AN ASSOCIATION OF SOCIO-DEMOGRAPHIC AND LIFESTYLE FACTORS WITH DIABETES AND HYPERTENSION IN PATIENTS WITH SCHIZOPHRENIA AND RELATED DISORDERS

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Background: Diabetes and hypertension are implicated in the shortened lifespan of patients with schizophrenia. While obesity and atypical antipsychotics are well-established risk factors, the roles of socio-demographic and lifestyle factors have not been examined systematically.

Design: A systematic review examining socio-demographic and lifestyle factors in diabetes and hypertension was carried out. A cross-sectional study examined the associations between socio-demographic and lifestyle factors, and diabetes and hypertension in patients with schizophrenia, their non-psychiatric first degree relatives, and non-psychiatric controls.

Methods: The systematic review was carried out using established guidelines. Cross-sectional data from the Diagnostic Interview for Genetic Studies were analyzed to examine associations between socio-demographic and lifestyle risk factors, and diabetes and hypertension in the three groups.

Results: The systematic review based on 26 studies showed a strong effect of age and African-American race on the prevalence of diabetes. Age was also associated with the metabolic syndrome, although the effect of race was equivocal. Sex was an effect modifier for diabetes and the metabolic syndrome in some, but not all studies, with higher rates in females.

Patients with schizophrenia had higher rates of diabetes and hypertension compared to controls. Multivariate analyses that included age, race, sex, years of schooling, marital status, occupational status, and living arrangement showed that only increasing age and African-American race were significant risk factors for diabetes and hypertension.

Patients with schizophrenia had higher rates of smoking, alcohol and marijuana use compared to controls. The rates of smoking and marijuana use in patients were also higher than the rates in their 1st degree relatives. Multivariate analyses that included age, race, sex and years of schooling, failed to show any significant associations for smoking, alcohol or marijuana use with diabetes or hypertension.

Conclusions: Only established non-modifiable factors, namely age and race, were confirmed as risk factors for diabetes and hypertension in the systematic review and cross-sectional study.

Public Health Significance: The dissertation confirms the need for developing services for minority, mainly African-American, patients with schizophrenia in order to reduce the disease burden and mortality associated with diabetes and hypertension.

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1.0 INTRODUCTION

1.1 SIGNIFICANCE OF THE PROBLEM

In 2006, the National Association of State Mental Health Program Directors (NASMHPD) conducted a study across 8 states and concluded that patients with severe mental illnesses (SMI include schizophrenia and related disorders such as schizoaffective and schizophreniform disorders, and bipolar disorders) died approximately 25 years earlier than populations from the same states (Parks et al., 2006). Contrary to popular belief, only a minority (30% to 40%) of this excess mortality was due to suicide and injury. The majority (60% to 70%) of premature deaths were attributable to chronic medical illnesses, namely cardiovascular diseases, diabetes, pulmonary, and infectious diseases.

Newman and Bland (1991) observed a 20% shorter life span (10 – 15 years) due to increased risk for death from medical causes in patients with schizophrenia. Although several other reports also observed shortened lifespan in patients with SMI as a consequence of co-morbid medical illnesses (Felker et al., 1996), the NASMHPD report highlighted the magnitude of the problem by providing empirical estimates of mortality based on comparisons with age- and gender-adjusted populations from the state. The medical illnesses specified in the NASMHPD report in large part result from modifiable lifestyle risk factors, namely smoking and other unhealthy behaviors like poor nutrition and inadequate physical activity, all of which occur

in high rates among patients with SMI (Brown et al., 1999). Furthermore, obesity, which occurs at alarmingly high rates in patients with SMI, is an important causative factor for the development of these medical illnesses (Chawastiak et al., 2009). These illnesses may also be a consequence of mental illness-related factors like poor communication and insight about health needs, non-adherence to treatment, and geographical factors affecting access (Ryan and Thakore, 2002).

High rates of under-diagnosed and under-treated medical problems in patients with SMI have been reported that may in part be due to issues related to physical health care (Folsom et al., 2002). Medical illnesses in this population are more likely to be treated in the acute phase when the disease is severe, painful or life threatening, rather than in its early, less severe phase (Munk-Jorgensen et al., 2000). Consequently, patients with co-morbid medical illnesses have longer stays in acute care facilities and a high overall use of inpatient and outpatient services (Kent et al., 1995). This disparate use of resources not only strains the healthcare system, but the absence of preventative care predicts a poorer prognosis for mentally ill patients with co-morbid medical illnesses (Dixon et al., 1999). Physical illnesses also have a detrimental effect on quality of life, self-esteem and compliance, thereby compromising the prognosis of the psychiatric illness (Dixon et al., 1999).

1.1.1 Socio-Demographic and Lifestyle Factors

The role of socio-demographic and lifestyle factors in the risk of developing several medical comorbidities is well-established in non-SMI populations. For example, obesity is associated with a higher risk of diabetes, cardiovascular disease, and some cancers (Mokdad et al., 2003). The risk for developing these comorbidities also increases with age (Redelmeier et al., 1998).

With regard to gender, it is known that the rates of some autoimmune diseases (Sjogren's syndrome and scleroderma), osteoarthritis, and Alzheimer's disease are higher among women than in men, whereas other illness such as epilepsies and aortic aneurysms are more common in men (Paeratakul et al., 2002). Similarly, race and ethnicity exert an influence on the development of some medical comorbidities. Diseases like sickle cell anemia are observed far more frequently among persons of African descent, whereas other diseases like cystic fibrosis are more common among Caucasians (Kittles and Weiss, 2003). Socioeconomic factors, namely economic impoverishment and employment, contribute significantly to the majority of chronic medical comorbidities (Kaplan and Keil, 1993).

Lifestyle factors such as smoking are linked to illnesses like Chronic Obstructive Pulmonary Disease (Fiel, 1996), lung cancer, and heart disease (Ornish et al., 1990). Other lifestyle factors like alcohol consumption increase the risk for liver disease, cardiovascular disease, and some cancers (Corrao et al., 2004). Chronic use of marijuana can increase apolipoprotein C-III and increase the risk for myocardial infarction and stroke (Jayanthi et al., 2008).

1.1.2 Genetic Factors

Genetic factors play an important role in the development of several medical comorbidities. Genetic disorders may be x-linked, i.e. involve the sex chromosome or autosomal chromosome (dominant or recessive). The vast numbers of medical comorbidities however are inherited through a combination of genetic and environmental factors. For example, an individual who has a family history of diabetes may develop the illness if he/she has additional risk factors such as obesity. Heart disease, stroke, and high blood pressure are other examples of inheritance

through dual genetic and environmental mechanisms. It is therefore important to study the rates of medical comorbidities in families in order to tease out the effect of genetic predisposition from environmental factors. First degree relatives that include parents, children, brothers and sisters have several factors in common, namely genetic, environmental and lifestyle factors. Studying groups of persons with shared genetic and environmental socio-demographic and perhaps lifestyle factors is the preferred methodology to control for the risk and bias that may result from those factors for the development of medical comorbidities.

1.1.3 Risk Factors for Medical Comorbidities in Schizophrenia

Socio-demographic, lifestyle and genetic factors associated with medical comorbidities (described above) are significant determinants of psychiatric disease in patients with schizophrenia and related disorders. Therefore, it may be hypothesized that the development of a SMI such as schizophrenia may further exacerbate the effect that socio-demographic and lifestyle risk factors may have on the development of medical comorbidities (Cohen, 1993). High rates of poverty, smoking, and alcohol consumption are frequent occurrences in these populations (Brown et al., 1999). Although some convergent evidence implicating some of these risk factors exists, the studies lack rigor (diagnostic characterization of subjects) and appropriate controls (to be discussed later). Moreover, the role of genetic predisposition for the development of medical comorbidities in patients with SRD has not been examined. A brief review of risk factors associated with medical comorbidities is presented.

1.1.4 Obesity and Related Factors

Obesity is an important cause for the development of several medical comorbidities. Risk factors associated with obesity also increase the risk for the development of medical comorbidities. The rates of obesity in the United States (US) have increased exponentially in the last 2 decades. With the exception of Washington, DC and Colorado, 20% or more of the population in all states and regions in the US is obese (Body Mass Index = > 30 kg/m2). The rates of obesity in Pennsylvania are 27.4% (Sherry et al., 2010).

The rates of obesity in patients with SRD have outpaced the national norms (Allison et al., 1999). Although antipsychotics are frequently implicated, higher rates of obesity observed in patients with SRD predate the development of these medications (Kraepelin, 1919). Risk factors associated with obesity also increase the risk for the development of medical comorbidities. These include atypical antipsychotic medications, diet and nutritional factors and physical inactivity.

1.1.4.1 Atypical Antipsychotic Medications

With the exception of molindone, all conventional (typical) antipsychotics have been linked with weight gain (Heikkinen et al., 1993; Baptista 1999). However, since the introduction of novel (atypical) antipsychotics, which are the treatment of choice for the management of psychosis, the rates of obesity have increased substantially. Most novel (atypical) antipsychotic medications, namely risperidone, olanzapine, clozapine and quetiapine, have been shown to cause weight gain (Nasarallah, 2003). Within this class of medication, the propensity for medication-related weight gain is highest with olanzapine and clozapine and lowest with risperidone. The exception to this class is aripiprazole, which is weight neutral (Marder et al., 2003).

1.1.4.2 Diet and Nutritional Factors

Poor dietary and nutritional habits have been implicated in the development of obesity in patients with schizophrenia (Brown et al.,1999). Patients with schizophrenia may eat infrequently, have a single large meal during the day, choose inexpensive high-calorie foods, and consume large quantities of sugar-rich drinks like soda and iced tea (Beebe et al., 2009). In a nutritional survey conducted at the Western Psychiatric Institute and Clinic, it was observed that patients with schizophrenia consumed larger quantities and hence more calories of the same foods compared to matched controls from the NHANES survey (Strassnig et al., 1993).

1.1.4.3 Physical Inactivity

The majority of patients with schizophrenia lead sedentary lives. This may be related to negative symptoms, such as apathy and social withdrawal, or due to medication-related sedation (Brown et al., 1999). Studies that have examined physical activity in patients with schizophrenia using pedometers have observed considerably lower activity levels as compared to norms (Kane et al., 2012).

1.1.5 Socio-Demographic and Clinical Factors

Few socio-demographic and clinical correlates of weight gain and obesity have been reported in patients with SRD. Contrary to non-psychiatric population norms, the rates of obesity are higher among women than men in patients with schizophrenia (Allison et al., 1999). In this survey, the rates among African-American women were significantly higher than among Caucasian women. It is also known that weight gain is precipitous in the first year of treatment with atypical antipsychotic medications, with 10 – 15 lbs gain observed in patients treated with clozapine and

15 – 20 lbs gain observed in patients treated with olanzapine. It has also been shown that patients who are of normal weight at the beginning of treatment are most likely to gain weight with antipsychotic treatment (Kinon et al., 2001). Furthermore, the rate of weight gain is highest in the first 90 days of treatment and may then level off (Kinon et al., 2001).

1.2 CRITICAL EVALUATION OF THE LITERATURE

The convergent evidence suggests that patients with SRD have higher rates of medical comorbidities, namely diabetes and hypertension, than individuals without psychiatric illness. With the exception of a few socio-demographic and clinical factors reviewed earlier that have shown an association with some medical comorbidities in patients with SRD, a study of other risk factors such as marital status, living arrangement, income/employment, smoking, alcohol and marijuana use has not been carried out. While these risk factors have been examined in non-psychiatric populations, systematic evidence in patients with SRD is lacking. Furthermore, with regard to the known association of medical comorbidities with other risk factors, studies examining such associations in patients with SRD lack rigor because of methodological limitations. Limitations are outlined below:

1.2.1 Study populations

Medical comorbidities and their associated risk factors have frequently been reported in hospital-based samples among individuals who are insured. It is not known whether this approach may have led to a systematic bias in the reported estimates. Estimates from other studies may have

been biased as racially homogenous populations were enrolled (Carney, Jones and Woolson, 2006).

1.2.2 Selection of controls

In some studies, samples of patients with SRD were compared with controls from national epidemiological surveys such as the NHANES (Strassnig et al., 2003). Controls enrolled from other geographical regions may differ in demographic and social factors from patients with SRD leading to systematic biases.

1.2.3 Ascertainment Bias

In studies where samples are culled from administrative or claims databases, biases with regard to 'case-finding' cannot be accounted for. It is also not possible to determine the extent to which rigorous methodology has been applied to the characterization of the psychiatric illness.

1.3 SIGNIFICANCE OF THE PROPOSED DISSERTATION

The Substance and Mental Health Services Administration has recognized the increased mortality resulting from chronic medical illnesses in patients with severe mental illnesses and is spearheading the "*10 X 10 Wellness Campaign*" to increase life expectancy by 10 years in 10 years (10 X 10) for people with mental illness. The following dimensions have been identified as possible areas of intervention and improvement to achieve this goal; social, physical,

emotional, spiritual, occupational, intellectual, environmental, and financial (http://www.promoteacceptance.samhsa.gov/10by10/default.aspx).

The NIH Roadmap for Medical Research emphasizes that in order to "*solve the puzzle of complex diseases and conditions*" research should be conducted by "*filling defined knowledge gaps*" (Zerhouni, 2003). The previous research on medical comorbidities in SRD has primarily focused on clinical factors, namely obesity-related medical comorbidities, which result from treatment with antipsychotic medications. Thus a "knowledge gap" in this literature exists with respect to other factors that may be associated with the development of medical comorbidities in patients with SRD. This dissertation examined whether socio-demographic and lifestyle factors were associated with an increased or decreased risk for the development of specific medical comorbidities in patients with SRD. Furthermore, the dissertation also explored how the risk of developing medical comorbidities was modified by the genetic predisposition associated with several medical comorbidities by comparing differences between the strength and nature of these associations in patients with SRD, their non-psychiatric first degree relatives, and unrelated non-psychiatric controls.

1.4 STRENGTHS AND WEAKNESSES

The dissertation examined socio-demographic and lifestyle factors that may have been associated with medical comorbidities in patients with SRD. Three groups, namely patients with SRD, their non-psychiatric first degree relatives, and unrelated non-psychiatric controls, were compared. These three groups were included in order to examine the following:

1.) What risk factors are associated with medical comorbidities in patients with SRD?

2.) Did risk factors that were associated with medical comorbidities in patients with SRD differ from those that were observed in unrelated non-psychiatric control subjects?

3.) To what extent did genetic predisposition account for the development of medical comorbidities in patients with SRD?

4.) Did first degree relatives of patients with SRD who did not have psychiatric illness have similar rates of medical comorbidities and risk factors as patients with SRD and unaffected controls?

1.4.1 Strengths

This is the first attempt to comprehensively assess many important risk factors that may be associated with the development of medical comorbidities in patients with SRD. A significant strength of the study is the uniformity with which the data were obtained. The Diagnostic Interview for Genetic Studies (DIGS; Nurnberger et al., 1994, described later) is an established tool for diagnostic characterization of subjects with mental illnesses. It was administered by trained raters across all studies with no systematic changes or modifications from study to study. Furthermore, the similarities in the inclusion/exclusion criteria across all studies also increased the confidence for pooling these data. There were no restrictions based on comorbid conditions, such as comorbid medical illnesses or comorbid alcohol or substance abuse/dependence, on the types of patients who could or could not be enrolled in these studies. Thus, these broad inclusion criteria vastly enhanced the external validity (generalizability) of the sample. This uniform strategy for ascertaining the Axis 1 diagnoses addressed the case-finding bias that was observed in the literature. Another significant strength of the study was the availability of information from first degree relatives without psychiatric illness(es). This allowed for the examination of

genetic predisposition as an additional risk for the development of medical comorbidities. Lastly, the availability of data from unrelated non-psychiatric controls who were enrolled contemporaneously from the same geographical area as patients with SRD or their relatives provided a unique opportunity for comparison of rates and risk factors in these groups. Thus, confounding that may have resulted from enrollment of non-contemporaneous controls or those derived from national epidemiological surveys was minimized.

