Assessment of risk for cardiovascular disease in a sample of schizophrenic patients

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Received 1 November 2016
Accepted 1 March 2017

Egyptian Journal of Psychiatry
2017, 38:131–137

Background
Interest in cardiovascular diseases (CVD) in schizophrenic patients has grown recently because of documented increased mortality. Causes of this mortality are most probably somatic diseases, particularly CVD. We aim to assess the risk for developing CVD in schizophrenic patients using C-reactive protein (CRP) and lipid profile by applying the Framingham Risk Score and correlate this risk with the severity of symptoms of schizophrenia.

Patients and methods
This is a cross-sectional study consisting of 62 schizophrenic patients who were recruited from the Kuwait Center for Mental Health inpatient departments. The structured Clinical Interview for DSM4 Axis of Disorders (SCID-I) and positive and negative syndrome scale were administered on all patients. Laboratory investigations for serum level of CRP, total cholesterol level, and high-density lipoprotein level were carried out. Cardiac risk was assessed on the basis of Framingham Risk Score.

Results
Twenty-one percent of patients had a risk for developing CVD as per the Framingham Risk Score. All patients had intermediate to high risk of developing CVD on the basis of baseline CRP. There was sex-related difference in cardiovascular risk as women had no risk, whereas 25% of men had a risk for developing CVD. There was no significant correlation between risk for CVD and severity of symptoms of schizophrenia.

Conclusion
Our study points to the measurement of CRP and screening of lipid levels as an improved method for identifying schizophrenic patients at risk for cardiovascular events.

Keywords:
C-reactive protein, cardiac risk, schizophrenic patients

Egypt J Psychiatr 38:131–137

1110-1105

Introduction

Schizophrenia is a serious neuropsychiatric disorder of uncertain etiology with a lifetime prevalence of ~0.7% (Tandon *et al.*, 2008). Schizophrenic patients have a mortality rate that is two to three times higher than that of the overall US population (Saha *et al.*, 2007). Causes for this premature mortality are most probably somatic diseases, particularly cardiovascular disease (CVD) (Osborn *et al.*, 2007).

This group of patients is characterized by low physical activity, poor diet, high frequency of smoking, as well as the side effects of commonly prescribed antipsychotic medications, which cause weight gain and alter glucose metabolism (Allison *et al.*, 1999, 2009; Compton *et al.*, 2006; Casagrande *et al.*, 2011). All of these lead to increased burden of cardiovascular risk factors, including obesity, dyslipidemia, hypertension, and diabetes.

In 2004, the American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, and North American Association for the Study of Obesity released guidelines for screening and monitoring somatic conditions among antipsychotic users, many of whom have serious mental illnesses such as schizophrenia. The American Diabetes Association/American Psychiatric Association consensus panel guidelines recommend more frequent screening for and monitoring of cardiovascular risk factors among antipsychotic users (American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, North American Association for the Study of Obesity, 2004). Thus, screening for cardiovascular risk factors in schizophrenic patients is an important first step for timely diagnosis and appropriate treatment for better outcomes.

 DOI: 10.4103/1110-1105.217211

The Framingham Risk Score is one of the scoring systems used to determine an individual's chances of developing CVD (National Cholesterol Education Program (NCEP), 2002). It is a sex-specific algorithm used to estimate the 10-year cardiovascular risk of an individual.

Recent research suggests that patients with elevated C-reactive protein (CRP) levels have increased risk f or hypertension and CVD (Danesh *et al.*, 2004).

CRP is an acute-phase reactant synthesized by the liver in response to cytokines released by damaged tissue. Production is controlled by interleukin-6, an inflammatory cytokine. CRP is commonly measured to screen for inflammation or infection. Traditional assays for CRP are insufficiently sensitive for measuring the lower serum values associated with atherosclerotic disease (Casas *et al.*, 2008). The newer high-sensitivity C-reactive protein testing has been shown to add to the predictive value of total cholesterol, low-density lipoprotein, and high-density lipoprotein (HDL), as well as the Framingham 10-year risk scores (Pearson *et al.*, 2003).

Aim

The aim of the study was to assess the risk of developing CVD in patients with schizophrenia for early prevention and better outcome and correlate this risk with the severity of symptoms of schizophrenia.

