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Association between Schizophrenia Clinical Severity and Obesity Risk: A Literature Review

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ABSTRACT

Obesity is a highly prevalent illness in schizophrenia patients. This review evaluates recent literature on the relationship between obesity risk and schizophrenia psychopathology. Ten studies were gathered using online resources like Google Scholar, PubMed, and the Brown University Library. Nine of the ten studies analyzed the relationship between obesity and schizophrenia severity with the factor of antipsychotics, while the last study excluded antipsychotic influence. While the nine studies with antipsychotic treatment indicate an association between improvement in overall symptom severity and weight gain, five studies specify negative symptoms to be more indicative of weight gain than positive symptoms, and two studies state the opposite. The last (tenth) study implies the existence of a relationship between weight and clinical severity independent from antipsychotic use. More research needs to be done on the connection between obesity and schizophrenia severity prior to antipsychotic treatment.

Introduction

Distinguished by a separation from reality in both thought and experience, schizophrenia is a debilitating mental disorder that affects approximately 1% of the global population. It can manifest in a plethora of symptoms, from hallucinations and delusions to avolition and disorganized speech, all of which prevent societal integration. The specific causes of schizophrenia are still unknown, but research supports an interplay between genetics, the environment, and chemical and structural changes in the brain (Patel et al., 2014). Though there is still no cure for this illness, medications and psychotherapy aim to lessen symptoms; antipsychotics, which affect brain chemicals (e.g. dopamine), are a vital part in schizophrenia treatment (Kapur et al., 2006).

A growing field of research confirms a high prevalence of obesity in patients with schizophrenia (Coodin, 2001; Cameron et al., 2017). According to a 2004 study, 40-60% of schizophrenia patients are either overweight or obese (Catapano & Castle, 2004), giving people with schizophrenia three times the risk of obesity compared to the typical population (Annamalai et al., 2017). Obesity, in turn, is associated with a higher risk of cardiometabolic disorders (Després, 2006), non-alcoholic fatty liver disease (Duseja & Chalasani, 2013), osteoarthritis (Felson et al., 1988), and cancer mortality (Calle et al., 2009), ultimately resulting in a decreased quality of life (Kolotkin et al., 2001; Hasan, 2019). The high prevalence of obesity in schizophrenia patients, therefore, warrants immediate attention. Despite the breadth of the issue, the specific relationship between obesity risk and schizophrenia symptomatology continues to lack consensus. To evaluate the association between obesity and schizophrenia severity, this study will assess existing literature on both disorders, as well as mention potential factors that contribute to the relationship. Intuitively, it would seem that greater rates of obesity are associated with more severe symptoms, as schizophrenia hinders normal functioning relating to exercise and diet control.

Methods

Literature was initially gathered through online resources such as the Brown University Library, Google Scholar, Elsevier, PubMed, ScienceDirect, SpringerLink, Oxford Academic, and Nature. The first ten pages of Google Scholar using keywords "PANSS" and "obesity" were searched. Findings were prioritized based on relevance and date published, as well as participant sample size and diversity in age and sex. Studies pertaining to obesity and schizophrenia had to be published after the year 2000, as the fields of psychiatric disorders, antipsychotic treatment, and public health are constantly evolving. Keywords entered in search engines include "Schizophrenia", "PANSS", "Women", "Men", "Age", "Obesity", "Overweight", and "AN-FEP". Studies concerning diseases related to obesity, schizophrenia, or schizoaffective disorder were accounted for in the research process to achieve a more comprehensive outlook. Discrepancies in article conclusions were noted and included in this review.

Schizophrenia symptom severity was measured using the Positive and Negative Syndrome Scale (PANSS), which consisted of three sections—positive symptoms, negative symptoms, and general psychopathology—and totaled 30 items which were each rated on a seven-point scale according to severity (Kay et al., 1987). Other scales were also used, such as the Brief Negative Symptom Scale (BNSS). Positive symptoms reveal the patient's inability to differentiate between reality and false perceptions, such as delusions and hallucinations; negative symptoms reveal a reduction in typical mental and social functioning, such as social withdrawal, speech impairment, and affective flattening.

Antipsychotics are categorized into two broad categories: typical (first-generation) and atypical (second-generation). Typical antipsychotics block the dopamine receptor D2 to reduce positive symptoms, but have a higher risk of motor side effects. Atypical antipsychotics, such as clozapine, olanzapine, and risperidone, block serotonin 5HT2A and dopamine D2 receptors, meaning that they improve both positive and negative symptoms. However, atypical antipsychotics have a higher risk of metabolic side effects (Chokhawala & Stevens, 2021). Atypical antipsychotics are usually considered the first-line of schizophrenia treatment (Moore et al., 2007).