Unlike several studies in the literature, the study sample was heterogeneous with respect to the distribution of demographic and social factors. Thus, the external validity (generalizability) of findings from such a sample was likely to be high.

1.4.2 Weaknesses

The proposed study has several weaknesses. First, the study was based on a cross-sectional examination of medical comorbidities and risk factors in three groups of subjects. Given this design, no assumptions of causality could be made as temporal precedence could not be established. Rather, the data only showed whether the risk factor(s) are associated with a particular medical comorbidity. Second, the characterization of medical disorders was based only on the subject's self-report. The diagnoses had not been corroborated or verified. Studies using this methodology usually result in an under-estimate of the outcome (Elliott and Huizinga, 1989). Therefore, lower than expected rates of medical comorbidities may have been observed. Third, although quite comprehensive in its scope, this study did not address all possible factors and mechanisms that may have accounted for the development of medical comorbidities in patients with SRD. Chiefly, a measure of body weight (or BMI) was not available and therefore, the role of obesity as a risk factor for the development of some medical comorbidities, for

example diabetes and cardiovascular disease, could not be accounted for. This limitation may have affected the validity of the relationship(s) between the other proposed risk factors and medical comorbidities because as previously stated, the rates of obesity are quite high in this population and body weight is only one of many potential factors that may lead to the development of medical comorbidities. These limitations notwithstanding, the comparison of various study groups was likely to have high internal validity because the biases apply to all subjects uniformly.

1.5 HYPOTHESES AND SPECIFIC AIMS

As part of this dissertation, a systematic review of published literature was carried out in order to examine socio-demographic and lifestyle factors (smoking, alcohol and marijuana use) that may be associated with diabetes, hypertension or the metabolic syndrome in patients with SRD. The dissertation also examined the associations between 1) socio-demographic factors, and 2) lifestyle factors with selected medical comorbidities in patients with SRD enrolled in genetic studies carried out at the Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine, Pittsburgh, PA (hereinafter referred to as probands). Additionally, these associations were examined in non-psychiatric first-degree relatives of the probands and in contemporaneously enrolled unrelated non-psychiatric controls from the same geographical areas. The following medical illnesses were included in these analyses; diabetes and hypertension. The specific aims and hypotheses were as follows:

Specific Aim 1: Examine the rates of hypertension and diabetes in patients with Schizophrenia, their 1st degree non-psychiatric relatives, and unrelated non-psychiatric controls.

Hypothesis 1: The rates of hypertension and diabetes are higher in patients with Schizophrenia and related disorders compared to 1) their non-psychiatric relatives and 2) unrelated healthy ***controls.***

Specific Aim 2: Compare the associations between socio-demographic risk factors and hypertension and diabetes in patients with Schizophrenia, their 1st degree non-psychiatric relatives, and unrelated non-psychiatric controls.

Hypothesis 2: Similar to associations observed in the general population, socio-demographic risk factors namely, age, race, gender, marital status, living arrangement, occupation and education are associated with hypertension and diabetes in patients with Schizophrenia and related disorders.

Specific Aim 3: Compare the associations between lifestyle factors and hypertension and diabetes in patients with Schizophrenia, their 1st degree non-psychiatric relatives, and unrelated non-psychiatric controls.

Hypothesis 3: Similar to associations observed in the general population, lifestyle factors namely, smoking, alcohol, and marijuana use are associated with hypertension and diabetes in patients with Schizophrenia and related disorders.

1.5.1 Rationale for Selection of Study Groups

Comparison of patients with SRD and unrelated non-psychiatric controls was carried out to show whether the association between the proposed risk factors and medical comorbidities varied in groups that were discordant for SRD and did not share genetic predisposition. Comparison of patients with SRD with their first degree non-psychiatric relatives was carried out to show whether the association between the proposed risk factors and medical illnesses varied in groups

that share a common genetic predisposition for the development of medical comorbidities, as well as several socio-demographic factors, but were discordant for the presence of psychiatric illness. Comparison of first degree relatives with unrelated non-psychiatric controls were carried out to inform the extent to which family history of psychiatric illness influenced the presence or absence of a medical comorbidity in individuals who did not have SRD.

1.5.2 Data for the Proposed Dissertation

The proposed dissertation is based on secondary data analysis of four large NIMH-funded genetic studies carried out by Vishwajit Nimgaonkar, MD, DPhil and colleagues at the University of Pittburgh. An exempt IRB approval from the University of Pittsburgh for secondary analysis of anonymized data was obtained.

These studies investigated the genetic basis for schizophrenia by enrolling patients with schizophrenia, their psychiatrically ill and non-psychiatric first degree relatives, and unrelated non-psychiatric controls from the same geographic area as the patients. The Diagnostic Interview for Genetic Studies (DIGS) was used to obtain socio-demographic and clinical information for diagnostic formulation of all study participants including the proband, their non-psychiatric first degree relatives, and unrelated non-psychiatric controls. The DIGS also elicits information about medical comorbidities. This uniform methodology facilitates the pooling of data in order to examine factors associated with medical comorbidities in all groups of interest. Details about the four studies are presented below:

1.) Candidate Gene Alleles: Associations with Schizophrenia (1K02MH000966; IRB#9509115): The objective of this study was to identify genetic susceptibility factors for schizophrenia using a combination of linkage and association studies in families with

one or more members affected with schizophrenia or schizoaffective disorder. Subjects of all races were recruited.

2.) Genetic Susceptibility in Schizophrenia (1R01MH056242; IRB#:020603): The objective of this study was to identify dopamine (DA) genes that may underlie liability to schizophrenia and related psychiatric disorders through analysis of a large sample of families with at least one member with schizophrenia or schizoaffective disorder, and an additional sample of unrelated control subjects. Subjects of all races were recruited.

3.) Schizophrenia Liability Genes among African Americans (1R01MH066263; IRB#:020526): The objective of this eight-institute collaborative study was to identify genes that underlie liability to schizophrenia in African American families with at least one member with schizophrenia or schizoaffective disorder.

4.) A Neurobehavioral Family Study of Schizophrenia (1R01MH063480; IRB#:010218): The objective of this two-site study (University of Pittsburgh and University of Pennsylvania) was to combine genetic and neurobiologic paradigms enabling detection and localization of genes that modulate susceptibility to schizophrenia or schizoaffective disorder in multiplex, multigenerational Caucasian families. In addition to the patients with schizophrenia (probands), only those first degree relatives who did not have psychiatric illness were included in the dissertation.

1.5.3 Diagnostic Interview for Genetic Studies

The Diagnostic Interview for Genetic Studies (DIGS) developed by the NIMH is a semi-structured interview for (poly-) diagnostic formulation using standard diagnostic criteria (Nurnberger et al., 1994). It can take 2-3 hours to complete and the time depends upon the

extent of the psychopathology and medical comorbidities. It also enables a detailed assessment of course of illness. The DIGS can be administered by individuals who have experience in interviewing and assessing manifest psychopathology. The kappa coefficients for test-retest reliability (4-10 day interval) of the scale for depression, bipolar disorder and schizophrenia, were 0.94, 0.96 and 0.75 respectively (Nurnberger et al., 1994).

The first section of the semi-structured interview (A. Demographics) capture socio-demographic information and the second section (B. Medical History) captures information related to medical comorbidities and smoking. Alcohol and marijuana use-related information is recorded in the I. Alcohol Use and Dependence and J. Drug Abuse and Dependence sections.

1.5.4 Psychiatric Diagnosis for Case Identification

Psychiatric diagnosis for case identification was culled from the DIGS for the following DSM-IV categories for "Schizophrenia and Other Psychotic Disorders (295.xx); 295.30 – Paranoid Type, 295.10 – Disorganized Type, 295.20 – Catatonic Type, 295.90 – Undifferentiated Type, 295.60 – Residual Type, 295.40 – Schizophreniform Disorder, 295.70 – Schizoaffective Disorder and 298.9 – Psychotic Disorder NOS. Other co-morbid Axis 1 diagnoses (for cases of 'Schizophrenia' identified above) were also extracted from the database.

1.5.5 Plan for Statistical Analysis

Prior to analyses, distributions of the variables were examined and data transformations done to reduce skewness. Other data reduction techniques including recoding and stratification were employed if necessary. The prevalence rates of diabetes and hypertension were calculated for

patients with SRD (probands), their non-psychiatric first degree relatives, and unrelated non-psychiatric controls and compared across the three groups.

The associations between demographic factors with diabetes or hypertension were examined in the following populations; probands, their non-psychiatric first degree relatives, and unrelated non-psychiatric controls. Specifically, the analyses examined whether the rates of various medical comorbidities were affected by age, gender, and ethnicity. Similar analyses for examining the association between social factors, namely, marital status, occupation (self, parent and head of household), and education were carried out. Similarly, the associations between lifestyle factors, namely smoking, marijuana and alcohol use, with diabetes or hypertension were examined.

1.5.6 Outline of the Dissertation

The dissertation consists of three separate manuscripts:

Manuscript 1: A systematic review of the literature examining the association between socio-demographic and lifestyle factors with diabetes, hypertension and the metabolic syndrome in patients with schizophrenia.

Manuscript 2: An investigation of the association of socio-demographic factors with diabetes and hypertension in patients with schizophrenia and related disorders, their 1st degree relatives and unrelated non-psychiatric controls.

Manuscript 3: An investigation of the association of lifestyle factors with diabetes and hypertension in patients with schizophrenia and related disorders, their 1st degree relatives and unrelated non-psychiatric controls.

1.6 LITERATURE CITED

See **BIBLIOGRAPHY**

2.0 A SYSTEMATIC REVIEW OF SOCIO-DEMOGRAPHIC AND LIFESTYLE FACTORS ASSOCIATED WITH DIABETES, HYPERTENSION AND THE METABOLIC SYNDROME IN PATIENTS WITH SCHIZOPHRENIA AND RELATED DISORDERS

2.1 ABSTRACT

Introduction: Diabetes, hypertension and the metabolic syndrome are important causes of early mortality in patients with schizophrenia. In addition to obesity and iatrogenic effects of atypical antipsychotic medications, socio-demographic factors such as age, race, gender, education, employment and marital status, and lifestyle factors such as smoking, alcohol and marijuana use, may add additional risk for the development of these disorders. A systematic review was carried out to examine the associations between these socio-demographic and lifestyle factors with diabetes mellitus, hypertension, and the metabolic syndrome in patients with schizophrenia and related disorders.

Methods: Articles published between 1989 and September 2012 were extracted from Medline and PsychINFO using broadly defined search terms. Relevant studies were selected using established methods for systematic reviews, from which primary studies with empirical findings were retrieved for further examination. Wide variations in study populations, designs and methodologies of retrieved studies precluded a meta-analytic quantitative summarization of

results. Results were summarized qualitatively for available socio-demographic and lifestyle factors associated with diabetes, hypertension and the metabolic syndrome.

Results: A total of 26 studies formed the basis of the systematic review. Convergent findings suggested that age increased the risk for diabetes mellitus, hypertension, and the metabolic syndrome. African-American race was consistently associated with a higher prevalence of diabetes, but its relationship with the metabolic syndrome varied. Some studies showed higher prevalence of the metabolic syndrome in African-American patients, while other studies showed higher rates among Hispanic and Caucasian patients. The results with respect to sex were equivocal, with a higher risk of diabetes and the metabolic syndrome for females and a higher risk for hypertension for males. Studies examining other socio-demographic and lifestyle factors were either too few or had not been done at all to yield meaningful conclusions.

Conclusions: Age and African-American race increase the risk for diabetes and hypertension in patients with schizophrenia. The majority of studies that examined the role of sex found that female patients were more likely to have higher rates of diabetes. The role of education, marital status, occupation, and living arrangement as effect modifiers could not be established in this review as there were too few studies that examined these characteristics. Similarly, there were too few or no studies examining lifestyle factors in diabetic and hypertensive patients with schizophrenia to determine their association with diabetes, hypertension, or the metabolic syndrome. Longitudinal studies must include these factors for a comprehensive assessment of diabetes, hypertension, and metabolic syndrome risk. Analyses stratified by important socio-demographic factors, for example sex, must be carried out in future studies in order to identify subgroups at highest risk for developing these disorders.

Public Health Significance: The study confirms the need for additional attention to address the high rates of diabetes and hypertension in African-American patients with schizophrenia.

2.2 INTRODUCTION

High rates of chronic medical conditions are associated with increased mortality in patients with schizophrenia as compared to the general population (Goldman, 1999). A recent survey of mortality data from state hospitals across 8 states using age and sex-matched controls, showed a 25 year lifespan gap among patients with schizophrenia and related disorders (SRD) attributable mainly to cardiovascular, cerebrovascular and pulmonary diseases (Parks et al., 2006). Moreover, treatment outcomes for chronic medical conditions in patients with SRD may be further compromised by poor access to physical health care and problems with medication compliance (Brown et al., 2000). Lastly, the high rates of cardiovascular risk factors such as obesity, poor nutrition, sedentary lifestyles and smoking in patients with schizophrenia also contribute to poor outcomes (Connolly and Kelly, 2005).

Atypical medication-related adiposity is frequently cited as an important reason for the development of several obesity-related chronic illnesses in patients with schizophrenia (Wirshing, 2004). Some, but not all, atypical medications have obesogenic effects that increase the likelihood for the development of diabetes and hypertension. There is also limited research to suggest that the medication-induced weight gain and dsyglycemia may be moderated by demographic characteristics, making some individuals more susceptible to the development of these sequelae (Saddichha et al., 2008).

Diabetes and hypertension, two prototypical chronic conditions that occur at high rates in patients with schizophrenia, have multifactorial etiologies (Hennekens et al., 2005). Known risk factors for the development of these disorders in the general population can broadly be divided

into two types; un-modifiable and modifiable. Un-modifiable factors include demographic characteristics such as age, race, sex and family history of diabetes. Marsh and colleagues observed that 20 percent of geriatric patients with schizophrenia had diabetes (Marsh et al., 1997). However, other studies have reported higher rates of diabetes among younger and middle-aged patients with schizophrenia but not in older patients (Jeste et al., 1996). The rates of cardiovascular diseases are also higher in patients with schizophrenia than in the general population (Dixon et al., 1999). Higher rates of these disorders have been found in older patients that also frequently account for medical hospitalization (Sajatovic et al., 1996). An age-dependent effect on the prevalence of hypertension has also been shown, although some studies have reported lower rates of hypertension, coronary heart disease and congestive heart failure in elderly patients with schizophrenia (Larco and Jeste, 1994).

