TITLE PAGE

CARDIOVASCULAR RISK PROFILE OF ADULTS WITH PSYCHOTIC DISORDERS IN ELDORET, KENYA

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Table of Contents

LIST OF ABBREVIATIONS

BMI - Body Mass Index

CIDI- Composite International Diagnostic Interview

CVD - Cardiovascular Disorders

CTQ-SF- Childhood Trauma Questionnaire- Short Form

DM – Diabetes Mellitus

DSM 5- Diagnostic Statistical Manual – version 5

FRS - Framingham risk score

HIV - Human Immunodeficiency Virus

HDL - High Density Lipoprotein

HPA - Hypothalamic - Pituitary _Adrenal Axis

LDL- Low Density Lipoprotein

LEC- Life events Checklist

LMIC- Low and Middle Income Countries

Mets - Metabolic Syndrome

MI- Myocardial Infarction

MINI - Mini International Neuropsychiatric Interview

MTRH - Moi Teaching and Referral Hospital

NCD - Non Communicable Diseases

NeuroGAP- Neuro Psychiatry Genetics of African Populations

OR- Odds Ratio

PGC - Psychiatric Genomics Consortium

RR- Relative Risk

REDcap- Research Data Capture

SES - Socioeconomic Status

SGA- second generation antipsychotics

SMI - Severe mental illness

SSA - Sub Saharan Africa

TB - Tuberculosis

TGs - Triglycerides

WHO - World Health Organization

UBACC - University of California, San Diego Brief Assessment of Capacity to Consent

UCT- University of Cape Town

UK - United Kingdom

US - United States

WORKING DEFINITION OF TERMS

Cardiovascular disorders: This term is used broadly to include all diseases that involve the heart or blood vessels and include coronary artery diseases such as angina and myocardial infarction, stroke, heart failure, hypertensive heart disease, rheumatic heart disease, cardiomyopathy, abnormal heart rhythms, heart valve disease, peripheral artery disease, thromboembolic disease, and venous thrombosis.

Metabolic disorders: For purposes of this study this refers to specific disorders that increase risk of cardiovascular disorders such as hypertension, diabetes, dyslipidaemia and obesity.

Conventional cardiovascular risk factors - This refers to conditions that are universally reported as to increase the probability of developing cardiovascular disorders, though not necessarily causal factors

Modifiable cardiovascular risk factors- They include smoking, hypertension diabetes, obesity, smoking, cigarette smoking.

Non Modifiable cardiovascular risk factors - These include age, Sex and social economic status

Non-conventional cardiovascular risk factors - For purposes of this study, these include trauma, psychological distress and chronic medical conditions.

Psychosis. For purposes of this thesis, psychosis refers to bipolar mood disorder, schizophrenia or schizoaffective disorder.

LIST OF TABLES

TABLE OF FIGURES

DECLARATION

I, Dr Edith Wanjiku Kamaru Kwobah, hereby declare that the work on which this dissertation is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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Signature: ..Signed by candidate..

6th October 2020

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"Show me a successful individual and I'll show you someone who had real positive influences in his or her life. I don't care what you do for a living—if you do it well I'm sure there was someone cheering you on or showing the way. A mentor." — *Denzel Washington*.

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For my literature review I utilised the UCT online library through the off campus log in service. The ViewIt@UCT on Google scholar enabled me to access relevant articles in full text for my citations.

ABSTRACT

Introduction: Cardiovascular disorders contribute significantly to mortality and morbidity amongst patient's psychotic disorders such as schizophrenia and bipolar mood disorders. In addition to conventional risk factors for cardiovascular disorders (smoking, alcohol use, inadequate physical activity, hypertension, diabetes, dyslipidaemia, obesity and metabolic syndrome, and non-modifiable factors such as sex, age and social-economic status) exposure to potentially traumatic events, psychological distress, comorbidity of other medical conditions, and use of antipsychotics may also increase cardiovascular risk in patients with psychosis. There is also evidence to suggest that intervention to mitigate such cardiovascular risk factors are suboptimal, hence contributing to poor outcomes.

Despite growing interest in cardiovascular health, there remains a paucity of data on the prevalence of the various cardiovascular risk factors among patients with psychosis in low resource settings such as Sub-Saharan Africa. This is likely to differ from high resource contexts given social-cultural and economic differences as well as differences in the health systems. In order to design contextually relevant cardiovascular risk screening, treatment and prevention guidelines that can be integrated into routine care of the mentally ill patients in low- and middle-income countries (LMICs), further work in this setting is warranted.

Objectives: The aim of this thesis was to establish the cardiovascular risk profile among patients treated for psychotic disorders at Moi Teaching and Referral Hospital (MTRH) in Eldoret, Western Kenya.

Specific objectives were as follows:

1. To conduct a literature review on the burden and etiological mechanisms of cardiovascular risk in patients with psychosis, with a focus on LMIC.
2. To compare the prevalence, as well as sociodemographic and clinical correlates, of conventional cardiovascular risk factors (smoking, alcohol intake, poor diet, and lack of exercise, diabetes mellitus, hypertension, obesity, dyslipidaemia and metabolic syndrome) in patients with psychosis versus matched controls.

3. To establish the prevalence and correlates of non-conventional risk factors; psychological distress, traumatic events (lifetime and childhood trauma) and comorbid medical disorders in patients with psychosis and controls, and to delineate how these risk factors contribute to the overall cardiovascular risk.

4. To describe current psychopharmacological treatments and explore potential associations with cardiovascular risk among patients with psychosis.

5. To explore the overall 10-year cardiovascular disease risk, as well as the social demographic and clinical correlates among patients and controls.

6 .To determine the proportion of untreated metabolic disorders (hypertension, diabetes mellitus, and dyslipidaemia) in patients with psychotic disorders and matched controls.

Methods: This was a cross-sectional descriptive survey comparing 300 patients with psychosis and 300 controls at Moi Teaching and Referral Hospital, Western Kenya. A paper based researcher-administered questionnaire was used to collect data on demographic variables (age, sex, education level, and marital status), and risk factors (smoking, alcohol intake, diet, physical activity). We used the Composite International Diagnostic Interview (CIDI) to assess for presence of other chronic medical disorders. Data on childhood trauma were obtained using the Childhood Trauma Questionnaire (CTQ) while the Life Events Checklist (LEC) was used to obtain data on lifetime exposure to potentially traumatic events. Data on psychological distress among controls were obtained using the Kessler-10 questionnaire. Measurements of weight, height, abdominal circumference and blood pressure were taken from each of the participants. Blood was drawn for measurement of glucose level and lipid profile. Data analysis was undertaken using Stata version 15. T-tests were used to compare continuous variables while Pearson chi-squared tests was used for categorical variables. Regression modelling was undertaken to assess associations between sociodemographic and clinical predictor variables and the cardiovascular risk factors.

Results: Data collection took place between July 2018 and March 2019. The mean age of patients was 33 years and of controls was 35 years. Compared to controls, patients were more likely to be unmarried

(46% vs 33% p<0.001), to have lower education levels education (25.6% vs 55% p<0.001), and were more likely to be unemployed (24.7% vs 48%, p<0.001). Compared to controls, patients were more likely to have smoked in their lifetime (9.9% vs 3.3%, p= 0.006) or to be current smokers (13.8% vs 7%, p=0.001). Most patients with psychosis consumed inadequate fruits and vegetables (97%); and had low physical activity (78%) and a good number had sedentary behaviour (48%).

Compared to controls, patients had a higher mean random blood glucose (5.23 vs 4.79, p=0.003), higher body mass index (5.23 vs 4.79, p=0.001), higher triglycerides (1.98 vs 1.56, p<0.001) larger waist circumference (89.23 vs 86.39, p=0.009) and lower high density lipoprotein (1.22 vs 1.32, p<0.001). Compared to controls, patients had a higher prevalence of metabolic syndrome (28.6% vs 19.8%, p=0.007) and obesity (15.4 vs 12.3 p=0.037). The odds of developing metabolic syndrome in patients were increased by psychosis (OR=2.09, p=0.006) and increasing age (OR=1.05, p< 0.001), and were reduced among females (OR 0.41 p<0.001) and those participants who were widowed/separated/ (OR 0.38, p=0. 0 13). The odds of having obesity in patients were increased by psychosis (OR 2.30, p<0.001) and female Sex (OR 2.67, P<0.001). Many participants (73% of patients and 80% of controls) reported having experienced at least one traumatic event in their lifetime. There was no significant association between trauma and any of the cardiovascular risk factors in this study. Controls with evidence of psychological distress were significantly less likely to have adequate physical activity (p=0.002). Patients had lower rates of reported medical conditions compared to controls, and the presence of medical conditions was not linked to increased CVD risk. On the Framingham risk scores, 4.4 % of the patients had an intermediate estimated 10 year risk of developing cardiovascular disorders (score 10-19) and 1 % had high risk (score >20). The estimated 10 year cardiovascular risk was significantly associated with female Sex (p=0.007), age (p<0.001), current tobacco smoking (p<0.001) and metabolic syndrome (P<0.001). Among the patients, 280 (94.3%) patients were on antipsychotics with the majority (86.5%) being treated with olanzapine. Of all the participants with diabetes 60% among patients and 22% among controls were not on treatment. Of the total number of participants with hypertension, 65% of patients and 47% controls were not on treatment

Conclusion: In the study setting of Eldoret, Western Kenya, patients with psychosis were found to have high levels of lifestyle cardiovascular risk factors such as smoking, inadequate intake of fruits and vegetables and inadequate physical activity. They were also found to have high rates of metabolic disorders such as hypertension, obesity, metabolic syndrome and dyslipidaemia. There was no evidence of increased cardiovascular risk among participants exposed to traumatic life events, with those experiencing psychological distress or those with other chronic medical disorders. The use of olanzapine was not significantly associated with increased cardiovascular risk in this setting. There was an identifiable gap in the treatment of cardiovascular risk factors in this setting. Given these findings, we recommend efforts to address these risk factors by development of protocols to ensure screening for these risk factors, adequate documentation and appropriate treatment.

CHAPTER 1: CARDIOVASCULAR RISK FACTORS IN THE GENERAL POPULATION

1.0 Introduction

This chapter will give an introduction to cardiovascular risk factors in general population. First the chapter will describe the conventional cardiovascular risk factors which include modifiable lifestyle factors and metabolic disorders, as well as the non-modifiable risk factors such as age, sex, and social economic status. Second, the chapter will highlight the non- conventional risk factors; trauma, psychological distress and comorbid chronic medical conditions. Third, the chapter will give an overview of cardiovascular risk prediction, narrowing down to Framingham risk scores.

1.1: Cardiovascular Risk Factors

According to the World Health Organization (WHO), cardiovascular disorders (CVDs) are the leading cause of death in the general population worldwide and accounted for an estimated 17.9 million deaths in 2016 only, a vast majority of these (85%) due to heart attack and stroke (WHO, Cardiovascular disorders 2017). Several factors are linked to increased CVD risk in the general population (Hennekens et al. 2005). The conventional/ traditional risks factors for CVD can be broadly divided into modifiable risk factors such as tobacco use, diabetes, hypertension, physical inactivity, unhealthy diet, dyslipidaemia, and obesity, and non-modifiable risk factors such as age, Sex and social economic status (El Fakiri 2005; Bager Tabei et al. 2014; A. S. Barnes 2013). However there are also non- conventional factors which are so regarded because though they contribute to increased cardiovascular risk though, they have not been included into the list of the modifiable /non modifiable risk factors (Lin et al. 2018).

1.1.1: Modifiable Cardiovascular risk factors

The conventional modifiable risk factors for CVD can further be classified into lifestyle factors like smoking, inadequate exercises, poor diet and harmful alcohol use, and specific metabolic disorders such as Diabetes Mellitus (DM) , hypertension, dyslipidaemia, obesity and the metabolic syndrome (MetS).

Life style cardiovascular risk factors

Smoking; According to the Centre for Disease Control and Prevention (CDC), smoking is one of the leading causes of premature deaths in the world (CDC TobaccoFree 2019). A systematic analysis from the Global Burden of Disease Study 2015 (including data from 195 countries) reported a 25% age-standardised prevalence of daily smoking; and ranked cigarette smoking among the five leading risk factors to ill health as measured by disability-adjusted life-years DALYS (GBD 2015 Tobacco collaborators, 2017). It is also recognised as one of the major contributors to CVD related mortality in general population (Mallaina et al. 2013) . Smoking contributes to CVD through a number of mechanisms, including increased oxidative stress and promotion of a pro-inflammatory state; leading to lipid oxidation, thrombogenesis, accelerated atherogenesis, increases in catecholamine release and activation of the sympathetic nervous system , which taken together, contribute to ischemia and arrhythmia risk, as well as acute myocardial infarction (MacDonald and Middlekauff 2019). Nicotine which is delivered into the body from tobacco or cigarette smoking affects the autonomic nervous system, resulting in increased sympathetic activity, and this may in turn be associated with increased heart rates, altered coronary blood flow and myocardial remodelling (Benowitz and Burbank 2016). Among nicotine users, increased catecholamine release has also been associated with fatal ventricular tachycardia and fibrillation resulting in sudden cardiac death (Katz and Grosbard 2006). In addition, nicotine leads to endothelial dysfunction and damage, induces vascular wall inflammation, and results in a shift towards a pro-coagulant state in the cardiovascular system (Messner and Bernhard 2014; Balakumar and Kaur 2009).

Harmful Alcohol use ; While many people in the world take alcohol, harmful drinking refers to alcohol consumption that results in physical or psychological harm (Reid, Fiellin, and O'Connor 1999) and is objectively defined as intake of alcohol greater than 100 grams per week or more than 6 standard drink (Wood et al. 2018) O'Keefe, Bybee, and Lavie 2007). Globally, it has been estimated that 3.8% of all deaths and 4.6% of disability-adjusted life-years are attributable to harmful alcohol use (Rehm et al.

2009; S. Bell et al. 2017; Mostofsky et al. 2016). Though some literature suggests that lower amounts of alcohol may be cardio-protective, there is no doubt that excess alcohol intake increases the risk of CVD (Cahill and Redmond 2012; Carnevale and Nocella 2012; Corrao et al. 2000; O'Keefe, Bybee, and Lavie 2007). A pattern of excess drinking has been associated with increased incidence of coronary heart disease (I. B. Puddey et al. 1999) (Griswold et al. 2018; Burton and Sheron 2018) . There is evidence for the role of alcohol on several specific steps that are core in the process of atherosclerosis including effects on lipid regulation, inflammation and oxidative stress, as well as the differential effects on endothelial cells and vascular smooth muscle cells which then results in CVD (Cahill and Redmond 2012; Piano 2017). Alcohol has been found to increase rates of hypertension, arrhythmias and dilated cardiomyopathy (Ricci et al. 2018; Ian B. Puddey and Beilin 2006; Y. Zhang and Ren 2011). A systematic review of 26 observational studies also reported that alcohol intake exceeding 3 standard drinks per day was associated with both haemorrhagic and ischemic stroke (Patra et al. 2010).

Inadequate physical activity and sedentary behaviour are both common contributors of many chronic diseases (Kyu et al. 2016) including CVD (F. W. Booth, Roberts, and Laye 2012) which play a significant role in morbidity and premature mortality in the general population (Ding et al. 2016). According to the WHO global strategy on diet, physical activity and health, adults aged 18–64 years should do at least 150 minutes of moderate-intensity aerobic physical activity throughout the week or do at least 75 minutes of vigorous-intensity aerobic physical activity in a week or an equivalent combination of moderate- and vigorous-intensity activity (WHO 2011b). Inadequate physical activity has been described in literature as an independent modifiable CVD risk factor (Myers et al. 2015, (A. J. Alves et al. 2016; Siscovick et al. 1997) . Adequate physical activity on the other hand has several positive health outcomes (Penedo and Dahn 2005 (Vanhees et al. 2012) and has over the years been demonstrated to be a cost effective way of promoting cardiovascular health (Myers 2003). For example, one meta-analysis of 36 studies (3, 439, 874 participants and 179, 393 events, during an average follow-up period of 12.3 years) reported that an increase from being inactive to achieving recommended 150 minutes of moderate-intensity aerobic activity per week was associated with lower risk of CVD mortality by 23%, CVD incidence by

17%, and type 2 DM incidence by 26% (Wahid Ahad et al. 2016). These benefits may result from direct and indirect cardio protective mechanisms such as an improvement in other cardiovascular risk factors (obesity, hypertension and diabetes) , improved endothelial function, and decreased sympathetic tone (Prasad and Das 2009). Physical activity reduces total and abdominal fat resulting in improved insulin sensitivity, reduces risk of DM and results in reduction in blood pressure (Stewart 2002). Further , regular exercise improves the endothelial integrity and dilator function thus resulting in athero-protection, preventing platelets and inflammatory cells from adhering to the vascular surface (Dimmeler Stefanie and Zeiher Andreas M. 2003). A recent meta-analysis of 16 prospective cohort studies (N= 1,005,791 individuals followed up for 2–18·years) suggested that engaging in intense physical activity (60-75 minutes) per day countered the harmful effect of prolonged sitting (e.g. for work purposes) (Ekelund et al. 2016).

Poor Diet; A poor diet, has been associated with poor health outcomes for many non-communicable diseases including CVD. Benefits of adequate fruits and vegetable intake (which is at least half a plate per day) in relation to CVD risk factors like DM and obesity is well documented (Krishnaswamy and Gayathri 2018), (Locke, Schneiderhan, and Zick 2018) (Bazzano, Serdula, and Liu 2003),. Fruits and vegetables supply dietary fibre which is linked to lower incidence of CVD, supply vitamins and minerals to the diet and are sources of phytochemicals that function as antioxidants and anti-inflammatory agents thus reducing the risk of CVD (Slavin and Lloyd 2012). A national prospective cohort study including 9,608 adults revealed that consuming fruit and vegetables more than 3 times per day compared with 1 time/day was associated with a 24% lower ischemic heart disease mortality, 27% lower cardiovascular disease mortality and a 15% lower all-cause mortality after adjustment for existing cardiovascular disease risk factors (Bazzano et al. 2002). A similar study that followed 3,876 women for 5 years reported a significant inverse association between fruit and vegetable intake and CVD risk after adjusting for age and smoking, with higher fruit and vegetable intake being associated with a lower risk of MI, with an adjusted RR of 0.62.(S. Liu et al. 2000). A recent meta-analysis of 10 studies (N= 24,013 cases of type 2 DM and N=434,342 controls) reported that the relative risk of Type 2 diabetes was 0.93, for an increase

of 1 serving of fruit per day; and the summary relative risk was 0.87, for an increase of 0.2 servings of green leafy vegetables consumed per day (M. Li et al. 2014). Similarly, a systematic review and meta-analysis of seventeen cohort studies and 563,277 participants reported an inverse relationship between fruit and vegetable intake, and weight gain, waist circumference and adiposity (Schwingshackl et al. 2015). A recent systematic review and dose-response meta-analysis of prospective studies (including 95 unique cohort studies) reported that – per 200 g/day of fruits and vegetables – the relative risk for coronary heart disease was 0.92; for stroke 0.84; for CVD 0.97; for all-cause mortality 0.90 (Aune et al. 2017). Another meta-analysis of 16 prospective cohort studies in the general population with follow-up periods ranging from 4.6 to 26 years reported an average reduction in risk of all-cause mortality by 5% for each additional serving of fruit and vegetables per day (up to five servings a day) after which the risk of death did not reduce further (Wang et al. 2014) .

Metabolic disorders that increase CVD risk

Diabetes Mellitus (DM) according to WHO, is characterized by persistently elevated plasma glucose (fasting levels above 7.0 mmol/l or random glucose above11.1mmol/l (WHO 2006). DM increases the risk of CVD through various mechanisms. Diabetes Mellitus (DM) is a major contributor for both macrovascular and microvascular pathologic processes that increase the risk of CVD (Petrie, Guzik, and Touyz 2018). First, DM contributes to macrovascular disease through atherosclerosis which then results in increased risk of strokes and myocardial infarction (Dokken 2008) . Second, hyperglycaemic state in blood increases production of pro-inflammatory cytokines such as interleukin 6, C reactive proteins and tumour necrosis factors which result in programmed cell death and recruitment of invasive leukocytes (Fernandez-Egea et al. 2009; Garcia-Rizo et al. 2012) (Esposito Katherine et al. 2002). Third, patients with DM are at risk of diabetic cardiomyopathy which is characterized by fibrosis, and hypertrophy and often results in left ventricular hypertrophy, diastolic and systolic dysfunction and eventually heart failure (Asghar et al. 2009a; Bertoni et al. 2006). Fourth, DM results in autonomic damage to the autonomic nerve fibres that innervate the heart and blood vessels (cardiovascular autonomic neuropathy and subsequent diastolic dysfunction) resulting in abnormalities in heart rate control and vascular dynamics

which predispose to cardiac arrhythmias and the risk of sudden death (Vinik, Erbas, and Casellini 2013), (Patil et al. 2011; Dinh et al. 2011; Rolim et al. 2008) (B. M. Leon and Maddox 2015), and has been linked to diabetic cardiomyopathy (Asghar et al. 2009b; Santra et al. 2011), and an increased incidence of myocardial infarction (Haffner et al. 1998). Insulin resistance that is associated with DM increase the risk of vascular damage (Pillinger et al. 2017; M. C. M. Ryan, Collins, and Thakore 2003; Greenhalgh et al. 2017). It is worth noting that hyperglycaemia (without established DM) also increases the risk of mortality in the general population. For example, one systematic review reported that patients with glucose concentrations ≥6·1–8·0 mmol/L (but without DM) had a 3.9-fold higher risk of death, versus those with lower glucose concentrations (Capes et al. 2000).

Hypertension; Hypertension, according to 'The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7), is characterized by persistent elevation of blood pressure above a systolic pressure of 140mm/hg and a diastolic pressure above 90mm/hg (National High Blood Pressure Education Program 2004). Hypertension is one of the strongest risk factors for CVD (Kjeldsen 2018; Lamprea-Montealegre Julio A. et al. 2018) and contributes significantly to incidences of coronary heart disease, cardiac arrhythmias including atrial fibrillation, cerebral stroke and renal failure (Vasan et al. 2001;Staessen et al. 1999), (Stamler, Stamler, and Neaton 1993). A study conducted in Taiwan (n= 77,389) showed that systolic blood pressures of 120 to 129mm Hg were associated with the lowest CVD mortality risks, while systolic blood pressure ≥160mm Hg, or diastolic blood pressure ≥90mm Hg significantly increased the CVD and expanded-CVD mortality risk (C.-Y. Wu et al. 2015). Hypertension contributes to CVD through various mechanisms. First, the persistently elevated blood pressure weakens the inner arterial wall promoting atherosclerosis and thrombosis which results in myocardial infarction, transient ischemic attacks and strokes. (Franklin and Wong 2013). Second, hypertension results in increases risk of left ventricular hypertrophy that results from chronic exposure to high blood pressure (Brook and Julius 2000; Berk, Fujiwara, and Lehoux 2007). Third, hypertension induced hemodynamic changes such as coronary insufficiency contributes to silent ischemia and risk of sudden death (Frohlich Edward D. 1999). In addition elevated blood pressure results

in mechanical damage to the blood vessel which results in vasoconstriction and further elevation in blood pressure (Drozdz and Kawecka-Jaszcz 2014). Fourth high blood pressure affects bioavailability of nitric oxide and increases vascular smooth muscle cell proliferation which results in stiffening of the arterial wall (Tedla et al. 2017). The loss of arterial elasticity results in increased pulse pressure, which in turn results in increase in the ventricular afterload, causes ventricular hypertrophy, and reduces coronary perfusion thus increasing the risk of cardiovascular events and mortality (Sipahioglu et al. 2012). Fifth, high blood pressure contributes to the risk of aneurysms (Elsa Kobeissi et al. 2019) as well as the eventual rupture of blood vessels which can be fatal (Takagi and Umemoto 2017).

Dyslipidaemia, Dyslipidaemia is characterized by an increase in the plasma concentration of Low Density Lipoprotein (LDL), total cholesterol and triglycerides, as well as reduction of High Density Lipoprotein HDL (Saari et al. 2004). Dyslipidaemia is known to increase the risk of cardiovascular diseases though various pathways (Badimon, Storey, and Vilahur 2011; Toth 2016). Products of lipid metabolism undergo changes that eventually lead to macrophage activation, foam cell formation and induction of inflammation (Tselepis and John Chapman 2002). LDL accumulates in the vascular wall and gets oxidized resulting in damage of the endothelium, and also triggers an inflammatory process which eventually results in the process of arteriosclerosis , a common feature of coronary artery disease, ischemic stroke, and peripheral vascular occlusive diseases (Marchio et al. 2019). On the other hand, HDL is reported to be cardio protective through reversing cholesterol transport, preventing endothelial dysfunction, inhibiting the homing of monocytes and preventing platelet activation and coalition on the vascular wall (Viles-Gonzalez et al. 2003). To illustrate this, an 8 year follow up study in Japan (n=5245) reported an incidence of 17.5 % of ischemic disease among participants with high levels of TGS and low HDL (Jeppesen Jørgen et al. 1997). The increased risk of CVD in patients with dyslipidaemia is also mediated by increased rates of DM (Warraich and Rana 2017) and hypertension (Halperin et al. 2006).

Obesity; Obesity is a growing challenge worldwide that affects close to 20 billion people (Hossain, Kawar, and El Nahas 2007). Obesity which is defined as excess accumulation of body fat is measured using the Body Mass Index (BMI), a function of the weight and height of an individual. It is categorized into 4 ;

underweight <18.5kg/m2, healthy weight 18.5-24.9kg/m2 , overweight, 25.0-29.9kg/m2, obese, and obese ≥30kg/m2 obese (World Health Organization 2000). Obesity is a well-known risk factor for various types of CVD (Ndumele et al. 2016) and has been associated with increased CVD related deaths (S. C. Smith 2007), (Hubert et al. 1983). Excess adipose tissue secrete leptin which is reported to alter myocardial metabolism, promote cardiomyocyte hypertrophy, and contribute to cardiac remodelling, thus increasing the risk of CVD (Wannamethee et al. 2011). It increases the risk of CVD, particularly heart failure and coronary heart disease, by causing changes in body composition that may alter hemodynamic and heart structure (Carbone et al. 2019) (Manson et al. 1990). Direct effects result from structural and functional adaptive changes of the cardiovascular system to accommodate excess weight (Koliaki, Liatis, and Kokkinos 2019; Van Gaal, Mertens, and De Block 2006). In addition, abnormal adipose tissue expansion has been linked to anti-inflammatory adipokines, resulting in the development of a chronic, low-grade inflammatory state and impaired mitochondrial function all which contribute to CVD (Nakamura, Fuster, and Walsh 2014). Pro-inflammatory cytokines which are produced by perivascular adipose tissue result in a reduction in vascular nitric oxide thus resulting in endothelial damage (Virdis et al. 2019). Obesity also contributes to insulin resistance (Ye 2013), abnormal glucose and lipid metabolism, (Singla, Bardoloi, and Parkash 2010) as well as hypertension (S.-Z. Jiang et al. 2016). It has also been found to increase both the aldosterone level and the mineralocorticoid receptor expression, each of which promotes interstitial cardiac fibrosis, platelet aggregation, and endothelial dysfunction (Csige et al. 2018).

Due to variations in the BMI across different body builds, the waist circumference, which measures central obesity, is also used to assess risk of CVD. Central obesity has been linked to insulin resistance and atherosclerosis (Rader 2007). According to a study done in Cameroon, central obesity is one of the key determinants of metabolic syndrome in some populations such as Africans (Fezeu et al. 2007).

Metabolic Syndrome (MetS); MetS**,** according to the National Cholesterol Education Program's Adult Treatment Panel III report (ATP III) is the occurrence of a combination of abdominal obesity, impaired glucose tolerance, hypertriglyceridemia, decreased High density Lipoprotein HDL and hypertension

(Beilby 2004a). This syndrome is now recognized as a major risk factor for CVD (Tune et al. 2017; Cornier et al. 2008)**.** The co-occurrence several CVD risk factors which constitute MetS makes it one of the greatest predictors of CVD (Robert H Eckel 2005). An 8 year cohort study reported that metabolic syndrome accounts for up to one third of CVD in men (Wilson Peter W.F. et al. 2005). A systematic review and meta- analysis that included 87 studies, and 951,083 patients reported that patients who have MetS have a 2-fold increase in CVD events and a 1.5-fold increase in all-cause mortality (Salvatore Motillo et al 2010). MetS is associated with inflammation as evidence by presence of inflammatory markers like C reactive protein (Steven Haffner 2005). Patients with MetS have an increased rate of thrombosis and atherogenesis which increases the risk of CVD event (Grundy Scott 2016)

1.1.2: Non Modifiable cardiovascular risk factors

Factors currently classified as non-modifiable cardiovascular risk factors include age, sex and social economic status (World Heart Federation 2017).

Age is believed to contribute to increased cardiovascular risk due to associated body changes with advancing years as well as accumulation of various risk factors in the course of time (North and Sinclair 2012). This may be reflective of the relationship between advancing age and increasing duration and intensity of exposure to other CVD risk factors (Dhingra and Vasan 2012b). For example, a multi-ethnic cardiac magnetic resonance imaging study in the US examining age-related differences in left ventricular structure and function in 5,004 participants reported that age was associated with left ventricular remodelling which was marked by increased mass-to-volume ratio, and accompanied by systolic as well as diastolic myocardial dysfunction (Susan Cheng et al. 2009). Further, a large Finnish cohort study of 14,786 men and women reported age-related differences in cholesterol level, blood pressure, BMI, and DM prevalence; and, taken together, these differences accounted for approximately one-third of the age-related increase in overall CVD risk (Jousilahti et al. 1999). The Framingham Heart Study in which enrolled participants were followed up for a total of 111,777 person-years indicated that having fewer

individual risk factors by age 50 was associated with a lower risk of developing CVD (Lloyd-Jones et al. 2006)

Sex plays an important role in shaping the CVD risk profile. WHO mortality and population data from 26 countries worldwide, demonstrated that coronary heart disease related deaths were up to five times higher in men than women while differences in mortality from stroke were approximately twice as high in men as compared with women (Bots, Peters, and Woodward 2017). One prospective Finnish study of 14,786 participants aged 25 to 64 years reported that smoking, total cholesterol and BMI were each higher in men, though this difference was found to decrease with increasing age (Jousilahti et al. 1999)**.** A meta-analysis of 37 studies of type 2 DM and fatal coronary heart disease (total N=447,064 patients) reported that the relative risk for fatal coronary heart disease associated with DM was 50% higher in females compared to men (Rachel Huxley et al 2006). Similarly, a meta- analysis of 64 cohort studies (N=representing 775,385 individuals) and 12,539 fatal and non-fatal strokes reported that the relative risk of stroke associated with diabetes was 2.28 in women and 1.83 in men (Sanne A E Peters et al 2014). In contrast to these studies, a New Yolk study done among 1,527 participants reported that black Latino women had lower prevalence of CVD risk factors than men, with less hypertension, lower triglycerides higher HDL and a greater likelihood of a healthy lifestyle, and were more likely not to smoke and to follow a healthy diet, thus highlighting the need to avoid generalizing the role of Sex in CVD risk but instead consider differences in various settings. Sex differences in CVD risk profile are also likely in an African populations. For example a study done among Nigerian and Ghanaian immigrants into Baltimore reported significant Sex differences in the CVD risk prevalence and reported that being employed and having health insurance were associated with lower CVD risk in women, while higher social support was associated with lower CVD risk in men (Commodore- Mensah Yvonne et al. 2016). A very recent study which enrolled 2,198 participants from 12 different Sub-Saharan countries reported higher rates of obesity and sedentary behaviour in women, and more cardiovascular complications in men (Diop et al. 2019). Similarly, a Tanzanian study done among 209 participants aged between 44 and 66 years revealed an excess of various CVD risk factors among women compared to men 13%: abdominal

obesity was 11%in men and 58% in women, women had three-fold greater odds of having metabolic syndrome compared to male counterparts, women had higher fasting blood glucose (Njelekela et al. 2009a). The differences in cardiovascular risk between men and women conditions is partly explained by the combined expression of genetic and hormonal differences between the two sexes (Shufelt C.L. et al. 2018; Kautzky-Willer, Harreiter, and Pacini 2016). It may also be associated with varying social and cultural experiences for men and women (Mark Woodward 2019). While initially the focus was mainly on the male Sex(Woodward 2019), recent evidence has described the Sex differences and brought to focus the cardiovascular risk issues related to female Sex (Mosca, Barrett-Connor, and Kass Wenger 2011).

Social economic status (SES) : The social economic status is one of the social determinants of health and has also been shown to influence cardiovascular health (Catalyst 2017)**.** For example, studies suggest that childhood poverty (G. E. Miller et al. 2011), as well as low SES in adulthood and cumulatively across the lifespan, may increase the risk of metabolic disorders (Chichlowska et al. 2009). This may be due – in part - to psychosocial distress and resultant neuroendocrine disturbances, as well as to poor nutritional status associated with low SES (Agardh et al. 2011).Similarly a relationship exists between SES such as unemployment and low education level and negative physical health outcomes which include increased CVD (Michael Marmot et al. 2008). Some association has been reported linking low SES with presence of CVD risk factors like low HDL, high cholesterol, high triglycerides, and hyperglycaemia (E. Brunner et al. 1999). Further, challenging social circumstances are reported to have an effect on behaviours such as smoking, diet, alcohol consumption, or physical activity which are known to increase the risk of CVD (Hemingway and Marmot 1999). For example low education level has also been associated with poor lifestyles that potentially increase the risk of cardiovascular disorders (Mucheru et al. 2018). It is reported that persons with lower employment levels are more likely to smoke, engage less in physical activity and to die from coronary heart disease compared to those in higher employment grades (M. Marmot et al. 2001). The Whitehall II study of 10,308 government workers in London aged 35–55 years reported that participants with a lower employment grade (which translates

to lower SES) were more likely to die from coronary heart disease (M. Marmot et al. 2001), compared to those who had higher employment grade. In the same study, employment grade was inversely associated with current history of smoking and physical inactivity; and with other metabolic risk factors such as low HDL, high cholesterol, high triglycerides, and hyperglycaemia (E. Brunner et al. 1999). The effect of unemployment on cardiovascular health may be related to the anxiety resulting from financial constraints, as well as a lack of structured activities; which may in turn increase the likelihood of adverse behaviours such as smoking and harmful alcohol use (Q. Wang, Shen, and Cochran 2016) , eventually increasing the overall cardiovascular risk (Weber and Lehnert 1997; R. L. Jin, Shah, and Svoboda 1997). A recent prospective cohort study (N=13,451) further demonstrated the link between unemployment and onset of acute cardiovascular events (Dupre et al. 2012). Similarly, another study that included 674 black and white women form Georgia, USA, reported that lower SES (defined by education level, annual household income, and employment status) increased the odds of poor cardiovascular health (S. K. Davis et al. 2014)

1.2: Non -conventional CVD risk factors; Trauma, Psychological distress and chronic medical conditions.

Beyond the traditional CVD risk factors described in the previous section, there are other factors that have been described in literature as contributing significant increase in cardiovascular risk. Some of these include marital status, exposure to potentially traumatic events, psychological distress and comorbid medical conditions.

1.2.1: Marital status

Marital status, while not considered a key conventional cardiovascular risk factor, has been documented as one of the factors that influence the cardiovascular risk profile in the general population. One systematic review that consisted of 34 studies with more than two million participants reported that compared with married participants, being unmarried was associated with increased odds of CVD , widowers were more likely to develop a stroke and single men and women with myocardial infarction

had increased mortality (Wong et al. 2018). The 2014 Ghana Demographic Health Survey (GDHS) that included 9,356 women and 4,374 men reported higher odds of hypertension for married, cohabiting and previously married women, and no significant association between any of the marital status cohorts and hypertension for men (Tuoyire and Ayetey 2019). In addition to affecting the risk profile, the marital status is reported to affect outcomes for those with established CVD. One prospective cohort study that included 6,051 patients undergoing cardiac catheterization for coronary artery disease who were followed up for about 3.7 years reported that being unmarried was associated with higher risk of all-cause mortality, cardiovascular death and myocardial infarction and these findings persisted even after adjustment for medications and other socioeconomic factors (Schultz et al. 2017). **Marital status** has been found to be associated with a number of health outcomes, including CVD. One recent prospective cohort study following 9,737 Iranian adults for 12 years reported a significant association between never having been married and higher risk of hypertension and all-cause mortality in men , widowed status was associated with a lower risk of Type 2 diabetes mellitus, and lower risk of hypertension in currently or previously married women (Ramezankhani, Azizi, and Hadaegh 2019). The role of marital status in CVD risk was also evident from the data sixth Korea National Health and Nutrition Examination Survey (2013–2014), that included 3,225 women aged 40–69 years which reported that widowed participants higher odds of getting MetS compared to their married counterparts (Jung et al. 2018) and in this setting, these differences were associated with socioeconomic and psychological factors (Cho et al. 2016). The Tehran lipid and glucose study that followed up 5,221 participants (2060 males and 3161 females) for a median of 9.6 years reported that marital transition including to or out of married status was associated with an increased prevalence of CVD, especially among employed females (Hosseinpour-Niazi et al. 2014). Other than the status, the quality of marital status also seem to play a role in influencing the CVD risk. As an example, Pittsburgh Healthy Women Study that involved 413 participants reported that lower scores in marital satisfaction (with regard to communication, satisfaction with sexual activity, agreement on financial matters, and similarity of interests, lifestyle, and temperament) were associated with higher odds of MetS (Troxel et al. 2005). The mechanism by which marital status may influence CDV risk profile

is not well researched. However it may result from the social economic benefits that a functional marriage may bring as described in the marriage protection theory (Waldron, Hughes, and Brooks 1996; N. Goldman, Korenman, and Weinstein 1995) thus affecting other CVD risk factors indirectly.

1.2.2 Exposure to Potentially traumatic Events

There is evidence indicating that exposure to potentially traumatic events (both lifetime and childhood) increase the risk of developing physical disorders, including CVD (Atwoli et al. 2016). Exposure to these traumatic events both in adulthood or childhood may result in significant changes in the Hypothalamus Pituitary Adrenal (HPA) axis (De Bellis and A.B. 2014). In such cases, chronic HPA axis activation results in increased release of catecholamines Second, HPA-axis dysregulation - as associated with chronic psychological distress – may result in immunological alterations and altered cytokine expression and other inflammatory markers such as the C- reactive protein , and alterations may, in turn, contribute to the development of obesity and MetS (Bose, Oliván, and Laferrère 2009). (Rozanski, Blumenthal, and Kaplan 1999). These inflammatory processes also contribute significantly to endothelial dysfunction (Black and Garbutt 2002), (Black 2006). Third, a stress-specific coronary syndrome, known as transient left ventricular apical ballooning cardiomyopathy or stress cardiomyopathy (Steptoe and Kivimäki 2012) may arise as a result of sympathetic nervous system hyper activation (Esler 2017). Stress related alteration in cortisol also contribute to increased risk of obesity, raised blood pressure and insulin resistance (Joseph and Golden 2017) (Dong et al. 2004) . In addition to these physiological changes, patients with posttraumatic stress disorder may resort to use of tobacco , alcohol and other drugs of abuse, physical inactivity, overeating, as strategies to alleviate anxiety and hyperarousal symptoms, further increasing the CVD risk (Edmondson and Cohen 2013; Dedert et al. 2010) (Halonen et al. 2015; C. Lee, Tsenkova, and Carr 2014; C. R. Davis et al. 2014).. A systematic review of 78 observational studies reported that posttraumatic stress resulted increased heart rate and raised blood pressure ultimately increasing CVD risk (Dedert et al. 2010). A well-powered prospective study following 49,978 women over 20-year period also reported increased odds of CVD events (including myocardial infarction and stroke) among those who had endorsed >4 PTSD symptoms (Sumner Jennifer A. et al. 2015). Data

from 10 countries participating in the WHO World Mental Health surveys (n=18,630) reported that two or more early childhood adversities were significantly associated with hypertension in adulthood (Stein et al. 2010). Further, there is evidence to suggest that childhood trauma not only increases the overall risk of developing metabolic syndrome, but also affects the number of specific symptoms that one develop (Etain et al. 2008b; Kesebir 2014). A cross-sectional study among patients with schizophrenia reported that exposure to trauma in childhood was associated with a sensitized state in adulthood characterized by elevated emotional and psychotic reactions to small daily life stressors, and this is likely to affect the cardiovascular system in the long term (Lardinois et al. 2011).

1.2.3 Psychological distress and cardiovascular risk

Psychological distress encompasses negative emotional experiences such as stress, anger, hostility, anxiety and depression experienced by an individual in response to a specific stressor or demand that results in harm to the person (Ridner 2004) . Psychological distress may contribute to increased risk of CVD and may, also influence the course and outcomes in those who develop CVD (Januzzi et al. 2000). First, stress has been found to be associated with pathophysiological changes in the cardiovascular system, which may result in cardiac dysregulation, myocardial ischemia, cardiac wall abnormalities, myocardial infarction and sudden death (Dimsdale 2008a).The suggested biological mechanisms underlying this include sympathetic activation, stimulation of the hypothalamic–pituitary axis, hyperventilation-induced coronary spasm, oxidative stress and increased inflammatory mediators (Olafiranye et al. 2011), (Esler Murray 2014).. The association between psychological distress and CVD risk has been well-documented in the current literature. For example, one study of 6,292 Japanese men reported that participants who displayed anger suppression and depressive symptoms had 1.5 increased odds of developing hypertension (Ohira 2010). Acute or chronic psychological distress has also been found to be associated with 40-60% increased risk of CVD, independent of conventional risk factors such as dyslipidaemia and hypertension (B. E. Cohen, Edmondson, and Kronish 2015),(W. Jiang 2015). Further, a number of cardiovascular events (including sudden death, myocardial infarction and myocardial ischemia) may be associated with psychological distress (Dimsdale 2008a).In addition

chronic stress may also be experienced in the absence of an actual threat, in the context of prior unsafe social networks or situations (Brosschot, Verkuil, and Thayer 2017). This may result in a chronically active sympathetic nervous system, which eventually also affects the cardiovascular system (Öhlin et al. 2004). Finally, psychological distress may increase CVD risk through poor lifestyle such as increase cigarette smoking, reduced physical activity, and increased alcohol intake, which may be part of negative coping skills in distressed individuals (Hamer, Molloy, and Stamatakis 2008).

1.2.4: Comorbid medical conditions and cardiovascular risk.

Co-occurrence of more than one medical condition (comorbidity also referred to as multimorbidity) is common in the general population (Navickas et al. 2016; Colombo, García-Goñi, and Schwierz 2016). As a result, the presence of several chronic conditions may be associated with increased disability, decreased quality of life, and increased risk of death (Johnston et al. 2019). According to a recent systematic review of 68 studies including data both from high-income and LMICs (Nguyen et al. 2019), the pooled prevalence of multimorbidity in the general population was found to be 33%. A large cross-sectional Dutch study (N=60,000 patients in general practice) also reported that the prevalence of multimorbidity was highly influenced by age, ranging from 10 % in young people to 78% in patients older than 80 years (van den Akker et al. 1998). Multimorbidity is also associated with a decline in general functioning of the affected individual. For example, one systemic review of 37 studies and (n=1,371,631 participants) reported that this decline was associated with the number of conditions affecting individual patients, as well as the severity of each condition (Ryan et al. 2015). Ultimately, multimorbidity may result in higher hospital utilization and increased financial burden (J. T. Lee et al. 2015).

Non-communicable as well as infectious diseases may play a role in increased CVD risk. As an example HIV-associated inflammation and immune activation are important mediators increasing cardiovascular risk 2 fold among those affected (Triant 2013; Mesquita et al. 2019). One prospective study of 2,960 Brazilian patients reported an increase in smoking, hypertension and obesity among HIV-positive patients, with an overall incidence rate of 6.75 per 1000 person-years (Diaz et al. 2016). A similar study following 3,384 HIV-infected individuals reported a CVD incidence rate of 11.10/1000 person years –

this was 4-fold higher at < 3 months' post-hospitalization for severe infections (Mesquita et al. 2019). HIV-positive patients are also likely to have a higher risk of cardiovascular disorders due to the interactions between traditional risk factors and the HI virus (Cerrato et al. 2015). For example, HIV-associated inflammation and immune activation (Triant 2013), as well increased rates of dyslipidaemia, hypertension and smoking, may account – in part – for the increased risk of CVD among HIV-positive patients (Freiberg and So-Armah 2016) . At the same time, mental illness increases the risk for HIV acquisition and the risk of negative health outcomes among (Remien et al. 2019). Infections such as Helicobacter Pylori which causes stomach ulcers may trigger the release of various pro-inflammatory mediators such as cytokines, bacterial lipopolysaccharide, heat shock proteins get into the systemic circulation, and trigger immune response in the arterial wall and contribute to atherosclerosis (Dunne 2004) (Whincup et al. 1996) Pasceri et al. 1998). This bacterium may also trigger the release of toxigenic nutrients such as vacuolating cytotoxic gen A, a nutrient which has been found to be involved in the formation of cholesterol patches in arteries, thus promoting atherosclerosis (Jamkhande, Gattani, and Farhat 2016).

Chronic inflammatory disorders such as allergies and asthma produce pro-inflammatory markers which may contribute to atherogenetic plagues thus increasing risk of CVD. For example, a systemic review and meta-analysis of 406,426 participants reported a relative risk for CVD among patients with asthma of 1.33 in women, 1.55 in men, and for both sexes combined (Mingzhu Xu, Jialiang Xu, and Xiangjun Yang 2017). Similarly, a multi-ethnic study following 6,792 participants for 9.1 years reported that patients with persistent asthma had a greater risk of CVD events than non-asthmatics (hazard ratio: 1.6), which persisted after adjustment for age, sex, ethnicity, CVD risk factors, and antihypertensive and lipid medication use (Tattersall Matthew C. et al. 2015). The mechanism of increased CVD risk among patients with asthma may be linked to inflammation - asthma is an inflammatory disorder; and its pro-inflammatory markers (e.g. leukotrienes) may contribute to atherogenetic plagues, thus increasing risk of CVD (Spanbroek et al. 2003)

A number of studies have also explored the association between Tuberculosis (TB) could also potentially increase CVD risk in affected individuals. A review of co-morbidity between infectious and chronic diseases in SSA reported that DM was associated with a 3-fold incident risk of tuberculosis (TB); and it is hypothesized that the TB may also increase the risk of developing the DM(Young et al. 2009a).

1.3: Estimating the 10 year risk of cardiovascular disorders

In order to quantify risk and to guide intervention, algorithms have been developed to estimate the absolute CVD risk (the probability that one develops a cardiovascular event in a defined period) and such estimates are determined by the synergistic effect of several cardiovascular risk factors present (Benowitz and Burbank 2016). An assessment of total risk of developing CVD which is based on the sum of all major risk factors has been found to be useful in clinical practice as it helps in identification of high-risk patients who require immediate attention and intervention, gives a clue to a patient's motivation to adhere to risk-reduction therapies, and can aid modification of intensity of risk-reduction efforts based on the total risk estimates (Grundy et al. 1999). Scores of the absolute 10 year CVD risk of developing cardiovascular disorders has been widely accepted as a guide for determining who to initiate on medication such as lipid-lowering statins in order to reduce the CVD risk (David P. J. et al. 2015).

Several of these scoring systems have been described in literature. They include the QRISK that was developed mainly for the United Kingdom (Collins and Altman 2010), the ASSIGN algorithm (Iglesia et al. 2011) , Reynolds risk score (Ridker et al. 2007) and the Framingham Risk Score (FRS).FRS is Sex specific multivariable risk factor algorithm that was initially developed for the Framingham study (n=8,491 mean age 49 years, women = 4522 women) among participants who attended a routine examination between 30 and 74 years of age and were free of CVD, and it is used to assess general CVD risk and risk of individual CVD events including coronary, cerebrovascular, and peripheral arterial disease as well as heart failure (D'Agostino Ralph B. et al. 2008). The FRS assesses the CVD risk level over 10 years by considering several risk factors; age, sex, total cholesterol, high density lipoprotein cholesterol, smoking habits, and systolic blood pressure (Jahangiry, Farhangi, and Rezaei 2017). The scores are then categorized as low (<10), intermediate (10-19) or high >20. The FRS has been found

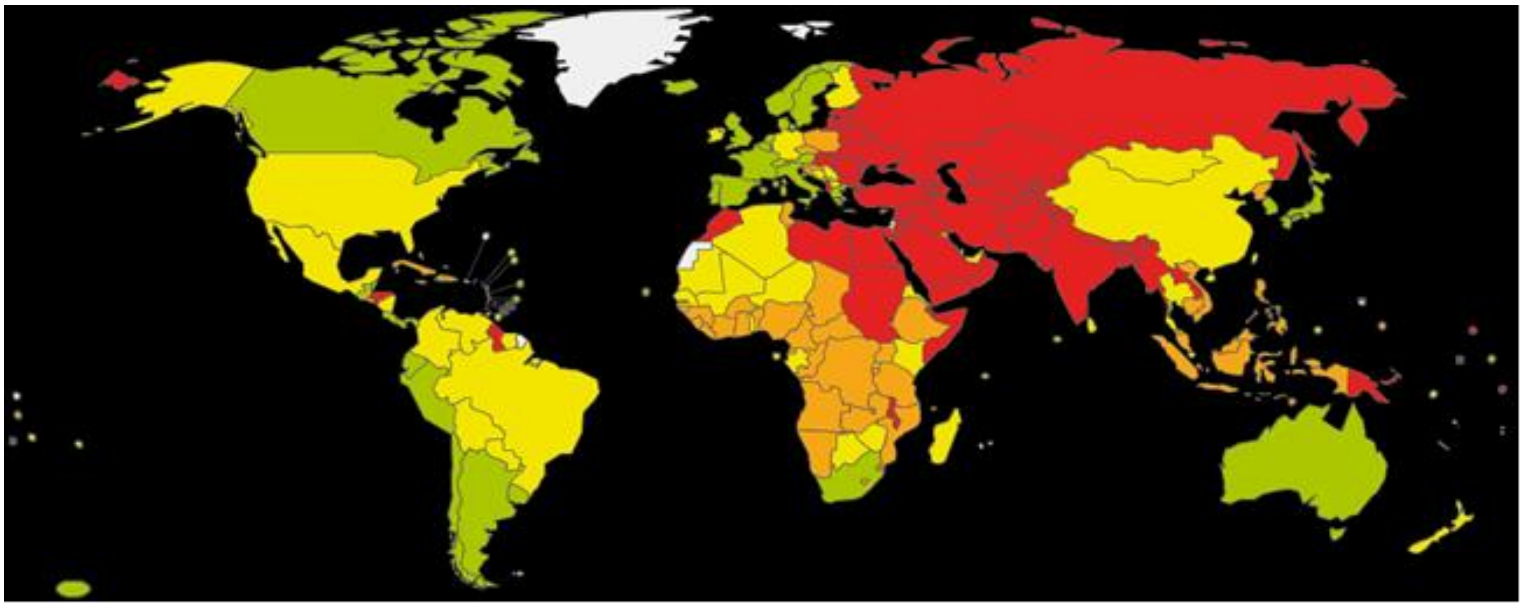
to be useful in assessing people in need of interventions to mitigate CVD risk such initiating statin treatment (Bosomworth 2011).

1.4: CVD Risk Factors in the Context of Low and Middle Income countries

Evidence indicates a rising trend of CVD risk factors in Africa and other LMIC in general populations. A WHO commissioned review of literature on the emerging non-communicable disease epidemic in Africa reported a rise in the prevalence of CVD risk factors over 6 years, (between 1998 and 2004); hypertension (3% to 30%) and diabetes (1% to 20%) as reported by (Mufunda et al. 2006). Further a systematic review of 1,201 studies on NCD in SSA reported a wide variation in prevalence: diabetes mellitus from 0 to 16%, hypertension from 6 to 48%, obesity from 0.4 to 43% and current smoking from 0.4 to 71% and an over representation in some countries such as South Africa (Dalal et al. 2011).

While the burden and outcomes of cardiovascular disorders can largely be reduced using cost effective methods, outcomes in many LMICs are poor with higher CVD related mortality rates being reported compared to high income countries. For example, the Prospective Urban Rural Epidemiologic (PURE) cohort study that included 150,000 adults in 17 high-, middle-, and low-income countries where participants were followed over 4 years reported that the rates of major CVD events were higher in LMIC compared to high income countries (6.43 vs 3.99 per 1000 person years), the case fatalities rates were also higher, (17.3% vs 6.5%) and the use of preventive medications to mitigate these risks was significantly more common in high-income countries than in middle- or low-income countries (Yusuf et al. 2014). Further WHO estimates that about 75% of the reported CVD deaths in the general population take place in LMIC (WHO, Cardiovascular disorders 2017) (See *figure 1 and 2 below*).

Figure 1: World map showing ischemic heart disease mortality rates

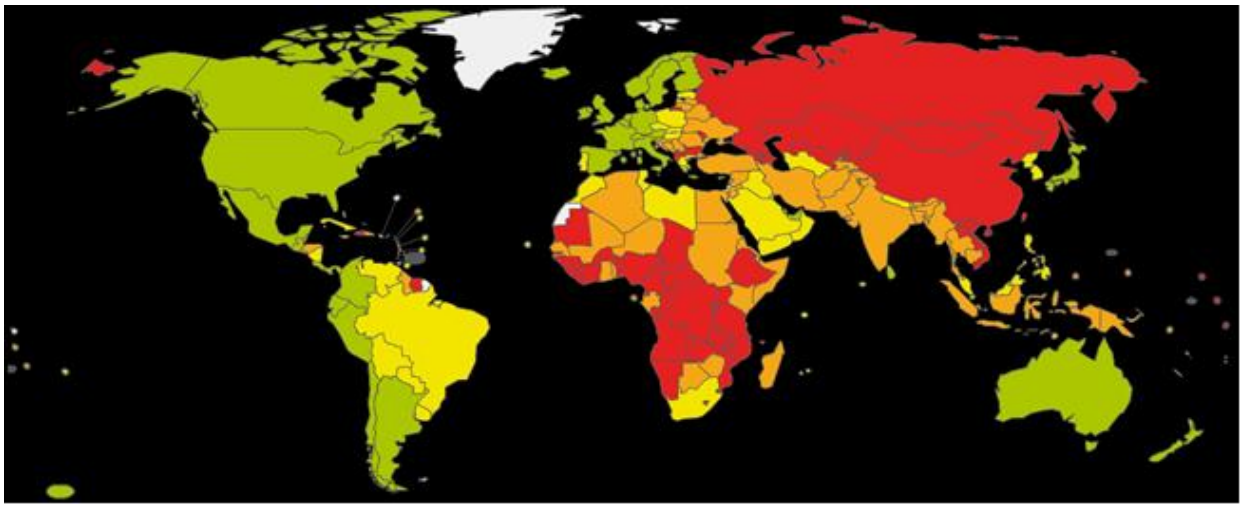


Age standardized, per 100 000)

Ischemic heart disease mortality (per 100 000)

- **12–74**
- **75–108**
- **109–151**
- **152–405**
- **Data not available**

Figure 2: World map showing cerebrovascular disease mortality rates



Age standardized, per 100,000)

Cerebrovascular disease mortality (per 100 000)

- **11–49**
- **50–88**
- **89–131**
- **132–240**
- **Data not available**

Both Figure 1 and 2 are reprinted with permission from Global Atlas on cardiovascular disease prevention and control. ISBN:9789241564373 page 17.

(*https://www.who.int/cardiovasculardiseases/publications/atlas cvd/en/* (WHO 2011a)

Several factors may contribute to poorer CVD-related outcomes in LMICs, compared to developed countries. First, there is lack of integrated care programs for early detection and treatment of CVD risk factors, thus limiting access to effective and equitable health care services. This is likely compounded by lower SES as well as low health literacy levels.

Conclusion

A large body of evidence exists on the factors increasing CVD risk – both in the general population .These include conventional modifiable and non- modifiable cardiovascular factors, as well as other non-conventional risk factors such as trauma exposure and psychological distress. Low and middle income countries suffer from the high burden of the CVD risk and yet the systems in these settings are not optimal hence resulting in poorer outcomes compared to high income settings.

CHAPTER 2: BURDEN AND ETIOLOGICAL MECHANISMS OF CARDIOVASCULAR RISK FACTORS AMONG PATIENTS WITH PSYCHOSIS.

2.0: Introduction

This chapter will describe the cardiovascular risk factors, as well as the etiological mechanisms for the excess risk among patients with psychosis. First the chapter introduces the subject of comorbidity of mental illness and cardiovascular disorders and how this comorbidity impacts outcomes. Second, the chapter describes the burden of each of the CVD risk factors and the reasons of their occurrence among mentally ill patients as currently documented in literature is highlighted, and the overlapping etiological mechanisms between mental illness and CVD risk factors. Third the chapter reports on documented evidence for the role of antipsychotics in increasing cardiovascular risk. Fourth, the chapter gives an overview of use Framingham risk scores to assess CVD risk among patients with psychosis. Fifth the chapter highlights the treatment gap for CVD risk factors among patients with mental illness. Lastly the chapter provides a summary of the gaps in the literature in Low and Middle income countries (LMICs), a conceptual framework and a list of the objectives of the study**.**

2.1: Multimorbidity and Excess Mortality among Patients with Mental Illness.

Patients with psychotic disorders such as schizophrenia have a 2 to 3 fold increased risk of dying compared to the general population and comorbid medical conditions play an important role in the excess mortality in this group (Saha, Chant, and McGrath 2007). A review including 17 large studies done among patients with bipolar disorders indicated a two fold increase in risk of premature death due to general medical conditions (Roshanaei-Moghaddam and Katon 2009). Similarly, a large longitudinal study done among 270,770 patients with psychiatric disorder in Denmark, Finland, and Sweden reported a reduced life expectancy (approximately 15 years shorter for women and 20 years shorter for men) in patients compared to the general population, and mortality due to medical conditions was increased two- to three-fold in patients (Nordentoft et al. 2013).