Many different characterizations of obesity exist, but the most commonly used is the definition established by the World Health Organization, which requires the calculation of body mass index (BMI). It is important to note that the cutoff BMI for obesity differs according to ethnicity, as well as environmental and cultural factors (WHO Expert Consultation, 2004; Davis et al., 2013). The studies mentioned in this review have been adjusted according to patient ethnicity, using different BMI criteria—such as the Chinese Working Group on Obesity in China (WGOC) diagnostic criteria for Han Chinese patients—to determine obesity.

Results

Ten studies were chosen for review. Six were cross-sectional, two were cohort studies, and two were clinical trials. Three reports included antipsychotic-naive and first-episode schizophrenia patients. Studies were summarized using study type, participant characteristics, antipsychotics taken during the study, ultimate results of the study, and limitations which may have impacted the results.

Table 1. Comprehensive Analysis of the Ten Studies Chosen for Review

Study Type	Sample	Antipsychotics Taken	Results	Key Limitations	Reference
Cross-sectional	633 Han Chinese inpatients with chronic schizophrenia.	Clozapine (n = 286) Risperidone (n = 134) Chlorpromazine (n = 52)	Negative relationship between BMI and PANSS total score,	More male patients than female patients were included in	(Tian et al., 2020)

	Average age was 47± 9.74 years. All participants were diagnosed with schizophrenia for at least one year. No participant had any drug or alcohol dependence.	Sulpiride (n = 34) Aripiprazole (n = 29) Perphenazine (n = 28) Quetiapine (n = 26) Loxapine (n = 14) Haloperidol (n = 9) Pipotiazine palmitate (n = 8) Olanzapine (n = 5) Other Antipsychotic (n = 8)	negative PANSS subscore and PANSS cognitive aspect.	the study. This is likely a reflection of the gender imbalance in schizophrenia as a whole, as schizophrenia is more prevalent in men than in women (Iacono & Beiser, 1992).	
Cross-sectional	377 Han Chinese inpatients. All patients met DSM-IV schizophrenia criteria and were on clozapine monotherapy for at least one year.	Clozapine (n=377)	Negative relationship between BMI and negative and general symptoms in male patients. No relationship found in female patients.	320 males and 57 female patients were included in the study, revealing a gender imbalance.	(Hui et al., 2015)
Clinical trial (longitudinal)	1,493 patients with chronic or recurrent schizophrenia from 57 U.S. sites. Type of antipsychotic drug was assigned randomly, and the trial was double-blind. Inclusion criteria specifies that patients must	Olanzapine Perphenazine Risperidone Quetiapine Ziprasidone	Statistically significant but clinically insignificant association between weight gain and decrease in PANSS total score.	Study was conducted when patients were switching antipsychotic medications. This time period is marked with relatively severe changes in psychopatholog y and weight (Mezquida et al., 2018).	(Hermes et al., 2011)

	be between 18-65 years and be diagnosed with DSM-IV criteria. Patients who continued treatment received follow-ups until eighteen months after treatment initiation.				
Clinical trial (longitudinal)	74 patients meeting the DSM-III-R schizophrenia criteria. The average age of the male patients was 34.7 ± 8.1 S.D. years, and the average age of the female patients was 36.2±11.6 S.D. years.	Clozapine (n=74)	Clinical symptom improvement was correlated with weight gain in both males and females.	Study was conducted when patients were switching antipsychotic medications. This time period is marked with relatively severe changes in psychopathology and weight (Mezquida et al., 2018).	(Meltzer et al., 2003)
Cross-sectional	206 Han Chinese inpatients (140 male, 66 female) from Beijing Hui-Long-Guan Hospital. This hospital is a psychiatric hospital owned by Beijing City. Inclusion criteria specifies that the participant must be 25-75 years old, with a DSM-IV diagnosis of schizophrenia.	Atypicals (such as clozapine, risperidone and olanzapine) Typicals	BMI was found to be negatively associated with the PANSS total and PANSS negative scores in men, but no relationship was found with women.	According to a 2005 study, mildly dependent smokers have a higher PANSS total score and less frequent positive symptoms relative to non-smokers and highly dependent smokers (Aguilar et al., 2005). This	(Li et al., 2016)