Patients and methods

This is a cross-sectional study aiming to assess the risk for developing CVD in schizophrenic patients. All patients were recruited from Kuwait Center for Mental Health after taking approval from the scientific and ethics committee of the hospital. The study was conducted from January 2013 to May 2013. The total number of patients was 62 after applying the inclusion and exclusion criteria.

Patients of either sex, aged 20 years or more, who had given written informed consent after being explained the aim of study were eligible for inclusion. Diagnosis was made according to *Diagnostic and statistical manual of mental disorders*, 4th ed., test revised (First *et al.*, 1996; El Missiry, 2003).

All patients with a known general acute or chronic medical condition, previous cardiac lesions, seizures, and neurological disorders as well as patients with substance abuse other than cigarette smoking and Axis II disorders including mental subnormality and personality disorders were excluded. In addition, women taking contraceptive pills were excluded as oral contraceptives can increase the serum CRP level.

Tools

Psychiatric assessment

Sociodemographic data and detailed medical and psychiatric history were gathered for all patients using a semistructured interview. The positive and negative syndrome scale (PANSS) (Fiszbein and Opler, 1987) was applied on all patients. Each scale comprises seven symptoms that are rated on a 1 (absent) to 7 (extreme) metric. The PANSS is a medical scale used for measuring symptom severity of patients with schizophrenia. As 1 rather than 0 is given as the lowest score for each item, the patient cannot score lower than 30 in the total PANSS score. Scores are often given separately for the positive items, negative items, and general psychopathology.

Cardiac assessment

Cardiac risk was assessed on the basis of the Framingham Risk Score (National Cholesterol Education Program (NCEP), 2002), which is a risk assessment tool for estimating the 10-year risk of having a heart attack.

This risk assessment tool uses information from the Framingham Heart Study to predict a person's chance of having a heart attack in the next 10 years. This tool is designed for adults aged 20 years or older who do not have heart disease or diabetes. The risk score is calculated by entering one's information in the calculator below.

Age:	years
Gender:	Female
	Male
Total Cholesterol:	mg/dL
HDL Cholesterol:	mg/dL
Smoker:	No
	Yes
Systolic Blood Pressure:	mm/Hg
Are you currently on any medication to treat high blood pressure.	No
	Yes

Total cholesterol: Total cholesterol is the sum of all the cholesterol in your blood. The higher the total cholesterol level, the greater the risk for heart disease. Less than 200 mg/dl is considered the desirable level, which puts you at lower risk for heart disease. A cholesterol level of 200 mg/dl or greater increases your risk. A level 200–239 mg/dl is considered borderline high, and a level 240 mg/dl and above is considered high blood cholesterol. A person with this level has more than twice the risk for heart disease compared with someone whose cholesterol is below 200 mg/dl.

HDL cholesterol: HDL is the good cholesterol. HDL carries cholesterol in the blood from other parts of the body back to the liver, which leads to its removal from the body. Thus, HDL helps keep cholesterol from building up in the walls of the arteries. An HDL level less than 40 mg/dl is considered a major risk factor for heart disease. An HDL of 60 mg/dl and above is considered protective against heart disease.

Smoker: A person who has smoked any cigarettes in the past month has to select the boxed marked 'yes'.

Systolic blood pressure: Systolic blood pressure is the first number of your blood pressure reading. For example, if your reading is 120/80 (120 over 80), your systolic blood pressure is 120.

Framingham Risk Score for women

Age (years)

On the basis of age the following scores are given: 20–34, −7 points; 35–39, −3 points; 40–44, 0 points; 45–49, 3 points; 50–54, 6 points; 55–59, 8 points; 60–64, 10 points; 65–69, 12 points; 70–74, 14 points; 75–79, 16 points.

Total cholesterol (mg/dl)

Scores on the basis of the level of total cholesterol for different age groups are as follows: For age 20–39 years – under 160, 0 points; 160–199, 4 points; 200–239, 8 points; 240–279, 11 points; 280 or higher, 13 points. For age 40–49 years – under 160, 0 points; 160–199, 3 points; 200–239, 6 points; 240–279, 8 points; 280 or higher, 10 points. For age 50–59 years – under 160, 0 points; 160–199, 2 points; 200–239, 4 points; 240–279, 5 points; 280 or higher, 7 points. For age 60–69 years – under 160, 0 points; 160–199, 1 point; 200–239, 2 points; 240–279, 3 points; 280 or higher, 4 points. For age 70–79 years – under 160, 0 points; 160–199, 1 point; 200–239, 1 point; 240–279, 2 points; 280 or higher, 2 points.