Co-occurrence of mental illness and physical conditions has been widely documented (Soreca et al. 2008; Kilbourne et al. 2004; ,C. P. Carney, Jones, and Woolson 2006) and may result in poor outcomes for both the physical and the mental illness (E. C. Harris and Barraclough 1998; Fagiolini and Goracci 2009a). The prevalence of medical conditions among the patients with mental illness is higher than among the general population in many settings (Janssen et al. 2015). According to the World Mental Health Survey of 17 countries (n=47,609 individuals, followed for 2,032,942 person-years), patients with mental illness were up to 3.5 times more likely to develop other physical conditions (K. M. Scott et al. 2016). Similarly, a large population-based study among patients with schizophrenia and schizoaffective disorder in the USA (n=1,074 cases and N=726,262) also reported that patients were twice more likely to have another chronic medical condition compared to controls (C. P. Carney, Jones, and Woolson 2006). Further, a national survey that included 1,037,946 patients attending primary care facilities in the United Kingdom linked multimorbidity with worsening health-related quality of life; and reported that the presence of a comorbid mental illness had a more adverse effect on health-related quality of life than any single comorbid physical condition (Mujica-Mota et al. 2015). This is in line with findings from the Patient Outcomes Research Team (Port) study in the US, which reported that comorbid physical and mental illness not only led to higher mortality, but also resulted in poorer perceived health status and worsening mental illness (Dixon et al. 1999).

Recent evidence indicate an excess risk of CVD among mentally ill patients compared to the general population (Barnett et al. 2007; McIntyre et al. 2005; Gardner-Sood et al. 2015; Mitchell, Vancampfort, Sweets, van Winkel, et al. 2013). These disorders are the leading physical disorders that contribute to mortality in patients with mental illness, as evidenced among patients receiving community psychiatry services across six states in the US (Colton and Manderscheid 2006). A recent meta-analysis of 3,211,768 patients and 113,383,368 controls reported that the pooled CVD prevalence in patients with severe mental illness (SMI) was 9.9%, while the cumulative CVD incidence was 3.6% (Correll et al. 2017). These disorders are believed to contribute significantly to the excess mortality that has been reported among patients with psychosis (Muhammad Chachal et al 2016), (Hennekens et al. 2005;

Risgaard et al. 2015), competing only with suicide (Ösby et al. 2000). For example, a cohort study done in the United Kingdom including 46,136 participants with severe mental illness (SMI) and 300, 426 without SMI, the hazard ratio for coronary heart disease mortality in people with SMI compared with controls was 3.22 and for stroke deaths, the hazard ratio was 2.53 (Osborn et al. 2007). Similarly a study that included 147,193 veteran affairs psychiatric patients in the US reported that 11,809 (8%) of these patients died from heart disease (Kilbourne Amy M. et al 2009). This therefore emphasizes the need for attention to CVD risk factors in order to reduce the mortality associated with CVD in this population.

Other comorbidities may also have a bearing The CVD risk profile of patients with psychosis. For example patients with psychosis have an increased risk of acquiring/transmitting TB, and with poorer adherence to anti-TB treatment; while a TB diagnosis may also increase the risk of psychiatric comorbidity (Doherty et al. 2013;,Pachi et al. 2013; Unwin 2016). TB among patients with psychosis may also have indirect effects on cardiovascular risk. For example, TB and diabetes mellitus have been found to be highly co-morbid - (Alebel et al. 2019). the TB bacterium may in fact alter carbohydrate metabolism by causing insulin deficiency and persistent hyperglycaemia (Young et al. 2009a; L. Bell et al. 2007). In addition, mental illness may increase the risk of smoking, which in turn may increases the risk both of TB and of CVD (Boon et al. 2007).

2.2: Conventional Cardiovascular Risk Factors among Patients with Psychosis

According to one narrative review, up to 9.7 million cases of CVD annually are attributable to well established CVD risk factors (Tzoulaki et al. 2016). Among patients with psychosis each of these risk factors exist in varying proportions, have different etiological mechanisms and have distinct pathways by which they contribute to the increased risk of developing CVD.

Socio-economic factors: The relationship between psychosis and low Social- economic Status (SES) has been described in literature (Hudson 2005) , with some evidence indicating that poverty and income inequality influence the prevalence and severity of psychosis in men and women across the life course (Lund et al. 2018). Poverty may also indirectly increase the risk of psychosis and the association has

been described for lower education levels, lack of employment, high cost of managing the disease, stigma and discrimination (Callander and Schofield 2015). An alternative explanation of the link between SES and cardiovascular health is that psychosis may impair one's ability to participate in income-generating activities, as demonstrated by large observational studies in Norway (Kaspersen et al. 2016), Finland, Poland, Spain (Leonardi et al. 2018), and the Netherlands (Leijten et al. 2015). Resultant job loss due to psychosis may then result in increased psychological distress, and ultimately increased CVD risk in affected individuals.

Smoking: Smoking is very common among patients with psychotic disorders (Wojtyna and Wiszniewicz 2013). There is evidence to suggest that more than half of patients on treatment schizophrenia and bipolar disorders smoke (J. de Leon and Diaz 2005; McClave et al. 2010; Uçok et al. 2004; Cooper et al. 2012). A recent meta-analysis which included 31 studies indicated a smoking rate of 58% among patients with mental illness (Myles et al. 2012a). Another study which compared the patients with psychosis and the general population reported that patients with schizophrenia are twice more likely to smoke (Ohi et al. 2019; Myles et al. 2012b). In addition to the number of cigarettes smoked per day by people with psychotic disorders, there is also evidence of higher nicotine intake as demonstrated by shorter inter puff periods and more puffs per cigarette amongst patients with mental illness (J. M. Williams et al. 2011).

The exact mechanisms underlying increased tobacco use in mentally ill patients remains complex and likely bidirectional (Quigley and MacCabe 2019). First, smoking itself may be a primary causative factor for psychosis, or may interact with other precipitating factors. A meta-analysis of 3,717 studies (total of N=14,555 tobacco users and N=273,162 non-users) reported that 57% of patients presenting with their first episode of psychosis were smokers; that smoking increased the risk of a psychotic disorder three fold; and that smoking was associated with an earlier age of onset of psychosis (Gurillo et al. 2015a). Second, patients with psychosis may smoke to self-medicate, i.e. to alleviate the negative experiences resulting from psychosis (such as anxiety and exaggerated startle reflex) (Choi, Ota, and Watanuki 2015). Third patients may also smoke to counter the cognitive impairment associated with psychosis, given

that nicotine has been shown to have cognitive-enhancing abilities by increasing dopamine release in the prefrontal cortex (Jasinska et al. 2014; Ghiasi et al. 2013). A meta-analysis including 41 double-blind, placebo-controlled laboratory studies found positive effects of smoking in fine motor functioning , alerting attention-accuracy and response time, orienting attention, short-term episodic memory, accuracy, and working memory response time (Heishman, Kleykamp, and Singleton 2010). Fourth, increased smoking in patients with psychosis may be mediated by specific genetic polymorphisms. For example, polymorphism of the IL-1beta-511C/T gene has been found to be associated with increased severity of nicotine dependence among male smokers with schizophrenia (Zhang et al. 2015). A polygenic analysis from the Psychiatric Genomics Consortium (PGC) Schizophrenia group has also revealed several shared genes between smoking and mental illness (J. Chen et al. 2016). Finally, nicotine use among mentally ill patients may be compounded by accompanying social difficulties, as demonstrated by a higher prevalence of smoking among socially disadvantaged patients (L. Hahn, Rigby, and Galletly 2014).

In addition the direct neurobiological mechanisms through which smoking increases CVD risk there are also a number of indirect mechanisms through which smoking may increase CVD risk among patients with psychosis. For example, smoking has been found to increase the activity of the cytochrome CYP 1A2 enzymes, thus decreasing the concentration of certain psychoactive agents such as clozapine and olanzapine, and increasing the clearance of fluphenazine and haloperidol (Šagud, Mihaljevi, and Vuksan 2009). As a result, dosages above the recommended therapeutic limits may be administered, resulting in higher risk of metabolic side effects associated with these drugs (McCloughen 2003; Tsuda, Saruwatari, and Yasui-Furukori 2014)

Harmful Alcohol use

While generally substance use disorders are very common among patients with mental illness (Toftdahl, Nordentoft, and Hjorthøj 2016), harmful alcohol use is one of the most commonly used substance among patients with psychotic disorders (Yang et al. 2018). One meta-analysis of 123 studies (N=165,811 participants) reported that 24% of patients with schizophrenia had a co-morbid alcohol use disorder

(Hunt et al. 2018); and 46.2% patients with bipolar I mood disorder have been reported also to have an alcohol use disorder (Sonne and Brady 2002). This , according to a nationwide prospective study done in Denmark that included 41,470 people with schizophrenia, 11,739 people with bipolar disorder, and 88 270 people with depression, is associated with higher standardized mortality rations (2 to 8 times higher) compared to patients without alcohol use (Hjorthøj et al. 2015).

The pathways underlying comorbid alcohol use disorder and psychotic disorders is likely multifaceted, including shared etiological mechanisms. Alcohol use may itself precipitate psychosis, and mental illness may increase the risk of alcohol use as self-medication (Sonne and Brady 2002). Alcohol has been found to target dopaminergic, glutamatergic and GABAergic transmission, all which are also involved in the pathophysiology of psychosis (Thoma and Daum 2013). Patients with schizophrenia may also tend to overvalue drug-like rewards (augmented by alterations in nicotinic, cholinergic, GABAergic, glutamatergic, and cannabinoid receptor function); and to devalue the potential negative consequences of substances, and this may be further complicated by detrimental decision-making and impulsive behaviour (Krystal et al. 2006). Distortions in reward processing and altered responses to substances of abuse may also increase the likelihood that individuals with schizophrenia will self-medicate in order to blunt or alleviate their psychotic symptoms (Potvin, Stip, and Roy 2003). Further, the greater euphoria and stimulatory effects in response to alcohol observed among patients with schizophrenia may also promote alcohol consumption among these patients (D'Souza et al. 2006). Genetic studies of both alcohol use and schizophrenia suggest a combination of multiple common and rare variants which may contribute to this co-morbidity (Polimanti, Agrawal, and Gelernter 2017; Levey et al. 2014; K. Wang, Luo, and Zuo 2014).

Inadequate physical activity; Current evidence indicates that patients with mental illness tend to have more sedentary behaviour and also perform less vigorous physical activity compared to the general population (Davy Vancampfort et al. 2017).. For example, a meta-analysis of 292 publications reported that patients with schizophrenia were less physically active than the general population (Ohi et al. 2018). A systematic review and meta-analysis including 2,033 participants with psychosis reported patients

spent on average 11hours in sedentary behaviour and this was about 2.8 hours more than the general population (Stubbs, Williams, et al. 2016). This less that optimal level of physical activity is likely to have implications both for physical health and for overall quality of life among patients with psychosis, (Martín-Sierra et al. 2011).

Several explanations have been put forth as contributors toward low physical activity level in this population. One large study of 204,186 adult patients with psychosis from 46 LMICs attributed the lower physical activity levels in these patients to certain symptoms and sequelae of psychosis, including impaired cognition, depression, mobility difficulties and self-care challenges, (Stubbs et al. 2017a). Reduced physical self-perception due to psychotic illness, as well as impaired physical capacity and health-related muscular fitness, may also play a role in reducing the ability of patients with psychosis to engage in adequate physical activities (Davy Vancampfort, Probst, et al. 2013). In addition, patients with schizophrenia have been found to have reduced cardiorespiratory fitness compared to healthy controls, (Heggelund et al. 2011; Strassnig, Brar, and Ganguli 2011), which may be worsened by the presence of other CVD risk factors such as obesity (D. Vancampfort, Sweers, et al. 2011) and DM (Davy Vancampfort, De Hert, et al. 2013). Low activity level may also precede the onset of illness as reported by a Finish birth cohort study which demonstrated that adolescents who later developed psychosis had low level of physical activity prior to the onset of the illness (Koivukangas et al. 2010) . The sedating effects of antipsychotics is also likely to reduce patients' physical activities thus increasing the time spent in sedentary behaviour and hence increasing the CVD risk further (D. D. Miller 2004).

Poor diet: Evidence suggests that patients with mental illness have high rates of *poor diet*. For example, a well powered self-reported health behaviours study conducted among 1, 935 Australian adults reported poor intake of fruits and vegetables among patients who scored highly on a psychological distress scale (D. Scott et al. 2013). This is collaborated by a systematic review of 31 articles assessing the dietary patterns of patients with schizophrenia which reported that these individuals often followed a poor diet (e.g. with increased intake of saturated fats and reduced intake of fruits and vegetables), thus augmenting the risk of metabolic disturbances (Dipasquale et al. 2013a).

Several factors contribute to poor dietary habits among patients with psychosis specifically. A case–control study that recruited patients with first episode psychosis from South-East London reported a positive association of poor dietary habits and unemployment (Samele et al. 2007). Poor dietary habits among mentally ill patients have also been attributed to substance use (which – as discussed previously – is highly comorbid in this population); to the negative symptoms of psychosis; or to economic challenges (Tune et al. 2017). According to an observational study of 1244 adults in Australia, another potential contributor of poor diet is low knowledge levels among patients with psychosis on physical health behaviours which is associated with poor dietary habits (Stanton, Scott, and Happell 2016). Further, cultural factors also play a role in shaping dietary habits as demonstrated by a case control study in Bahrain (n=240) that reported similar dietary habits between patients with schizophrenia and controls ,a finding they attributed to the practice of serving certain fruits and vegetables in every meal and in community cerebrations (Jahrami et al. 2017).

Diabetes: Hyperglycaemia and DM are common among patients with schizophrenia and schizoaffective disorder (D. Cohen et al. 2006), with a recent meta-analysis (N=438,245 individuals) reporting a prevalence of DM of 10.2% (Davy Vancampfort et al. 2016). This is in agreement with findings of a study done in Wales among 3,170 patients with schizophrenia which reported a double incidence of DM among the patients compared to the general population (Le Noury et al. 2008). Similarly, a 10-year nationwide population-based prospective cohort study that was conducted in Taiwan among 367 patients with bipolar mood disorder, 417 patients with major depressive disorder , and 1,993 patients with schizophrenia reported that patients with bipolar mood disorder and schizophrenia had significantly increased risks of initiation of anti-diabetic and anti-hyperlipidaemia treatment compared to controls and patients with major depressive disorder (Bai et al. 2013).

The relationship between DM and mental illness is bidirectional with DM increasing risk of mental illness and mental illness medication increasing risk of DM (Balhara 2011). There is also evidence that there are several shared etiological pathways that contribute to the comorbidity (Y. Liu et al. 2013). The use of antipsychotics - particularly olanzapine and clozapine - has been linked to increased prevalence of

DM (Lamberti et al. 2004; Lamberti et al. 2005; Guo et al. 2006). Antipsychotics may contribute to impaired glucose control through pancreatic beta cell dysfunction, reduced insulin sensitivity , increased hepatic glucose production and decreased peripheral glucose utilization (Chintoh et al. 2009). However, there is also evidence of impaired glucose levels in up to 15% of patients who have not been exposed to such neuroleptics, suggesting an alternative etiological mechanism for DM in patients with psychosis (Mukherjee et al. 1996). One hypothesis is linked to the deficiency of insulin-like growth factor in patients with schizophrenia, which is believed to contribute to insulin resistance and thus also to impaired glucose tolerance (Gastaldelli, Gaggini, and DeFronzo 2017; Venkatasubramanian et al. 2007; Kirkpatrick et al. 2012). Further, a positive family history of DM has been found to be associated with a positive family history of schizophrenia, suggesting potentially shared heritability (Nuevo et al. 2011), (Foley et al. 2016). In addition , a functional genetic variant of the melatonin receptor 1B (*MTNR1B*) gene, which increases vulnerability for elevated fasting plasma glucose, has been reported to be shared between bipolar mood disorder and schizophrenia (Hukic et al. 2016).

Hypertension: The prevalence of hypertension is estimated to be up to two times higher among patients with mental illness compared to the general population (Sugai et al. 2016a; Ayerbe et al. 2018). Other evidence indicates that hypertension is one of the most common medical comorbidities in patients with schizophrenia (Nishanth et al. 2017) and bipolar mood disorder (Goldstein et al. 2009). A recent meta-analysis reported an increased incidence of hypertension in patients with bipolar mood disorders (Ayerbe et al. 2018) with a Japanese nationwide survey indicating a 2 to 3 fold increased risk among patients with schizophrenia (Sugai et al. 2016a). Data from the 2001-2002 National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) study reported that the prevalence of hypertension among patients with bipolar mood disorder is 22% (Goldstein et al. 2009).

The mechanism underlying increased risk of hypertension in patients with psychosis are varied. Antipsychotic use resulting in disrupted dopamine activity may be a significant contributor to the increased risk of hypertension in patients with schizophrenia (B. B. Alves et al. 2019) . This may be underpinned by the absence of inhibitory tone on sympathetic outflow (mediated by D2 dopamine receptors) in the

vascular smooth muscle (Li et al. 2001). In addition, emotional distress which is common in patients with psychosis results in HPA axis dysregulation hence contributing to development of hypertension (Ojike et al. 2016). Given the high heritability both of hypertension (30-60% (Kupper et al. 2005; Shih and O'Connor 2008), and of schizophrenia (81%) (Sullivan, Kendler, and Neale 2003), genetic risk factors may also contribute to their co-morbidity (Kotchen et al. 2000) .

Obesity; Studies done in high income settings indicate that patients with schizophrenia are twice as likely to experience obesity and dyslipidaemia, compared to the general population (Cameron et al. 2017; Association 2004). A small but growing evidence base suggests that this trend may also exist in general populations in SSA. For example, one population-based cross-sectional survey by Kavishe et al. of 2,011 participants from rural Tanzania and Uganda reported high rates of hypertension, cigarette smoking, harmful alcohol use , and increased BMI (Kavishe et al. 2015).

The high rates of obesity reported among patients with psychosis has been linked to a shared biological vulnerability between mental illness and abnormal metabolic processes, unhealthy lifestyles and antipsychotic use (Bradshaw and Mairs 2014). As is the case for DM, it is likely that co-morbid obesity and psychosis is largely attributable to antipsychotic use, particularly clozapine and olanzapine (Gianfrancesco et al. 2003; Wirshing 2004; Rummel-Kluge et al. 2010a). In this regard, a number of studies that have been conducted among patients with first episode psychosis before medication initiation have consistently demonstrated lower prevalence of obesity among unmedicated patients compared to patients on antipsychotics (Padmavati, McCreadie, and Tirupati 2010), (Sengupta et al. 2008). Another mechanism that could explain the high prevalence of obesity among patients with psychosis is dopamine dysregulation as described in the dopamine theory of schizophrenia (Howes and Kapur 2009). Impairment in dopaminergic pathways that regulate neuronal systems associated with reward sensitivity and control of food intake may result in overeating and hence obesity in this population (Volkow, Wang, and Baler 2011), (Wise 2006).

Dyslipidaemia; Several studies have demonstrated a derangement in lipids among patients with psychosis (Koro et al. 2002). A study done among 1,642 Australians with psychosis and 8,866 controls showed that patients with psychosis had lower a HDL-cholesterol than controls (18). Another survey conducted in South Africa among 84 long-term mentally ill patients reported that half of the participants had high Low Density Lipoprotein (LDL) (Maaroganye et al. 2013). A similar study of 276 participants in Durban, Kwazulu-Natal reported high LDL and low HDL among the mentally ill persons (Saloojee, Burns, and Motala 2016a).

The dyslipidaemia among patients with psychosis has strongly been linked to use of antipsychotics especially atypical antipsychotics with olanzapine and clozapine being on the lead (Attux, Quintana, and Chaves 2007; Birkenaes et al. 2008; J. de Leon et al. 2007). In support of the role of medication in altering the lipid metabolism, a comparative meta-analysis including twenty-six studies with 2,548 patients who were taking medication and 19 studies with 1,325 unmedicated patients reported that the dyslipidaemia is more prevalent after medication initiation (Lange and Steck 1994). Antipsychotics are believed to alter lipid metabolism by promoting synthesis and accumulation of total cellular cholesterol by reducing the cholesterol level within the cell endoplasmic reticulum (Mitchell, Vancampfort, De Herdt, et al. 2013a). Another potential mechanism of antipsychotic medication on lipid metabolism is the upregulation of genes controlled by the sterol regulatory element-binding protein (SREBP) transcription factors(J. Fernø et al. 2005 ; Johan Fernø et al. 2009).

Metabolic syndrome; Patients with psychosis demonstrate a higher prevalence of (MetS) compared with the general population (Toalson et al. 2004, (Jakovljević et al. 2007; McEvoy et al. 2005; Ohaeri and Akanji 2011). According to one large meta-analysis (N=256,920 individuals), the prevalence of MetS was reported to be 32.5% among patients with schizophrenia and related disorders (Mitchell, Vancampfort, Sweers, et al. 2013) and 37.3% among patients being treated for bipolar mood disorder (Davy Vancampfort, Vansteelandt, et al. 2013).

In patients with mental illness, the strongest evidence of association has been with prescribed medication (Ventriglio et al. 2015). Other contributors to high rates of MetS among patients with mental illness can be linked to the individual risk factors such as DM and dyslipidaemia in these patients (Davy Vancampfort, Vansteelandt, et al. 2013), (Beilby 2004b). Others have hypothesized that sleep disturbance in psychosis could lead to impaired energy balance due to impairment of sleep regulated hormones like leptin and ghrelin (Garaulet and Madrid 2009). Important to note however, is that the prevalence of MetS in neuroleptic-naïve psychotic patients and in those with first-episode psychosis has been found to be approximately 10%, thus suggesting additional etiological mechanisms (Mitchell, Vancampfort, De Herdt, et al. 2013b). The risk at diagnosis is however likely to be worsened as the illness takes a more chronic course as indicated by a meta-analysis that included123 publications which reported a higher prevalence of MetS among more chronic patients with schizophrenia compared to first episode and unmedicated schizophrenia (Mitchell et al. 2013).

2.3: Psychopharmacological treatment and cardiovascular risk

Mental illness in itself has an association with CVD risk as demonstrated by presence of CVD risk factors like diabetes, dyslipidaemia and obesity even before the onset of antipsychotic use (Osby et al. 2014; Bushe and Holt 2004. However the use of antipsychotics in these patients markedly affects metabolism leading to weight gain, dyslipidaemia and diabetes mellitus (DB Allison, JL Mentore, M Heo 1999; Ballon et al. 2014).

Antipsychotics, both first generation and second generation, remain the main mode of treatment for schizophrenia, bipolar disorders and other psychotic disorders (Lally and MacCabe 2015). Unfortunately, most antipsychotics are associated with an increase in CVD risk factors such as obesity, weight gain, hypertension and DM (Rojo et al. 2015), thus the need to understand, assess, and subsequently manage metabolic complications of antipsychotics in order to mitigate the excess CVD related morbidity and mortality among patients using these drugs (Abosi et al. 2018). A recent meta-analysis of 307 clinical trials reported that almost all antipsychotics assessed resulted in increased body weight and BMI, particularly with longer duration of antipsychotic use - (the exceptions in this case were amisulpride,

aripiprazole and ziprasidone, which remained weight-neutral with increasing duration of antipsychotic use). However, different antipsychotic show different alteration in metabolic profile, with olanzapine being most implicated. For example an observational Chinese study comparing risperidone, olanzapine, ziprasidone chlorpromazine, haloperidol and trifluoperazine showed that olanzapine was associated with the highest increment in cholesterol and triglycerides (Edwin Lee, Lai-Yin Chow, and Chi-Ming Leung 2011) .Further, antipsychotic-naïve patients exhibited the greatest incremental weight gain and increase in BMI with increased duration of medication use (Maarten Bak et al. 2014). This is similar to findings of a small Spanish longitudinal study (N=170) of patients with first episode psychosis, which demonstrated that metabolic changes occurred early in treatment, with maximal increases of weight gain and lipids occurring in the first year , and stabilizing thereafter (Pérez-Iglesias et al. 2014). Though most of the literature is from developed nations, findings of increased CVD risk with antipsychotic use has also been reported in LMIC settings. For example an observational study conducted in Ethiopia among 356 patients reported that 56% of the patients developed cardiovascular related side effects (Wubeshet, Mohammed, and Desse 2019).

A number of mechanisms underlie antipsychotic-induced metabolic changes and increased CVD risk. For example, antipsychotics may affect glucose homeostasis by perturbing both the central and peripheral nervous systems that are involved in glucose metabolism (Kowalchuk et al. 2018). Antipsychotic-induced weight gain as well as alteration of lipid and glucose metabolism results from blockade of serotonin (5HT2c) and histamine (H1, H3) receptors in the nervous system (Shen- Chieh Chang et all 2012; Wesley Kroeze 2003; Chao Deng 2010; Gavin P Reynolds et all 2006). Antipsychotics also result in results in increased appetite and weight gain, as well as binding at 5-HT1A, muscarinic M3, dopamine D2 which has been linked to insulin resistance (Shen- Chieh Chang et all 2012). The antipsychotic-related metabolic effects are seen in patients using most antipsychotics but are more prominent with the second generation antipsychotics like olanzapine and clozapine (Rummel-Kluge et al. 2010b).

It has also been suggested that reduction in prolactin levels that occurs with use of atypical antipsychotics due to reduction in serotonin level also plays a role in aetiology of DM (Oberweis and Gragnoli 2012). In addition, antipsychotics may increase the risk of weight gain and obesity by inducing a hypermetabolic state (increasing appetite and caloric intake), which is a result of alteration of neurotransmitters such as histamine(H), adiponectin, serotonin(5HT) and dopamine (D) which play a role in obesity (Manu et al. 2015). It has also been reported that the antagonistic effects of antipsychotics on 5-HT2C, muscarinic, and H1 receptors alter the gut microbiota composition, which in turn leads to changes in appetite and emotions and eventually increased weight gain (Bretler et al. 2019). Further, given that antipsychotics target dopamine receptors, and that D1, D3 and D4 receptors interact directly with the renin-angiotensin-aldosterone system whereas D2 and D5 receptors interact with the sympathetic nervous system to regulate blood pressure, use of dopaminergic agonists or antagonists has the potential to interfere with the regulation of blood pressure thus increasing CVD risk (Gonsai et al. 2018; B. B. Alves et al. 2019). Molecular studies have also indicated that second generation antipsychotics interfere with energy glucose metabolism at the mitochondrial level (the cellular organelle responsible for energy production) thus accelerating development of MetS (del Campo et al. 2018) . Antipsychotic-related weight gain has also been linked to certain variants in genes coding for antipsychotic pharmacodynamics targets such as the dopamine and serotonin receptors. A meta-analysis of 72 articles (N=6700 participants) reported at least 9 genes and 13 Singel Nucleotide Polymorphisms (SNPs) associated with antipsychotic-induced weight gain (J.-P. Zhang et al. 2016). Antipsychotic effect on cardiovascular risk factors may also augment an already existing vulnerability. For example one Chinese study that compared antipsychotic naïve patients with schizophrenia and the general population reported that patients with schizophrenia are more likely to have insulin resistance and dysfunction of lipid metabolism when compared to the control population, even before onset of treatment (S. Chen et al. 2013).

2.4: Exposure to Potentially Traumatic Events among Patients with Psychosis

There is evidence that patients with psychosis are more likely to experience potentially traumatic events in their lifetime, when compared to the general population (Mueser et al. 2002) (Floen and Elklit 2007b).. There is also evidence to suggest that traumatic experiences increase the risk of schizophrenia and bipolar mood disorders- particularly among those with genetic predisposition - by increasing stress vulnerability, and dysfunction in the HPA axis (Okkels et al. 2017**;** Shevlin et al. 2008). A study done in South Africa among patients with first episode psychosis demonstrated that both the witnessing of a seriously violent act (and a history of sexual assault were associated with high positive symptoms in patients (Burns et al. 2011). In addition, childhood trauma is also common among patients with psychosis but the etiological mechanisms remain poorly understood (Etain et al. 2008a**;** Craig Morgan and Fisher 2007; Friedman and Tin 2007). Childhood trauma has also been found to be associated with the development of mental illness later in life (Larkin and Read 2008; Spataro et al. 2004). One meta-analysis of 36 studies (n=81,253) reported that such exposure to trauma may increase the risk of psychosis by almost three fold (Varese et al. 2012). This risk is likely due to distressing interpretations of ambiguous external events (Whitfield et al. 2005a; Larkin and Read 2008). In addition childhood trauma has been linked with impairment in working memory, executive function, verbal learning, and attention in schizophrenia patients (2019). The Adverse Childhood Experiences study (ACE) documented the positive relationship between the dose of traumatic experience in childhood and the severity of negative mental health outcome in adulthood (Whitfield et al. 2005b). Similarly, data from the second British National Survey of Psychiatric Morbidity suggested that patients with psychosis were more likely to report traumatic experiences in their childhood than were those without psychosis, with sexual abuse being most frequently reported (Bebbington et al. 2004) Data from the environmental risk longitudinal twin study in United Kingdom , which followed 2,232 twin children reported a three-fold increase in risk of psychotic symptoms among patients who were maltreated in childhood (Arseneault et al. 2011). One brain imaging study of children who were maltreated postulated that childhood trauma may contribute to psychopathology by resulting in changes in brain regions involved in emotional regulation, ability to

accurately attribute thoughts or intentions and self-awareness (Teicher et al. 2014). An Irish prospective cohort study involving 1,112 adolescents reported a bidirectional relationship between trauma and psychotic experiences, a dose-response relationship between severity of bullying and risk of psychotic experiences as well as incidence of psychotic experiences decreasing significantly in individuals whose exposure to trauma ceased over the course of the study (Kelleher et al. 2013).

2.5: Estimating the Overall Cardiovascular Risk in Patients with Psychosis

Framingham Risk Score (FRS) is the most commonly used in patients with mental illness (Foguet-Boreu et al. 2016) (Lloyd-Jones et al. 2004; Wilson Peter W. F. et al. 1998). The Clinical Trials of Antipsychotic Treatment Effectiveness (CATIE) schizophrenia study, reported significantly elevated FRS scores among patients with schizophrenia compared to controls, both for males (9.4% in patients vs 7.0% in controls) and females (6.3% vs. 4.2%) (Goff et al. 2005). Similarly, a Lebanon study of 329 patients with schizophrenia reported that 31.6% of the participants had intermediate risk of developing CVD, while 7.6% had high risk (Haddad et al. 2017). A Chinese study (83 patients and 243 controls) also reported that patients with schizophrenia had a higher mean 10-year CVD risk (4.6%), compared to controls (3.1%) (Tay, Nurjono, and Lee 2013).

2.6: Treatment Gap for Cardiovascular Risk Factors among Patients with Psychosis

While the burden of CVD risk factors is high among patients with psychosis, there is evidence for interventions that have potential to reduce this in this population. For example a UK wellbeing support program that was initiated among 966 patients with SMI reported a significant improvement in physical activity and a reduction in smoking(S. Smith et al. 2007). A Chinese randomized controlled trial that involved 128 adults with schizophrenia assigned to 12 weeks of either placebo, 750 mg/d of metformin alone, 750 mg/d of metformin and lifestyle intervention, or lifestyle intervention only, demonstrated that a combination of metformin and lifestyle intervention (psychoeducational, dietary and exercise programs) was effective in reducing weight, BMI and waist circumference (Wu Ren Rong 2008). In addition, a study done in Boston comparing the quality of care between 214 patients with schizophrenia and 3594 controls

indicated that patients with schizophrenia can actually receive high quality care for DM in well-organized settings (Weiss et al. 2006).

Despite the recognized burden of CVD among patients with psychosis and evidence for interventions that could reduce this burden, current systems for the assessment and treatment of these disorders in this group are limited (Hennekens 2007). According to data from the CATIE: Schizophrenia study, rates of non-treatment were 30.2% for diabetes mellitus, 62.4% for hypertension, and 88.0% for dyslipidaemia (Nasrallah Henry et all 2006). A study of patients with Type 2 DM including 100 patients with schizophrenia, 101 with a major depressive mood disorder, and 99 without SMI reported that patients were less likely to be prescribed for cholesterol-lowering statin medications, angiotensin-converting enzyme inhibitors, and angiotensin receptor blocking agents than diabetes patients without SMI and that patients with both diabetes and SMI are treated less aggressively for high cardiovascular risk than diabetes patients without mental disorders (Kreyenbuhl et al. 2006). Similarly, a study of psychiatric inpatients in Southampton (n=100) reported low documented screening for cardiovascular risk factors, with only 32% of patients having blood pressure on record, 16% with measured glucose, 19% with lipids assessed and 2% with weight recorded in a one-year period (Holt et al. 2010). Further, a study in Maudsley (n=606) reported that 11% of patients with diabetes mellitus had not been previously diagnosed (David Taylor, Corina Young, Radia Mohamed, Carol Paton, Rebecca Walwyn 2005). Similarly, a population-based record-linkage study of 210,129 users of mental health services in Western Australia reported that - compared to the general population - patients with psychosis were less likely to receive interventions for acute cardiovascular events such as revascularization (David M. Lawrence et al. 2003).

The low rate of screening ,diagnosis and treatment for cardiovascular risk factors amongst patients with psychosis many settings may be due to a number of interrelated factors (D. J. Smith et al. 2013; DE HERT et al. 2011; Druss et al. 2001). First , there may be lack of co-located medical and mental health services, and cultural challenges such as providers' adopting a biomedical – rather than a holistic – approach to patient care (Druss and Newcomer 2007), (Druss 2007). Second , patients with psychosis

tend to exhibit lower utilization of healthcare services and higher use of emergency services, which may suggest missed opportunities for recognition and management of CVD risk factors (Motsinger et al. 2006; Thomas R. E. Barnes et al. 2007). In such settings, physical examination may not be comprehensive as clinicians may focus instead on the presenting emotional or behavioural disturbance, neglecting symptoms that may indicate cardiovascular ill health (R. Carney, Bradshaw, and Yung 2015). Third, impaired cognition that is associated with psychosis may also adversely affect health seeking behaviour and reporting of CVD related physical symptoms (Räsänen et al. 2003; Mensah et al. 2015). Third, due to the mental illness most patients are less likely to adhere to medication prescribed to control the cardio metabolic disorders thus contributing to poorer outcomes. Fourth, both perceived and experienced stigma for mental illness may contribute to the patients not receiving adequate care for the cardiovascular risk factors (Knaak, Mantler, and Szeto 2017).

However, even when healthcare facilities are accessed by patients with psychosis, screening for physical disorders in these settings is limited. For example, despite the American Diabetes Association (ADA) consensus statement recommending metabolic monitoring for patients treated with second generation antipsychotics (SGA,) screening rates among mentally ill patients in the US have been found to be as low as 20% for glucose and 10% for lipids (Morrato et al. 2009) . This is similar to findings of a UK-based clinician audit, which reported recorded measurement within the previous year for blood pressure in 26% of patients (total N=1966), for obesity in 17%, for blood glucose (or HbA1c) in 28% and for plasma lipids in 22%; with all four measures documented in only 11% (Thomas R. E. Barnes et al. 2007; Motsinger et al. 2006). Label warnings of antipsychotics may also not be effective in increasing screening rates - in a cross-state US cohort study of 109,451 individuals receiving Medicaid who were initiated on SGA treatment, labelled warning was not associated with a significant increase in glucose testing; and only marginally increased lipid testing rates (1.7%; p=0.02) (Morrato et al. 2010). These gaps in care likely contributes to excess CVD related mortality and morbidity in this population.

2.7 : Study Justification

While there is substantial literature on the prevalence and determinants of CVD risk factors in the developed world, there is a notable underrepresentation of data available from LMICs and SSA; and the literature on the burden of conventional cardiovascular risk factors among patients with psychosis in SSA is scanty. There are also minimal data for SSA on the role of trauma and psychological distress in shaping cardiovascular risk profile; and on the contribution of comorbid medical conditions to cardiovascular risk among patients with psychosis. Data on prescription patterns in SSA and how this affects the cardiovascular risk profile among patients with mental illness is not existent. Efforts to address the cardiovascular risk factors among mentally ill patients in LMIC and SSA, are also not well documented in literature. The current study therefore addresses the knowledge gap on the risk of CVD among patients treated for psychosis in a SSA setting.

The dearth of evidence emerging from LMICs and SSA has likely contributed to limited clinical programs addressing the cardiovascular health of mentally ill patients in these settings. In future, the burden and sequelae of CVDs may largely be reduced through simple and cost-effective methods such as lifestyle modification (e.g. smoking cessation, improved diet and physical activity, substance use interventions); as well as timely treatment for disorders such as hypertension, DM, and hyperlipidaemia. However, in order to design contextually relevant screening, treatment and prevention guidelines that may ultimately be integrated into routine care of the mentally ill in SSA, further work on the prevalence of CVD risk factors is needed.

2.8: Study aim and objectives

The aim of this study was to assess the cardiovascular risk profile among patients treated for psychotic disorders at Moi Teaching and Referral Hospital (MTRH) in Eldoret, Western Kenya.

To achieve this aim, the specific objectives of the study were as follows:

1. To compare the prevalence, as well as sociodemographic and clinical correlates, of conventional cardiovascular risk factors (smoking, alcohol intake, poor diet, and lack of exercise, DM, hypertension, obesity, dyslipidaemia and metabolic syndrome) in patients with psychosis versus matched controls.
2. To explore the prevalence and correlates of non-conventional risk factors; psychological distress, traumatic events (lifetime and childhood trauma) and comorbid medical disorders in patients with psychosis and controls, and to delineate how these risk factors contribute to the overall cardiovascular risk.
3. To describe current psychopharmacological treatments in patients with psychosis and explore potential associations with cardiovascular risk among patients with psychosis.
4. To estimate the overall 10-year cardiovascular disease risk, as well as the social demographic and clinical correlates among patients and controls.
5. To establish the proportion of untreated metabolic disorders (hypertension, diabetes mellitus, and dyslipidaemia) in patients with psychotic disorders and matched controls.

2.9: Conceptual Frame work

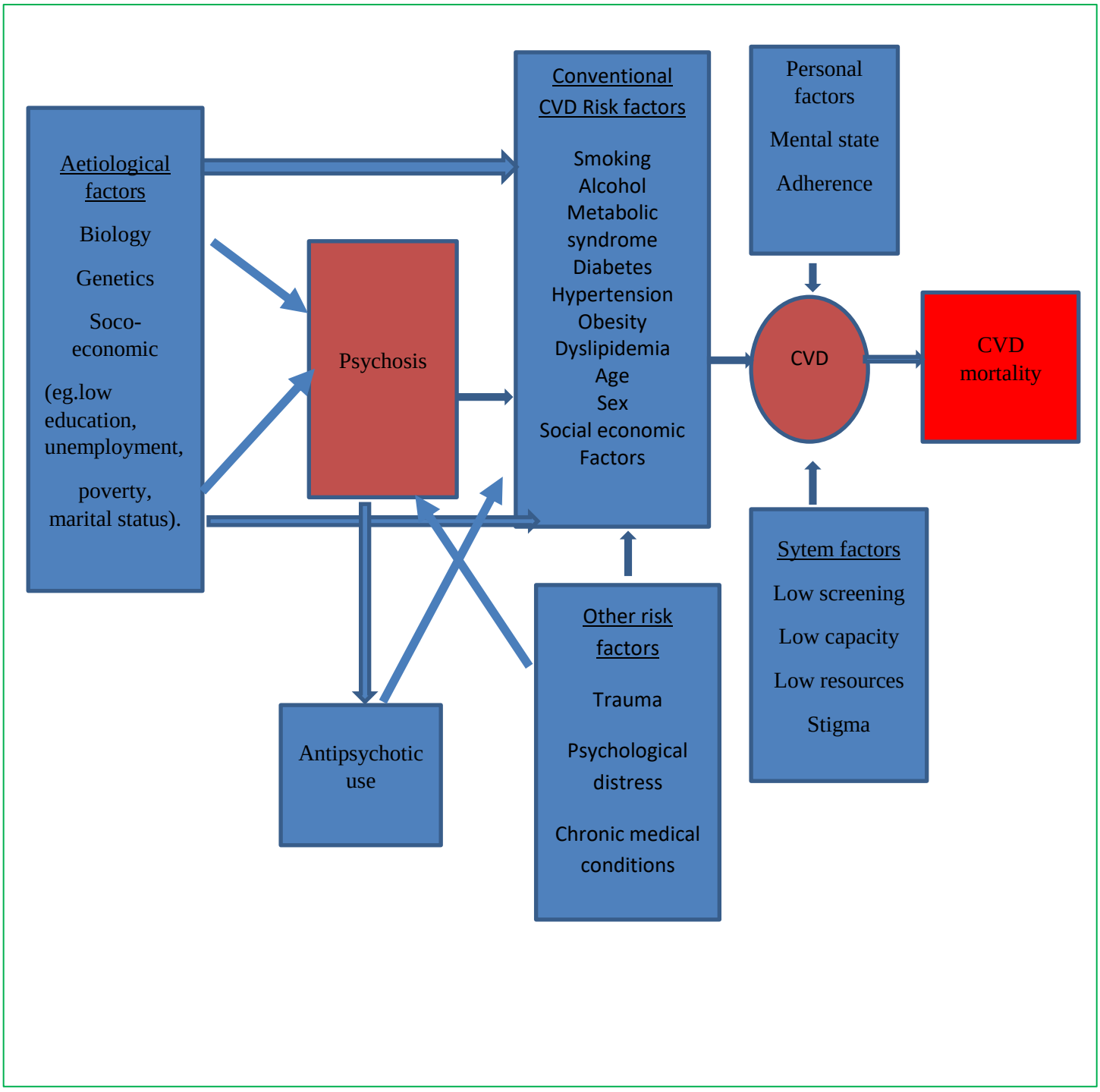


Figure 3 : Conceptual Framework

Source: Authors compilation

A number of inter-related factors have been found to contribute to cardiovascular risk among patients with psychosis. **Figure 3** above summarizes the various aspects of the CVD risk profile of patients with psychosis. There are shared biological, socio-economic, and environmental factors that contribute to the risk of both psychosis and CVD risk factors (De Hert, Detraux, and Vancampfort 2018). Antipsychotic medication augment these factors thus increasing the CVD risk further (Newcomer and Haupt 2006). Additionally, individual, social and systemic factors may impede optimal implementation of interventions, thus resulting in increased morbidity and mortality in patients with psychosis (Ringen et al. 2014). Understanding these interrelated factors is the first step in planning for programs to mitigate CVD risk factors. This study therefore is an important step in informing programs to promote cardiovascular health among patients with psychosis in Kenya and SSA.

CHAPTER 3: MATERIALS AND METHODS

3.0: Introduction

This chapter will highlight the research design. It will also give a description of the study site, and the study population. A detailed description of the study procedures will be provided as well as the data analysis that was undertaken.

3.1: Study Design

This was a cross-sectional descriptive survey comparing a group of patients with psychotic disorders (patients) and a group of participants without psychotic disorders (controls). This study was nested within the Neuropsychiatric Genetics of African Populations (NeuroGAP) study, which aims to explore the genes that are associated with psychotic disorders in African populations (Dalvie et al. 2015; Stevenson et al. 2019). (https://www.broadinstitute.org/stanley-center-psychiatric-research/NeuroGAP/NeuroGAP-psychosis). In summary, NeuroGAP is an ongoing multi-site case control study, in which data collection is being undertaken in South Africa, Uganda, Ethiopia and Kenya in collaboration with Harvard School of public health. For the current thesis, patients who had already been recruited for NeuroGAP were eligible for inclusion.

The patient group comprised of persons being actively followed up for the treatment of either schizophrenia, schizoaffective disorder or bipolar mood disorders at Moi Teaching and Referral Hospital (MTRH). Clinical diagnoses were obtained from patient records, as documented by the primary doctor, and confirmed using a subset of questions adapted from the Mini International Neuropsychiatry Interview (MINI). The MINI is a short semi-structured interview for diagnosing mental illness in line with the Diagnostic and Statistical Manual, version 5 (DSM 5 (Lecrubier et al. 1997). The MINI has been shown to be reliable and comparable to the Structured Clinical Interview for DSM (SCID) and the Composite International Diagnostic Interview (CIDI), but with a shorter administration time (Sheehan et al. 1997)

The control group consisted of members of the public who had never been treated for a mental illness. They were recruited from patients attending general clinics in MTRH, hospital visitors and relatives of

patients, who were believed to live in the same geographic region as the study group participants. They were matched with the study group for age and Sex in order to ensure similar distribution of confounders.

3.2: Study Setting

The study was conducted at Moi Teaching and Referral Hospital (MTRH). MTRH is located in Eldoret town, Uasin Gishu County, and it is the fifth largest town in Kenya, situated in the Western part of the country *(see Figure 4).*

Figure 4: Map of Kenya showing the location of Eldoret

Source: Uploaded by World Environment 2019; 9(1): 19-27 (Wilfred Omollo 2019)

MTRH is the second largest referral hospital in Kenya and has a catchment population of >15 million. The hospital serves as a referral facility for peripheral hospitals in the Western part of Kenya and as the primary care centre for the local community. Further, MTRH serves patients both from rural and urban

settings, including diverse ethnic groups. Thus, this study setting was appropriate to maximize generalizability of research findings.

Figure 5 : Inpatient mental unit of MTRH and NeuroGAP team

The photo includes members of the Moi NeuroGAP study team, as well as visiting members from the Stanley Centre at the Broad Institute.

(With permission) From Left to Right: Stella Gichuru, NeuroGAP study coordinator; Amantia Ametaj, post doc fellow NeuroGAP, Broad Institute; Eunice Jeptanui, one of the three NeuroGAP research assistants; Edith Kwobah, author; Carter Newman, Broad institute; Anne Stevenson , Broad Institute.

The hospital serves as a referral facility for peripheral hospitals in the Western part of Kenya and as the primary care centre for the local community. Further, MTRH serves patients both from rural and urban settings, including diverse ethnic groups. Thus, this study setting was appropriate to maximize generalizability of research finding MTRH has a well-established mental health service providing both

inpatient and outpatient services. There is a booked psychiatric outpatient clinic that operates every Wednesday and - according to the hospital records - serves an average of 75 patients per week and 300 patients per month. This clinic is complemented by a daily walk-in mental health clinic that serves an average of 20 patients daily. The inpatient service is a ward (*see Figure 5 above*) with a 70-bed capacity which admits severely ill patients. According to hospital records, more than 70% of the patients treated in this facility have psychotic disorders. At MTRH the patients with mental illness are managed by a multidisciplinary mental health team (psychiatrists, mental health clinical officers, nurses, psychologists and occupational therapist). A patient presenting with a medical condition in addition to the mental illness is either managed by the psychiatrist or referred to a medical outpatient clinic which runs on a different day of the week.

3.3 Study Population

The study targeted all adult patients who at the time of recruitment, were on management for schizophrenia, schizoaffective disorder or bipolar mood disorder. The control group targeted adults who had never been treated for mental illness.

3.4: Inclusion and Exclusion Criteria

Patients were eligible for inclusion if they were (i) aged 18 years or older; (ii) had been on follow up in the MTRH outpatients' service for a minimum of 6 months and (iii) the diagnosis (as made by a psychiatrist) was either schizophrenia, schizoaffective disorder or bipolar mood disorder. Diagnoses were obtained from patient records after an assessment by the primary psychiatrist and were then confirmed using the MINI. Patients receiving medical treatment for acute alcohol or drug intoxication were excluded. Pregnant women were excluded due to evidence that substantial CVD-related changes may occur in pregnancy including insulin resistance, raised serum glucose and changes in lipid metabolism (Lain and Kristine Y, Catalano, Patrick 2007). Those who did not have capacity to consent on the University of California, San Diego Brief Assessment of Capacity to Consent (UBACC) were also excluded from participation. The UBACC (*see Appendix 1c*) is a 10-item scale with good internal consistency, interrater reliability and

concurrent validity (Jeste et al. 2007). It also has a relatively brief administration time and simple language, in order to optimize ease of administration in study settings such as this. For each of the responses on the 10 UBACC items a patient is given a score of 0 (implying no understanding),1 (partial understanding) and 2 (full understanding) of the concept, a total score less than 14.5 indicates cognitive inability to consent (Megan M. Campbell et al. 2017).

Controls were eligible for inclusion if they were adults aged 18 years and older and had provided informed consent to participate. Individuals known to have a mental illness and those taking any psychiatric medication at the time of recruitment (as determined by self-report or medical record review) were excluded. Individuals receiving medical treatment for acute alcohol or drug intoxication, as well as pregnant women, were also excluded.

3.5: Participant recruitment

Being a nested study, all participants who were recruited into this cardiovascular study had already completed the NeuroGAP study interview. These were patients who were attending booked outpatient consultant clinic at MTRH. Routinely, and in order to ensure timely services during the clinic day, files of all booked patients are retrieved on Tuesdays (i.e. the day before the outpatient clinic) and transported from the records library to the outpatient clinic reception desk. Research assistants were thus able to review these retrieved files on Wednesday mornings. Files with a documented diagnosis of any of the psychotic disorders of interests were tagged with a study sticker. On the clinic day, all participants with a marked file were then identified from the waiting bay, given more information on both studies and requested to participate. Patients had the option of participating only on the NeuroGAP study or both studies. Those who agreed to participate were taken to a private room for clarifications on the study procedures and consenting. Clarification was made on the two studies. All participants were requested to provide written informed consent (*see Appendix 1*).

Like participants, controls who were recruited also participated in the NeuroGAP study. Recruitment of control participants took place every day of the week apart from Wednesdays, which was dedicated to

recruitment of patients. Posters were displayed on the hospital notice boards informing members of the public of the study; and asking those who were interested to contact the research assistant on the telephone number provided (*see Appendix 2*). In addition, controls were also recruited from hospital waiting bays. Clarification was made on the two studies, and participants had the option of participating only on the NeuroGAP study or both studies. Those who expressed interest in participating were given more details about the study; and upon agreeing to participate, written informed consent was provided.

3.6: Sample size and sampling procedure

For this study, convenience sampling was undertaken. The target sample size was 286 participants in the study group and 286 participants in the control group, based on prior sample size calculations i.e.: N = 10 k/p , where k is the number of covariates and p is the proportion of cases in the population (Peduzzi et al. 1996). Using an estimated prevalence of MetS in the general population in Kenya of approximately 35% (Kaduka et al. 2012) and 10 covariates in the data collection tool: N = 10×10/0.35 = 285.7. This sample size is comparable to one prior study conducted in South Africa by Saloojee and colleagues, which employed a design similar to this (Saloojee, Burns, and Motala 2016a). In order to allow for missing data and quality control procedures, we aimed to recruit 300 patients and 300 controls.

3.7: Data Collection tools

Demographic data were obtained on age, sex, level of education, employment status, smoking, marital status, other physical medication, dietary habits and exercise. Items assessing diet and exercise were adapted from the WHO Steps Survey, a tool used to measure risk factors for non-communicable disease ("WHO , The STEPS Instrument and Support Materials"). The Alcohol use Identification Test (AUDIT – C) was used to screen for harmful alcohol use (Bradley et al. 2007b). The AUDIT-C comprises three questions, each scored on a 5-points Likert scale (minimum score = 0; maximum score = 4), with the total score ranging from 0 to 12. A score of 4 in men and 3 in women is optimal for identifying an alcohol use disorder (Bush et al. 1998), (Bradley et al. 2007a)

Exposure to lifetime potentially traumatic events was assessed using the Live Events Checklist (LEC) for DSM 5, a tool with acceptable psychometric properties (Gray et al. 2004) and has been used in a African setting (Mhlongo et al. 2018). A history of childhood trauma was assessed using the Childhood Trauma Questionnaire-Short Form (CTQ-SF) a reliable and valid self-report measure for assessing exposure to childhood abuse and/or neglect in patients with schizophrenia (Kim et al. 2013). The CTQ is a 28-item retrospective inventory comprising five subscales - three assessing abuse (emotional, physical, and sexual) and two assessing neglect (emotional and physical). Each subscale score ranges from 5 (no history of abuse or neglect) to 25 (very extreme history of abuse and neglect), (Bernstein et al. 2003), (Devi et al. 2019).

For patient only information on primary psychiatric diagnosis, current psychotropic medication and any other medication was obtained from patient self-report and from hospital records. In both groups, the WHO Composite International Diagnostic Interview (CIDI) screener for chronic diseases was used to establish presence of other chronic physical disorders ("About the WHO WMH-CIDI – WHO WMH-CIDI") (https://www.hcp.med.harvard.edu/wmhcidi/about-the-who-wmh-cidi/)

Psychosocial distress in the control group only was assessed using the Kessler-10 (K10), a tool validated for use in individuals with no known mental illness. Each item is scored on a Likert scale ranging from 1 (none of the time) to 5 (all of the time). Total scores range from 10 to 50; those scoring under 20 are likely to be well; those scoring 20-24 are likely to have a mild distress; those scoring 25-29 are likely to have moderate distress; and those scoring 30 and over are likely to have severe distress (Gavin Andrews and Tim Slade 2001)

In addition to the interviews, measurements for weight, height, abdominal circumference and blood pressure were taken; and blood was drawn for blood sugar and a non-fasting lipid profile. A non-fasting assessment was undertaken due to anticipated difficulties in ensuring or ascertaining a fasted state among mentally ill participants. There is evidence to suggest that in assessing for cardiovascular risk ,

non- fasting lipid profile is adequate, time saving, and patient-friendly and a fasting test is then recommended only for those with triglycerides > 5 mmol/L (Mora 2016; Nordestgaard 2017)

For clarity, it is important to highlight that though some of the tools we used were also used on the NeuroGAP study whose protocol has been published (Stevenson et al. 2019), the social demographic questionnaire was modified. In addition we had extra tools like the CTQ, and we collected blood while this was not done in NeuroGAP. CVD study the tools were printed into hard copy for ease of data access and retrieval for analysis, while the Neuro-Gap study data collected into an IPad and submitted to Broad Institute, and needed a specific approval mechanism to analyse the data.

Table 1 below gives a summary of the data collection tools:

Table 1: Summary of data collection tools used in CVD and NGAP study

	Tool	CVD Patients	CVD Controls	NeuroGAP study
1.	Social Demographic Questionnaire	✓	✓	✓ modified
2.	AUDIT-C	✓	✓	×
3.	Kessler 10	×	✓	✓
4.	Childhood Trauma Questionnaire-Short Form	✓	✓	×
5.	Live Events Checklist	✓	✓	✓
6.	Current psychotropic medication	✓	×	✓
7.	CIDI screener for chronic diseases	✓	✓	✓
8.	Anthropometric measurements and blood pressure	✓	✓	✓ modified
9.	Blood for lipid Profile and Glucose levels.	✓	✓	×

✓ Administered

× Not administered.

3.8: Study procedures

Data were collected by three trained NeuroGAP research assistants - a graduate psychologist, a graduate nurse and a clinical officer (equivalent to a physician assistant in other settings), all who were not primary care providers for these patients. They were trained on research ethics and the protection of human subjects.

The research assistants explained in detail the purpose of the study and the procedures to be undertaken. They then confirmed that the individual was ready to participate. For the controls, the consent form was given to participants to review and sign. For the patients, the UBACC was administered in order to ascertain capacity to consent. The UBACC was administered a maximum of 4 times with more explanations for questions where one scored 0. If the participant scored above 14.5 the participant was deemed fit to consent. If the scores remained below 14.5 on the 4^{th} attempt, the patient was not interviewed. The consent form was signed in duplicate, allowing the participant to retain one copy, while the other copy was attached to the data collection tool and was kept by the research assistant. The participant was also assigned a unique study identifying number, which was included on the signed consent and the study questionnaire.

Following informed consenting, the research assistants then administered the complete study interview battery (as described above). Upon completion of the interview, two readings of blood pressure were taken using an Omron compact upper arm blood pressure monitor. To draw blood, a tourniquet was placed around the arm, a vein was identified, the injection site was sterilized using alcohol swab and 10 millimetres of blood was drawn into a 10 ml plain vacutainer. The vacutainer was labelled using the participant's study ID.

The participant was then asked to remove footwear to enable accurate measurement of weight and height. The weight of the participant was measured with a 762 dial bathroom floor scale and recorded in kilograms. The height (in centimetres) was measured with a mechanical roll-up measuring tape with feet together, heels against the measuring wall and knees straight. Finally, the waist circumference was measured on the exposed abdomen with the participant standing and both arms lifted. It was measured

in centimetres at the midpoint between the iliac crests and the lower rib laterally and passing over the umbilicus anteriorly. The participant was then given a chance to ask any questions and once these were addressed the participant was thanked, and the session came to an end.

Research assistants delivered blood samples to the Academic Model Providing Access to Healthcare (AMPATH) reference laboratory for analysis immediately after completion of the interview. They also followed up with the laboratory, collected the results, and attached them to each participant's questionnaire. The laboratory results were then reviewed by the study psychiatrist. Any participant with elevated blood pressure, elevated glucose, or dyslipidaemia was contacted via mobile telephone by the psychiatrist and the results discussed. In instances of elevated blood pressure or elevated glucose, for which intervention was urgently needed, the psychiatrist initiated treatment with medication before referring the patient to the medical outpatient clinic of MTRH. In cases in which measurements were abnormal but there was need for a repeat, or more investigations the participant was advised of this, and referred appropriately.

3.9: Data management and analysis

Data were entered into REDcap, (Research Electronic Data Capture) a secure, web-based software platform designed to support data capture for research studies and also provides an intuitive interface for validated data capture, audit trails for tracking data manipulation, and automated export procedures for seamless data downloads to common statistical packages (P. A. Harris et al. 2009). Once in REDcap, the data were then cleaned and exported into Stata version 15 for analysis (Statistical Software: Release 14. College Station, TX: StataCorp LP).

The Wilcoxon sum rank tests a non- parametric test was used to assess whether the distribution of age differed between patients and controls; while Pearson chi squared tests were used to assess associations between categorical variables. Fisher's exact tests was only used in cases where the expected cell counts were small.

The frequencies of various cardiovascular risk factors were calculated (i.e. smoking, alcohol intake, psychosocial distress, trauma, poor diet and lack of exercise, diabetes, hypertension, dyslipidaemia and metabolic syndrome); and Person's chi squared tests was used to determine the differences in these frequencies between patients with psychosis versus controls. T-tests were undertaken to determine the differences in the means of lipids, blood sugar and blood pressure between the patients and the controls. **Table 2** below shows the cut-off parameters that were used for analyses of outcome variables.