	No participant had any drug or alcohol dependence.			study had a significantly higher ratio of smokers in men than in women. Thus, the disparity in smoking could have impacted the study results. Furthermore, there was a gender imbalance in the number of women represented in the study, and all participants were taken from one hospital.	
Cross-sectional	62 patients with schizophrenia were recruited from a European multicenter study. The four centers were located in Cambridge, Oviedo, and Barcelona. All participants had an illness duration of at least four years.	Olanzapine (n=8) Clozapine (n=54)	Negative symptoms on the BNSS scale were negatively associated with BMI, but there was no association between PANSS and BMI.	Relatively smaller sample size.	(Mezquida et al., 2018)
Cross-sectional	206 Han Chinese patients (140 male, 66 female) from Beijing Hui-Long-Guan Hospital. This hospital is a psychiatric hospital owned	Clozapine (n=92) Risperidone (n=28) Mixed (n=7) Typical (n=79)	Negative association between BMI and PANSS negative and total scores.	This study had a significantly higher ratio of smokers in men than in women—only 2.5% of female patients were active smokers,	(Li et al., 2017)

	by Beijing City. The average age was 51.7 years, but ranged from 30 to 71 years. Inclusion criteria specify that the participant has a DSM-IV diagnosis of schizophrenia, as well as at least one year of illness. 51 patients were active smokers.			while 35% of male patients were active smokers. Thus, the disparity in smoking could have impacted the study results. Furthermore, there was a gender imbalance in the number of women represented in the study, and all participants were taken from one hospital.	
Cohort	22 antipsychotic-naive first-episode psychosis (AN-FEP) patients with schizophrenia (thirteen males, nine females). The average participant age was 27.6±8.31 years. All patients met DSM-IV diagnosis criteria, and all patients never received any sort of antipsychotic or antidepressant. The mean length of follow-up after enrollment was 6.04±2.16 years. The study was	Not listed but were used.	Increase in BMI after follow-up was positively associated with positive symptoms before antipsychotic treatment. No relation was found between BMI and baseline negative symptoms.	Study size lacked significant statistical power. The study was naturalistic; the treatment and follow-up time was not constant among patients.	(Lin et al., 2021)

	done in the department of psychiatry in the medical center in southern Taiwan.				
Cohort	174 AN-FEP patients recruited from the outpatient and inpatient psychiatric facilities of Marques de Valdecilla University Hospital in Spain. Patients were experiencing their first episode of psychosis and met DSM-IV criteria. All patients never received any sort of antipsychotic treatment. Average age was 27.3 years; 61% of patients were male; 97% of patients were white Caucasian. Patients were diagnosed with schizophrenia, schizophreniform, schizoaffective, brief psychotic episode, or unspecified psychotic disorder at the six month follow-up. Follow-ups continued until	In the beginning of the study: Haloperidol (32% of patients) Olanzapine (32%) Risperidone (36%) Patients discontinued their medications as time went on. At the end of follow-up: Haloperidol (10%) Olanzapine (31%) Risperidone (35%) Quetiapine (7%) Ziprasidone (6%) Amisulpride (2%) Clozapine (4%) Aripiprazole (3%) Other (2%)	Lack of response for negative symptoms was positively associated with weight gain. Lack of response for positive symptoms was negatively associated with weight gain.	Adherence to medication was self-reported, which could have led to an overestimation in medication compliance. There was also consistent treatment switching during the three year period. Other obesity factors, such as genetics and exercise, were not controlled nor recorded. All participants were from one hospital.	(Pérez-Iglesias et al., 2014)

	the third year of treatment.				
Cross-sectional	297 Han Chinese first-episode and drug-naive (FEDN) inpatients with schizophrenia from the First Affiliated Hospital of Shanxi Medical University. Inclusion criteria required the diagnosis of the Chinese DSM-IV (SCID). All patients had an illness duration of five years or less. The average age was 27.11±8.71 years, and all patients were between 25-75 years old. Patients had no antipsychotic drug history. There were 325 Han Chinese controls from local communities. They were aged 17-45 years old.	No antipsychotics used from onset to admission.	BMI had a positive association with positive symptoms, general psychopathology, and PANSS total.	Did not control or quantitatively record factors related to obesity like diet and exercise. The ages of the control and FEDN participants did not match up, and age is a significant contributor to obesity. The participants were all from one hospital and its local communities.	(Tian et al., 2021)

Across all ten studies, 3,544 schizophrenia patients were evaluated, assuming no overlap in participants. Nine studies included the factor of antipsychotics, while one did not. Five cross-sectional studies found a lower severity in negative symptoms to be associated with a higher BMI—two of these studies found this association to be true for only men. One cohort study found an association between higher initial positive symptom severity and weight gain after antipsychotic use. Another cohort study found an association between a higher severity in negative symptoms and weight gain. The single study that did not include antipsychotic treatment found that a higher BMI was associated with more severe symptoms, positive symptoms and general psychopathology in particular.