With regard to gender, some studies have shown higher rates of diabetes in female patients compared with males (Philippe et al., 2005). Rates of the metabolic syndrome are also higher in female patients compared to males (McEvoy et al., 2005). The metabolic syndrome, also called Syndrome X, is a clustering of risk factors that increase the risk for coronary artery disease, stroke and type-2 diabetes (Alberti et al., 2005). In order to meet diagnostic criteria for the metabolic syndrome as set forth by the National Cholesterol Education Program (Adult Treatment Protocol III), three or more of the following criteria must be present; 1) Abdominal obesity: Men > 40 inches, Women > 35 inches, 2) fasting triglycerides $\geq$ 150 mg/dL, 3) high density lipoprotein cholesterol (HDL-C): Men < 40 mg/dL, Women < 50 mg /dL, 4) blood pressure $\geq$ 130/85 mm Hg or an antihypertensive medication, and 5) fasting glucose > 110 mg/dL or on insulin or hypoglycemic medication (Expert Panel on Detection, 2001). Metabolic syndrome was included for this systematic review as both comorbidities of interest, diabetes and

hypertension, are part of the cluster that collectively increase the risk for coronary artery disease and type-2 diabetes. Since 2000, there has been a increase in the number of studies examining the metabolic syndrome in patients with schizophrenia and related disorders (De Hert et al., 2009). It is thus imperative that the metabolic syndrome be included in any comprehensive evaluation of cardiovascular risk factors. Similar to diabetes and hypertension, the rates of the metabolic syndrome in patients with schizophrenia are at least 1.5 to 2-fold the rates observed in the general population (De Hert et al., 2009).

Minority patient populations, both African-American and Hispanic, have higher rates of diabetes and hypertension compared to Caucasian populations. A few studies however, have shown higher prevalence of the metabolic syndrome among Caucasian patients compared to African-American patients. In a study by Meyers and colleagues, a higher proportion of white patients met criteria for the metabolic syndrome compared to non-white patients with schizophrenia (61.5% vs 44.6%, $p < 0.05$; Meyer, Pandina et al., 2005).

Modifiable factors that afford environmental risk include educational attainment, obesity, smoking and alcohol use (Wilson et al., 1998). Social supports such as marital status and solitary living are additional modifiable factors that not only increase the risk for the development of chronic medical conditions like diabetes or hypertension, but also impact outcomes (Sherbourne and Hays, 1990).

Whereas an association between antipsychotic medication-related adiposity and diabetes and hypertension has been shown in patients with schizophrenia (Citrome et al., 2007), the effect of socio-demographic factors, such as age, race, sex, education, marital status and occupation on the relationship have not been examined. Moreover, the contribution of lifestyle factors, namely,

smoking, alcohol and marijuana, in the development of these disorders in patients with SRD, although suggested anecdotally, remains unclear.

In the general population, smoking is an independent risk factor for both diabetes and hypertension (Rosen et al., 2006; Willi et al., 2009). Similarly, heavy use of alcohol also increases the risk for hypertension (Puddey et al., 1985). This risk is compounded if alcohol is consumed in the absence of food, adding additional vulnerability for patients with schizophrenia who have poor dietary habits (Stranges et al., 2004; Peet, 2004). The role of marijuana use in the development of diabetes and hypertension is less clear. A recent report of an inverse association between marijuana use and diabetes is intriguing but requires replication in the general population (Rajavashisth et al., 2012). On the other hand, the relationship between heavy marijuana use and the increased risk for myocardial infarction and stroke in the general population is well established (Sidney et al., 2002; Frishman et al., 2003).

The cumulative risk afforded by socio-demographic and lifestyles factors for the development of diabetes, hypertension, and the metabolic syndrome in a population of mentally ill patients, who have a substantial pre-existing liability for these disorders from psychotropic medications, is likely to be high. It is also essential that the evaluation of socio-demographic and lifestyle factors that are associated with diabetes and hypertension be carried out within the context of the same study so that confounding factors, if any, are uniformly applied while testing all associations. Given the large numbers of socio-demographic and lifestyle risk factors that may be associated with diabetes or hypertension, a study of substantial size where uniform methodology has been applied for data collection is ideal. However, in the absence of such a study, a systematic review or a meta-analysis may be carried out by combining and contrasting the results obtained from different studies. Results obtained from multiple studies may either be

summarized quantitatively using statistical techniques (Meta-analysis), or summarized qualitatively (Systematic review).

This review examined the relationship between socio-demographic and lifestyle factors and diabetes, hypertension, and the metabolic syndrome in patients with schizophrenia and related disorders by conducting a systematic review of all available evidence.

2.3 METHODS

2.3.1 Search Strategy

Data for the study were retrieved from Medline and PsychINFO databases using the OVID interface. Studies published between 1989 and September 2012 were included. The starting year 1989 was selected to coincide with the approval of clozapine, the first prototypical antipsychotic medication, which also had pronounced obesogenic effects (Choc et al., 1990). In the ensuing period, there has been a renewed interest in examining cardiovascular risk factors attributable to the increased risk for development chronic medical conditions. The systematic review is intended to examine socio-demographic (age, race, sex, education, occupation, martial status, living arrangement) and lifestyle factors (smoking, alcohol and marijuana use) associated with the high rates of diabetes, hypertension and the metabolic syndrome in patients with schizophrenia and related disorders.

Search terms used for the retreival of studies included *schizophrenia, schizoaffective disorder, schizophreniform disorder, severe mental illness* and *serious mental illness*. In order to identify articles related to diabetes, hypertension, and the metabolic syndrome the following

search terms were used; *diabetes, hyperglycemia, dysglycemia, metabolic syndrome, syndrome X, hypertension,*and *high blood pressure*. The two searches, articles of schizophrenia and studies of diabetes, hypertension and the metabolic syndrome, were combined. Next, articles that addressed socio-demographic and lifestyle factors were extracted using the following terms; *age, age-adjusted, age-stratified, race, ethnicity, sex, gender, education, schooling, marital status, spouse, living arrangement, smoking, nicotine, tobacco, alcohol, ethanol, marijuana,* and *cannabis*. A dataset was created that included articles with schizophrenia, diabetes, hypertension or the metabolic syndrome with the articles that addressed any one or more of the socio-demographic or lifestyle factors. The title and abstracts of articles to be included were reviewed and in the case where it could not be ascertained whether a particular socio-demographic or lifestyle factor was examined, the full articles was examined. In addition, the bibliographies of published articles were also examined to include studies that may not have been retrieved through the Ovid search. Articles that included one or more socio-demographic or lifestyle factors of interest were selected.

2.3.2 Inclusion and Exclusion Criteria

Cross-sectional studies including case-control and retrospective chart reviews and longitudinal studies including cohort studies and randomized controlled trials were included. Narrative reviews, case reports, commentaries and editorials were excluded from the systematic review as were studies published in foreign languages. Studies on type-1 diabetes, which results from a different etio-pathogenic mechanism and has shown an inverse relationship with schizophrenia, have not been included in this review (Juvonen et al, 2007).

2.3.3 Qualitative Assessment of Studies

Findings from selected studies were summarized in tables using criteria that represented sample size, sample characteristics, type of study, demographic profile and primary finding related to the factor of interest. Results of factors that yielded very few studies were summarized narratively.

Because of the nature of this study, only the author was involved in searching for and retreiving available articles, and culling data to include in the systematic review. The search for retrieval of studies was done at least twice to ensure that the methodology used may be reproducible.

2.4 RESULTS

2.4.1 Search Results

The search results are summarized in Figure 1.

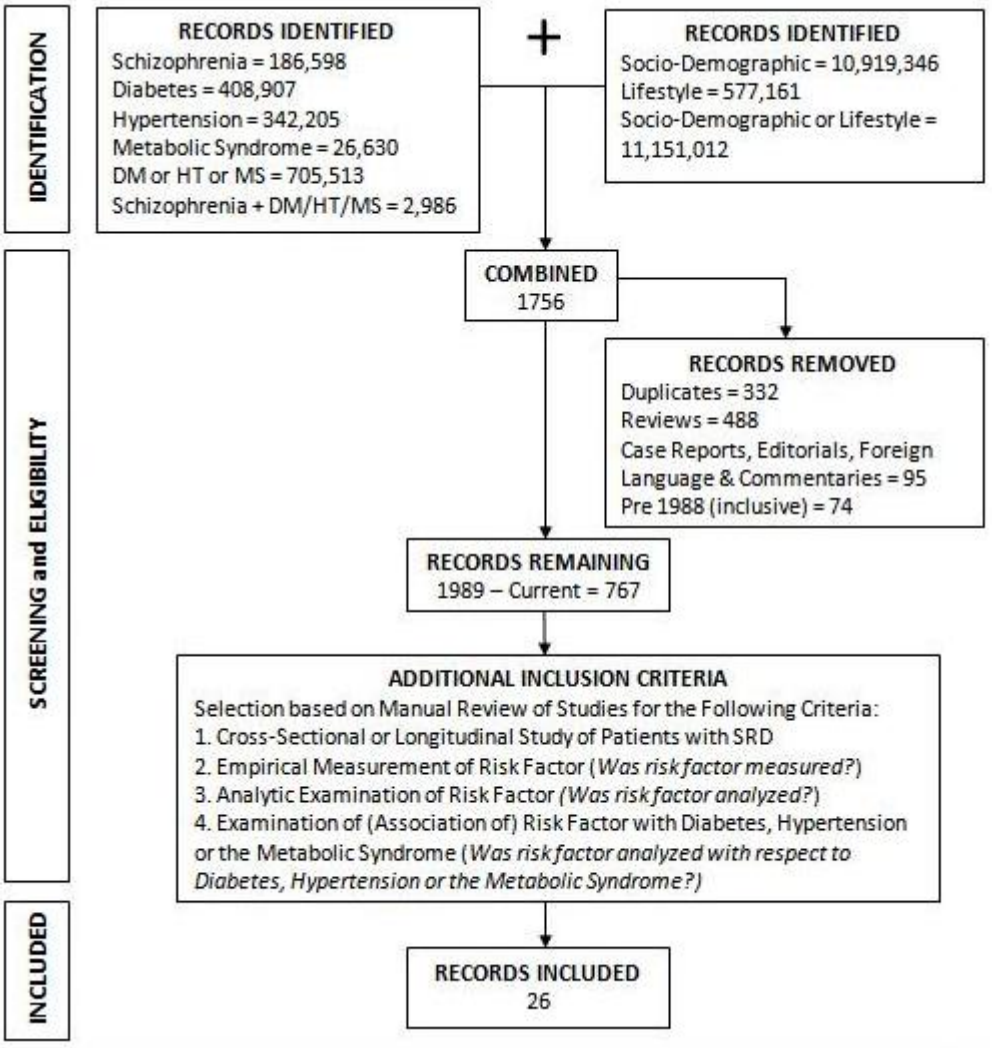

Figure 1. Search Results

A total of 186,598 articles were identified for schizophrenia and related disorders and 705,513 for diabetes or hypertension or the metabolic syndrome using the search terms described earlier. The combination of these two data-sets yielded 2,986 articles. In a separate search 10,919,346 articles were identified for any socio-demographic factor of interest and 577,161 for any lifestyle factor. Combination of the socio-demographic and lifestyle data-sets with the schizophrenia plus diabetes or hypertension data-set yielded 1756 articles.

After removing duplicates, review articles, case reports, editorials and commentaries and limiting the search to English language articles published between 1989 to September 2012, 767 articles remained. As the search targeted title and abstract fields instead of keywords, all publications in which an assortment of search terms appeared were retrieved. The majority of these articles did not have any empirical measurement of any of the socio-demographic or lifestyle factors of interest, or cases with diabetes, hypertension or the metabolic syndrome. However, from this data-set, only articles that included an analytic examination of any one or more of the socio-demographic or lifestyle factors in patients with schizophrenia, hypertension or the metabolic syndrome, were selected.

A total of 26 studies were included in the systematic review. No additional articles were identified by reviewing the bibliographies of review articles and published studies that were not included in the original searches.

2.4.2 Systematic Review of Socio-Demographic Risk Factors

Effect of Age: A total of 10 studies addressed the association between age and diabetes, hypertension or the metabolic syndrome in patients with schizophrenia and related disorders. These studies are reviewed in Table 1.

Table 1. Effect of Age

Study	N	Sample	Design	Age Mean + SD	Race % Caucasian / A-A / Other	Sex % M	Conclusion
Studies of Diabetes							
Dixon et al., 2000	20967	I-P, O-P	C-S	UNK	41 to 80 / 20 to 59	34 to 37	Positive association with age
Subramaniam et al., 2003	194	O-P	C-S	55.5 + 12.7	Unknown	80	*Higher rates in all age strata but lower in $\geq$ 70
Voruganti et al., 2007	1123	O-P	C-S	44.2 + 12.6	82/18	63	Positive association with age
Chien et al., 2009	4417	ND	C-S	S-d	Taiwanese	55	*Higher rates in all age strata but lower in $\geq$ 70
Okumura et al., 2010	3489	ND	C-S	44.5 + 14.3	Japanese	49	*Higher rates in all age strata
Hsu et al., 2011	3150	ND	C-S	S-d	Taiwanese	-	*Higher rates in all age strata
Studies of the Metabolic Syndrome							
Straker et al., 2005	89	I-P	C-S	39.8+ 15.3	32/28/20	50	Positive association
McEvoy et al., 2005	689	I-P, O-P	Long	40.4 + 11.2	60/40	74	Positive association
Bermudes et al., 2006	102	I-P	Long	38 + 10.8	51/49	50	Positive association
Studies of Hypertension							
Lan et al., 2012	1030	I-P	C-S	48 + 12.2	Taiwanese	60	*Higher rates in all age strata

UNK = Unknown; N = Sample Size; S-d: (Age) Stratified in Deciles,
I-P = Inpatient; O-P = Outpatient; ND = National Database
C-S = Cross-Sectional including Case Control studies
Long = Longitudinal including cohort studies and randomized controlled trials
DM = Diabetes, HT = Hypertension, MS = Metabolic Syndrome
Race % Cauc / A-A / Other = Percent of Caucasian / African-American / Other.
(In the case only two numbers are presented = Caucasian / African-American)
Sex % M = Percent of Males
* = Incremental increase, i.e. a positive relationship between 2 variables

Increasing age was associated with incrementally higher risk for diabetes, the metabolic syndrome and hypertension. Studies that compared these associations to those observed in the general population also showed much higher rates of diabetes among younger age groups in patients with schizophrenia (Subramaniam et al., 2003, Chien et al., 2009). These studies also observed lower prevalence rates among older patients greater than 70 years of age compared to population norms. Although it is unclear why such trends exist, it may be the result of a 'survivor effect' where healthy individuals are more likely to survive into their older years compared with unhealthy individuals who die earlier (Richardson et al., 2004).

An incremental association with age was also observed for hypertension and the metabolic syndrome (Lan et al., 2012; McEvoy et al., 2005). These trends with age were present in all populations that included European, American, Taiwanese and Japanese samples. Studies that presented age-corrected prevalence rates were not reviewed as the relationship between age and diabetes, hypertension or the metabolic syndrome could not be ascertained (Liao et al, 2011).

Effect of Race: A total of 17 studies addressed the association between race and diabetes or hypertension or the metabolic syndrome in patients with schizophrenia and related disorders. These studies are reviewed in Table 2.