Table 2: Cut off Parameters for metabolic disorders

Disorder	Cut-off parameter
Diabetes (WHO 2006).	Random blood sugar ≥11.1 mmol/l or treatment for diabetes
Hypertension (B. Williams et al. 2018)	On treatment for hypertension with a documented diagnosis, or newly-diagnosed hypertension, i.e. 3 or more readings of systolic blood pressure ≥140 mmHg, or diastolic blood pressure ≥90 mmHg
Dyslipidaemia according to †NCEP ATP III Cholesterol guidelines (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults 2001)	Total cholesterol > 200 mg/dl or > 5.17mmol/l) and/or increased LDL cholesterol > 100 mg/dl or >2.59 mmol/l and/or decreased HDL cholesterol < 40mg/dl or <1 mmol/l)
Obesity	Overweight: BMI >25-30 Obese: BMI >30-40 Morbidly obese: BMI>40. Central obesity = waist circumference > 88cm in women and > 102cm in men.
Metabolic syndrome According to the Adult Treatment Panel III (Grundy et al. 2004)	Abdominal obesity > 102 cm in men, > 88cm in women. TGS ≥150mg/dl HDL < 40mg/dl or <1mmol/l in men, < 50mg/dl or <1.3mmol/l in women. BP ≥130/≥85mmHg or current treatment for hypertension Fasting glucose- ≥110mg/dl or current treatment for diabetes. Random blood glucose ≥11.1 mmol/l

In computing FRS we used the age, sex, total cholesterol, high density lipoprotein cholesterol, smoking habits, DM and systolic blood pressure. The scores were then categorized as low (<10), intermediate (10-19) or high >20. T-tests were used to determine the differences in the means of the Framingham 10-year estimated risk for cardiovascular disorders between the patients and the controls. Logistic regression modelling was then undertaken to explore the predictors of FRS statistically higher among patients than controls.

In analyses of trauma and cardiovascular risk, the prevalence of a number traumatic experiences was calculated. Pearson Chi-squared tests were carried out to establish differences in the prevalence of trauma exposure between patients and controls.

Prescription patterns were explored by calculating the proportions of participants being treated with specific medications of interest. Chi squared tests (or and Fishers exact tests where applicable) were carried out to determine the association between olanzapine use and a number cardiovascular risk factors.

The treatment gap was assessed by calculating the number of participants with untreated hypertension, diabetes mellitus and dyslipidaemia, as a proportion of the total number of individuals with any of these conditions in both groups (patients and controls). The proportion of those who had never been treated for these disorders was also calculated.

3.10: Ethical Considerations

Ethics review and approval was obtained from the MTRH/Moi University School of Medicine Institutional Research and Ethics Committee (IREC/2017/90) and from the Human Research Ethics Committee of the University of Cape Town (HREC/286/2017). This was renewed annually during the study period. Permission to carry out the proposed procedures was also obtained from the management of MTRH. Informed Consent was provided by all participants (see Appendix 1). As previously discussed, ability to consent was assessed using the UBACC. Participation was entirely voluntary and participants were free to withdraw at any point of the study without forfeiting any benefits of receiving required care. Compensation of 10 US dollars for transport expenditure and time inconvenience (a total of about 2.5 hours was required to complete both interviews) was offered by NeuroGAP Study. Confidentiality was maintained by using assigned study ID numbers and entering only de-identified data into REDCap. The study posed minimal risk of pain during blood sample collection; as well as psychological distress due to painful memories of traumatic life events being potentially elicited. All participants with abnormal results were reviewed by the study psychiatrist, initiated on medication where urgently needed, and referred to the relevant medical outpatient clinic for physician review. Participants who developed psychological distress secondary to the interview process were also assessed by the psychiatrist, managed and referred appropriately. All study documents were safely stored in a lockable cabinet; and soft copies of the data was stored in a password-protected electronic database with controlled access. All potentially identifiable data were appropriately de-identified before analysis.

CHAPTER 4: RESULTS

4.0: Introduction

Data were collected between July 2018 and March 2019. A total of 1,700 participants were treated for psychosis at the MTRH psychiatry outpatient clinic during the study period. During the same period, the hospital served about 200 000 patients for other medical conditions and had several visitors. After 8 months of data collection, a total of 600 participants consented and were recruited into the study - 300 patients with psychosis and 300 controls. Three patients were excluded from analyses as two had epilepsy-induced psychosis and one had substance-induced psychosis.

This chapter will give a detailed report of relevant study findings. First, sociodemographic characteristics of the study participants will be described. Second, findings of the prevalence and correlates of conventional cardiovascular lifestyle risk factors and metabolic disorders will be presented. Third, the results pertaining to the three non-conventional cardiovascular risk factors (i.e. exposure to traumatic events, psychological distress and comorbid medical conditions) will be reported. Fourth, the estimated 10-year risk of developing cardiovascular disorders in this study sample will be described. Fifth, prescription patterns and associated cardiovascular risk will be reported. Finally the treatment gap for CVD risk factors in patients with mental illness will be presented.

4.1: Conventional non modifiable CVD risk factors and other demographic characteristics.

Participants in this study sample were relatively young, with a mean age of 33 years among the patients and 35 years among the controls. Patients were more likely to be unmarried (47% vs 33%, $p<0.001$). While most participants had formal education (77% patients and 82% controls), patients were less likely to have tertiary education compared to controls (26% vs 56%, $p<0.001$), with most having only primary school education. Further patients were more likely to be unemployed (48% vs 24.7% of controls) and controls were more likely to be in formal employment (48% vs 14.5% of patients), and these differences were statistically significant ($p<0.001$) **Table 3** below summarizes the characteristics of both patients and controls.

Table 3: Socio-demographic characteristics of the study participants

Variable	Total	Patients	Control	p-value
Age in years	34 (26,42)	33 (26,40)	35 (26.5,41)	0.383[3]
Sex				0.238[1]
Male	265 (44.4)	139 (46.8)	126 (42.0)	
Female	332 (55.6)	158 (53.2)	174 (58.0)	
Marital status				**<0.001[1]**
Married	269 (45.1)	103 (34.7)	166 (55.3)	
Never married	239 (40)	139 (46.8)	100 (33.3)	
Widow/separated/divorced	89 (14.9)	55 (18.5)	34 (11.3)	
Highest level of Education				**<0.001[1]**
None	35 (5.9)	23 (7.7)	12 (4)	
Primary	147 (24.6)	106 (35.7)	41 (13.7)	
Secondary	172 (28.8)	92 (31)	80 (26.7)	
Tertiary	243 (40.7)	76 (25.6)	167 (55.7)	
Occupation				**<0.001[1]**
Unemployed	217 (36.3)	143 (48.1)	74 (24.7)	
Formal	187 (31.3)	43 (14.5)	144 (48)	
Self	193 (32.3)	11(17.4)	82 (27.3)	

1 Chi square test 2 Fishers' exact test 3 Wilcoxon rank sum test

4.2. Lifestyle factors

Compared to controls, patients were more likely to have ever smoked (13.8% patients vs 7 % controls, p=0.006) or to be current smokers (9.8% vs 3.3%, p=0.001. Most patients with psychosis had consumed inadequate fruits and vegetables (97%); had inadequate physical activity (78%) and had significant

sedentary behaviour (48%). However, significant differences in physical activity and dietary habits were not demonstrated between patients and controls), **Table 4**.

Table 4: Lifestyle risk factors

	Total	**Cases**	**Control**	**p-value**
Variable	**Freq %)**	**Freq (%)**	**Freq (%)**	
Current smoker				**0.001[1]**
No	558 (93.5)	268 (90.2)	290 (96.7)	
Yes	39 (6.5)	29 (9.8)	10 (3.3)	
Ever smoker				**0.006[1]**
No	535 (89.6)	256 (86.2)	279 (93)	
Yes	62 (10.4)	41 (13.8)	21 (7)	
Harmful alcohol				0.648[2]
No	579 (97)	289 (97.3)	290 (96.7)	
Yes	18 (3)	8 (2.7)	10 (3.3)	
Poor diet				0.352[2]
No	11 (1.8)	7 (2.4)	4 (1.3)	
Yes	586 (98.2)	290 (97.6)	296 (98.7)	
Inadequate exercise				0.084[1]
No	114 (19.1)	65 (21.9)	49 (16.3)	
Yes	483 (80.9)	232 (78.1)	251 (83.7)	
Time spent sitting				0.906[1]
< 3 hours in a day	311 (52.1)	154 (51.9)	157 (52.3)	
More than 3 hours in a day	286 (47.9)	143 (48.1)	143 (47.7)	

[1] Chi square test [2] Fishers' exact test

4.3: Metabolic disorders

Metabolic disorders were common among patients, with abnormal LDL being the most prevalent (65%) followed by elevated triglycerides (47%) and abnormal BMI (45%), **Figure 6.**

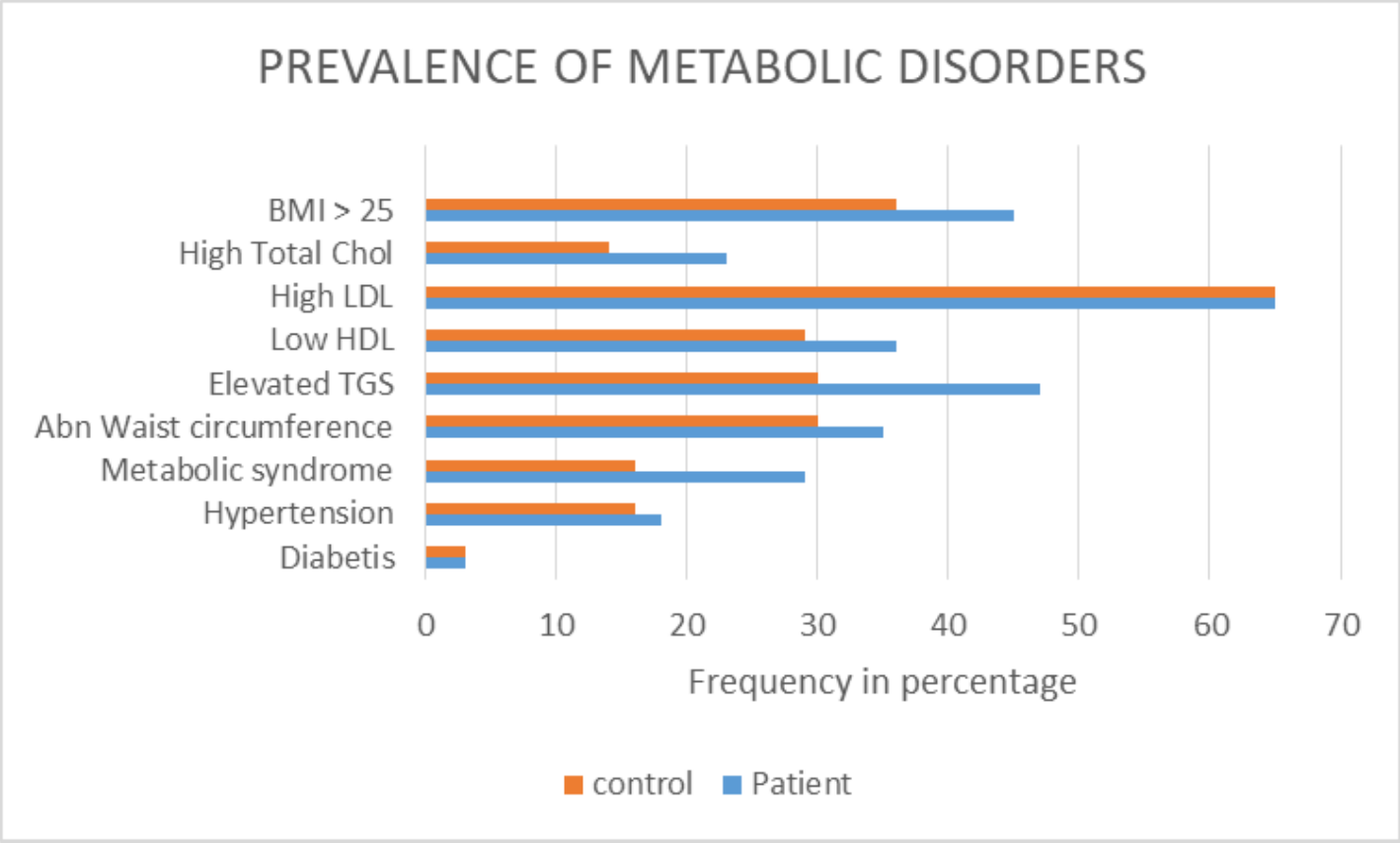


Figure 6: Prevalence of metabolic disorders among patients

Met Syndrome - Metabolic Syndrome

BMI -Abnormal Body mass index

LDL - Low High density Lipoproteins

HDL - High density Lipoproteins

TGS - Triglycerides

Cho l- Cholesterol

As shown in **Table 5** below, there were significant differences in the means of a number of metabolic risk parameters. Compared to controls, patients had higher mean random blood sugar (5.23 vs 4.79**,** p=0.003), BMI (5.23 vs 4.79 p=0.001), TGs (1.98 vs 1.56,p<0.001) and waist circumference (89.23 vs 86.39 p=0.009)), but were found to have lower HDL (1.22 vs 1.32, p<0.001).

Table 5: A comparison of the means of metabolic parameters

Variable	Total	Patient	Control	t-test p-value
	Mean (SD)	**Mean (SD)**	**Mean (SD)**	
Systolic BP	119.19 (14.98)	119.6 (13.76)	118.78 (16.1)	0.504
Diastolic BP	76.04 (11.17)	76.09 (10.11)	76 (12.15)	0.916
RBS[1]	**5.01 (1.85)**	**5.23 (2)**	**4.79 (1.67)**	**0.003**
BMI[2]	**24.82 (6.13)**	**25.63 (7.15)**	**24.03 (4.81)**	**0.001**
HDL[3]	**1.27 (0.48)**	**1.22 (0.49)**	**1.32 (0.46)**	**0.008**
LDL[4]	2.98 (0.92)	3.01 (0.98)	2.95 (0.85)	0.405
Chol[5]	4.46 (1.79)	4.59 (2.37)	4.34 (0.89)	0.089
TG[6]	**1.77 (1.29)**	**1.98 (1.41)**	**1.56 (1.12)**	**<0.001**
Waist circum[7]	**87.81 (13.31)**	**89.23 (13.43)**	**86.39 (13.06)**	**0.009**

[1]Random blood sugar [2]Body mass index [3]High density lipoprotein [4] Low Density Lipoprotein [5]Cholesterol [6]Triglycerides [7] Waist circumference

Compared to controls, patients were more likely to have elevated total cholesterol (23.6 vs 14.7, p=0.006), higher triglycerides (47.1 vs 30.3, p<0.001), higher rates of MetS (28.6 vs 19, p=0.007) and obesity (45.1 vs 35.6, p=0.037), **Table 6**.

Table 6: **Comparing prevalence of cardio metabolic disorders of patients and controls**

	Patients	**Controls**	**P-value**
Variable	**Freq (Col%)**	**Freq (Col%)**	
Diabetes			0.798[2]
No	287 (96.6)	291 (97)	
Yes	10 (3.4)	9 (3)	
Hypertension			0.412[1]
No	243 (81.8)	253 (84.3)	
Yes	54 (18.2)	47 (15.7)	
Metabolic Syndrome			**0.007[1]**
No MetS	262 (71.4)	243 (81.0)	
MetS	35 (28.6)	57 (19.0)	
Waist circumference			0.162[1]
Normal	193 (65)	211 (70.3)	
High	104 (35)	89 (29.7)	
TGS			**<0.001[1]**
Normal	**157 (52.9)**	**209 (69.7)**	
High	**140 (47.1**	**91 (30.3)**	
HDL			0.067[1]
Normal	190 (64)	213 (71)	
Low	107 (36)	87 (29)	
LDL			0.997[1]
Normal	104 (35)	105 (35)	
High	193 (65)	195 (65)	
Cholesterol			**0.006[1]**
Normal	**227 (76.4)**	**256 (85.3)**	
High	**70 (23.6)**	**44 (14.7)**	
BMI			**0.037[2]**
Underweight	**7 (2.4)**	**18 (6.0)**	
Normal	**152 (51.9)**	**175 (58.3)**	
Overweight	**89 (30.4)**	**70 (23.3)**	
Obese	**43 (14.7)**	**36 (12.0)**	
Morbid	**2(0.7)**	**1 (0.3)**	

[1] Chi square test [2] Fishers' exact test

After adjusting for other variables in a logistic regression model, factors associated with increased odds of having MetS were psychosis (OR=2.09, p=0.006), and age (OR=1.05, p< 0.001). Factors that were associated with decreased odds of MetS were female Sex (OR 0.41 p<0.001), and being widowed/separated/divorced (OR 0.38, P=013)**, Table 7**.

Table 7: Factors associated with the presence of metabolic syndrome

Variable	**Adjusted Odds Ratio**	**p-Value**	**[95% Conf. Interval]**	
Psychosis	**2.09**	**0.006**	**1.23**	**3.55**
Age in yrs	**1.05**	**<0.001**	**1.02**	**1.07**
Male	1.00			
Female	**0.41**	**<0.001**	**0.25**	**0.67**
Never married	0.52	0.031	0.28	0.94
Widow/separated/divorced	**0.38**	**0.013**	**0.17**	**0.81**
Primary education	0.48	0.112	0.19	1.19
Secondary education	0.43	0.071	0.17	1.07
Tertiary education	0.60	0.270	0.24	1.48
Currently smoking	1.18	0.701	0.51	2.76
Harmful alcohol	0.94	0.925	0.24	3.72
Physical exercise	0.80	0.442	0.45	1.42
Spent >3 hours sitting	0.94	0.791	0.58	1.51

After adjusting for other variables in a regression model, factors associated with increased odds of having elevated BMI were psychosis (OR 2.30, p<0.001), age (OR1.05, p<0.001) and female Sex (OR 2.67, p<0.001) **Table 8**. Having never been married (or being windowed/ separated/ divorced) was associated with decreased odd of having an abnormal BMI (OR 0.44, p= 0.003)**.**

Table 8: Factors associated with abnormal BMI

Variable	**Odds Ratio**	**P-value**	**[95% Conf. Interval**	
Psychosis	**2.30**	**<0.001**	**1.55**	**3.43**
Age in years	**1.05**	**<0.001**	**1.02**	**1.07**
Female	**2.67**	**<0.001**	**1.82**	**3.92**
Never married	0.52	0.005	0.33	0.82
Widow/separated/divorced	**0.44**	**0.003**	**0.26**	**0.75**
Primary	0.86	0.703	0.39	1.90
Secondary	0.91	0.807	0.41	2.00
Tertiary	1.43	0.374	0.65	3.14
Currently smoking	0.94	0.871	0.43	2.03
Harmful alcohol use	1.48	0.457	0.53	4.11
Poor diet	0.86	0.830	0.21	3.49
Inadequate physical exercise	0.90	0.639	0.57	1.41
Spent >3 hours sitting	1.05	0.770	0.74	1.51

4.4. Trauma and cardiovascular risk

4.4.1.: Lifetime Exposure to potentially traumatic events

Among all participants, physical assault was the most commonly reported potentially traumatic live event (30%), followed by transport accidents (28.3%) and life threatening illness or injury (28.1%), **Table 9.** Patients reported significantly lower prevalence of a number of traumatic events compared to controls, including natural disasters (p=0.009), fire explosion (p=0.005), transport accidents (p<0.001), accident at work or home (p=0.001), life threatening injury (p=0.008), exposure to war (p=0.022), severe human suffering (p=0.007), sudden violent death 0.029) and other unspecified stressors (p=0.002).

Table 9 : Exposure to potentially traumatic life events

Event	Total	Patients	Control	P-value
	Freq (%)	Freq (%)	Freq (%)	
Natural disaster	**71 (11.9)**	**25 (8.4)**	**46 (15.3)**	**0.009**
Fire or explosion	120 (20.1)	46 (15.5)	74 (24.7)	0.005
Transportation accident	**169 (28.3)**	**61 (20.5)**	**108 (36)**	**<0.001**
Serious accident at work, home or recreation	**63 (10.6)**	**19 (6.4)**	**44 (14.7)**	**0.001**
Exposure to toxic substance	22 (3.7)	11 (3.7)	11 (3.7)	0.981
Physical assault	182 (30.5)	86 (29)	96 (32)	0.419
Assault with a weapon	91 (15.2)	39 (13.1)	52 (17.3)	0.153
Sexual assault	41 (6.9)	21 (7.1)	20 (6.7)	0.845
Other sexual experience	37 (6.2)	15 (5.1)	22 (7.3)	0.247
Combat or exposure to war	**33 (5.5)**	**10 (3.4)**	**23 (7.7)**	**0.022**
Captivity	9 (1.5)	4 (1.3)	5 (1.7)	0.748
Life threatening illness or injury	**168 (28.1)**	**69 (23.2)**	**99 (33)**	**0.008**
Severe human suffering	**97 (16.2)**	**36 (12.1)**	**61 (20.3)**	**0.007**
Sudden violent death	**74 (12.4)**	**28 (9.4)**	**46 (15.3)**	**0.029**
Sudden accidental death	70 (11.7)	29 (9.8)	41 (13.7)	0.138
Serious injury, harm or death you caused	10 (1.7)	4 (1.3)	6 (2.0)	0.534
Any other stressful event	**110 (18.4)**	**40 (13.5)**	**70 (23.3)**	**0.002**

As shown in Figure **7** below, 73% of patients and 80% of controls reported having experienced at least one traumatic event in their lifetimes.

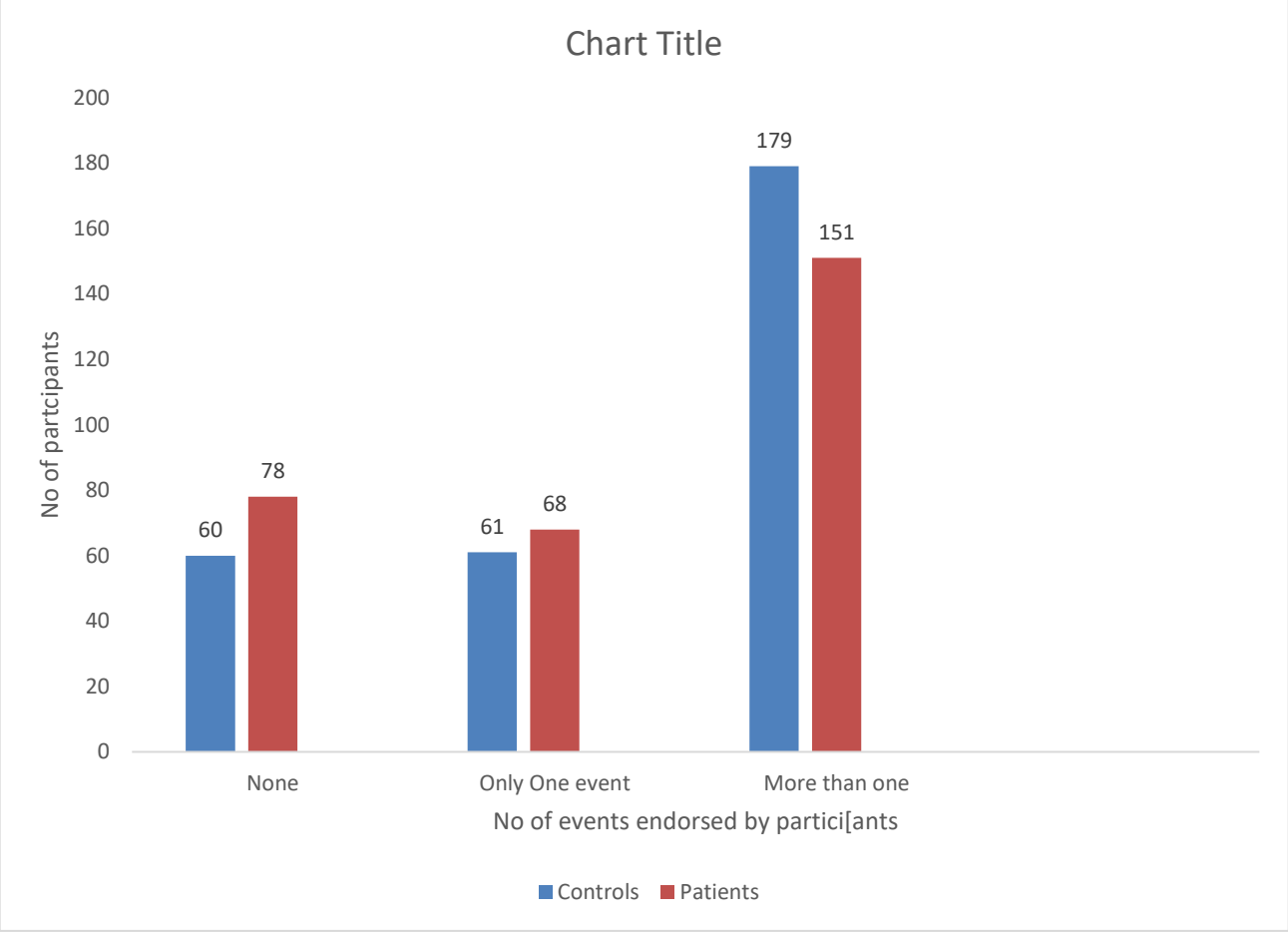


Figure 7. Number of events endorsed on the LEC by patients and controls.

Among patients, there was a significant association between exposure to potentially traumatic life events and smoking **Table 10**

Table 10: Lifetime traumatic life events and other cardiovascular risk factors- patients

Variable	Traumatic life events controls			P-value
	None	One	More than One	
	Freq (Col %)	Freq (Col %)	Freq (Col %)	
MS				0.875
No MS	63(80.8)	53(779)	122(80.8)	
MS	15(19.2)	15(22.1)	29(19.2)	
Diabetes				0.954
No	75(96.2)	66(97.1)	146(96.7)	
Yes	2(3.8)	2(2.9)	5(3.3)	
Hypertension				0.743
No	62(79.5)	55(80.9)	128(83.4)	
Yes	16(20.5)	13(19.1)	25(16.6)	
HDL				0.106
Normal	57(73.1)	44(64.7)	89(58.9)	
Elevated	21(26.1)	24(35.3)	62(41.1)	
LDL				0.052
Normal	19(24.4)	29(42.6)	56(37.1)	
Elevated	59(75.6)	39(57.4)	95(62.9)	
Cholesterol				0.449
Normal	61(78.2)	55(80.9)	111(73.5)	
Elevated	17(21.8)	13(19.1)	40(26.5)	
Current smoker				**0.035**
No	76(97.4)	61(89.7)	131(86.8)	
Yes	2(2.6)	7 (10.3)	20 (13.2)	
Harmful alcohol				0.661
No	77(98.7)	66(97.1)	146(96.7)	
Yes	1(1.3)	2(2.9)	5(3.3)	

There was no significant association between exposure to potentially traumatic life events and any of the cardiovascular risk factors of interest was demonstrated among controls, **Table 11**

Table 11 **Lifetime traumatic life events and other cardiovascular risk factors- controls**

Variable	Traumatic life events			P-value
	None	One	More than One	
	Freq (Col %)	Freq (Col %)	Freq (Col %)	
MS				0.391
No MS	49(81,7)	55(90.2)	155(86.6)	
MS	11(18.3	6(9,8)	24(13.4)	
Diabetes				0.968
No	58 (96.7)	59(96.7)	174(97.2)	
Yes	2(3.3)	2(3.3)	5(2.8)	
Hypertension				0.556
No	49(81.7)	54(88.5)	150(83.8)	
Yes	11(8.3	7 (11.5)	29(16.2)	
HDL				0.990
Normal	43(71.7)	43(70.5)	127(70.9)	
Elevated	17(28.3	18(29.5)	52(29.1)	
LDL				0.343
Normal	20(33.3)	17(27.9)	68(38.0)	
Elevated	40(66.7)	44(72.1)	111(62.0)	
Cholesterol				0.895
Normal	51 (85.0)	51(83.6)	154(86.0	
Elevated	9 (15.0)	10(16.4)	25(14)	
Current smoker				0.712
No	57(95.)	59(96.7)	171(95.5)	
Yes	3(5.0)	2(3.3)	8(4.5)	
Harmful alcohol				0.712
No	60 (100	59 (96.7	171 (95.5)	
Yes	0	2. (3.3)	8(4.5)	

4.4.2: Childhood trauma

Severe physical abuse was reported among 9% of controls and 8.8% of patients. Severe emotional abuse was reported among 5.7% of patients and 4.3% of controls, while severe sexual abuse was reported in 4.7% of patients and 6.3% of controls. Almost half of the participants (49.2% of controls and 56.1) of patients endorsed items on the CTQ pertaining to childhood neglect; about half reporting physical neglect. No significant differences in overall reported childhood trauma was found between patients and controls **Table 12**.

Table 12: Childhood trauma exposure (by specific categories of abuse/neglect)

Variable	Patients Freq (Col %)	Controls Freq (Col %)	P-value
Childhood trauma			
Emotional abuse			0.295[2]
None	214 (72.3)	208 (69.6)	
Low	47 (15.9)	64 (21.4)	
Moderate	18 (6.1)	14 (4.7)	
Severe	17 (5.7)	13 (4.3)	
Physical abuse			0.979[2]
None	206 (69.6)	212 (70.7)	
Low	42 (14.2)	39 (13)	
Moderate	22 (7.4)	22 (7.3)	
Severe	26 (8.8)	27 (9)	
Sexual abuse			0.055[2]
None	243 (82.1)	219 (73)	
Low	17 (5.7)	31 (10.3)	
Moderate	22 (7.4)	31 (10.3)	
Severe	14 (4.7)	19 (6.3)	
Emotional neglect			0.234[2]
None	130 (43.9)	155 (51.8)	
Low	122 (41.2)	101 (33.8)	
Moderate	34 (11.5)	32 (10.7)	
Severe	10 (3.4)	11 (3.7)	
Physical neglect			0.683[2]
None	149 (50.2)	153 (51.2)	
Low	50 (16.8)	57 (19.1)	
Moderate	56 (18.9)	46 (15.4)	
Severe	42 (14.1)	43 (14.4)	

On the CTQ, patients endorsed wearing dirty clothes significantly more than controls (51.5% vs 39.7% , p=0.004) and endorsed 3 questions on sexual abuse significantly less than controls; sexual touch (10.4 patients vs 18.0 controls), being forced to do or watch sexual things (7.7 patients vs13% controls , p=0.035), and being molested (7.1 patients vs12.3% controls , p=0.031) **Table 13**.

Table 13: Childhood trauma exposure (itemized by the CTQ)

When I was growing up	Total	Patients	Controls	p-value
	Freq (%)	**Freq (%)**	**Freq (%)**	
Physical Neglect				
1. I didn't have enough to eat.	244 (40.9)	117 (39.4)	127 (42.3)	0.465
2. I knew there was someone to take care of me and protect me	580 (97.2)	288 (97)	292 (97.3)	0.789
4. My parents were too drunk or high to take care of me.	133 (22.3)	69 (23.2)	64 (21.4)	0.592
6. I had to wear dirty clothes.	**272 (45.6)**	**153 (51.5)**	**119 (39.7)**	**0.004**
26. There was someone to take me to the doctor if I needed it.	573 (96)	286 (96.3)	287 (95.7)	0.695
Emotional Neglect				
5. There was someone in my family who helped me feel important or special.	573 (96)	286 (96.3)	287 (95.7)	0.695
7. I felt loved.	569 (95.3)	284 (95.6)	285 (95)	0.719
13. People in my family looked out for each other.	549 (92.1)	277 (93.3)	272 (91)	0.298
19. People in my family felt close to each other.	554 (93)	278 (93.9)	276 (92.0)	0.360
28. My family was a source of strength and support.	588 (98.5)	293 (98.7)	295 (98.3)	0.748
Emotional abuse				
3. People in my family called me things like "stupid", "lazy", or "ugly".	210 (35.2)	108 (36.4)	102 (34)	0.545
8. I thought that my parents wished I had never been born.	88 (14.8)	45 (15.2)	43 (14.4)	0.791
14. People in my family said hurtful or insulting things to me.	179 (30)	87 (29.4)	92 (30.7)	0.734

18. I felt that someone in my family hated me.	187 (31.3)	96 (32.3)	91 (30.3)	0.600
25. I believe that I was emotionally abused.	162 (27.1)	88 (29.6)	74 (24.7)	0.173
Physical abuse				
9. I got hit so hard by someone in my family that I had to see a doctor or go to the hospital.	95 (15.9)	50 (16.8)	45 (15)	0.540
11. People in my family hit me so hard that it left bruises or marks.	103 (17.3)	52 (17.6)	51 (17)	0.855
12. I was punished with a belt, a board, a cord, or some hard object.	216 (36.2)	108 (36.4)	108 (36)	0.926
15. I believe that I was physically abused.	137 (22.9)	72 (24.2)	65 (21.7)	0.454
17. I got hit or beaten so badly that it was noticed by someone like a teacher, neighbour, or doctor.	87 (14.6)	38 (12.8)	49 (16.3)	0.220
Sexual abuse				
20. Someone tried to touch me in a sexual way, or tried to make me touch them.	**85 (14.2)**	**31 (10.4)**	**54 (18.0)**	**0.008**
21. Someone threatened to hurt me or tell lies about me unless I did something sexual with them.	42 (7)	23 (7.7)	19 (6.3)	0.500
23. Someone tried to make me do sexual things or make me watch sexual things.	**62 (10.4)**	**23 (7.7)**	**39 (13)**	**0.035**
24. Someone molested me.	**58 (9.7)**	**21 (7.1)**	**37 (12.3)**	**0.031**
27. I believe that I was sexually abused	49 (8.2)	24 (8.1)	25 (8.3)	0.911
Minimization				
10. There was nothing I wanted to change about my family.	338 (56.7)	163 (55.1)	175 (58.3)	0.421
16. I had the perfect childhood.	543 (91.3)	272 (92.2)	271 (90.3)	0.419
22. I had the best family in the world.	558 (93.5)	279 (93.9)	279 (93.0)	0.642

No significant association between childhood trauma and any of the other cardiovascular risk factors of interest was found in the study sample, **Table 14.**

Table 14: Association between childhood trauma and CVD risk factors among patients

Variable	Childhood trauma		P-value
	No	Yes	
	Freq (Col %)	Freq (Col %)	
MS			0.533
No MS	63(77.8)	175(81.0)	
MS	18(22.8)	41(19.0)	
Diabetes			0.599
No	79(97.5)	208(96.3)	
Yes	2(2.5)	8(307)	
Hypertension			0.110
No	71(87.7)	172(79.6)	
Yes	10(12.3)	44(20.4)	
HDL			0.160
Normal	57(70.4)	133(61.6)	
Elevated	24(29.6)	83(38.4)	
LDL			0.710
Normal	27(33.3)	77(35.6)	
Elevated	54 (66.7)	139 (64.4)	
Cholesterol			0.780
Normal	61(75.3)	166(76.90	
Elevated	20(24.7)	50(23.1)	
Current smoker			0.690
No	74(91.4)	194(89.8)	
Yes	7(8.6)	22(10.2)	
Harmful alcohol			0.884
No	79(97.5)	210(97.2)	
Yes	2(2.5)	6(2.8)	

No significant association between childhood trauma and any of the other cardiovascular risk factors of interest was found in the study sample, **Table 15.**

Table 15: **Childhood trauma and CVD risk factors among controls**

Variable	Childhood trauma		P-value
	No	Yes	
	Freq (Col %)	Freq (Col %)	
MS			0.646
No MS	67(84.8)	192(86.9)	
MS	12(15.2)	29(13.1)	
Diabetes			0.776
No	77(97.5)	214(96.8)	
Yes	2(2.5	7(3.2)	
Hypertension			0.822
No	66(83.5)	187(84.6)	
Yes	13(16.5)	63(28.5)	
HDL			0.753
Normal	55(69.6)	158(71.5)	
Elevated	20(30.4)	63(28.5)	
LDL			0.923
Normal	28(35.4)	77(34.8)	
Elevated	51(64.6)	144(65.2)	
Cholesterol			0.878
Normal	67(84.8)	189(85.5)	
Elevated	12(15.2)	32(14.5)	
Current smoker			0.231
No	78(98.7)	212(95.9)	
Yes	1(1.3)	9(4.1)	
Harmful alcohol			0.318
No	75(94.9)	215(97.3)	
Yes	4(5.1)	6(2.7)	

4.5: Psychological distress among controls

As shown on **Figure 8** below, 11% of the controls had mild distress, 5.7% had moderate distress and 3.3 % had severe distress.

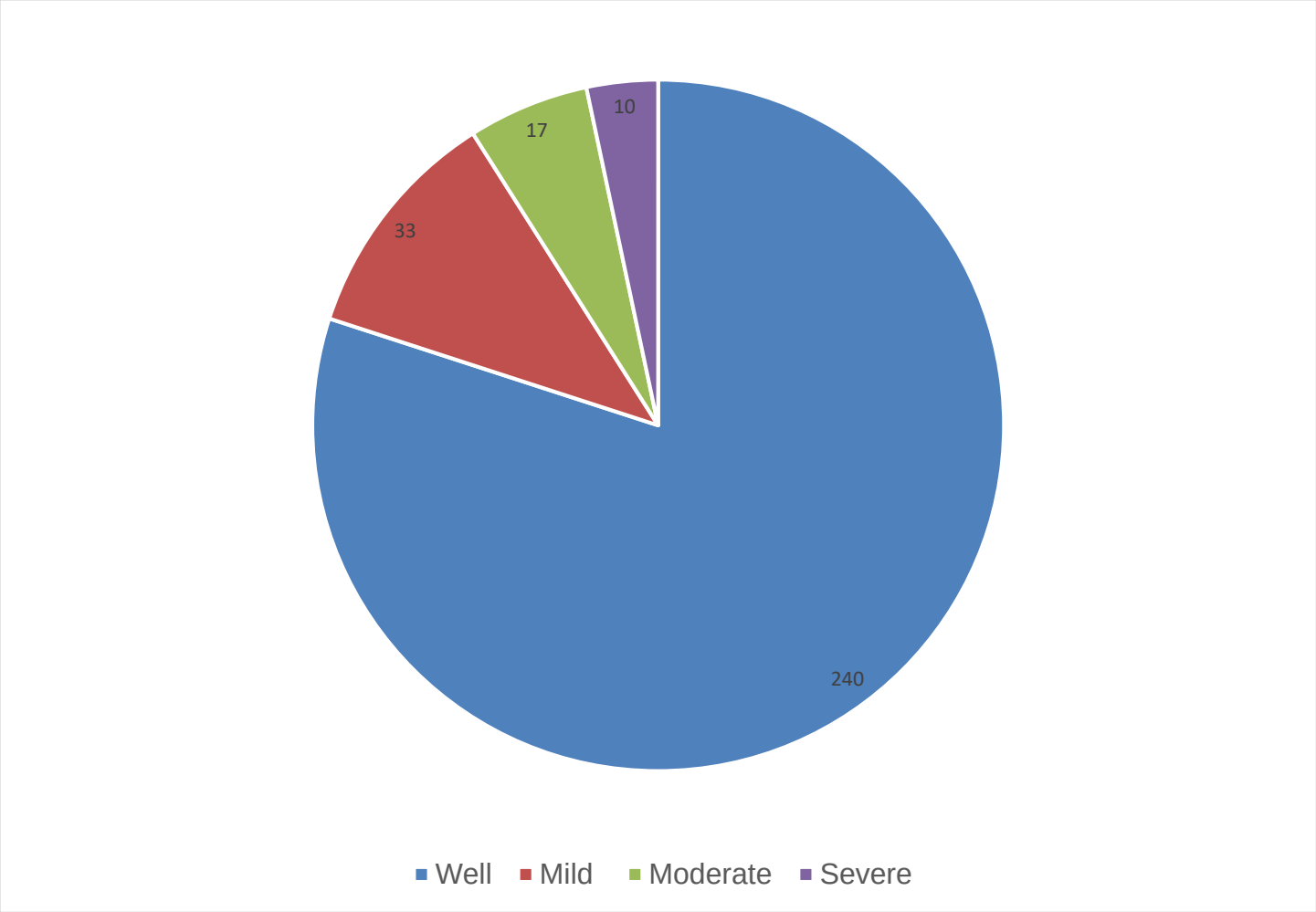


Figure 8 .Psychological distress among controls as measured using K10 Scores

Well: under 20. Mild: 20-24. Moderate: score 25-29. Severe: 30 and above

Those participants who did score highly on the psychological distress scale were significantly less likely to have adequate physical activity (p=0.002), **Table 16**. A significant association between psychological distress and education level (p=0.001) was also demonstrated.

Table 16: Psychological distress and cardiovascular risk factors

	Total	Distress	No distress	P-value
Variable	**Freq (%)**	**Freq (%)**	**Freq (%)**	
Sex				0.219[1]
Male	126 (42)	21 (35)	105 (43.8)	
Female	174 (58)	39 (65)	135 (56.3)	
Marital status				0.107[2]
Married	166 (55.3)	26 (43.3)	140 (58.3)	
Never married	100 (33.3)	26 (43.3)	74 (30.8)	
Widow/separated/divorced	34 (11.3)	8 (13.3)	26 (10.8)	
Education level				**0.001[2]**
None	12 (4)	4 (6.7)	8 (3.3)	
Primary	41 (13.7)	1 (1.7)	40 (16.7)	
Secondary	80 (26.7)	10 (16.7)	70 (29.2)	
Tertiary	167 (55.7)	45 (75)	122 (50.8)	
Currently smoking				0.421[2]
No	290 (96.7)	57 (95)	233 (97.1)	
Yes	10 (3.3)	3 (5)	7 (2.9)	
Harmful alcohol				0.108[2]
No	290 (96.7)	56 (93.3)	234 (97.5)	
Yes	10 (3.3)	4 (6.7)	6 (2.5)	
Poor diet				0.131[2]
No	4 (1.3)	2 (3.3)	2 (0.8)	
Yes	296 (98.7)	58 (96.7)	238 (99.2)	
Inadequate Exercise				**0.002[2]**
No	49 (16.3)	2 (3.3)	47 (19.6)	
Yes	251 (83.7)	58 (96.7)	193 (80.4)	
Time spent sitting				0.488[1]
Less than 3 hours	157 (52.3)	29 (48.3)	128 (53.3)	
More than 3 hours	143 (47.7)	31 (51.7)	112 (46.7)	
MS				0.737[2]
No MS	259 (86.3)	51 (85)	208 (86.7)	
MS	41 (13.7)	9 (15)	32 (13.3)	

4.6: Comorbid chronic medical conditions

In general, patients with psychosis reported a lower prevalence of medical conditions compared to those without psychosis. Specifically, patients were found to have significantly lower prevalence of reported tuberculosis (1% in patients vs 4.4% in controls, p=0.025), HIV (4.7% in patients vs 14.4%in controls p<0.001), seasonal allergies (17% in patients vs 27%in controls p=0.015), asthma (2.7% in patients vs 7.4% in controls, p=0.032) and ulcers (10.4% in patients vs 20.1% in controls p=0.002). **Table 17**

Table 17: Reported medical conditions as captured on CIDI screener.

Variable	Total	Patients	Control	
	Freq (Col %)	Freq (Col %)	Freq (Col %)	P-value
Ever been admitted to the hospital				0.018[1]
No	408 (31.4)	217 (73.1)	191 (64.1)	
Yes	187 (100)	80 (26.9)	107 (35.9)	
Number of previous hospitalizations				**0.016[2]**
1	115 (18)	58 (73.4)	57 (54.8)	
2	33 (10.9)	11 (13.9)	22 (21.2)	
3	20 (3.8)	9 (11.4)	11 (10.6)	
4	7 (4.4)	1 (1.3)	6 (5.8)	
5	8 (100)	0 (0)	8 (7.7)	
Arthritis or rheumatism				0.228[2]
Yes	11 (97.8)	3 (1)	8 (2.7)	
No	582 (0.2)	294 (99)	288 (96.6)	
Don't know	1 (0.2)	0 (0)	1 (0.3)	
Refused to answer	1 (100)	0 (0)	1 (0.3)	
Chronic back or neck problems				0.645[2]
Yes	39 (93)	17 (5.7)	22 (7.4)	
No	554 (0.3)	279 (93.9)	275 (92)	
Don't know	2 (0.2)	1 (0.3)	1 (0.3)	
Refused to answer	1 (100)	0 (0)	1 (0.3)	
Frequent or severe headaches				0.187[2]
Yes	98 (83.1)	43 (14.5)	55 (18.4)	
No	495 (0.3)	254 (85.5)	241 (80.6)	
Don't know	2 (0.2)	0 (0)	2 (0.7)	
Refused to answer	1 (100)	0 (0)	1 (0.3)	
Any other chronic pain				0.414[2]
Yes	36 (93.5)	14 (4.7)	22 (7.4)	

No	557 (0.3)	282 (94.9)	275 (92)	
Don't know	2 (0.2)	1 (0.3)	1 (0.3)	
Refused to answer	1 (100)	0 (0)	1 (0.3)	
Seasonal allergies eg hay fever				**0.015[2]**
Yes	132 (77)	51 (17.2)	81 (27.1)	
No	459 (0.7)	243 (81.8)	216 (72.2)	
Don't know	4 (0.2)	3 (1)	1 (0.3)	
Refused to answer	1 (100)	0 (0)	1 (0.3)	
A stroke				0.171[2]
Yes	4 (98.8)	0 (0)	4 (1.3)	
No	589 (0.3)	296 (99.7)	293 (98)	
Don't know	2 (0.2)	1 (0.3)	1 (0.3)	
Refused to answer	1 (100)	0 (0)	1 (0.3)	
A heart attack				0.574[2]
Yes	2 (99.3)	1 (0.3)	1 (0.3)	
No	592 (0.2)	296 (99.7)	296 (99)	
Don't know	1 (0.2)	0 (0)	1 (0.3)	
Refused to answer	1 (100)	0 (0)	1 (0.3)	
Heart disease				0.297[2]
Yes	6 (98.5)	1 (0.3)	5 (1.7)	
No	586 (0.3)	295 (99.3)	291 (97.7)	
Don't know	2 (0.2)	1 (0.3)	1 (0.3)	
Refused to answer	1 (100)	0 (0)	1 (0.3)	
Asthma				0.032[2]
Yes	30 (94.6)	8 (2.7)	22 (7.4)	
No	563 (0.2)	288 (97)	275 (92.3)	
Don't know	1 (0.2)	1 (0.3)	0 (0)	
Refused to answer	1 (100)	0 (0)	1 (0.3)	
High Blood Pressure				0.597[2]
Yes	44 (92.1)	19 (6.4)	25 (8.4)	
No	548 (0.3)	277 (93.3)	271 (90.9)	
Don't know	2 (0.2)	1 (0.3)	1 (0.3)	
Refused to answer	1 (100)	0 (0)	1 (0.3)	
Tuberculosis				**0.025[2]**
Yes	16 (96.8)	3 (1)	13 (4.4)	
No	576 (0.3)	292 (98.3)	284 (95.3)	
Don't know	2 (0.2)	2 (0.7)	0 (0)	
Refused to answer	1 (100)	0 (0)	1 (0.3)	
COPD or emphysema				0.390[3]
Yes	4 (99)	1 (0.3)	3 (1)	
No	589 (0.2)	296 (99.7)	293 (98.3)	
Don't know	1 (0.2)	0 (0)	1 (0.3)	
Refused to answer	1 (100)	0 (0)	1 (0.3)	
Diabetes or high blood sugar				0.608[2]
Yes	11 (97)	4 (1.3)	7 (2.3)	

No	577 (1)	290 (97.6)	287 (96.3)	
Don't know	6 (0.2)	3 (1)	3 (1)	
Refused to answer	1 (100)	0 (0)	1 (0.3)	
Ulcer in your stomach or intestine				**0.002[2]**
Yes	91 (84)	31 (10.4)	60 (20.1)	
No	500 (0.7)	265 (89.2)	235 (78.9)	
Don't know	4 (100)	1 (0.3)	3 (1)	
HIV infection or AIDS				**<0.001[2]**
Yes	57 (86.7)	14 (4.7)	43 (14.4)	
No	517 (3.5)	275 (92.6)	242 (80.9)	
Don't know	21 (0.2)	8 (2.7)	13 (4.3)	
Refused to answer	1 (100)	0 (0)	1 (0.3)	
Epilepsy or seizures				0.125[2]
Yes	10 (97.5)	8 (2.7)	2 (0.7)	
No	581 (0.7)	286 (96.3)	295 (98.7)	
Don't know	4 (0.2)	3 (1)	1 (0.3)	
Refused to answer	1 (100)	0 (0)	1 (0.3)	
Cancer				0.133[2]
Yes	3 (89.7)	0 (0)	3 (1)	
No	534 (9.6)	272 (91.9)	262 (87.6)	
Don't know	57 (0.2)	24 (8.1)	33 (11)	
Refused to answer	1 (100)	0 (0)	1 (0.3)	
Other Conditions				0.769[2]
No	583 (1.9)	291 (98.3)	292 (98)	
Yes	11 (100)	5 (1.7)	6 (2)	

[1] Chi-square test [2] Fishers' exact test

There was no significant association between comorbid medical conditions and metabolic syndrome or other cardiovascular risk factors among the participants.

4.7: Pharmacological treatment patterns and cardiovascular risk

The vast majority (94.3%) of patients were being treated with an antipsychotic medication at the time of assessment, while the remaining patients were treated with antidepressants only. As shown in **Figure 9,** below, most (86.5%) patients were treated with olanzapine.

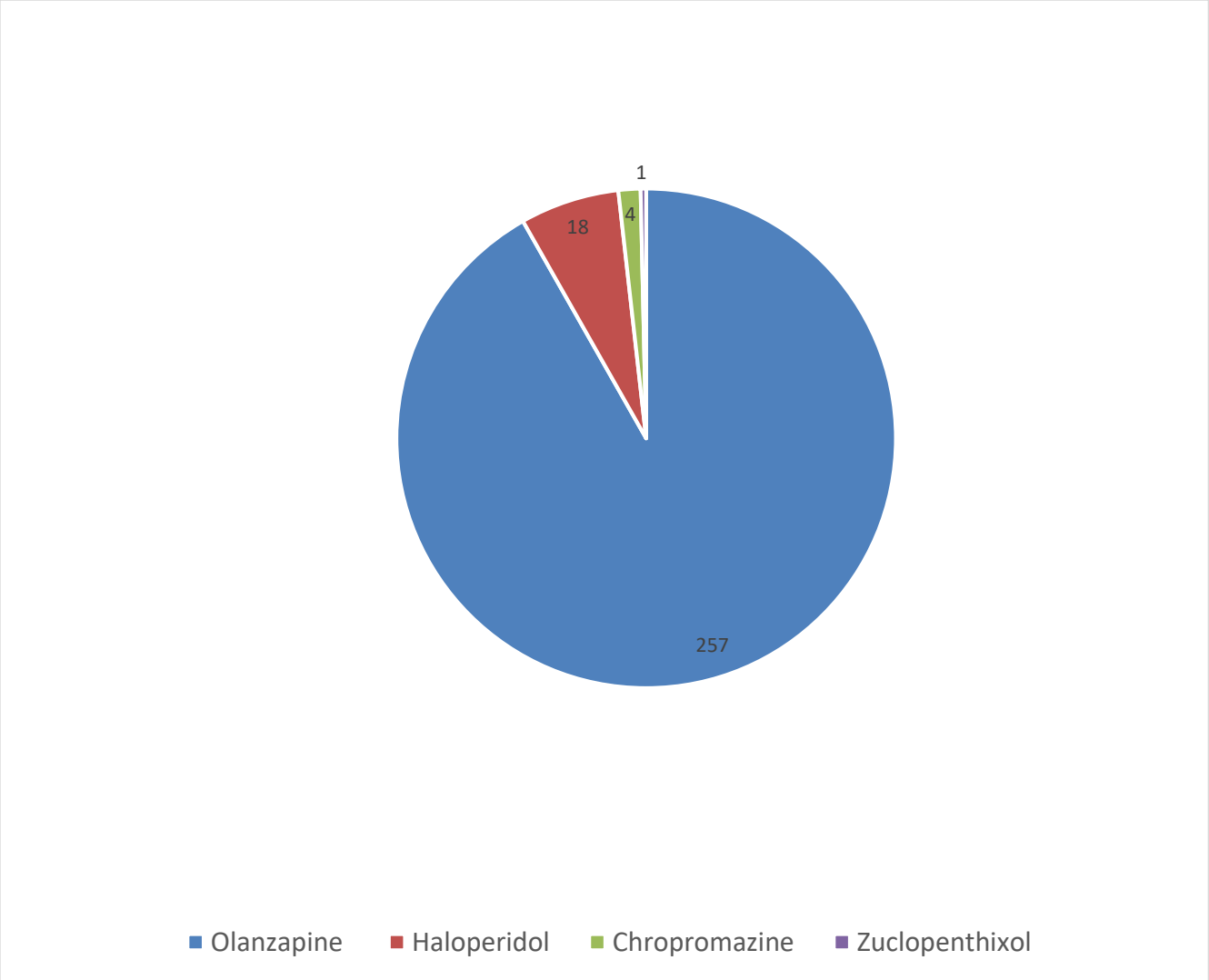


Figure 9: Antipsychotic prescription patterns among patients with psychosis.

Neither olanzapine use, nor olanzapine dosage was significantly associated with increased cardiovascular risk, **Table 18**; and an inverse relationship between olanzapine use and hypertension (p=0.029) was in fact noted.

Table 18: Association between olanzapine dosage and cardiovascular risk

	Olanzapine dosage			
	None	**<=10**	**>10**	
Variable	**Freq (Col %)**	**Freq (Col %)**	**Freq (Col %)**	**P-value**
MS				0.376[1]
No MS	25 (62.5)	134 (72)	53 (74.6)	
MS	15 (37.5)	52 (28)	18 (25.4)	
Diabetes				0.192[2]
No	38 (95)	178 (95.7)	71 (100)	
Yes	2 (5)	8 (4.3)	0 (0)	
Hypertension				**0.029[2]**
No	27 (67.5)	154 (82.8)	62 (87.3)	
Yes	13 (32.5)	32 (17.2)	9 (12.7)	
HDL				0.678[1]
Normal	28 (70)	118 (63.4)	44 (62)	
Elevated	12 (30)	68 (36.6)	27 (38)	
LDL				0.324[1]
Normal	14 (35)	60 (32.3)	30 (42.3)	
Elevated	26 (65)	126 (67.7)	41 (57.7)	
Cholesterol				0.948[1]
Normal	31 (77.5)	141 (75.8)	55 (77.5)	
Elevated	9 (22.5)	45 (24.2)	16 (22.5)	
BMI				0.261[2]
Underweight	2 (5)	5 (2.7)	0 (0)	
Normal	17 (42.5)	96 (52.5)	39 (55.7)	
Overweight	10 (25)	57 (31.1)	22 (31.4)	
Obese	10 (25)	24 (13.1)	9 (12.9)	
Morbid obesity	1 (2.5)	1 (0.5)	0 (0)	

[1] Chi square test [2] Fishers' exact test

4.8: 10 year estimated risk of developing cardiovascular disorders

In this study the scores of the Framingham 10-year estimated risk of developing CVD among patients with psychosis was 3.16, which was comparable to that in the control group (2.93), **Table 19**.

Table 19: Framingham risk scores

FRS	N	Mean	SD	t-test p-value
Control	300	2.93	4.55	0.534
Patients	297	3.16	4.23	
Total	597	3.04	4.39	

Most patients (94.6%) had a low risk score (<10), 4.4 % had an intermediate risk and 1% had high risk for CVD in this study, **Table 20.**

Table 20: A comparison of Framingham Risk Score severity

Framingham Score	Total	Patients	Control	p-value
	Freq (%)	Freq (%)	Freq (%)	
Low risk	563 (94.3)	281 (94.6)	282 (94.0)	1.000
Intermediate	27 (4.5)	13 (4.4)	14 (4.7)	
High Risk	7 (1.2)	3 (1.0)	4 (1.3)	

In terms of Sex comparisons of the FRS, Female patients were found to have a significantly higher risk compared to controls (p=0.008); while no difference between male patients and male controls was evident, **Table 21**

Table 21: Framingham 10 year cardiovascular disease risk by Sex

Sex	**Arm**	**N**	**Mean**	**SD**	**t-test p-value**
Male	Control	126	4.55	6.13	0.317
	Patients	139	3.86	5.19	
Female	**Control**	**174**	**1.76**	**2.29**	**0.008**
	Patients	158	2.54	3.03	
Total		597	3.04	4.39	

In a linear regression model adjusted for covariates, the estimated 10-year cardiovascular risk among patients was significantly associated with female Sex (p=0.007), age (p<0.001), current tobacco smoking (p<0.001) and metabolic syndrome (p<0.001), **Table 22**. It was not found to be associated with harmful alcohol use, or with olanzapine dose.

Table 22: Factors associated with higher 10 year FRS scores among patients

Variable	Coefficient	p value	95% Confidence interval
Female vs male	**0.888**	**0.007**	**1.528 -0.248**
Age in years	**0.239**	**<0.001**	**0.2090 0. 268**
Employment ; formal vs none	0.476	0.307	-1.413 0.460
Education: secondary vs none	0.184	0.770	-1.433 1.064
Obese vs normal weight	0.466	0.176	-0.210 1.142
Current tobacco use	**3.817**	**<0.001**	**2.717 4.917**
Harmful alcohol use	0.884	0.369	_1.051 2.819
Metabolic syndrome	3.092	<0.001	2.319 3.865
Olanzapine dose			
< 10mg vs none	0.438	0.337	0.458 1.335
>10mg vs none	0.367	0.478	0.651 1.385
Childhood trauma	0.668	0.058	-0.022 1.359
Traumatic life events	-0/218	0.550	-0.937 0.500

4.9: Treatment Gap for CVD risk factors.

Out of 10 patients who had DM, 6 (60%) were not previously diagnosed hence were not on treatment. Out of 9 controls who had DM, 2(22%) were not previously diagnosed hence were not on treatment. Out

of all the 54 patients who we found to have hypertension, 35 (65%) were not on treatment, while out of the controls 47 controls who had hypertension 22 (47%)of them were not on treatment. **Table 23.**

We found no record of treatment with lipid lowering drugs; or of any other medication to reduce the adverse cardiovascular effects of antipsychotic treatment in this study sample.

Table 23: Proportion of treated and untreated cardio metabolic disorders❄

Variable	Patients Freq (Col %)	Controls Freq (Col %)	P-value
Diabetes Mellitus			0.115[2]
Treated	4 (40%)	7 (78%)	
Untreated	6 (60%)	2 (22%)	
Total Diabetes	10 (100 %)	9 (100%)	
Hypertension			0.069[1]
Treated	19 (35%)	25 (53%)	
Untreated	35 (65%)	22 (47%)	
Total Hypertension	54 (100%)	47 (100)	

❄*Patient records were reviewed for documented evidence of treatment of the cardiovascular risk factors. This was complemented by patients' self-report of other medication they were taking; and was compared with the laboratory tests and anthropometric measurements*

CHAPTER 5: DISCUSSION

5.0 Introduction

The purpose of this chapter is to interpret and describe the significance of the key study findings, in light of existing literature on cardiovascular risk factors and psychosis. First, we discuss sociodemographic characteristics of the participants, highlighting the overall young age of the study sample, and the impact on cardiovascular risk. Second, we explore the prevalence and correlates of both conventional and non-conventional cardiovascular risk factors, noting the high prevalence of several factors among the participants. Third, we discuss antipsychotic use and its association with cardiovascular risk, highlighting the unexpected absence of a significant association between olanzapine and increased cardiovascular risk. Fourth, we discuss the overall estimated 10-year risk of developing CVD, noting the significant relationship between age, sex, metabolic syndrome and cigarette smoking on the FRS. Fifth, we describe the interventions for metabolic disorders among mentally ill patients in the study setting, as well as treatment gaps identified in this study. Sixth, we summarize methodological limitations which should be considered when interpreting the findings of this study. Finally, we discuss the translational potential of these findings; and how these may impact on clinical care; as well as directions for future research in this field.

