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# The Impact of Blood Glucose and Cholesterol Levels on the Manifestation of Psychiatric Disorders

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**Abstract:** This study examined possible association of fasting glucose and lipid abnormalities in psychiatric patients on conventional antipsychotic medications. A total of 305 subjects were used for the study, comprising 203 clinically diagnosed psychiatric patients and 102 non-psychiatric subjects used as control at the psychiatric clinic at Komfo Anokye Teaching Hospital (KATH). Questionnaires were administered, blood pressure and anthropometric measurements undertaken. Fasting blood samples were taken for glucose and total cholesterol. The patients included those treated with conventional antipsychotic agents. It was noted, that there were higher rates of diabetes (22.17%) and lipid abnormalities (42.43%) with lower rate of hypertension (5.91%) and obesity (5.91%) across the sample as compared to control. This finding suggests that the high prevalence of diabetes and lipid abnormalities, in a young, psychiatrically ill population makes the case for aggressive screening.

**Key words:** Diabetes, hypercholesterolemia, risk factors, psychiatric disorder, obesity

## INTRODUCTION

Metabolic syndrome is associated with increased risk of cardiovascular morbidity and mortality and is defined by the International Diabetic Federation (IDF) as having obesity and presence of two or more of the following factors: hyperlipidaemia, raised blood pressure and/or raised blood glucose (NCEP III, 2001). Other factors that are non modifiable such as: age above forty, male gender, Asian or Black racial origin and a family history of diabetes mellitus, further increase the risk of this syndrome (Allison *et al*., 1999; Mukherjee *et al*., 1996).

Sedentary life style, smoking, poor dietary habits, reduced access to medical care, poor judgement of health status and medications (antipsychotics, antidepressants and mood stabilisers) contribute to the increased prevalence of metabolic syndrome and its fatal consequences (Allison *et al*., 1999; Mukherjee *et al*., 1996) in people with enduring and severe mental illnesses. Thus hyperlipidaemia, type 2 diabetes, ischaemic heart disease and obesity are more common in patients with psychiatric disorders than in the general population. Reports have suggested that people with severe mental illness are up to five times more likely to have diabetes and twice as likely to die from cardiovascular disease.

The antipsychotic class of drugs has been used for the treatment of psychiatric disorders thus enabling numerous patients to live in the community rather than in psychiatric centers. Recently, antipsychotic agents have been linked to several forms of morbidity, including obesity; hyperlipidaemia; type 2 diabetes mellitus and diabetic ketoacidosis (Allison and Casey, 2001; Mir and Taylor, 2001). The earliest report indicating that antipsychotics might directly interfere with glucose metabolism was based on animal data (Norman and Hiestand, 1955; Lebovitz, 2003). It was reported that diabetic mice treated with chlorpromazine had elevated blood glucose levels and higher mortality rates when compared with diabetic mice not treated with chlorpromazine. Compared with the general population, life expectancy in patients with psychiatric disorders is shorter by as much as 20%, attributable to higher rates of suicide, accidental deaths and natural causes such as cardiovascular disease, infectious disease and endocrine disorders (Harris and Barraclough, 1998; Newman and Bland, 1991).

Lebovitz (2003) suggested monitoring of body weight, plasma fasting glucose and lipids with the initiation of antipsychotics and continuing monitoring throughout treatment (Lebovitz, 2003). Others have

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supported baseline and continuation monitoring of body weight, Body Mass Index (BMI), fasting blood glucose and fasting lipid profile (Casey *et al*., 2004; Marder *et al*., 2002; Menza *et al*., 2004). However, a recent study revealed that less than half of hospitalised patients prescribed antipsychotic drugs were tested for diabetes. We conducted this study to evaluate glucose dysregulation and lipid abnormalities in psychiatry patients on conventional antipsychotic medications.

## MATERIALS AND METHODS

**Subjects:** This study was carried out at the Out-Patient Department of the Psychiatric Clinic at the Komfo Anokye Teaching Hospital, Kumasi-Ghana over a 3 month period (January to March 2006). The study was conducted among those diagnosed at the psychiatric clinic as suffering from one form or the other of a psychiatric condition using the International Classification of Diseases (ICD-10) criteria and attending the psychiatric clinic for treatment. All patients had been on monotherapy with a conventional antipsychotic drug (i.e., chlorpromazine, fluphenazine, haloperidol or trifluoperazine). Patients on more than one antipsychotic were excluded. A total of (305) individuals were sampled for this study. Two hundred and three subjects were diagnosed as psychiatric patients and 102 non-psychiatric subjects. The 102 non-psychiatric subjects were used as control group. All confirmed psychiatric patients were on monotherapy with conventional antipsychotic medication. The participation of the respondents was voluntary and informed consent was obtained from each of them. The study was approved by the Committee on Human Research, Publication and Ethics of the School of Medical Sciences and the Komfo Anokye Teaching Hospital, Kumasi.