Table 2. Effect of Race

Study	N	Sample	Design	Race % Caucasian /A-A/Other	Sex % M	Conclusion
Studies of Diabetes						
Dixon et al., 2000	20967	I-P, O-P	C-S	41 to 80 / 20 to 59	34-37	Higher in A-A
Regenold et al., 2002	243	I-P	C-S	49 / 51	35	No difference
Subramaniam et al., 2003	194	O-P	C-S	Unknown	80	No association with Asian ethnicities
Sernyak et al., 2003	121	O-P	Long	90 / 10	9	Higher in A-A
Kreyenbuhl et al., 2006	143	O-P	C-S	57 / 43	52	Higher in nonwhites
Ramaswamy et al, 2007	140951	Med	Long	77 / 15 /8	47	Higher in A-A
Studies of the Metabolic Syndrome						
Basu et al., 2004	33	O-P	C-S	61 / 36 / 3	51	No differences
Kato et al., 2004	48	O-P	C-S	25/ 10 / 65	50	Higher in Hispanics
McEvoy et al., 2005	689	I-P,O-P	Long	60 / 40	74	Higher in A-A
Straker et al., 2005	89	I-P	C-S	52 / 28 / 20	50	No Differences
Lambert et al., 2005	3663	Med	Long	49 / 21 / 30	47	Higher in A-A and Hispanics
Meyer et al., 2005 (a)	1231	I-P, O-P	C-S	74 / 26	59	Higher in Whites
Meyer et al., 2005 (b)	121	O-P	C-S	49 / 51	54	Higher in Whites
Lamberti et al., 2006	93	O-P	C-S	80 / 20	67	No differences
Bermudes et al., 2006	102	I-P	Long	51 / 49	50	Higher in Caucasians
Corell et al., 2008	111	I-P	C-S	84 / 16	49	No Differences
Meyer et al., 2009	314	O-P	Long	57 / 27 / 16	70	Higher in A-A
Rivas-Vazquez et al., 2011	122	O-P	C-S	80% Hispanics	72	Highest in Cuban Americans
Studies of Hypertension						
McEvoy et al., 2005	689	I-P,O-P	Long	60 / 40	74	Higher in A-A

N = Sample Size; S-d: (Age) Stratified in Deciles,
I-P = Inpatient; O-P = Outpatient; ND = National Database
C-S = Cross-Sectional including Case Control studies, Long = Longitudinal studies
DM = Diabetes, HT = Hypertension, MS = Metabolic Syndrome, DKA = Diabetic Ketoacidosis
Race % Cauc / A-A / Other = Percent of Caucasian / African-American / Other.
(In the case only two numbers are presented = Caucasian / African-American)
Sex % M = Percent of Males

Most cross-sectional studies showed higher rates of diabetes in African-American patients with schizophrenia. African-American patients also had higher odds for developing diabetes following antipsychotic treatment (Lambert et al., 2005). Studies with diverse populations including Medicaid and Medicare recipients consistently show higher rates of diabetes among African-American patients with schizophrenia (Dixon et al., 2000). These racial differences were also observed in the prevalence of undiagnosed diabetes and diabetic ketoacidosis (Sernyak et al., 2003, Ramaswamy et al., 2007).

Racial differences were less consistent for association with the metabolic syndrome, with some studies showing higher rates among African-American patients (Meyer et al., 2009, Lambert et al., 2005) or Hispanic patients (Kato et al., 2004, Rivas-Vazquez et al., 2011), with other studies showing higher prevalence among Caucasian patients (Meyer et al., 2005(a); Meyer et al., 2005(b), Bermudes et al., 2006). Some studies also failed to show any racial differences in the prevalence of the metabolic syndrome (Lamberti et al., 2006, Corell et al., 2008). With regard to hypertension, only one study presented racial differences with higher rates among African-American patients (McEvoy et al., 2005).

Effect of Sex: A total of 12 studies addressed the association between sex and diabetes or hypertension or the metabolic syndrome in patients with schizophrenia and related disorders. These studies are reviewed in Table 3.

Table 3. Effect of Sex

Study	N	Sample	Design	Race % Caucasian / A-A / Other	Sex % M	Conclusion
Studies of Diabetes						
Dixon et al., 2000	20967	I-P, O-P	C-S DM	41 to 80 / 20 to 59	34 to 37	Higher in females
Subramaniam et al., 2003	194	O-P	C-S	Unknown	80	No differences
Voruganti et al., 2007	1123	O-P	C-S	82 / 18	63	No differences
Chien et al., 2009	4417	ND	C-S	Taiwanese	55	Higher in females
Okumura et al., 2010	3489	ND	C-S	Japanese	49	Higher in Males 30-49 and females 40-59
Hsu et al., 2011	3150	ND	C-S	Taiwanese	50	Higher in females
Studies of the Metabolic Syndrome						
McEvoy et al., 2005	689	I-P, O-P	Long	60 / 40	74	Higher in females
Straker et al., 2005	89	I-P	C-S	52 / 28 / 20	50	No differences
Meyer et al., 2005 (a)	1231	I-P, O-P	C-S	74 / 26	59	Higher in females
Meyer et al., 2005 (b)	121	O-P	C-S	49 / 51	54	No differences
Corell et al., 2008	111	I-P	C-S	84 / 16	49	No differences
Studies of Hypertension						
Lan et al., 2012	1030	I-P	C-S	Taiwanese	60	Higher in males

N = Sample Size; S-d: (Age) Stratified in Deciles,
I-P = Inpatient; O-P = Outpatient; ND = National Database
C-S = Cross-Sectional including Case Control studies
Long = Longitudinal including cohort studies and randomized controlled trials
DM = Diabetes, HT = Hypertension, MS = Metabolic Syndrome
Race % Cauc / A-A / Other = Percent of Caucasian / African-American / Other.
(In the case only two numbers are presented = Caucasian / African-American)
Sex % M = Percent of Males
DKA = Diabetic Ketoacidosis

About half the studies that examined gender differences in patients with schizophrenia found higher prevalence of diabetes and the metabolic syndrome in female patients (McEvoy et al., 2005, Chein et al., 2009; Hsu et al., 2011, Lan et al., 2012). The remaining studies did not

find gender differences. Larger gender differences were also observed in Asian populations. The rates of diabetes among women with schizophrenia (10.3%) were almost twice the rates among men (5.9%; Chien et al., 2009) and 1.5 times higher than the rates among women in the general population (Hsu et al., 2011).

Only one study examined gender differences in the prevalence of hypertension and observed higher rates among male patients (Lan et al., 2012).

Effect of Education: Only three studies examined the relationship between educational status and the prevalence of diabetes in patients with schizophrenia. Lower education was associated with a higher risk of having diabetes (Dixon et al., 2000, Suvasaari et al., 2008). The third study did not find such an association (Voruganti et al., 2007).

Effect of Employment: Occupation or employment status as a risk factor for diabetes, hypertension or the metabolic syndrome in patients with schizophrenia was not examined in any of the studies reviewed.

Effects of Marital Status and Living Arrangement: Only one study examined marital status and found that the rates of diabetes were almost two-fold among patients who were 'ever married' compared to those who were 'never married' (Dixon et al., 2000) . In one study, independent housing, i.e. living on one's own, did not show any association with diabetes in patients with schizophrenia (Voruganti et al., 2007).

Effects of Lifestyle Factors: None of the studies included in the review examined the relationships between smoking or marijuana use and diabetes, hypertension or the metabolic syndrome in patients with schizophrenia. Two studies examined alcohol use; one showed a higher odds of having diabetes with alcohol consumption (Suvasaari et al., 2008) and the other

showed no relationship of alcohol with the metabolic syndrome in patients with schizophrenia (Meyer, Nasrallah et al., 2005).

2.4.3 Subgroup and Sensitivity analysis

Given the variations in sampling, design and methodology, a sensitivity analysis was not carried out. However, comparison of broadly defined subgroups, for example, inpatient vs. outpatient studies, or cross-sectional vs. longitudinal studies, revealed essentially similar results.

2.4.4 Publication Bias

Publication bias cannot be ruled out because unpublished reports and studies printed in foreign languages were not included. A funnel plot, a graphical technique used to assess publication bias (Light and Pillemer, 1984), was not constructed as there were marked dissimilarities in the methodologies and the resulting effect sizes for associations observed from different studies.

2.5 DISCUSSION

The systematic review included 26 studies on diabetes, hypertension and the metabolic syndrome in patients with schizophrenia. Age, race and sex were the most frequently investigated socio-demographic factors. Convergent findings suggested that age increased the risk for diabetes mellitus, hypertension and the metabolic syndrome in patients with schizophrenia and related disorders. African-American compared to Caucasian race was consistently associated with a

higher prevalence of diabetes but its relationship with the metabolic syndrome varied. Although a majority of studies trended towards higher rates for the metabolic syndrome in minority populations, several studies failed to find these trends. Female sex also emerged as a significant effect modifier associated with higher rates of co-occurring diabetes or the metabolic syndrome in some, but not all, studies. The findings with regard to age and race were robust and did not change based on patient status, inpatient or outpatient, or study design, cross-sectional or longitudinal. No conclusions could be drawn for other social or lifestyle factors because of the virtual lack of studies that examined these characteristics.

2.5.1 Diabetes, Hypertension and the Metabolic Syndrome in Schizophrenia

Higher rates of diabetes and glucose intolerance were reported in patients with schizophrenia prior to the introduction of antipsychotic medications (Raphael and Parcels, 1921). The rates of diabetes increased exponentially after the introduction of the first atypical antipsychotic medication clozapine in 1989 (Safferman et al., 1991). Several other atypicals have been introduced subsequently, most of which, with the exception of a few, have varying degrees of propensity to cause weight gain, insulin resistence and diabetes (McIntyre et al, 2001). Therefore, this review was limited to an examination of risk factors associated with diabetes, hypertension and the metabolic sydrome in the 'new' era of pharmacotherapy where atypical antipsychotic medications are the mainstay of treatment, and estimates of obesity and its related sequalae, namely diabetes, hypertension and the metabolic syndrome, have been examined systematically using established diagnostic criteria.

Several studies have shown high rates of hypertension in patients with schizophrenia (Hennekens 2007). In a survey of 101 long-term mentally ill adults, Kendrick and colleagues

found that about 25 percent of patients were obese, about 50 percent were smokers and about 10 percent were hypertensive (Kendrick, 1996). Corell and colleagues (2008) observed that 60% of patients who met the criteria for the metabolic syndrome had hypertension (Corell et al., 2008). In addition to adiposity, treatment with psychotropic medications also increases the incidence of hypertension (McEvoy et al., 2007). A third of patients in the CATIE Study were hypertensive, of which only 37.6% were receiving treatment (Nasarallah et al., 2006).

Some studies have failed to show an increased risk for hypertension in patients with schizophrenia (Cohn et al., 2004). In a study using data extracted from the Danish Psychiatric Central Research Register, higher rates for hypertension were observed among patients with bipolar disorder and anxiety disorders but not among patients with schizophrenia (Johannessen et al., 2006). Studies that report lower rates of hypertension in schizophrenia are usually associated with under-diagnosis secondary to a lack of awareness by patients and care providers (Munk-Jorgensen et al., 2000).

2.5.2 Effect of Age, Race and Sex

The effect of age on the risk for diabetes and hypertension in the general population is well established. A higher number of medical comorbidities have been observed in older patients with schizophrenia (Jeste et al., 1996). The effect of age on the incrementally higher risk for diabetes has been demonstrated in patients with schizophrenia treated with atypical antipsychotic agents (Basu and Meltzer, 2006). In studies that have examined stratified age groups, age-specific prevalence rates of diabetes increased steadily from 4% in the group aged 30 to 39 years to 17.3% in the group aged 40 to 49, to 50.0% in the group aged 50 to 59% (Subramanium et al. 2003).

In patients with schizophrenia, higher rates of obesity and related disorders are seen in minority populations (Kumunyika, 2012). The higher risk for developing medical comorbidities in racial minorities stems from several physiological and environmental factors. In addition to genetic factors, poor access to care, low health literacy and cultural competence, socio-economic factors, and diet play an etiological role (Liem et al., 1978). An additive risk model for diabetes that includes ethnicity, family history of diabetes, history of glucose dysregulation and pre-existing hypertension has also been proposed (Lindenmayer et al., 2001).

Higher levels of insulin resistance, a precursor to the development of diabetes, have been observed in women compared with men in the general population (Mittendorfer, 2005). Furthermore, the risk for developing coronary artery disease is also higher among diabetic women than diabetic men in the general population (Cubbon et al., 2007). Among patients with schizophrenia, women are also more likely than men to gain weight with antipsychotic treatment (Covell et al., 2004). The CATIE trial showed higher rates of the metabolic syndrome in women (52%) compared to men (36%; McEvoy et al., 2005). In a study not included in the systemic review because it compared diabetic patients with schizophrenia to diabetic patients without schizophrenia, it was observed that patients with schizophrenia were 10 years younger and more likely to be female with a higher representation of African-American patients (Kreyenbuhl et al., 2010).

2.5.3 Effect of Social and Lifestyle Factors

Poor social supports and solitary living are related to poor psychiatric outcomes in patients with severe mental illnesses (Liem and Liem, 1978). It may be speculated that patients who are unmarried or live by themselves have higher rates of chronic medical conditions. Among social

support deficits, living alone is the strongest factor associated with poor adherence and poorer physical quality of life in patients with schizophrenia (Suttajit and Pilakanta, 2010; Kilian et al., 2001). A systematic evaluation of these risk factors has not been carried out so far. Furthermore, despite the high rates of unemployment in patients with mental illness (Strum et al., 1999), an association with co-occurring medical conditions has also not been demonstrated.

It has been speculated that the high rates of cardiovascular illnesses in patients with schizophrenia may be associated with various risk factors, for example, smoking, alcohol use, poor diet, and lack of exercise (Davidson, 2002; Ryan and Thakore, 2002). Whereas moderate alcohol use has been shown to be cardio-protective, heavy use increases the risk for hypertension, coronary artery disease, and ischemic stroke in the general population (Cargiulo, 2007). Heavy use of alcohol increases cardiovascular risk by exerting its effects on the sympathetic nervous system (Randin et al., 1995). The systematic review did not include sufficient amount of empirical evidence to examine whether alcohol was a risk factor for diabetes, hypertension or the metabolic syndrome in patients with schizophrenia and related disorders. With regard to marijuana, longitudinal studies have shown that the risk for developing schizophrenia increases with marijuana use in a dose dependent manner (Andreasson et al., 1987). Heavy marijuana use is known to increase cardiovascular risk in the general population (Aryana and Williams, 2007). However, the risk attributable to marijuana use for the development of medical comorbidities in patients with schizophrenia has not been examined.

2.5.4 Effect of Socio-Demographic and Lifestyle Factors on Mortality

Medical illnesses in this population are more likely to be treated in the acute phase when the disease is severe, painful or life threatening, rather than in its early, less severe phase (Munk-

Jorgensen et al., 2000). Consequently, patients with co-morbid medical illnesses have longer stays in acute care facilities and a high overall use of inpatient and outpatient services (Kent et al., 1995). This disparate use of resources not only strains the healthcare system, but the absence of preventative care bodes for a poorer prognosis for mentally ill patients with co-morbid medical illnesses (Dixon et al., 1999). Physical illnesses also have a detrimental effect on quality of life, self-esteem and compliance thereby compromising the prognosis of the psychiatric illness (Dixon et al., 1999).

Kelly and colleagues (2011) observed that cardiac causes most frequently accounted for mortality among smokers with schizophrenia. The types of cardiovascular disorders however, were not enumerated. A recent meta-analysis concluded that smoking was associated with poor psychiatric outcomes but did not examine whether these outcomes were mediated by the development of chronic medical disorders (Cerimele and Katon., 2012).

Mortality among diabetic patients with schizophrenia is associated with age, low use of primary care services, male gender, and being unmarried (Copeland et al., 2009). Mortality associated with cigarette smoking increases with age and is higher in males (Kelly et al., 2011). Smoking, diabetes and hypertension were associated with an increased 10-year cardiovascular risk (Goff et al., 2005). Birkenas and colleagues observed high rates of age-adjusted cardiovascular risk parameters despite higher levels of education in patients with schizophrenia compared to the general population (Birkenas et al., 2007). These illnesses may also be a consequence of mental illness-related factors like poor communication and insight about health needs, non-adherence to treatment, and geographical factors affecting access to care (Ryan and Thakore, 2002). High rates of under-diagnosed and under-treated medical problems in patients with severe mental illnesses have been reported that may in part be due to issues related to

physical health care (Folsom et al., 2002). In the CATIE trial, the rate of diabetes under-treatment in non-white women (50%) was considerably higher compared to the undertreatment rate in non-white men (18%, Nasarallah et al., 2006).