If cigarette smoker (years)

On the basis of cigarette smoking the scores are as follows for different age groups: 20–39, 9 points; 40–49, 7 points; 50–59, 4 points; 60–69, 2 points; 70–79, 1 point.

All nonsmokers

Nonsmokers are given a score of 0.

High-density lipoprotein cholesterol (mg/dl)

On the basis of the level of HDL cholesterol the scores are as follows: 60 or higher, −1 point; 50–59, 0 points; 40–49, 1 point; under 40, 2 points.

Systolic blood pressure (mmHg)

The scores for untreated systolic blood pressure are as follows: under 120, 0 points; 120–129, 1 point; 130–139, 2 points; 140–159, 3 points; 160 or higher, 4 points. The scores for treated systolic blood pressure are as follows: under 120, 0 points; 120–129, 3 points; 130–139, 4 points; 140–159, 5 points; 160 or higher, 6 points.

Ten-year risk (%)

The 10-year risk was determined on the basis of the total scores as follows: under 9 points, <1; 9–12 points, 1; 13–14 points, 2; 15 points, 3; 16 points, 4; 17 points, 5; 18 points, 6; 19 points, 8; 20 points, 11; 21 points, 14; 22 points, 17; 23 points, 22; 24 points, 27; greater than 25 points, over 30.

Framingham Risk Score for men

Age (years)

On the basis of age the Framingham Risk Scores for men are as follows: 20–34, −9 points; 35–39, −4 points; 40–44, 0 points; 45–49, 3 points; 50–54, 6 points; 55–59, 8 points; 60–64, 10 points; 65–69, 11 points; 70–74, 12 points; 75–79, 13 points.

Total cholesterol (mg/dl)

On the basis of the level of total cholesterol the scores for different age groups are as follows: age 20–39 years – under 160, 0 points; 160–199, 4 points; 200–239, 7 points; 240–279, 9 points; 280 or higher, 11 points. Age 40–49 years – under 160, 0 points; 160–199, 3 points; 200–239, 5 points; 240–279, 6 points; 280 or higher, 8 points. Age 50–59 years – under 160, 0 points; 160–199, 2 points; 200–239, 3 points; 240–279, 4 points; 280 or higher, 5 points. Age 60–69 years – under 160, 0 points; 160–199, 1 point; 200–239, 1 point; 240–279, 2 points; 280 or higher, 3 points. Age 70–79 years – under 160, 0 points; 160–199, 0 points; 200–239, 0 points; 240–279, 1 point; 280 or higher, 1 point.

If cigarette smoker (years)

On the basis of cigarette smoking the scores for different age groups are as follows: age 20–39, 8 points; 40–49, 5 points; 50–59, 3 points; 60–69, 1 point; 70–79, 1 point.

All nonsmokers

All nonsmokers were given scores of 0.

High-density lipoprotein cholesterol (mg/dl)

On the basis of HDL cholesterol, the scores were as follows: 60 or higher, −1 point; 50–59, 0 points.40–49, 1 point; under 40, 2 points.

Systolic blood pressure (mmHg)

The scores for untreated systolic blood pressure are as follows: under 120, 0 points; 120–129, 0 points; 130–139, 1 point; 140–159, 1 point; 160 or higher, 2 points. Treated – under 120: 0 points; 120–129, 1 point; 130–139, 2 points; 140–159, 2 points; 160 or higher, 3 points.

Ten-year risk (%)

The 10-year risk in men was calculated on the basis of the total score as follows: 0 point, &lt 1–4 points, 1; 5–6 points, 2; 7 points, 3; 8 points, 4; 9 points, 5; 10 points, 6; 11 points, 8; 12 points, 10; 13 points, 12; 14 points, 16; 15 points, 20; 16 points, 25; 17 points or more, over 30.

High-sensitivity C-reactive protein level

Blood serum levels were obtained. We used the lower of two readings obtained at least 2 weeks apart to estimate stable CRP value. The relative risk for future cardiovascular events based on high-sensitivity C-reactive protein testing is estimated as follows: low risk, CRP less than 1.0 mg/l; intermediate risk, CRP 1.0–3.0 mg/l; and high risk, CRP greater than 3.0 mg/l. Acute inflammation is a CRP greater than 10.0 mg/l (Pearson *et al.*, 2003).