**Sample collection and preparation:** Venous blood samples were collected after an overnight fast (12-16 h). About 5 mL of venous blood was collected and dispensed into fluoride oxalate tubes and vacutainer® plain tubes for separation into plasma and serum, respectively. This was then taken to the laboratory and centrifuged at 500 g for 15 min within 30 min of sample collection for plasma and serum, respectively. Biochemical assays on the serum and plasma were performed with the ATAC® 8000 Random Access Chemistry System (Elan Diagnostics, Smithfield, RI, USA). Parameters that were determined include: Total Cholesterol (T-CHOL) for the serum sample and fasting blood sugar for the plasma sample. Serum total cholesterol was estimated using Cholesterol Oxidase/Peroxidase method Trinder (1969) and glucose was determined using glucose oxidase/peroxidase method (Trinder, 1969).

**Anthropometric variables:** Anthropometric measurements included height, measured without shoes and weight to nearest 0.1 kg in light clothing. Subjects were weighed on a bathroom scale (Zhongshan Camry Electronic Co. Ltd., Guangdong, China) and their height measured with a wall-mounted ruler. BMI was calculated by dividing weight (kg) by height squared ($m^2$). On the basis of BMI, all subjects were divided into four groups: under weight (BMI<19 kg $m^{-2}$), normal (BMI between 19 and 24.9 kg $m^{-2}$), overweight (BMI between 25 and 29.9 kg $m^{-2}$) and obese (BMI = 30 kg $m^{-2}$).

Blood pressure was taken by qualified psychiatric nurses using a mercury sphygmomanometer and stethoscope. Measurements were taken from the left upper arm after subjects had been sitting for >5 min in accordance with the recommendation of the American Heart Association (Kirkendall *et al*., 1967). Duplicate measurements were taken with a 5 min rest interval between measurements and the mean value was recorded to the nearest 2.0 mmHg.

**Statistical analysis:** Values for the continuous variables are expressed as their Mean±SEM. Comparisons of the psychiatry subjects with the control group were performed using unpaired students t-tests, a level of $p<0.05$ was considered as statistically significant. Pearson rank correlation was used to examine the relationship between Fasting Blood Sugar (FBS), T-CHOL, BMI and Blood Pressure (BP). GraphPad Prism version 5.00 for windows was used for statistical analysis (GraphPad software, San Diego California USA, www.graphpad.com).

## RESULTS

This study involved 305 subjects of whom 203 were diagnosed using the International Classification of Diseases (ICD-10) as having psychiatric disorders and 102 non-psychiatric subjects who served as study control. The age distribution for the psychiatric patients ranged between 7 and 79 years. Females constituted 58% of the study population and 13% of the subjects were reporting as new cases whilst 87% of them were old cases coming for review at the psychiatric clinic. The 20-40 year group accounted for about 60% of the total psychiatry patient population (Fig. 1d). The majority of psychiatric patients in the sample were unemployed (n = 145; 71.5%), single (n = 113; 55.7%) and had no family history of psychiatry (n = 173; 85.2%) as shown in Fig. 1a-c, respectively.