5.1: Conventional non-modifiable CVD risk factors and other social demographic characteristics

5.1.1: Age

The overall young age (below 40 years of age) of participants in this study may be attributed to the fact that generally Kenya has a very young population with more than three quarters of Kenyan citizens being younger than 30 years of age (World population Review 2019). In this study age was positively correlated with MetS, abnormal BMI and FRS. Evidence suggests that age affects the overall CVD risk because several CVD risk factors are more common among older than younger populations resulting in a cumulative effect (Gurven et al. 2012; Pinto 2007a). As an example population-based retrospective cohort study in Canada amongst 379, 003 Canadians with diabetes and 9, 018, 082 persons without

diabetes reported that patients with diabetes get into a high CVD risk after the age of 40 (G. L. Booth et al. 2006). Similarly, a study done in South Africa reported that MetS prevalence was significantly higher in patients aged above 55 years(Saloojee, Burns, and Motala 2016b). Further hypertension is reported to increase with age, due to age related alteration in sodium haemostasis, arterial stiffness and increased pulse pressure (Frame and Wainford 2018; Baker et al. 2016). Given that age is a key predictor of CVD risk both in our study and in other studies (Dhingra and Vasan 2012a; Sniderman and Furberg 2008) , the findings of this study should be interpreted in that context, bearing in mind that an older population of mentally ill patients may display a different cardiovascular risk profile.

5.1.2: Sex

This study demonstrated that sex may play a significant role in shaping the cardiovascular risk profile of patients with psychosis. While a number CVD risk factors were common in both men and women, female sex was positively correlated with a higher BMI and increased risk scores. These findings are in agreement with a study done among 169 patients with in Baltimore among patients with severe mental illness which reported a positive correlation between female sex and abnormal BMI (Dickerson et al. 2006). Similarly, higher rates of obesity were reported among female patients with severe mental illness in a study involving 272 patients in Maryland (Daumit et al. 2003). While in our study we found MetS to be positively correlated with male sex, other studies have reported higher rates of Mets among females. For example, an observation study done among 500 patients in India reported a positive correlation between Mets and female sex (Beigh and Jain 2012). Similarly, a Mexican study showed that females patients with psychosis were 3 times more likely to develop metabolic syndrome compared to men (Díaz-Domínguez et al. 2013). The sex differences in this study supports the existing literature which recommends a Sex sensitive approach to diagnosis and interventions of CVD risk factors.

5.1.3: Socioeconomic and marital status:

In understanding the cardiovascular risk profile of the study participants, this study explored three aspects of social economic environment that may play a key role in determining health outcomes: employment status, education level and marital status (WHO ; S. M. Marmot 2018).

There were higher rates of unemployment among patients with psychosis compared to controls. These findings are in agreement with other studies that have demonstrated that people with mental illness are more likely to be unemployed compared to their healthy counterparts (Mallett et al. 2002). This is in agreement with a study done among 546 African-Caribbean participants (224 patients with psychosis and 322 controls) which demonstrated that unemployment is common among patients with psychosis (Reininghaus et al. 2008). Although this was not demonstrated in this study, other studies have reported an indirect link between unemployment and physical as well as mental health (Tøge 2016; Batic-Mujanovic et al. 2017; López del Amo González, Benítez, and Martín-Martín 2018).

Patients had lower level of education compared to those who had no psychosis. In this study, having a secondary education was associated with lower odds of having metabolic syndrome. This is in line with other literature that has described a relationship between education level and physical and mental health (Kurtze, Eikemo, and Kamphuis 2013). For example, a Chinese observational study that involved 10,054 community residents reported that patients with lower educational level had a higher risk of developing metabolic syndrome (Zhan et al. 2012). However it is in contrast to the Interheart African study that was conducted among (578) were matched to 785 controls by age and sex in 9 SSA countries, which showed that high education level was associated with increased risk of CVD. Similarly A nationwide Spanish cohort study (n=9,226) reported that DM, hypertension and BMI mediated the association between education and CVD incidence, accounting for 26% of the association (Dégano et al. 2017). Further, a Mendelian randomization study that included 217, 013 white British participants reported that every additional standard deviation of education (3.6 years) was associated with a 13% lower risk of coronary heart disease in observational analysis and a 37% lower risk in Mendelian randomization analysis and that BMI, systolic blood pressure and smoking were the main mediators (Carter et al. 2019). It is believed that educated persons are more likely to access screening and

treatment for cardiovascular risk factors compared to those with lower educating, implying that better educated people are likely to have better health outcomes (Oguoma et al. 2015)

Patients in this study were more likely never to have been married or to be separated compared to those who had no psychosis. This is consistent with findings of case control study done in Denmark (n=5,341) which demonstrated that patients with schizophrenia were more likely not to be married both at diagnosis and even several years later after initiation of treatment (Agerbo et al. 2004). Similarly a recent observational study conducted in Ethiopia among 245 patients with severe mental illness indicated that marital status was associated with presence of metabolic syndrome components (Teshome, Kassa, and Hirigo 2020). Mental illness is believed to result in a state of social disadvantage associated with the symptomatology of the disease, like the cognitive impairment , difficulty with social interactions, as well as the stigma for mental illness, which affects their ability to get into marital commitments (C. Morgan et al. 2008.). Being married has been associated with better quality of life due to the social support that it brings (Salokangas et al. 2001), and married psychotic patients tend to present with less severe symptoms compared to those who are not married (Nyer et al. 2010) . In the current study those who were divorced, separated or windowed had reduced odds of having metabolic syndrome and abnormal BMI. This is contrary to other studies that have found that unmarried people (divorced, widowed, or separated) have higher odds of developing metabolic syndrome. For example , the sixth Korea National Health and Nutrition Examination Survey that involved 3,225 women aged 40–69 years reported that the OR for metabolic syndrome in the widowed participants compared to the married group was 4.8, possibly related to social economic factors and other health behaviours (Jung et al. 2018). At the same time, the conditions in the marriage can also shape the cardiovascular health of the individuals. As an example, the Stockholm female coronary risk study showed a nearly 3 time increase in cardiac events associated with marital distress (Orth-Gomér et al. 2000)..

These findings imply that in implementing any efforts to improve the cardiovascular profile of patients with psychosis, it is important to also explore the role the social economic and marital circumstances play in shaping the individuals cardiovascular profile.

5.2: Conventional modifiabl CVD risk factors

5.2.1: Lifestyle risk factors

Smoking

In this study, 13.8 % of patients reported cigarette smoking. This finding is comparable to the prevalence of smoking in the general population in Kenya which is 13.5% according to the WHO STEP survey (Ngaruiya et al. 2018). However it is lower that what other studies among patients with psychosis have reported. This is lower than findings of a study done among patients with schizophrenia in Nigeria which reported a lifetime prevalence of 25% (Aguocha et al. 2015). Similarly, a review and meta-analysis including 61 studies comprising 72 samples and an overall sample of 14,555 tobacco users and 273,162 non-users reported a 57% prevalence of smoking amongst patients with first episode psychosis (Gurillo et al. 2015b). The lower prevalence in the current study may be due to underreporting of nicotine use that may be associated with both perceived and internalized stigma for substance use in the study setting.

When compared to controls, this study reported a significantly higher prevalence of smoking among patients and that cigarette smoking was associated with higher FRS. The higher prevalence among patients versus controls is in line with a well stablished evidence base. Several studies across the globe have demonstrated that patients with psychotic disorders have very high rates of smoking (Gurillo et al. 2015b**;** Addington et al. 2014**;** Vanable et al. 2003) with patients being 4 to 6 times more likely to smoke compared to those without psychosis (Hartz et al. 2014).

The findings of this study agree with other literature that smoking is a common cardiovascular risk factor among patients with psychosis supporting the need for continuous efforts to promote smoking cessation in order to improve the cardiovascular health of this group.

Harmful alcohol use

In the current study, only 2.7% of the patients with psychosis had harmful alcohol use as defined by an Audit score greater than 4 in men and 3 in women. This prevalence is notably lower than expected, given that a community based study done in the same region of Western Kenya indicated that the prevalence

of harmful alcohol was 12% (Kwobah et al. 2017). In addition a large body of evidence indicates a higher burden of harmful alcohol use among patients with psychosis than in the general population affecting more than one third of patients with schizophrenia (Menezes et al. 1996). A study done in Ethiopia among patients with bipolar mood disorder reported that 24.5% had alcohol use disorder (Tensae et al. 2018). Similarly meta-analysis that included 60 studies estimated that the prevalence of harmful alcohol use among patients with schizophrenia is 20% (Koskinen et al. 2009). Evidence suggests that the higher prevalence of alcohol in patients with bipolar mood disorders as well as schizophrenia is part of self-medication to relieve distressing symptoms (Maremmani et al. 2018; James M. Bolton, Jennifer Robinson, and Jitender Sareen 2009). This discordant finding in our study sample highlights the methodological limitation of self-reported assessments for alcohol use and the stigma that surrounds alcohol use in the study setting. Other studies have demonstrated that many persons who use alcohol are likely to underreport their drinking especially when they are drinking heavily (Boniface, Kneale, and Shelton 2014) mainly due to perceived stigma (Northcote and Livingston 2011). The findings of this study underscore the need for a more objective way of assessing for harmful alcohol use among patients with psychosis (such as blood or urine tests) in order to avoid under estimating the role excess alcohol use plays in shaping the cardiovascular risk profile in this population.

Poor dietary habits

In this study most patients with psychosis reported eating less than one serving of fruits in a week, and having less than 3 servings of vegetables in a week. This finding is in line with the 2015 national survey of 2015 in Kenya that reported that 99% of the participants had less than the recommended intake of fruits and vegetables (Haregu et al. 2018). This pattern of low intake of fruits and vegetables is similar to findings of the second Australia national survey on psychosis (Margolese et al. 2004) which showed that 74% of the patients had very low intake of fruits and vegetables. This has been attributed to the symptoms of the illness especially the negative symptoms and the cognitive impairment, as well as the low financial abilities which would limit the purchasing power for healthy meals (L. A. Hahn et al. 2014) .

While only fruits and vegetables intake was used to assess diet in this study, existing evidence report other poor forms of dietary habits among patients with psychosis, which may result in increased cardiovascular risk (Dipasquale et al. 2013b). These include consuming diet with excess salt and saturated fats further increasing the cardiovascular risk (Nenke et al. 2015). According to a German study the patients with schizophrenia were more likely to eat a snack for dinner , consume instant meals and eat healthy groceries more rarely (Roick et al. 2007). This pattern of poor dietary habits may be due to many factors including social dysfunction which is common among these patients (Mucheru et al. 2017a). According to the survey of high impact psychosis in Australia, patients who are isolated and lonely were more likely to miss essential meals like breakfast and also eat diet with low fruits and vegetable levels compared to the general population (Mucheru et al. 2017b). Other factors that may result in poor dietary habits are financial constraints as demonstrated by a study done in South East London which associated the poor diet with unemployment (Samele et al. 2007).

These findings are important as they highlights the importance of including in the care of mentally ill patients in this setting, efforts to improve intake of healthy diet in order to promote cardiovascular health.

Inadequate physical activity and sedentary behaviour

This study reports a very high rate of inadequate exercise in terms of physical activities per week as well as hours spent sitting. This is consistent with the 2015 WHO Steps survey that reported that up to 80% of the population in Kenya do not engage in adequate physical activity (Wekesah et al. 2018). A review including 2,033 people with psychosis revealed that many patients with psychosis may spend up to 9 hours of their wakefulness in sedentary state and at least 2 hours more is spent in sedentary state compared to the general population (Stubbs, Williams, et al. 2016). The WHO mental health survey conducted among 204,186 participants from several LMICs reported that the low physical activity was common among patients with a diagnosis of psychosis ,especially male patients, and this was associated with mobility difficulties, self-care difficulties , depression , cognitive impairment, changes in sleep and energy levels in that order (Stubbs et al. 2017b). A review including 25 articles associated low physical

activity in patients with psychosis with negative symptoms such as anhedonia ,side-effects of antipsychotic medication, lack of knowledge on cardiovascular disease risk factors, lack of belief in the health benefits, a lower self-efficacy, and social isolation (D. Vancampfort et al. 2012). A different review including 35 studies representing 3,453 individuals with schizophrenia associated the low physical activity levels with old age as well as depressive symptoms (Stubbs, Firth, et al. 2016). The level of physical activity is also affected by obesity which is prevalent in patients with psychosis, as well as patients perceptions in terms of perceived competence physical self-worth(D. Vancampfort, Probst, et al. 2011).

These findings mean that there is work to be done in this kind of setting to identify and implement ways of promoting physical activity among patients with psychosis in order to reduce risk of CVD.

5.2.2: Metabolic disorders

Diabetes Mellitus; The prevalence of DM in our study sample (3.4%) was low but comparable to the findings of the National Steps survey on NCD risk factors that was carried out in Kenya in 2015 among 4069 participants aged between 18 and 69 years, which reported a 2.4% diabetes (Mohamed, Mwangi, et al. 2018). This is also within the range that was reported by one review that included 143 articles which indicated that the prevalence of diabetes in patients with psychotic disorders ranges widely ,from 1·26% to 50% across studies (median 13%) (Ward and Druss 2015). Other contrasting studies indicate a higher prevalence among patients with mental illness compared to the general population. One observational study done in Taiwan that involved 246 patients with schizophrenia reported that the prevalence of DM was 9.8% (Chi-FaHunga, Ching-Kuan, and WuabPao-Yen 2005). Another large population based Canadian study (28,755 patients with psychotic disorder and 2,281,636 controls) reported a 10% prevalence of diabetes among patients with psychosis compared to 6% among controls (Bresee et al. 2010). Similarly a smaller study done in Singapore among patients with schizophrenia reported a prevalence of 19.1%.(Shafie et al. 2018). One possible contribution to the lower prevalence in the current study sample could be the use of random blood sugar cut off while in essence some of the patients may actually have been in a fasting state, having not eaten for more than 6 hours. While in this current study there was no relationship between DM and FRS, the Framingham study established that the presence of

DM increases the risk of cardiovascular disease twice in men and three times in women compared to those with no diabetes (W B Kannel and McGee 1979).

These findings point to the need for better assessments of presence of DM, for example by use of HB1Ac, before conclusions that indeed patients with psychosis in this setting have a low prevalence of DM.

High blood Pressure; This study found that 18.2% of the patients with psychosis had elevated blood pressure. This is lower than a prevalence of 24% that was reported by the national survey in Kenya in 2015 (Mohamed, Mutua, et al. 2018) in the general population. Though not demonstrated in this study, other evidence suggests that the rates of hypertension in patients with psychosis are likely higher than the general population owing to several shared etiological pathways between hypertension and mental illness (Rihmer, Gonda, and Döme 2017). For example, a nationwide survey in Japan amongst patients with schizophrenia found a prevalence of hypertension of 30% (Sugai et al. 2016b), and a multisite study done in France among older patients reported a prevalence of 43% (Abou Kassm et al. 2019). The lower prevalence of hypertension in the current study might be accounted for by the relatively younger age of the participants. Current evidence suggests that blood pressure changes by 20 mm Hg systolic and 10 mm Hg diastolic increment from age 30 to 65 years (William B. Kannel 1996). These changes in blood pressure with increasing age have been linked to the various changes at the cellular level that aging brings such as alterations in second messengers calcium and magnesium that affect the tone of the small arteries (Barbagallo et al. 2000), and the structural changes especially large artery stiffness (Pinto 2007b).

These findings indicate the need for monitoring blood pressure among patients with psychosis in similar setting, and a need to do for more studies among older patients with psychosis who might be more at risk than the young population that this study engaged.

Dyslipidaemia; This study found a high prevalence of dyslipidaemia (65% had elevated LDL, 47% had elevated triglycerides and 36% had low HDL) among patients with psychosis and both cholesterol and triglyceride levels were significantly higher among patients compared to controls. These findings are higher than what would be expected in the general population in a similar setting as exemplified by a systematic review and meta-analysis of 177 studies (n=294063) from across that reported 28·6% elevated of LDL, 37·4% of low HDL, and 17·0% of triglycerides (Noubiap et al. 2018) , and findings of the Health and Demographic Surveillance System (HDSS) site in Western Kenya which reported that only 15% of the population had elevated plasma lipids (Chege 2016). They are comparable to findings of a Saudi Arabian cross sectional study that included 992 patients with mental illness reported that 32.8% had elevated triglycerides and 52.5 % had low HDL cholesterol (Alosaimi et al. 2017). The high prevalence of dyslipidaemia in this study is a clear indicator for the need for continuous monitoring and management of lipids in patients with psychosis in this setup in order to reduce the associated risk of CVD.

Obesity; This study found a high prevalence of elevated BMI (45%) This is higher than a meta-analysis of obesity in general population in Africa (n=48,823) that estimated the prevalence to be 21.8% (Tulp et al. 2018). A cross sectional study done in Australia (n=189) demonstrated higher prevalence where most of the participants (78%) were either overweight or obese (Nenke et al. 2015).In the current study, the prevalence of abnormal BMI was significantly higher among patients than controls. This is similar to study done in Yale that included 326 patients with schizophrenia and 1899 controls reported which reported that 58% of the patients were obese compared to 27% of the controls (Annamalai, Kosir, and Tek 2017). This study established that abnormal BMI was positively associated with female Sex. This is similar to findings of an ecological analysis of internationally comparable obesity prevalence for adult men and women from the 2010 WHO Global Infobase which reported that in 87% of the 151 countries involved, female prevalence exceeded that of males (Garawi et al. 2014). While data on mentally ill females patients is limited, evidence for excess obesity among females has been reported in studies done in general populations in Turkey (Erem et al. 2004), Spain (Martínez, Moreno, and Martínez-

González 2004), and Malawi (Alison J Price et al. 2018) and Kenya (Asiki et al. 2018). In addition to high rates of elevated BMI, the study also established a high prevalence of central obesity as indicated by abnormal waist circumference (35%). Similarly an observational study done in China among patients with schizophrenia reported that almost half of the participants had central obesity (Bressington et al. 2016) This has significance as abdominal obesity is believed to have the highest impact on metabolic profile in some populations such as Africans (Handlos et al. 2012). These findings indicate the need to screen for obesity bearing in mind the Sex differences, and the need to put mechanisms in place to lower these rates in order to promote cardiovascular health in similar settings.

Metabolic syndrome; In this study we found that 28.6 % of the patients had MetS. In a Kenyan setting, these findings are lower than 34.6% which was reported in a cross-sectional study among urban dwellers in Nairobi (Kaduka et al. 2012) but higher than the prevalence of 19.2% among HIV infected individuals in the same setting (Kiama et al. 2018). Among patients with mental illness, these findings are comparable to an earlier South African study done among 276 patients with SMI which reported a prevalence of 23% (Saloojee, Burns, and Motala 2016a) an Ethiopian study which reported a prevalence of 28.9 (Asaye et al. 2018) and a very recent cross sectional study done in Uganda among 309 patients with SMI which reported a prevalence of 24% (Agaba et al. 2019). The prevalence in this study is also comparable to cross- sectional studies done in Taiwan and Singapore which reported that 26% of patients with psychosis had MetS (Tseng et al. 2014),(Seow et al. 2017) and in in Belgium which reported a prevalence of 28.4% (Marc A de Heart et all 2006).

In this study the metabolic syndrome was associated with psychosis and increasing age. Of note is that males were more likely to have MetS than females which is contrary to other work in the field. For example a study done in South Africa reported that the prevalence of MetS among black African women with SMI were more than three times more compared to men in the same setting (Saloojee, Burns, and Motala 2017) and a study done in Tanzania in the general population reported that 13% of males and 35% of females had metabolic syndrome (Njelekela et al. 2009b). Similarly data from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Schizophrenia Trial, reported higher rates of metabolic

syndrome among females, (51.6 % females vs 36%) (McEvoy et al. 2005). These findings indicate the need to consider sex differences in assessment and interventions for MetS.

5.3: Trauma, Psychological distress and Comorbid medical conditions

5.3.1: Exposure to potentially traumatic events

In this study, most participants (73% of patients and 80% of controls) reported having experienced at least one potentially traumatic event in their life. There were also several participants who reported having experienced potentially traumatic events in childhood. These findings of high prevalence of traumatic experiences among the patients is in agreement with other studies. For example, one review of literature including 46 studies reported that there is a wide range of reported prevalence of childhood trauma among patients with psychosis, ranging between 28% and 73% (Bendall et al. 2008). Another study done among schizophrenia patients in community mental health centres in central Indiana reported that 98% of the participants had at least one traumatic life event and 36% had childhood traumatic experiences(Resnick, Bond, and Mueser 2003). Similarly, a study done in New Yolk among patients with psychosis reported that 69% had trauma exposure, with 29% being exposed to at least three lifetime traumatic events, and 32.2% were exposed to childhood traumas before age 16 (Neria et al. 2002). Further, a Dutch study reported that 97.0% of the participants had experienced at least one traumatic event during their lifetime, 81.8% at least two, traumatic events and 60.6% at least three traumatic events (Lommen and Restifo 2009).

In our study, the commonest traumatic even experienced by patients was physical assault and may be partly related to high rates of Sex based violence in SSA settings (Melissa A. Smigelsky et al. 2014).. These findings are similar to findings of a study done in Norway (n=139) which also reported that physical assault and childhood neglect were among the commonest traumas reported by patients in the acute ward of a public psychiatric hospital (Floen and Elklit 2007a). Similarly, a study done among 399 patients with schizophrenia and schizoaffective disorder admitted in the Veterans Affairs inpatient psychiatric unit endorsed physical trauma most, with war zone trauma coming second (Calhoun et al.

2007). This is however different from a study done among patients with SMI in a community public mental health service in New Jersey (n=851) where the most endorsed traumatic events were childhood sexual abuse and sudden loss of a loved one (Lu et al. 2013).

Patients in this study recorded less traumatic events both in child hood and in their lifetime than controls. This is in contrast to the findings of the Genomics of Schizophrenia in the South African Xhosa people study, which reported that patients with schizophrenia had 2.44 odds of having experienced Childhood trauma compared to controls (Mall et al. 2020). . Similarly a review of literature reported that trauma and post-traumatic stress disorder (PTSD) are highly prevalent among individuals with SMI relative to the general population, and that this is associated with negative clinical functioning and increased healthcare burden (Grubaugh et al. 2011).

Patients in this study endorsed physical neglect (wearing dirty clothes) much more than the controls. This finding is in agreement with a small study done in France which reported that almost a fifth of the patients on management for schizophrenia had experienced physical neglect (Bennouna-Greene et al. 2011) . On the contrary, a study done among 305, patients with psychotic disorders in Norway reported that 82% of the patients had experienced one or more Childhood traumatic events, the most frequent subtype of trauma being emotional neglect (Larsson et al. 2013)

In the currents study, among the patients, there was an association between exposure to traumatic experiences and smoking. The association between smoking and traumatic experiences has been described in literature though mostly in the general population as demonstrated by the study done in Germany among 4075 participants (Hapke et al. 2005). This has been attributed to the need to reduce the negative effects of trauma experienced by the victims of trauma (Feldner et al. 2007). In this study however there was no evidence of an association between trauma with psychosis status. Other literature has suggested a bilateral relationship between psychosis and exposure to trauma , where psychosis may increase the risk of trauma while traumatic experiences may contribute to psychopathology (Mayo et al. 2017). On the same breadth, traumatic experiences have been reported to contribute to CVD risk by

promoting physiological changes such as dysregulation of the hypothalamic-pituitary-adrenal axis, autonomic nervous system dysfunction, and increased inflammation, which results in obesity, and hypertension. The findings of high rates of traumatic experiences in this study suggest the need to include trauma history in the diagnosis and management of patients with mental illness.

5.3.2: Psychological distress and cardiovascular risk

Psychological distress was reported in 11.7% of controls and was found to be associated with reduced physical activity and lower education level, both potential contributors to increased CVD risk. This is in agreement with A Brazilian study done among 506 military officers which demonstrated that psychological distress was significantly associated with less sport and leisure exercises (Martins and Lopes 2013). A number of other observational studies have demonstrated association between cardiovascular risk and psychological distress (Dimsdale 2008b), (McLachlan and Gale 2018). Similarly, the Whitehall study that followed up participants of varying social economic status in London demonstrated that social economic challenges such as poor living environment would impact the cardiovascular risk significantly by increasing cholesterol, smoking, blood pressure, body mass index and blood glucose among the socially disadvantaged,(E. J. Brunner 2017). A Finish Prospective study that followed up employee who were free from CVD at baseline for 25 years reported that psychological distress that results from job strain and effort-reward imbalance can be result in a doubling of the risk of CVD related death, as well as contribute to adverse changes in biological factors such as cholesterol concentration and body mass index among employees who were free from overt cardiovascular diseases at baseline (Kivimäki et al. 2002) . In line with this line of thought, one South Korean study including 1071 workers study associated high work demand with low decision latitude with increased risk of hyperlipidaemia and higher levels of homocysteine, implying an increased risk of CVD (Gun Kang et al. 2005).

5.3.3: Comorbid medical conditions.

Patients in this study reported notably lower rates of most chronic disorders with significantly lower rates of HIV, TB, stomach ulcers and allergies.

HIV: The lower rates of HIV among patients compared to controls that were reported in this study differ from that in other studies that have demonstrated an excess of HIV in patients with mental illness (DE HERT et al. 2011). For example a South African study demonstrated that patients with severe mental illness have an almost three times greater prevalence of HIV than the general population, after controlling for age and Sex (Singh, Berkman, and Bresnahan 2009). This is agreement with findings of a population based cohort study in Denmark that followed up more than two and a half million people demonstrated that HIV increased risk of schizophrenia 4 times and acute psychosis 7 times (Helleberg et al. 2015). Similarly, a descriptive study done in the US including 191,625 patients with severe mental illness and 100,000 participants without mental illnesses established that the crude odds of having an HIV diagnosis were twice as high among patients who had diagnoses of serious mental illness as among patients who did not have serious mental illness diagnoses (Himelhoch et al. 2007) . The prevalence of HIV among mentally ill patients has been attributed to engagement in risky sexual behaviour especially among bipolar patients , but may also be due to the fact that there may be impairment in understanding what safety entails or making decisions to promote safe Sex among mentally ill patients (Mamabolo et al. 2012), (Henning, Krüger, and Fletcher 2012).

The unexpected findings of lower reported rates in this study could be due to the fact that we did not test but instead asked about HIV status. Stigma to report HIV status is possible (Hamra et al. 2005) (L. Li et al. 2013), but it is also likely that routine screening for HIV is less in patients with mental illness in Kenya than in the general population . In the setting of the study one needs to be mentally stable to undergo the pre-test and post-test counselling in order to understand the test and appreciate the results, and this could have implications on the rates of diagnosis for HIV among patients with psychosis. The low levels of reported HIV could also point to difficulties with sexual interaction either due to cognitive impairment or due to side effects of medication.

Tuberculosis: In this study patients with psychosis reported significantly lower rates of TB compared to those without psychosis again contrasting other published studies. For example, one review and meta-analysis that included 40 studies from 20 different countries reported that 25% of multidrug-resistant tuberculosis patients experienced depression 24% experienced anxiety 10% experienced psychosis (Alene et al. 2018). Other small studies have also reported higher rates of mental illness among tuberculosis patients compared to the general population (Duko, Gebeyehu, and Ayano 2015) , (Ambaw et al. 2017). Further Psychosis due to TB meningitis or TB medication such as Isoniazid therapy has also been documented (Masood et al. 2011), (R., Garg, and Verma 2008),(Gomes et al. 2019),(Deribew et al. 2010). The low rates in this study could indicate low levels of screening and diagnosis for physical disorders among patients with mental illness. This may be associated with cognitive impairments in patients with psychosis which impairs ability to appreciate, describe and report physical symptoms such as those of TB (L. S. Goldman 1999). It could also be an indicator of failure of the existing the health systems to put mechanisms in place to screen and treat for physical disorders among the mentally ill patients (Fagiolini and Goracci 2009b). Such challenges in screening and care for the comorbidity were demonstrated in a global survey conducted in 26 different countries which reported low levels of screening for the comorbidity of mental health and TB and these were associated with knowledge gap for need to screen , limited resources and social stigma for TB (c et al. 2019).

Asthma: Patients reported lower rates of asthma compared to controls. Like all the other medical conditions above, this may be attributed to low screening of medical conditions in the study setting. Other studies have indicated that patients with asthma have an increased risk of developing psychosis. For example, a nationwide longitudinal study in Taiwan involving 75,069 subjects reported that asthma was associated with significantly greater hazard ratio for incident schizophrenia 1.40 (W.-C. Wang et al. 2017).

In this study, we found no significant association between the presence of selected medical conditions and FRS, with Mets S or other CVD risk factors. This was unexpected given existing evidence that existing comorbid infectious and non- infectious medical conditions among patients with psychosis are

likely to impact on the cardiovascular risk profile through direct effects of the medical condition on the cardiovascular system or due to medication prescribed for the comorbid medical condition (Young et al. 2009b).

These findings point to the need to interrogate further the practice of screening and treatment for these conditions among patients with mental illness.

5.4: Antipsychotic treatment and cardiovascular risk.

We found that 87% of the participants were on olanzapine with only a minority being on other antipsychotics. This is likely due to the widespread availability of the agent in the study setting (Olanzapine is available as a donation to the hospital), in which cost and availability of a drug are very important consideration in prescribing.

Contrary to existing evidence olanzapine use in this study was not associated with any of the cardiovascular risk factors nor did it significantly affect the estimated 10 year CVD risk. A number of observational and longitudinal studies have reported that antipsychotics affect metabolism of patients on management of psychosis hence increasing the overall cardiovascular risk. (B. L. Lambert et al. 2005), (Emsley et al. 2015: Henderson 2002; Komossa et al. 2010). For example, a one year prospective study comparing weight gain of patients initiated on neuroleptics and heathy controls demonstrated a higher weight gain among those on neuroleptics with majority of the weight gain being associated to olanzapine use (Strassnig et al. 2007). Similarly a three year prospective cohort study done in Belgium comparing patients with first and second generation antipsychotics reported a 3 fold increase in MetS among patients with second generation antipsychotics compared to first generation antipsychotics (De Hert et al. 2008). Even among the second generation antipsychotics, there are reported differences among the various drugs on the effect on metabolism. Specifically olanzapine and clozapine have been linked with the highest risk of metabolic side effects compared to other antipsychotics (Haupt et al 2006), (R.-R. Wu et al. 2006). A Chinese prospective, comparative, longitudinal study with a minimum antipsychotic treatment period of 8 weeks and assessments of participants at baseline and 8 weeks after inclusion

demonstrated that antipsychotics are associated with an increase of insulin, C-peptide, and insulin resistance index , increased cholesterol and triglyceride levels, with the effects of clozapine and olanzapine on the glucose and lipid metabolism outweighing those of risperidone and sulpiride (R.-R. Wu et al. 2006).

In this study, lower prevalence of hypertension was found among patients treated with olanzapine compared those who were not on olanzapine. This could be due to a switch from olanzapine for patients whose high blood pressure is noted to be high. Other studies have reported higher rates of hypertension in patients with antipsychotics that is believed to be due to the effect on dopamine on the renin angiotensin pathways (Gonsai et al. 2018), as well as its effect on the sympathetic nervous system where D2 receptor blockade results in persistently increased sympathetic tone, hence increase in blood pressure (Scigliano and Ronchetti 2013).

These findings imply the need for further studies to establish if olanzapine induced metabolic effects are different in the Kenyan/ SSA setting and whether there is need to reconsider safety warnings related to metabolic complication that has seen olanzapine loose favour as a first line treatment for at risk populations with psychosis.

5.5: Estimated 10 year cardiovascular risk

The estimated 10 year risk of developing cardiovascular related events among the patients in this study was low. This may be partly explained by the likelihood of generally low risk of CVD in the study setting as demonstrated by a cross-sectional survey done among slum dwellers in Nairobi which established that the risk score was CVD was low with only 1.7% having a high risk (Vusirikala et al. 2019). The findings of this study are similar to a study done in Brazil among patients with psychosis reported that only 1.2% had severe Framingham risk scores (Benseñor et al. 2012). However in contrast to a study done among 363 Spanish patients with schizophrenia where 22% of the participants had high Framingham risk scores, (Bobes et al. 2007). The lower FRS scores are likely related to the young age of the participants in this study, which could explain lower rates of most of the CVD risk factors like

hypertension, diabetes and obesity, all of which tend to increase with age (Jousilahti Pekka et al. 1999).One Italian study done among 595 men and 748 women showed that older age was associated with higher levels of interleukin-6 IL-1 receptor antagonist, C-reactive protein and fibrinogen, resulting in a pro-inflammatory state that increases the risk of CVD (Ferrucci et al. 2005)

This study found that the absolute estimated 10 year risk of developing CVD between patients and control was comparable and that the female patients had higher risk scores compared to controls while there was no difference between male patients and controls. This in contrast with the findings that the Clinical Trials of Antipsychotic Treatment Effectiveness (CATIE) study that reported significantly higher FRS between patients and controls generally and that both male and female patients had higher scores than male and female controls (Goff et al. 2005).

In this study FRS scores were significantly associated with female Sex, smoking and MetS. These findings are comparable to the findings of a Chinese study that compared 83 patients with schizophrenia and 243 controls that reported that smoking and MetS were the leading contributors of increased CVD risk (Tay, Nurjono, and Lee 2013). Similarly a study done in Malaysia among 270 patients with Schizophrenia reported FRS scores among patients with MetS compared to those without MetS (Said et al. 2012).The FRS were also associated with age, in agreement with existing literature that indicate that the estimation of absolute CVD risk is highly dependent an age. As an example a study done among 179 patients with psychosis in San Diego revealed that the FRS was increased by 50% due to age (H. Jin et al. 2011). These findings indicate a need to reconsider the best way to evaluate CVD risk in a setting with young participants.

5.6 **The treatment gap for metabolic disorders**

In this study sample, most of patients with hypertension as well as diabetes were not previously diagnosed hence were not on medication. Further, no documentation of prevention or treatment for dyslipidaemia was found on review of patients' files who had evidence of dyslipidaemia and obesity, suggesting a potential gap in the identification and management of CVD risk factors in the study setting.

This finding supports the fact that the rate of screening for CVD risk factors is wanting in many settings as reported by a study done in Durban South Africa among 331 patients who were treated with antipsychotics for SMI for at least 6 months which reported very low rates of screening for components of MetS; 0.6% for abdominal obesity,, 3.9% for hyperglycaemia and 1.8% for dyslipidaemia (Saloojee, Burns, and Motala 2014). Similar findings have been reported in developed countries such as the US, in which diabetes care and hypertension control was found to be 14-49% lower among patients with mental illness compared to unaffected controls (J. Liu et al. 2017). One review also reported that mentally ill persons are 30% less likely to be investigated or to receive care for CVD risk factors, both before and after initiation of antipsychotics (D. Scott, Platania-Phung, and Happell 2012). An observational study done among 76,799 patients with DM and mental illness and 236,827 patients with DM but no mental illness reported lower DM care among patients with mental illness compared to those without mental illness(Frayne et al. 2005). Like in our study low treatment with statins among patients has also been documented. For example, a study done among 40,992 patients with psychosis in Maryland reported that about half of patients with lipid derangements did not receive treatment with statins (Kreyenbuhl et al. 2008). A number of other studies have documented sub-optimal care for cardiovascular risk factors among patients with mental illness - this could be due to individual factors such as stigma; de-prioritisation of psychiatric (versus biomedical) symptoms; or patients' inability to describe their symptoms due to their mental illness (Marc De Hert et al. 2011). Systemic challenges such as lack of capacity (in terms of knowledge and infrastructure) for monitoring the physical illness; and limited time and human resources may also contribute to the treatment gap for CVD risk factors (M. De Hert et al. 2009). This may ultimately result in increased costs related to treating complications (McIntyre et al. 2006).

5.7: Relevance of the Study to Clinical Practice and Recommendations.

This study established that patients with psychosis have high prevalence of CVD risk factors and that there are gaps in interventions to address these risk factors in the context of MTRH, Eldoret. This is in agreement with the findings of the Lancet commission for protecting physical health in people with mental illness, which in summary, reported a 1.4 to 2 increased risk of obesity, and CVD as well as an increased risk of lifestyle factors such as smoking, sedentary behaviour and alcohol use among patients with mental illness, and also observed that that people with mental illness are likely to receive lower quality of care compared to the general population , and gave several suggestions for addressing these risk factors using a multidisciplinary approach (Firth et al. 2019).

To address the burden of specific CVD risk factors in the setting of Eldoret there is a need to consider implementing a number of suggested solutions put forward in the Lancet commission as well as in earlier literature (Samele 2004).

Inclusion of simple strategies that are achievable even in resource limited setting is a potentially good place to start , for example; active assessment of physical health symptoms and CVD risk factor symptoms by use of checklists for physical health as well as routine systematic questioning (Phelan M et al. 2004). **Table 24** summarises possible solutions to improve cardiovascular health among patients with psychosis.

Table 24: Addressing the cardiovascular health of patients with psychosis

Cardiovascular risk factors	**Potential solution**
Biological, genetics Immune factors	Early screening and prevention
Lifestyle: Smoking, Poor diet, Exercise, harmful alcohol use	Individualised/ Flexible interventions Education, Nicotine replacement therapy Nutritional education Prescribe and monitor exercise programs Motivational interviews as part of care Addiction counselling
Medication induced CVD risk	Risk assessment early on before initiation of medication Routine screening, avoid polypharmacy, use drugs with low risk for metabolic derangement
System factors	Multidisciplinary approach Integrated care Capacity building among health care workers Allocate finances to allow investigations and management Use of technology Putting in place appropriate policies
Lack of Support systems Stigma	Family education and involvement Education to reduce stigma for mental illness.

There is also need to consider incorporating into routine care lifestyle modification activities with attention to diet and exercise – both of which promote the mental wellbeing and cardiovascular health of patients with psychosis (Bonfioli et al. 2012) This may include targeted behavioural weight loss (Daumit et al. 2013),(Bartels et al. 2015), in which physicians collaboratively identify physical activity goals for a specific client, reinforce efforts to reach the targets, and continuously address barriers to physical activity (Richardson et al. 2005). To demonstrate this, the Life Goal Corroborated Care Trial reported improved blood pressure and reduction in mental symptoms associated with semi-structured guidance on managing physical and mental health symptoms through healthy behaviour changes augmented by ongoing care (Kilbourne et al. 2017), (Kilbourne et al. 2013). Clinicians should routinely discuss and encourage healthy and culturally appropriate diets (such as fresh fruit and vegetables and meals made at home) and discourage unhealthy foods (such as fast foods and hotel foods) (Pérez-Martínez et al. 2017). Early involvement of nutritionists for individual and group support (where possible) is also key in promoting healthy diets (Teasdale et al. 2017). Strategies should be employed to mitigate potential poor adherence to these lifestyle changes such as psychoeducation group sessions and use of incentives (Andrade 2016) , as the lifestyle changes need to be sustained over long periods in order translate into long-term reduction in CVD risk (Patnode et al. 2017).

Prevention or cessation of alcohol consumption and cigarette smoking should also be incorporated into the care of patients with psychosis (Compton, Daumit, and Druss 2006). Although smoking cessation is an effective and cost-effective way to improve cardiovascular health (H. Lee and Son 2019), cessation therapies are not widely implemented partly due to the perception that smoking is a “lifestyle choice”, or relapse is common (Erhardt 2009). Medication to assist smoking cessation, such as bupropion, varenicline and nicotine replacement therapies - as well as group and individual psychotherapies - should also be routinely incorporated into care where feasible (Tsoi, Porwal, and Webster 2013).

Antipsychotic treatment should also be optimised, by encouraging monotherapy, use of minimum effective doses and attention to increased risk. For vulnerable groups e.g. children, the elderly and patients with a genetic predisposition to metabolic disorders, medication with lower risk of metabolic side

effects should be considered e.g. first-generation antipsychotics are often cost effective, as effective as second generation antipsychotics , but with a lower risk of metabolic adverse effects (Naber and Lambert 2009), (Linmarie Sikich et al. 2008). Metformin may also be prescribed in cases of refractory metabolic symptoms as this agent has demonstrated efficacy (Praharaj et al. 2011), (Zheng et al. 2015), and is available and affordable in most settings (Siskind et al. 2016).

Mechanisms of early identification of high-risk patients, as well as routine monitoring of the metabolic effects of medication, should be implemented (Marc De Hert et al. 2009). When initiating antipsychotic treatment, baseline weight, blood pressure, and fasting triglycerides should be measured; and an electrocardiogram done due to the risk of arrhythmias in patients with existing heart disease (Warnier et al. 2015), (Rabkin 2015). Patients should also be assessed for a family history of type 2 DM, hypertension and obesity, in order to avoid medications that increase risk of these disorders. Weight and BMI should then be monitored at each follow-up visit; and fasting blood glucose and lipid profile should be checked at week 12 after treatment initiation, and annually thereafter (Jesus, Jesus, and Agius 2015) .

Integration of care for CVD and psychosis, employing a multidisciplinary team approach, is a potential mechanism for addressing current treatment gaps globally (T. J. R. Lambert and Newcomer 2009), (Vreeland 2007). Capacity building and skills development are also key, in order to ensure that health professionals treating patients with mental illness are equipped to screen for CVD risk factors, and to initiate care or refer adequately. Continuous evaluation of care (e.g. via audit-based, quality improvement programmes and customised feedback to participating mental health services) could also complement the strategies highlighted above (T R E Barnes et al. 2015). A holistic approach that gives weight to both physical and mental wellbeing is key in optimising outcomes (Seeman 2016).

Finally, education and involvement of patients and their families are integral to optimising adherence to the prescribed health promotion activities (Khasawneh and Shankar 2014). Provision of adequate motivation will also be vital in ensuring that patients remain committed to prescribed interventions (Mamakou et al. 2018).

5.8: Strength and limitations of the study, and suggestions for future research.

A number of methodological limitations should be borne in mind when interpreting these study findings. First, an observational study design was undertaken. As a result, potential causal relationships between psychosis and CVD risk could not be ascertained. In future, longitudinal studies of patients with newly-diagnosed psychosis would enable more reliable estimates of the incidence of cardiovascular risk factors in this patient group, as well as enabling tests of causality.

Second, convenience sampling was employed mainly and this could have resulted in selection bias as those who were available to participate may have had a different risk profile from those who were not available.

Third, most data collected were self-reported (e.g. chronic medical conditions, tobacco use, alcohol consumption, exercise and diet). This is likely to have introduced a reporting bias. Future studies utilizing objective measures such as laboratory testing for chronic disorders and pedometers for exercise could mitigate the latter bias.

Fourth, random blood glucose measurement was used to establish the presence of DM. While this was undertaken in order to overcome the challenge of ascertaining a fasted state among the patients, it is possible that some participants were actually in a fasted state hence excluded from the random sugar cut off of DM , hence giving a lower prevalence. In future, glycated haemoglobin (HbA1c) measurement could be undertaken to get more accurate assessments of the prevalence of DM in the study setting.

Fifth, most patients in our study sample were being treated with olanzapine. Thus, we were unable to compare the impact of different antipsychotics on cardiovascular risk profile in the study setting. Future studies stratifying patients according to antipsychotic medication would allow for comparison.

Sixth, the use of records to establish treatment for dyslipidaemia (as was the case in our study) is inherently limited by the documentation itself. Thus, it may be that our study findings were reflective of

incomplete records, rather than a true treatment gap. In future, qualitative patient discussions centred on interventions implemented could be undertaken to complement hospital records.

Seventh, the use of absolute scores to describe CVD risk has its limitations. For example FRS our patient group is quite low and can give a false impression of CVD risk of the setting, yet it may only be explained by the young age of the participants. In addition Framingham risk scores represent average values without considering individual variability in risk. Further, several other factors not included in the Framingham scores potentially modify absolute risk for individual for example the social economic status. Future studies could assess the FRS among older participants in the same setting and also compare different risk score estimating formulae.

Eighth, there are variations in recommended cut off for various metabolic parameters like DM and hypertension and this has potential to give varying prevalence of metabolic disorders in different studies.

These limitations notwithstanding, the current study provides novel and clinically relevant preliminary data of cardiovascular risk profile among patients with psychosis in Eldoret, Kenya. One of the strengths of this study is the assessment of several cardiovascular risk indicators, given that most studies focus one or two CVD risk factors. The second novel thing is the inclusion of nonconventional CVD risk factors in assessing the cardiovascular risk profile. Work such as this may ultimately provide insight into the cardiovascular risk profile of patients in LMIC settings, thus contributing to an important research gap in this context.

5.9: Conclusion

In the LMIC setting of Eldoret, patients with psychosis exhibited a high burden of a number of key CVD risk factors. Of note the prevalence of MetS, smoking and obesity were found to be significantly more prevalent than in the general population. In this setting smoking and MetS, as well as age and female Sex contributed significantly to increased Framingham risk scores. It is worth noting that in this study smoking was the only CVD risk factor that was associated with exposure to potentially traumatic experiences. However our study did not establish a relationship between psychological distress, comorbid medical conditions or use of olanzapine with CVD risk factors. A number of gaps in current practice – both in terms of undiagnosed and of untreated metabolic disorders – were also identified. In future, routine screening for various CVD risk factors could improve early identification of high risk patients. Thereafter, coordinated and integrated interventions, drawing on multidisciplinary approaches and guided by contextually appropriate standardized guidelines, could be effective in improving patient outcome and overall quality of life of patients with psychosis.

REFERENCES

Abosi, Oluchi, Sneha Lopes, Samantha Schmitz, and Jess G. Fiedorowicz. 2018. "Cardiometabolic Effects of Psychotropic Medications." *Hormone Molecular Biology and Clinical Investigation* 36 (1). https://doi.org/10.1515/hmbci-2017-0065.

Abou Kassm, Sandra, Nicolas Hoertel, Wadih Naja, Kibby McMahon, Sarah Barrière, Yvonne Blumenstock, Christophe Portefaix, et al. 2019. "Metabolic Syndrome among Older Adults with Schizophrenia Spectrum Disorder: Prevalence and Associated Factors in a Multicenter Study." *Psychiatry Research* 275 (May): 238–46. https://doi.org/10.1016/j.psychres.2019.03.036.

"About the WHO WMH-CIDI – WHO WMH-CIDI." n.d. Accessed December 11, 2019. https://www.hcp.med.harvard.edu/wmhcidi/about-the-who-wmh-cidi/.

Addington, Jean, Nevicia Case, Majid M. Saleem, Andrea M. Auther, Barbara A. Cornblatt, and Kristin S. Cadenhead. 2014. "Substance Use in Clinical High Risk for Psychosis: A Review of the Literature." *Early Intervention in Psychiatry* 8 (2): 104–12. https://doi.org/10.1111/eip.12100.

Agaba, David Collins, Richard Migisha, Rosemary Namayanja, Godfrey Katamba, Henry Mark Lugobe, Hillary Aheisibwe, Godfrey Twesigomwe, and Scholastic Ashaba. 2019. "Prevalence and Associated Factors of Metabolic Syndrome among Patients with Severe Mental Illness Attending a Tertiary Hospital in Southwest Uganda." Research Article. BioMed Research International. 2019. https://doi.org/10.1155/2019/1096201.

Agerbo, Esben, Majella Byrne, William W. Eaton, and Preben B. Mortensen. 2004. "Marital and Labor Market Status in the Long Run in Schizophrenia." *Archives of General Psychiatry* 61 (1): 28–33. https://doi.org/10.1001/archpsyc.61.1.28.

Aguocha, C. M., J. K. Aguocha, M. Igwe, R. U. Uwakwe, and G. M. Onyeama. 2015. "Prevalence and Correlates of Cigarette Smoking among Patients with Schizophrenia in Southeast Nigeria." *Acta Psychiatrica Scandinavica* 131 (3): 206–12. https://doi.org/10.1111/acps.12334.

Akker, Marjan van den, Frank Buntinx, Job F. M. Metsemakers, Sjef Roos, and J. André Knottnerus. 1998. "Multimorbidity in General Practice: Prevalence, Incidence, and Determinants of Co-Occurring Chronic and Recurrent Diseases." *Journal of Clinical Epidemiology* 51 (5): 367–75. https://doi.org/10.1016/S0895-4356(97)00306-5.

Alebel, Animut, Amsalu Taye Wondemagegn, Cheru Tesema, Getiye Dejenu Kibret, Fasil Wagnew, Pammla Petrucka, Amit Arora, Amare Demsie Ayele, Mulunesh Alemayehu, and Setegn Eshetie. 2019. "Prevalence of Diabetes Mellitus among Tuberculosis Patients in Sub-Saharan Africa: A Systematic Review and Meta-Analysis of Observational Studies." *BMC Infectious Diseases* 19 (March). https://doi.org/10.1186/s12879-019-3892-8.

Alene, Kefyalew Addis, Archie C A Clements, Emma S McBryde, Ernesto Jaramillo, Knut Lönnroth, Debebe Shaweno, Amelia Gulliver, and Kerri Viney. 2018. "Mental Health Disorders, Social Stressors, and Health-Related Quality of Life in Patients with Multidrug-Resistant Tuberculosis: A Systematic Review and Meta-Analysis." *Journal of Infection* 77 (5): 357–67. https://doi.org/10.1016/j.jinf.2018.07.007.

Alison J Price, Debbie A Lawlor, Elenaus Mwaiyeghele, Lawrence Nkhwazi, Liam Smeeth, Neil Pearce, Elizabeth Munthali, Beatrice M Mwagomba, Charles Mwansambo, Judith R Glynn, Shabbar Jaffar, Moffat Nyirenda, and Alison J Price*, Amelia C Crampin*, Alemayehu Amberbir, Ndoliwe Kayuni-Chihana, Crispin Musicha, Terence Tafatatha, Keith Branson,Debbie A Lawlor, Elenaus Mwaiyeghele, Lawrence Nkhwazi, Liam Smeeth, Neil Pearce, Elizabeth Munthali, Beatrice M Mwagomba,Charles Mwansambo, Judith R Glynn, Shabbar Jaffar, Moffat Nyirenda. 2018. "Prevalence of Obesity, Hypertension, and Diabetes, and Cascade of Care in Sub-Saharan Africa: A Cross-Sectional, Population-Based Study in Rural and Urban Malawi- ClinicalKey." *Lancet Diabetis Endocrinolology* 6: 288–222.

Alosaimi, Fahad D., Mohammed Abalhassan, Bandar Alhaddad, Nasser Alzain, Ebtihaj Fallata, Abdulhadi Alhabbad, and Mohammed Z. Alassiry. 2017. "Prevalence of Metabolic Syndrome and Its Components among Patients with Various Psychiatric Diagnoses and Treatments: A Cross-Sectional Study." *General Hospital Psychiatry* 45 (March): 62–69. https://doi.org/10.1016/j.genhosppsych.2016.12.007.

Alves, Alberto J, João L Viana, Suiane L Cavalcante, Nórton L Oliveira, José A Duarte, Jorge Mota, José Oliveira, and Fernando Ribeiro. 2016. "Physical Activity in Primary and Secondary Prevention of Cardiovascular Disease: Overview Updated." *World Journal of Cardiology* 8 (10): 575–83. https://doi.org/10.4330/wjc.v8.i10.575.

Alves, Beatriz Beretta, Giovana de Padua Oliveira, Milton Gabriel Moreira Neto, Roberta Bonamim Fiorilli, and Elizabeth do Espírito Santo Cestário. 2019. "Use of Atypical Antipsychotics and Risk of Hypertension: A Case Report and Review Literature." *SAGE Open Medical Case Reports* 7 (January): 2050313X1984182. https://doi.org/10.1177/2050313X19841825.

Ambaw, Fentie, Rosie Mayston, Charlotte Hanlon, and Atalay Alem. 2017. “Burden and Presentation of Depression among Newly Diagnosed Individuals with TB in Primary Care Settings in Ethiopia.” *BMC Psychiatry* 17 (1): 57. https://doi.org/10.1186/s12888-017-1231-4.

Andrade, Chittaranjan. 2016. “Cardiometabolic Risks in Schizophrenia and Directions for Intervention, 2: Nonpharmacological Interventions.” *The Journal of Clinical Psychiatry* 77 (8): 964–67. https://doi.org/10.4088/JCP.16f11060.

Annamalai, Aniyizhai, Urska Kosir, and Cenk Tek. 2017. “Prevalence of Obesity and Diabetes in Patients with Schizophrenia.” *World Journal of Diabetes* 8 (8): 390–96. https://doi.org/10.4239/wjd.v8.i8.390.

Arseneault, Louise, Mary Cannon, Helen L. Fisher, Guilherme Polanczyk, Terrie E. Moffitt, and Avshalom Caspi. 2011. “Childhood Trauma and Children’s Emerging Psychotic Symptoms: A Genetically Sensitive Longitudinal Cohort Study.” *American Journal of Psychiatry* 168 (1): 65–72. https://doi.org/10.1176/appi.ajp.2010.10040567.

Asaye, Sintayehu, Shiferaw Bekele, Daniel Tolessa, and Waqtola Cheneke. 2018. “Metabolic Syndrome and Associated Factors among Psychiatric Patients in Jimma University Specialized Hospital, South West Ethiopia.” *Diabetes & Metabolic Syndrome: Clinical Research & Reviews* 12 (5): 753–60. https://doi.org/10.1016/j.dsx.2018.04.037.

Asghar, Omar, Ahmed Al-Sunni, Kaivan Khavandi, Ali Khavandi, Sarah Withers, Adam Greenstein, Anthony M. Heagerty, and Rayaz A. Malik. 2009a. “Diabetic Cardiomyopathy.” *Clinical Science (London, England : 1979)* 116 (Pt 10): 741–60. https://doi.org/10.1042/CS20080500.

———. 2009b. “Diabetic Cardiomyopathy.” *Clinical Science (London, England : 1979)* 116 (Pt 10): 741–60. https://doi.org/10.1042/CS20080500.

Asiki, Gershim, Shukri F. Mohamed, David Wambui, Caroline Wainana, Stella Muthuri, and Michelle Ramsay. 2018. “Sociodemographic and Behavioural Factors Associated with Body Mass Index among Men and Women in Nairobi Slums: AWI-Gen Project.” *Global Health Action* 11 (Suppl 2). https://doi.org/10.1080/16549716.2018.1470738.

Association, American Diabetes. 2004. “Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes.” *Diabetes Care* 27 (2): 596–601. https://doi.org/10.2337/diacare.27.2.596.

Attux, Cecília, Maria Inês Quintana, and Ana Cristina Chaves. 2007. “Weight Gain, Dyslipidemia and Altered Parameters for Metabolic Syndrome on First Episode Psychotic Patients after Six-Month Follow-Up.” *Brazilian Journal of Psychiatry* 29 (4): 346–49. https://doi.org/10.1590/S1516-44462006005000061.

Atwoli, Lukoye, Jonathan M. Platt, Archana Basu, David R. Williams, Dan J. Stein, and Karestan C. Koenen. 2016. “Associations between Lifetime Potentially Traumatic Events and Chronic Physical Conditions in the South African Stress and Health Survey: A Cross-Sectional Study.” *BMC Psychiatry* 16 (July): 214. https://doi.org/10.1186/s12888-016-0929-z.

Aune, Dagfinn, Edward Giovannucci, Paolo Boffetta, Lars T. Fadnes, NaNa Keum, Teresa Norat, Darren C. Greenwood, Elio Riboli, Lars J. Vatten, and Serena Tonstad. 2017. “Fruit and Vegetable Intake and the Risk of Cardiovascular Disease, Total Cancer and All-Cause Mortality—a Systematic Review and Dose-Response Meta-Analysis of Prospective Studies.” *International Journal of Epidemiology* 46 (3): 1029–56. https://doi.org/10.1093/ije/dyw319.

Ayerbe, Luis, Ivo Forgnone, Juliet Addo, Ana Siguero, Stefano Gelati, and Salma Ayis. 2018. “Hypertension Risk and Clinical Care in Patients with Bipolar Disorder or Schizophrenia; a Systematic Review and Meta-Analysis.” *Journal of Affective Disorders* 225 (January): 665–70. https://doi.org/10.1016/j.jad.2017.09.002.

Badimon, L., Robert F. Storey, and Gemma Vilahur. 2011. “Update on Lipids, Inflammation and Atherothrombosis.” *Thrombosis and Hemostasis* 105 (suppl 1): s34–42. https://doi.org/doi:10.1160/THS10-11-0717.

Bager Tabei, Seyeed Mohammad, Sara Senemar, Babak Saffari, Zeinab Ahmadi, and Somayeh Haqparast. 2014. “Non-Modifiable Factors of Coronary Artery Stenosis in Late Onset Patients with Coronary Artery Disease in Southern Iranian Population.” *Journal of Cardiovascular and Thoracic Research; ISSN 2008-6830*. https://doi.org/10.5681/jcvtr.2014.010.

Bai, Ya-Mei, Tung-Ping Su, Mu-Hong Chen, Tzeng-Ji Chen, and Wen-Han Chang. 2013. “Risk of Developing Diabetes Mellitus and Hyperlipidemia among Patients with Bipolar Disorder, Major Depressive Disorder, and Schizophrenia: A 10-Year Nationwide Population-Based Prospective Cohort Study.” *Journal of Affective Disorders* 150 (1): 57–62. https://doi.org/10.1016/j.jad.2013.02.019.

Baker, Sarah E., Jacqueline K. Limberg, Sushant M. Ranadive, and Michael J. Joyner. 2016. “Neurovascular Control of Blood Pressure Is Influenced by Aging, Sex, and Sex Hormones.” *American Journal of Physiology - Regulatory, Integrative and Comparative Physiology* 311 (6): R1271–75. https://doi.org/10.1152/ajpregu.00288.2016.