Discussion

In contrast to the original hypothesis, most recent studies have found obesity to have a negative correlation with clinical symptoms, particularly negative symptoms (Tian et al., 2020; Hermes et al., 2011; Meltzer et al., 2003; Mezquida et al., 2018; Li et al., 2017; Li et al., 2016; Hui et al., 2015). Literature in this field still holds disagreement when it comes to sex differences in this association. Two studies report no relationship between PANSS score and BMI in women; however, both studies had a limited number of female participants, suggesting caution when interpreting the lack of correlation between women, obesity, and clinical severity.

It is important to note that in the studies mentioned above, all patients were on antipsychotics before enrollment. The relationship between antipsychotics and obesity is relatively well researched (Bak et al., 2014; Allison et al., 1999; Łopuszańska & Makara-Studzińska, 2017). Antipsychotics—clozapine, amisulpride, olanzapine, zotepine, and risperidone in particular—significantly reduce schizophrenia symptoms but collaterally induce weight gain and contribute to metabolic disorders (Huhn et al., 2019; Larsen et al., 2017). The exact mechanisms behind this relationship are still unclear, but there are several well-backed postulations.

One popular explanation states that as a result of the decreased symptom severity from taking antipsychotics, schizophrenia patients experience a greater sense of motivation and pleasure, which consequently leads to greater weight gain (Meltzer et al., 2003). This is supported by the finding that patients with more severe negative symptoms have reduced adaptive coding of the brain, which in turn contributes to uncertainty in reward response (Kirschner et al., 2016). In short, patients with lessened negative symptoms would adapt and respond better to food reward, making them more susceptible to overeating (Alonso-Alonso et al., 2015).

Furthermore, antipsychotics are proposed to cause dysregulation in visceral adipose tissue, a type of body fat that is packed around internal organs; for example, atypical antipsychotics are specifically suggested to increase adipose tissue lipogenesis and differentiation (Gonçalves et al., 2015). Lipogenesis is the synthesis of fatty acids and triglycerides—an increase in these molecules strongly contributes to obesity (Boden, 2008; Klop et al., 2013). Adipose stem cells give rise to adipocytes, or fat cells (Berry et al., 2013). Atypical antipsychotics have the ability to stimulate this process of differentiation, leading to an increase in adipose tissue, and subsequently, obesity risk (Hemmrich et al., 2011; Fried & Kral, 1987).

Interestingly, studies that began with AN-FEP (Antipsychotic-Naive First Episode Psychosis) patients revealed slightly different results than studies that simply analyzed antipsychotic-using patients. Out of the selected studies, two studies started off with AN-FEP patients and recorded the changes in clinical severity and weight gain as the patients began antipsychotic treatment. One study found that weight gain after antipsychotic treatment was associated with more severe positive symptoms before antipsychotic treatment, thereby suggesting a possible link between treatment effectiveness and more severe initial positive symptoms (Lin et al., 2021). A greater initial severity in illness has been associated with greater antipsychotic efficacy and consequent symptom reduction (Haddad & Correll, 2018). Thus, the association between an increase in BMI and a reduction in positive symptom severity may be in partial agreement with the former studies (Tian et al., 2020; Hermes et al., 2011; Meltzer et al., 2003; Mezquida et al., 2018; Li et al., 2017; Li et al., 2016; Hui et al., 2015), as all studies point to the conclusion that symptom improvement/reduction is associated with weight gain.

The other study found that a decrease in negative symptoms after using antipsychotics was associated with less weight gain, while a decrease in positive symptoms was associated with more weight gain (Pérez-Iglesias et al., 2014). These results may hint at several theories; first, that people with more severe negative symptoms have less physical activities and are thus vulnerable to weight gain; second, that people with more severe positive symptoms may tend to have a lower rate of medication adherence (Pérez-Iglesias et al., 2014). The results of this cohort study are seemingly half-contradictory to the conclusions of the studies mentioned prior (Tian et al., 2020; Hermes et al., 2011; Meltzer et al., 2003; Mezquida et al., 2018; Li et al., 2017; Li et al., 2016; Hui et al., 2015); while it conjectures

the relationship between overall symptom improvement/reduction and weight gain, it finds that positive symptoms are more associated with weight gain than negative symptoms.

It is crucial to mention that both studies investigated weight and clinical changes during the onset of schizophrenia, when changes in symptomatology and weight are relatively severe (Mezquida et al., 2018). The 2014 study also had many instances of medication switching, which also causes severe weight and symptom changes. Thus, it is likely that the contradictory results of the studies were at least partially caused by the differing situations they were conducted in (e.g. during illness onset versus during long-term stable antipsychotic use).