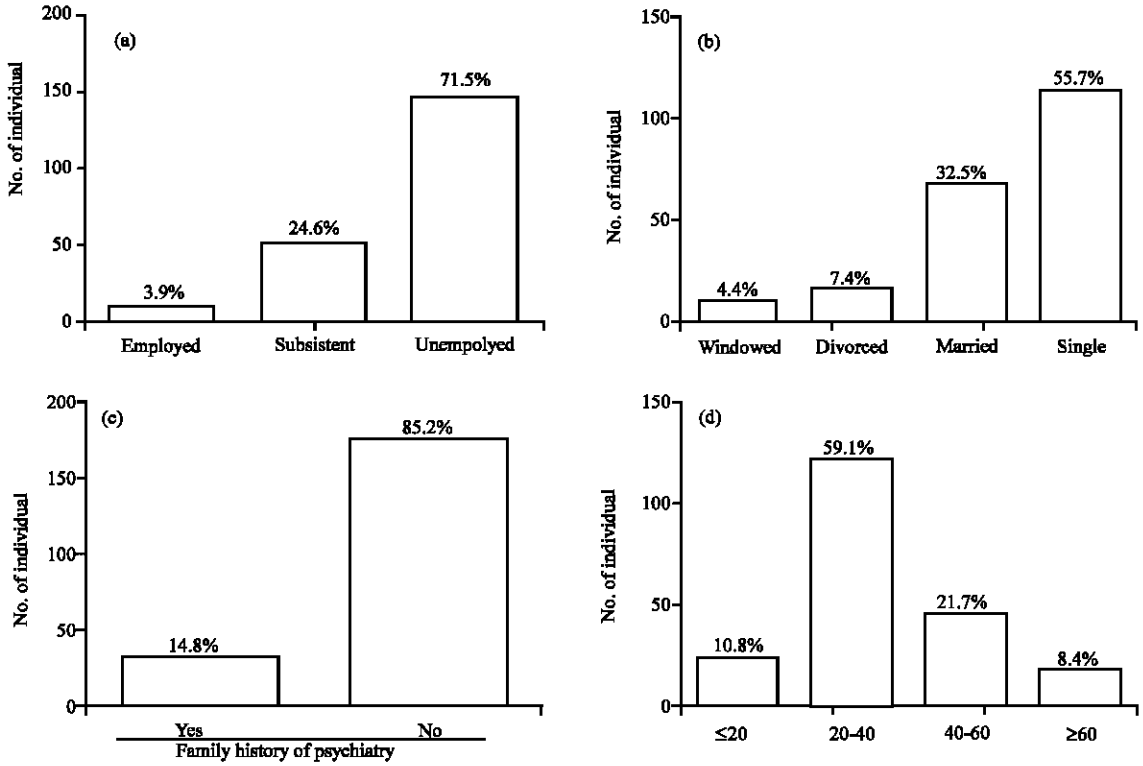


Fig. 1: Occupational distribution (a) marital status, (b) family history of psychiatry, (c) age distribution and (d) among the psychiatry patients

Table 1: General characteristic and prevalence of components of the metabolic syndrome among psychiatric subjects and non-psychiatric control

| Parameters | Control | Total | Male | Female |
|---|---|---|---|---|
| **Mean value** | | | | |
| T-CHOL | 183.50±4.01 | 196.90±3.72* | 195.40±6.39 | 197.90±4.45 |
| FBS | 5.27±0.10 | 5.53±0.11 | 5.59±0.17 | 5.49±0.14 |
| BMI | 22.97±0.52 | 23.18±0.31 | 21.97±0.31 | 23.82±0.45** |
| SBP | 119.20±1.89 | 119.10±0.97 | 121.50±1.34 | 117.40±1.34** |
| DBP | 74.71±1.19 | 79.72±0.73** | 80.50±1.07 | 79.15±0.99 |
| **Prevalence(%)** | | | | |
| Dyslipidaemia | 22(21.57%) | 85(42.43%) | 35(40.70%) | 50(42.74%) |
| Diabetes | 7(6.86%) | 45(22.17%) | 17(19.77%) | 28(23.93%) |
| Underweight | 7(6.86%) | 21(10.34%) | 8(9.30%) | 13(11.11%) |
| Overweight | 27(26.47%) | 48(23.64%) | 17(19.77%) | 31(26.49%) |
| Obese | 17(16.67%) | 12(5.91%) | 1(1.16%) | 11(9.40%) |
| SBP | 19(18.63%) | 15(7.39%) | 7(8.14%) | 8(6.84%) |
| DBP | 19(18.63%) | 31(15.27%) | 12(13.95%) | 19(16.24) |
| Hypertension | 14(13.73%) | 12(5.91%) | 5(5.81%) | 7(5.98%) |

T-Chol: Total cholesterol; FBS: Fasting blood sugar; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure, *: $p<0.05$; **: $p<0.001$ when total psychiatric subjects were compared to the control group and **: $p<0.001$ when female subjects were compared to the male subjects

In reviewing the comorbid medical conditions in this sample, it was found that the psychiatric patients had significantly higher total cholesterol and diastolic hypertension as compared to the control group. However, when the psychiatric patients were stratified based on sex, it was found that even though the female had significantly lower systolic blood pressure as compared to the male, the female (23.82±0.45) were significantly heavier than their male (21.97±0.31) counterparts (Table 1). The prevalence of the comorbid medical conditions was 22.17% for diabetes (i.e., ~3 times relative risk of developing diabetic compared to non-psychiatric patients), 5.91% for hypertension and obesity (~3 times less likely to develop hypertension and obesity) and a 42.43% for dyslipidaemia (~2 times relative risk of developing hypercholesterolemia) (Table 1). When stratified based on sex, the female had higher percentage prevalence of all the comorbid medical conditions as compared to the male counterpart (Table 1).

