinger et al. identified 29 genes associated with diabetes type 2 and schizophrenia. They postulated, that both disorders have the same genetic loci [40].

Calkin et al. maintain that type 2 diabetes is three times more common in patients with bipolar disorder than in those without bipolar disorder, becoming one of the leading causes of death in this group [41].

Another issue is the relationship between type 2 diabetes and depression. Carnethon et al. in long-term studies have shown that the severity of depression symptoms is associated with an increased risk of developing type 2 diabetes. The risk of developing hyperglycemia is 37% higher in people suffering from depression than in people without depressive disorders [42]. It has been shown that depressive disorders have a negative impact on glucose metabolism through increased secretion of hormones that control glucose transport disorders and increased activity of inflammatory factors, which may lead to the phenomenon of insulin resistance [43]. It should be
added that people suffering from depressive disorders tend to lead an unhygienic lifestyle that may lead to the development of chronic diseases [44].

**Metabolic syndrome**

In recent years, there have been many scientific publications on the subject of metabolic disorders in people with mental illness. This is undoubtedly related to the growing awareness that some antipsychotic drugs contribute to weight gain in patients suffering from mental disorders, which in turn leads to the development of many interrelated somatic factors such as: abdominal obesity, impaired glucose tolerance, hypertriglyceridemia and hypertension [45-46].

MetS is more common in people with mental disorders. It is assumed that in the group of people with SMI about three times more often than in the population of people without SMI [47].

The highest incidence rate is noted in patients with schizophrenia, schizoaffective disorders, then in people with bipolar disorder and also in people with depression. Knowledge of MetS prevalence in other psychiatric diseases is very low and requires further research [49].

It is assumed that the prevalence of individual MetS components in the group of people with schizophrenia is obesity (45% -55%), hypertension (19% -58%), type 2 diabetes (10% -15%), and lipid disorders (25% -69%) [50]. In the meta-analysis of Malhotra et al. it has been shown that the incidence of MetS in the group of patients treated for schizophrenia ranges from 11% to 69%, and in those not taking antipsychotic drugs from 4% to 26% [51].

MetS prevalence in affective disorder ranges from 16.7% up to 67%, depending on various studies [52]. There are fewer publications in the presence of MetS in depression. Extensive German study in the group of 1,673 people with depression showed that the prevalence rate of MetS was 2.4 times higher than in the control group and amounted to 41% [53].

**Summary**

SMI are linked with metabolic disorders. Cause of this association is mostly determinated by pharmacological treatment, especially using atypical antipsychotics, which lead to weight gain and induced proinflammatory process which can lead to some metabolic disorders like: obesity, diabetes type 2, CVDs. On the other hand, metabolic disorders, are observed in persons with SMI
before starting treatment. It is assumed, that some persons with SMI can have genetic predisposition to overweight and obesity.

The scientists' reports described above imply that there is a relationship between depression, mental disorders and type 2 diabetes, and this fact should be taken into account in the treatment of these diseases.