There was one 2021 study that was devoid of antipsychotic drug influence throughout the entire process. This study found that in FEDN (First-Episode Drug Naive) patients, BMI was positively correlated with positive symptoms, general psychopathology, and overall symptom severity (Tian et al., 2021). The results of this study piece together a more holistic perspective by illustrating that the relationship between weight and clinical severity exists even when antipsychotics are not in play.

The seemingly inherent relationship between obesity and schizophrenia could be in part explained by cortisol and its relations to both disorders. Cortisol is a hormone that is crucial in regulating many processes, of which include metabolism and stress response. Produced in the cortex of the adrenal glands, cortisol is regulated by the hypothalamic-pituitary-adrenal axis (HPA axis), which represents the cooperation between the hypothalamus, pituitary gland, and adrenal glands. Chronic physiological stress—such as that caused by the nerve-wracking symptoms and experiences of schizophrenia—can result in cortisol dysregulation (Aschbacher et al., 2013). This dysregulation, in turn, can cause weight gain and obesity (Aschbacher et al., 2012).

Conclusion

In conclusion, while there is some discrepancy between studies, most support an association between weight gain and improvement in clinical symptoms. Underlying mechanisms of antipsychotic-induced weight gain may include the reward system and visceral adipose tissue dysregulation. Mechanisms of antipsychotic-independent weight gain may include cortisol dysregulation. More research needs to be done to track patients from the AN-FEP stage to stable antipsychotic use with a large-sample longitudinal design. The relationship between psychopathology and obesity without the compounding factor of antipsychotics needs to be explored further, and more research should be done with female schizophrenia patients. To the author's knowledge, this is the first comprehensive literature review focusing on obesity and schizophrenia severity.

Limitations

Important limitations of this review include the disproportionate amount of male patients compared to female patients. In addition, six of the ten studies focused on Chinese patients; since cultural and ethnic factors contribute to obesity as a whole, more research needs to be done on non-Chinese and non-Caucasian schizophrenia patients. Most studies were cross-sectional, meaning that they can only imply association and not causation. Publication bias is another limitation. The varying types of antipsychotics used in each study also affected the results, as certain antipsychotics—such as clozapine and olanzapine—have a higher propensity to cause weight gain (Dayabandara et al., 2017). Besides antipsychotics, there are many factors which contribute to obesity. Schizophrenia patients tend to have poor diets with high amounts of saturated fat (Dipasquale et al., 2013), as well as reduced engagement in physical activity (Ho et al., 2018). The numerous risk factors of obesity were difficult to control throughout all ten studies, so there were likely other compounding characteristics that were not accounted for.

References

Aguilar, M. C., Gurpegui, M., Diaz, F. J., & de Leon, J. (2005). Nicotine dependence and symptoms in schizophrenia: Naturalistic study of complex interactions. *The British Journal of Psychiatry: The Journal of Mental Science*, *186*, 215–221. https://doi.org/10.1192/bjp.186.3.215

Allison, D. B., Mentore, J. L., Heo, M., Chandler, L. P., Cappelleri, J. C., Infante, M. C., & Weiden, P. J. (1999). Antipsychotic-induced weight gain: A comprehensive research synthesis. *The American Journal of Psychiatry*, *156*(11), 1686–1696. https://doi.org/10.1176/ajp.156.11.1686

Alonso-Alonso, M., Woods, S. C., Pelchat, M., Grigson, P. S., Stice, E., Farooqi, S., Khoo, C. S., Mattes, R. D., & Beauchamp, G. K. (2015). Food reward system: Current perspectives and future research needs. *Nutrition Reviews*, *73*(5), 296–307. https://doi.org/10.1093/nutrit/nuv002

Annamalai, A., Kosir, U., & Tek, C. (2017). Prevalence of obesity and diabetes in patients with schizophrenia. *World Journal of Diabetes*, *8*(8), 390–396. https://doi.org/10.4239/wjd.v8.i8.390

Aschbacher, K., Adam, E. K., Crofford, L. J., Kemeny, M. E., Demitrack, M. A., & Ben-Zvi, A. (2012). Linking disease symptoms and subtypes with personalized systems-based phenotypes: A proof of concept study. *Brain, Behavior, and Immunity*, *26*(7), 1047–1056. https://doi.org/10.1016/j.bbi.2012.06.002

Aschbacher, K., O'Donovan, A., Wolkowitz, O. M., Dhabhar, F. S., Su, Y., & Epel, E. (2013). Good Stress, Bad Stress and Oxidative Stress: Insights from Anticipatory Cortisol Reactivity. *Psychoneuroendocrinology*, *38*(9), 1698–1708. https://doi.org/10.1016/j.psyneuen.2013.02.004