Among the conditions schizophrenia was the most commonly reported case accounting for 59.61% followed by psychosis (17.24%), hypomania (8.37%), depression (8.37%) and others (6.41%). The others comprise of those presenting with epilepsy, mental retardation, dementia, anxiety disorder and somatism (Table 2). Patients with schizophrenia, hypomania and psychosis each have about two times relative risk of developing dyslipidaemia (hypercholesterolemia) compared with the control group. With regard to diabetes, schizophrenic patients have about four times relative risk of developing diabetes; hypomania, psychosis and others each have about three

Table 2: The prevalence of comorbid medical conditions among the various psychiatric conditions

| Parameters | Control (102) | Schizophrenia (121) | Hypomania (17) | Depression (17) | Psychosis (35) | Others (13) |
|---|---|---|---|---|---|---|
| Prevalence | 0/102(0.00%) | 121/203(59.61%) | 17/203(8.37%) | 17/203(8.37%) | 35/203(17.24%) | 13/203(6.41%) |
| Dyslipidaemia | 22/102(21.57%) | 54/121(44.63%) | 8/17(47.06%) | 5/17(29.41%) | 13/35(37.14%) | 4/13(30.77%) |
| Diabetes | 7/102(6.86%) | 28/121(23.14%) | 3/17(17.65%) | 6/17(35.29%) | 6/35(17.14%) | 2/13(15.38%) |
| Underweight | 7/102(6.86%) | 11/121(9.09%) | 1/17(5.88%) | 2/17(11.76%) | 5/35(14.29%) | 2/13(15.38%) |
| Overweight | 27/102(26.47%) | 31/121(25.62%) | 1/17(5.88%) | 5/17(29.41%) | 8/35(22.86%) | 3/13(23.08%) |
| Obese | 17/102(16.67%) | 6/121(4.96%) | 2/17(11.76%) | 1/17(5.88%) | 2/35(5.71%) | 1/13(7.69%) |
| Hypertension | 14/102(13.73%) | 8/121(6.61%) | 1/17(5.88%) | 3/17(17.65%) | 0/35(0.00%) | 0/13(0.00%) |
| Psychiatry Hist. | 5/102(4.90%) | 18/121(14.88%) | 3/17(17.65%) | 2/17(11.76%) | 5/35(14.29%) | 2/13(15.38%) |
| Female | 73/102(71.57%) | 71/121(58.68%) | 9/17(52.94%) | 10/17(58.82%) | 18/35(51.43%) | 9/13(69.23%) |

Table 3: Pearson correlation coefficients of clinical variables and anthropometric measurement for psychiatric subjects (upper right-hand side) and control group (lower left-hand side)

| Parameters | T CHOL | FBS | BMI | SBP | DBP |
|---|---|---|---|---|---|
| T CHOL | | -0.06 | 0.24** | 0.17* | 0.07 |
| FBS | -0.08 | | 0.14* | 0.08 | 0.10 |
| BMI | 0.14 | 0.10 | | 0.28*** | 0.18* |
| SBP | 0.12 | 0.18* | 0.22** | | 0.67*** |
| DBP | 0.17* | 0.18* | 0.19* | 0.70*** | |

T-Chol: Total cholesterol; FBS: Fasting blood sugar; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure. *p = 0.05, **p = 0.001, ***p = 0.01

times relative risk of developing diabetes and about five times relative risk of developing diabetes was experienced in depressed patients (Table 2). However, the psychiatric patients were zero to four times less likely to develop obesity and hypertension compared to the control group (Table 2).

From the correlation matrix in Table 3, blood pressure showed significant positive correlations with BMI and total cholesterol in both the control group and psychiatric subjects. Blood pressure, however, showed a significant positive correlation with fasting blood sugar in only the control group. BMI also showed a significant positive correlation with total cholesterol and fasting blood sugar among the psychiatric subjects only (Table 3).

## DISCUSSION

In this study, the 20-40 year age group constituted about 60% of the psychiatric patients and 72% of the psychiatric patients were unemployed whilst 24% were engaged in subsistence trading, whereas only 4% were gainfully employed. It may be presumed, therefore, that unemployment and low household income may be a significant determinant for the development of the psychiatric disorders in conformity with the report of other studies (Oyane *et al*., 2005).