Balakumar, Pitchai, and Jagdeep Kaur. 2009. “Is Nicotine a Key Player or Spectator in the Induction and Progression of Cardiovascular Disorders?” *Pharmacological Research* 60 (5): 361–68. https://doi.org/10.1016/j.phrs.2009.06.005.

Balhara, Yatan Pal Singh. 2011. “Diabetes and Psychiatric Disorders.” *Indian Journal of Endocrinology and Metabolism* 15 (4): 274. https://doi.org/10.4103/2230-8210.85579.

Ballon, Jacob S., Utpal Pajvani, Zachary Freyberg, Rudolph L. Leibel, and Jeffrey A. Lieberman. 2014. “Molecular Pathophysiology of Metabolic Effects of Antipsychotic Medications.” *Trends in Endocrinology & Metabolism* 25 (11): 593–600. https://doi.org/10.1016/j.tem.2014.07.004.

Barbagallo, Mario, Raj K. Gupta, Ligia J. Dominguez, and Lawrence M. Resnick. 2000. “Cellular Ionic Alterations with Age: Relation to Hypertension and Diabetes.” *Journal of the American Geriatrics Society* 48 (9): 1111–16. https://doi.org/10.1111/j.1532-5415.2000.tb04788.x.

Barnes, Ann Smith. 2013. “Emerging Modifiable Risk Factors for Cardiovascular Disease in Women.” *Texas Heart Institute Journal* 40 (3): 293–95.

Barnes, T R E, S F Bhatti, R Adroer, and C Paton. 2015. “Screening for the Metabolic Side Effects of Antipsychotic Medication: Findings of a 6-Year Quality Improvement Programme in the UK.” *BMJ Open* 5 (10). https://doi.org/10.1136/bmjopen-2015-007633.

Barnes, Thomas R. E., Carol Paton, Mary-Rose Cavanagh, Elizabeth Hancock, and David M. Taylor. 2007. “A UK Audit of Screening for the Metabolic Side Effects of Antipsychotics in Community Patients.” *Schizophrenia Bulletin* 33 (6): 1397–1403. https://doi.org/10.1093/schbul/sbm038.

Bartels, Stephen J., Sarah I. Pratt, Kelly A. Aschbrenner, Laura K. Barre, John A. Naslund, Rosemarie Wolfe, Haiyi Xie, et al. 2015. “Pragmatic Replication Trial of Health Promotion Coaching for Obesity in Serious Mental Illness and Maintenance of Outcomes.” *The American Journal of Psychiatry* 172 (4): 344–52. https://doi.org/10.1176/appi.ajp.2014.14030357.

Batic-Mujanovic, Olivera, Samir Poric, Nurka Pranjic, Enisa Ramic, Esad Alibasic, and Enisa Karic. 2017. “Influence of Unemployment on Mental Health of the Working Age Population.” *Materia Socio-Medica* 29 (2): 92–96. https://doi.org/10.5455/msm.2017.29.92-96.

Bazzano, Lydia A., Jiang He, Lorraine G. Ogden, Catherine M. Loria, Suma Vupputuri, Leann Myers, and Paul K. Whelton. 2002. “Fruit and Vegetable Intake and Risk of Cardiovascular Disease in US Adults: The First National Health and Nutrition Examination Survey Epidemiologic Follow-up Study.” *The American Journal of Clinical Nutrition* 76 (1): 93–99. https://doi.org/10.1093/ajcn/76.1.93.

Bazzano, Lydia A., Mary K. Serdula, and Simin Liu. 2003. “Dietary Intake of Fruits and Vegetables and Risk of Cardiovascular Disease.” *Current Atherosclerosis Reports* 5 (6): 492–99. https://doi.org/10.1007/s11883-003-0040-z.

Beigh, Seerat Hussain, and Saroj Jain. 2012. “Prevalence of Metabolic Syndrome and Sex Differences.” *Bioinformation* 8 (13): 613–16. https://doi.org/10.6026/97320630008613.

Beilby, John. 2004a. “Definition of Metabolic Syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association Conference on Scientific Issues Related to Definition.” *The Clinical Biochemist Reviews* 25 (3): 195–98.

———. 2004b. “Definition of Metabolic Syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association Conference on Scientific Issues Related to Definition.” *The Clinical Biochemist Reviews* 25 (3): 195–98.

Bell, Luis, Vishnu Bhat, Grace George, Abolade Ajani Awotedu, and Bomkazi Gqaza. 2007. “Sluggish Glucose Tolerance in Tuberculosis Patients.” *South African Medical Journal = Suid-Afrikaanse Tydskrif Vir Geneeskunde* 97 (5): 374–77.

Bell, Steven, Marina Daskalopoulou, Eleni Rapsomaniki, Julie George, Annie Britton, Martin Bobak, Juan P Casas, et al. 2017. “Association between Clinically Recorded Alcohol Consumption and Initial Presentation of 12 Cardiovascular Diseases: Population Based Cohort Study Using Linked Health Records.” *The BMJ* 356 (August). https://doi.org/10.1136/bmj.j909.

Bendall, Sarah, Henry J. Jackson, Carol A. Hulbert, and Patrick D. McGorry. 2008. “Childhood Trauma and Psychotic Disorders: A Systematic, Critical Review of the Evidence.” *Schizophrenia Bulletin* 34 (3): 568–79. https://doi.org/10.1093/schbul/sbm121.

Bennouna-Greene, Mehdi, Valerie Bennouna-Greene, Fabrice Berna, and Luc Defranoux. 2011. “History of Abuse and Neglect in Patients with Schizophrenia Who Have a History of Violence.” *Child Abuse & Neglect* 35 (5): 329–32. https://doi.org/10.1016/j.chiabu.2011.01.008.

Benowitz, Neal L., and Andrea D. Burbank. 2016. “Cardiovascular Toxicity of Nicotine: Implications for Electronic Cigarette Use.” *Trends in Cardiovascular Medicine* 26 (6): 515–23. https://doi.org/10.1016/j.tcm.2016.03.001.

Benseñor, Isabela M., André R. Brunoni, Luis Augusto Pilan, Alessandra C. Goulart, Geraldo F. Busatto, Paulo A. Lotufo, Márcia Scazufca, and Paulo R. Menezes. 2012. “Cardiovascular Risk Factors in Patients with First-Episode Psychosis in São Paulo, Brazil.” *General Hospital Psychiatry* 34 (3): 268–75. https://doi.org/10.1016/j.genhosppsych.2011.12.010.

Berk, Bradford C, Keigi Fujiwara, and Stephanie Lehoux. 2007. “ECM Remodeling in Hypertensive Heart Disease.” *The Journal Of Clinical Investigation* 117 (3): 568–75.

Bernstein, David P., Judith A. Stein, Michael D. Newcomb, Edward Walker, David Pogge, Taruna Ahluvalia, John Stokes, et al. 2003. “Development and Validation of a Brief Screening Version of the Childhood Trauma Questionnaire.” *Child Abuse & Neglect* 27 (2): 169–90. https://doi.org/10.1016/s0145-2134(02)00541-0.

Bertoni, Alain G., Jr David C. Goff, Ralph B. D&amp, apos, Jr Agostino, Kiang Liu, W. Gregory Hundley, et al. 2006. “Diabetic Cardiomyopathy and Subclinical Cardiovascular Disease: The Multi-Ethnic Study of Atherosclerosis (MESA).” *Diabetes Care*, March. https://link.galegroup.com/apps/doc/A143240976/AONE?sid=lms.

Birkenaes, Astrid B., Kåre I. Birkeland, John A. Engh, Ann Færden, Halldora Jonsdottir, Petter Andreas Ringen, Svein Friis, Stein Opjordsmoen, and Ole A. Andreassen. 2008. “Dyslipidemia Independent of Body Mass in Antipsychotic-Treated Patients Under Real-Life Conditions:” *Journal of Clinical Psychopharmacology* 28 (2): 132–37. https://doi.org/10.1097/JCP.0b013e318166c4f7.

Black, Paul H. 2006. “The Inflammatory Consequences of Psychologic Stress: Relationship to Insulin Resistance, Obesity, Atherosclerosis and Diabetes Mellitus, Type II.” *Medical Hypotheses* 67 (4): 879–91. https://doi.org/10.1016/j.mehy.2006.04.008.

Black, Paul H., and Lisa D. Garbutt. 2002. “Stress, Inflammation and Cardiovascular Disease.” *Journal of Psychosomatic Research* 52 (1): 1–23.

Bobes, Julio, Celso Arango, Pedro Aranda, Rafael Carmena, Margarida Garcia-Garcia, and Javier Rejas. 2007. “Cardiovascular and Metabolic Risk in Outpatients with Schizophrenia Treated with Antipsychotics: Results of the CLAMORS Study.” *Schizophrenia Research* 90 (1): 162–73. https://doi.org/10.1016/j.schres.2006.09.025.

Bonfioli, Elena, Loretta Berti, Claudia Goss, Francesca Muraro, and Lorenzo Burti. 2012. “Health Promotion Lifestyle Interventions for Weight Management in Psychosis: A Systematic Review and Meta-Analysis of Randomised Controlled Trials.” *BMC Psychiatry* 12 (1): 78. https://doi.org/10.1186/1471-244X-12-78.

Boniface, Sadie, James Kneale, and Nicola Shelton. 2014. “Drinking Pattern Is More Strongly Associated with Under-Reporting of Alcohol Consumption than Socio-Demographic Factors: Evidence from a Mixed-Methods Study.” *BMC Public Health* 14 (December). https://doi.org/10.1186/1471-2458-14-1297.

Boon, Saskia den, Suzanne Verver, Ben J. Marais, Donald A. Enarson, Carl J. Lombard, Eric D. Bateman, Elvis Irusen, et al. 2007. “Association Between Passive Smoking and Infection With Mycobacterium Tuberculosis in Children.” *Pediatrics* 119 (4): 734–39. https://doi.org/10.1542/peds.2006-1796.

Booth, Frank W., Christian K. Roberts, and Matthew J. Laye. 2012. “Lack of Exercise Is a Major Cause of Chronic Diseases.” *Comprehensive Physiology* 2 (2): 1143. https://doi.org/10.1002/cphy.c110025.

Booth, Gillian L, Moira K Kapral, Kinwah Fung, and Jack V Tu. 2006. “Relation between Age and Cardiovascular Disease in Men and Women with Diabetes Compared with Non-Diabetic People: A Population-Based Retrospective Cohort Study.” *The Lancet* 368 (9529): 29–36. https://doi.org/10.1016/S0140-6736(06)68967-8.

Bose, Mousumi, Blanca Oliván, and Blandine Laferrère. 2009. “Stress and Obesity: The Role of the Hypothalamic–Pituitary–Adrenal Axis in Metabolic Disease.” *Current Opinion in Endocrinology, Diabetes, and Obesity* 16 (5): 340–46. https://doi.org/10.1097/MED.0b013e32832fa137.

Bosomworth, N. John. 2011. “Practical Use of the Framingham Risk Score in Primary Prevention.” *Canadian Family Physician* 57 (4): 417–23.

Bots, Sophie H., Sanne A. E. Peters, and Mark Woodward. 2017. “Sex Differences in Coronary Heart Disease and Stroke Mortality: A Global Assessment of the Effect of Ageing between 1980 and 2010.” *BMJ Global Health* 2 (2). https://doi.org/10.1136/bmjgh-2017-000298.

Bradley, Katharine A., Anna F. DeBenedetti, Robert J. Volk, Emily C. Williams, Danielle Frank, and Daniel R. Kivlahan. 2007a. “AUDIT-C as a Brief Screen for Alcohol Misuse in Primary Care.” *Alcoholism: Clinical and Experimental Research* 31 (7): 1208–17. https://doi.org/10.1111/j.1530-0277.2007.00403.x.

———. 2007b. “AUDIT-C as a Brief Screen for Alcohol Misuse in Primary Care.” *Alcoholism, Clinical and Experimental Research* 31 (7): 1208–17. https://doi.org/10.1111/j.1530-0277.2007.00403.x.

Bradshaw, Tim, and Hilary Mairs. 2014. “Obesity and Serious Mental Ill Health: A Critical Review of the Literature.” *Healthcare* 2 (2): 166–82. https://doi.org/10.3390/healthcare2020166.

Bresee, Lauren C., Sumit R. Majumdar, Scott B. Patten, and Jeffrey A. Johnson. 2010. “Prevalence of Cardiovascular Risk Factors and Disease in People with Schizophrenia: A Population-Based Study.” *Schizophrenia Research* 117 (1): 75–82. https://doi.org/10.1016/j.schres.2009.12.016.

Bressington, Daniel, Jolene Mui, Mei Ling Tse, Richard Gray, Eric F. C. Cheung, and Wai Tong Chien. 2016. "Cardiometabolic Health, Prescribed Antipsychotics and Health-Related Quality of Life in People with Schizophrenia-Spectrum Disorders: A Cross-Sectional Study." *BMC Psychiatry* 16 (1): 411. https://doi.org/10.1186/s12888-016-1121-1.

Bretler, Tali, Hagar Weisberg, Omry Koren, and Hadar Neuman. 2019. "The Effects of Antipsychotic Medications on Microbiome and Weight Gain in Children and Adolescents." *BMC Medicine* 17 (1): 112. https://doi.org/10.1186/s12916-019-1346-1.

Brook, Robert D., and Stevo Julius. 2000. "Autonomic Imbalance, Hypertension, and Cardiovascular Risk." *American Journal of Hypertension* 13 (S4): 112S-122S. https://doi.org/10.1016/S0895-7061(00)00228-4.

Brosschot, Jos F., Bart Verkuil, and Julian F. Thayer. 2017. "Exposed to Events That Never Happen: Generalized Unsafety, the Default Stress Response, and Prolonged Autonomic Activity." *Neuroscience & Biobehavioral Reviews*, Stress, Behavior and the Heart, 74 (March): 287–96. https://doi.org/10.1016/j.neubiorev.2016.07.019.

Brunner, E., M. J. Shipley, D. Blane, G. D. Smith, and M. G. Marmot. 1999. "When Does Cardiovascular Risk Start? Past and Present Socioeconomic Circumstances and Risk Factors in Adulthood." *Journal of Epidemiology & Community Health* 53 (12): 757–64. https://doi.org/10.1136/jech.53.12.757.

Brunner, Eric John. 2017. "Social Factors and Cardiovascular Morbidity." *Neuroscience & Biobehavioral Reviews*, Stress, Behavior and the Heart, 74 (March): 260–68. https://doi.org/10.1016/j.neubiorev.2016.05.004.

Burns, Jonathan Kenneth, Khatija Jhazbhay, Tonya Esterhuizen, and Robin Emsley. 2011. "Exposure to Trauma and the Clinical Presentation of First-Episode Psychosis in South Africa." *Journal of Psychiatric Research* 45 (2): 179–84. https://doi.org/10.1016/j.jpsychires.2010.05.014.

Burton, Robyn, and Nick Sheron. 2018. "No Level of Alcohol Consumption Improves Health." *The Lancet* 392 (10152): 987–88. https://doi.org/10.1016/S0140-6736(18)31571-X.

Bush, Kristen, Daniel R. Kivlahan, Mary B. McDonell, Stephan D. Fihn, and Katharine A. Bradley. 1998. "The AUDIT Alcohol Consumption Questions (AUDIT-C): An Effective Brief Screening Test for Problem Drinking." *Archives of Internal Medicine* 158 (16): 1789–95. https://doi.org/10.1001/archinte.158.16.1789.

c, A. C., J. Galea, S. S. Shin, C. Driver, R. A. Dlodlo, A. Karpati, and M. L. Wainberg. 2019. "Integrating Tuberculosis and Mental Health Services: Global Receptivity of National Tuberculosis Program Directors." *The International Journal of Tuberculosis and Lung Disease : The Official Journal of the International Union against Tuberculosis and Lung Disease* 23 (5): 600–605. https://doi.org/10.5588/ijtld.18.0530.

Cahill, Paul A., and Eileen M. Redmond. 2012. "Alcohol and Cardiovascular Disease—Modulation of Vascular Cell Function." *Nutrients* 4 (4): 297–318. https://doi.org/10.3390/nu4040297.

Calhoun, Patrick S., Karen M. Stechuchak, Jennifer Strauss, Hayden B. Bosworth, Christine E. Marx, and Marian I. Butterfield. 2007. "Interpersonal Trauma, War Zone Exposure, and Posttraumatic Stress Disorder among Veterans with Schizophrenia." *Schizophrenia Research* 91 (1): 210–16. https://doi.org/10.1016/j.schres.2006.12.011.

Callander, Emily J., and Deborah J. Schofield. 2015. "Psychological Distress and the Increased Risk of Falling into Poverty: A Longitudinal Study of Australian Adults." *Social Psychiatry and Psychiatric Epidemiology* 50 (10): 1547–56. https://doi.org/10.1007/s00127-015-1074-6.

Cameron, Isobel M., Ross J. Hamilton, Gordon Fernie, and Stephen A. MacGillivray. 2017. "Obesity in Individuals with Schizophrenia: A Case Controlled Study in Scotland." *BJPsych Open* 3 (5): 254–56. https://doi.org/10.1192/bjpo.bp.116.003640.

Campo, Andrea del, Catalina Bustos, Carolina Mascayano, Claudio Acuña-Castillo, Rodrigo Troncoso, and Leonel E. Rojo. 2018. "Metabolic Syndrome and Antipsychotics: The Role of Mitochondrial Fission/Fusion Imbalance." *Frontiers in Endocrinology* 9. https://doi.org/10.3389/fendo.2018.00144.

Capes, Sarah E, Dereck Hunt, Klas Malmberg, and Hertzel C Gerstein. 2000. "Stress Hyperglycaemia and Increased Risk of Death after Myocardial Infarction in Patients with and without Diabetes: A Systematic Overview." *The Lancet* 355 (9206): 773–78. https://doi.org/10.1016/S0140-6736(99)08415-9.

Carbone, Salvatore, Justin M Canada, Hayley E Billingsley, Mohammad S Siddiqui, Andrew Elagizi, and Carl J Lavie. 2019. "Obesity Paradox in Cardiovascular Disease: Where Do We Stand?" *Vascular Health and Risk Management* Volume 15 (May): 89–100. https://doi.org/10.2147/VHRM.S168946.

Carnevale, Roberto, and Cristina Nocella. 2012. "Alcohol and Cardiovascular Disease: Still Unresolved Underlying Mechanisms." *Vascular Pharmacology* 57 (2–4): 69–71. https://doi.org/10.1016/j.vph.2012.06.005.

Carney, Caroline P, Laura Jones, and Robert F Woolson. 2006. "Medical Comorbidity in Women and Men with Schizophrenia." *Journal of General Internal Medicine* 21 (11): 1133–37. https://doi.org/10.1111/j.1525-1497.2006.00563.x.

Carney, Rebekah, Tim Bradshaw, and Alison R. Yung. 2015. “Monitoring of Physical Health in Services for Young People at Ultra-High Risk of Psychosis.” *Early Intervention in Psychiatry*, October. https://doi.org/10.1111/eip.12288.

Carter, Alice R., Dipender Gill, Neil M. Davies, Amy E. Taylor, Taavi Tillmann, Julien Vaucher, Robyn E. Wootton, et al. 2019. “Understanding the Consequences of Education Inequality on Cardiovascular Disease: Mendelian Randomisation Study.” *BMJ* 365 (May). https://doi.org/10.1136/bmj.l1855.

Catalyst, NEJM. 2017. “Social Determinants of Health (SDOH).” *NEJM Catalyst*, December. https://catalyst.nejm.org/doi/abs/10.1056/CAT.17.0312.

CDC. 2019. “Health Effects of Cigarette Smoking.” Centers for Disease Control and Prevention. March 4, 2019. https://www.cdc.gov/tobacco/data_statistics/fact_sheets/health_effects/effects_cig_smoking/index.htm.

Cerrato, Enrico, Andrea Calcagno, Fabrizio D’Ascenzo, Giuseppe Biondi-Zoccai, Massimo Mancone, Walter Grosso Marra, Daniela Demarie, et al. 2015. “Cardiovascular Disease in HIV Patients: From Bench to Bedside and Backwards.” *Open Heart* 2 (1): e000174. https://doi.org/10.1136/openhrt-2014-000174.

Chao Deng. 2010. “The Role of Histaminergic H1 and H3 Receptors in Food Intake: A Mechanism for Atypical Antipsychotic-Induced Weight Gain? - ScienceDirect.” 2010. https://www-sciencedirect-com.ezproxy.uct.ac.za/science/article/pii/S0278584609003959.

Chege, Pm. 2016. “Multiple Cardiovascular Disease Risk Factors in Rural Kenya: Evidence from a Health and Demographic Surveillance System Using the WHO STEP-Wise Approach to Chronic Disease Risk Factor Surveillance.” *South African Family Practice* 58 (2): 54–61. https://doi.org/10.1080/20786190.2015.1114703.

Chen, Jingchun, Silviu-Alin Bacanu, Hui Yu, Zhongming Zhao, Peilin Jia, Kenneth S. Kendler, Henry R. Kranzler, et al. 2016. “Genetic Relationship between Schizophrenia and Nicotine Dependence.” *Scientific Reports* 6 (May). https://doi.org/10.1038/srep25671.

Chen, Song, Dong Broqueres-You, Guigang Yang, Zhiren Wang, Yanli Li, Ning Wang, Xiangyang Zhang, Fude Yang, and Yunlong Tan. 2013. “Relationship between Insulin Resistance, Dyslipidaemia and Positive Symptom in Chinese Antipsychotic-Naive First-Episode Patients with Schizophrenia.” *Psychiatry Research* 210 (3): 825–29. https://doi.org/10.1016/j.psychres.2013.08.056.

Chichlowska, Kristal L., Kathryn M. Rose, Ana V. Diez-Roux, Sherita H. Golden, Annie M. McNeill, and Gerardo Heiss. 2009. “Life Course Socioeconomic Conditions and Metabolic Syndrome in Adults: The Atherosclerosis Risk in Communities (ARIC) Study.” *Annals of Epidemiology* 19 (12): 875–83. https://doi.org/10.1016/j.annepidem.2009.07.094.

Chi-FaHunga, Ching-Kuan, and WuabPao-Yen. 2005. “Diabetes Mellitus in Patients with Schizophrenia in Taiwan.” *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 29 (4): 523–27. https://doi.org/10.1016/j.pnpbp.2005.01.003.

Chintoh, Araba F., Steve W. Mann, Loretta Lam, Adria Giacca, Paul Fletcher, Jose Nobrega, and Gary Remington. 2009. “Insulin Resistance and Secretion in Vivo: Effects of Different Antipsychotics in an Animal Model.” *Schizophrenia Research* 108 (1): 127–33. https://doi.org/10.1016/j.schres.2008.12.012.

Cho, Kyoung Im, Bo Hyun Kim, Hyung Gon Je, Jae Sik Jang, and Yong Hyun Park. 2016. “Sex-Specific Associations between Socioeconomic Status and Psychological Factors and Metabolic Syndrome in the Korean Population: Findings from the 2013 Korean National Health and Nutrition Examination Survey.” *BioMed Research International* 2016. https://doi.org/10.1155/2016/3973197.

Choi, Damee, Shotaro Ota, and Shigeki Watanuki. 2015. “Does Cigarette Smoking Relieve Stress? Evidence from the Event-Related Potential (ERP).” *International Journal of Psychophysiology: Official Journal of the International Organization of Psychophysiology* 98 (3 Pt 1): 470–76. https://doi.org/10.1016/j.ijpsycho.2015.10.005.

Cohen, Beth E., Donald Edmondson, and Ian M. Kronish. 2015. “State of the Art Review: Depression, Stress, Anxiety, and Cardiovascular Disease.” *American Journal of Hypertension* 28 (11): 1295–1302. https://doi.org/10.1093/ajh/hpv047.

Cohen, Dan, Ronald P. Stolk, Diederick E. Grobbee, and Christine C. Gispen-de Wied. 2006. “Hyperglycemia and Diabetes in Patients with Schizophrenia or Schizoaffective Disorders.” *Diabetes Care* 29 (4): 786–91.

Collins, G. S., and D. G. Altman. 2010. “An Independent and External Validation of QRISK2 Cardiovascular Disease Risk Score: A Prospective Open Cohort Study.” *BMJ* 340 (may13 2): c2442–c2442. https://doi.org/10.1136/bmj.c2442.

Colombo, Francesca, Manuel García-Goñi, and Christoph Schwierz. 2016. “Addressing Multimorbidity to Improve Healthcare and Economic Sustainability.” *Journal of Comorbidity* 6 (1): 21–27. https://doi.org/10.15256/joc.2016.6.74.

Colton, Craig W, and Ronald W Manderscheid. 2006. “Congruencies in Increased Mortality Rates, Years of Potential Life Lost, and Causes of Death Among Public Mental Health Clients in Eight States.” *Preventing Chronic Disease* 3 (2). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1563985/.

Commodore-Mensah Yvonne, Hill Martha, Allen Jerilyn, Cooper Lisa A., Blumenthal Roger, Agyemang Charles, and Himmelfarb Cheryl Dennison. 2016. “Sex Differences in Cardiovascular Disease Risk of Ghanaian- and Nigerian-Born West African Immigrants in the United States: The Afro-Cardiac Study.” *Journal of the American Heart Association* 5 (2): e002385. https://doi.org/10.1161/JAHA.115.002385.

Compton, Michael T., Gail L. Daumit, and Benjamin G. Druss. 2006. “Cigarette Smoking and Overweight/Obesity Among Individuals with Serious Mental Illnesses: A Preventive Perspective:” *Harvard Review of Psychiatry* 14 (4): 212–22. https://doi.org/10.1080/10673220600889256.

Cooper, Jae, Serafino G Mancuso, Ron Borland, Tim Slade, Cherrie Galletly, and David Castle. 2012. “Tobacco Smoking among People Living with a Psychotic Illness: The Second Australian Survey of Psychosis.” *Australian & New Zealand Journal of Psychiatry* 46 (9): 851–63. https://doi.org/10.1177/0004867412449876.

Cornier, Marc-Andre, Dana Dabelea, Teri L. Hernandez, Rachel C. Lindstrom, Amy J. Steig, Nicole R. Stob, Rachael E. Van Pelt, Hong Wang, and Robert H. Eckel. 2008. “The Metabolic Syndrome.” *Endocrine Reviews* 29 (7): 777–822. https://doi.org/10.1210/er.2008-0024.

Corrao, Giovanni, Luca Rubbiati, Vincenzo Bagnardi, Antonella Zambon, and Kari Poikolainen. 2000. “Alcohol and Coronary Heart Disease: A Meta-Analysis.” *Addiction* 95 (10): 1505–23. https://doi.org/10.1046/j.1360-0443.2000.951015056.x.

Correll, Christoph U., Marco Solmi, Nicola Veronese, Beatrice Bortolato, Stella Rosson, Paolo Santonastaso, Nita Thapa-Chhetri, et al. 2017. “Prevalence, Incidence and Mortality from Cardiovascular Disease in Patients with Pooled and Specific Severe Mental Illness: A Large-scale Meta-analysis of 3,211,768 Patients and 113,383,368 Controls.” *World Psychiatry* 16 (2): 163–80. https://doi.org/10.1002/wps.20420.

Csige, Imre, Dóra Ujvárosy, Zoltán Szabó, István Lőrincz, György Paragh, Mariann Harangi, and Sándor Somodi. 2018. “The Impact of Obesity on the Cardiovascular System.” *Journal of Diabetes Research* 2018 (November): 1–12. https://doi.org/10.1155/2018/3407306.

D’Agostino Ralph B., Vasan Ramachandran S., Pencina Michael J., Wolf Philip A., Cobain Mark, Massaro Joseph M., and Kannel William B. 2008. “General Cardiovascular Risk Profile for Use in Primary Care.” *Circulation* 117 (6): 743–53. https://doi.org/10.1161/CIRCULATIONAHA.107.699579.

Dalal, Shona, Juan Jose Beunza, Jimmy Volmink, Clement Adebamowo, Francis Bajunirwe, Marina Njelekela, Dariush Mozaffarian, et al. 2011. “Non-Communicable Diseases in Sub-Saharan Africa: What We Know Now.” *International Journal of Epidemiology* 40 (4): 885–901. https://doi.org/10.1093/ije/dyr050.

Dalvie, Shareefa, Nastassja Koen, Laramie Duncan, Catherine Abbo, Dickens Akena, Lukoye Atwoli, Bonginkosi Chiliza, et al. 2015. “Large Scale Genetic Research on Neuropsychiatric Disorders in African Populations Is Needed.” *EBioMedicine* 2 (10): 1259–61. https://doi.org/10.1016/j.ebiom.2015.10.002.

Daumit, Gail L., Jeanne M. Clark, Donald M. Steinwachs, Camelia M. Graham, Anthony Lehman, and Daniel E. Ford. 2003. “Prevalence and Correlates of Obesity in a Community Sample of Individuals with Severe and Persistent Mental Illness:” *The Journal of Nervous and Mental Disease* 191 (12): 799–805. https://doi.org/10.1097/01.nmd.0000100923.20188.2d.

Daumit, Gail L., Faith B. Dickerson, Nae-Yuh Wang, Arlene Dalcin, Gerald J. Jerome, Cheryl A. M. Anderson, Deborah R. Young, et al. 2013. “A Behavioral Weight-Loss Intervention in Persons with Serious Mental Illness.” *The New England Journal of Medicine* 368 (17): 1594–1602. https://doi.org/10.1056/NEJMoa1214530.

David M. Lawrence, Cashel D’Arcy, J. Holman, Assen V. Jablensky, and Michael S. T. Hobbs. 2003. “Death Rate from Ischaemic Heart Disease in Western Australian Psychiatric Patients 1980–1998” 182 (1): 31–36.

David P. J., Osborn, David P. J. Osborn, PhD1,2; Sarah Hardoon, PhD1,3; Rumana Z. Omar, PhD4; et al, and Rumana Z. Omar. 2015. “Cardiovascular Risk Prediction Models for People With Severe Mental Illness: Results From the Prediction and Management of Cardiovascular Risk in People With Severe Mental Illnesses (PRIMROSE) Research Program | Bipolar and Related Disorders | JAMA Psychiatry | JAMA Network.” *JAMA Psychiatry* 72 (2). https://jamanetwork-com.ezproxy.uct.ac.za/journals/jamapsychiatry/fullarticle/2043173.

David Taylor, Corina Young, Radia Mohamed, Carol Paton, Rebecca Walwyn. 2005. “Undiagnosed Impaired Fasting Glucose and Diabetes Mellitus amongst Inpatients Receiving Antipsychotic Drugs - David Taylor, Corina Young, Radia Mohamed, Carol Paton, Rebecca Walwyn, 2005” 19 (2). https://journals-sagepub-com.ezproxy.uct.ac.za/doi/abs/10.1177/0269881105049039.

Davis, Cynthia R., Eric Dearing, Nicole Usher, Sarah Trifiletti, Lesya Zaichenko, Elizabeth Ollen, Mary T. Brinkoetter, et al. 2014. “Detailed Assessments of Childhood AdversityEnhance Prediction of Central Obesity Independent of Sex, Race, Adult Psychosocial Risk and Health Behaviors.” *Metabolism: Clinical and Experimental* 63 (2): 199–206. https://doi.org/10.1016/j.metabol.2013.08.013.

Davis, Sharon K., Samson Gebreab, Rakale Quarells, and Gary H. Gibbons. 2014. “Social Determinants of Cardiovascular Health among Black and White Women Residing in Stroke Belt and Buckle Regions of the South.” *Ethnicity & Disease* 24 (2): 133–43.

DB Allison, JL Mentore, M Heo. 1999. “Antipsychotic-Induced Weight Gain: A Comprehensi... - Google Scholar.” 1999. https://scholar.google.com/scholar_lookup?title=Antipsychotic-induced%20weight%20gain%3A%20a%20comprehensive%20research%20synthesis&publication_year=1999&author=D.B.%20Allison&author=J.L.%20Mentore&author=M.%20Heo&author=L.P.%20Chandler&author=J.C.%20Cappelleri&author=M.C.%20Infante&author=P.J.%20Weiden.

De Bellis, Michael D., and Abigail Zisk A.B. 2014. “‘The Biological Effects of Childhood Trauma.’” *Child and Adolescent Psychiatric Clinics of North America* 23 (2): 185–222. https://doi.org/10.1016/j.chc.2014.01.002.

DE HERT, MARC, CHRISTOPH U. CORRELL, JULIO BOBES, MARCELO CETKOVICH-BAKMAS, DAN COHEN, ITSUO ASAI, JOHAN DETRAUX, et al. 2011. “Physical Illness in Patients with Severe Mental Disorders. I. Prevalence, Impact of Medications and Disparities in Health Care.” *World Psychiatry* 10 (1): 52–77.

De Hert, Marc, Johan Detraux, and Davy Vancampfort. 2018. “The Intriguing Relationship between Coronary Heart Disease and Mental Disorders.” *Dialogues in Clinical Neuroscience* 20 (1): 31–40.

De Hert, Marc, Vincent Schreurs, Kim Sweers, Dominique Van Eyck, Linda Hanssens, Sebastjan Šinko, Martien Wampers, Andre Scheen, Joseph Peuskens, and Ruud van Winkel. 2008. “Typical and Atypical Antipsychotics Differentially Affect Long-Term Incidence Rates of the Metabolic Syndrome in First-Episode Patients with Schizophrenia: A Retrospective Chart Review.” *Schizophrenia Research* 101 (1): 295–303. https://doi.org/10.1016/j.schres.2008.01.028.

Dedert, Eric A., Patrick S. Calhoun, Lana L. Watkins, Andrew Sherwood, and Jean C. Beckham. 2010. “Posttraumatic Stress Disorder, Cardiovascular and Metabolic Disease: A Review of the Evidence.” *Annals of Behavioral Medicine : A Publication of the Society of Behavioral Medicine* 39 (1): 61–78. https://doi.org/10.1007/s12160-010-9165-9.

Dégano, Irene R., Jaume Marrugat, Maria Grau, Betlem Salvador-González, Rafel Ramos, Alberto Zamora, Ruth Martí, and Roberto Elosua. 2017. “The Association between Education and Cardiovascular Disease Incidence Is Mediated by Hypertension, Diabetes, and Body Mass Index.” *Scientific Reports* 7 (September). https://doi.org/10.1038/s41598-017-10775-3.

Deribew, Amare, Markos Tesfaye, Yohannes Hailmichael, Ludwig Apers, Gemeda Abebe, Luc Duchateau, and Robert Colebunders. 2010. “Common Mental Disorders in TB/HIV Co-Infected Patients in Ethiopia.” *BMC Infectious Diseases* 10 (July): 201. https://doi.org/10.1186/1471-2334-10-201.

Devi, Fiona, Shazana Shahwan, Wen Lin Teh, Rajeswari Sambasivam, Yun Jue Zhang, Ying Wen Lau, Say How Ong, et al. 2019. “The Prevalence of Childhood Trauma in Psychiatric Outpatients.” *Annals of General Psychiatry* 18 (August). https://doi.org/10.1186/s12991-019-0239-1.

Dhingra, Ravi, and Ramachandran S. Vasan. 2012a. “Age as a Cardiovascular Risk Factor.” *The Medical Clinics of North America* 96 (1): 87–91. https://doi.org/10.1016/j.mcna.2011.11.003.

———. 2012b. “Age As a Risk Factor.” *Medical Clinics of North America* 96 (1): 87–91. https://doi.org/10.1016/j.mcna.2011.11.003.

Diaz, Chanelle M., Eddy R. Segura, Paula M. Luz, Jesse L. Clark, Sayonara R. Ribeiro, Raquel De Boni, Leonardo Eksterman, et al. 2016. “Traditional and HIV-Specific Risk Factors for Cardiovascular Morbidity and Mortality among HIV-Infected Adults in Brazil: A Retrospective Cohort Study.” *BMC Infectious Diseases* 16 (August). https://doi.org/10.1186/s12879-016-1735-4.

Díaz-Domínguez, Daniel Alejandro, Francisco De La Rosa-Donlucas, Laura Romans-Demaria, José Ramón Grajales-Almeida, Tizbé Sauer-Vera, and Gabriel Eugenio Sotelo-Monroy. 2013. “Prevalence of Metabolic Syndrome and Associated Risk Factors in Hospitalized Patients with Schizophrenia in Mexico.” *International Journal of Mental Health* 42 (4): 95–104. https://doi.org/10.2753/IMH0020-7411420405.

Dickerson, F. B., C. H. Brown, J. A. Kreyenbuhl, L. Fang, R. W. Goldberg, K. Wohlheiter, and L. B. Dixon. 2006. “Obesity among Individuals with Serious Mental Illness.” *Acta Psychiatrica Scandinavica* 113 (4): 306–13. https://doi.org/10.1111/j.1600-0447.2005.00637.x.

Dimmeler Stefanie, and Zeiher Andreas M. 2003. “Exercise and Cardiovascular Health.” *Circulation* 107 (25): 3118–20. https://doi.org/10.1161/01.CIR.0000074244.82874.A0.

Dimsdale, Joel E. 2008a. “Psychological Stress and Cardiovascular Disease.” *Journal of the American College of Cardiology* 51 (13): 1237–46. https://doi.org/10.1016/j.jacc.2007.12.024.

———. 2008b. “Psychological Stress and Cardiovascular Disease.” *Journal of the American College of Cardiology* 51 (13): 1237–46. https://doi.org/10.1016/j.jacc.2007.12.024.

Ding, Ding, Kenny D Lawson, Tracy L Kolbe-Alexander, Eric A Finkelstein, Peter T Katzmarzyk, Willem van Mechelen, and Michael Pratt. 2016. “The Economic Burden of Physical Inactivity: A Global Analysis of Major Non-Communicable Diseases.” *The Lancet* 388 (10051): 1311–24. https://doi.org/10.1016/S0140-6736(16)30383-X.

Dinh, W., R. Füth, M. Lankisch, L. Bansemir, W. Nickl, T. Scheffold, A. Bufe, T. Krahn, and D. Ziegler. 2011. “Cardiovascular Autonomic Neuropathy Contributes to Left Ventricular Diastolic Dysfunction in Subjects with Type 2 Diabetes and Impaired Glucose Tolerance Undergoing Coronary Angiography.” *Diabetic Medicine* 28 (3): 311–18. https://doi.org/10.1111/j.1464-5491.2010.03221.x.

Diop, I. B., M. Antignac, C. Nhavoto, A. Sidy Ali, D. Balde, J. P. Empana, A. Dzudie, et al. 2019. “P3459Research Network in Africa (RNA): Sex Differences in Cardiovascular Risk Factors and Complications in 12 African Countries.” *European Heart Journal* 40 (Supplement_1). https://doi.org/10.1093/eurheartj/ehz745.0332.

Dipasquale, Salvatore, Carmine M. Pariante, Paola Dazzan, Eugenio Aguglia, Philip McGuire, and Valeria Mondelli. 2013a. “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.

———. 2013b. “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.

Dixon, LISA M. D., LETICIA Postrado, JANINE M. A. Delahanty, PAMELA J. Fischer, and ANTHONY M. D. Lehman. 1999. “The Association of Medical Comorbidity in Schizophrenia with Poor Physical and Mental Health.” *Journal of Nervous* 187 (8): 496–502.

Doherty, Anne M., John Kelly, Colm McDonald, Anne Marie O’Dywer, Joseph Keane, and John Cooney. 2013. “A Review of the Interplay between Tuberculosis and Mental Health.” *General Hospital Psychiatry* 35 (4): 398–406. https://doi.org/10.1016/j.genhosppsych.2013.03.018.

Dokken, Betsy B. 2008. “The Pathophysiology of Cardiovascular Disease and Diabetes: Beyond Blood Pressure and Lipids.” *Diabetes Spectrum* 21 (3): 160–65. https://doi.org/10.2337/diaspect.21.3.160.

Dong, Maxia, Wayne H. Giles, Vincent J. Felitti, Shanta R. Dube, Janice E. Williams, Daniel P. Chapman, and Robert F. Anda. 2004. “Insights Into Causal Pathways for Ischemic Heart Disease: Adverse Childhood Experiences Study.” *Circulation* 110 (13): 1761–66. https://doi.org/10.1161/01.CIR.0000143074.54995.7F.

Drozdz, Dorota, and Kalina Kawecka-Jaszcz. 2014. “Cardiovascular Changes during Chronic Hypertensive States.” *Pediatric Nephrology (Berlin, Germany)* 29 (9): 1507–16. https://doi.org/10.1007/s00467-013-2614-5.

Druss, Benjamin G. 2007. “Improving Medical Care for Persons with Serious Mental Illness: Challenges and Solutions.” *The Journal of Clinical Psychiatry* 68 Suppl 4: 40–44.

Druss, Benjamin G., W. David Bradford, Robert A. Rosenheck, Martha J. Radford, and Harlan M. Krumholz. 2001. “Quality of Medical Care and Excess Mortality in Older Patients With Mental Disorders.” *Archives of General Psychiatry* 58 (6): 565–72. https://doi.org/10.1001/archpsyc.58.6.565.

Druss, Benjamin G., and John W. Newcomer. 2007. “Challenges and Solutions to Integrating Mental and Physical Health Care.” *The Journal of Clinical Psychiatry* 68 (4): e09.

D’Souza, Deepak C., Roberto B. Gil, Steven Madonick, Edward B. Perry, Kimberlee Forselius-Bielen, Gabriel Braley, Lia Donahue, et al. 2006. “Enhanced Sensitivity to the Euphoric Effects of Alcohol in Schizophrenia.” *Neuropsychopharmacology* 31 (12): 2767–75. https://doi.org/10.1038/sj.npp.1301207.

Duko, Bereket, Abebaw Gebeyehu, and Getnet Ayano. 2015. “Prevalence and Correlates of Depression and Anxiety among Patients with Tuberculosis at WolaitaSodo University Hospital and Sodo Health Center, WolaitaSodo, South Ethiopia, Cross Sectional Study.” *BMC Psychiatry* 15 (1): 214. https://doi.org/10.1186/s12888-015-0598-3.

Dunne, Michael. 2004. *INFECTIOUS AGENTS AND CARDIOVASCULAR DISEASE*. National Academies Press (US). https://www.ncbi.nlm.nih.gov/books/NBK83710/.

Dupre, Matthew E., Linda K. George, Guangya Liu, and Eric D. Peterson. 2012. “The Cumulative Effect of Unemployment on Risks for Acute Myocardial Infarction.” *Archives of Internal Medicine* 172 (22): 1731–37. https://doi.org/10.1001/2013.jamainternmed.447.

Edmondson, Donald, and Beth E. Cohen. 2013. “Posttraumatic Stress Disorder and Cardiovascular Disease.” *Progress in Cardiovascular Diseases* 55 (6): 548–56. https://doi.org/10.1016/j.pcad.2013.03.004.

Edwin Lee, Lai-Yin Chow, and Chi-Ming Leung. 2011. “Metabolic Profile of First and Second Generation Antipsychotics among Chinese Patients- ClinicalKey.” *Psychiatry Research* 185 (3): 456–58.

Ekelund, Ulf, Jostein Steene-Johannessen, Wendy J Brown, Morten Wang Fagerland, Neville Owen, Kenneth E Powell, Adrian Bauman, and I-Min Lee. 2016. "Does Physical Activity Attenuate, or Even Eliminate, the Detrimental Association of Sitting Time with Mortality? A Harmonised Meta-Analysis of Data from More than 1 Million Men and Women." *The Lancet* 388 (10051): 1302–10. https://doi.org/10.1016/S0140-6736(16)30370-1.

El Fakiri, F. 2005. "Prevention of Cardiovascular Diseases: Focus on Modifiable Cardiovascular Risk." *Heart* 92 (6): 741–45. https://doi.org/10.1136/hrt.2005.068114.

Elsa Kobeissi, Han Pan, Dagfnn Aune, and Makoto Hibino. 2019. "Blood Pressure, Hypertension and the Risk of Abdominal Aortic Aneurysms: A Systematic Review and Meta-Analysis of Cohort Studies | SpringerLink." *European Journal of Epidemiology* 34 (16): 547–55. https://doi.org/10654-019-00510-9.

Emsley, Robin, Laila Asmal, Bonginkosi Chiliza, Stefan du Plessis, Jonathan Carr, Martin Kidd, Anil K. Malhotra, Matthijs Vink, and Rene S. Kahn. 2015. "Changes in Brain Regions Associated with Food-Intake Regulation, Body Mass and Metabolic Profiles during Acute Antipsychotic Treatment in First-Episode Schizophrenia." *Psychiatry Research* 233 (2): 186–93. https://doi.org/10.1016/j.pscychresns.2015.06.014.

Erem, Cihangir, Cengiz Arslan, Arif Hacihasanoglu, Orhan Deger, Murat Topbaş, Kubilay Ukinc, Halil Önder Ersöz, and Münir Telatar. 2004. "Prevalence of Obesity and Associated Risk Factors in a Turkish Population (Trabzon City, Turkey)." *Obesity Research* 12 (7): 1117–27. https://doi.org/10.1038/oby.2004.140.

Erhardt, Leif. 2009. "Cigarette Smoking: An Undertreated Risk Factor for Cardiovascular Disease." *Atherosclerosis* 205 (1): 23–32. https://doi.org/10.1016/j.atherosclerosis.2009.01.007.

Esler Murray. 2014. "Sympathetic Nervous System Moves Toward Center Stage in Cardiovascular Medicine." *Hypertension* 63 (3): e25–32. https://doi.org/10.1161/HYPERTENSIONAHA.113.02439.

Esler, Murray. 2017. "Mental Stress and Human Cardiovascular Disease." *Neuroscience & Biobehavioral Reviews*, Stress, Behavior and the Heart, 74 (March): 269–76. https://doi.org/10.1016/j.neubiorev.2016.10.011.

Esposito Katherine, Nappo Francesco, Marfella Raffaele, Giugliano Giovanni, Giugliano Francesco, Ciotola Myriam, Quagliaro Lisa, Ceriello Antonio, and Giugliano Dario. 2002. "Inflammatory Cytokine Concentrations Are Acutely Increased by Hyperglycemia in Humans." *Circulation* 106 (16): 2067–72. https://doi.org/10.1161/01.CIR.0000034509.14906.AE.

Etain, Bruno, Chantal Henry, Frank Bellivier, Flavie Mathieu, and Marion Leboyer. 2008a. "Beyond Genetics: Childhood Affective Trauma in Bipolar Disorder." *Bipolar Disorders* 10 (8): 867–76. https://doi.org/10.1111/j.1399-5618.2008.00635.x.

———. 2008b. "Beyond Genetics: Childhood Affective Trauma in Bipolar Disorder." *Bipolar Disorders* 10 (8): 867–76. https://doi.org/10.1111/j.1399-5618.2008.00635.x.

Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. 2001. "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 (Adult Treatment Panel III)." *JAMA* 285 (19): 2486–97.

Fagiolini, Andrea, and Arianna Goracci. 2009a. "The Effects of Undertreated Chronic Medical Illnesses in Patients with Severe Mental Disorders." *The Journal of Clinical Psychiatry* 70 Suppl 3: 22–29. https://doi.org/10.4088/JCP.7075su1c.04.

———. 2009b. "The Effects of Undertreated Chronic Medical Illnesses in Patients With Severe Mental Disorders." *The Journal of Clinical Psychiatry* 70 (suppl 3): 22–29. https://doi.org/10.4088/JCP.7075su1c.04.

Feldner, Matthew T., Kimberly A. Babson, Michael J. Zvolensky, Anka A. Vujanovic, Sarah F. Lewis, Laura E. Gibson, Candice M. Monson, and Amit Bernstein. 2007. "Posttraumatic Stress Symptoms and Smoking to Reduce Negative Affect: An Investigation of Trauma-Exposed Daily Smokers." *Addictive Behaviors* 32 (2): 214–27. https://doi.org/10.1016/j.addbeh.2006.03.032.

Fernandez-Egea, Emilio, Miguel Bernardo, Thomas Donner, Ignacio Conget, Eduard Parellada, Azucena Justicia, Enric Esmatjes, Clemente Garcia-Rizo, and Brian Kirkpatrick. 2009. "Metabolic Profile of Antipsychotic-Naive Individuals with Non-Affective Psychosis." *The British Journal of Psychiatry* 194 (5): 434–38. https://doi.org/10.1192/bjp.bp.108.052605.

Fernø, J., M. B. Raeder, A. O. Vik-Mo, S. Skrede, M. Glambek, K.-J. Tronstad, H. Breilid, et al. 2005. "Antipsychotic Drugs Activate SREBP-Regulated Expression of Lipid Biosynthetic Genes in Cultured Human Glioma Cells: A Novel Mechanism of Action?" *The Pharmacogenomics Journal* 5 (5): 298. https://doi.org/10.1038/sj.tpj.6500323.

Fernø, Johan, Audun O. Vik-Mo, Goran Jassim, Bjarte Håvik, Kjetil Berge, Silje Skrede, Oddrun A. Gudbrandsen, et al. 2009. "Acute Clozapine Exposure in Vivo Induces Lipid Accumulation and Marked Sequential Changes in the Expression of SREBP, PPAR, and LXR Target Genes in Rat Liver." *Psychopharmacology* 203 (1): 73–84. https://doi.org/10.1007/s00213-008-1370-x.

Ferrucci, Luigi, Annamaria Corsi, Fulvio Lauretani, Stefania Bandinelli, Benedetta Bartali, Dennis D. Taub, Jack M. Guralnik, and Dan L. Longo. 2005. "The Origins of Age-Related Proinflammatory State." *Blood* 105 (6): 2294–99. https://doi.org/10.1182/blood-2004-07-2599.

Fezeu, Leopold, Beverley Balkau, André-Pascal Kengne, Eugène Sobngwi, and Jean-Claude Mbanya. 2007. "Metabolic Syndrome in a Sub-Saharan African Setting: Central Obesity May Be the Key Determinant." *Atherosclerosis* 193 (1): 70–76. https://doi.org/10.1016/j.atherosclerosis.2006.08.037.

Firth, Joseph, Najma Siddiqi, Ai Koyanagi, Dan Siskind, Simon Rosenbaum, Cherrie Galletly, Stephanie Allan, et al. 2019. "The Lancet Psychiatry Commission: A Blueprint for Protecting Physical Health in People with Mental Illness." *The Lancet Psychiatry* 6 (8): 675–712. https://doi.org/10.1016/S2215-0366(19)30132-4.

Floen, Silje K, and Ask Elklit. 2007a. "Psychiatric Diagnoses, Trauma, and Suicidiality." *Annals of General Psychiatry* 6 (April): 12. https://doi.org/10.1186/1744-859X-6-12.

———. 2007b. "Psychiatric Diagnoses, Trauma, and Suicidiality." *Annals of General Psychiatry* 6 (1). https://doi.org/10.1186/1744-859X-6-12.

Foguet-Boreu, Quintí, Maria Isabel Fernandez San Martin, Gemma Flores Mateo, Edurne Zabaleta del Olmo, Luís Ayerbe García-Morzon, Maria Perez-Piñar López, Luis Miguel Martin-López, Javier Montes Hidalgo, and Concepción Violán. 2016. "Cardiovascular Risk Assessment in Patients with a Severe Mental Illness: A Systematic Review and Meta-Analysis." *BMC Psychiatry* 16 (May). https://doi.org/10.1186/s12888-016-0833-6.

Foley, Debra L., Andrew Mackinnon, Vera A. Morgan, Gerald F. Watts, David J. Castle, Anna Waterreus, and Cherrie A. Galletly. 2016. "Common Familial Risk Factors for Schizophrenia and Diabetes Mellitus." *The Australian and New Zealand Journal of Psychiatry* 50 (5): 488–94. https://doi.org/10.1177/0004867415595715.

Frame, Alissa A., and Richard D. Wainford. 2018. "Mechanisms of Altered Renal Sodium Handling in Age-Related Hypertension." *American Journal of Physiology-Renal Physiology* 315 (1): F1–6. https://doi.org/10.1152/ajprenal.00594.2017.

Franklin, Stanley S., and Nathan D. Wong. 2013. "Hypertension and Cardiovascular Disease: Contributions of the Framingham Heart Study." *Global Heart*, Framingham Legacy Issue, 8 (1): 49–57. https://doi.org/10.1016/j.gheart.2012.12.004.

Frayne, Susan M., Jewell H. Halanych, Donald R. Miller, Fei Wang, Hai Lin, Leonard Pogach, Erica J. Sharkansky, et al. 2005. "Disparities in Diabetes Care: Impact of Mental Illness." *Archives of Internal Medicine* 165 (22): 2631–38. https://doi.org/10.1001/archinte.165.22.2631.

Freiberg, Matthew S., and Kaku So-Armah. 2016. "HIV and Cardiovascular Disease: We Need a Mechanism, and We Need a Plan." *Journal of the American Heart Association* 5 (3). https://www.ahajournals.org/doi/abs/10.1161/JAHA.116.003411.

Friedman, Trevor, and Nyunt Nyunt Tin. 2007. "Childhood Sexual Abuse and the Development of Schizophrenia." *Postgraduate Medical Journal* 83 (982): 507–8. https://doi.org/10.1136/pgmj.2006.054577.

Frohlich Edward D. 1999. "Risk Mechanisms in Hypertensive Heart Disease." *Hypertension* 34 (4): 782–89. https://doi.org/10.1161/01.HYP.34.4.782.

Garaulet, Marta, and Juan A Madrid. 2009. "Chronobiology, Genetics and Metabolic Syndrome:" *Current Opinion in Lipidology* 20 (2): 127–34. https://doi.org/10.1097/MOL.0b013e3283292399.

Garawi, F, K Devries, N Thorogood, and R Uauy. 2014. "Global Differences between Women and Men in the Prevalence of Obesity: Is There an Association with Sex Inequality?" *European Journal Of Clinical Nutrition* 68 (10): 1101–6. https://doi.org/10.1038/ejcn.2014.86.

Garcia-Rizo, Clemente, Emilio Fernandez-Egea, Cristina Oliveira, Azucena Justicia, Miguel Bernardo, and Brian Kirkpatrick. 2012. "Inflammatory Markers in Antipsychotic-Naïve Patients with Nonaffective Psychosis and Deficit vs. Nondeficit Features." *Psychiatry Research* 198 (2): 212–15. https://doi.org/10.1016/j.psychres.2011.08.014.

Gastaldelli, Amalia, Melania Gaggini, and Ralph A. DeFronzo. 2017. "Role of Adipose Tissue Insulin Resistance in the Natural History of Type 2 Diabetes: Results From the San Antonio Metabolism Study." *Diabetes* 66 (4): 815–22. https://doi.org/10.2337/db16-1167.

Gavin Andrews and Tim Slade. 2001. "Interpreting Scores on the Kessler Psychological Distress Scale (K10) -." *Journal of Public Health* 25 (16): 494–97.

Gavin P Reynolds et all. 2006. "The 5-HT2C Receptor and Antipsychoticinduced Weight Gain – Mechanisms and Genetics - Gavin P. Reynolds, Matthew J. Hill, Shona L. Kirk, 2006." 2006. https://journals-sagepub-com.ezproxy.uct.ac.za/doi/abs/10.1177/1359786806066040.

GBD 2015 Tobacco collaborators. 2017. “Smoking Prevalence and Attributable Disease Burden in 195 Countries and Territories, 1990–2015: A Systematic Analysis from the Global Burden of Disease Study 2015.” *Lancet (London, England)* 389 (10082): 1885–1906. https://doi.org/10.1016/S0140-6736(17)30819-X.

Ghiasi, Faramarz, Sara Farhang, Alireza Farnam, and Salman Safikhanlou. 2013. “The Short Term Effect of Nicotine Abstinence on Visuospatial Working Memory in Smoking Patients with Schizophrenia.” *Nordic Journal of Psychiatry* 67 (2): 104–8. https://doi.org/10.3109/08039488.2012.687765.

Gianfrancesco, Frank, Richard White, Ruey-hua Wang, and Henry A. Nasrallah. 2003. “Antipsychotic-Induced Type 2 Diabetes: Evidence from a Large Health Plan Database.” *Journal of Clinical Psychopharmacology* 23 (4): 328–35. https://doi.org/10.1097/01.jcp.0000085404.08426.3a.

Goff, Donald C., Lisa M. Sullivan, Joseph P. McEvoy, Jonathan M. Meyer, Henry A. Nasrallah, Gail L. Daumit, Steven Lamberti, et al. 2005. “A Comparison of Ten-Year Cardiac Risk Estimates in Schizophrenia Patients from the CATIE Study and Matched Controls.” *Schizophrenia Research* 80 (1): 45–53. https://doi.org/10.1016/j.schres.2005.08.010.

Goldman, Larry S. 1999. “Medical Illness in Patients With Schizophrenia.” *The Journal of Clinical Psychiatry* 60 (suppl 21): 10–15.

Goldman, Noreen, Sanders Korenman, and Rachel Weinstein. 1995. “Marital Status and Health among the Elderly.” *Social Science & Medicine* 40 (12): 1717–30. https://doi.org/10.1016/0277-9536(94)00281-W.

Goldstein, Benjamin I, Andrea Fagiolini, Patricia Houck, and David J Kupfer. 2009. “Cardiovascular Disease and Hypertension among Adults with Bipolar I Disorder in the United States.” *Bipolar Disorders* 11 (6): 657–62. https://doi.org/10.1111/j.1399-5618.2009.00735.x.

Gomes, Joana, Diana Durães, André Sousa, and Hugo Afonso. 2019. “Isoniazid-Induced Acute Psychosis in a Patient with Pleural Tuberculosis.” *Case Reports in Psychiatry* 2019 (February). https://doi.org/10.1155/2019/4272941.

Gonsai, N. H., V. H. Amin, C. G. Mendpara, R. Speth, and G. M. Hale. 2018. “Effects of Dopamine Receptor Antagonist Antipsychotic Therapy on Blood Pressure.” *Journal of Clinical Pharmacy and Therapeutics* 43 (1): 1–7. https://doi.org/10.1111/jcpt.12649.

Gray, Matt J., Brett T. Litz, Julie L. Hsu, and Thomas W. Lombardo. 2004. “Psychometric Properties of the Life Events Checklist.” *Assessment* 11 (4): 330–41. https://doi.org/10.1177/1073191104269954.

Greenhalgh, Anne Marie, Leticia Gonzalez-Blanco, Clemente Garcia-Rizo, Emilio Fernandez-Egea, Brian Miller, Miguel Bernardo Arroyo, and Brian Kirkpatrick. 2017. “Meta-Analysis of Glucose Tolerance, Insulin, and Insulin Resistance in Antipsychotic-Naïve Patients with Nonaffective Psychosis.” *Schizophrenia Research* 179 (January): 57–63. https://doi.org/10.1016/j.schres.2016.09.026.