Statistical analysis

Data were collected, coded, and entered into an IBM compatible computer using SPSS (SPSS, Inc., Chicago), version 22 for Windows. The entered data were checked for accuracy and normality, using the Kolmogorov–Smirnov and Shapiro–Wilk tests; they were normally distributed. Qualitative variables were expressed as number and percentage and quantitative variables were expressed as mean ($\overline{X}$) and SD.

The arithmetic mean ($\overline{X}$) was used as a measure of central tendency, whereas the SD was used as a measure of dispersion.

The following statistical tests were used:

(1) Independent-samples *t*-test was used as a parametric test of significance for comparison between two sample means, after performing the Levene's test for equality of variances.
(2) The χ^2-test (or likelihood ratio) was used as a nonparametric test of significance for comparison between the distribution of two qualitative variables.

A 5% level was chosen as the level of significance.

Results

The total sample consisted of 62 schizophrenic patients. The age range of the patients was 28–64 years (mean 48.66±8.164). All patients were on atypical antipsychotics. Table 1 shows the sociodemographic data of the patients. Table 2 shows that 21% of patients had a 10-year risk for developing CVD by Framingham Risk Score. Table 3 shows risk for developing CVD as measured

Table 1 Sociodemographic and clinical data of the studied group

Variables	*N* (%)
Sex	
Male	51 (82.3)
Female	11 (17.7)
Marital status	
Single	48 (77.4)
Married	8 (12.9)
Divorced	5 (8.1)
Widow	1 (1.6)
Education	
Illiterate	10 (16.1)
Can read and write	1 (1.6)
Low-grade school	34 (54.8)
High-grade school	14 (22.6)
University	3 (4.8)
Occupation	
Jobless	47 (75.8)
Retired	15 (24.2)
Nationality	
Kuwaiti	44 (71.0)
Non-Kuwaiti	18 (29.0)
Smoking	
Yes	35 (56.5)
No	27 (43.5)
Treatment for hypertension	
Yes	27 (43.0)
No	35 (56.5)

Table 2 10-year risk for developing cardiovascular disease

Risk	*N* (%)
0.00	49 (79.0)
1.00	6 (9.7)
2.00	2 (3.2)
3.00	1 (1.6)
4.00	1 (1.6)
5.00	1 (1.6)
25.00	2 (3.2)
Subtotal with risk	13 (21)

Table 3 C-reactive protein and risk for cardiovascular disease

CRP (mean=5.5±3.7)	*N* (%)
Intermediate risk	15 (24.2)
High risk	47 (75.8)

CRP, C-reactive protein.

by baseline CRP; all patients were in the range of intermediate to high risk. Table 4 shows that there was no significant correlation between 10-year risk for developing CVD and PANSS scores. Further, there was no significant correlation between CRP level and Framingham Risk Score. Table 5 shows sex-related difference in cardiovascular risk; women had no risk, whereas 25% of men had a risk for developing CVD.

Discussion

Schizophrenic patients have a shorter life span than the general population and are associated with higher risk for respiratory, infectious, and CVDs (Joshi *et al.*, 2013). Standardized mortality rates are elevated in schizophrenia compared with the general population. The incidence of coronary heart disease (CHD) and the relative contribution of CHD to increased mortality in schizophrenia patients are not clear, despite recent concerns about metabolic complications of certain atypical antipsychotics (Goff *et al.*, 2005).

In our study when we applied Framingham assessment to detect the 10-year risk to develop CVDs we found that 79% of the patients had no risk and 21% had a risk for developing CVD. Our study is inconsistent with other studies that tried to detect the risk for CVD in schizophrenic patients as our study detected more risk. In a study conducted by McCreadie (2003) assessing Framingham Risk Score for 84 patients, the mean 10-year risk for CHD in men was 10.5% (compared with that of the general population of 6.4) and that in women was 7% (compared with that of the general population of 4.1%).

Also Goff *et al.* (2005) tried to detect the 10-year risk for CHD in 689 schizophrenic patients who participated in the Clinical Trials of Antipsychotic Treatment Effectiveness using the Framingham CHD risk assessment. The patients were compared with age-matched, race-matched and sex-matched controls from the National Health and Nutrition Examination Survey. The authors found that 10-year CHD risk was significantly elevated in male (9.4 vs. 7.0%) and female (6.3 vs. 4.2%) schizophrenic patients compared with controls. Also schizophrenic patients had significantly higher rates of smoking (68 vs. 35%).