References
1. Choo CC, Chew PKH, Ho CS, Ho RC. Quality of Life in Patients With a Major Mental Disorder in Singapore. Front Psychiatry. 2019;9:727. DOI http://dx.doi.org/10.3389/fpsyt.2018.00727
2. Etkin A, Gyurak A, O'Hara R. A neurobiological approach to the cognitive deficits of psychiatric disorders. Dialogues Clin Neurosci. 2013;15(4):419-429.
3. Richardson T, Elliott P, Roberts R, Jansen M. A Longitudinal Study of Financial Difficulties and Mental Health in a National Sample of British Undergraduate Students. Community Ment Health J. 2017;53(3):344-352. DOI http://dx.doi.org/10.1007/s10597-016-0052-0
4. Luciano A, Meara E. Employment status of people with mental illness: national survey data from 2009 and 2010. Psychiatr Serv. 2014;65(10):1201-1209. DOI http://dx.doi.org/10.1176/appi.ps.201300335
5. Lomholt LH, Andersen DV, Sejrsgaard-Jacobsen C, et al. Mortality rate trends in patients diagnosed with schizophrenia or bipolar disorder: a nationwide study with 20 years of follow-up. Int J Bipolar Disord. 2019;7(1):6. DOI http://dx.doi.org/10.1186/s40345-018-0140-x
6. Viron MJ, Stern TA. The impact of serious mental illness on health and healthcare. Psychosomatics. 2010;51(6):458-65. DOI http://dx.doi.org/10.1176/appi.psy.51.6.458
7. De Hert M, Correll ChU, Bobes J, Cetkovich-Bakmas M, Cohen D, et al. Physical illness in patients with severe mental disorders. I. Prevalence, impact of medications and disparities in health care, Wolrd Psychiatry 2011, 52-77. DOI http://dx.doi.org/10.1002/j.2051-5545.2011.tb00014.x
8. Heald A, Pendlebury J, Anderson S, et al. Lifestyle factors and the metabolic syndrome in Schizophrenia: a cross-sectional study. Ann Gen Psychiatry. 2017;16:12. DOI http://dx.doi.org/10.1186/s12991-017-0134-6
9. Lake J, Turner MS. Urgent Need for Improved Mental Health Care and a More Collaborative Model of Care. Perm J. 2017;21:17-024. DOI http://dx.doi.org/10.7812/TPP/17-024
10. Lawrence D, Kisely S. Inequalities in healthcare provision for people with severe mental illness. J Psychiatr Pract. 2010;24(4 Suppl):61-68. DOI http://dx.doi.org/10.7812/TPP/17-024
11. Holt RIG. The Management of Obesity in People with Severe Mental Illness: An Unresolved Conundrum. Psychother Psychosom. 2019;88(6):327-332. DOI http://dx.doi.org/10.1159/000503835
12. De Hert M, Detraux J, Vancampfort D. The intriguing relationship between coronary heart disease and mental disorders. Dialogues Clin Neurosci. 2018;20(1):31-40. DOI http://dx.doi.org/10.31887/DCNS.2018.20.1/mdehert
13. Kohen D. Diabetes mellitus and schizophrenia: historical perspective. BJP 2004; 184: 64–66.
14. Allison D, Fontaine K, Moonseong H et al. The distribution of body mass index among individuals with and without schizophrenia. J Clin Psychiatry 1999; 60: 215- 220.
15. Freyberg Z, Aslanoglou D, Shah R, Ballon JS. Intrinsic and Antipsychotic Drug-Induced Metabolic Dysfunction in Schizophrenia. Front Neurosci. 2017;11:432. DOI http://dx.doi.org/10.3389/fnins.2017.00432
16. Vancampfort D, Wampers M, Mitchell AJ, et al. A meta-analysis of cardio-metabolic abnormalities in drug naïve, first-episode and multi-episode patients with schizophrenia versus general population controls. World Psychiatry. 2013;12(3):240-250. DOI http://dx.doi.org/10.1002/wps.20069
17. Chen J, Tan L, Long Z, Wang L, Hu L, Yang D. Drug-naive patients with schizophrenia have metabolic disorders that are not associated with polymorphisms in the LEP (-2548G/A) and 5-HTR2C (-759C/T) genes. Int J Clin Exp Pathol. 2018;11(12):5969-5980.
18. Maina G, Salvi V, Vitalucci A. Prevalence and correlates of overweight in drug-naïve patients with bipolar disorder. J Affect Disord. 2008;110:149–155.
19. Lin CH, Chen CC, Wong J, McIntyre RS. Both body weight and BMI predicts improvement in symptom and functioning for patients with major depressive disorder. J Affect Disord. 2014;161:123-6. DOI http://dx.doi.org/10.1016/j.jad.2014.02.039.
20. Roberts RE, Deleger S, Strawbridge WJ, Kaplan GA. Prospective association between obesity and depression: evidence from the Alameda County Study. Int J Obes Relat Metab Disord. 2003; 27(4):514-21. DOI http://dx.doi.org/10.1038/sj.ijo.0802204.

21. Marmorstein NR, Iacono WG, Legrand L. Obesity and depression in adolescence and beyond: reciprocal risks. Int J Obes (Lond). 2014; 38(7):906-11. DOI http://dx.doi.org/10.1038/ijo.2014.19.

22. Every-Palmer S, Huthwaite MA, Elmslie JL, Grant E, Romans SE. Long-term psychiatric inpatients' perspectives on weight gain, body satisfaction, diet and physical activity: a mixed methods study. BMC Psychiatry. 2018;18(1):300. DOI http://dx.doi.org/10.1186/s12888-018-1878-5.