Griswold, Max G, Nancy Fullman, Caitlin Hawley, Nicholas Arian, Stephanie R M Zimsen, Hayley D Tymeson, Vidhya Venkateswaran, et al. 2018. “Alcohol Use and Burden for 195 Countries and Territories, 1990–2016: A Systematic Analysis for the Global Burden of Disease Study 2016.” *The Lancet* 392 (10152): 1015–35. https://doi.org/10.1016/S0140-6736(18)31310-2.

Grubaugh, Anouk L., Heidi M. Zinzow, Lisa Paul, Leonard E. Egede, and B. Christopher Frueh. 2011. “Trauma Exposure and Posttraumatic Stress Disorder in Adults with Severe Mental Illness: A Critical Review.” *Clinical Psychology Review* 31 (6): 883–99. https://doi.org/10.1016/j.cpr.2011.04.003.

Grundy Scott. 2016. “Metabolic Syndrome Update - ScienceDirect.” 2016. https://www-sciencedirect-com.ezproxy.uct.ac.za/science/article/pii/S1050173815002492.

Grundy, Scott M., H. Bryan Brewer, James I. Cleeman, Sidney C. Smith, and Claude Lenfant. 2004. “Definition of Metabolic Syndrome.” *Circulation* 109 (3): 433–38. https://doi.org/10.1161/01.CIR.0000111245.75752.C6.

Grundy, Scott M, Richard Pasternak, Philip Greenland, Sidney Smith, and Valentin Fuster. 1999. “Assessment of Cardiovascular Risk by Use of Multiple-Risk-Factor Assessment Equations.” *Circulation* 100 (13): 1481–92.

Gun Kang, Myung, Sang Baek Koh, Bong Suk Cha, Jong Ku Park, Soon Koo Baik, and Sei Jin Chang. 2005. “Job Stress and Cardiovascular Risk Factors in Male Workers.” *Preventive Medicine* 40 (5): 583–88. https://doi.org/10.1016/j.ypmed.2004.07.018.

Guo, Jeff J., Paul E. Keck, Patricia K. Corey-Lisle, Hong Li, Dongming Jiang, Raymond Jang, and Gilbert J. L’Italien. 2006. “Risk of Diabetes Mellitus Associated with Atypical Antipsychotic Use among Patients with Bipolar Disorder: A Retrospective, Population-Based, Case-Control Study.” *The Journal of Clinical Psychiatry* 67 (7): 1055–61.

Gurillo, Pedro, Sameer Jauhar, Robin M Murray, and James H MacCabe. 2015a. “Does Tobacco Use Cause Psychosis? Systematic Review and Meta-Analysis.” *The Lancet. Psychiatry* 2 (8): 718–25. https://doi.org/10.1016/S2215-0366(15)00152-2.

———. 2015b. “Does Tobacco Use Cause Psychosis? Systematic Review and Meta-Analysis.” *The Lancet. Psychiatry* 2 (8): 718–25. https://doi.org/10.1016/S2215-0366(15)00152-2.

Gurven, Michael, Aaron D. Blackwell, Daniel Eid Rodríguez, Jonathan Stieglitz, and Hillard Kaplan. 2012. “Does Blood Pressure Inevitably Rise With Age?: Longitudinal Evidence Among Forager-Horticulturalists.” *Hypertension* 60 (1): 25–33. https://doi.org/10.1161/HYPERTENSIONAHA.111.189100.

Haddad, Chadia, Souheil Hallit, Pascale Salameh, Tarek Bou-Assi, and Marouan Zoghbi. 2017. “Coronary Heart Disease Risk in Patients with Schizophrenia: A Lebanese Cross-Sectional Study.” *Journal of Comorbidity* 7 (1): 79–88. https://doi.org/10.15256/joc.2017.7.107.

Haffner, Steven M., Seppo Lehto, Tapani Rönnemaa, Kalevi Pyörälä, and Markku Laakso. 1998. “Mortality from Coronary Heart Disease in Subjects with Type 2 Diabetes and in Nondiabetic Subjects with and without Prior Myocardial Infarction.” *New England Journal of Medicine* 339 (4): 229–34. https://doi.org/10.1056/NEJM199807233390404.

Hahn, Lisa A, Cherrie A Galletly, Debra L Foley, Andrew Mackinnon, Gerald F Watts, David J Castle, Anna Waterreus, and Vera A Morgan. 2014. “Inadequate Fruit and Vegetable Intake in People with Psychosis.” *Australian & New Zealand Journal of Psychiatry* 48 (11): 1025–35. https://doi.org/10.1177/0004867414553950.

Hahn, Lisa, Ashlee Rigby, and Cherrie Galletly. 2014. “Determinants of High Rates of Smoking among People with Psychosis Living in a Socially Disadvantaged Region in South Australia.” *Australian & New Zealand Journal of Psychiatry* 48 (1): 70–79. https://doi.org/10.1177/0004867413491158.

Halonen, Jaana I., Sari Stenholm, Jaana Pentti, Ichiro Kawachi, S. V. Subramanian, Mika Kivimäki, and Jussi Vahtera. 2015. “Childhood Psychosocial Adversity and Adult Neighborhood Disadvantage as Predictors of Cardiovascular DiseaseClinical Perspective: A Cohort Study.” *Circulation* 132 (5): 371–79. https://doi.org/10.1161/CIRCULATIONAHA.115.015392.

Halperin, Ruben O., Howard D. Sesso, Jing Ma, Julie E. Buring, Meir J. Stampfer, and J. Michael Gaziano. 2006. “Dyslipidemia and the Risk of Incident Hypertension in Men.” *Hypertension* 47 (1): 45–50. https://doi.org/10.1161/01.HYP.0000196306.42418.0e.

Hamer, Mark, Gerard J. Molloy, and Emmanuel Stamatakis. 2008. “Psychological Distress as a Risk Factor for Cardiovascular Events: Pathophysiological and Behavioral Mechanisms.” *Journal of the American College of Cardiology* 52 (25): 2156–62. https://doi.org/10.1016/j.jacc.2008.08.057.

Hamra, M., M. W. Ross, K. Karuri, M. Orrs, and A. D’Agostino. 2005. “The Relationship between Expressed HIV/AIDS-Related Stigma and Beliefs and Knowledge about Care and Support of People Living with AIDS in Families Caring for HIV-Infected Children in Kenya.” *AIDS Care* 17 (7): 911–22. https://doi.org/10.1080/09540120500100593.

Handlos, Line N., Daniel R. Witte, David L. Mwaniki, Michael K. Boit, Beatrice Kilonzo, Henrik Friis, Andreas W. Hansen, Knut Borch-Johnsen, Inge Tetens, and Dirk L. Christensen. 2012. “Abdominal Obesity Has the Highest Impact on Metabolic Profile in an Overweight African Population.” *Annals of Human Biology* 39 (6): 530–33. https://doi.org/10.3109/03014460.2012.720279.

Hapke, Ulfert, Anja Schumann, Hans-Juergen Rumpf, Ulrich John, Uwe Konerding, and Christian Meyer. 2005. “Association of Smoking and Nicotine Dependence With Trauma and Posttraumatic Stress Disorder in a General Population Sample:” *The Journal of Nervous and Mental Disease* 193 (12): 843–46. https://doi.org/10.1097/01.nmd.0000188964.83476.e0.

Haregu, Tilahun Nigatu, Frederick M Wekesah, Shukri F Mohamed, Martin K Mutua, Gershim Asiki, and Catherine Kyobutungi. 2018. “Patterns of Non-Communicable Disease and Injury Risk Factors in Kenyan Adult Population: A Cluster Analysis.” *BMC Public Health* 18 (Suppl 3). https://doi.org/10.1186/s12889-018-6056-7.

Harris, E. C., and B. Barraclough. 1998. “Excess Mortality of Mental Disorder.” *The British Journal of Psychiatry: The Journal of Mental Science* 173 (July): 11–53.

Harris, Paul A., Robert Taylor, Robert Thielke, Jonathon Payne, Nathaniel Gonzalez, and Jose G. Conde. 2009. “Research Electronic Data Capture (REDCap)—A Metadata-Driven Methodology and Workflow Process for Providing Translational Research Informatics Support.” *Journal of Biomedical Informatics* 42 (2): 377–81. https://doi.org/10.1016/j.jbi.2008.08.010.

Hartz, Sarah M., Carlos N. Pato, Helena Medeiros, Patricia Cavazos-Rehg, Janet L. Sobell, James A. Knowles, Laura J. Bierut, and Michele T. Pato. 2014. “Comorbidity of Severe Psychotic Disorders with Measures of Substance Use.” *JAMA Psychiatry* 71 (3): 248–54. https://doi.org/10.1001/jamapsychiatry.2013.3726.

Haupt, Dan W. 2006. “Differential Metabolic Effects of Antipsychotic Treatments.” *European Neuropsychopharmacology*, From the Clinic to the Community: Treating the Whole Schizophrenic Patient and Innovation in Psychiatric Therapy: The Promise of the New Antipsychotics, 16 (September): S149–55. https://doi.org/10.1016/j.euroneuro.2006.06.003.

Heggelund, Jørn, Jan Hoff, Jan Helgerud, Geir E. Nilsberg, and Gunnar Morken. 2011. “Reduced Peak Oxygen Uptake and Implications for Cardiovascular Health and Quality of Life in Patients with Schizophrenia.” *BMC Psychiatry* 11: 188. https://doi.org/10.1186/1471-244X-11-188.

Heishman, Stephen J., Bethea A. Kleykamp, and Edward G. Singleton. 2010. “Meta-Analysis of the Acute Effects of Nicotine and Smoking on Human Performance.” *Psychopharmacology* 210 (4): 453–69. https://doi.org/10.1007/s00213-010-1848-1.

Helleberg, Marie, Marianne G. Pedersen, Carsten B. Pedersen, Preben B. Mortensen, and Niels Obel. 2015. “Associations between HIV and Schizophrenia and Their Effect on HIV Treatment Outcomes: A Nationwide Population-Based Cohort Study in Denmark.” *The Lancet. HIV* 2 (8): e344-350. https://doi.org/10.1016/S2352-3018(15)00089-2.

Hemingway, Harry, and Michael Marmot. 1999. “Psychosocial Factors in the Aetiology and Prognosis of Coronary Heart Disease: Systematic Review of Prospective Cohort Studies.” *BMJ* 318 (7196): 1460–67. https://doi.org/10.1136/bmj.318.7196.1460.

Henderson, David C. 2002. “Diabetes Mellitus and Other Metabolic Disturbances Induced by Atypical Antipsychotic Agents.” *Current Diabetes Reports* 2 (2): 135–40.

Hennekens, Charles H. 2007. “Increasing Global Burden of Cardiovascular Disease in General Populations and Patients With Schizophrenia.” *The Journal of Clinical Psychiatry* 68 (suppl 4): 4–7.

Hennekens, Charles H., Alissa R. Hennekens, Danielle Hollar, and Daniel E. Casey. 2005. “Schizophrenia and Increased Risks of Cardiovascular Disease.” *American Heart Journal* 150 (6): 1115–21. https://doi.org/10.1016/j.ahj.2005.02.007.

Henning, M. P., C. Krüger, and L. Fletcher. 2012. “HIV Sero-Positivity in Recently Admitted and Long-Term Psychiatric in-Patients: Prevalence and Diagnostic Profile.” *African Journal of Psychiatry* 15 (1): 47–53. http://dx.doi.org/10.4314/ajpsy.v15i1.7.

Hert, M. De, J. M. Dekker, D. Wood, K. G. Kahl, R. I. G. Holt, and H.-J. Möller. 2009. “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).” *European Psychiatry* 24 (6): 412–24. https://doi.org/10.1016/j.eurpsy.2009.01.005.

Hert, Marc De, Dan Cohen, Julio Bobes, Marcelo Cetkovich-Bakmas, Stefan Leucht, David M. Ndetei, John W. Newcomer, et al. 2011. “Physical Illness in Patients with Severe Mental Disorders. II. Barriers to Care, Monitoring and Treatment Guidelines, plus Recommendations at the System and Individual Level.” *World Psychiatry* 10 (2): 138–51. https://doi.org/10.1002/j.2051-5545.2011.tb00036.x.

Hert, Marc De, Vincent Schreurs, Davy Vancampfort, and Ruud Van Winkel. 2009. “Metabolic Syndrome in People with Schizophrenia: A Review.” *World Psychiatry* 8 (1): 15.

Himelhoch, Seth, John F. McCarthy, Dara Ganoczy, Deborah Medoff, Lisa B. Dixon, and Frederic C. Blow. 2007. “Understanding Associations Between Serious Mental Illness and HIV Among Patients in the VA Health System.” *Psychiatric Services* 58 (9): 1165–72. https://doi.org/10.1176/ps.2007.58.9.1165.

Hjorthøj, Carsten, Marie Louise Drivsholm Østergaard, Michael Eriksen Benros, Nanna Gilliam Toftdahl, Annette Erlangsen, Jon Trærup Andersen, and Merete Nordentoft. 2015. “Association between Alcohol and Substance Use Disorders and All-Cause and Cause-Specific Mortality in Schizophrenia, Bipolar Disorder, and Unipolar Depression: A Nationwide, Prospective, Register-Based Study.” *The Lancet Psychiatry* 2 (9): 801–8. https://doi.org/10.1016/S2215-0366(15)00207-2.

Holt, Rig, T. Abdelrahman, M. Hirsch, Z. Dhesi, T. George, T. Blincoe, and Rc Peveler. 2010. “The Prevalence of Undiagnosed Metabolic Abnormalities in People with Serious Mental Illness.” *Journal of Psychopharmacology* 24 (6): 867–73. https://doi.org/10.1177/0269881109102788.

Hossain, Parvez, Bisher Kawar, and Meguid El Nahas. 2007. “Obesity and Diabetes in the Developing World — A Growing Challenge.” *New England Journal of Medicine* 356 (3): 213–15. https://doi.org/10.1056/NEJMp068177.

Hosseinpour-Niazi, Somayeh, Parvin Mirmiran, Farhad Hosseinpanah, Arefeh Fallah-ghohroudy, and Fereidoun Azizi. 2014. “Association of Marital Status and Marital Transition With Metabolic Syndrome: Tehran Lipid and Glucose Study.” *International Journal of Endocrinology and Metabolism* 12 (4). https://doi.org/10.5812/ijem.18980.

Howes, Oliver D., and Shitij Kapur. 2009. “The Dopamine Hypothesis of Schizophrenia: Version III—The Final Common Pathway.” *Schizophrenia Bulletin* 35 (3): 549–62. https://doi.org/10.1093/schbul/sbp006.

Hubert, HELEN B. M. P. H., MANNING M. D. Feinleib, PATRICIA M. Mcnamara, and WILLIAM P. M. D. Castelli. 1983. “Obesity as an Independent Risk Factor for Cardiovascular Disease: A 26-Year Follow-up of Participants in the Framingham Heart Study.” *Circulation* 67 (5): 968–77.

Hudson, Christopher G. 2005. “Socioeconomic Status and Mental Illness: Tests of the Social Causation and Selection Hypotheses.” *American Journal of Orthopsychiatry* 75 (1): 3–18. https://doi.org/10.1037/0002-9432.75.1.3.

Hukic, Dzana S., Catharina Lavebratt, Louise Frisén, Lena Backlund, Agneta Hilding, Harvest F. Gu, Claes-Göran Östenson, et al. 2016. "Melatonin Receptor 1B Gene Associated with Hyperglycemia in Bipolar Disorder." *Psychiatric Genetics*, March. https://doi.org/10.1097/YPG.0000000000000131.

Hunt, Glenn E., Matthew M. Large, Michelle Cleary, Harry Man Xiong Lai, and John B. Saunders. 2018. "Prevalence of Comorbid Substance Use in Schizophrenia Spectrum Disorders in Community and Clinical Settings, 1990-2017: Systematic Review and Meta-Analysis." *Drug and Alcohol Dependence* 191: 234–58. https://doi.org/10.1016/j.drugalcdep.2018.07.011.

Iglesia, Beatriz de la, John F. Potter, Neil R. Poulter, Margaret M. Robins, and Jane Skinner. 2011. "Performance of the ASSIGN Cardiovascular Disease Risk Score on a UK Cohort of Patients from General Practice." *Heart* 97 (6): 491–99. https://doi.org/10.1136/hrt.2010.203364.

Jahangiry, Leila, Mahdieh Abbasalizad Farhangi, and Fatemeh Rezaei. 2017. "Framingham Risk Score for Estimation of 10-Years of Cardiovascular Diseases Risk in Patients with Metabolic Syndrome." *Journal of Health, Population and Nutrition* 36 (1). https://doi.org/10.1186/s41043-017-0114-0.

Jahrami, Haitham Ali, Mo'ez Al-Islam Ezzat Faris, Zahraa Qassim Saif, and Laila Habib Hammad. 2017. "Assessing Dietary and Lifestyle Risk Factors and Their Associations with Disease Comorbidities among Patients with Schizophrenia: A Case–Control Study from Bahrain." *Asian Journal of Psychiatry* 28 (August): 115–23. https://doi.org/10.1016/j.ajp.2017.03.036.

Jakovljević, Miro, Zeljka Crncević, Dulijano Ljubicić, Dragan Babić, Radmila Topić, and Marija Sarić. 2007. "Mental Disorders and Metabolic Syndrome: A Fatamorgana or Warning Reality?" *Psychiatria Danubina* 19 (1–2): 76–86.

James M. Bolton, second Jennifer Robinson, and Jitender Sareen. 2009. "Self-Medication of Mood Disorders with Alcohol and Drugs in the National Epidemiologic Survey on Alcohol and Related Conditions- ClinicalKey" 115: 367–75.

Jamkhande, Prasad G., Surendra G. Gattani, and Shaikh Ayesha Farhat. 2016. "Helicobacter Pylori and Cardiovascular Complications: A Mechanism Based Review on Role of Helicobacter Pylori in Cardiovascular Diseases." *Integrative Medicine Research* 5 (4): 244. https://doi.org/10.1016/j.imr.2016.05.005.

Janssen, Ellen M., Emma E. McGinty, Susan T. Azrin, Denise Juliano-Bult, and Gail L. Daumit. 2015. "Review of the Evidence: Prevalence of Medical Conditions in the United States Population with Serious Mental Illness." *General Hospital Psychiatry* 37 (3): 199–222. https://doi.org/10.1016/j.genhosppsych.2015.03.004.

Januzzi, James L., Theodore A. Stern, Richard C. Pasternak, and Roman W. DeSanctis. 2000. "The Influence of Anxiety and Depression on Outcomes of Patients With Coronary Artery Disease." *Archives of Internal Medicine* 160 (13): 1913–21. https://doi.org/10.1001/archinte.160.13.1913.

Jasinska, Agnes J., Todd Zorick, Arthur L. Brody, and Elliot A. Stein. 2014. "Dual Role of Nicotine in Addiction and Cognition: A Review of Neuroimaging Studies in Humans." *Neuropharmacology* 0 (September): 111–22. https://doi.org/10.1016/j.neuropharm.2013.02.015.

Jeppesen Jørgen, Hein Hans Ole, Suadicani Poul, and Gyntelberg Finn. 1997. "Relation of High TG–Low HDL Cholesterol and LDL Cholesterol to the Incidence of Ischemic Heart Disease." *Arteriosclerosis, Thrombosis, and Vascular Biology* 17 (6): 1114–20. https://doi.org/10.1161/01.ATV.17.6.1114.

Jeste, Dilip V., Barton W. Palmer, Paul S. Appelbaum, Shahrokh Golshan, Danielle Glorioso, Laura B. Dunn, Kathleen Kim, Thomas Meeks, and Helena C. Kraemer. 2007. "A New Brief Instrument for Assessing Decisional Capacity for Clinical Research." *Archives of General Psychiatry* 64 (8): 966–74. https://doi.org/10.1001/archpsyc.64.8.966.

Jesus, Cátia, Inês Jesus, and Mark Agius. 2015. "A Review of the Evidence for the Use of Metformin in the Treatment of Metabolic Syndrome Caused by Antipsychotics." *Psychiatria Danubina* 27 Suppl 1 (September): S489-491.

Jiang, Shu-Zhong, Wen Lu, Xue-Feng Zong, Hong-Yun Ruan, and Yi Liu. 2016. "Obesity and Hypertension." *Experimental and Therapeutic Medicine* 12 (4): 2395–99. https://doi.org/10.3892/etm.2016.3667.

Jiang, Wei. 2015. "Emotional Triggering of Cardiac Dysfunction: The Present and Future." *Current Cardiology Reports* 17 (10): 91. https://doi.org/10.1007/s11886-015-0635-3.

Jin, Hua, David Folsom, Alana Sasaki, Sunder Mudaliar, Robert Henry, Monique Torres, Shah Golshan, Danielle K. Glorioso, and Dilip Jeste. 2011. "Increased Framingham 10-Year Risk of Coronary Heart Disease in Middle Aged and Older Patients with Psychotic Symptoms." *Schizophrenia Research* 125 (2–3): 295–99. https://doi.org/10.1016/j.schres.2010.10.029.

Jin, Robert L., Chandrakant P. Shah, and Tomislav J. Svoboda. 1997. "The Impact of Unemployment on Health: A Review of the Evidence." *Journal of Public Health Policy* 18 (3): 275–301. https://doi.org/10.2307/3343311.

Johnston, Marjorie C., Michael Crilly, Corri Black, Gordon J. Prescott, and Stewart W. Mercer. 2019. "Defining and Measuring Multimorbidity: A Systematic Review of Systematic Reviews." *European Journal of Public Health* 29 (1): 182–89. https://doi.org/10.1093/eurpub/cky098.

Joseph, Joshua J., and Sherita H. Golden. 2017. “Cortisol Dysregulation: The Bidirectional Link between Stress, Depression, and Type 2 Diabetes Mellitus.” *Annals of the New York Academy of Sciences* 1391 (1): 20–34. https://doi.org/10.1111/nyas.13217.

Jousilahti Pekka, Vartiainen Erkki, Tuomilehto Jaakko, and Puska Pekka. 1999. “Sex, Age, Cardiovascular Risk Factors, and Coronary Heart Disease.” *Circulation* 99 (9): 1165–72. https://doi.org/10.1161/01.CIR.99.9.1165.

Jousilahti, Pekka, Erkki Vartiainen, Jaakko Tuomilehto, and Pekka Puska. 1999. “Sex, Age, Cardiovascular Risk Factors, and Coronary Heart Disease: A Prospective Follow-Up Study of 14 786 Middle-Aged Men and Women in Finland.” *Circulation* 99 (9): 1165–72. https://doi.org/10.1161/01.CIR.99.9.1165.

Jung, Young-Ah, Li-Ly Kang, Ha-Nui Kim, Hoon-Ki Park, Hwan-Sik Hwang, and Kye-Yeung Park. 2018. “Relationship between Marital Status and Metabolic Syndrome in Korean Middle-Aged Women: The Sixth Korea National Health and Nutrition Examination Survey (2013–2014).” *Korean Journal of Family Medicine* 39 (5): 307–12. https://doi.org/10.4082/kjfm.17.0020.

Kaduka, Lydia U., Yeri Kombe, Eucharia Kenya, Elizabeth Kuria, John K. Bore, Zipporah N. Bukania, and Moses Mwangi. 2012. “Prevalence of Metabolic Syndrome Among an Urban Population in Kenya.” *Diabetes Care* 35 (4): 887–93. https://doi.org/10.2337/dc11-0537.

Kannel, W B, and D L McGee. 1979. “Diabetes and Cardiovascular Risk Factors: The Framingham Study.” *Circulation* 59 (1): 8–13. https://doi.org/10.1161/01.CIR.59.1.8.

Kannel, William B. 1996. “Blood Pressure as a Cardiovascular Risk Factor: Prevention and Treatment.” *JAMA* 275 (20): 1571–76. https://doi.org/10.1001/jama.1996.03530440051036.

Kaspersen, Silje L., Kristine Pape, Gunnhild Å. Vie, Solveig O. Ose, Steinar Krokstad, David Gunnell, and Johan H. Bjørngaard. 2016. “Health and Unemployment: 14 Years of Follow-up on Job Loss in the Norwegian HUNT Study.” *The European Journal of Public Health* 26 (2): 312–17. https://doi.org/10.1093/eurpub/ckv224.

Katz, Amos, and Aviva Grosbard. 2006. “Does It All Go up in Smoke? Cigarette Smoking and Tachyarrhythmias.” *Journal of Cardiovascular Electrophysiology* 17 (9): 937–39. https://doi.org/10.1111/j.1540-8167.2006.00573.x.

Kautzky-Willer, Alexandra, Jürgen Harreiter, and Giovanni Pacini. 2016. “Sex and Sex Differences in Risk, Pathophysiology and Complications of Type 2 Diabetes Mellitus.” *Endocrine Reviews* 37 (3): 278–316. https://doi.org/10.1210/er.2015-1137.

Kavishe, Bazil, Samuel Biraro, Kathy Baisley, Fiona Vanobberghen, Saidi Kapiga, Paula Munderi, Liam Smeeth, et al. 2015. “High Prevalence of Hypertension and of Risk Factors for Non-Communicable Diseases (NCDs): A Population Based Cross-Sectional Survey of NCDS and HIV Infection in Northwestern Tanzania and Southern Uganda.” *BMC Medicine* 13 (May). https://doi.org/10.1186/s12916-015-0357-9.

Kelleher, Ian, Helen Keeley, Paul Corcoran, Hugh Ramsay, Camilla Wasserman, Vladimir Carli, Marco Sarchiapone, Christina Hoven, Danuta Wasserman, and Mary Cannon. 2013. “Childhood Trauma and Psychosis in a Prospective Cohort Study: Cause, Effect, and Directionality.” *American Journal of Psychiatry* 170 (7): 734–41. https://doi.org/10.1176/appi.ajp.2012.12091169.

Kesebir, Sermin. 2014. “Metabolic Syndrome and Childhood Trauma: Also Comorbidity and Complication in Mood Disorder.” *World Journal of Clinical Cases : WJCC* 2 (8): 332–37. https://doi.org/10.12998/wjcc.v2.i8.332.

Khasawneh, Fadi T., and Gollapudi S. Shankar. 2014. “Minimizing Cardiovascular Adverse Effects of Atypical Antipsychotic Drugs in Patients with Schizophrenia.” Research article. Cardiology Research and Practice. 2014. https://doi.org/10.1155/2014/273060.

Kiama, Catherine Nduku, Joyce Njeri Wamicwe, Elvis Omondi Oyugi, Mark Odhiambo Obonyo, Jane Githuku Mungai, Zeinab Gura Roka, and Ann Mwangi. 2018. “Prevalence and Factors Associated with Metabolic Syndrome in an Urban Population of Adults Living with HIV in Nairobi, Kenya.” *The Pan African Medical Journal* 29 (January). https://doi.org/10.11604/pamj.2018.29.90.13328.

Kilbourne, Amy M., Michelle M. Barbaresso, Zongshan Lai, Kristina M. Nord, Margretta Bramlet, David E. Goodrich, Edward P. Post, Daniel Almirall, and Mark S. Bauer. 2017. “Improving Physical Health in Patients with Chronic Mental Disorders: 12-Month Results from a Randomized Controlled Collaborative Care Trial.” *The Journal of Clinical Psychiatry* 78 (1): 129–37. https://doi.org/10.4088/JCP.15m10301.

Kilbourne, Amy M., Jack R. Cornelius, Xiaoyan Han, Harold A. Pincus, Mujeeb Shad, Ihsan Salloum, Joseph Conigliaro, and Gretchen L. Haas. 2004. “Burden of General Medical Conditions among Individuals with Bipolar Disorder.” *Bipolar Disorders* 6 (5): 368–73. https://doi.org/10.1111/j.1399-5618.2004.00138.x.

Kilbourne Amy M. et al. 2009. “Excess Heart-Disease-Related Mortality in a National Study of Patients with Mental Disorders: Identifying Modifiable Risk Factors - ScienceDirect.” *Elsevier* 31 (6): 555–63.

Kilbourne, Amy M., David E. Goodrich, Zongshan Lai, Edward P. Post, Karen Schumacher, Kristina M. Nord, Margretta Bramlet, Stephen Chermack, David Bialy, and Mark S. Bauer. 2013. "Randomized Controlled Trial to Reduce Cardiovascular Disease Risk for Patients with Bipolar Disorder: The Self-Management Addressing Heart Risk Trial (SMAHRT)." *The Journal of Clinical Psychiatry* 74 (7): e655–62. https://doi.org/10.4088/JCP.12m08082.

Kim, Daeho, Hwallip Bae, Changwoo Han, Hyun Young Oh, and Kai Macdonald. 2013. "Psychometric Properties of the Childhood Trauma Questionnaire-Short Form (CTQ-SF) in Korean Patients with Schizophrenia." *Schizophrenia Research* 144 (1–3): 93–98. https://doi.org/10.1016/j.schres.2012.12.020.

Kirkpatrick, Brian, Brian J. Miller, Clemente Garcia-Rizo, Emilio Fernandez-Egea, and Miguel Bernardo. 2012. "Is Abnormal Glucose Tolerance in Antipsychotic-Naïve Patients With Nonaffective Psychosis Confounded by Poor Health Habits?" *Schizophrenia Bulletin* 38 (2): 280–84. https://doi.org/10.1093/schbul/sbq058.

Kivimäki, Mika, Päivi Leino-Arjas, Ritva Luukkonen, Hilkka Riihimäi, Jussi Vahtera, and Juhani Kirjonen. 2002. "Work Stress and Risk of Cardiovascular Mortality: Prospective Cohort Study of Industrial Employees." *BMJ* 325 (7369): 857. https://doi.org/10.1136/bmj.325.7369.857.

Kjeldsen, Sverre E. 2018. "Hypertension and Cardiovascular Risk: General Aspects." *Pharmacological Research* 129 (March): 95–99. https://doi.org/10.1016/j.phrs.2017.11.003.

Knaak, Stephanie, Ed Mantler, and Andrew Szeto. 2017. "Mental Illness-Related Stigma in Healthcare: Barriers to Access and Care and Evidence-Based Solutions." *Healthcare Management Forum* 30 (2): 111–16. https://doi.org/10.1177/0840470416679413.

Koivukangas, J., T. Tammelin, M. Kaakinen, P. Mäki, I. Moilanen, A. Taanila, and J. Veijola. 2010. "Physical Activity and Fitness in Adolescents at Risk for Psychosis within the Northern Finland 1986 Birth Cohort." *Schizophrenia Research* 116 (2): 152–58. https://doi.org/10.1016/j.schres.2009.10.022.

Koliaki, Chrysi, Stavros Liatis, and Alexander Kokkinos. 2019. "Obesity and Cardiovascular Disease: Revisiting an Old Relationship." *Metabolism*, Obesity: the 21st century epidemic, 92 (March): 98–107. https://doi.org/10.1016/j.metabol.2018.10.011.

Komossa, Katja, Christine Rummel-Kluge, Heike Hunger, Franziska Schmid, Sandra Schwarz, Lorna Duggan, Werner Kissling, and Stefan Leucht. 2010. "Olanzapine versus Other Atypical Antipsychotics for Schizophrenia." *The Cochrane Database of Systematic Reviews*, no. 3: CD006654. https://doi.org/10.1002/14651858.CD006654.pub2.

Koro, Carol E., Donald O. Fedder, Gilbert J. L'Italien, Sheila Weiss, Laurence S. Magder, Julie Kreyenbuhl, Dennis Revicki, and Robert W. Buchanan. 2002. "An Assessment of the Independent Effects of Olanzapine and Risperidone Exposure on the Risk of Hyperlipidemia in Schizophrenic Patients." *Archives of General Psychiatry* 59 (11): 1021–26. https://doi.org/10.1001/archpsyc.59.11.1021.

Kotchen, T. A., J. M. Kotchen, C. E. Grim, V. George, M. L. Kaldunski, A. W. Cowley, P. Hamet, and T. H. Chelius. 2000. "Genetic Determinants of Hypertension: Identification of Candidate Phenotypes." *Hypertension (Dallas, Tex.: 1979)* 36 (1): 7–13.

Kowalchuk, Chantel, Laura N. Castellani, Araba Chintoh, Gary Remington, Adria Giacca, and Margaret K. Hahn. 2018. "Antipsychotics and Glucose Metabolism: How Brain and Body Collide." *American Journal of Physiology-Endocrinology and Metabolism* 316 (1): E1–15. https://doi.org/10.1152/ajpendo.00164.2018.

Kreyenbuhl, Julie, Faith B. Dickerson, Deborah R. Medoff, Clayton H. Brown, Richard W. Goldberg, LiJuan Fang, Karen Wohlheiter, Leena P. Mittal, and Lisa B. Dixon. 2006. "Extent and Management of Cardiovascular Risk Factors in Patients With Type 2 Diabetes and Serious Mental Illness:" *The Journal of Nervous and Mental Disease* 194 (6): 404–10. https://doi.org/10.1097/01.nmd.0000221177.51089.7d.

Kreyenbuhl, Julie, Deborah R. Medoff, Stephen L. Seliger, and Lisa B. Dixon. 2008. "Use of Medications to Reduce Cardiovascular Risk among Individuals with Psychotic Disorders and Type 2 Diabetes." *Schizophrenia Research* 101 (1): 256–65. https://doi.org/10.1016/j.schres.2008.02.004.

Krishnaswamy, Kamala, and Rajagopal Gayathri. 2018. "Nature's Bountiful Gift to Humankind: Vegetables & Fruits & Their Role in Cardiovascular Disease & Diabetes." *The Indian Journal of Medical Research* 148 (5): 569–95. https://doi.org/10.4103/ijmr.IJMR_1780_18.

Krystal, John H., D. Cyril D'Souza, JÜrgen Gallinat, Naomi Driesen, Anissa Abi-Dargham, Ismene Petrakis, Andreas Heinz, and Godfrey Pearlson. 2006. "The Vulnerability to Alcohol and Substance Abuse in Individuals Diagnosed with Schizophrenia." *Neurotoxicity Research* 10 (3): 235–52. https://doi.org/10.1007/BF03033360.

Kupper, Nina, Gonneke Willemsen, Harriëtte Riese, Daniëlle Posthuma, Dorret I. Boomsma, and Eco J. C. de Geus. 2005. "Heritability of Daytime Ambulatory Blood Pressure in an Extended Twin Design." *Hypertension* 45 (1): 80–85. https://doi.org/10.1161/01.HYP.0000149952.84391.54.

Kurtze, Nanna, Terje A. Eikemo, and Carlijn B. M. Kamphuis. 2013. “Educational Inequalities in General and Mental Health: Differential Contribution of Physical Activity, Smoking, Alcohol Consumption and Diet.” *European Journal of Public Health* 23 (2): 223–29. https://doi.org/10.1093/eurpub/cks055.

Kwobah, Edith, Steve Epstein, Ann Mwangi, Debra Litzelman, and Lukoye Atwoli. 2017. “PREVALENCE of Psychiatric Morbidity in a Community Sample in Western Kenya.” *BMC Psychiatry* 17 (January). https://doi.org/10.1186/s12888-017-1202-9.

Kyu, Hmwe H., Victoria F. Bachman, Lily T. Alexander, John Everett Mumford, Ashkan Afshin, Kara Estep, J. Lennert Veerman, et al. 2016. “Physical Activity and Risk of Breast Cancer, Colon Cancer, Diabetes, Ischemic Heart Disease, and Ischemic Stroke Events: Systematic Review and Dose-Response Meta-Analysis for the Global Burden of Disease Study 2013.” *BMJ* 354 (August). https://doi.org/10.1136/bmj.i3857.

Lain, and Kristine Y, Catalano,Patrick. 2007. “Metabolic Changes in Pregnancy | Ovid.” *Clinical Obstetrics and Gynecology* 57 (4): 938–48.

Lally, John, and James H. MacCabe. 2015. “Antipsychotic Medication in Schizophrenia: A Review.” *British Medical Bulletin* 114 (1): 169–79. https://doi.org/10.1093/bmb/ldv017.

Lambert, Bruce L., Chia-Hung Chou, Ken-Yu Chang, Eskinder Tafesse, and William Carson. 2005. “Antipsychotic Exposure and Type 2 Diabetes among Patients with Schizophrenia: A Matched Case-Control Study of California Medicaid Claims.” *Pharmacoepidemiology and Drug Safety* 14 (6): 417–25. https://doi.org/10.1002/pds.1092.

Lambert, Tim J. R., and John W. Newcomer. 2009. “Are the Cardiometabolic Complications of Schizophrenia Still Neglected? Barriers to Care.” *The Medical Journal of Australia* 190 (4): 39.

Lamberti, J. Steven, G. Oana Costea, David Olson, John F. Crilly, Kumar Maharaj, Xin Tu, Adrienne Groman, et al. 2005. “Diabetes Mellitus among Outpatients Receiving Clozapine: Prevalence and Clinical-Demographic Correlates.” *The Journal of Clinical Psychiatry* 66 (7): 900–906.

Lamberti, J. Steven, John F. Crilly, Kumar Maharaj, David Olson, Karen Wiener, Stephen Dvorin, G. Oana Costea, Margaret P. Bushey, and Marci B. Dietz. 2004. “Prevalence of Diabetes Mellitus among Outpatients with Severe Mental Disorders Receiving Atypical Antipsychotic Drugs.” *The Journal of Clinical Psychiatry* 65 (5): 702–6.

Lamprea-Montealegre Julio A., Zelnick Leila R., Hall Yoshio N., Bansal Nisha, and de Boer Ian H. 2018. “Prevalence of Hypertension and Cardiovascular Risk According to Blood Pressure Thresholds Used for Diagnosis.” *Hypertension* 72 (3): 602–9. https://doi.org/10.1161/HYPERTENSIONAHA.118.11609.

Lange, Yvonne, and Theodore L. Steck. 1994. “Cholesterol Homeostasis. Modulation by Amphiphiles.” *Journal of Biological Chemistry* 269 (47): 29371–29374.

Lardinois, M., T. Lataster, R. Mengelers, J. Van Os, and I. Myin-Germeys. 2011. “Childhood Trauma and Increased Stress Sensitivity in Psychosis.” *Acta Psychiatrica Scandinavica* 123 (1): 28–35. https://doi.org/10.1111/j.1600-0447.2010.01594.x.

Larkin, W., and J. Read. 2008. “Childhood Trauma and Psychosis: Evidence, Pathways, and Implications.” *Journal of Postgraduate Medicine* 54 (4): 287–93.

Larsson, Sara, Ole A. Andreassen, Monica Aas, Jan I. Røssberg, Erlend Mork, Nils E. Steen, Elizabeth A. Barrett, et al. 2013. “High Prevalence of Childhood Trauma in Patients with Schizophrenia Spectrum and Affective Disorder.” *Comprehensive Psychiatry* 54 (2): 123–27. https://doi.org/10.1016/j.comppsych.2012.06.009.

Le Noury, Joanna, Afshan Khan, Margaret Harris, Winnie Wong, Dawn Williams, Tony Roberts, Richard Tranter, and David Healy. 2008. “The Incidence and Prevalence of Diabetes in Patients with Serious Mental Illness in North West Wales: Two Cohorts, 1875–1924 & 1994–2006 Compared.” *BMC Psychiatry* 8 (1): 67. https://doi.org/10.1186/1471-244X-8-67.

Lecrubier, Y, DV Sheehan, E Weiller, P Amorim, I Bonora, K Harnett Sheehan, J Janavs, and GC Dunbar. 1997. “The Mini International Neuropsychiatric Interview (MINI). A Short Diagnostic Structured Interview: Reliability and Validity According to the CIDI.” *European Psychiatry* 12 (5): 224–31. https://doi.org/10.1016/S0924-9338(97)83296-8.

Lee, Chioun, Vera Tsenkova, and Deborah Carr. 2014. “Childhood Trauma and Metabolic Syndrome in Men and Women.” *Social Science & Medicine (1982)* 105 (March): 122–30. https://doi.org/10.1016/j.socscimed.2014.01.017.

Lee, Hyeonju, and Youn-Jung Son. 2019. “Influence of Smoking Status on Risk of Incident Heart Failure: A Systematic Review and Meta-Analysis of Prospective Cohort Studies.” *International Journal of Environmental Research and Public Health* 16 (15). https://doi.org/10.3390/ijerph16152697.

Lee, John Tayu, Fozia Hamid, Sanghamitra Pati, Rifat Atun, and Christopher Millett. 2015. “Impact of Noncommunicable Disease Multimorbidity on Healthcare Utilisation and Out-Of-Pocket Expenditures in Middle-Income Countries: Cross Sectional Analysis.” *PLoS ONE* 10 (7). https://doi.org/10.1371/journal.pone.0127199.

Leijten, Fenna R. M., Astrid de Wind, Swenne G. van den Heuvel, Jan Fekke Ybema, Allard J. van der Beek, Suzan J. W. Robroek, and Alex Burdorf. 2015. "The Influence of Chronic Health Problems and Work-Related Factors on Loss of Paid Employment among Older Workers." *J Epidemiol Community Health* 69 (11): 1058–65. https://doi.org/10.1136/jech-2015-205719.

Leon, Benjamin M, and Thomas M Maddox. 2015. "Diabetes and Cardiovascular Disease: Epidemiology, Biological Mechanisms, Treatment Recommendations and Future Research." *World Journal of Diabetes* 6 (13): 1246–58. https://doi.org/10.4239/wjd.v6.i13.1246.

Leon, Jose de, and Francisco J. Diaz. 2005. "A Meta-Analysis of Worldwide Studies Demonstrates an Association between Schizophrenia and Tobacco Smoking Behaviors." *Schizophrenia Research* 76 (2): 135–57. https://doi.org/10.1016/j.schres.2005.02.010.

Leon, Jose de, Margaret T. Susce, Maria Johnson, Mike Hardin, Lana Pointer, Gualberto Ruaño, Andreas Windemuth, and Francisco J. Diaz. 2007. "A Clinical Study of the Association of Antipsychotics with Hyperlipidemia." *Schizophrenia Research* 92 (1): 95–102. https://doi.org/10.1016/j.schres.2007.01.015.

Leonardi, Matilde, Davide Guido, Rui Quintas, Fabiola Silvaggi, Erika Guastafierro, Andrea Martinuzzi, Somnath Chatterji, et al. 2018. "Factors Related to Unemployment in Europe. A Cross-Sectional Study from the COURAGE Survey in Finland, Poland and Spain." *International Journal of Environmental Research and Public Health* 15 (4). https://doi.org/10.3390/ijerph15040722.

Levey, D. F., H. Le-Niculescu, J. Frank, M. Ayalew, N. Jain, B. Kirlin, R. Learman, et al. 2014. "Genetic Risk Prediction and Neurobiological Understanding of Alcoholism." *Translational Psychiatry* 4 (5): e391. https://doi.org/10.1038/tp.2014.29.

Li, Li, Chunqing Lin, Jihui Guan, and Zunyou Wu. 2013. "Implementing a Stigma Reduction Intervention in Healthcare Settings." *Journal of the International AIDS Society* 16 (3S2): 18710. https://doi.org/10.7448/IAS.16.3.18710.

Li, Xiao Xi, Martin Bek, Laureano D. Asico, Zhiwei Yang, David K. Grandy, David S. Goldstein, Marcelo Rubinstein, Gilbert M. Eisner, and Pedro A. Jose. 2001. "Adrenergic and Endothelin B Receptor-Dependent Hypertension in Dopamine Receptor Type-2 Knockout Mice." *Hypertension* 38 (3): 303–8. https://doi.org/10.1161/01.HYP.38.3.303.

Lin, Jennifer S., Corinne V. Evans, Eric Johnson, Nadia Redmond, Brittany U. Burda, Erin L. Coppola, and Ning Smith. 2018. *Nontraditional Risk Factors in Cardiovascular Disease Risk Assessment: A Systematic Evidence Report for the U.S. Preventive Services Task Force*. *Nontraditional Risk Factors in Cardiovascular Disease Risk Assessment: A Systematic Evidence Report for the U.S. Preventive Services Task Force [Internet]*. Evidence Synthesis 166. Agency for Healthcare Research and Quality (US). https://www.ncbi.nlm.nih.gov/books/NBK525929/.

Linmarie Sikich, M. D., M. D. Jean A. Frazier, M. D. Jon McClellan, M. D. Robert L. Findling, M. D. Benedetto Vitiello, M. B. A. Louise Ritz, M. D. Denisse Ambler, et al. 2008. "Double-Blind Comparison of First- and Second-Generation Antipsychotics in Early-Onset Schizophrenia and Schizo-Affective Disorder: Findings From the Treatment of Early-Onset Schizophrenia Spectrum Disorders (TEOSS) Study." *American Journal of Psychiatry*, November. https://doi.org/10.1176/appi.ajp.2008.08050756.

Liu, Junqing, Jonathan Brown, Suzanne Morton, D. E. B. Potter, Lisa Patton, Milesh Patel, Rita Lewis, and Sarah Hudson Scholle. 2017. "Disparities in Diabetes and Hypertension Care for Individuals with Serious Mental Illness." *The American Journal of Managed Care* 23 (5): 304–8.

Liu, Simin, JoAnn E. Manson, I.-Min Lee, Stephen R. Cole, Charles H. Hennekens, Walter C. Willett, and Julie E. Buring. 2000. "Fruit and Vegetable Intake and Risk of Cardiovascular Disease: The Women's Health Study." *The American Journal of Clinical Nutrition* 72 (4): 922–28. https://doi.org/10.1093/ajcn/72.4.922.

Liu, Yanli, Zezhi Li, Meixia Zhang, Youping Deng, Zhenghui Yi, and Tieliu Shi. 2013. "Exploring the Pathogenetic Association between Schizophrenia and Type 2 Diabetes Mellitus Diseases Based on Pathway Analysis." *BMC Medical Genomics* 6 (1): S17. https://doi.org/10.1186/1755-8794-6-S1-S17.

Lloyd-Jones, Donald M., Eric P. Leip, Martin G. Larson, Ralph B. D'Agostino, Alexa Beiser, Peter W.F. Wilson, Philip A. Wolf, and Daniel Levy. 2006. "Prediction of Lifetime Risk for Cardiovascular Disease by Risk Factor Burden at 50 Years of Age." *Circulation* 113 (6): 791–98. https://doi.org/10.1161/CIRCULATIONAHA.105.548206.

Lloyd-Jones, Donald M, Peter W.F Wilson, Martin G Larson, Alexa Beiser, Eric P Leip, Ralph B D'Agostino, and Daniel Levy. 2004. "Framingham Risk Score and Prediction of Lifetime Risk for Coronary Heart Disease." *The American Journal of Cardiology* 94 (1): 20–24. https://doi.org/10.1016/j.amjcard.2004.03.023.

Locke, Amy, Jill Schneiderhan, and Suzanna M. Zick. 2018. "Diets for Health: Goals and Guidelines." *American Family Physician* 97 (11): 721–28.

Lommen, Miriam J. J., and Kathleen Restifo. 2009. “Trauma and Posttraumatic Stress Disorder (PTSD) in Patients with Schizophrenia or Schizoaffective Disorder.” *Community Mental Health Journal* 45 (6): 485–96. https://doi.org/10.1007/s10597-009-9248-x.

López del Amo González, M. Puerto, Vivian Benítez, and José J. Martín-Martín. 2018. “Long Term Unemployment, Income, Poverty, and Social Public Expenditure, and Their Relationship with Self-Perceived Health in Spain (2007–2011).” *BMC Public Health* 18 (January). https://doi.org/10.1186/s12889-017-5004-2.

Lu, Weili, Philip T. Yanos, Steven M. Silverstein, Kim T. Mueser, Stanley D. Rosenberg, Jennifer D. Gottlieb, Stephanie Marcello Duva, et al. 2013. “Public Mental Health Clients with Severe Mental Illness and Probable Posttraumatic Stress Disorder: Trauma Exposure and Correlates of Symptom Severity.” *Journal of Traumatic Stress* 26 (2): 266–73. https://doi.org/10.1002/jts.21791.

Lund, Crick, Carrie Brooke-Sumner, Florence Baingana, Emily Claire Baron, Erica Breuer, Prabha Chandra, Johannes Haushofer, et al. 2018. “Social Determinants of Mental Disorders and the Sustainable Development Goals: A Systematic Review of Reviews.” *The Lancet Psychiatry* 5 (4): 357–69. https://doi.org/10.1016/S2215-0366(18)30060-9.

Maaroganye, K., M. Mohapi, C. Krüger, and P. Rheeder. 2013. “The Prevalence of Metabolic Syndrome and Its Associated Factors in Long-Term Patients in a Specialist Psychiatric Hospital in South Africa.” *African Journal of Psychiatry* 16 (6). http://dx.doi.org/10.4314/ajpsy.v16i6.53.

Maarten Bak, Annemarie Fransen, Jouke Janssen, Jim van Os, and Marjan Drukker. 2014. “Almost All Antipsychotics Result in Weight Gain: A Meta-Analysis.” *PLOS ONE* 9 (4). https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0094112.

MacDonald, Andrea, and Holly R Middlekauff. 2019. “Electronic Cigarettes and Cardiovascular Health: What Do We Know so Far?” *Vascular Health and Risk Management* 15 (June): 159–74. https://doi.org/10.2147/VHRM.S175970.

Mall, Sumaya, Jonathan M. Platt, Henk Temmingh, Eustasius Musenge, Megan Campbell, Ezra Susser, and Dan J. Stein. 2020. “The Relationship between Childhood Trauma and Schizophrenia in the Genomics of Schizophrenia in the Xhosa People (SAX) Study in South Africa.” *Psychological Medicine* 50 (9): 1570–77. https://doi.org/10.1017/S0033291719001703.

Mallaina, Pablo, Christos Lionis, Hugo Rol, Renzo Imperiali, Andrew Burgess, Mark Nixon, and Franco Mondello Malvestiti. 2013. “Smoking Cessation and the Risk of Cardiovascular Disease Outcomes Predicted from Established Risk Scores: Results of the Cardiovascular Risk Assessment among Smokers in Primary Care in Europe (CV-ASPIRE) Study.” *BMC Public Health* 13 (1): 362. https://doi.org/10.1186/1471-2458-13-362.

Mallett, Rosemarie, Julian Leff, Dinesh Bhugra, Dong Pang, and Jing Hua Zhao. 2002. “Social Environment, Ethnicity and Schizophrenia.” *Social Psychiatry and Psychiatric Epidemiology* 37 (7): 329–35. https://doi.org/10.1007/s00127-002-0557-4.

Mamabolo, M. M., T. G. Magagula, C. Krüger, and L. Fletcher. 2012. “A Survey of Risk Behaviour for Contracting HIV among Adult Psychiatric Patients. A South African Study - Part 1.” *African Journal of Psychiatry* 15 (5): 329–34. http://dx.doi.org/10.4314/ajpsy.v15i5.40.

Mamakou, V., A. Thanopoulou, F. Gonidakis, N. Tentolouris, and V. Kontaxakis. 2018. “Schizophrenia and Type 2 Diabetes Mellitus.” *Psychiatrike = Psychiatriki* 29 (1): 64–73. https://doi.org/10.22365/jpsych.2018.291.64.

Manson, JoAnn E., Graham A. Colditz, Meir J. Stampfer, Walter C. Willett, Bernard Rosner, Richard R. Monson, Frank E. Speizer, and Charles H. Hennekens. 1990. “A Prospective Study of Obesity and Risk of Coronary Heart Disease in Women.” *New England Journal of Medicine* 322 (13): 882–89. https://doi.org/10.1056/NEJM199003293221303.

Marc A de Heart et all. 2006. “Prevalence of the Metabolic Syndrome in Patients with Schizophrenia Treated with Antipsychotic Medication - ScienceDirect.” 2006. https://www-sciencedirect-com.ezproxy.uct.ac.za/science/article/pii/S092099640600003X.

Marchio, Patricia, Sol Guerra-Ojeda, José M. Vila, Martín Aldasoro, Victor M. Victor, and Maria D. Mauricio. 2019. “Targeting Early Atherosclerosis: A Focus on Oxidative Stress and Inflammation.” *Oxidative Medicine and Cellular Longevity* 2019 (July). https://doi.org/10.1155/2019/8563845.

Maremmani, Angelo G. I., Silvia Bacciardi, Julian M. Somers, Mohammadali Nikoo, Christian Schütz, Kerry L. Jang, and Michael Krausz. 2018. “Substance Dependence Among Bipolar, Unipolar Depression and Psychotic Homeless: A Canadian National Study.” *Frontiers in Psychiatry* 9 (December). https://doi.org/10.3389/fpsyt.2018.00701.

Margolese, Howard C., Leslie Malchy, Juan Carlos Negrete, Raymond Tempier, and Kathryn Gill. 2004. “Drug and Alcohol Use among Patients with Schizophrenia and Related Psychoses: Levels and Consequences.” *Schizophrenia Research* 67 (2): 157–66. https://doi.org/10.1016/S0920-9964(02)00523-6.

Mark woodward. 2019. “Rationale and Tutorial for Analysing and Reporting Sex Differences in Cardiovascular Associations | Heart.” *BMJ Heart* 105 (22): 1701–8.

Marmot, M., M. Shipley, E. Brunner, and H. Hemingway. 2001. “Relative Contribution of Early Life and Adult Socioeconomic Factors to Adult Morbidity in the Whitehall II Study.” *Journal of Epidemiology & Community Health* 55 (5): 301–7. https://doi.org/10.1136/jech.55.5.301.

Marmot, Michael, Sharon Friel, Ruth Bell, Tanja AJ Houweling, and Sebastian Taylor. 2008. “Closing the Gap in a Generation: Health Equity through Action on the Social Determinants of Health.” *The Lancet* 372 (9650): 1661–69. https://doi.org/10.1016/S0140-6736(08)61690-6.

Marmot, Sir Michael. 2018. “‘Why Treat People and Send Them Back to the Conditions That Made Them Sick in the First Place?,’” 7.

Martínez, J. A., B. Moreno, and M. A. Martínez-González. 2004. “Prevalence of Obesity in Spain.” *Obesity Reviews* 5 (3): 171–72. https://doi.org/10.1111/j.1467-789X.2004.00146.x.

Martins, Lilian Cristina X., and Claudia S. Lopes. 2013. “Rank, Job Stress, Psychological Distress and Physical Activity among Military Personnel.” *BMC Public Health* 13 (1): 716. https://doi.org/10.1186/1471-2458-13-716.

Martín-Sierra, Ana, Davy Vancampfort, Michel Probst, Julio Bobes, Katrien Maurissen, Kim Sweers, Els De Schepper, and Marc De Hert. 2011. “Walking Capacity Is Associated with Health Related Quality of Life and Physical Activity Level in Patients with Schizophrenia: A Preliminary Report.” *Actas Espanolas De Psiquiatria* 39 (4): 211–16.

Masood, Imran, Sanjay Bhat, Aadil Beigh, and Veena Gupta. 2011. “Isoniazid-Induced Psychosis in a Patient on DOTS Therapy.” *Annals of Tropical Medicine and Public Health* 4 (2): 126. https://doi.org/10.4103/1755-6783.85769.

Mayo, Danessa, Sarah Corey, Leah H. Kelly, Seghel Yohannes, Alyssa L. Youngquist, Barbara K. Stuart, Tara A. Niendam, and Rachel L. Loewy. 2017. “The Role of Trauma and Stressful Life Events among Individuals at Clinical High Risk for Psychosis: A Review.” *Frontiers in Psychiatry* 8 (April). https://doi.org/10.3389/fpsyt.2017.00055.

McClave, Annette K., Lela R. McKnight-Eily, Shane P. Davis, and Shanta R. Dube. 2010. “Smoking Characteristics of Adults With Selected Lifetime Mental Illnesses: Results From the 2007 National Health Interview Survey.” *American Journal of Public Health* 100 (12): 2464–72. https://doi.org/10.2105/AJPH.2009.188136.

McCloughen, Andrea. 2003. “The Association between Schizophrenia and Cigarette Smoking: A Review of the Literature and Implications for Mental Health Nursing Practice.” *International Journal of Mental Health Nursing* 12 (2): 119–29. https://doi.org/10.1046/j.1440-0979.2003.00278.x.

McEvoy, Joseph P., Jonathan M. Meyer, Donald C. Goff, Henry A. Nasrallah, Sonia M. Davis, Lisa Sullivan, Herbert Y. Meltzer, John Hsiao, T. Scott Stroup, and Jeffrey A. Lieberman. 2005. “Prevalence of the Metabolic Syndrome in Patients with Schizophrenia: Baseline Results from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Schizophrenia Trial and Comparison with National Estimates from NHANES III.” *Schizophrenia Research* 80 (1): 19–32. https://doi.org/10.1016/j.schres.2005.07.014.

McIntyre, Roger S, Jakub Z Konarski, Joanna K Soczynska, Kathryn Wilkins, Gulshan Panjwani, Beverley Bouffard, Alexandra Bottas, and Sidney H Kennedy. 2006. “Medical Comorbidity in Bipolar Disorder: Implications for Functional Outcomes and Health Service Utilization.” *PSYCHIATRIC SERVICES* 57 (8): 5.

McLachlan, Kyle J. J., and Catharine R. Gale. 2018. “The Effects of Psychological Distress and Its Interaction with Socioeconomic Position on Risk of Developing Four Chronic Diseases.” *Journal of Psychosomatic Research* 109 (June): 79–85. https://doi.org/10.1016/j.jpsychores.2018.04.004.

Megan M. Campbell, Ezra Susser, Sumaya Mall, Sibonile G, Mqulwana, Michael M, Mndini, et al. 2017. “Using Iterative Learning to Improve Understanding during the Informed Consent Process in a South African Psychiatric Genomics Study.” *PLoS ONE* 12 (11). https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0188466.

Menezes, Paulo R., Sonia Johnson, Graham Thornicroft, Jane Marshall, David Prosser, Paul Bebbington, and Elizabeth Kuipers. 1996. “Drug and Alcohol Problems among Individuals with Severe Mental Illnesses in South London.” *The British Journal of Psychiatry* 168 (5): 612–19. https://doi.org/10.1192/bjp.168.5.612.

Mensah, George A., Gregory A. Roth, Uchechukwu K. A. Sampson, Andrew E. Moran, Valery L. Feigin, Mohammed H. Forouzanfar, Mohsen Naghavi, Christopher J. L. Murray, and GBD 2013 Mortality and Causes of Death Collaborators. 2015. “Mortality from Cardiovascular Diseases in Sub-Saharan Africa, 1990-2013: A Systematic Analysis of Data from the Global Burden of Disease Study 2013.” *Cardiovascular Journal of Africa* 26 (2 Suppl 1): S6-10. https://doi.org/10.5830/CVJA-2015-036.