Bak, M., Fransen, A., Janssen, J., Os, J. van, & Drukker, M. (2014). Almost All Antipsychotics Result in Weight Gain: A Meta-Analysis. *PLOS ONE*, *9*(4), e94112. https://doi.org/10.1371/journal.pone.0094112

Berry, D. C., Stenesen, D., Zeve, D., & Graff, J. M. (2013). The developmental origins of adipose tissue. *Development (Cambridge, England)*, *140*(19), 3939–3949. https://doi.org/10.1242/dev.080549

Boden, G. (2008). Obesity and Free Fatty Acids (FFA). *Endocrinology and Metabolism Clinics of North America*, *37*(3), 635–ix. https://doi.org/10.1016/j.ecl.2008.06.007

Calle, E. E., Rodriguez, C., Walker-Thurmond, K., & Thun, M. J. (2003). Overweight, Obesity, and Mortality from Cancer in a Prospectively Studied Cohort of U.S. Adults. *The New England Journal of Medicine*. https://doi.org/10.1056/NEJMoa021423

Cameron, I. M., Hamilton, R. J., Fernie, G., & MacGillivray, S. A. (2017). Obesity in individuals with schizophrenia: A case controlled study in Scotland. *BJPsych Open*, *3*(5), 254–256. https://doi.org/10.1192/bjpo.bp.116.003640

Catapano, L., & Castle, D. (2004). Obesity in Schizophrenia: What can be Done About it? *Australasian Psychiatry*, *12*(1), 23–25. https://doi.org/10.1046/j.1039-8562.2003.02054.x

Chokhawala, K., & Stevens, L. (2021). Antipsychotic Medications. In *StatPearls*. StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK519503/

Coodin, S. (2001). Body Mass Index in Persons with Schizophrenia. *The Canadian Journal of Psychiatry*, *46*(6), 549–555. https://doi.org/10.1177/070674370104600610

Davis, J., Juarez, D., & Hodges, K. (2013). Relationship of Ethnicity and Body Mass Index with the Development of Hypertension and Hyperlipidemia. *Ethnicity & Disease*, *23*(1), 65–70.

Dayabandara, M., Hanwella, R., Ratnatunga, S., Seneviratne, S., Suraweera, C., & de Silva, V. A. (2017). Antipsychotic-associated weight gain: Management strategies and impact on treatment adherence. *Neuropsychiatric Disease and Treatment*, *13*, 2231–2241. https://doi.org/10.2147/NDT.S113099

Després, J.-P. (2006). Abdominal obesity: The most prevalent cause of the metabolic syndrome and related cardiometabolic risk. *European Heart Journal Supplements*, *8*(suppl_B), B4–B12. https://doi.org/10.1093/eurheartj/sul002

Dipasquale, S., Pariante, C. M., Dazzan, P., Aguglia, E., McGuire, P., & Mondelli, V. (2013). The dietary pattern of patients with schizophrenia: A systematic review. *Journal of Psychiatric Research*, *47*(2), 197–207. https://doi.org/10.1016/j.jpsychires.2012.10.005

Duseja, A., & Chalasani, N. (2013). Epidemiology and risk factors of nonalcoholic fatty liver disease (NAFLD). *Hepatology International*, *7*(2), 755–764. https://doi.org/10.1007/s12072-013-9480-x

Felson, D. T., Anderson, J. J., Naimark, A., Walker, A. M., & Meenan, R. F. (1988). Obesity and knee osteoarthritis. The Framingham Study. *Annals of Internal Medicine*, *109*(1), 18–24. https://doi.org/10.7326/0003-4819-109-1-18

Fried, S. K., & Kral, J. G. (1987). Adipose Tissue of Morbidly Obese Patients: Clinical Implications of Distribution, Morphology, and Metabolism. *Gastroenterology Clinics*, *16*(2), 207–213. https://doi.org/10.1016/S0889-8553(21)00286-7

Gonçalves, P., Araújo, J. R., & Martel, F. (2015). Antipsychotics-induced metabolic alterations: Focus on adipose tissue and molecular mechanisms. *European Neuropsychopharmacology*, *25*(1), 1–16. https://doi.org/10.1016/j.euroneuro.2014.11.008

Haddad, P. M., & Correll, C. U. (2018). The acute efficacy of antipsychotics in schizophrenia: A review of recent meta-analyses. *Therapeutic Advances in Psychopharmacology*, *8*(11), 303–318. https://doi.org/10.1177/2045125318781475