2.5.5 Limitations and Future Directions

This review has several limitations. Antipsychotic medication use, an important factor for the development of diabetes, hypertension and the metabolic syndrome in patients with schizophrenia, was not included in this review. Although medications have a significant role to play in the development of both diabetes and hypertension, the majority of studies only consider the antipsychotic used at the time of enrollment, ignoring the cumulative exposure that medications may have had over their lifetime. Thus, in the absence of lifetime antipsychotic exposure, knowledge of current medications is minimally useful. The following factors that are closely linked with diabetes, hypertension and the metabolic syndrome were not included in this review: measure of adiposity, measure of physical inactivity, diet and nutrition, and family history of diabetes or hypertension. Metabolic syndrome is fueled by these risk factors that are known to cluster in patients with schizophrenia (McCreadie, 2003).

It is important to note that that studies of diabetes, hypertension, and the metabolic syndrome may not be comparable because of changes in the diagnostic criteria for these conditions. For example, the change from the standard 75 mg oral glucose tolerance test to fasting glucose and more recently to glycosylated hemoglobin (HbA1c) may account for differences in the rates of diagnosed diabetes (Jorgensen et al., 2010).

Despite the limitations, this review draws renewed attention for health services and policy plannning with the intent to create preventative services for racial minorities to minimize

poor outcomes associated with chronic medical conditions such as diabetes and the metabolic syndrome. In keeping with the goals of the SAMHSA 10 X 10 campaign, a pre-emptive approach for providing integrated services that include special programs to address behavioral risk factors such as obesity, physical inactivity and smoking will go a long way in reducing the morbidity and mortality associated with co-occurring medical disorders in patients with schizophrenia.

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3.0 AN ASSOCIATION OF SOCIO-DEMOGRAPHIC CHARACTERISTISTICS WITH DIABETES AND HYPERTENSION IN PATIENTS WITH SCHIZOPHRENIA AND RELATED DISORDERS

3.1 ABSTRACT

Introduction: Socio-demographic risk factors associated with diabetes and hypertension in patients with schizophrenia in comparison with contemporaneously enrolled non-psychiatric healthy controls have not been investigated systematically. Furthermore, the effect of family history of schizophrenia on the prevalence of diabetes and hypertension is not known. A retrospective and cross-sectional study with pooled data from 4 major genetic studies was carried out to ascertain the prevalence rates of diabetes and hypertension in patients with schizophrenia, their non-psychiatric unaffected 1st degree relatives, and unrelated healthy controls and to examine the association of socio-demographic factors with both diabetes and hypertension.

Methods: Data were extracted from the Diagnostic Interview for Genetic Studies (DIGS) questionnaire, which was used for diagnostic formulation of all cases. Data for diabetes and hypertension were extracted from text fields using a large set of search terms. The rates of diabetes and hypertension in the three study groups were compared using contingency statistics. Associations between socio-demographic risk factors, namely age, race, sex, marital status, living arrangement, years of schooling and occupation, and diabetes or hypertension were

examined in each study group separately and in the combined sample using multivariate logistic regression analysis. Stepwise regression with backward elimination was used to find the best fitting model.

Results: The rates for diabetes in patients with schizophrenia, their first degree relatives and healthy controls were 10.6%, 9.1% and 6.5%, respectively, and for hypertension were 17.8%, 8.6% and 9.5%, respectively. The rates for diabetes and hypertension were significantly higher in patients with schizophrenia compared to healthy controls. The rates for hypertension were also higher for patients compared to their 1st degree relatives. All study groups showed higher rates of diabetes and hypertension among African-American subjects compared to Caucasian subjects. Multivariate analyses showed that of all socio-demographic factors examined, only increasing age and African-American race were significant risk factors for diabetes and hypertension. In addition, being disabled was a significant risk factor for diabetes but not for hypertension.

Conclusions: Similar to previous studies, the roles of increasing age and African-American race as significant risk factors for diabetes and hypertension in all study groups were confirmed. The multivariate analyses failed to show higher rates for both disorders among 1st degree relatives compared to controls, suggesting that a family history of schizophrenia did not confer a higher risk for the development of either disorder. Sex, marital status, years of schooling, and living arrangement were not associated with either diabetes or hypertension in any group.

Public Health Significance: Pursuant to the SAMHSA 10 X 10 Wellness campaign, these results underscore the need for heightened awareness and resource allocation for African-American patients with schizophrenia in order to reduce diabetes and hypertension-related mortality in this underserved population.

3.2 INTRODUCTION

Latent genetic, lifestyle and socio-demographic factors mediate the clustering of diabetes and hypertension (Whiting et al., 2010; Carmelli et al., 1994). These two disorders affect the same target organs increasing the risk for developing coronary artery disease, stroke, peripheral vascular disease, heart failure, and eye and kidney damage. In a medically underserved population such as patients with serious mental illness, poor outcomes for these two disorders frequently result from inadequate treatment and management and non-treatment related logistic factors (Nasrallah et al., 2006). These disorders also account for the excess mortality in patients with schizophrenia and related disorders (Brown, 1997; Brown et al., 1999).

3.2.1 Diabetes in Schizophrenia

Similar to the rates in the US population, the rates of diabetes in patients with schizophrenia have increased substantially in the last few years (Schoepf et al., 2012). These high rates of diabetes mimic the high rates of obesity observed in schizophrenia patients treated with atypical antipsychotic medications, with the greatest risk afforded by olanzapine and clozapine and the lowest by aripiprazole (Lindenmeyer et al., 2003; VanWinkel et al., 2008). Although most risk factors that are associated with obesity may also be applied to diabetes, the disorder may also result from mechanisms that are independent of adiposity (Bushe and Holt, 2004). Atypical antipsychotic medication may interfere with the action of the glucose transporter protein or may cause hyperglycemia by antagonism of the serotonin 5-$HT1_A$ receptor (Dwyer et al, 1999;

Liebzeit et al., 2001). There are several case reports describing the rapid onset of diabetic ketoacidosis (DKA) in schizophrenia patients who began treatment with an atypical antipsychotic medication (Jin, Meyer and Jeste, 2002). The etio-pathogenesis of DKA in these cases is poorly understood, although the direct effect of the medication on beta-cell function has been proposed as a possible mechanism (Cohen et al., 2006).

The socio-demographic and clinical risk profile for diabetes to a large extent parallels that for obesity. Factors that may increase the risk for diabetes include ethnicity with a higher risk in non-white populations, history of gestational diabetes and history of delivering a baby > 9 pounds, hypertension: BP > 140/90 mm Hg, dyslipidemia: HDL-C < 35 mg/dL or triglycerides > 250 mg/dL, and smoking (Wannamethee et al., 1998). However, these factors have not been examined in schizophrenia patients with diabetes.

Genetic factors also play an important role in the development of diabetes. First degree relatives of persons with diabetes are 2 to 3 times more likely to develop diabetes than those without (Tarn et al., 1988). Interestingly, a higher rate of diabetes has been observed in first degree relatives of patients with schizophrenia than the rates of diabetes among first degree relatives of non-schizophrenic persons suggesting that a genetic commonality may exist in the inheritance for these two disorders (Mukerjee et al., 1996).

3.2.2 Cardiovascular Diseases in Schizophrenia

The rates of several cardiovascular disorders, for example atherosclerotic coronary artery disease, angina, and hypertension, occur at higher rates in patients with schizophrenia than in the general population (Hennekens et al., 2005). In fact, the steady increase in mortality from 1976 to 1995, with the highest increase in the last 5 year period, is attributed to cardiovascular causes

in patients with schizophrenia and related disorders (Osby et al., 2000). Similar to the risk for diabetes, the risk for developing these cardiovascular disorders also increases with obesity. In addition, atypical antipsychotic medications may also increase the risk for the development of hyperlipidemias through both adiposity-mediated and direct mechanisms (Koro et al., 2002). Furthermore, cardiac rhythm abnormalities, particularly those arising from Q-wave changes or QT interval prolongation, have been reported in association with certain atypical antipsychotic agents, for example ziprasidone (Taylor, 2003).

3.2.3 Socio-Demographic Factors for Diabetes and Hypertension

The role of socio-economic factors such as low educational attainment and unemployment, which are associated with chronic diseases such as diabetes and hypertension (Whiting et al., 2010), and are commonly observed in patients with schizophrenia, have not been investigated. A genetic connection between schizophrenia and some medical disorders also has been proposed but not investigated (Newman et al., 1987; Dixon et al., 2000). Furthermore, a systematic review that was conducted as part of this dissertation showed that there were either too few or no studies that examined the roles of education, marital status, occupation and living arrangement as effect modifiers for diabetes and hypertension in patients with schizophrenia.

3.2.4 Hypotheses

This study examines the rates of diabetes and hypertension in three groups; patients with schizophrenia, their unaffected (non-psychiatric) first-degree relatives (including siblings and

parents), and contemporaneously enrolled unrelated and unaffected controls. The associations between socio-demographic factors, such as age, race, gender, years of education, marital status and occupation, and diabetes and hypertension in the three study groups is also examined. It is hypothesized that the rates of hypertension and diabetes are higher in patients with Schizophrenia and related disorders compared to their non-psychiatric 1st degree relatives and unrelated healthy controls. Furthermore, similar to associations observed in the general population, socio-demographic risk factors namely, age, gender, ethnicity, marital status, living arrangement, occupation and education are likely to be associated with hypertension and diabetes in patients with schizophrenia and related disorders and their first degree relatives.

3.3 METHODS

3.3.1 Data for the Study

Data for this study were culled from four large NIMH-funded genetic studies (1. Candidate Gene Alleles: Association with Schizophrenia (1K02MH000966), 2. Genetic Susceptibility in Schizophrenia (1R01MH056242), 3. Schizophrenia Liability Genes among African-Americans (1R01MH066263), and 4. A Neurobehavioral Family Study of Schizophrenia (1R01MH063480)) conducted at the Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine, Pittsburgh, PA. An exempt IRB approval from the University of Pittsburgh for secondary analysis of anonymized data was obtained. These studies investigated the genetic basis for schizophrenia by enrolling patients with schizophrenia, their non-psychiatric

first degree relatives, and unrelated non-psychiatric controls from the same geographic area as the patients.

3.3.2 Diagnostic Interview for Genetic Studies

The Diagnostic Interview for Genetic Studies (DIGS) was used to obtain socio-demographic and clinical information for diagnostic formulation of all study participants including the proband, their non-psychiatric first degree relatives, and unrelated non-psychiatric controls (Nurnberger et al., 1994). The Diagnostic Interview for Genetic Studies (DIGS) developed by the NIMH is a semi-structured interview for (poly-) diagnostic formulation using standard diagnostic criteria (Nurnberger et al., 1994). Sections A and B capture demographic information and medical history respectively. The kappa coefficients for test-retest reliability (4-10 day interval) of the scale for depression, bipolar disorder and schizophrenia, is 0.94, 0.96 and 0.75 respectively (Nurnberger et al., 1994).

As per recommendations, the DIGS was administered by staff who were experienced in psychiatric interviewing and assessing manifest psychopathology. The broad similarities in the inclusion and exclusion criteria of the 4 studies facilitated the pooling of data in order to examine 4 separate data sets as one single sample. One of the studies enrolled only African-American subjects (1R01MH066263), while another study enrolled only Caucasian subjects (1R01MH063480).

3.3.3 Case Definition and Study Samples

Psychiatric diagnosis for case identification was culled from the DIGS for the following DSM-IV categories for "Schizophrenia and Other Psychotic Disorders (295.xx); 295.30 – Paranoid Type, 295.10 – Disorganized Type, 295.20 – Catatonic Type, 295.90 – Undifferentiated Type, 295.60 – Residual Type, 295.40 – Schizophreniform Disorder, and 295.70 – Schizoaffective Disorder. Other co-morbid Axis 1 diagnoses (for cases of 'Schizophrenia' identified above) were also extracted from the database. The diagnosis for each case was confirmed after consensus between two psychiatrists. Family history of psychiatric illness, particularly schizophrenia, was ruled out for healthy controls recruited for all studies.

Two study samples were examined. The first sample excluded subjects with the following Axis 1 psychiatric diagnoses: psychotic disorder NOS, delusional disorder, brief psychotic disorder, psychotic disorder due to a medical condition or substance-induced psychotic disorder, all dementias (290.xx), dementia due to medical condition and dementia NOS, and mental retardation. The second sample excluded subjects with any Axis I or Axis II disorder. The rationale for extracting these two samples was to compare the results of a 'generalizable' sample (which included subjects with other Axis 1 diagnoses) to a 'pure' sample (which excluded subjects with any Axis 1 or 2 disorder). All analyses were carried out for both samples. Differences in results obtained for the two samples, if any, are highlighted.

3.3.4 Data Extraction

Prior to analysis, distribution of the variables was examined and data transformations completed to reduce skewness. Other data reduction techniques including recoding and stratification were

also carried out. Diabetes and hypertension were recorded on the DIGS in a text field. These variables were extracted from text fields, coded, and added to the database. These disorders were recorded in response to Item B1 in Section B. Medical History: Have you ever had any serious physical illness or medical problems? Search terms used for diabetes included: diabetes, DM, T2DM, type-2 diabetes, sugar diabetes, NIDDM (non-insulin dependent diabetes), maturity-onset diabetes, gestational diabetes, DKA or diabetic ketoacidosis, hyperglycemia, pre-diabetes, or insulin resistance. Type-1 diabetes was excluded. Search terms used for hypertension included: hypertension, HT, HTN, blood pressure, or high blood pressure.

3.3.5 Statistical Methods

The demographic characteristics of the study sample were examined using descriptive statistics using one-way ANOVA for continuous variables and n X k tables for categorical variables. A Mantel-Haenszel modified chi-square was also used for comparison of two dichotomous categorical variables controlling for a third categorical factor. Analyses within each study group (Patients with schizophrenia, 1st degree relatives and Controls) were carried out using multivariate logistic regression with diabetes or hypertension (coded 1=present and 0=absent) as the dependent variable and 'socio-demographic risk factors' as independent variables. Independent variables that were significantly associated with diabetes or hypertension were selected for inclusion in the regression model. These analyses produced a regression coefficient (β) for each independent variable, for example $P\{y=1\} = 1/(1+\exp(-(\beta 0 + \beta 1.\text{Age} + \beta 2.\text{Gender} + \beta 3.\text{Race} + \beta 4.\text{Years of Schooling....} + \beta k*Xk))$, the exponential conversion of which yielded an odds ratio. A 95% confidence interval for each Odds Ratio was also obtained. The calibration

of the multivariate logistic regression model was examined using the Hosmer-Lemeshow test for goodness of fit.

In order to examine the differential effect(s) that risk factors may have in various study groups, another set of multivariate logistic regression using diabetes or hypertension as the dependent variable and 'socio-demographic risk factor' and 'group' as independent variables was performed. This model allowed the examination of the effect that group membership (patients with schizophrenia, 1st degree relatives and controls) may have had on associations with diabetes or hypertension along with other socio-demographic factors. A stepwise regression using backward elimination was performed in all cases to find the best fitting model. All results were interpreted with an alpha level set at 0.05.

3.4 RESULTS

Although separate analyses were performed for the two study samples ('generalizable' sample with Axis 1 comorbidities and 'pure' sample without Axis 1 or 2 comorbidities) results of only the 'generalizable' sample are presented. Results for the two samples were essentially similar for all the analyses performed.