Mesquita, Emersom Cicilini, Lara Esteves Coelho, Rodrigo Teixeira Amancio, Valdilea Veloso, Beatriz Grinsztejn, Paula Luz, and Fernando Augusto Bozza. 2019. “Severe Infection Increases Cardiovascular Risk among HIV-Infected Individuals.” *BMC Infectious Diseases* 19 (1): 319. https://doi.org/10.1186/s12879-019-3894-6.

Messner, Barbara, and David Bernhard. 2014. “Smoking and Cardiovascular Disease: Mechanisms of Endothelial Dysfunction and Early Atherogenesis.” *Arteriosclerosis, Thrombosis, and Vascular Biology* 34 (3): 509–15. https://doi.org/10.1161/ATVBAHA.113.300156.

Mhlongo, Mpho D, Andrew Tomita, Lindokuhle Thela, Varsha Maharaj, Jonathan K Burns, and Mpho Mhlongo. 2018. “Sexual Trauma and Post-Traumatic Stress among African Female Refugees and Migrants in South Africa.” *Open Access*, 4.

Miller, Del D. 2004. “Atypical Antipsychotics: Sleep, Sedation, and Efficacy.” *Primary Care Companion to The Journal of Clinical Psychiatry* 6 (suppl 2): 3–7.

Miller, Gregory E., Margie E. Lachman, Edith Chen, Tara L. Gruenewald, Arun S. Karlamangla, and Teresa E. Seeman. 2011. “PATHWAYS TO RESILIENCE: MATERNAL NURTURANCE AS A BUFFER AGAINST THE EFFECTS OF CHILDHOOD POVERTY ON METABOLIC SYNDROME AT MIDLIFE.” *Psychological Science* 22 (12): 1591–99. https://doi.org/10.1177/0956797611419170.

Mingzhu Xu, Jialiang Xu, and Xiangjun Yang. 2017. “Asthma and Risk of Cardiovascular Disease or All-Cause Mortality: A Meta-Analysis.” *Annals of Sauidi Medicine* 37 (2): 99–105.

Mitchell, Alex J., Davy Vancampfort, Amber De Herdt, Weiping Yu, and Marc De Hert. 2013a. “Is the Prevalence of Metabolic Syndrome and Metabolic Abnormalities Increased in Early Schizophrenia? A Comparative Meta-Analysis of First Episode, Untreated and Treated Patients.” *Schizophrenia Bulletin* 39 (2): 295–305. https://doi.org/10.1093/schbul/sbs082.

———. 2013b. “Is the Prevalence of Metabolic Syndrome and Metabolic Abnormalities Increased in Early Schizophrenia? A Comparative Meta-Analysis of First Episode, Untreated and Treated Patients.” *Schizophrenia Bulletin* 39 (2): 295–305. https://doi.org/10.1093/schbul/sbs082.

Mitchell, Alex J., Davy Vancampfort, Kim Sweers, Ruud van Winkel, Weiping Yu, and Marc De Hert. 2013. “Prevalence of Metabolic Syndrome and Metabolic Abnormalities in Schizophrenia and Related Disorders—A Systematic Review and Meta-Analysis.” *Schizophrenia Bulletin* 39 (2): 306. https://doi.org/10.1093/schbul/sbr148.

Mohamed, Shukri F., Martin K. Mutua, Richard Wamai, Frederick Wekesah, Tilahun Haregu, Pamela Juma, Loise Nyanjau, Catherine Kyobutungi, and Elijah Ogola. 2018. “Prevalence, Awareness, Treatment and Control of Hypertension and Their Determinants: Results from a National Survey in Kenya.” *BMC Public Health* 18 (Suppl 3). https://doi.org/10.1186/s12889-018-6052-y.

Mohamed, Shukri F., Martin Mwangi, Martin K. Mutua, Joseph Kibachio, Abubakar Hussein, Zachary Ndegwa, Scholastica Owondo, Gershim Asiki, and Catherine Kyobutungi. 2018. “Prevalence and Factors Associated with Pre-Diabetes and Diabetes Mellitus in Kenya: Results from a National Survey.” *BMC Public Health* 18 (3): 1215. https://doi.org/10.1186/s12889-018-6053-x.

Mora, Samia. 2016. “Nonfasting for Routine Lipid Testing: From Evidence to Action.” *JAMA Internal Medicine* 176 (7): 1005–6. https://doi.org/10.1001/jamainternmed.2016.1979.

Morgan, C., J. Kirkbride, G. Hutchinson, T. Craig, K. Morgan, P. Dazzan, J. Boydell, et al. 2008. “Cumulative Social Disadvantage, Ethnicity and First-Episode Psychosis: A Case-Control Study.” *Psychological Medicine* 38 (12): 1701–15. https://doi.org/10.1017/S0033291708004534.

Morgan, Craig, and Helen Fisher. 2007. “Environment and Schizophrenia: Environmental Factors in Schizophrenia: Childhood Trauma—A Critical Review.” *Schizophrenia Bulletin* 33 (1): 3–10. https://doi.org/10.1093/schbul/sbl053.

Morrato, Elaine H., Benjamin Druss, Daniel M. Hartung, Robert J. Valuck, Richard Allen, Elizabeth Campagna, and John W. Newcomer. 2010. “Metabolic Testing Rates in 3 State Medicaid Programs After FDA Warnings and ADA/APA Recommendations for Second-Generation Antipsychotic Drugs.” *Archives of General Psychiatry* 67 (1): 17–24. https://doi.org/10.1001/archgenpsychiatry.2009.179.

Morrato, Elaine H., John W. Newcomer, Siddhesh Kamat, Onur Baser, James Harnett, and Brian Cuffel. 2009. “Metabolic Screening After the American Diabetes Association’s Consensus Statement on Antipsychotic Drugs and Diabetes.” *Diabetes Care* 32 (6): 1037–42. https://doi.org/10.2337/dc08-1720.

Mostofsky, Elizabeth, Harpreet S. Chahal, Kenneth J. Mukamal, Eric B. Rimm, and Murray A. Mittleman. 2016. “Alcohol and Immediate Risk of Cardiovascular Events: A Systematic Review and Dose-Response Meta-Analysis.” *Circulation* 133 (10): 979–87. https://doi.org/10.1161/CIRCULATIONAHA.115.019743.

Motsinger, Charles, Michael Slack, Melanie Weaver, and Morgan Reed. 2006. “Physician Patterns of Metabolic Screening for Patients Taking Atypical Antipsychotics: A Retrospective Database Study.” *Primary Care Companion to The Journal of Clinical Psychiatry* 8 (4): 220–23.

Mucheru, Doreen, Mary-Claire Hanlon, Linda E. Campbell, Mark McEvoy, and Lesley MacDonald-Wicks. 2017a. “Social Dysfunction and Diet Outcomes in People with Psychosis.” *Nutrients* 9 (1). https://doi.org/10.3390/nu9010080.

———. 2017b. “Social Dysfunction and Diet Outcomes in People with Psychosis.” *Nutrients* 9 (1). https://doi.org/10.3390/nu9010080.
———. 2018. “Cardiovascular Disease Lifestyle Risk Factors in People with Psychosis: A Cross-Sectional Study.” *BMC Public Health* 18 (June). https://doi.org/10.1186/s12889-018-5649-5.
Mueser, Kim T., Stanley D. Rosenberg, Lisa A. Goodman, and Susan L. Trumbetta. 2002. “Trauma, PTSD, and the Course of Severe Mental Illness: An Interactive Model.” *Schizophrenia Research* 53 (1): 123–43. https://doi.org/10.1016/S0920-9964(01)00173-6.
Mufunda, Jacob, Rufaro Chatora, Yustina Ndambakuwa, Peter Nyarango, Andrew Kosia, Jephat Chifamba, Antoinie Filipe, Abdulmumini Usman, and V. Harvey Sparks. 2006. “Emerging Non-Communicable Disease Epidemic in Africa: Preventive Measures from the WHO Regional Office for Africa.” *Ethnicity & Disease* 16 (2): 521–26.
Muhammad Chachal et al. 2016. “Cardiovascular Diseases among Patients with Schizophrenia - ScienceDirect” 19 (February): 28–36.
Mujica-Mota, R. E., M. Roberts, G. Abel, M. Elliott, G. Lyratzopoulos, M. Roland, and J. Campbell. 2015. “Common Patterns of Morbidity and Multi-Morbidity and Their Impact on Health-Related Quality of Life: Evidence from a National Survey.” *Quality of Life Research* 24 (4): 909–18. https://doi.org/10.1007/s11136-014-0820-7.
Mukherjee, S., P. Decina, V. Bocola, F. Saraceni, and P. L. Scapicchio. 1996. “Diabetes Mellitus in Schizophrenic Patients.” *Comprehensive Psychiatry* 37 (1): 68–73.
Myers, Jonathan. 2003. “Exercise and Cardiovascular Health.” *Circulation* 107 (1). https://doi.org/10.1161/01.CIR.0000048890.59383.8D.
Myers, Jonathan, Paul McAuley, Carl J. Lavie, Jean-Pierre Despres, Ross Arena, and Peter Kokkinos. 2015. “Physical Activity and Cardiorespiratory Fitness as Major Markers of Cardiovascular Risk: Their Independent and Interwoven Importance to Health Status.” *Progress in Cardiovascular Diseases*, 2013 Global Congress on Physical Activity - All Hearts Need Exercise: A Global Call to Action by the AHA, 57 (4): 306–14. https://doi.org/10.1016/j.pcad.2014.09.011.
Myles, Nicholas, Hannah D. Newall, Jackie Curtis, Olav Nielssen, David Shiers, and Matthew Large. 2012a. “Tobacco Use before, at, and after First-Episode Psychosis: A Systematic Meta-Analysis.” *The Journal of Clinical Psychiatry* 73 (4): 468–75. https://doi.org/10.4088/JCP.11r07222.
———. 2012b. “Tobacco Use Before, At, and After First-Episode Psychosis: A Systematic Meta-Analysis [CME].” *The Journal of Clinical Psychiatry* 73 (4): 468–75. https://doi.org/10.4088/JCP.11r07222.
Naber, Dieter, and Martin Lambert. 2009. “The CATIE and CUtLASS Studies in Schizophrenia: Results and Implications for Clinicians.” *CNS Drugs* 23 (8): 649–59. https://doi.org/10.2165/00023210-200923080-00002.
Nakamura, Kazuto, José J. Fuster, and Kenneth Walsh. 2014. “Adipokines: A Link between Obesity and Cardiovascular Disease.” *Journal of Cardiology* 63 (4): 250–59. https://doi.org/10.1016/j.jjcc.2013.11.006.
Nasrallah Henry et all. 2006. “Low Rates of Treatment for Hypertension, Dyslipidemia and Diabetes in Schizophrenia: Data from the CATIE Schizophrenia Trial Sample at Baseline - ScienceDirect.” 2006. https://www-sciencedirect-com.ezproxy.uct.ac.za/science/article/pii/S0920996406002982.
National High Blood Pressure Education Program. 2004. *Classification of Blood Pressure*. National Heart, Lung, and Blood Institute (US). https://www.ncbi.nlm.nih.gov/books/NBK9633/.
Navickas, Rokas, Vesna-Kerstin Petric, Andrea B. Feigl, and Martin Seychell. 2016. “Multimorbidity: What Do We Know? What Should We Do?” *Journal of Comorbidity* 6 (1): 4–11. https://doi.org/10.15256/joc.2016.6.72.
Ndumele, Chiadi E., Kunihiro Matsushita, Mariana Lazo, Natalie Bello, Roger S. Blumenthal, Gary Gerstenblith, Vijay Nambi, et al. 2016. “Obesity and Subtypes of Incident Cardiovascular Disease.” *Journal of the American Heart Association: Cardiovascular and Cerebrovascular Disease* 5 (8). https://doi.org/10.1161/JAHA.116.003921.
Nenke, Marni A., Lisa A. Hahn, Campbell H. Thompson, Dennis Liu, and Cherrie A. Galletly. 2015. “Psychosis and Cardiovascular Disease: Is Diet the Missing Link?” *Schizophrenia Research* 161 (2): 465–70. https://doi.org/10.1016/j.schres.2014.12.012.
Neria, Yuval, Evelyn J. Bromet, Sylvia Sievers, Janet Lavelle, and Laura J. Fochtmann. 2002. “Trauma Exposure and Posttraumatic Stress Disorder in Psychosis: Findings from a First-Admission Cohort.” *Journal of Consulting and Clinical Psychology* 70 (1): 246–51. https://doi.org/10.1037/0022-006X.70.1.246.
Newcomer, John W, and Dan W Haupt. 2006. “The Metabolic Effects of Antipsychotic Medications.” *The Canadian Journal of Psychiatry* 51 (8): 480–91. https://doi.org/10.1177/070674370605100803.
Ngaruiya, Christine, Hussein Abubakar, Dorcas Kiptui, Ann Kendagor, Melau W. Ntakuka, Philip Nyakundi, and Gladwell Gathecha. 2018. “Tobacco Use and Its Determinants in the 2015 Kenya WHO STEPS Survey.” *BMC Public Health* 18 (3): 1223. https://doi.org/10.1186/s12889-018-6058-5.

Nishanth, K. N., R. K. Chadda, M. Sood, A. Biswas, and R. Lakshmy. 2017. “Physical Comorbidity in Schizophrenia & Its Correlates.” *The Indian Journal of Medical Research* 146 (2): 281. https://doi.org/10.4103/ijmr.IJMR_1510_15.

Njelekela, Marina A, Rose Mpembeni, Alfa Muhihi, Nuru L Mligiliche, Donna Spiegelman, Ellen Hertzmark, Enju Liu, et al. 2009a. “Sex-Related Differences in the Prevalence of Cardiovascular Disease Risk Factors and Their Correlates in Urban Tanzania.” *BMC Cardiovascular Disorders* 9 (July): 30. https://doi.org/10.1186/1471-2261-9-30.

———. 2009b. “Sex-Related Differences in the Prevalence of Cardiovascular Disease Risk Factors and Their Correlates in Urban Tanzania.” *BMC Cardiovascular Disorders* 9 (July): 30. https://doi.org/10.1186/1471-2261-9-30.

Nordentoft, Merete, Kristian Wahlbeck, Jonas Hällgren, Jeanette Westman, Urban Ösby, Hassan Alinaghizadeh, Mika Gissler, and Thomas Munk Laursen. 2013. “Excess Mortality, Causes of Death and Life Expectancy in 270,770 Patients with Recent Onset of Mental Disorders in Denmark, Finland and Sweden.” *PLOS ONE* 8 (1): e55176. https://doi.org/10.1371/journal.pone.0055176.

Nordestgaard, Børge G. 2017. “A Test in Context: Lipid Profile, Fasting Versus Nonfasting.” *Journal of the American College of Cardiology* 70 (13): 1637–46. https://doi.org/10.1016/j.jacc.2017.08.006.

North, Brian J., and David A. Sinclair. 2012. “The Intersection Between Aging and Cardiovascular Disease.” *Circulation Research* 110 (8): 1097–1108. https://doi.org/10.1161/CIRCRESAHA.111.246876.

Northcote, Jeremy, and Michael Livingston. 2011. “Accuracy of Self-Reported Drinking: Observational Verification of ‘Last Occasion’ Drink Estimates of Young Adults.” *Alcohol and Alcoholism* 46 (6): 709–13. https://doi.org/10.1093/alcalc/agr138.

Noubiap, Jean Jacques, Jean Joel Bigna, Jobert Richie Nansseu, Ulrich Flore Nyaga, Eric Vounsia Balti, Justin B Echouffo-Tcheugui, and André Pascal Kengne. 2018. “Prevalence of Dyslipidaemia among Adults in Africa: A Systematic Review and Meta-Analysis.” *The Lancet Global Health* 6 (9): e998–1007. https://doi.org/10.1016/S2214-109X(18)30275-4.

Nuevo, Roberto, Somnath Chatterji, David Fraguas, Emese Verdes, Nirmala Naidoo, Celso Arango, and José Luis Ayuso-Mateos. 2011. “Increased Risk of Diabetes Mellitus among Persons with Psychotic Symptoms: Results from the WHO World Health Survey.” *The Journal of Clinical Psychiatry* 72 (12): 1592–99. https://doi.org/10.4088/JCP.10m06801.

Nyer, Maren, John Kasckow, Ian Fellows, Edith C Lawrence, Shah Golshan, Ellen Solorzano, and Sidney Zisook. 2010. “The Relationship of Marital Status and Clinical Characteristics in Middle-Aged and Older Patients with Schizophrenia and Depressive Symptoms.” *Annals of Clinical Psychiatry* 22 (3): 172–75.

Oberweis, Brandon, and Claudia Gragnoli. 2012. “Potential Role of Prolactin in Antipsychotic-Mediated Association of Schizophrenia and Type 2 Diabetes.” *Journal of Cellular Physiology* 227 (8): 3001–6. https://doi.org/10.1002/jcp.24023.

Oguoma, Victor Maduabuchi, Ezekiel Uba Nwose, Timothy Chas Skinner, Kester Awharentomah Digban, Innocent Chukwu Onyia, and Ross Stuart Richards. 2015. “Prevalence of Cardiovascular Disease Risk Factors among a Nigerian Adult Population: Relationship with Income Level and Accessibility to CVD Risks Screening.” *BMC Public Health* 15 (April): 397. https://doi.org/10.1186/s12889-015-1709-2.

Ohaeri, Jude U., and Abayomi O. Akanji. 2011. “Metabolic Syndrome in Severe Mental Disorders.” *Metabolic Syndrome and Related Disorders* 9 (2): 91–98. https://doi.org/10.1089/met.2010.0053.

Ohi, Kazutaka, Yuzuru Kataoka, Takamitsu Shimada, Aki Kuwata, Hiroaki Okubo, Kohei Kimura, Toshiki Yasuyama, Takashi Uehara, and Yasuhiro Kawasaki. 2018. “Meta-Analysis of Physical Activity and Effects of Social Function and Quality of Life on the Physical Activity in Patients with Schizophrenia.” *European Archives of Psychiatry and Clinical Neuroscience*, May, 1–11. https://doi.org/10.1007/s00406-018-0903-5.

Ohi, Kazutaka, Takamitsu Shimada, Aki Kuwata, Yuzuru Kataoka, Hiroaki Okubo, Kohei Kimura, Toshiki Yasuyama, Takashi Uehara, and Yasuhiro Kawasaki. 2019. “Smoking Rates and Number of Cigarettes Smoked per Day in Schizophrenia: A Large Cohort Meta-Analysis in a Japanese Population.” *International Journal of Neuropsychopharmacology* 22 (1): 19–27. https://doi.org/10.1093/ijnp/pyy061.

Ohira, Tetsuya. 2010. “Psychological Distress and Cardiovascular Disease: The Circulatory Risk in Communities Study (CIRCS).” *Journal of Epidemiology* 20 (3): 185–91. https://doi.org/10.2188/jea.JE20100011.

Öhlin, B., P. M. Nilsson, J.-Å Nilsson, and G. Berglund. 2004. “Chronic Psychosocial Stress Predicts Long-Term Cardiovascular Morbidity and Mortality in Middle-Aged Men.” *European Heart Journal* 25 (10): 867–73. https://doi.org/10.1016/j.ehj.2004.03.003.

Ojike, Nwakile, James R. Sowers, Azizi Seixas, Joseph Ravenell, G. Rodriguez-Figueroa, M. Awadallah, F. Zizi, Girardin Jean-Louis, Olugbenga Ogedegbe, and Samy I. McFarlane. 2016. “Psychological Distress and Hypertension: Results from

the National Health Interview Survey for 2004-2013." *Cardiorenal Medicine* 6 (3): 198–208. https://doi.org/10.1159/000443933.

O'Keefe, James H., Kevin A. Bybee, and Carl J. Lavie. 2007. "Alcohol and Cardiovascular Health: The Razor-Sharp Double-Edged Sword." *Journal of the American College of Cardiology* 50 (11): 1009–14. https://doi.org/10.1016/j.jacc.2007.04.089.

Okkels, Niels, Betina Trabjerg, Mikkel Arendt, and Carsten Bøcker Pedersen. 2017. "Traumatic Stress Disorders and Risk of Subsequent Schizophrenia Spectrum Disorder or Bipolar Disorder: A Nationwide Cohort Study." *Schizophrenia Bulletin* 43 (1): 180–86. https://doi.org/10.1093/schbul/sbw082.

Olafiranye, O, G Jean-Louis, F Zizi, J Nunes, and MT Vincent. 2011. "Anxiety and Cardiovascular Risk: Review of Epidemiological and Clinical Evidence." *Mind & Brain : The Journal of Psychiatry* 2 (1): 32–37.

Orth-Gomér, Kristina, Sarah P. Wamala, Myriam Horsten, Karin Schenck-Gustafsson, Neil Schneiderman, and Murray A. Mittleman. 2000. "Marital Stress Worsens Prognosis in Women With Coronary Heart Disease: The Stockholm Female Coronary Risk Study." *JAMA* 284 (23): 3008–14. https://doi.org/10.1001/jama.284.23.3008.

Osborn, David P. J., Gus Levy, Irwin Nazareth, Irene Petersen, Amir Islam, and Michael B. King. 2007. "Relative Risk of Cardiovascular and Cancer Mortality in People With Severe Mental Illness From the United Kingdom's General Practice Research Database." *Archives of General Psychiatry* 64 (2): 242–49. https://doi.org/10.1001/archpsyc.64.2.242.

Ösby, Urban, Nestor Correia, Lena Brandt, Anders Ekbom, and Pär Sparén. 2000. "Mortality and Causes of Death in Schizophrenia in Stockholm County, Sweden." *Schizophrenia Research* 45 (1): 21–28. https://doi.org/10.1016/S0920-9964(99)00191-7.

P. Manu, L. Dima, M. Shulman, D. Vancampfort, M. De Hert, and C. U. Correll. 2015. "Weight Gain and Obesity in Schizophrenia: Epidemiology, Pathobiology, and Management - Manu - 2015 - Acta Psychiatrica Scandinavica - Wiley Online Library." *Acta Psychiatrica Scandinavica* 132 (2): 97–108.

Pachi, Argiro, Dionisios Bratis, Georgios Moussas, and Athanasios Tselebis. 2013. "Psychiatric Morbidity and Other Factors Affecting Treatment Adherence in Pulmonary Tuberculosis Patients." *Tuberculosis Research and Treatment* 2013. https://doi.org/10.1155/2013/489865.

Padmavati, Ramachandran, Robin G. McCreadie, and Srinivasan Tirupati. 2010. "Low Prevalence of Obesity and Metabolic Syndrome in Never-Treated Chronic Schizophrenia." *Schizophrenia Research* 121 (1): 199–202. https://doi.org/10.1016/j.schres.2010.05.010.

Pasceri, Vincenzo, Giovanni Cammarota, Giuseppe Patti, Lucio Cuoco, Antonio Gasbarrini, Rita L Grillo, Giuseppe Fedeli, Giovanni Gasbarrini, and Attilio Maseri. 1998. "Association of Virulent Helicobacter Pylori Strains With Ischemic Heart Disease." *Circulation* 97: 1675–79.

Patil, Virendra C., Harsha V. Patil, Kuldeep B. Shah, Jay D. Vasani, and Pruthvi Shetty. 2011. "Diastolic Dysfunction in Asymptomatic Type 2 Diabetes Mellitus with Normal Systolic Function." *Journal of Cardiovascular Disease Research* 2 (4): 213–22. https://doi.org/10.4103/0975-3583.89805.

Patnode, Carrie D., Corinne V. Evans, Caitlyn A. Senger, Nadia Redmond, and Jennifer S. Lin. 2017. *Behavioral Counseling to Promote a Healthful Diet and Physical Activity for Cardiovascular Disease Prevention in Adults Without Known Cardiovascular Disease Risk Factors: Updated Systematic Review for the U.S. Preventive Services Task Force*. U.S. Preventive Services Task Force Evidence Syntheses, Formerly Systematic Evidence Reviews. Rockville (MD): Agency for Healthcare Research and Quality (US). http://www.ncbi.nlm.nih.gov/books/NBK476368/.

Patra, Jayadeep, Benjamin Taylor, Hyacinth Irving, Michael Roerecke, Dolly Baliunas, Satya Mohapatra, and Jürgen Rehm. 2010. "Alcohol Consumption and the Risk of Morbidity and Mortality for Different Stroke Types - a Systematic Review and Meta-Analysis." *BMC Public Health* 10 (May): 258. https://doi.org/10.1186/1471-2458-10-258.

Peduzzi, P., J. Concato, E. Kemper, T. R. Holford, and A. R. Feinstein. 1996. "A Simulation Study of the Number of Events per Variable in Logistic Regression Analysis." *Journal of Clinical Epidemiology* 49 (12): 1373–79.

Penedo, Frank J, and Jason R Dahn. 2005. "Exercise and Well-Being: A Review of Mental and Physical Health Benefits Associated with Physical Activity:" *Current Opinion in Psychiatry* 18 (2): 189–93. https://doi.org/10.1097/00001504-200503000-00013.

Pérez-Iglesias, Rocio, Obdulia Martínez-García, Gema Pardo-Garcia, Jose Antonio Amado, M. Teresa Garcia-Unzueta, Rafael Tabares-Seisdedos, and Benedicto Crespo-Facorro. 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." *The International Journal of Neuropsychopharmacology* 17 (01): 41–51. https://doi.org/10.1017/S1461145713001053.

Pérez-Martínez, Pablo, Dimitri P. Mikhailidis, Vasilios G. Athyros, Mónica Bullo, Patrick Couture, María I. Covas, Lawrence de Koning, et al. 2017. "Lifestyle Recommendations for the Prevention and Management of Metabolic Syndrome: An International Panel Recommendation." *Nutrition Reviews* 75 (5): 307–26. https://doi.org/10.1093/nutrit/nux014.

Peter W.F. Wilson, Ralph B. D'Agostino, Helen Parise, Lisa Sullivan, and James B. Meigs. 2005. "Metabolic Syndrome as a Precursor of Cardiovascular Disease and Type 2 Diabetes Mellitus | Circulation." 2005. https://www.ahajournals.org/doi/full/10.1161/circulationaha.105.539528.

Petrie, John R., Tomasz J. Guzik, and Rhian M. Touyz. 2018. "Diabetes, Hypertension, and Cardiovascular Disease: Clinical Insights and Vascular Mechanisms." *The Canadian Journal of Cardiology* 34 (5): 575–84. https://doi.org/10.1016/j.cjca.2017.12.005.

Phelan M, Stradins L, Amin D, Isadore R, Hitrov C, Doyle A, and Inglis R. 2004. "The Physical Health Check: A Tool for Mental Health Workers." *Journal of Mental Health* 13 (3): 277–84.

Piano, Mariann R. 2017. "Alcohol's Effects on the Cardiovascular System." *Alcohol Research : Current Reviews* 38 (2): 219–41.

Pillinger, Toby, Katherine Beck, Cristian Gobjila, Jacek Donocik, Sameer Jauhar, and Oliver Howes. 2017. "Impaired Glucose Homeostasis in First-Episode Schizophrenia: A Systematic Review and Meta-Analysis." *JAMA Psychiatry* 74 (3): 261–69. https://doi.org/10.1001/jamapsychiatry.2016.3803.

Pinto, Elisabete. 2007a. "Blood Pressure and Ageing." *Postgraduate Medical Journal* 83 (976): 109–14. https://doi.org/10.1136/pgmj.2006.048371.

———. 2007b. "Blood Pressure and Ageing." *Postgraduate Medical Journal* 83 (976): 109–14. https://doi.org/10.1136/pgmj.2006.048371.

Polimanti, Renato, Arpana Agrawal, and Joel Gelernter. 2017. "Schizophrenia and Substance Use Comorbidity: A Genome-Wide Perspective." *Genome Medicine* 9 (March). https://doi.org/10.1186/s13073-017-0423-3.

Popovic, David, Andrea Schmitt, Lalit Kaurani, Fanny Senner, Sergi Papiol, Berend Malchow, Andre Fischer, Thomas G. Schulze, Nikolaos Koutsouleris, and Peter Falkai. 2019. "Childhood Trauma in Schizophrenia: Current Findings and Research Perspectives." *Frontiers in Neuroscience* 13. https://doi.org/10.3389/fnins.2019.00274.

Potvin, S., E. Stip, and J.-Y. Roy. 2003. "[Schizophrenia and addiction: An evaluation of the self-medication hypothesis]." *L'Encephale* 29 (3 Pt 1): 193–203.

Praharaj, Samir Kumar, Amlan Kusum Jana, Nishant Goyal, and Vinod Kumar Sinha. 2011. "Metformin for Olanzapine-Induced Weight Gain: A Systematic Review and Meta-Analysis." *British Journal of Clinical Pharmacology* 71 (3): 377–82. https://doi.org/10.1111/j.1365-2125.2010.03783.x.

Prasad, Ds, and Bc Das. 2009. "Physical Inactivity : A Cardiovascular Risk Factor." *Indian Journal of Medical Sciences* 63 (1): 33. https://doi.org/10.4103/0019-5359.49082.

Puddey, I. B., V. Rakic, S. B. Dimmitt, and L. J. Beilin. 1999. "Influence of Pattern of Drinking on Cardiovascular Disease and Cardiovascular Risk Factors--a Review." *Addiction* 94 (5): 649. https://doi.org/10.1046/j.1360-0443.1999.9456493.x.

Puddey, Ian B., and Lawrence J. Beilin. 2006. "Alcohol Is Bad for Blood Pressure." *Clinical and Experimental Pharmacology & Physiology* 33 (9): 847–52. https://doi.org/10.1111/j.1440-1681.2006.04452.x.

Quigley, Harriet, and James H. MacCabe. 2019. "The Relationship between Nicotine and Psychosis." *Therapeutic Advances in Psychopharmacology* 9 (July). https://doi.org/10.1177/2045125319859969.

R., Prasad, Rajiv Garg, and Sanjay Kumar Verma. 2008. "Isoniazid- and Ethambutol-Induced Psychosis." *Annals of Thoracic Medicine* 3 (4): 149–51. https://doi.org/10.4103/1817-1737.43083.

Rabkin, Simon W. 2015. "Impact of Age and Sex on QT Prolongation in Patients Receiving Psychotropics." *Canadian Journal of Psychiatry. Revue Canadienne de Psychiatrie* 60 (5): 206–14.

Rachel Huxley et al. 2006. "Excess Risk of Fatal Coronary Heart Disease Associated with Diabetes in Men and Women: Meta-Analysis of 37 Prospective Cohort Studies | The BMJ." *2006* 332 (73). https://www-bmj-com.ezproxy.uct.ac.za/content/332/7533/73.

Rader, Daniel J. 2007. "Effect of Insulin Resistance, Dyslipidemia, and Intra-Abdominal Adiposity on the Development of Cardiovascular Disease and Diabetes Mellitus." *The American Journal of Medicine*, Modifying Cardiovascular and Metabolic Risk Factors: The Role of the Endocannabinoid System and Cannabinoid Receptors, 120 (3, Supplement 1): S12–18. https://doi.org/10.1016/j.amjmed.2007.01.003.

Ramezankhani, Azra, Fereidoun Azizi, and Farzad Hadaegh. 2019. "Associations of Marital Status with Diabetes, Hypertension, Cardiovascular Disease and All-Cause Mortality: A Long Term Follow-up Study." *PLoS ONE* 14 (4). https://doi.org/10.1371/journal.pone.0215593.

Räsänen, Sami, Helinä Hakko, Kaisa Viilo, V. Benno Meyer-Rochow, and Juha Moring. 2003. "Excess Mortality among Long-Stay Psychiatric Patients in Northern Finland." *Social Psychiatry and Psychiatric Epidemiology* 38 (6): 297–304. https://doi.org/10.1007/s00127-003-0635-2.

Rehm, Jürgen, Colin Mathers, Svetlana Popova, Montarat Thavorncharoensap, Yot Teerawattananon, and Jayadeep Patra. 2009. "Global Burden of Disease and Injury and Economic Cost Attributable to Alcohol Use and Alcohol-Use Disorders." *The Lancet* 373 (9682): 2223–33. https://doi.org/10.1016/S0140-6736(09)60746-7.

Reid, M. Carrington, David A. Fiellin, and Patrick G. O'Connor. 1999. "Hazardous and Harmful Alcohol Consumption in Primary Care." *Archives of Internal Medicine* 159 (15): 1681–89. https://doi.org/10.1001/archinte.159.15.1681.

Reininghaus, Ulrich A., Craig Morgan, Jayne Simpson, Paola Dazzan, Kevin Morgan, Gillian A. Doody, Dinesh Bhugra, et al. 2008. "Unemployment, Social Isolation, Achievement–Expectation Mismatch and Psychosis: Findings from the ÆSOP Study." *Social Psychiatry and Psychiatric Epidemiology* 43 (9): 743–51. https://doi.org/10.1007/s00127-008-0359-4.

Remien, Robert H., Michael J. Stirratt, Nadia Nguyen, Reuben N. Robbins, Andrea N. Pala, and Claude A. Mellins. 2019. "Mental Health and HIV/AIDS: The Need for an Integrated Response." *AIDS* 33 (9): 1411. https://doi.org/10.1097/QAD.0000000000002227.

Resnick, Sandra G., Gary R. Bond, and Kim T. Mueser. 2003. "Trauma and Posttraumatic Stress Disorder in People with Schizophrenia." *Journal of Abnormal Psychology* 112 (3): 415–23. https://doi.org/10.1037/0021-843X.112.3.415.

Ricci, Cristian, Angela Wood, David Muller, Marc J Gunter, Antonio Agudo, Heiner Boeing, Yvonne T van der Schouw, et al. 2018. "Alcohol Intake in Relation to Non-Fatal and Fatal Coronary Heart Disease and Stroke: EPIC-CVD Case-Cohort Study." *The BMJ* 361 (May). https://doi.org/10.1136/bmj.k934.

Richardson, Caroline R., Guy Faulkner, Judith McDevitt, Gary S. Skrinar, Dori S. Hutchinson, and John D. Piette. 2005. "Integrating Physical Activity Into Mental Health Services for Persons With Serious Mental Illness." *Psychiatric Services* 56 (3): 324–31. https://doi.org/10.1176/appi.ps.56.3.324.

Ridker, Paul M., Julie E. Buring, Nader Rifai, and Nancy R. Cook. 2007. "Development and Validation of Improved Algorithms for the Assessment of Global Cardiovascular Risk in Women: The Reynolds Risk Score." *JAMA* 297 (6): 611–19. https://doi.org/10.1001/jama.297.6.611.

Ridner, Sheila H. 2004. "Psychological Distress: Concept Analysis." *Journal of Advanced Nursing* 45 (5): 536–45. https://doi.org/10.1046/j.1365-2648.2003.02938.x.

Rihmer, Zoltán, Xénia Gonda, and Péter Döme. 2017. "Is Mania the Hypertension of the Mood? Discussion of A Hypothesis." *Current Neuropharmacology* 15 (3): 424–33. https://doi.org/10.2174/1570159X14666160902145635.

Ringen, Petter Andreas, John A. Engh, Astrid B. Birkenaes, Ingrid Dieset, and Ole A. Andreassen. 2014. "Increased Mortality in Schizophrenia Due to Cardiovascular Disease – A Non-Systematic Review of Epidemiology, Possible Causes, and Interventions." *Frontiers in Psychiatry* 5 (September). https://doi.org/10.3389/fpsyt.2014.00137.

Risgaard, Bjarke, Kristine Waagstein, Bo Gregers Winkel, Reza Jabbari, Thomas Hadberg Lynge, Charlotte Glinge, Christine Albert, et al. 2015. "Sudden Cardiac Death in Young Adults with Previous Hospital-Based Psychiatric Inpatient and Outpatient Treatment: A Nationwide Cohort Study from Denmark." *The Journal of Clinical Psychiatry* 76 (9): e1122-1129. https://doi.org/10.4088/JCP.14m09742.

Robert H Eckel. 2005. "The Metabolic Syndrome - ScienceDirect." 2005. https://www-sciencedirect-com.ezproxy.uct.ac.za/science/article/pii/S0140673605663787.

Roick, Christiane, Anita Fritz-Wieacker, Herbert Matschinger, Dirk Heider, Jana Schindler, Steffi Riedel-Heller, and Matthias C. Angermeyer. 2007. "Health Habits of Patients with Schizophrenia." *Social Psychiatry and Psychiatric Epidemiology* 42 (4): 268–76. https://doi.org/10.1007/s00127-007-0164-5.

Rojo, Leonel E., Pablo A. Gaspar, H. Silva, L. Risco, Pamela Arena, Karen Cubillos-Robles, and Belen Jara. 2015. "Metabolic Syndrome and Obesity among Users of Second Generation Antipsychotics: A Global Challenge for Modern Psychopharmacology." *Pharmacological Research*, Country in focus: Pharmacology in Chile, 101 (November): 74–85. https://doi.org/10.1016/j.phrs.2015.07.022.

Rolim, Luiz Clemente de Souza Pereira, João Roberto de Sá, Antonio Roberto Chacra, and Sérgio Atala Dib. 2008. "Diabetic Cardiovascular Autonomic Neuropathy: Risk Factors, Clinical Impact and Early Diagnosis." *Arquivos Brasileiros de Cardiologia* 90 (4): e24–32. https://doi.org/10.1590/S0066-782X2008000400014.

Roshanaei-Moghaddam, Babak, and Wayne Katon. 2009. "Premature Mortality From General Medical Illnesses Among Persons With Bipolar Disorder: A Review." *Psychiatric Services* 60 (2): 147–56. https://doi.org/10.1176/ps.2009.60.2.147.

Rozanski, Alan, James A. Blumenthal, and Joan Kaplan. 1999. "Impact of Psychological Factors on the Pathogenesis of Cardiovascular Disease and Implications for Therapy." *Circulation* 99 (16): 2192–2217.

Rummel-Kluge, Christine, Katja Komossa, Sandra Schwarz, Heike Hunger, Franziska Schmid, Claudia Asenjo Lobos, Werner Kissling, John M Davis, and Stefan Leucht. 2010a. "Head-to-Head Comparisons of Metabolic Side Effects of Second Generation Antipsychotics in the Treatment of Schizophrenia: A Systematic Review and Meta-Analysis." *Schizophrenia Research* 123 (2–3): 225–33. https://doi.org/10.1016/j.schres.2010.07.012.

Rummel-Kluge, Christine, Katja Komossa, Sandra Schwarz, Heike Hunger, Franziska Schmid, Claudia Asenjo Lobos, Werner Kissling, John M. Davis, and Stefan Leucht. 2010b. "Head-to-Head Comparisons of Metabolic Side Effects of Second Generation Antipsychotics in the Treatment of Schizophrenia: A Systematic Review and Meta-Analysis." *Schizophrenia Research* 123 (2): 225–33. https://doi.org/10.1016/j.schres.2010.07.012.

Ryan, Aine, Emma Wallace, Paul O'Hara, and Susan M. Smith. 2015. "Multimorbidity and Functional Decline in Community-Dwelling Adults: A Systematic Review." *Health and Quality of Life Outcomes* 13 (October). https://doi.org/10.1186/s12955-015-0355-9.

Ryan, Martina C.M., Patrick Collins, and Jogin H. Thakore. 2003. "Impaired Fasting Glucose Tolerance in First-Episode, Drug-Naive Patients With Schizophrenia." *American Journal of Psychiatry* 160 (2): 284–89. https://doi.org/10.1176/appi.ajp.160.2.284.

Saari, K., J. Jokelainen, J. Veijola, H. Koponen, P. B. Jones, M. Savolainen, M.-R. Järvelin, L. Lauren, M. Isohanni, and S. Lindeman. 2004. "Serum Lipids in Schizophrenia and Other Functional Psychoses: A General Population Northern Finland 1966 Birth Cohort Survey." *Acta Psychiatrica Scandinavica* 110 (4): 279–85. https://doi.org/10.1111/j.1600-0447.2004.00358.x.

Šagud, Marina, Alma Mihaljevi, and Bjanka Vuksan. 2009. "SMOKING AND SCHIZOPHRENIA" 21 (3): 5.

Saha, Sukanta, David Chant, and John McGrath. 2007. "A Systematic Review of Mortality in Schizophrenia: Is the Differential Mortality Gap Worsening Over Time?" *Archives of General Psychiatry* 64 (10): 1123–31. https://doi.org/10.1001/archpsyc.64.10.1123.

Said, Mas Ayu, Ahmad Hatim Sulaiman, Mohd Hussain Habil, Srijit Das, Abdul Kadir Abu Bakar, Rosliwati Yusoff, Tsui Huei Loo, and Shamshunnisah Abu Bakar. 2012. "Metabolic Syndrome and Cardiovascular Risk among Patients with Schizophrenia Receiving Antipsychotics in Malaysia," 7.

Salokangas, R. K. R., T. Honkonen, E. Stengård, and A.-M. Koivisto. 2001. "To Be or Not to Be Married – That Is the Question of Quality of Life in Men with Schizophrenia." *Social Psychiatry and Psychiatric Epidemiology* 36 (8): 381–90. https://doi.org/10.1007/s001270170028.

Saloojee, Shamima, Jonathan K. Burns, and Ayesha A. Motala. 2014. "Very Low Rates of Screening for Metabolic Syndrome among Patients with Severe Mental Illness in Durban, South Africa." *BMC Psychiatry* 14 (1): 228. https://doi.org/10.1186/s12888-014-0228-5.

Saloojee, Shamima, Jonathan K Burns, and Ayesha A Motala. 2016a. "Metabolic Syndrome in South African Patients with Severe Mental Illness: Prevalence and Associated Risk Factors." *PLoS ONE* 11 (2). https://doi.org/10.1371/journal.pone.0149209.

Saloojee, Shamima, Jonathan K. Burns, and Ayesha A. Motala. 2016b. "Metabolic Syndrome in South African Patients with Severe Mental Illness: Prevalence and Associated Risk Factors." *PLOS ONE* 11 (2): e0149209. https://doi.org/10.1371/journal.pone.0149209.

———. 2017. "High Risk of Metabolic Syndrome among Black South African Women with Severe Mental Illness." *The South African Journal of Psychiatry : SAJP : The Journal of the Society of Psychiatrists of South Africa* 23 (April). https://doi.org/10.4102/sajpsychiatry.v23i0.1089.

Salvatore Motillo et al. 2010. "The Metabolic Syndrome and Cardiovascular Risk: A Systematic Review and Meta-Analysis - ScienceDirect." 2010. https://www.sciencedirect.com/science/article/pii/S0735109710026380.

Samele, Chiara. 2004. "Factors Leading to Poor Physical Health in People with Psychosis." *Epidemiologia e Psichiatria Sociale* 13 (3): 141–45. https://doi.org/10.1017/S1121189X00003407.

Samele, Chiara, Maxine Patel, Jane Boydell, Morven Leese, Simon Wessely, and Robin Murray. 2007. "Physical Illness and Lifestyle Risk Factors in People with Their First Presentation of Psychosis." *Social Psychiatry and Psychiatric Epidemiology* 42 (2): 117–24. https://doi.org/10.1007/s00127-006-0135-2.

Sanne A E Peters et al. 2014. "Diabetes as a Risk Factor for Stroke in Women Compared with Men: A Systematic Review and Meta-Analysis of 64 Cohorts, Including 775 385 Individuals and 12 539 Strokes - ScienceDirect" 383 (9933): 1973–80.

Santra, Sukamal, Asish Kumar Basu, Pradip Roychowdhury, Ramtanu Banerjee, Pankaj Singhania, Sudhakar Singh, and Utpal Kumar Datta. 2011. "Comparison of Left Ventricular Mass in Normotensive Type 2 Diabetes Mellitus Patients with That in the Nondiabetic Population." *Journal of Cardiovascular Disease Research* 2 (1): 50–56. https://doi.org/10.4103/0975-3583.78597.

Schultz, William M., Salim S. Hayek, Ayman Samman Tahhan, Yi-An Ko, Pratik Sandesara, Mosaab Awad, Kareem H. Mohammed, et al. 2017. "Marital Status and Outcomes in Patients With Cardiovascular Disease." *Journal of the American Heart Association: Cardiovascular and Cerebrovascular Disease* 6 (12). https://doi.org/10.1161/JAHA.117.005890.

Schwingshackl, Lukas, Georg Hoffmann, Tamara Kalle-Uhlmann, Maria Arregui, Brian Buijsse, and Heiner Boeing. 2015. "Fruit and Vegetable Consumption and Changes in Anthropometric Variables in Adult Populations: A Systematic Review and Meta-Analysis of Prospective Cohort Studies." *PLoS ONE* 10 (10). https://doi.org/10.1371/journal.pone.0140846.

Scigliano, Giulio, and Gabriele Ronchetti. 2013. "Antipsychotic-Induced Metabolic and Cardiovascular Side Effects in Schizophrenia: A Novel Mechanistic Hypothesis." *CNS Drugs* 27 (4): 249–57. https://doi.org/10.1007/s40263-013-0054-1.

Scott, David, Brenda Happell, Sheree Strange, and Chris Platania-Phung. 2013. "Investigating Self-Reported Health Behaviors in Australian Adults with Mental Illness." *Behavioral Medicine* 39 (3): 60–65. https://doi.org/10.1080/08964289.2012.726289.

Scott, David, Chris Platania-Phung, and Brenda Happell. 2012. "Quality of Care for Cardiovascular Disease and Diabetes amongst Individuals with Serious Mental Illness and Those Using Antipsychotic Medications." *Journal for Healthcare Quality: Official Publication of the National Association for Healthcare Quality* 34 (5): 15–21. https://doi.org/10.1111/j.1945-1474.2011.00155.x.

Scott, Kate M., Carmen Lim, Ali Al-Hamzawi, Jordi Alonso, Ronny Bruffaerts, José Miguel Caldas-de-Almeida, Silvia Florescu, et al. 2016. "Association of Mental Disorders With Subsequent Chronic Physical Conditions: World Mental Health Surveys From 17 Countries." *JAMA Psychiatry* 73 (2): 150–58. https://doi.org/10.1001/jamapsychiatry.2015.2688.

Seeman, Mary V. 2016. "Obesity in Schizophrenia." *Journal of Obesity Management* 1 (1): 10. https://doi.org/10.14302/issn.2574-450X.jom-16-1039.

Sengupta, Sarojini, Maria A. Parrilla-Escobar, Ruby Klink, Ferid Fathalli, Ying Kin Ng, Emmanuel Stip, Trino Baptista, Ashok Malla, and Ridha Joober. 2008. "Are Metabolic Indices Different between Drug-Naïve First-Episode Psychosis Patients and Healthy Controls?" *Schizophrenia Research* 102 (1): 329–36. https://doi.org/10.1016/j.schres.2008.02.013.

Seow, Lee Seng Esmond, Siow Ann Chong, Peizhi Wang, Saleha Shafie, Hui Lin Ong, and Mythily Subramaniam. 2017. "Metabolic Syndrome and Cardiovascular Risk among Institutionalized Patients with Schizophrenia Receiving Long Term Tertiary Care." *Comprehensive Psychiatry* 74 (April): 196–203. https://doi.org/10.1016/j.comppsych.2017.01.017.

Shafie, Saleha, Siau Pheng Lee, Samantha Bee Cheng Ong, Peizhi Wang, Esmond Seow, Hui Lin Ong, Siow Ann Chong, and Mythily Subramaniam. 2018. "Prevalence and Correlates of Diabetes Mellitus and Dyslipidaemia in a Long-Stay Inpatient Schizophrenia Population in Singapore." *Singapore Medical Journal* 59 (9): 465–71. https://doi.org/10.11622/smedj.2018020.

Sheehan, DV, Y Lecrubier, K Harnett Sheehan, J Janavs, E Weiller, A Keskiner, J Schinka, E Knapp, MF Sheehan, and GC Dunbar. 1997. "The Validity of the Mini International Neuropsychiatric Interview (MINI) According to the SCID-P and Its Reliability." *European Psychiatry* 12 (5): 232–41. https://doi.org/10.1016/S0924-9338(97)83297-X.

Shen- Chieh Chang et all. 2012. "Metabolic and Cardiovascular Adverse Effects Associated with Treatment with Antipsychotic Drugs - ScienceDirect." 2012. https://www-sciencedirect-com.ezproxy.uct.ac.za/science/article/pii/S1878331712000253#bib29.

Shevlin, Mark, James E. Houston, Martin J. Dorahy, and Gary Adamson. 2008. "Cumulative Traumas and Psychosis: An Analysis of the National Comorbidity Survey and the British Psychiatric Morbidity Survey." *Schizophrenia Bulletin* 34 (1): 193–99. https://doi.org/10.1093/schbul/sbm069.

Shih, Pei-an Betty, and Daniel T. O'Connor. 2008. "Hereditary Determinants of Human Hypertension." *Hypertension* 51 (6): 1456–64. https://doi.org/10.1161/HYPERTENSIONAHA.107.090480.

Shufelt C.L., Pacheco C, Tweet M.S.., and Miller V.M. 2018. "Sex-Specific Physiology and Cardiovascular Disease | SpringerLink." In *Sex-Specific Physiology and Cardiovascular Disease*, 433–54. SPringer, Cham. https://link.springer.com/chapter/10.1007%2F978-3-319-77932-4_27#citeas.

Singh, Dinesh, Alan Berkman, and Michaeline Bresnahan. 2009. "Seroprevalence and HIV-Associated Factors among Adults with Severe Mental Illness – a Vulnerable Population." *South African Medical Journal = Suid-Afrikaanse Tydskrif Vir Geneeskunde* 99 (7): 523–27.

Singla, Parul, Animesh Bardoloi, and Anuj A Parkash. 2010. "Metabolic Effects of Obesity: A Review." *World Journal of Diabetes* 1 (3): 76–88. https://doi.org/10.4239/wjd.v1.i3.76.

Sipahioglu, M. H., H. Kucuk, A. Unal, M. G. Kaya, F. Oguz, B. Tokgoz, O. Oymak, and C. Utas. 2012. "Impact of Arterial Stiffness on Adverse Cardiovascular Outcomes and Mortality in Peritoneal Dialysis Patients." *Peritoneal Dialysis International* 32 (1): 73–80. https://doi.org/10.3747/pdi.2010.00186.

Siscovick, David S., Linda Fried, Maurice Mittelmark, Gale Rutan, Diane Bild, and Daniel H. O'Leary. 1997. "Exercise Intensity and Subclinical Cardiovascular Disease in the ElderlyThe Cardiovascular Health Study." *American Journal of Epidemiology* 145 (11): 977–86. https://doi.org/10.1093/oxfordjournals.aje.a009066.

Siskind, Dan J., Janni Leung, Anthony W. Russell, Daniel Wysoczanski, and Steve Kisely. 2016. "Metformin for Clozapine Associated Obesity: A Systematic Review and Meta-Analysis." *PLoS ONE* 11 (6). https://doi.org/10.1371/journal.pone.0156208.

Slavin, Joanne L., and Beate Lloyd. 2012. "Health Benefits of Fruits and Vegetables1." *Advances in Nutrition* 3 (4): 506–16. https://doi.org/10.3945/an.112.002154.

Smith, Daniel J., Julie Langan, Gary McLean, Bruce Guthrie, and Stewart W. Mercer. 2013. "Schizophrenia Is Associated with Excess Multiple Physical-Health Comorbidities but Low Levels of Recorded Cardiovascular Disease in Primary Care: Cross-Sectional Study." *BMJ Open* 3 (4): e002808. https://doi.org/10.1136/bmjopen-2013-002808.

Smith, Shubulade, David Yeomans, Chris J.P. Bushe, Cecilia Eriksson, Tom Harrison, Robert Holmes, Laurence Mynors-Wallis, Helen Oatway, and Gary Sullivan. 2007. "A Well-Being Programme in Severe Mental Illness. Reducing Risk for Physical Ill-Health: A Post-Programme Service Evaluation at 2years." *European Psychiatry* 22 (7): 413–18. https://doi.org/10.1016/j.eurpsy.2007.07.002.

Smith, Sidney C. 2007. "Multiple Risk Factors for Cardiovascular Disease and Diabetes Mellitus." *The American Journal of Medicine*, Modifying Cardiovascular and Metabolic Risk Factors: The Role of the Endocannabinoid System and Cannabinoid Receptors, 120 (3, Supplement 1): S3–11. https://doi.org/10.1016/j.amjmed.2007.01.002.

Sniderman, Allan D, and Curt D Furberg. 2008. "Age as a Modifiable Risk Factor for Cardiovascular Disease." *The Lancet* 371 (9623): 1547–49. https://doi.org/10.1016/S0140-6736(08)60313-X.

Sonne, Susan C., and Kathleen T. Brady. 2002. "Bipolar Disorder and Alcoholism." *Alcohol Research & Health* 26 (2): 103–8.

Soreca, Isabella, Andrea Fagiolini, Ellen Frank, Patricia R. Houck, Wesley K. Thompson, and David J. Kupfer. 2008. "Relationship of General Medical Burden, Duration of Illness and Age in Patients with Bipolar I Disorder." *Journal of Psychiatric Research* 42 (11): 956–61. https://doi.org/10.1016/j.jpsychires.2007.10.009.

Spanbroek, R., R. Grabner, K. Lotzer, M. Hildner, A. Urbach, K. Ruhling, M. P. W. Moos, et al. 2003. "Expanding Expression of the 5-Lipoxygenase Pathway within the Arterial Wall during Human Atherogenesis." *Proceedings of the National Academy of Sciences* 100 (3): 1238–43. https://doi.org/10.1073/pnas.242716099.

Spataro, Josie, Paul E. Mullen, Philip M. Burgess, David L. Wells, and Simon A. Moss. 2004. "Impact of Child Sexual Abuse on Mental Health." *The British Journal of Psychiatry* 184 (5): 416–21. https://doi.org/10.1192/bjp.184.5.416.

Staessen, Jan A., Lutgarde Thijs, Robert Fagard, Eoin T. O'Brien, Denis Clement, Peter W. de Leeuw, Giuseppe Mancia, et al. 1999. "Predicting Cardiovascular Risk Using Conventional vs Ambulatory Blood Pressure in Older Patients With Systolic Hypertension." *JAMA* 282 (6): 539–46. https://doi.org/10.1001/jama.282.6.539.

Stamler, Jeremiah, Rose Stamler, and James D. Neaton. 1993. "Blood Pressure, Systolic and Diastolic, and Cardiovascular Risks: US Population Data." *Archives of Internal Medicine* 153 (5): 598–615. https://doi.org/10.1001/archinte.1993.00410050036006.

Stanton, Robert, David Scott, and Brenda Happell. 2016. "Low Knowledge of Physical Health Behaviours Is Associated with Poor Diet and Chronic Illness in Adults." *Australian Journal Of Primary Health* 22 (3): 226–32. https://doi.org/10.1071/PY14132.

Stein, Dan J., Kate Scott, Josep M. Haro Abad, Sergio Aguilar-Gaxiola, Jordi Alonso, Matthias Angermeyer, Koen Demytteneare, et al. 2010. "Early Childhood Adversity and Later Hypertension: Data from the World Mental Health Survey." *Annals of Clinical Psychiatry : Official Journal of the American Academy of Clinical Psychiatrists* 22 (1): 19–28.

Steptoe, Andrew, and Mika Kivimäki. 2012. "Stress and Cardiovascular Disease." *Nature Reviews Cardiology* 9 (6): 360–70. https://doi.org/10.1038/nrcardio.2012.45.

Steven Haffner. 2005. "The Metabolic Syndrome: Inflammation, Diabetes Mellitus, and Cardiovascular Disease - ScienceDirect." 2005. https://www-sciencedirect-com.ezproxy.uct.ac.za/science/article/pii/S000291490502028X.

Stevenson, Anne, Dickens Akena, Rocky E Stroud, Lukoye Atwoli, Megan M Campbell, Lori B Chibnik, Edith Kwobah, et al. 2019. "Neuropsychiatric Genetics of African Populations-Psychosis (NeuroGAP-Psychosis): A Case-Control Study Protocol and GWAS in Ethiopia, Kenya, South Africa and Uganda." *BMJ Open* 9 (2). https://doi.org/10.1136/bmjopen-2018-025469.

Stewart, Kerry J. 2002. “Exercise Training and the Cardiovascular Consequences of Type 2 Diabetes and Hypertension: Plausible Mechanisms for Improving Cardiovascular Health.” *JAMA* 288 (13): 1622–31. https://doi.org/10.1001/jama.288.13.1622.

Strassnig, Martin, Jaspreet S. Brar, and Rohan Ganguli. 2011. “Low Cardiorespiratory Fitness and Physical Functional Capacity in Obese Patients with Schizophrenia.” *Schizophrenia Research* 126 (1–3): 103–9. https://doi.org/10.1016/j.schres.2010.10.025.

Strassnig, Martin, Jean Miewald, Matcheri Keshavan, and Rohan Ganguli. 2007. “Weight Gain in Newly Diagnosed First-Episode Psychosis Patients and Healthy Comparisons: One-Year Analysis.” *Schizophrenia Research* 93 (1–3): 90–98. https://doi.org/10.1016/j.schres.2007.02.024.

Stubbs, Brendon, Joseph Firth, Alexandra Berry, Felipe B. Schuch, Simon Rosenbaum, Fiona Gaughran, Nicola Veronesse, et al. 2016. “How Much Physical Activity Do People with Schizophrenia Engage in? A Systematic Review, Comparative Meta-Analysis and Meta-Regression.” *Schizophrenia Research* 176 (2): 431–40. https://doi.org/10.1016/j.schres.2016.05.017.

Stubbs, Brendon, Ai Koyanagi, Felipe Schuch, Joseph Firth, Simon Rosenbaum, Fiona Gaughran, James Mugisha, and Davy Vancampfort. 2017a. “Physical Activity Levels and Psychosis: A Mediation Analysis of Factors Influencing Physical Activity Target Achievement Among 204 186 People Across 46 Low- and Middle-Income Countries.” *Schizophrenia Bulletin* 43 (3): 536–45. https://doi.org/10.1093/schbul/sbw111.

———. 2017b. “Physical Activity Levels and Psychosis: A Mediation Analysis of Factors Influencing Physical Activity Target Achievement Among 204 186 People Across 46 Low- and Middle-Income Countries.” *Schizophrenia Bulletin* 43 (3): 536–45. https://doi.org/10.1093/schbul/sbw111.

Stubbs, Brendon, Julie Williams, Fiona Gaughran, and Tom Craig. 2016. “How Sedentary Are People with Psychosis? A Systematic Review and Meta-Analysis.” *Schizophrenia Research* 171 (1): 103–9. https://doi.org/10.1016/j.schres.2016.01.034.