The difference in the ratio between our study and others may be due to differences in the sex distribution as 82.3% of the sample was male. In addition, cultural variations, difference in risk factors in the form of smoking, diet, and sedentary life, and the effect of psychotropic medication, were not discussed in our study.

All the studied patients had intermediate to higher risk of developing CVD by measurement of baseline CRP. That is confirmed by a meta-analysis of all cross-sectional studies of serum and plasma CRP levels in schizophrenic patients compared with healthy patients. Longitudinal studies were conducted on CRP levels before and after antipsychotic use. This meta-analysis included a total of 26 cross-sectional and longitudinal studies comprising 85 000 participants. It found that CRP levels were moderately increased in persons with schizophrenic regardless of the use of antipsychotics (Fernandes *et al.*, 2015).

In addition, our result was supported by Joshi *et al.* (2013) who detected CRP in 45 schizophrenic patients

Table 4 Correlation between 10-year risk for cardiovascular disease and subscales of positive and negative syndrome scale and C-reactive protein level

Variables	*R*	*P*
Positive subscale of PANSS (mean=18.37±7.41)	0.117	0.364
Negative subscale of PANSS (mean=30.03±11.29)	0.108	0.402
General psychopathology scale (mean=38.56±9.77)	0.108	0.403
CRP level	−0.065	0.614

CRP, C-reactive protein; PANSS, positive and negative syndrome scale.

Table 5 Gender difference in cardiovascular risk

Variables	Equation (CVR)							
	0.00	1.00	2.00	3.00	4.00	5.00	25.00	Total
Sex(*n*)								
Male	38 (77.6)	6 (100)	2 (100)	1 (100)	1 (100)	1 (100)	2 (100)	51 (82.3)
Female	11 (22.4)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00(	0 (0.00)	11 (17.7)
Total	49	6	2	1	1	1	2	62 (100)

CVR, cardiovascular risk.

compared with control groups. They found that high-sensitive CRP level was significantly higher in the patient group. The study also suggested that CRP may play a role in the underlying inflammation and that inflammation is a possible contributing factor in disease pathogenesis.

Although all the studied patients had intermediate to higher risk of developing CVD by measurement of baseline CRP, we could not find a significant correlation between CRP levels and the Framingham CHD risk assessments of patients. This is inconsistent with the results of Mainar *et al.* (2013) who found that high CRP levels were associated with both known CVD and high/very high 10-year risk for a CVD event in patients with schizophrenia, suggesting that CRP could be a marker of CVD in this psychiatric disorder. But Danesh *et al.* (2004) found no significant correlation and concluded that CRP is a relatively moderate predictor of CHD.

In our study there was no significant correlation between risk for CVD and severity of symptoms of schizophrenia. We attempted to find a relation between negative symptoms of schizophrenia and risk for CVD, as a sedentary lifestyle and lack of physical exercise due to negative symptoms may contribute to metabolic syndrome (MetS) development, which could increase the risk for CVD. Mainar *et al.* (2015) found a relation between MetS and negative symptoms in schizophrenic patients by a retrospective cohort study using electronic medical records. PANNS was used as a framework for characterizing negative symptoms. MetS was defined using the National Cholesterol Education Program Adult Treatment Panel III diagnostic criteria. Patients were distributed into two groups according to the presence or absence of negative symptoms: group 1 for patients presenting one or more negative symptoms, and group 2 for patients without negative symptoms. One or more negative symptoms were present in 52.5% of a sample of 1120 patients; the overall prevalence of MetS was 38.6% and it was significantly higher in those patients with negative symptoms (43.9 vs. 34.9%, P=0.002). MetS was significantly associated with the presence of negative symptoms.

In our study there was a significant difference between men and women as regards cardiovascular risk. Our result is contrary to the result of McCreadie (2003) who found no significant sex-related differences in the 10-year risk for CHD or stroke. But our results are consistent with that of Goff *et al.* (2005), who found increased risk in men compared with women.

Our study points to the measurement of CRP and screening of lipid levels as an improved method for identifying schizophrenic patients at risk for cardiovascular events.