3.4.1 Socio-Demographic Characteristics

The socio-demographic characteristics of the study sample are presented in Table 4.

Table 4.Description of the Study Sample (Mean + SD or percentage)

Factor		Schizophrenia n=1524	1st Degree n=778	Controls n=527	X^2 / F	p
AGE (Years)		38.8+10.6	42.9+16.1	43.0+15.6	34.9	< 0.001
SCHOOLING (Years)		12.5+2.6	12.6+2.7	13.3+2.9	17.1	< 0.001
RACE	Caucasian	51.9%	19.4%	20.7%		
	A-A	45.4%	79.9%	78.4%	340.8	< 0.001
	Other	2.7%	0.6%	0.9%		
SEX	Male	57.2%	34.7%	41.9%	114.7	< 0.001
	Female	42.8%	65.3%	58.1%		
RELIGION	Catholic	21.5%	10.1%	15.3%		
	Protestant	59.1%	71.1%	68.1%		
	Jewish	1.8%	0.6%	1.7%	69.5	< 0.001
	Moslem	0.7%	0.6%	0.6%		
	Not Affiliated	5.9%	2.8%	2.7%		
	Other	11.8%	14.9%	11.6%		
MARITAL STATUS						
	Currently Married	12.0%	29.8%	31.9%	211.4	< 0.001
	In the Past	22.2%	30.8%	25.3%		
	Never Married	65.8%	39.4%	42.8%		
LIVE ALONE	Alone	41.9%	18.8%	25.3%	134.3	< 0.001
	With Others	58.1%	81.2%	74.7%		
OCCUPATION						
	Employed	24.5%	64.7%	69.0%	739.4	< 0.001
	Disabled	59.5%	13.2%	5.7%		
	Not Employed	16%	22.1%	25.3%		

The 'generalizable' sample comprised of 1524 subjects with schizophrenia or related disorders, 778 1st degree relatives and 527 controls. The following variables were recoded; Marital Status – reduced from 5 categories to 3, Living Alone – reduced from 8 categories to 2,

and Occupation – reduced from 22 categories to 3. Categories for these variables were reduced to prevent over-fitting the model as there were several subgroups with very few (< 5) or no cases.

Patients with schizophrenia were significantly younger than their 1st degree relatives and controls. It is important to note that while several 1st degree relatives may have been enrolled in the genetic studies, only one unaffected (non-psychiatric) 1st degree relative was chosen for inclusion in this study. The 1st degree relative who was an adult (> 18 years of age) sibling and closest in age to the proband (patient with schizophrenia) was preferably chosen. In the absence of an adult sibling, a parent was chosen.

There was a significant over-representation of African-American subjects especially among 1st degree relatives and controls. This was a result of a larger representation of African-American subjects from one of the four studies (1R01MH066263 – this enrolled only African-American subjects with schizophrenia, their 1st degree relatives and healthy controls) from which the study sample was derived. Controls had significantly higher mean years of education as compared with patients with schizophrenia and 1st degree relatives, groups that did not differ from one another. Although a significant result for religion was observed, this factor was not included in subsequent analyses because 1) there was no theoretical basis in the literature for its inclusion as a risk factor for diabetes or hypertension, and 2) there were cells with very small numbers that could not be grouped together. Marital status was also significantly different between groups with almost two-thirds of patients who were never married. Occupational status also differed significantly between groups with high employment in the 1st degree and control groups and high rates of disability in patients with schizophrenia. All of these factors with the exception of religion were included in multivariate logistic regression models as independent variables.

3.4.2 Rates of Diabetes and Hypertension

The rates of diabetes and hypertension in the three study groups are presented in Table 5.

Table 5. Raw and Age-Adjusted Rates of Diabetes and Hypertension in the Study Sample

		Schizophrenia n = 1524	1st Degree n = 778	Controls n = 527	P
DIABETES	Unadjusted (Raw)	10.6%	9.1%	6.5%	0.02
	Age-Adjusted	11.4%	8.2%	5.5%	<0.001
HYPERTENSION	Unadjusted (Raw)	17.8%	8.6%	9.5%	< 0.001
	Age-Adjusted	18.8%	7.6%	8.4%	<0.001

There were significant differences in the unadjusted and age-adjusted rates of both diabetes and hypertension in the three study groups. Post-hoc differences in unadjusted rates between groups were obtained by comparing the column proportions using Bonferroni procedure with an adjusted 'p' (significance). The unadjusted rates of diabetes in patients with schizophrenia were significantly (1.6 times) higher than controls. There were however no significant differences between the unadjusted rates for diabetes in patients with schizophrenia and their 1st degree relatives. The unadjusted rates for hypertension were significantly higher in patients with schizophrenia compared to their 1st degree relatives (2.1 times) and healthy control subjects (1.9 times). Post-hoc comparisons of age-adjusted rates showed significantly higher rates for both diabetes and hypertension in patients with schizophrenia as compared with both their first degree relatives and controls.

As patients with schizophrenia were younger than their first degree relatives and controls, age-specific rates of diabetes and hypertension were also examined the three groups. The results are presented in Table 6.

Table 6. Age-Specific Rates of Diabetes and Hypertension

Age Range (years)	Schizophrenia n = 1524		1st Degree n = 778		Controls n = 527	
	Diabetes	Hypertension	Diabetes	Hypertension	Diabetes	Hypertension
≤ 20	3.6%	10.7%	0.0%	0.0%	0.0%	3.8%
21 to 30	3.8%	11.3%	1.4%	2.2%	1.8%	1.8%
31 to 40	9.3%	13.4%	7.1%	5.0%	3.1%	7.2%
41 to 50	13.4%	21.3%	8.2%	6.8%	6.5%	7.2%
51 to 60	20.5%	33.5%	15.7%	13.9%	8.6%	21.0%
> 60	11.5%	23.1%	21.1%	23.7%	18.1%	18.1%

An incrementally higher rate of diabetes and hypertension was observed for both diabetes and hypertension for each higher age strata to the age of 60 years in all three groups. In the age group 60 years and older, the rates of both diabetes and hypertension in patients with schizophrenia were lower that the rates in the preceding age group, 51 to 60 years. Similar trends have been reported in other studies and have been attributed to a 'survivor effect' where only healthy individuals (who are free from disease) may survive (Subramaniam et al., 2003; Richardson et al., 2004).

Given the over-representation of African-American subjects in the study sample, these differences were separately examined in the two racial groups. The results are presented in Table 7.

Table 7. Rates of Diabetes and Hypertension in Racial Groups

	Race	Schizophrenia n = 1524	1st Degree n = 778	Controls n = 527
Diabetes	Caucasian	8.3%	5.3%	4.6%
	African-American	13.1%	10.1%	7.0%
Hypertension	Caucasian	6.8%	4.6%	5.5%
	African-American	30.8%	9.6%	10.7%

Trends similar to those observed in the combined sample were also observed in the racial groups separately. The rates for diabetes and hypertension were higher among African-

American subjects compared to Caucasian subjects in all study groups. The rates for both diabetes and hypertension were also higher in patients with schizophrenia compared to controls of the same race.

3.4.3 Risk Factors for Diabetes and Hypertension in Study Groups Examined Separately

Risk factors for diabetes and hypertension were examined in each of the study groups separately. The independent variables (risk factors) included in these analyses were age, race, marital status, years of schooling, living alone, and occupation. A summary of these results is presented in Table 8.

Table 8. Risk Factors for Diabetes in Study Groups Separately

STUDY GROUP	**Schizophrenia**		**1st Degree Relatives**		**Controls**	
Risk factors (Independent Variables)	**(B) p**	**OR / Exp (B)**	**(B) p**	**OR / Exp (B)**	**(B) p**	**OR / Exp (B)**
Age (years)	<0.001	1.05*	< 0.001	1.06	0.001	1.06*
Race (RC = Caucasian)	0.004	1.69*	0.029	2.55	0.103	2.56
Sex (RC = Male)	0.29	1.13	0.39	0.76	0.39	0.86
Marital Status (RC = Married)	0.86		0.64		0.31	
Years of Schooling	0.65	0.98	0.46	1.04	0.91	1.04
Living Alone (RC = Alone)	0.92	0.98	0.78	0.91	0.57	1.49
Occupation (RC = Employed)	0.21		0.11		0.029	
Disabled		1.14		2.19	0.008	1.47*

RC = Reference Category
(B) p = Significance for the regression coefficient associated with the independent variable
OR / Exp (B) = Odds Ratio derived from exponentiation of the regression coefficient.
* = Odds Ratios that did not include the null value (‘1’) .

In patients with schizophrenia, (increasing) age and (African-American) race were significant risk factors for diabetes. This model also included sex, marital status, years of schooling, living status (living alone) and occupation. A stepwise regression using backward elimination also confirmed that age and race were the two best risk factors for diabetes. Similar

results were found in the group of 1st degree relatives. In the control group however, age but not race was a significant risk factor. In addition, occupational status, particularly disability (category = being disabled) was also a significant risk factor of diabetes. Stepwise regression with backward elimination confirmed the significance of these risk factors in all cases.

The adjusted odds ratios derived from exponentiation of the regression coefficient, for age for all three study groups, for race, for patients with schizophrenia and their 1st degree relatives, and for disability in controls are also presented in Table 4. The corresponding 95th percent confidence intervals for these odds ratios did not include '1'. In patients with schizophrenia and their 1st degree relatives, age and race were significant risk factors for diabetes. However, in controls, age and being disabled were significant risk factors of diabetes. Race was not a significant risk factor of diabetes for controls.

The risk factors for hypertension in the three study groups are presented in Table 9.

Table 9. Risk Factors for Hypertension in Study Groups Separately

	Schizophrenia		1st Degree Relatives		Controls	
Risk factors (Independent Variables)	**(B) p**	**OR / Exp (B)**	**(B) p**	**OR / Exp (B)**	**(B) p**	**OR / Exp (B)**
Age (years)	< 0.001	1.04*	< 0.001	1.06*	0.001	1.05*
Race (RC = Caucasian)	< 0.001	6.67*	0.003	4.20*	0.005	4.13*
Sex (RC = Male)	0.16	0.8	0.28	1.4	0.07	1.88
Marital Status (RC = Married)	0.46		0.50		0.64	
Years of Schooling	0.61	1.02	0.12	1.08	0.15	1.08
Living Alone (RC = Alone)	0.13	0.79	0.39	1.42	0.63	0.82
Occupation (RC = Employed)	0.34		0.62		0.59	

RC = Reference Category.
(B) p = Significance for the regression coefficient associated with the independent variable
OR / Exp (B) = Odds Ratio derived from exponentiation of the regression coefficient.
*= Odds Ratios that did not include the null value ('1').

Similar to the results for diabetes, (increasing) age and (African-American) race were significant risk factors for hypertension in patients with schizophrenia, their 1st degree relatives

and controls. This model also included sex, marital status, years of schooling, living status (living alone) and occupation. In these analyses, stepwise regression with backward elimination confirmed the significance of these risk factors in all groups.

The adjusted odds ratios for age and race for all three groups are presented in Table 5. In patients with schizophrenia, African-American race (in comparison to Caucasian) was associated with a 6.7 times higher likelihood of having hypertension, controlling for age, marital status, years of schooling, living alone, and marital status.

3.4.4 Risk Factors for Diabetes and Hypertension in the Combined Sample

The results of multivariate logistic regressions using group assignments as an additional independent variable for associations with diabetes and hypertension are presented in Table 10. In these analyses, the study group comprising of patients with schizophrenia was used as the reference category.

Table 10. Risk Factors for Diabetes and Hypertension in Combined Sample

	Diabetes		Hypertension	
Risk factors (Independent Variables)	**(B) p**	**OR / Exp (B)**	**(B) p**	**OR / Exp (B)**
Age (years)	< 0.001	1.05*	< 0.001	1.05*
Race (RC = Caucasian)	< 0.001	1.84*	< 0.001	6.11*
Sex (RC = Male)	0.80	1.04	0.95	0.99
Marital Status (RC = Married)	0.43		0.20	
Years of Schooling	0.83	1.01	0.09	1.04
Living Alone (RC = Alone)	0.90	1.02	0.86	0.86
Occupation (RC = Employed)	0.024		0.12	
Disabled	0.015	1.6*	0.056	1.40
Study Group (RC = Patients with Schizophrenia)	< 0.001		< 0.001	
1st Degree Relatives	0.003	0.55*	< 0.001	0.20*
Controls	<0.001	0.41*	< 0.001	0.23*

RC = Reference Category.
(B) p = Significance for the regression coefficient associated with the independent variable
OR / Exp (B) = Odds Ratio, *= Odds Ratios that did not include the null value ('1').

In these models, (increasing) age and (African-American) race were significant risk factors for both diabetes and hypertension. Occupation (category = being disabled) was a significant risk factor for diabetes but not for hypertension. Both models also showed that the risk for both diabetes and hypertension was lower among 1st degree relatives, and in controls compared to the risk in patients with schizophrenia. The corresponding 95th percent confidence intervals of the odds ratios for any of the significant risk factors did not include '1'.

The analyses using the smaller ('pure') sample in which all co-morbid Axis 1 and Axis 2 disorders were excluded yielded essentially similar results to that obtained in the inclusive ('generalizable') sample. Magnitudes of the significant associations in the 'pure' sample were either smaller in size, or were reduced to trends (p = 0.05 thru 0.1) but were in the predicted directions to the associations observed in the 'generalizable' sample. Given the similarities in findings between the two samples, the results for the 'pure' sample have not been presented.

3.5 DISCUSSION

This study compared the rates for diabetes and hypertension, and provided a comprehensive assessment of associated socio-demographic risk factors, in patients with schizophrenia, their 1st degree relatives, and contemporaneously enrolled healthy controls. The age-adjusted rates for diabetes and hypertension in patients with schizophrenia (11.4% and 18.8% respectively) were higher than the rates observed in healthy control subjects (5.5% and 8.4% respectively). Although higher rates for diabetes and hypertension in patients with schizophrenia have been reported previously, wide variations in study population, sampling techniques and study

design/methodology and diagnostic criteria used have produced varying estimates for both disorders. Furthermore, methods for ascertaining diabetes also have varied and have ranged from conducting glucose tolerance tests in prospective studies, to enumeration of recorded diagnoses in insurance and administrative databases in retrospective studies. These factors make comparison of prevalence rates across studies challenging, and emphasize the need to only compare studies that share critical characteristics.

The observed rates for both diabetes and hypertension are lower in comparison to studies that are similar in scope and have included a comparison group. Nasrallah and colleagues (2006) observed diabetes rates of 14% and 7% in patients with schizophrenia and controls in contrast to 11.4% and 5.5% observed in this study. Similarly, another study showed hypertension rates of 20% and 15% for patients with schizophrenia and healthy controls in contrast to rates of 18.8% and 8.4% respectively, observed in this study (Lumby et al., 2007). One possible explanation for the lower rates observed here may be the effect of condensing data acquired over approximately 20 years into a single cross-sectional estimate. Therefore, the observed estimates in this study may not accurately reflect the point prevalence for diabetes and hypertension. Despite this limitation, comparisons of rates across contemporaneously enrolled groups of 1st degree relatives and controls within the same time-frame remain valid.