Females constituted about 58% of the psychiatric patients in this study. The high proportion of females among the psychiatric patients in this study is also consistent with the findings of Oyane *et al*. (2005) who indicated that female gender, low educational level and unemployment leading to low household income are some of the determinant factors for psychiatric disorders. This high female prevalence may also be attributed to the emotionally fragile nature of women who are known to internalize and brood over problems compared to men (Gore-Felton *et al*., 2001).

From the study, schizophrenia was the most prevalent psychiatric condition commonly reported accounting for 59%. This finding is also consistent with a study conducted independently in Ghana by Turkson and Asante (1997). Schizophrenia is a destructive disorder; thus the families of the affected individual are much more concerned and disturbed and as a result, seek mental care for their family members. Other conditions like dementia are associated with old age and people usually do not bother to report because it is considered as normal for neurodegenerative disease to occur in old age. This could possibly explain why schizophrenia is the most prevalent psychiatric condition, even though other conditions might also have relatively high prevalence.

This study found the prevalence of diabetes among the subjects to be 22% and hypercholesterolemia to be 42%, both of which are higher than in the nonpsychiatric population. Whether diabetes or hypercholesterolaemia are associated with the antipsychotic agents remains to be fully investigated. Prospective controlled studies measuring insulin resistance are more likely to provide clues to this question. There is speculation that antipsychotic-induced alterations in glucose regulation may exacerbate preexisting glucoregulatory disturbances associated with schizophrenia (Newcomer *et al*., 1999). Others suggest that the association of antipsychotics with diabetes is a function of drug affinity for the five hydroxytryptamine (5-HT) receptors, which are also involved in glucose homeostasis (Wirshing *et al*., 1998).

The schizophrenic population has been shown to have a two to four times relative risk of developing diabetes mellitus compared with the general population (McKee *et al*., 1986; Mukherjee *et al*., 1996) and this has been confirmed by this study. This study found a 23.14% prevalence of type 2 diabetes mellitus among schizophrenics, a finding which is consistent with the literature. In a previous naturalistic study, in which patients 55 years and older within the schizophrenia spectrum were followed on a 6-monthly basis with

measures of side effects, cognition and symptoms, a 19% prevalence of type 2 diabetes mellitus was noted (Gupta *et al*., 2003). They suggest that the antipsychotic agents as a group may unmask or precipitate diabetes in susceptible psychotic patients.

In this study, the psychiatric patients presented with a low BMI compared to the control. This is probably due to the stigma and superstition associated with psychiatric conditions in this part of the world thereby leading to the neglect of the patients. In most Ghanaian families, psychiatric patients are often shunned by their nuclear as well as extended families because the condition is traditionally associated with superstition. It may be argued that due to the high incidence of low education achievement as well as unemployment among psychiatric patients, they tend to be poor and hence malnourished. This observation however may require further qualitative research to exclude any social desirability bias. Among both the psychiatric patients and controls in this study, an increase in body weight correlated with an increase in the total cholesterol, fasting blood sugar, systolic blood pressure as well as diastolic blood pressure.

Researchers have identified several biologaboutic risk factors for psychiatric disorders, including a family history of the disease and certain neurological changes in the elderly (Cooper, 1997). From this study, only 14% of the patients had a family history of any psychiatric disorder and 86% were having their condition as the first occurrence in the family. Also, 9% of the psychiatric patients are above 60 years and their condition can be a physiological neurological degeneration associated with the elderly.

## CONCLUSION

The peak age for psychiatric disorders in this study was 20-40 years with schizophrenia being the most commonly presented condition (60%). The study also showed that psychiatric conditions were more prevalent in women contrary to WHO mental health report (Brundtland, 2001) which indicates that there were no gender differences in the occurrence of psychiatric disorders. This study has also confirmed that unemployment is associated with psychiatric disorders. The subjects had about 2 to 3 times relative risk of developing diabetes mellitus and hypercholesterolemia compared to control.

Historically, people with severe and enduring mental illness are less likely to access the primary care services. Their main point of contact remains the psychiatric services. It is, therefore, imperative that the mental health services take up this challenge proactively. Early identification of patients with high risk factors and the appropriate management of the indicators of the metabolic syndrome can go a long way in improving the physical health of these patients.

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## REFERENCES

Allison, D.B., K.R. Fontaine, M. Heo, J.L. Mentore and J.C. Cappelleri *et al*., 1999. The distribution of body mass index among individuals with and without schizophrenia. J. Clin. Psychiatry, 60: 215-220.