Study limitation

(1) There was no control group against which the risk for CVD in schizophrenic patients could be compared.
(2) In the patient population, factors like physical activity or dietary habits were not controlled; hence, the effect of these factors on CVD risk could not be described.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

References

Allison DB, Mentore JL, Heo M, Chandler LP, Cappelleri JC, Infante MC, Weiden PJ (1999). Antipsychotic-induced weight gain: a comprehensive research synthesis. Am J Psychiatry 156:341–350.

Allison D, Newcomer JW, Dunn AL, Blumenthal JA, Fabricatore AN, Daumit GL, *et al.* (2009). Obesity among those with mental disorders: a national institute of mental health meeting report. Am J Prev Med 36:341–350.

American Diabetes Association, American Psychiatric Association, American Association of Clinical Edocrinologists, North American Association for the Study of Obesity (2004). Consensus development conference for antipsychotic drugs and obesity and diabetes. Diabetes Care 27:596–601.

Casagrande SS, Anderson CA, Appel L, Jerome G, Dickerson FB, Daumit GL (2011). Dietary intake of adults with serious mental illness. Psychiatr Rehabil J 35:137–140.

Casas JP, Shah T, Hingorani AD, Danesh J, Pepys MB (2008). C-reactive protein and coronary heart disease: a critical review. J Intern Med 264: 295–314.

Compton MT, Daumit GL, Druss BG (2006). Cigarette smoking and overweight/obesity among individuals with serious mental illness: a preventive perspective. Harv Rev Psychiatry 14:212–222.

Danesh J, Wheeler JG, Hirschfield GM, Eda S, Eiriksdottir G, Rumley A *et al.* (2004). C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. N Engl J Med 350:1387–1397.

El Missiry A (2003). Homicide and psychiatric illness, an Egyptian study [MD thesis]. Cairo: Faculty of Medicine, Ain Shams University.

Fernandes BS, Steiner J, Bernstein HG, Dodd S, Pasco JA, Dean OM *et al.* (2015). C-reactive protein is increased in schizophrenia but is not altered by antipsychotics: meta-analysis and implications. Mol Psychiatry 21:554–564.

First MB, Spitzer RL, Gibbon M, Williams JBW (1996). Structured Clinical Interview for DSM-IV Axis I Disorders, Clinician Version (SCID-CV). Washington, DC: American Psychiatric Press Inc.

Fiszbein A, Opler LA (1987). The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 13:261–276.

Goff DC, Sullivan LM, McEvoy JP, Meyer JM, Nasrallah HA, Daumit GL *et al.* (2005). A comparison of ten-year cardiac risk estimates in schizophrenia patients from the CATIE study and matched controls. Schizophr Res 80:45–53.

Joshi KB, Nillawar A, Thorat AP (2013). Cardiovascular disease risk in schizophrenia patients: a case control study. J Clin Diagn Res 7: 2694–2696.

Mainar SA, Gutiérrez RJ, Artieda NR, Blanca-Tamayo M (2013). C-reactive protein as a marker of cardiovascular disease in patients with a schizophrenia spectrum disorder treated in routine medical practice. Eur Psychiatry 28:161–167.

Mainar SA, Maurino J, Beato ER, Artieda RN (2015). Prevalence of metabolic syndrome according to the presence of negative symptoms in patients with schizophrenia. Neuropsychiatr Dis Treat 11:51–57.

McCreadie RG (2003). Diet, smoking and cardiovascular risk in people with schizophrenia. Br J Psychiatry 183:534–539.

National Cholesterol Education Program (NCEP) (2002). Expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III). Circulation 106:3143–314.

Osborn DP, Levy G, Nazareth I, Petersen I, Islam A, King MB (2007). Relative risk of cardiovascular and cancer mortality in people with severe mental illness from the United Kingdom's general practice database. Arch Gen Psychiatry 64:242–249.

Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO, Criqui M, *et al.* (2003). Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation 107: 499–511.

Saha S, Chant D, McGrath J (2007). A systematic review of mortality in schizophrenia: is the differential mortality gap worsening over time? Arch Gen Psychiatry 64:1123–1131.

Tandon R, Keshavan MS, Nasrallah HA (2008). Schizophrenia, 'Just the Facts' what we know in 2008. 2. Epidemiology and etiology. Schizophr Res 102:1–18.