23. Bradshaw T, Mairs H. Obesity and Serious Mental Ill Health: A Critical Review of the Literature. Healthcare (Basel). 2014;2(2):166-182. DOI http://dx.doi.org/10.3390/healthcare2020166.

24. Jessica Tyrrell, Anwar Mulugeta, Andrew R Wood, Ang Zhou, Robin N Beaumont, et al. Using genetics to understand the causal influence of higher BMI on depression, International Journal of Epidemiology, 2019; 48(3): 834–848,. DOI https://doi.org/10.1093/ije/dvy223.

25. Ibrahim MA, Asuka E, Jialal I. Hypercholesterolemia. [Updated 2020 Aug 30]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK459188/ (access 22.10.2020).

26. Lee Y, Siddiqui WJ. Cholesterol Levels. [Updated 2020 Jul 26]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK542294/ (access 22.10.2020).

27. Llorente ML, Urrutia V, Diabetes, Psychiatric Disorders, and the Metabolic Effects of Antipsychotic Medications, Clinical Diabetes. 2006; 24(1): 18-24. DOI http://dx.doi.org/10.2337/diaclin.24.1.18.

28. Wirshing DA, Boyd JA, Meng LR, Ballon JS, Marder SR, Wirshing WC. The effects of novel antipsychotics on glucose and lipid levels. J Clin Psychiatry. 2002; 63(10):856-65. DOI http://dx.doi.org/10.4088/jcp.v63n1002.

29. Vanderlip ER, Fiedorowicz JG, Haynes WG. Screening, diagnosis, and treatment of dyslipidemia among persons with persistent mental illness: a literature review. Psychiatr Serv. 2012; 63(7):693-701. DOI http://dx.doi.org/10.1176/appi.ps.201100475.
30. Nasrallah HA, Meyer JM, Goff DC, McEvoy JP, Davis SM, Stroup TS, Lieberman JA. Low rates of treatment for hypertension, dyslipidemia and diabetes in schizophrenia: data from the CATIE schizophrenia trial sample at baseline. Schizophr Res. 2006;86(1-3):15-22. DOI http://dx.doi.org/10.1016/j.schres.2006.06.026.

31. Canadian Diabetes Association Clinical Practice Guidelines Expert Committee, Robinson DJ, Luthra M, Vallis M. Diabetes and mental health. Can J Diabetes. 2013; 37 Suppl 1:S87-92. DOI http://dx.doi.org/10.1016/j.jcjd.2013.01.026.

32. Srihari VH, Tek C. Glucose metabolism dysregulation at the onset of mental illness is not limited to first episode psychosis: A systematic review and meta-analysis. Early Interv Psychiatry. 2019 Oct;13(5):1021-1031. DOI http://dx.doi.org/10.1111/eip.12749.

33. Kooy FH. Hyperglycemia in mental disorders. Brain 1919; 42: 214-289.

34. Kohen D. Diabetes mellitus and schizophrenia: historical perspective, BJP 2004, 184: 64-66. DOI: https://doi.org/10.1192/bjp.184.47.s64

35. Turner T. Chlorpromazine: unlocking psychosis. BMJ. 2007; 334 Suppl 1: 7. DOI http://dx.doi.org/10.1136/bmj.39034.609074.94.

36. Dobkin, A.B., Fisher, L.M. & Wyant, G.M. The effect of chlorpromazine on haemostasis. Can. Anaes. Soc. J. 4, 352 (1957). DOI https://doi.org/10.1007/BF03021121

37. Whicher CA, Price HC, Holt RIG. Mechanisms in endocrinology: Antipsychotic medication and type 2 diabetes and impaired glucose regulation. Eur J Endocrinol. 2018; 178(6):R245-R258. DOI http://dx.doi.org/10.1530/EJE-18-0022.

38. Gough SC, O'Donovan MC. Clustering of metabolic comorbidity in schizophrenia: a genetic contribution? J Psychopharmacol. 2005; 19(6 Suppl):47-55. DOI http://dx.doi.org/10.1177/0269881105058380.

39. Suvisaari J, Perälä J, Saarni SI, Härkänen T, Pirkola S, Joukamaa M, Koskinen S, Lönnqvist J, Reunanen A. Type 2 diabetes among persons with schizophrenia and other psychotic disorders in a general population survey. Eur Arch Psychiatry Clin Neurosci. 2008; 258(3):129-36. DOI http://dx.doi.org/10.1007/s00406-007-0762-y.