Sugai, Takuro, Yutaro Suzuki, Manabu Yamazaki, Kazutaka Shimoda, Takao Mori, Yuji Ozeki, Hiroshi Matsuda, et al. 2016a. “High Prevalence of Obesity, Hypertension, Hyperlipidemia, and Diabetes Mellitus in Japanese Outpatients with Schizophrenia: A Nationwide Survey.” *PLoS ONE* 11 (11). https://doi.org/10.1371/journal.pone.0166429.

———. 2016b. “High Prevalence of Obesity, Hypertension, Hyperlipidemia, and Diabetes Mellitus in Japanese Outpatients with Schizophrenia: A Nationwide Survey.” *PLoS ONE* 11 (11). https://doi.org/10.1371/journal.pone.0166429.

Sullivan, Patrick F., Kenneth S. Kendler, and Michael C. Neale. 2003. “Schizophrenia as a Complex Trait: Evidence From a Meta-Analysis of Twin Studies.” *Archives of General Psychiatry* 60 (12): 1187–92. https://doi.org/10.1001/archpsyc.60.12.1187.

Sumner Jennifer A., Kubzansky Laura D., Elkind Mitchell S.V., Roberts Andrea L., Agnew-Blais Jessica, Chen Qixuan, Cerdá Magdalena, et al. 2015. “Trauma Exposure and Posttraumatic Stress Disorder Symptoms Predict Onset of Cardiovascular Events in Women.” *Circulation* 132 (4): 251–59. https://doi.org/10.1161/CIRCULATIONAHA.114.014492.

Susan Cheng, Susan Cheng, MD; Veroˆnica R.S. Fernandes, MD, PhD; David A. Bluemke, MD, PhD;, Robyn L. McClelland, PhD; Richard A. Kronmal, PhD; Joa˜o A.C. Lima, MD, Robyn L. McClelland, PhD; Richard A. Kronmal, PhD; Joa˜o A.C. Lima, MD, Susan Cheng, and Susan Cheng. 2009. “Age-Related Left Ventricular Remodeling and Associated Risk for Cardiovascular Outcomes: The Multi-Ethnic Study of Atherosclerosis.” *Circulation, Cardiovascular Inaging* 2 (3): 191–98.

Takagi, Hisato, and Takuya Umemoto. 2017. “Association of Hypertension with Abdominal Aortic Aneurysm Expansion.” *Annals of Vascular Surgery* 39 (February): 74–89. https://doi.org/10.1016/j.avsg.2016.04.019.

Tattersall Matthew C., Guo Mengye, Korcarz Claudia E., Gepner Adam D., Kaufman Joel D., Liu Kiang J., Barr R. Graham, et al. 2015. “Asthma Predicts Cardiovascular Disease Events.” *Arteriosclerosis, Thrombosis, and Vascular Biology* 35 (6): 1520–25. https://doi.org/10.1161/ATVBAHA.115.305452.

Tay, Yi Hang, Milawaty Nurjono, and Jimmy Lee. 2013. “Increased Framingham 10-Year CVD Risk in Chinese Patients with Schizophrenia.” *Schizophrenia Research* 147 (1): 187–92. https://doi.org/10.1016/j.schres.2013.03.023.

Teasdale, Scott B., Philip B. Ward, Simon Rosenbaum, Katherine Samaras, and Brendon Stubbs. 2017. “Solving a Weighty Problem: Systematic Review and Meta-Analysis of Nutrition Interventions in Severe Mental Illness.” *The British Journal of Psychiatry* 210 (2): 110–18. https://doi.org/10.1192/bjp.bp.115.177139.

Tedla, Yacob G., Yuichiro Yano, Mercedes Carnethon, and Philip Greenland. 2017. “Association Between Long-Term Blood Pressure Variability and 10-Year Progression in Arterial Stiffness: The Multiethnic Study of Atherosclerosis.” *Hypertension* 69 (1): 118–27. https://doi.org/10.1161/HYPERTENSIONAHA.116.08427.

Teicher, Martin H., Carl M. Anderson, Kyoko Ohashi, and Ann Polcari. 2014. “Childhood Maltreatment: Altered Network Centrality of Cingulate, Precuneus, Temporal Pole and Insula.” *Biological Psychiatry* 76 (4): 297–305. https://doi.org/10.1016/j.biopsych.2013.09.016.

Tensae, Debebe W., Haddis Solomon, Berhanu Boru, and Wondale Getinet. 2018. “Prevalence and Correlates of Alcohol Use Disorders among Bipolar Patients at Amanuel Mental Specialized Hospital, Addis Ababa (Ethiopia): A Cross-Sectional Institution Based Study.” *Journal of Public Health in Africa* 9 (3). https://doi.org/10.4081/jphia.2018.829.

Teshome, Tesfaye, Dejene Hailu Kassa, and Agete Tadewos Hirigo. 2020. “Prevalence and Associated Factors of Metabolic Syndrome Among Patients with Severe Mental Illness at Hawassa, Southern-Ethiopia.” *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy* 13 (February): 569–79. https://doi.org/10.2147/DMSO.S235379.

Thoma, Patrizia, and Irene Daum. 2013. “Comorbid Substance Use Disorder in Schizophrenia: A Selective Overview of Neurobiological and Cognitive Underpinnings.” *Psychiatry and Clinical Neurosciences* 67 (6): 367–83. https://doi.org/10.1111/pcn.12072.

Toalson, Patrick, Saeeduddin Ahmed, Thomas Hardy, and Gary Kabinoff. 2004. “The Metabolic Syndrome in Patients With Severe Mental Illnesses.” *The Primary Care Companion to The Journal of Clinical Psychiatry* 06 (04): 152–58. https://doi.org/10.4088/PCC.v06n0402.

Toftdahl, Nanna Gilliam, Merete Nordentoft, and Carsten Hjorthøj. 2016. “Prevalence of Substance Use Disorders in Psychiatric Patients: A Nationwide Danish Population-Based Study.” *Social Psychiatry and Psychiatric Epidemiology* 51 (1): 129–40. https://doi.org/10.1007/s00127-015-1104-4.

Tøge, Anne G. 2016. “Health Effects of Unemployment in Europe During the Great Recession: The Impact of Unemployment Generosity.” *International Journal of Health Services* 46 (4): 614–41. https://doi.org/10.1177/0020731416664688.

Toth, Peter P. 2016. “Triglyceride-Rich Lipoproteins as a Causal Factor for Cardiovascular Disease.” *Vascular Health and Risk Management* 12 (May): 171–83. https://doi.org/10.2147/VHRM.S104369.

Triant, Virginia A. 2013. “Cardiovascular Disease and HIV Infection.” *Current HIV/AIDS Reports* 10 (3): 199–206. https://doi.org/10.1007/s11904-013-0168-6.

Troxel, Wendy M., Karen A. Matthews, Linda C. Gallo, and Lewis H. Kuller. 2005. “Marital Quality and Occurrence of the Metabolic Syndrome in Women.” *Archives of Internal Medicine* 165 (9): 1022–27. https://doi.org/10.1001/archinte.165.9.1022.

Tselepis, Alexandros D, and M John Chapman. 2002. “Inflammation, Bioactive Lipids and Atherosclerosis: Potential Roles of a Lipoprotein-Associated Phospholipase A2, Platelet Activating Factor-Acetylhydrolase.” *Atherosclerosis Supplements* 3 (4): 57–68. https://doi.org/10.1016/S1567-5688(02)00045-4.

Tseng, Ping-Tao, Hung-Yu Wang, Yu-Shian Cheng, Feng-Chih Shen, Pao-Yen Lin, and Ching-Kuan Wu. 2014. “The Metabolic Syndrome and Risk of Coronary Artery Disease in Patients with Chronic Schizophrenia or Schizoaffective Disorder in a Chronic Mental Institute.” *The Kaohsiung Journal of Medical Sciences* 30 (11): 579–86. https://doi.org/10.1016/j.kjms.2014.09.002.

Tsoi, Daniel T., Mamta Porwal, and Angela C. Webster. 2013. “Interventions for Smoking Cessation and Reduction in Individuals with Schizophrenia.” *Cochrane Database of Systematic Reviews*, no. 2. https://doi.org/10.1002/14651858.CD007253.pub3.

Tsuda, Yoshiyuki, Junji Saruwatari, and Norio Yasui-Furukori. 2014. “Meta-Analysis: The Effects of Smoking on the Disposition of Two Commonly Used Antipsychotic Agents, Olanzapine and Clozapine.” *BMJ Open* 4 (3). https://doi.org/10.1136/bmjopen-2013-004216.

Tulp, Orien L., Olayide F. Obidi, Temitope C. Oyesile, and George P. Einstein. 2018. “The Prevalence of Adult Obesity in Africa: A Meta-Analysis.” *Gene Reports* 11 (June): 124–26. https://doi.org/10.1016/j.genrep.2018.03.006.

Tune, Johnathan D., Adam G. Goodwill, Daniel J. Sassoon, and Kieren J. Mather. 2017. “Cardiovascular Consequences of Metabolic Syndrome.” *Translational Research : The Journal of Laboratory and Clinical Medicine* 183 (May): 57–70. https://doi.org/10.1016/j.trsl.2017.01.001.

Tuoyire, Derek Anamaale, and Harold Ayetey. 2019. “SEX DIFFERENCES IN THE ASSOCIATION BETWEEN MARITAL STATUS AND HYPERTENSION IN GHANA.” *Journal of Biosocial Science* 51 (3): 313–34. https://doi.org/10.1017/S0021932018000147.

Tzoulaki, Ioanna, Paul Elliott, Vasilis Kontis, and Majid Ezzati. 2016. “Worldwide Exposures to Cardiovascular Risk Factors and Associated Health Effects: Current Knowledge and Data Gaps.” *Circulation* 133 (23): 2314–33. https://doi.org/10.1161/CIRCULATIONAHA.115.008718.

Uçok, Alp, Aslihan Polat, Oya Bozkurt, and Handan Meteris. 2004. “Cigarette Smoking among Patients with Schizophrenia and Bipolar Disorders.” *Psychiatry and Clinical Neurosciences* 58 (4): 434–37. https://doi.org/10.1111/j.1440-1819.2004.01279.x.

Unwin, Catherine R. Stevenson, Julia A. Critchley, Nita G. Forouhi, Gojka Roglic, Brian G. Williams, Christopher Dye, Nigel C. 2016. “Diabetes and the Risk of Tuberculosis: A Neglected Threat to Public Health? - Catherine R. Stevenson, Julia A. Critchley, Nita G. Forouhi, Gojka Roglic, Brian G. Williams, Christopher Dye, Nigel C. Unwin, 2007.” *Chronic Illness*, June. http://journals.sagepub.com/doi/abs/10.1177/1742395307081502.

Van Gaal, Luc F., Ilse L. Mertens, and Christophe E. De Block. 2006. “Mechanisms Linking Obesity with Cardiovascular Disease.” *Nature* 444 (7121): 875–80. https://doi.org/10.1038/nature05487.

Vanable, Peter A., Michael P. Carey, Kate B. Carey, and Stephen A. Maisto. 2003. “Smoking Among Psychiatric Outpatients: Relationship to Substance Use, Diagnosis, and Illness Severity.” *Psychology of Addictive Behaviors : Journal of the Society of Psychologists in Addictive Behaviors* 17 (4): 259–65. https://doi.org/10.1037/0893-164X.17.4.259.

Vancampfort, D., J. Knapen, M. Probst, T. Scheewe, S. Remans, and M. De Hert. 2012. “A Systematic Review of Correlates of Physical Activity in Patients with Schizophrenia.” *Acta Psychiatrica Scandinavica* 125 (5): 352–62. https://doi.org/10.1111/j.1600-0447.2011.01814.x.

Vancampfort, D., M. Probst, K. Sweers, K. Maurissen, J. Knapen, and M. De Hert. 2011. “Relationships between Obesity, Functional Exercise Capacity, Physical Activity Participation and Physical Self-Perception in People with Schizophrenia.” *Acta Psychiatrica Scandinavica* 123 (6): 423–30. https://doi.org/10.1111/j.1600-0447.2010.01666.x.

Vancampfort, D., K. Sweers, M. Probst, K. Maurissen, J. Knapen, P. Minguet, and M. De Hert. 2011. “Association of the Metabolic Syndrome with Physical Activity Performance in Patients with Schizophrenia.” *Diabetes & Metabolism* 37 (4): 318–23. https://doi.org/10.1016/j.diabet.2010.12.007.

Vancampfort, Davy, Christoph U. Correll, Britta Galling, Michel Probst, Marc De Hert, Philip B. Ward, Simon Rosenbaum, Fiona Gaughran, John Lally, and Brendon Stubbs. 2016. “Diabetes Mellitus in People with Schizophrenia, Bipolar Disorder and Major Depressive Disorder: A Systematic Review and Large Scale Meta-analysis.” *World Psychiatry* 15 (2): 166–74. https://doi.org/10.1002/wps.20309.

Vancampfort, Davy, Marc De Hert, Kim Sweers, Amber De Herdt, Johan Detraux, and Michel Probst. 2013. “Diabetes, Physical Activity Participation and Exercise Capacity in Patients with Schizophrenia.” *Psychiatry and Clinical Neurosciences* 67 (6): 451–56. https://doi.org/10.1111/pcn.12077.

Vancampfort, Davy, Joseph Firth, Felipe B. Schuch, Simon Rosenbaum, James Mugisha, Mats Hallgren, Michel Probst, et al. 2017. “Sedentary Behavior and Physical Activity Levels in People with Schizophrenia, Bipolar Disorder and Major Depressive Disorder: A Global Systematic Review and Meta-Analysis.” *World Psychiatry* 16 (3): 308–15. https://doi.org/10.1002/wps.20458.

Vancampfort, Davy, Michel Probst, Amber De Herdt, Rui Manuel Nunes Corredeira, Attilio Carraro, Dirk De Wachter, and Marc De Hert. 2013. “An Impaired Health Related Muscular Fitness Contributes to a Reduced Walking Capacity in Patients with Schizophrenia: A Cross-Sectional Study.” *BMC Psychiatry* 13 (January): 5. https://doi.org/10.1186/1471-244X-13-5.

Vancampfort, Davy, Kristof Vansteelandt, Christoph U. Correll, Alex J. Mitchell, Amber De Herdt, Pascal Sienaert, Michel Probst, and Marc De Hert. 2013. “Metabolic Syndrome and Metabolic Abnormalities in Bipolar Disorder: A Meta-Analysis of Prevalence Rates and Moderators.” *The American Journal of Psychiatry* 170 (3): 265–74. https://doi.org/10.1176/appi.ajp.2012.12050620.

Vanhees, L, N Geladas, D Hansen, E Kouidi, J Niebauer, Ž Reiner, V Cornelissen, S Adamopoulos, E Prescott, and M Börjesson. 2012. “Importance of Characteristics and Modalities of Physical Activity and Exercise in the Management of Cardiovascular Health in Individuals with Cardiovascular Risk Factors: Recommendations from the EACPR (Part II).” *European Journal of Preventive Cardiology* 19 (5): 1005–33. https://doi.org/10.1177/1741826711430926.

Varese, Filippo, Feikje Smeets, Marjan Drukker, Ritsaert Lieverse, Tineke Lataster, Wolfgang Viechtbauer, John Read, Jim van Os, and Richard P. Bentall. 2012. “Childhood Adversities Increase the Risk of Psychosis: A Meta-Analysis of Patient-Control, Prospective- and Cross-Sectional Cohort Studies.” *Schizophrenia Bulletin* 38 (4): 661–71. https://doi.org/10.1093/schbul/sbs050.

Vasan, Ramachandran S., Martin G. Larson, Eric P. Leip, Jane C. Evans, Christopher J. O’Donnell, William B. Kannel, and Daniel Levy. 2001. “Impact of High-Normal Blood Pressure on the Risk of Cardiovascular Disease.” *New England Journal of Medicine* 345 (18): 1291–97. https://doi.org/10.1056/NEJMoa003417.

Venkatasubramanian, Ganesan, Seetharamaiah Chittiprol, Narendran Neelakantachar, Magadi N. Naveen, Jagadisha Thirthall, Bangalore N. Gangadhar, and K. Taranath Shetty. 2007. "Insulin and Insulin-Like Growth Factor-1 Abnormalities in Antipsychotic-Naive Schizophrenia." *American Journal of Psychiatry* 164 (10): 1557–60. https://doi.org/10.1176/appi.ajp.2007.07020233.

Ventriglio, Antonio, Alessandro Gentile, Eleonora Stella, and Antonello Bellomo. 2015. "Metabolic Issues in Patients Affected by Schizophrenia: Clinical Characteristics and Medical Management." *Frontiers in Neuroscience* 9 (September). https://doi.org/10.3389/fnins.2015.00297.

Viles-Gonzalez, Juan F., Valentin Fuster, Roberto Corti, and Juan J. Badimon. 2003. "Emerging Importance of HDL Cholesterol in Developing High-Risk Coronary Plaques in Acute Coronary Syndromes:" *Current Opinion in Cardiology* 18 (4): 286–94. https://doi.org/10.1097/00001573-200307000-00008.

Vinik, Aaron I., Tomris Erbas, and Carolina M. Casellini. 2013. "Diabetic Cardiac Autonomic Neuropathy, Inflammation and Cardiovascular Disease." *Journal of Diabetes Investigation* 4 (1): 4–18. https://doi.org/10.1111/jdi.12042.

Virdis, Agostino, Stefano Masi, Rocchina Colucci, Martina Chiriacò, Monica Uliana, Ilaria Puxeddu, Nunzia Bernardini, Corrado Blandizzi, and Stefano Taddei. 2019. "Microvascular Endothelial Dysfunction in Patients with Obesity." *Current Hypertension Reports* 21 (4): 32. https://doi.org/10.1007/s11906-019-0930-2.

Volkow, Nora D., Gene-Jack Wang, and Ruben D. Baler. 2011. "Reward, Dopamine and the Control of Food Intake: Implications for Obesity." *Trends in Cognitive Sciences* 15 (1): 37–46. https://doi.org/10.1016/j.tics.2010.11.001.

Vreeland, Betty. 2007. "Bridging the Gap between Mental and Physical Health: A Multidisciplinary Approach." *The Journal of Clinical Psychiatry* 68 Suppl 4: 26–33.

Vusirikala, Amoolya, Frederick Wekesah, Catherine Kyobutungi, and Oyinlola Oyebode. 2019. "Assessment of Cardiovascular Risk in a Slum Population in Kenya: Use of World Health Organisation/International Society of Hypertension (WHO/ISH) Risk Prediction Charts - Secondary Analyses of a Household Survey." *BMJ Open* 9 (9): e029304. https://doi.org/10.1136/bmjopen-2019-029304.

Wahid Ahad, Manek Nishma, Nichols Melanie, Kelly Paul, Foster Charlie, Webster Premila, Kaur Asha, et al. 2016. "Quantifying the Association Between Physical Activity and Cardiovascular Disease and Diabetes: A Systematic Review and Meta-Analysis." *Journal of the American Heart Association* 5 (9): e002495. https://doi.org/10.1161/JAHA.115.002495.

Waldron, Ingrid, Mary Elizabeth Hughes, and Tracy L. Brooks. 1996. "Marriage Protection and Marriage Selection—Prospective Evidence for Reciprocal Effects of Marital Status and Health." *Social Science & Medicine* 43 (1): 113–23. https://doi.org/10.1016/0277-9536(95)00347-9.

Wang, Kesheng, Xingguang Luo, and Lingjun Zuo. 2014. "Genetic Factors for Alcohol Dependence and Schizophrenia: Common and Rare Variants." *Austin Journal of Drug Abuse and Addiction* 1 (1). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4976769/.

Wang, Qing, Jay J. Shen, and Chris Cochran. 2016. "Unemployment Rate, Smoking in China: Are They Related?" *International Journal of Environmental Research and Public Health* 13 (1). https://doi.org/10.3390/ijerph13010113.

Wang, Wei-Chen, Mong-Liang Lu, Vincent Chin-Hung Chen, Mei-Hing Ng, Kuo-You Huang, Ming-Hong Hsieh, Meng-Jer Hsieh, Roger S. McIntyre, Yena Lee, and Charles Tzu-Chi Lee. 2017. "Asthma, Corticosteroid Use and Schizophrenia: A Nationwide Population-Based Study in Taiwan." Edited by Ping-Hsun Wu. *PLOS ONE* 12 (3): e0173063. https://doi.org/10.1371/journal.pone.0173063.

Wang, Xia, Yingying Ouyang, Jun Liu, Minmin Zhu, Gang Zhao, Wei Bao, and Frank B. Hu. 2014. "Fruit and Vegetable Consumption and Mortality from All Causes, Cardiovascular Disease, and Cancer: Systematic Review and Dose-Response Meta-Analysis of Prospective Cohort Studies." *BMJ* 349 (July): g4490. https://doi.org/10.1136/bmj.g4490.

Wannamethee, S. Goya, A. Gerald Shaper, Peter H. Whincup, Lucy Lennon, and Naveed Sattar. 2011. "Obesity and Risk of Incident Heart Failure in Older Men With and Without Pre-Existing Coronary Heart Disease: Does Leptin Have a Role?" *Journal of the American College of Cardiology* 58 (18): 1870–77. https://doi.org/10.1016/j.jacc.2011.06.057.

Ward, Martha, and Benjamin Druss. 2015. "The Epidemiology of Diabetes in Psychotic Disorders." *The Lancet Psychiatry* 2 (5): 431–51. https://doi.org/10.1016/S2215-0366(15)00007-3.

Warnier, Miriam Jacoba, Frans Hendrik Rutten, Patrick Cyriel Souverein, Anthonius de Boer, Arno Wilhelmus Hoes, and Marie Louise De Bruin. 2015. "Are ECG Monitoring Recommendations before Prescription of QT-Prolonging Drugs Applied in Daily Practice? The Example of Haloperidol." *Pharmacoepidemiology and Drug Safety* 24 (7): 701–8. https://doi.org/10.1002/pds.3792.

Warraich, Haider J., and Jamal S. Rana. 2017. "Dyslipidemia in Diabetes Mellitus and Cardiovascular Disease." *Cardiovascular Endocrinology & Metabolism* 6 (1): 27–32. https://doi.org/10.1097/XCE.0000000000000120.

Weber, A., and G. Lehnert. 1997. “Unemployment and Cardiovascular Diseases: A Causal Relationship?” *International Archives of Occupational and Environmental Health* 70 (3): 153–60. https://doi.org/10.1007/s004200050201.
Weiss, Anthony P., David C. Henderson, Jeffrey B. Weilburg, Donald C. Goff, James B. Meigs, Enrico Cagliero, and Richard W. Grant. 2006. “Treatment of Cardiac Risk Factors Among Patients With Schizophrenia and Diabetes.” *Psychiatric Services* 57 (8): 1145–52. https://doi.org/10.1176/ps.2006.57.8.1145.
Wekesah, Frederick M, Loise Nyanjau, Joseph Kibachio, Martin K Mutua, Shukri F Mohamed, Diederick E Grobbee, Kerstin Klipstein-Grobusch, et al. 2018. “Individual and Household Level Factors Associated with Presence of Multiple Non-Communicable Disease Risk Factors in Kenyan Adults.” *BMC Public Health* 18 (Suppl 3). https://doi.org/10.1186/s12889-018-6055-8.
WEsley Kroeze. 2003. “H1-Histamine Receptor Affinity Predicts Short-Term Weight Gain for Typical and Atypical Antipsychotic Drugs | Neuropsychopharmacology.” 2003. https://www.nature.com/articles/1300027.
Whincup, P. H., M. A. Mendall, I. J. Perry, D. P. Strachan, and M. Walker. 1996. “Prospective Relations between Helicobacter Pylori Infection, Coronary Heart Disease, and Stroke in Middle Aged Men.” *Heart* 75 (6): 568. https://doi.org/10.1136/hrt.75.6.568.
Whitfield, Charles L., Shanta R. Dube, Vincent J. Felitti, and Robert F. Anda. 2005a. “Adverse Childhood Experiences and Hallucinations.” *Child Abuse & Neglect* 29 (7): 797–810. https://doi.org/10.1016/j.chiabu.2005.01.004.
———. 2005b. “Adverse Childhood Experiences and Hallucinations.” *Child Abuse & Neglect* 29 (7): 797–810. https://doi.org/10.1016/j.chiabu.2005.01.004.
WHO. 2006. “WHO | Definition and Diagnosis of Diabetes Mellitus and Intermediate Hyperglycaemia.” WHO. 2006. http://www.who.int/diabetes/publications/diagnosis_diabetes2006/en/.
———. 2011a. “WHO | Global Atlas on Cardiovascular Disease Prevention and Control.” 2011. https://www.who.int/cardiovascular_diseases/publications/atlas_cvd/en/.
———. 2011b. “WHO | Physical Activity and Adults.” WHO. 2011. https://www.who.int/dietphysicalactivity/factsheet_adults/en/.
———. n.d. “WHO | The Determinants of Health.” WHO. Accessed January 27, 2020. https://www.who.int/hia/evidence/doh/en/.
“WHO | The STEPS Instrument and Support Materials.” n.d. WHO. Accessed September 6, 2016. http://www.who.int/chp/steps/instrument/en/.
WHO, Cardivascular disorders. 2017. “Cardiovascular Diseases (CVDs).” 2017. https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds).
Wilfred Omollo. 2019. “Solid Waste Management in the Informal Settlements: A Land Use Planning Perspective.” *World Environment* 9 (1): 19–27. https://doi.org/10.5923/j.env.20190901.03.
Williams, Bryan, Giuseppe Mancia, Wilko Spiering, Enrico Agabiti Rosei, Michel Azizi, Michel Burnier, Denis L. Clement, et al. 2018. “2018 ESC/ESH Guidelines for the Management of Arterial Hypertension.” *European Heart Journal* 39 (33): 3021–3104. https://doi.org/10.1093/eurheartj/ehy339.
Williams, Jill M., Kunal K. Gandhi, Shou-En Lu, Supriya Kumar, Marc L. Steinberg, Brett Cottler, and Neal L. Benowitz. 2011. “Shorter Interpuff Interval Is Associated with Higher Nicotine Intake in Smokers with Schizophrenia.” *Drug and Alcohol Dependence* 118 (0): 313–19. https://doi.org/10.1016/j.drugalcdep.2011.04.009.
Wilson Peter W. F., D’Agostino Ralph B., Levy Daniel, Belanger Albert M., Silbershatz Halit, and Kannel William B. 1998. “Prediction of Coronary Heart Disease Using Risk Factor Categories.” *Circulation* 97 (18): 1837–47. https://doi.org/10.1161/01.CIR.97.18.1837.
Wilson Peter W.F., D’Agostino Ralph B., Parise Helen, Sullivan Lisa, and Meigs James B. 2005. “Metabolic Syndrome as a Precursor of Cardiovascular Disease and Type 2 Diabetes Mellitus.” *Circulation* 112 (20): 3066–72. https://doi.org/10.1161/CIRCULATIONAHA.105.539528.
Wincup, Ph, Ma Mendall, Ij Perry, Dp Strachan, and M Walker. 1997. “Prospective Relations between Helicobacter Pylori Infection, Coronary Heart Disease and Stroke in Middle-Aged Men.” *Heart* 77 (3): 294.
Wirshing, Donna A. 2004. “Schizophrenia and Obesity: Impact of Antipsychotic Medications.” *The Journal of Clinical Psychiatry* 65 (suppl 18): 13–26.
Wise, Roy A. 2006. “Role of Brain Dopamine in Food Reward and Reinforcement.” *Philosophical Transactions of the Royal Society B: Biological Sciences* 361 (1471): 1149–58. https://doi.org/10.1098/rstb.2006.1854.
Wojtyna, Ewa, and Agnieszka Wiszniewicz. 2013. “The Characteristics of Nicotine Addiction Among Patients with Schizophrenia.” *Mental Disorders - Theoretical and Empirical Perspectives*, January. https://doi.org/10.5772/54308.

Wong, Chun Wai, Chun Shing Kwok, Aditya Narain, Martha Gulati, Anastasia S. Mihalidou, Pensee Wu, Mirvat Alasnag, Phyo Kyaw Myint, and Mamas A. Mamas. 2018. "Marital Status and Risk of Cardiovascular Diseases: A Systematic Review and Meta-Analysis." *Heart* 104 (23): 1937–48. https://doi.org/10.1136/heartjnl-2018-313005.

Wood, Angela M, Stephen Kaptoge, Adam S Butterworth, Peter Willeit, Samantha Warnakula, Thomas Bolton, Ellie Paige, et al. 2018. "Risk Thresholds for Alcohol Consumption: Combined Analysis of Individual-Participant Data for 599 912 Current Drinkers in 83 Prospective Studies." *The Lancet* 391 (10129): 1513–23. https://doi.org/10.1016/S0140-6736(18)30134-X.

Woodward, Mark. 2019. "Cardiovascular Disease and the Female Disadvantage." *International Journal of Environmental Research and Public Health* 16 (7). https://doi.org/10.3390/ijerph16071165.

World HealthOganization. 2000. *Obesity: Preventing and Managing the Global Epidemic*. World Health Organization.

World Heart Federation. 2017. "Cardiovascular Disease Risk Factors | World Heart Federation." 2017. http://www.world-heart-federation.org/press/fact-sheets/cardiovascular-disease-risk-factors/.

World population Review. 2019. "Kenya Population 2019 (Demographics, Maps, Graphs)." 2019. http://worldpopulationreview.com/countries/kenya-population/.

Wu, Chen-Yi, Hsiao-Yun Hu, Yiing-Jenq Chou, Nicole Huang, Yi-Chang Chou, and Chung-Pin Li. 2015. "High Blood Pressure and All-Cause and Cardiovascular Disease Mortalities in Community-Dwelling Older Adults." *Medicine* 94 (47). https://doi.org/10.1097/MD.0000000000002160.

Wu Ren Rong. 2008. "Lifestyle Intervention and Metformin for Treatment of Antipsychotic-Induced Weight Gain: A Randomized Controlled Trial | Lifestyle Behaviors | JAMA | JAMA Network." 2008. https://jamanetwork-com.ezproxy.uct.ac.za/journals/jama/fullarticle/1380162.

Wu, Ren-Rong, Jing-Ping Zhao, Zhe-Ning Liu, Jin-Guo Zhai, Xiao-Feng Guo, Wen-Bing Guo, and Jing-Song Tang. 2006. "Effects of Typical and Atypical Antipsychotics on Glucose–Insulin Homeostasis and Lipid Metabolism in First-Episode Schizophrenia." *Psychopharmacology* 186 (4): 572–78. https://doi.org/10.1007/s00213-006-0384-5.

Wubeshet, Yirgalem Shewakena, Oumer Sada Mohammed, and Tigestu Alemu Desse. 2019. "Prevalence and Management Practice of First Generation Antipsychotics Induced Side Effects among Schizophrenic Patients at Amanuel Mental Specialized Hospital, Central Ethiopia: Cross-Sectional Study." *BMC Psychiatry* 19 (January). https://doi.org/10.1186/s12888-018-1999-x.

Yang, Ping, Rui Tao, Chengsen He, Shen Liu, Ying Wang, and Xiaochu Zhang. 2018. "The Risk Factors of the Alcohol Use Disorders—Through Review of Its Comorbidities." *Frontiers in Neuroscience* 12 (May). https://doi.org/10.3389/fnins.2018.00303.

Ye, Jianping. 2013. "Mechanisms of Insulin Resistance in Obesity." *Frontiers of Medicine* 7 (1): 14–24. https://doi.org/10.1007/s11684-013-0262-6.

Young, Fiona, Julia A. Critchley, Lucy K. Johnstone, and Nigel C. Unwin. 2009a. "A Review of Co-Morbidity between Infectious and Chronic Disease in Sub Saharan Africa: TB and Diabetes Mellitus, HIV and Metabolic Syndrome, and the Impact of Globalization." *Globalization and Health* 5 (1): 9. https://doi.org/10.1186/1744-8603-5-9.

Young, Fiona, Julia A Critchley, Lucy K Johnstone, and Nigel C Unwin. 2009b. "A Review of Co-Morbidity between Infectious and Chronic Disease in Sub Saharan Africa: TB and Diabetes Mellitus, HIV and Metabolic Syndrome, and the Impact of Globalization." *Globalization and Health* 5 (September): 9. https://doi.org/10.1186/1744-8603-5-9.

Yusuf, Salim, Sumathy Rangarajan, Koon Teo, Shofiqul Islam, Wei Li, Lisheng Liu, Jian Bo, et al. 2014. "Cardiovascular Risk and Events in 17 Low-, Middle-, and High-Income Countries." *New England Journal of Medicine* 371 (9): 818–27. https://doi.org/10.1056/NEJMoa1311890.

Zhan, Yiqiang, Jinming Yu, Ruoqing Chen, Junling Gao, Rongjing Ding, Yuanyuan Fu, Lijun Zhang, and Dayi Hu. 2012. "Socioeconomic Status and Metabolic Syndrome in the General Population of China: A Cross-Sectional Study." *BMC Public Health* 12 (1): 921. https://doi.org/10.1186/1471-2458-12-921.

Zhang, Jian-Ping, Todd Lencz, Ryan X. Zhang, Masahiro Nitta, Lawrence Maayan, Majnu John, Delbert G. Robinson, et al. 2016. "Pharmacogenetic Associations of Antipsychotic Drug-Related Weight Gain: A Systematic Review and Meta-Analysis." *Schizophrenia Bulletin* 42 (6): 1418–37. https://doi.org/10.1093/schbul/sbw058.

Zhang, Xiang Yang, Da-Chun Chen, Yun-Long Tan, Shu-ping Tan, Xingguang Luo, Lingjun Zuo, Wenwang Rao, et al. 2015. "A Functional Polymorphism in the Interleukin-1beta and Severity of Nicotine Dependence in Male Schizophrenia: A Case-Control Study." *Journal of Psychiatric Research* 64 (May): 51–58. https://doi.org/10.1016/j.jpsychires.2015.03.015.

Zhang, Yingmei, and Jun Ren. 2011. "ALDH2 in Alcoholic Heart Diseases: Molecular Mechanism and Clinical Implications." *Pharmacology & Therapeutics* 132 (1): 86–95. https://doi.org/10.1016/j.pharmthera.2011.05.008.

Zheng, Wei, Xian-Bin Li, Yi-Lang Tang, Ying-Qiang Xiang, Chuan-Yue Wang, and Jose de Leon. 2015. “Metformin for Weight Gain and Metabolic Abnormalities Associated With Antipsychotic Treatment: Meta-Analysis of Randomized Placebo-Controlled Trials.” *Journal of Clinical Psychopharmacology* 35 (5): 499–509. https://doi.org/10.1097/JCP.0000000000000392.

APPENDICES

Appendix 1 consent

Appendix 1a: Patient Consent

You are being invited to participate in a research study on the things that increase the likelihood of developing heart-related problems among patients on management for mental illness as compared to the general population. The study is important as it will be useful in developing treatments and strategies of improving the physical health of people with mental illness. This study will involve 600 participants. There is no very special reason why you are being asked to participate except that you fit in the criteria required for the study.

This work is being done as part of a PHD program for Dr Edith Kwobah who is a consultant psychiatrist at the MTRH.

If you agree to participate, the study will take at most 2 hours of your time. There will be an initial interview in which several questions concerning your physical and psychological health, including negative experiences in the past will be asked. Subsequently you will have your weight, height, waist circumference, and blood pressure taken. A blood sample will also be taken to measure your sugar and fat levels. We will also carry out an examination of the heart that involves putting several metallic knobs on your chest. It is called an electrocardiogram, it assesses how the heart functions and it is painless.

The benefit of participating in this study to you as an individual, is to get to know your health status with respect to your sugar levels, blood pressure, blood fat levels, weight and heart function. Your results will be communicated to you by Dr E Kwobah.

Participating in this research is entirely voluntary. You may terminate your participation at any point during the study without losing any benefits.

This research has minimal risk to you, it will cause no grave harm. You may experience mild discomfort and pain during drawing of your blood samples. The interview will contain some questions of a sensitive nature which may cause you psychological discomfort .You will also spend more time in the hospital than usual in order to complete these study activities. However, the research team is prepared to help you deal with any physical or psychological pain that may arise. This information will be confidential but should

you choose not to answer, it will in no way affect your relations with the clinic.

There are no costs to you for participating in the study. You will also not receive any payments for participating in the study.

The blood samples drawn for this study will be stored for a minimum of the two years duration of the study. Any further study done using the sample will strictly be upon approval by the ethics committee. The results of the study will be stored in a computer that is password protected and only accessible by those conducting the study. No one will be able to identify you or your results. Should the results be published, none of your individual information will be disclosed. You will not get the results of the study individually.

If you have any questions about the study, please contact Dr. Edith Kwobah (phone no: 0721763412) at Moi Teaching and Referral Hospital. The Institutional Review and Ethics Committee of Moi University and Moi Teaching & Referral Hospital has reviewed this request to conduct this project. You may also contact the ethics committee at Moi Teaching & Referral Hospital building, 2nd floor. Door No. 219, P.O. Box. 3-30100 Eldoret, Kenya, Office line: 0787723677, Email: irecmtrh@gmail.com or contact@irec.or.ke

By signing this document, you are voluntarily agreeing to participate in this study.

I have understood the explanation given to me regarding the study. ALL OF MY QUESTIONS HAVE BEEN SATISFACTORILY ANSWERED, AND I WANT TO TAKE PART IN THIS RESEARCH STUDY. By signing below, I agree to participate in this study and I also permit the publication of the results of the study. I also accept that future research may be conducted using the sample stored during this study, on condition that such a study is approved by the ethical committees involved.

Signature of the participant _____ **Date** _____

Signature of researcher _____ **Date**_____

Appendix 1b: Control Consent

You are being invited to participate in a research study comparing the risk of developing heart-related problems among patients on management for mental illness and participants without mental illness. The study is important as it will be useful in developing treatments and strategies of improving the physical health of people with mental illness. This study will involve 600 participants. There is no very special reason why you are being asked to participate except that you fit in the criteria required for the study.

This work is being done as part of a PHD program for Dr Edith Kwobah who is a consultant psychiatrist at the MTRH.

The study will take at most 2 hours of your time. There will be an initial interview in which questions concerning your physical and psychological health, including negative experiences in the past will be asked. Subsequently you will have your weight, height, waist circumference, and blood pressure taken. A blood sample will also be taken to measure your sugar and fat levels. We will also carry out an examination of the heart that involves putting several metallic knobs on your chest. It is called an electrocardiogram, it assesses how the heart functions and it is painless.

The benefit of participating in this study to you as an individual, is to get to know your health status with respect to your sugar levels, blood pressure, blood fat levels, weight and heart function. Your results will be communicated to you by Dr E Kwobah. If any of these is found to be abnormal, you will either be initiated on medication or be referred to the relevant clinic for help.

Participating in this research is entirely voluntary. You may terminate your participation at any point during the study without affecting your relationship or interaction with the hospital.

This research has minimal risk to you and will cause no grave harm. You will, however, experience mild discomfort and pain during drawing of your blood samples. The interview will contain some questions of a sensitive nature which may cause you psychological discomfort .You will also spend time in the hospital in order to complete these study activities. However, the research team is prepared to help you deal with any physical or psychological pain that may arise. This information will be confidential but should you

choose not to answer, it will in no way affect your future relations with the hospital or the staff.

There are no costs to you for participating in the study. You will also not receive any payments for participating in the study.

The results of the study will be stored in a computer that is password protected and only accessible by those conducting the study. No one will be able to identify you or your results. Should the results be published, none of your individual information will be disclosed. You will not get the results of the study individually.

If you have any questions about the study, please contact Dr Edith Kwobah (phone no: 0721763412) at Moi Teaching and Referral Hospital. The Institutional Review and Ethics Committee of Moi University and Moi Teaching & Referral Hospital has reviewed this request to conduct this project. You may also contact the ethics committee at Moi Teaching & Referral Hospital building, 2nd floor. Door No. 219, P.O. Box. 3-30100 Eldoret, Kenya, Office line: 0787723677, Email: irecmtrh@gmail.com or contact@irec.or.ke

By signing this document, you are voluntarily agreeing to participate in this study.

I have understood the explanation given to me regarding the study. ALL OF MY QUESTIONS HAVE BEEN SATISFACTORILY ANSWERED, AND I WANT TO TAKE PART IN THIS RESEARCH STUDY. By signing below, I agree to participate in this study and I also permit the publication of the results of the study. I also accept that future research may be conducted using the sample stored during this study, on condition that such a study is approved by the ethical committees involved.

Signature of the participant _____ **Date** _____

Signature of researcher _____ **Date**_____

Appendix 1c : University of California Brief Assessment of Capacity to Consent (UBACC)

1. What is the purpose of the study that was just described to you?	**Circle**
Response: Two key concepts (1) risk of heart diseases. (2) Look at causes of heart disease among patients with mental illness. Neither concept One concept – either (1) OR (2) Link both concepts 1) TO (2)	Score 0 1 2
2. What makes you want to consider participating in this study?	
Response: Two key concepts: (1) Increase people's knowledge about heart disease among patients with mental OR (2) possibility of finding improved treatments in the future. Neither concept , Give my blood or time for money, or get treatment One concept Two concepts	Score 0 1 2
3. Do you believe this is primarily research or primarily treatment?	
Response: Treatment; I don't know; both; Research	Score 0 2
4. **Do you have to be in this study**?	
Response: Yes; I don't know No	Score 0 2
5. If you withdraw from the study, will you still receive regular treatment?	
Response: No; I don't know Yes	Score 0 2

6. If you participate in this study, what will you be asked to do?	
Response: Two tasks: (1) Answer questions about myself; (2) give blood None of the above One task either 1) OR (2) Both tasks 1) AND (2)	Score 0 1 2
7. Please describe some of the risks or discomforts that you may experience?	
Response: Two key concepts: (1) Answering questions about myself could be uncomfortable; (2) Pain when blood is being withdrawn None of the above One concept Two concepts	Score 0 1 2
8. Please describe some of the possible benefits of this study	
Response: Two key concepts: (1) helping humanity – increase knowledge about heart disease OR (2) improved treatments in the future Neither concept: I will be paid to participate One concept – (1) helping humanity Two concepts (1) increased knowledge AND (2) improved treatments	Score 0 1 2
9. Is it possible that being in this study will not have any benefit to you?	
Response: No, I don't know (0) Yes (2)	Score 0 2
10. Do you have to agree to have your details used in publications	
Response: No; I don't know Yes: In order to participate in this study I do	Score 0 2

TOTAL SCORE Research staff to add up scores from right-hand column. Write number in box here.	→
NEXT STEPS FOR RESEARCH STAFF 1. If participant scores **less than 20,** review the questions that were not fully understood and re-administer those questions. 2. Continue to explain and re-administer the specific questions not understood up to **four times** or until the participant receives a perfect score. 3. If after four times the participant scores **above 14.5,** he or she can continue with the study. If after four times the participant scores **below** 14.5, **STOP!** He or she may not fully understand the study and should therefore not be invited to continue.	

Appendix 2: Study Announcement

A research team in MTRH is conducting a research study on the risks of developing heart-related diseases.

The study is seeking adults above 18 years of age.

The study will involve an interview of about 45 minutes asking questions on physical and psychological well-being. Blood with be taken to measure blood sugar and body fat. Interested participants will have their blood sample taken to give and an electrocardiogram (ECG), a test of the heart function, done.

The benefit of participating is that you get to know if you have high blood sugar, abnormal body fat, high blood pressure and whether your weight or body fat is increasing your risk of getting a heart disease. Anyone who is found to have an abnormality will be referred appropriately for care.

Any interested participant may call the research coordinator on 0700 675 961 from 8am to 5pm on any weekday for further information.

Appendix 3: Data Collection Tool

Academic Model Providing Access to Healthcare
Telephone: 254 53 2033471/2P.O. BOX 4606, ELDORET Fax: 254 53 2060727

CVD Data Collection Tool

PARTICIPANTS Category ☐ Control ☐ Patient

P ID CVD ……. P ID NGAP…….. Telephone No……

Clinical diagnosis (Patients only) …….

Demographics

1. Age in years……..
2. Sex……
   A) Male…….
   B) Female ……
3. Marital status
   A) Currently Married
   B) Never married
   C) Widowed
   D) Divorced
   E) Separated
   F) Other (Specify): …….
4. Highest level of Education
   A) No formal schooling
   B) Less than primary school
   C) Primary school completed
   D) Secondary school completed
   E) High school completed
   F) College/University completed
   G) Post graduate degree
5. What kind of work do you do?
   A) Unemployed (Unable to work)
   B) Unemployed (Able to work)
   C) Formal employment (permanent or contract, 8am-5pm jobs)
   D) Self-employed (business and farming)
   E) Retired

Kessler 10 **(controls only)**

Please tick the answer that is correct for you:	All of the time (score 5)	Most of the time (score 4)	Some of the time (score 3)	A little of the time (score 2)	None of the time (score 1)
1. In the past 4 weeks, about how often did you feel tired out for no good reason?					
2. In the past 4 weeks, about how often did you feel nervous?					
3. In the past 4 weeks, about how often did you feel so nervous that nothing could calm you down?					
4. In the past 4 weeks, about how often did you feel hopeless?					
5. In the past 4 weeks, about how often did you feel restless or fidgety?					
6. In the past 4 weeks, about how often did you feel so restless you could not sit still?					
7. In the past 4 weeks, about how often did you feel depressed?					
8. In the past 4 weeks, about how often did you feel that everything was an effort?					
9. In the past 4 weeks, about how often did you feel so sad that nothing could cheer you up?					
10. In the past 4 weeks, about how often did you feel worthless?					

LIFE EVENTS Checklist

Listed below are a number of difficult or stressful things that sometimes happen to people. For each event check one or more of the boxes to the right to indicate that: (a) it *happened to you* personally; (b) you *witnessed it* happen to someone else; (c) you *learned about it* happening to a close family member or close friend; (d) you were exposed to it as *part of your job* (for example, paramedic, police, military, or other first responder); or (e) you're *not sure* if it fits.

Be sure to consider your *entire life* (growing up as well as adulthood) as you go through the list of events.

Event	*Happened to me*	*Witnessed it*	*Learned about it*	*Part of my job*	*Not Sure*
1. Natural disaster (for example, flood, hurricane, tornado, earthquake)					
2. Fire or explosion					
3. Transportation accident (for example, car accident, boat accident, train wreck, plane crash)					
4. Serious accident at work, home, or during recreational activity					
5. Exposure to toxic substance (for example, dangerous chemicals, radiation)					
6. Physical assault (for example, being attacked, hit, slapped, kicked, beaten up)					
7. Assault with a weapon (for example, being shot, stabbed, threatened with a knife, gun, bomb)					
8. Sexual assault (rape, attempted rape, made to perform any type of sexual act through force or threat of harm)					
9. Other unwanted or uncomfortable sexual experience					
10. Combat or exposure to a war-zone (in the military or as a civilian)					
11. Captivity (for example, being kidnapped, abducted, held hostage, prisoner of war)					
12. Life-threatening illness or injury					
13. Severe human suffering					
14. Sudden violent death (for example, homicide, suicide)					
15. Sudden accidental death					
16. Serious injury, harm, or death you caused to someone else					
17. Any other very stressful event or experience					

Tobacco use

1. Do you currently use any tobacco products such as chewing tobacco, snuffing tobacco, smoking cigarettes, shisha, betel nuts or pipes?
A) Yes, if yes specify the type used…… frequency amount per day ……
B) No

2. In the past, did you ever use tobacco products such as chewing tobacco, snuffing tobacco, smoking cigarettes, shisha, betel nuts or pipes?
A) Yes, if yes specify the type used…… frequency……..amount per day ……..
B) No

Alcohol Use (Audit-C)

I) How often do you have a drink containing alcohol?
(0) Never *(Skip the rest of the questions)*
(1) Monthly or less
(2) 2 to 4 times a month
(3) 2 to 3 times a week
(4) 4 or more times a week

II) How many drinks containing alcohol do you have on a typical day when you are drinking?
(0) 1 or 2
(1) 3 or 4
(2) 5 or 6
(3) 7, 8, or 9
(4) 10 or more

III) How often do you have six or more drinks on one occasion?
(0) Never
(1) Less than monthly
(2) Monthly
(3) Weekly
(4) Daily or almost daily

Other substances used:……Frequency……..

Diet

1. A) In a typical week, on how many days do you eat fruits?.....
   B) What quantity of fruits do you eat (in terms of pieces of fruits, types of fruits).
   ……..

2. 1. A) In a typical week, on how many days do you eat vegetables?.....
B) What quantity of vegetables do you eat (in terms of plates, types of vegetables.
…….

CIDI-Chronic Disease Screener

Have you ever been admitted to the hospital for a general medical condition?
Yes No

How many previous hospitalizations have you had?
1 2 3 4 5

If yes, for what reason were you admitted?

The next few questions are about health problems you might have had at any time in your life. Have you ever had any of the following?

Arthritis or rheumatism?
Yes No Don't know Refused to answer

Chronic back or neck problems?
Yes No Don't know Refused to answer

Frequent or severe headaches?
Yes No Don't know Refused to answer

Any other chronic pain?
Yes No Don't know Refused to answer

Seasonal allergies like hay fever?
Yes No Don't know Refused to answer

A stroke?
Yes No Don't know Refused to answer

A heart attack?
Yes No Don't know Refused to answer

Did a doctor or other health professional ever tell you that you had any of the following illnesses?

Heart disease?
Yes No Don't know Refused to answer

High Blood Pressure?
Yes No Don't know Refused to answer

Asthma?
Yes No Don't know Refused to answer

Tuberculosis?
Yes No Don't know Refused to answer

Any other chronic lung disease, like COPD or emphysema?
Yes No Don't know Refused to answer

Diabetes or high blood sugar?
Yes No Don't know Refused to answer

An ulcer in your stomach or intestine?
Yes No Don't know Refused to answer

HIV infection or AIDS?
Yes No Don't know Refused to answer
Epilepsy or seizures?
Yes No Don't know Refused to answer

Cancer?
Yes No Don't know Refused to answer

Other conditions?
Yes No

Please list other conditions
_____

Neuroleptic use (for patients only)

What medications are you currently using? *[May confirm with the notes in the file]*

a) Olanzapine	dose	mg/24 hours	date of onset_____
b) Chropromazine	dose	mg/24 hours	date of onset_____
c) Haloperidol	dose	mg/24 hours	date of onset_____
d) Fluphenazine decanoate	dose	mg/24 hours	date of onset_____
e) Zuclopenthixol	dose	mg/24 hours	date of onset_____
f).Amitriptiline	dose	mg/24 hours	date of onset_____
g) Fluoxetine	dose	mg/24 hours	date of onset_____

h) Others:
Name …….. Dose ……mg/24hrs date of onset_____
Name ……Dose ……mg/24hrs date of onset_____

Section E: Physical activity

1. In a typical week, on how many days do you do vigorous-intensity activities that increase your breathing and heart rate, as part of your work?
A) 3-7 days
B) <3 days

2. In a typical week, on how many days do you walk or bicycle for at least 10 minutes continuously to get to and from places?
A) 3-7 days
B) <3 days

3. In a typical week, on how many days do you do vigorous-intensity sports, fitness or recreational (leisure) activities?
A) 3-7 days
B) <3 days

4. How much time do you usually spend sitting or reclining
A) Less than 3 hours in a day
B) More than 3 hours in a day

Childhood Trauma Questionnaire – Short Form (CTQ-SF)

When I was growing up	Never True	Rarely True	Sometimes	Often True	Very Often
1. I didn't have enough to eat.	1	2	3	4	5
2. I knew there was someone to take care of me and protect me	1	2	3	4	5
3. People in my family called me things like "stupid", "lazy", or "ugly".	1	2	3	4	5
4. My parents were too drunk or high to take care of me.	1	2	3	4	5
5. There was someone in my family who helped me feel important or special.	1	2	3	4	5
6. I had to wear dirty clothes.	1	2	3	4	5
7. I felt loved.	1	2	3	4	5
8. I thought that my parents wished I had never been born.	1	2	3	4	5
9. I got hit so hard by someone in my family that I had to see a doctor or go to the hospital.	1	2	3	4	5
10. There was nothing I wanted to change about my family.	1	2	3	4	5
11. People in my family hit me so hard that it left bruises or marks.	1	2	3	4	5
12. I was punished with a belt, a board, a cord, or some hard object.	1	2	3	4	5
13. People in my family looked out for each other.	1	2	3	4	5
14. People in my family said hurtful or insulting things to me.	1	2	3	4	5
15. I believe that I was physically abused.	1	2	3	4	5
16. I had the perfect childhood.	1	2	3	4	5
17. I got hit or beaten so badly that it was noticed by someone like a teacher, neighbor, or doctor.	1	2	3	4	5
18. I felt that someone in my family hated me.	1	2	3	4	5
19. People in my family felt close to each other.	1	2	3	4	5
20. Someone tried to touch me in a sexual way, or tried to make me touch them.	1	2	3	4	5
21. Someone threatened to hurt me or tell lies about me unless I did something sexual with them.	1	2	3	4	5
22. I had the best family in the world.	1	2	3	4	5
23. Someone tried to make me do sexual things or make me watch sexual things.	1	2	3	4	5
24. Someone molested me.	1	2	3	4	5
25. I believe that I was emotionally abused.	1	2	3	4	5
26. There was someone to take me to the doctor if I needed it.	1	2	3	4	5
27. I believe that I was sexually abused	1	2	3	4	5
28. My family was a source of strength and support.	1	2	3	4	5

Section I: Physical measurements

Measurement		
1. Height in centimeters		
2. Weight in Kilograms		
3. Waist circumference in Centimeters		
4. Blood pressure in mmhg		
1st reading	Systolic	Diastolic
2nd reading	Systolic	Diastolic
3rd reading	Systolic	Diastolic
Average blood pressure		

Section J: Biochemical measurements (units in mmol/l)

2. Random Blood Sugar _____
3. Total Cholesterol _____
4. Triglycerides _____
5. LDL _____
6. HDL _____

Appendix 4: Procedures for various study measurements

a) Random blood sugar, lipid profile

The procedure of withdrawing blood will be as follows:

- The participant will remain in sitting position for 15 minutes prior to blood collection.
- The arm will be exposed to search for a vein.
- Tourniquet will be placed around the arm
- Injection site will be sterilized using alcohol swab.
- A 20 or 22 gauge needle will be inserted into the identified vein.
- Immediately after the insertion, the tourniquet will be released.
- 10 mls of blood will be drawn into a 10 ml plain vacutainer,
- The needle will be removed and an adhesive bandage placed on the puncture site.

The Vacutainer will be labelled appropriately. Blood will be taken to the laboratory for analysis by the research nurse. Analysis will be done on the same day so no need for storage.

b) The weight of participants will be taken in order to calculate body mass index (BMI), i.e. Weight relative to the height. The weight will be measured with a 762 Dial Bathroom Floor Scale.

Below are the steps that will be followed in measuring weight:

- The scale will be placed on a firm, flat surface.
- Participant will be asked to remove their footwear (shoes, slippers, sandals).
- The participant will be asked to step onto scale with one foot on each side of the scale.
- Participant will be asked to: stand still, face forward, place arms on the side and wait until they will be asked to step off.
- The weight in kilograms will be recorded on the participant's file.
- The participant will be asked to step off the scale.

c). The height of participants will be measured as a composite of body mass index (BMI). The height will be measured with a Mechanical roll-up measuring tape (Seca 260).

The steps that will be followed in measuring height will be as follows:

- The participant will be asked to remove their footwear (shoes, slippers, sandals, etc.) and head gear (hat, cap, hair bows, comb, and ribbons). However, those with a scarf or veil shall not be asked to remove them (measurement may be taken over light fabric).

- Participant will be asked stand next to the measuring wall facing the research assistant/ investigator.
- Participant will be asked to stand with: feet together, heels against the measuring board/wall, knees straight.
- Participant will be asked to look straight ahead and not tilt their head up.
- The research assistant/ investigator will make sure eyes are the same level as the ears.
- The measure arm will be moved gently down onto the head of the participant and the participant asked to breathe in and stand tall.
- The height will be read in centimetres at the exact point.
- The participant will be asked to step away from the measuring board/wall.
- The height measurement in centimetres will be recorded in the participant's file

d) Waist circumference: A standard tape measure will be used. Patient will be instructed to expose the abdomen fully while standing and lift both arms. The RA will then measure the waist circumference in centimetres at the midpoint between the iliac crests and the lower rib laterally and passing over the umbilicus anteriorly.

e) Blood pressure ; This will be taken using an Omron M2 compact upper arm blood pressure (BP) monitor (Omron Healthcare, Inc., 1200 Lakeside Drive, Bannockburn, Illinois 60015). Patients will be required to have had at least 15 minutes' rest in a quiet place and in a relaxed sitting position with no tight fitting clothing on the upper arm, or any thick clothing such as a sweater.

Steps that will be followed are as follows:

- Participant will be seated upright with the back straight and right arm placed on the table so that the cuff will be on the same level as the heart.
- Cuff will be wrapped on the arm so that the bottom of the cuff will be at least 1cm above the elbow. The cuff will then be fastened snugly.
- Start button will then be pressed and the cuff will automatically inflate to take the blood pressure reading.
- Blood pressure and pulse rate results will be displayed on the on the screen of the machine.
- Blood pressure readings will be recorded on the pro-forma.

In case an error occur during the process, the cuff will be deflated and the process repeated.

At least two readings will be take, one minute apart.

Appendix 5: Management and referral of participants with positive results

As soon as the results are out (immediately for blood pressure, and random blood sugar, and later for lipid profile), the research nurse will inform Dr Kwobah.

Dr Kwobah will contact the client face to face or on the provided contact.

She will inform the participants of the abnormal results.

She will discuss the need for care.

She will initiate treatment, in consultation with a physician, where urgent care is needed. She will also fill the MTRH consultation form for a booking to the appropriate clinic; general medical outpatient clinic or cardiology clinic.

In case of psychological distress resulting from the study procedures or otherwise, Dr Kwobah will assess the client and determine the appropriate course of action. She will either manage the patient or link them to a psychologist in the hospital for relevant psychological support.

Appendix 6: Sample handling and storage

(1) Blood will be collected into a Vacutainer by the research assistant (nurse or clinical officer). The vacutainer will be labelled appropriately sing the participants study ID.

(2) The blood will be taken to the Laboratory

3. It will be allowed to stand for a minimum of 45 min at room temperature to allow complete clotting and clot retraction.

(3) It will be centrifuged by the laboratory technician.

4. Serum will be analyses for the lipids appropriately.

5. Any extra sample will be stored at -80°C for the period of the study which is 2 years.