Age was a significant risk factor for diabetes and hypertension. It is a known risk factor for these two disorders and for cardiovascular diseases in general. In patients with schizophrenia, cross-sectional age-stratified rates for diabetes show a 10-fold increase from 4% in patients aged 30-39 years, to 50% in patients aged 50 to 59 years (Subramaniam et al. 2003). African-American race was also a significant risk factor for both diabetes and hypertension. This is consistent with higher rates for diabetes in African-American patients with schizophrenia

reported in both cross-sectional and longitudinal studies (Dixon et al., 2000; Kreyenbuhl et al., 2006; Lambert et al., 2005; Ramaswamy et al., 2006). The role of disability as an effect modifier for diabetes remains unclear, although it may be speculated that it is a likely consequence of diabetes rather than a factor that affords risk.

Although bivariate analyses showed that rates for diabetes in 1st degree relatives did not differ significantly from the rates in patients with schizophrenia, and were numerically higher than the rates in controls, these differences were not borne out in multivariate logistic regression analyses that included socio-demographic factors and group membership with 1st degree relatives as the reference group. The rates for hypertension in 1st degree relatives were essentially similar to the rates in healthy controls and significantly lower than the rates in patients with schizophrenia.

Age-, race-, and sex-stratified rates of hypertension in patients with schizophrenia for purposes of comparison are unavailable. However, the similarities in the results of risk factors for diabetes and hypertension confirm the roles of age and race as important factors for both disorders. Interestingly, none of the other risk factors, namely marital status, living arrangement and years of schooling, showed associations either with diabetes or hypertension, although each factor differed significantly between the study groups.

A significant strength of the study is the uniformity with which the data were collected, fastidious diagnostic case ascertainment, similarities in the inclusion/exclusion criteria for the different studies from which the data were pooled, and the size and uniqueness of the study sample. Additionally, confounding that may result from enrollment of non-contemporaneous controls or those derived from national epidemiological surveys is minimized. Unlike several studies in the literature, the study sample is heterogeneous with respect to distribution of

demographic and social characteristics. Thus, the external validity (generalizability) of findings from such a sample is likely to be high.

The proposed study also has several weaknesses. First, no assumptions of causality can be made in this cross-sectional study as temporal precedence cannot be established. Second, the characterization of diabetes and hypertension is based only on the subject's self-report to an open-ended question without any additional corroboration. Studies using this methodology usually result in an under-estimate of the outcome (Elliott and Huizinga, 1989). This may have also accounted for the lower than expected rates of diabetes and hypertension. Third, although quite comprehensive in its scope, this study does not address all possible factors and mechanisms that may account for the development of medical comorbidities in patients with schizophrenia. Chiefly, a measure of body weight (or Body Mass Index (BMI)) is not available and therefore, the role of obesity as a risk factor for the development of diabetes and hypertension cannot be accounted for. This limitation is unlikely to affect the validity of the relationship(s) between the other proposed risk factors and diabetes and hypertension because as previously stated, the rates of obesity are quite high in this population and body weight is only one of many potential factors that may lead to the development of diabetes or hypertension. Furthermore, the range of socio-demographic variables included in this study is limited and restricted only to the data obtained using the DIGS. These limitations notwithstanding, the comparison of various study groups continues to have high internal validity because the biases apply to all subjects uniformly.

Racial disparities in cardiovascular diseases are well-documented (Keppel et al., 2002). In addition to a higher genetic predisposition for diabetes and hypertension, socio-economic factors and reduced access to care also contribute to disease burden borne by African-American patients (Williams et al., 2010). The Substance and Mental Health Services Administration has

recognized the increased mortality resulting from chronic medical illnesses in patients with severe mental illnesses and is spearheading the "10 X 10 Wellness Campaign" to increase life expectancy by 10 years in 10 years (10 X 10) for people with mental illness. To that end, this study further makes the case for increased attention and resources for adequate treatment and ongoing management of diabetes and hypertension in African-American patients with schizophrenia.

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4.0 AN ASSOCIATION OF SMOKING, ALCOHOL, AND MARIJUANA USE WITH DIABETES AND HYPERTENSION IN PATIENTS WITH SCHIZOPHRENIA AND RELATED DISORDERS

4.1 ABSTRACT

Introduction: The rates of smoking, alcohol and marijuana use in patients with schizophrenia are higher than in the general population. The role that these factors play in contributing to poor clinical and social outcomes in this population is well documented, but their effects on physical health outcomes have not been examined systematically. Diabetes and hypertension, two common prototypical chronic medical conditions that co-occur at high rates in schizophrenia are related to premature mortality in patients. Associations between lifestyle factors and diabetes and hypertension, if any, may help to elucidate the effect that these factors have in contributing to the increased mortality in this population.

Methods: A retrospective cross-sectional study with pooled data from four major genetic studies was carried out to examine the associations that lifestyle factors, such as smoking, alcohol and marijuana use, have with diabetes mellitus and hypertension in patients with schizophrenia, their non-psychiatric unaffected 1st degree relatives and unrelated healthy controls. Data were extracted from the Diagnostic Interview for Genetic Studies (DIGS) questionnaire which was used for diagnostic formulation of all cases. Data for diabetes and hypertension were extracted

from text fields using a large set of search terms. Two measures for each lifestyle factor were selected, one noting the presence or absence of the factor and the other its severity or duration. Contingency statistics were used to compare the rates of smoking, alcohol and marijuana use in the study groups. In the case where these associations were examined while controlling for a stratifying variable, a Mantel Haenszel chi-square test was used. Associations between lifestyle risk factors and diabetes or hypertension, controlling for socio-demographic factors, were examined using multivariate logistic regression analysis. Stepwise regression with backward elimination was used to find the best fitting model.

Results: The rates of smoking, alcohol, and marijuana use were significantly higher in patients with schizophrenia than the rates in contemporaneously recruited controls. The rates of smoking and marijuana in 1st degree relatives were similar to the rates observed in controls and significantly lower than the rates in patients with schizophrenia. However, the rates of alcohol use in 1st degree relatives were higher than in controls and marginally lower than the rates in patients. Although bivariate analyses between lifestyle factors and diabetes or hypertension in the pooled sample showed an inverse relationship between marijuana use and diabetes, and a direct relationship between smoking and hypertension, unconditional multivariate logistic regression analyses that adjusted for socio-demographic factors did not show any association between any of the lifestyle factors and diabetes or hypertension.

Conclusions: These data support the high rates of smoking, alcohol and marijuana use observed in patients with schizophrenia. First degree relatives of patients with schizophrenia did not differ from controls in smoking and marijuana use. The rates of alcohol use in 1st degree relatives were higher than in controls. Multivariate analyses that controlled for socio-demographic factors did not show any associations between smoking, alcohol or marijuana use, and diabetes or

hypertension. However, future studies must re-examine these relationships by including important factors such as family history of diabetes or hypertension, a measure of adiposity, and lifetime use of obesogenic and diabetogenic psychotropic medications.

Public Health Significance: High rates of substance abuse in patients with schizophrenia contribute to poor behavioral and physical outcomes, and underscore the need for primary and secondary prevention measures in order to reduce premature mortality in this population.

4.2 INTRODUCTION

Lifestyle factors such as poor diet and nutrition, physical inactivity, and smoking contribute to the increased mortality observed in patients with schizophrenia (Brown, 1997; Brown et al., 1999; Brown et al., 2000). Despite the high rates of these lifestyle factors, the morbidity and mortality associated with other lifestyle factors such as alcohol and marijuana use in patients with schizophrenia have not been systematically examined (Regier et al., 1990). In the absence of longitudinal data, a cross-sectional association between these common lifestyle factors and chronic medical illnesses such as diabetes mellitus and hypertension may shed some light on the role that these risk factors might have on the premature mortality in this population.

The rationale for selecting diabetes mellitus (herein referred to as diabetes) and hypertension has been discussed in an earlier study (Brar, Paper 2). In that study, higher rates of diabetes and hypertension were observed in patients with schizophrenia compared to healthy controls, and the rates of both disorders increased with age and African-American race (Brar, Paper 2). If preliminary associations between common lifestyle factors such as smoking, alcohol, and marijuana use with diabetes or hypertension are observed, and a cause-and-effect relationship is borne out by longitudinal studies, the need to develop specialized services to address these modifiable risk factors will take on renewed importance.

4.2.1 Smoking in Schizophrenia

The rates of smoking in patients with schizophrenia range from 58% to 90%, rates that are 2 to 3 times higher than those observed in the general population (Moeller-Saxone, 2008; Chaves and Shirakawa, 2008). Furthermore, patients with schizophrenia also tend to be heavy smokers drawing higher levels of nicotine from cigarettes (de Leon et al., 1995). These high rates result from several psychological, behavioral and environmental causes that make smoking cessation a challenging endeavor in this population (William and Foulds, 2007; Fagerstrom and Aubin, 2009). Cigarette smoking in patients has been linked with higher than expected rates of chronic obstructive pulmonary disease and other respiratory and heart diseases (Oud and Meyboom-de Jong, 2009).

4.2.2 Association of Smoking with Diabetes or Hypertension

Smoking has been listed along with diabetes and hypertension as an important risk factor for cardiovascular disease (Wilson, 2010). However, a recent meta-analysis has shown that smoking is in fact an independent risk factor for the development of diabetes mellitus (Willi et al., 2009). Smoking has been shown to affect beta cell functions and cause insulin resistance thereby increasing the risk for the development of diabetes (Facchini et al., 1992; Attvall et al. 1993). Smoking has also been linked to incident hypertension and decreased regional left ventricular function (Rosen et al., 2006; Bowman et al., 2007).

A clustering of smoking, diabetes, hypertension and other lifestyle risk factors has been reported to explain premature mortality in patients with schizophrenia (Connolly and Kelly, 2005). A recent review and an accompanying editorial have also suggested an independent role

of smoking for the increased prevalence of diabetes and hypertension, but this has not been empirically investigated (Wildgust et al., 2010; Wildgust and Beary, 2010).

4.2.3 Alcohol Use in Schizophrenia

Alcohol is the second commonest substance abused by patients with schizophrenia after smoking (Batel, 1995). Although a third of patients with schizophrenia meet diagnostic criteria for an alcohol use disorder (AUD), the number of patients who drink is considerably higher (Regier et al., 1990). Similar to smoking, alcohol use in schizophrenia is also associated with psychological, behavioral and environmental causes (Drake and Meuser, 2002), and is associated with medication non-compliance, frequent hospitalization, risk of violence, and poor overall health and functioning in patients with schizophrenia (Drake et al., 1989).

4.2.4 Association of Alcohol Use with Diabetes or Hypertension

While moderate drinking is associated with a lower risk of diabetes (Kopper et al., 2005), heavy drinking can lead to obesity and insulin resistance (Shah et al., 1988). A recent meta-analysis has shown that abstainers and heavy alcohol drinkers had a higher risk for developing diabetes in comparison to moderate drinkers (Baliunas et al., 2009). This U-shaped relationship was true for both men and women (Baliunas et al., 2009). Moderate drinking exerts a protective effect for the development of diabetes by improving insulin sensitivity (Kiechl et al., 1996). Alcohol consumption also has a J-shaped association with cardiovascular disease outcomes including mortality (Costanzo et al., 2010). Similar to diabetes, moderate alcohol consumption may also have a beneficial effect on blood pressure (Xin et al., 2001). This may result from vasodilation,

an acute effect of alcohol consumption. On the other hand, regular drinking over a prolonged period of time may have a linear effect on blood pressure increasing the incidence of hypertension (Puddey et al., 1985; Puddey and Beilin, 2006). Furthermore, the risk of hypertension increases when alcohol is consumed in the absence of food (Stranges et al., 2004).

The associations between alcohol use and diabetes or hypertension have not been examined in patients with schizophrenia. However, it can be speculated that the risk for both disorders in patients who consume alcohol may be high because of heavy drinking and poor dietary habits observed in this population (Drake et al., 1990; Peet, 2004).

4.2.5 Marijuana Use in Schizophrenia

Marijuana use has been shown to increase the risk for developing schizophrenia (Kuepper et al., 2011). After smoking and alcohol, it is the next most common substance for abuse in patients with schizophrenia (Reiger et al., 1990). Prevalence rates for marijuana use vary considerably by sample composition, recruitment source, method for diagnosis and data collection (Green et al., 2005). A review of cannabis use and misuse studies estimated the lifetime prevalence rates in patients with schizophrenia to be 42.1% and 22%, respectively (Green et al., 2005). Another cohort study estimated the lifetime cannabis use to be 66.2% (Foti et al., 2010). This study also showed that ongoing cannabis use was associated with a worse outcome with respect to positive (psychotic) symptoms in patients with schizophrenia (Foti et al., 2010).

4.2.6 Association of Marijuana Use with Diabetes or Hypertension

A recently published study has shown that the prevalence of diabetes was lower among marijuana users compared to non-users (Rajavashisth et al., 2012). The authors examined data from 10,896 adults who participated in the third National Health and Nutrition Examination Survey (NHANES-III, 1988 – 1994) and found that marijuana users had a lower age-adjusted prevalence of diabetes compared to non-users (Odds Ratio = 0.42, 95th % confidence interval = 0.33 – 0.55). The authors of this study postulated that the decreased prevalence diabetes was possibly related to the anti-inflammatory and antioxidant effect of bioactive cannabinoids in marijuana. The only other published study that has examined the association between marijuana use and diabetes found similar glucose levels in users and non-users (Rodondi et al., 2006). Short-term effects of marijuana on the cardiovascular system include tachycardia, spike in blood pressure, and orthostatic hypotension, but the effects on blood pressure are attenuated with long-term use (Sidney, 2002; Frishman et al., 2003). Heavy marijuana use may trigger the onset of myocardial infarction and increase the risk for stroke (Sidney, 2002; Frishman et al., 2003). The study by Rajavashisth and colleagues (2012) did not find an association between marijuana use and hypertension.

A systematic review that was conducted as part of this dissertation showed that there were either too few or no studies that examined the roles of lifestyle factors, namely smoking, alcohol and marijuana use as effect modifiers for diabetes and hypertension in patients with schizophrenia.

4.2.7 Hypotheses

This study examined the associations between lifestyle risk factors of smoking, alcohol and marijuana use and diabetes and hypertension in patients with schizophrenia, their unaffected (non-psychiatric) first-degree relatives (including siblings and parents), and contemporaneously enrolled unrelated and unaffected controls. The confounding effects that socio-demographic factors such as age, race, sex and years of schooling may have on the associations between lifestyle factors and diabetes and hypertension are also examined. It is hypothesized that lifestyle factors will show associations with diabetes and hypertension similar to that observed in the general population. Furthermore, the associations between lifestyle risk factors and diabetes and hypertension are likely to be strongest in patients with schizophrenia as the prevalence of these factors is expected to be higher in that group.

4.3 METHODS

4.3.1 Data for the Study

Data extraction procedures for this study have been described previously (Brar, Paper 2). Briefly, data pooled from four large NIMH-funded studies investigating the genetic basis for schizophrenia were analyzed. Three study groups were assembled: patients with schizophrenia and related disorders (probands), their non-psychiatric first degree relatives, and unrelated non-psychiatric controls who were recruited from the same geographic area as the patients.

4.3.2 Diagnostic Interview for Genetic Studies

The Diagnostic Interview for Genetic Studies (DIGS) was used to obtain socio-demographic and clinical information for diagnostic formulation of all study participants including the proband, their non-psychiatric first degree relatives, and unrelated non-psychiatric controls (Nurnberger et al., 1994). This instrument has a high test-retest reliability for schizophrenia (Nurnberger et al., 1994). Procedures for the extraction of socio-demographic and medical variables (diagnosis of diabetes and hypertension) used for this study have been described previously (Brar, Paper 2).