Hasan, A. A.-H. (2019). The correlation between the quality of life and clinical variables among outpatients with schizophrenia. *Psychiatry Research*, *271*, 39–45. https://doi.org/10.1016/j.psychres.2018.09.062

Hemmrich, K., Kappel, B. A., Paul, N. E., Goy, D., Luckhaus, C., Pallua, N., & Fehsel, K. (2011). Antipsychotic Drugs Increase Adipose Stem Cell Differentiation-Implications for Treatment With Antipsychotic Drugs. *Journal of Clinical Psychopharmacology*, *31*(5), 663–665. https://doi.org/10.1097/JCP.0b013e31822bf0a5

Hermes, E., Nasrallah, H., Davis, V., Meyer, J., McEvoy, J., Goff, D., Davis, S., Stroup, T. S., Swartz, M., Lieberman, J., & Rosenheck, R. (2011). The association between weight change and symptom reduction in the CATIE schizophrenia trial. *Schizophrenia Research*, *128*(1), 166–170. https://doi.org/10.1016/j.schres.2011.01.022

Ho, P. A., Dahle, D. N., & Noordsy, D. L. (2018). Why Do People With Schizophrenia Exercise? A Mixed Methods Analysis Among Community Dwelling Regular Exercisers. *Frontiers in Psychiatry*, *9*. https://doi.org/10.3389/fpsyt.2018.00596

Huhn, M., Nikolakopoulou, A., Schneider-Thoma, J., Krause, M., Samara, M., Peter, N., Arndt, T., Bäckers, L., Rothe, P., Cipriani, A., Davis, J., Salanti, G., & Leucht, S. (2019). Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: A

systematic review and network meta-analysis. *The Lancet*, *394*(10202), 939–951. https://doi.org/10.1016/S0140-6736(19)31135-3

Hui, L., Ye, M., Tang, W., Chen, D.-C., Tan, Y.-L., Zhang, F., Liu, J., Liu, L., Chen, Y., Yang, F.-D., & Zhang, X. Y. (2015). Obesity correlates with fewer symptoms in schizophrenia treated with long-term clozapine: Gender difference. *Psychiatry Research*, *225*(3), 741–742. https://doi.org/10.1016/j.psychres.2014.12.035

Iacono, W. G., & Beiser, M. (1992). Are males more likely than females to develop schizophrenia? *The American Journal of Psychiatry*, *149*(8), 1070–1074. https://doi.org/10.1176/ajp.149.8.1070

Kapur, S., Agid, O., Mizrahi, R., & Li, M. (2006). How antipsychotics work—From receptors to reality. *NeuroRx*, *3*(1), 10–21. https://doi.org/10.1016/j.nurx.2005.12.003

Kay, S. R., Fiszbein, A., & Opler, L. A. (1987). The Positive and Negative Syndrome Scale (PANSS) for Schizophrenia. *Schizophrenia Bulletin*, *13*(2), 261–276. https://doi.org/10.1093/schbul/13.2.261

Kirschner, M., Hager, O. M., Bischof, M., Hartmann-Riemer, M. N., Kluge, A., Seifritz, E., Tobler, P. N., & Kaiser, S. (2016). Deficits in context-dependent adaptive coding of reward in schizophrenia. *Npj Schizophrenia*, *2*(1), 1–8. https://doi.org/10.1038/npjschz.2016.20

Klop, B., Elte, J. W. F., & Castro Cabezas, M. (2013). Dyslipidemia in Obesity: Mechanisms and Potential Targets. *Nutrients*, *5*(4), 1218–1240. https://doi.org/10.3390/nu5041218

Kolotkin, R. L., Meter, K., & Williams, G. R. (2001). Quality of life and obesity. *Obesity Reviews*, *2*(4), 219–229. https://doi.org/10.1046/j.1467-789X.2001.00040.x

Larsen, J. R., Vedtofte, L., Jakobsen, M. S. L., Jespersen, H. R., Jakobsen, M. I., Svensson, C. K., Koyuncu, K., Schjerning, O., Oturai, P. S., Kjaer, A., Nielsen, J., Holst, J. J., Ekstrøm, C. T., Correll, C. U., Vilsbøll, T., & Fink-Jensen, A. (2017). Effect of Liraglutide Treatment on Prediabetes and Overweight or Obesity in Clozapine- or Olanzapine-Treated Patients With Schizophrenia Spectrum Disorder: A Randomized Clinical Trial. *JAMA Psychiatry*, *74*(7), 719–728. https://doi.org/10.1001/jamapsychiatry.2017.1220