40. Hackinger, S., Prins, B., Mamakou, V. et al. Evidence for genetic contribution to the increased risk of type 2 diabetes in schizophrenia. Transl Psychiatry 8, 252 (2018). DOI https://doi.org/10.1038/s41398-018-0304-6
41. Calkin CV, Gardner DM, Ransom T, Alda M. The relationship between bipolar disorder and type 2 diabetes: more than just co-morbid disorders. Ann Med. 2013; 45(2):171-81. DOI http://dx.doi.org/10.3109/07853890.2012.687835.

42. Carnethon MR, Biggs ML, Barzilay JI, Smith NL, Vaccarino V, Bertoni AG, Arnold A, Siscovick D. Longitudinal association between depressive symptoms and incident type 2 diabetes mellitus in older adults: the cardiovascular health study. Arch Intern Med. 2007; 167(8):802-7. DOI http://dx.doi.org/10.1001/archinte.167.8.802.

43. Webb M, Davies M, Ashra N, et al. The association between depressive symptoms and insulin resistance, inflammation and adiposity in men and women. PLoS One. 2017; 12(11):e0187448. DOI http://dx.doi.org/10.1371/journal.pone.0187448.

44. Mulugeta A, Zhou A, Power C, Hyppönen E. Obesity and depressive symptoms in mid-life: a population-based cohort study. BMC Psychiatry. 2018;18(1):297. DOI http://dx.doi.org/10.1186/s12888-018-1877-6.

45. Penninx BWJH, Lange SMM. Metabolic syndrome in psychiatric patients: overview, mechanisms, and implications. Dialogues Clin Neurosci. 2018; 20(1): 63-73. DOI http://dx.doi.org/10.31887/DCNS.2018.20.1/bpenninx.

46. Padmavati R. Metabolic syndrome, serious mental illnesses & lifestyle. Indian J Med Res. 2016;143(4):395-397. DOI http://dx.doi.org/10.4103/0971-5916.184280.

47. Kamkar MZ, Sanagoo A, Zargarani F, Jouybari L, Marjani A. Metabolic syndrome in patients with severe mental illness in Gorgan. J Nat Sci Biol Med. 2016;7(1):62-67. DOI http://dx.doi.org/10.4103/0976-9668.175073.

48. Carrà G, Bartoli F, Carretta D, Crocamo C, Bozzetti A, Clerici M, Bebbington PE. The prevalence of metabolic syndrome in people with severe mental illness: a mediation analysis. Soc Psychiatry Psychiatr Epidemiol. 2014; 49(11):1739-46. DOI http://dx.doi.org/10.1007/s00127-014-0835-y.

49. Łopuszańska UJ, Skorzyńska-Dziduszko K, Lupa-Zatwarnicka K, Makara-Studzińska M. Mental illness and metabolic syndrome--a literature review. Ann Agric Environ Med. 2014;21(4):815-21. DOI http://dx.doi.org/10.5604/12321966.1129939.

50. De Hert M, Dekker JM, Wood D, Kahl KG, Holt RI, Möller HJ. Cardiovascular disease and diabetes in people with severe mental illness position statement from the European Psychiatric Association (EPA), supported by the European Association for the Study of Diabetes
(EASD) and the European Society of Cardiology (ESC). Eur Psychiatry. 2009;24(6):412-24. DOI http://dx.doi.org/10.1016/j.eurpsy.2009.01.005

51. Malhotra N, Grover S, Chakrabarti S, Kulhara P. Metabolic syndrome in schizophrenia. Indian J Psychol Med. 2013; 35(3):227-40. DOI http://dx.doi.org/10.4103/0253-7176.119471

52. Grover S, Malhotra N, Chakrabarti S, Kulhara P. Metabolic syndrome in bipolar disorders. Indian J Psychol Med. 2012; 34(2): 110-118. DOI http://dx.doi.org/10.4103/0253-7176.101767

53. Kahl KG, Greggersen W, Schweiger U, Cordes J, Balijepalli C, Lösch C, Moebus S. Prevalence of the metabolic syndrome in unipolar major depression. Eur Arch Psychiatry Clin Neurosci. 2012; 262(4):313-20. DOI http://dx.doi.org/10.1007/s00406-011-0277-4