Allison, D.B. and D.E. Casey, 2001. Antipsychotic-induced weight gain: A review of the literature. J. Clin. Psychiatry, 62: 22-31.

Brundtland, G.H., 2001. From the world health organization. Mental health: New understanding, new hope. JAMA., 286: 2391-2391.

Casey, D.E., D.W. Haupt, J.W. Newcomer, D.C. Henderson and M.J. Sernyak *et al*., 2004. Antipsychotic-induced weight gain and metabolic abnormalities: implications for increased mortality in patients with schizophrenia. J. Clin. Psychiatry, 65: 4-18.

Cooper, S.A., 1997. Epidemiology of psychiatric disorders in elderly compared with younger adults with learning disabilities. Br. J. Psychiatry, 170: 375-380.

Gore-Felton, C., C. Koopman, E. McGarvey, N. Hernandez and R.J. Jr. Canterbury, 2001. Relationships of sexual, physical and emotional abuse to emotional and behavioral problems among incarcerated adolescents. J. Child Sex. Abus., 10: 73-88.

Gupta, S., C. Steinmeyer, B. Frank, K. Lockwood, B. Lentz and K. Schultz, 2003. Older patients with schizophrenia: Nature of dwelling status and symptom severity. Am. J. Psychiatry, 160: 383-384.

Harris, E.C. and B. Barraclough, 1998. Excess mortality of mental disorder. Br. J. Psychiatry, 173: 11-53.

Kirkendall, W.M., A.C. Burton, F.H. Epstein and E.D. Freis, 1967. Recommendations for human blood pressure determination by sphygmomanometers. Circulation, 36: 980-988.

Lebovitz, H.E., 2003. Metabolic consequences of atypical antipsychotic drugs. Psychiatry Q., 74: 277-290.

Marder, S.R., S.M. Essock, A.L. Miller, R.W. Buchanan and J.M. Davis *et al*., 2002. The Mount Sinai conference on the pharmacotherapy of schizophrenia. Schizophr. Bull., 28: 5-16.

McKee, H.A., P.F. D'Arcy and P.J. Wilson, 1986. Diabetes and schizophrenia-a preliminary study. J. Clin. Hosp. Pharm., 11: 297-299.

Menza, M., B. Vreeland, S. Minsky, M. Gara, D.R. Radler and M. Sakowitz, 2004. Managing atypical antipsychotic-associated weight gain: 12-month data on a multimodal weight control program. J. Clin. Psychiatry, 65: 471-477.

Mir, S. and D. Taylor, 2001. Atypical antipsychotics and hyperglycaemia. Int. Clin. Psychopharmacol., 16: 63-73.

Mukherjee, S., P. Decina, V. Bocola, F. Saraceni and P.L. Scapicchio, 1996. Diabetes mellitus in schizophrenic patients. Compr. Psychiatry, 37: 68-73.

NCEP III, 2001. Expert panel on detection, evaluation and treatment of high blood cholesterol in adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation and treatment of high blood cholesterol in adults. J. Am. Med. Assoc., 285: 2486-2497.

Newcomer, J.W., S. Craft, R. Fucetola, S.O. Moldin, G. Selke, L. Paras and R. Miller, 1999. Glucose-induced increase in memory performance in patients with schizophrenia. Schizophr. Bull., 25: 321-335.

Newman, S.C. and R.C. Bland, 1991. Mortality in a cohort of patients with schizophrenia: A record linkage study. Can. J. Psychiatry, 36: 239-245.

Norman, D. and W.A. Hiestand, 1955. Glycemic effects of chlorpromazine in the mouse, hamster and rat. Proc. Soc. Exp. Biol. Med., 90: 89-91.

Oyane, N.M., F. Holsten, R. Ursin and B. Bjorvatn, 2005. Seasonal variations in mood and behaviour associated with gender, annual income and education: The Hordaland health study. Eur. J. Epidemiol., 20: 929-937.

Trinder, P., 1969. Determination of glucose in blood using glucose oxidase with an alternative oxygen acceptor. Ann. Clin. Biochem., 62: 24-27.

Turkson, S.N. and K. Asante, 1997. Psychiatric disorders among offender patients in the Accra Psychiatric Hospital. West Afr. J. Med., 16: 88-92.

Wirshing, D.A., B.J. Spellberg, S.M. Erhart, S.R. Marder and W.C. Wirshing, 1998. Novel antipsychotics and new onset diabetes. Biol. Psychiatry, 44: 778-783.