Li, Q., Chen, D., Liu, T., Walss-Bass, C., de Quevedo, J. L., Soares, J. C., Zhao, J., & Zhang, X. Y. (2016). Sex Differences in Body Mass Index and Obesity in Chinese Patients With Chronic Schizophrenia. *Journal of Clinical Psychopharmacology*, *36*(6), 643–648. https://doi.org/10.1097/JCP.0000000000000594

Li, Q., Du, X., Zhang, Y., Yin, G., Zhang, G., Walss-Bass, C., Quevedo, J., Soares, J. C., Xia, H., Li, X., Zheng, Y., Ning, Y., & Zhang, X. Y. (2017). The prevalence, risk factors and clinical correlates of obesity in Chinese patients with schizophrenia. *Psychiatry Research*, *251*, 131–136. https://doi.org/10.1016/j.psychres.2016.12.041

Lin, S.-H., Tseng, H.-H., Tsai, H. C., Chi, M. H., Lee, I. H., Chen, P. S., Chen, K. C., & Yang, Y. K. (2021). Positive Symptoms in Antipsychotic-naïve Schizophrenia are Associated with Increased Body Mass Index after Treatment. *Clinical Psychopharmacology and Neuroscience*, *19*(1), 155–159. https://doi.org/10.9758/cpn.2021.19.1.155

Łopuszańska, U., & Makara-Studzińska, M. (2017). Relationship between antipsychotic medication, obesity and cognitive functions. *Current Problems of Psychiatry*, *18*(4), 272–278. https://doi.org/10.1515/cpp-2017-0020

Meltzer, H. Y., Perry, E., & Jayathilake, K. (2003). Clozapine-induced weight gain predicts improvement in psychopathology. *Schizophrenia Research*, *59*(1), 19–27. https://doi.org/10.1016/S0920-9964(01)00326-7

Mezquida, G., Savulich, G., Garcia-Rizo, C., Garcia-Portilla, M. P., Toll, A., Garcia-Alvarez, L., Bobes, J., Mané, A., Bernardo, M., & Fernandez-Egea, E. (2018). Inverse association between negative symptoms and body mass index in chronic schizophrenia. *Schizophrenia Research*, *192*, 69–74. https://doi.org/10.1016/j.schres.2017.04.002

Moore, T. A., Buchanan, R. W., Buckley, P. F., Chiles, J. A., Conley, R. R., Crismon, M. L., Essock, S. M., Finnerty, M., Marder, S. R., Miller, D. D., McEvoy, J. P., Robinson, D. G., Schooler, N. R., Shon, S. P., Stroup, T. S., & Miller, A. L. (2007). The Texas Medication Algorithm Project antipsychotic algorithm for schizophrenia: 2006 update. *The Journal of Clinical Psychiatry*, *68*(11), 1751–1762. https://doi.org/10.4088/jcp.v68n1115

Patel, K. R., Cherian, J., Gohil, K., & Atkinson, D. (2014). Schizophrenia: Overview and Treatment Options. *Pharmacy and Therapeutics*, *39*(9), 638–645.

Pérez-Iglesias, R., Martínez-García, O., Pardo-Garcia, G., Amado, J. A., Garcia-Unzueta, M. T., Tabares-Seisdedos, R., & Crespo-Facorro, B. (2014). Course of weight gain and metabolic abnormalities in first treated episode of psychosis: The first year is a critical period for development of cardiovascular risk factors. *International Journal of Neuropsychopharmacology*, *17*(1), 41–51. https://doi.org/10.1017/S1461145713001053

Tian, Y., Liu, D., Wang, D., Wang, J., Xu, H., Dai, Q., Andriescue, E. C., Wu, H. E., Xiu, M., Chen, D., Wang, L., Chen, Y., Yang, R., Wu, A., Wei, C. W., & Zhang, X. (2020). Obesity in Chinese patients with chronic schizophrenia: Prevalence, clinical correlates and relationship with cognitive deficits. *Schizophrenia Research*, *215*, 270–276. https://doi.org/10.1016/j.schres.2019.10.017

Tian, Y., Wang, D., Wei, G., Wang, J., Zhou, H., Xu, H., Dai, Q., Xiu, M., Chen, D., Wang, L., & Zhang, X. Y. (2021). Prevalence of obesity and clinical and metabolic correlates in first-episode schizophrenia relative to healthy controls. *Psychopharmacology*, *238*(3), 745–753. https://doi.org/10.1007/s00213-020-05727-1

WHO Expert Consultation. (2004). Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet (London, England)*, *363*(9403), 157–163. https://doi.org/10.1016/S0140-6736(03)15268-3