4.3.3 Extraction of Data Related to Lifestyle Factors

Data for smoking, alcohol use and marijuana use were extracted from sections 'A. Demographics', 'I. Alcohol Abuse and Dependence' and 'J. Drug Abuse and Dependence', respectively. For each lifestyle factor, two variables were selected. The first variable selected most closely approximated lifetime use of the lifestyle factor, the second represented its severity. In the absence of a good measure of severity, lifetime duration of use was chosen as a surrogate marker.

Smoking-related information is recorded in section 'A. Demographics' of the DIGS. Each subject is asked 3 questions; 1) had the subject ever smoked cigarettes (recorded as 'No', 'Yes, Currently', and 'Yes, In the Past', 2) number of packs smoked per day and, 3) number of years smoked. A severity measure of 'Pack-Years' is then calculated as the product of 'packs smoked per day' and 'number of years smoked'. For the first measure (had the subject ever smoked cigarettes), the three categories were reduced to a dichotomous response (Yes or No) by combining 'Yes, Currently' and 'Yes, In the Past'. The categories were collapsed because 1)

both smoking currently or in the past was likely to have exerted similar effects on the development of chronic medical conditions such as diabetes or hypertension and 2) to align this variable with similar variables obtained from alcohol and marijuana use representing lifetime use. 'Pack-Years' was selected as the measure of severity of smoking, in addition to the dichotomous variable.

Alcohol use-related information was extracted from two questions in section 'I. Alcohol Abuse and Dependence'. Question 5 in this section inquired whether the subject ever drank regularly (at least once a week for six months or more) – with a dichotomous response of Yes or No. If the response to this question was 'Yes', the next question asked the age at which the subject started to drink regularly. Age of onset of regular drinking was selected as a measure of severity for alcohol use.

Marijuana use-related information was extracted from two questions in the 'Marijuana' section in 'J. Drug Abuse and Dependence'. Question 1 inquired whether the subject ever used marijuana – with a dichotomous response of Yes or No. The marijuana section of the DIGS further elicits the duration of marijuana use that is accompanied by contemporaneous experiences involving any two of the following; preoccupation with obtaining marijuana, a broad range of psychological problems relating to marijuana use, feeling jumpy, startled or nervous, inability to cut down use of marijuana, gradually requiring larger quantities of marijuana, experiencing co-occurring physical symptoms (such as insomnia, nervousness, sweating, nausea or diarrhea), putting oneself in situations that could cause harm after using marijuana, family and friends objecting to marijuana use, reduced family and social interactions, under the influence of marijuana at school or work, or legal problems related to marijuana. The number of years that

the subject had any two these experiences at the same time is calculated and recorded on the DIGS. This variable was used as a surrogate marker for severity.

It is important to note that probands, i.e. patients with schizophrenia, who had a concurrent diagnosis of alcohol or substance abuse and/or dependence were not enrolled in the genetic studies. Similarly, unrelated non-psychiatric controls who also had a concurrent diagnosis of alcohol or substance abuse and/or dependence were not enrolled. However, these exclusionary criteria did not apply to 1st degree relatives of patients with schizophrenia.

4.3.4 Case Definition and Study Samples

Case definition and assembly of the study sample have been described previously (Brar, Paper 2). The group of patients with schizophrenia and related disorders consisted of subjects who met DSM-IV diagnostic criteria for any of the schizophrenia subtypes, schizophreniform disorder or schizoaffective disorder. Subjects with an Axis 1 diagnosis of psychotic disorder, NOS, delusional disorder, brief psychotic disorder, psychotic disorder due to a medical condition or substance-induced psychotic disorder, all dementias (290.xx), dementia due to medical condition and dementia NOS, and mental retardation were excluded from the sample. The diagnosis for each case was confirmed only after there was consensus between two psychiatrists. Family history of psychiatric illness, particularly schizophrenia and related disorders, was ruled out for healthy controls recruited for the genetic studies.

4.3.5 Data Extraction

Data reduction techniques including recoding and stratification of variables and extraction of medical information relating to a diagnosis of diabetes and hypertension have been described previously (Brar, Paper 2).

4.3.6 Statistical Methods

Descriptive statistics were used to examine the demographic characteristics of the study sample. These included one-way analysis of variance (ANOVA) for continuous variables and n X k tables for categorical variables. Contingency statistics (2 X 3 tables using crosstab) were used to examine differences in the rates of lifestyle factors between study groups. Differences in the severity measures of lifestyle factors were compared using an F-test of a one-way ANOVA. The associations between lifestyle factors and diabetes or hypertension were examined using odds ratios and their corresponding 95^{th} percent Confidence Interval. In order to examine the association between lifestyle factors and diabetes or hypertension in the pooled sample, a Mantel-Haenszel Chi-Square test was used. This test is applicable for stratified categorical data and allows for the comparison of two groups (categorical variables) while controlling for a third categorical variable (Mantel and Haenszel, 1959). The association between lifestyle factors and diabetes or hypertension was examined after controlling for study group membership.

Multivariate logistic regression was used to examine the associations of lifestyle and socio-demographic factors with diabetes or hypertension. Diabetes or hypertension (coded 1=present and 0=absent, the dependent variable) was regressed using both categorical and continuous lifestyle and socio-demographic factors. An odds ratio for each independent factor

was obtained by the exponential conversion of its regression coefficient (β). A corresponding 95% Confidence Interval for each Odds Ratio was also obtained. The calibration of the multivariate logistic regression model was examined using the Hosmer-Lemeshow test for Goodness of Fit. A stepwise regression using backward elimination of the multivariate logistic model was carried out to determine the model with the highest association. All results were interpreted with an alpha level set at 0.05.

The following reference categories were used for the discrete variables in the multivariate models; Caucasian for Race, male for Sex, and patients with schizophrenia for study group membership.

4.4 RESULTS

4.4.1 Socio-Demographic Characteristics

The socio-demographic characteristics of the study sample are presented in Table 11. The sample consisted of 1524 subjects with schizophrenia or related disorders, 778 1st degree relatives, and 527 controls.

Table 11. Description of the Study Sample (Mean + SD or percentage)

Factor	Schizophrenia n=1524	1st Degree n=778	Controls n=527	X^2 / F	p
AGE (Years)	38.8+10.6	42.9+16.1	43.0+15.6	34.9	< 0.001
SCHOOLING (Years)	12.5+2.6	12.6+2.7	13.3+2.9	17.1	< 0.001
RACE Caucasian African-American Other	51.9% 45.4% 2.7%	19.4% 79.9% 0.6%	20.7% 78.4% 0.9%	340.8	< 0.001
SEX Male Female	57.2% 42.8%	34.7% 65.3%	41.9% 58.1%	114.7	< 0.001

There were significant differences in the socio-demographic characteristics in the study groups. Patients with schizophrenia were significantly younger than their 1st degree relatives and controls. A large proportion of 1st degree relatives and controls included in the study sample were recruited for a study that enrolled African-American subjects only (R01MH066263). This resulted in a significant over-representation of African-American subjects among 1st degree relatives and controls than would be expected from a random sampling of the population. The proportion of females among 1st degree relatives and controls was also significantly higher than the proportion of females among patients with schizophrenia. Controls in the sample also had significantly higher mean years of schooling compared with patients with schizophrenia and 1st degree relatives. The latter two groups did not differ in mean years of schooling from one another.

4.4.2 Rates of Diabetes and Hypertension

The rates of diabetes and hypertension in the study sample have been described previously (Brar, Paper 2). Briefly, patients with schizophrenia had significantly higher rates of diabetes than

control subjects but not their 1st degree relatives. The rates of hypertension in patients with schizophrenia were higher than both their 1st degree relatives and controls. These differences persisted when examined separately in Caucasian and African-American subjects (Brar, Paper 2).

4.4.3 Smoking, Alcohol, and Marijuana Use

The rate and severity or duration of each lifestyle factor was examined separately in the three study groups. Results are presented in Tables 12.

Table 12. Rates of Smoking, Alcohol, and Marijuana Use

Lifestyle Factors		Schizophrenia n = 1524	1st Degree Relatives n = 778	Controls n = 527	X^2 (2df)	p
Smoking	Yes	1007 (68.9%)	398 (53.9%)	252 (48.3%)	89.4	< 0.001
	No	455 (31.1%)	341 (46.1%)	270 (51.7%)		
Alcohol Use	Yes	702 (51.7%)	324 (46.6%)	192 (38.3%)	26.8	< 0.001
	No	655 (48.3%)	371 (53.4%)	309 (61.7%)		
Marijuana Use	Yes	998 (68.5%)	432 (58.1%)	288 (54.8%)	41.8	< 0.001
	No	459 (31.5%)	311 (41.9%)	238 (45.2%)		

The sample sizes for the analyses of associations between diabetes and hypertension with smoking, alcohol and marijuana use differ, and are smaller than the complete sample because of missing data for lifestyle factors. An examination of missing data prior to the analyses revealed that the data were missing at random.

The rates of smoking in patients with schizophrenia (68.9%) were significantly higher than the rates in 1st degree relatives (53.9%) and controls (48.3%). The rates in 1st degree relatives and controls did not differ significantly from one another. The rates of alcohol use in patients with schizophrenia (51.7%) and their 1st degree relatives (46.6%) were significant higher

than the rates in controls (38.3%) but did not differ significant from one another. The rates of marijuana use in patients with schizophrenia (68.5%) were also significantly higher than both the rates in their 1st degree relatives (58.1%) and controls (54.8%). There were no statistically significant differences in the rates of marijuana use between 1st degree relatives and controls.

Differences in the severity or duration of smoking, alcohol and marijuana use are presented in Table 13.

Table 13. Severity or Duration of Smoking, Alcohol, and Marijuana Use

Lifestyle Factors	Measure	Schizophrenia n = 1524	1st Degree Relatives n = 778	Controls n = 527	F Test	p
Smoking	Pack-Years[1]	19.2 + 22.2	16.2 + 37.2	14.9 + 18.1	6.2	0.002
Alcohol Use	AOO[2]	19.03 + 5.3	21.8 + 7.5	21.01 + 5.6	23.4	< 0.001
Marijuana Use	Duration[3]	6.4 + 7.4	5.6 + 7.9	7.4 + 9.2	0.49	ns

Pack-Years = packs per day X years smoked
AOO = Age of Onset, age at which subject started drinking regularly
Duration in years = Use accompanied by 2 symptoms of disturbance repeatedly for at least 1 month

The severity of smoking measured by mean 'Pack-Years' was significantly higher in patients with schizophrenia compared with both their 1st degree relatives and controls. Similarly, the mean age at which patients with schizophrenia started drinking alcohol regularly was lower than that in 1st degree relatives and controls. The latter two groups did not differ from one another. No differences in the severity of marijuana use were observed between the study groups. Both variables, one determining rate of each lifestyle factor (Categorical, in Table 2), and the other measuring the severity/duration of the lifestyle factor (Continuous, in Table 3) were included in multivariate analyses to examine risk factors for diabetes or hypertension.

The associations of lifestyle factors with diabetes were examined separately within each group and across groups. The results are presented in Table 14.

Table 14. Associations (Odds Ratios and 95th% CI) Between Lifestyle Factors and Diabetes

	Schizophrenia n = 1524	1st Degree Relatives n = 778	Controls n = 527	Pooled; Mantel-Haenszel Test
Smoking	0.91 (0.64 – 1.29)	1.19 (0.73 – 1.95)	1.08 (0.54 – 2.16)	1.01 (0.77 – 1.31)
Alcohol Use	1.3 (0.92 – 1.83)	0.88 (0.52 – 1.48)	0.52 (0.23 – 1.17)	1.04 (0.80 – 1.36)
Marijuana Use	0.73 (0.52 – 1.03)	0.67 (0.41 – 1.11)	0.59 (0.29 – 1.20)	0.69* (0.53 – 0.90)

*= 95th percent Confidence Intervals for the Odds Ratios that do not include null value (1).

Smoking and alcohol use were not associated with diabetes in any of the study groups examined separately or in the pooled sample controlling for study group membership. Marijuana use was not associated with diabetes when examined in the study groups separately but an inverse (protective effect) association was observed in the pooled sample that controlled for study group membership. There was a 0.69 times lower likelihood of having diabetes in subjects who used marijuana in the study sample after controlling for study group membership (Mantel-Haenszel $X^2 = 7.2$ (1df), $p = 0.007$).

The associations of lifestyle factors with hypertension were examined separately within each group and across groups. The results are presented in Table 15.

Table 15. Associations (ORs and 95th% CI) Between Lifestyle Factors and Hypertension

	Schizophrenia n = 1524	1st Degree Relatives n = 778	Controls n = 527	Pooled; Mantel-Haenszel Test
Smoking	1.38* (1.02 – 1.87)	1.03 (0.62 – 1.71)	1.29 (0.72 – 2.31)	1.29* (1.01 – 1.63)
Alcohol Use	1.12 (0.85 – 1.48)	0.87 (0.52 – 1.48)	1.46 (0.79 – 2.70)	1.11 (0.88 – 1.39)
Marijuana Use	1.29 (0.96 – 1.74)	0.29* (0.17 – 0.50)	0.62 (0.35 – 1.12)	0.85 (0.67 - 1.06)

* = 95th percent Confidence Intervals for the Odds Ratios that do not include null value (1).

Smoking was associated with a higher likelihood of hypertension (OR = 1.38) in patients with schizophrenia but not in 1st degree relatives and controls. The pooled sample that controlled for study group membership also showed a similar significant association between smoking and hypertension (Mantel-Haenszel X^2 (1df) = 4.02, p = 0.045). Alcohol use was not associated with hypertension in any of the study groups separately or in the pooled study sample. Marijuana use was not associated with hypertension in patients with schizophrenia or controls but an inverse association was observed in 1st degree relatives. However, there was no association in the pooled sample controlling for study group membership (Mantel-Haenszel X^2 (1df) = 1.86, p = ns).

4.4.4 Lifestyle Factors Associated with Diabetes and Hypertension

In order to examine the associations between lifestyle factors and diabetes and hypertension after controlling for the effect(s) of socio-demographic factors, bi-variate analyses were performed to select factors (independent variables) that should be included in multivariate models (data not shown). Socio-demographic factors which were significantly associated with smoking included race (both Caucasian and African-American in different groups), male sex, age (↑), and years of schooling (↓). All socio-demographic factors also showed similar associations with alcohol and marijuana use, and were included in multivariate analyses examining risk factors for diabetes and hypertension.

Lifestyle factors associated with diabetes or hypertension were examined in each of the study groups separately and in the combined sample. The independent factors included all socio-demographic variables and the categorical (Yes/No) or continuous (severity or duration) variable related to each lifestyle factor. Data for severity or duration of each lifestyle factor were only

available for subjects who were coded as 'Yes' for the lifestyle factor. For example, 'Pack-Years' was relevant only for subjects who had a history of smoking (coded 'Yes') and not for non-smokers (coded 'No'). Because of this multicollinearity between the categorical and continuous variables for each lifestyle factor, only one variable (either the categorical or the continuous) was used in each multivariate model. Analysis for the combined sample included study group (membership) as an independent factor.

Results of multivariate analyses examining the association for smoking, alcohol use and marijuana use with diabetes are presented in Table 16.

Table 16. Socio-Demographic and Lifestyle Factors Associated with Diabetes

	Smoking		Alcohol Use		Marijuana Use	
Independent Risk factors	**(B) p**	**OR / Exp (B)**	**(B) p**	**OR / Exp (B)**	**(B) p**	**OR / Exp (B)**
Age (years)	< 0.001	1.06*	< 0.001	1.06*	< 0.001	1.06*
Race (RC = Caucasian)	< 0.001	2.01*	< 0.001	2.03*	< 0.001	1.99*
Sex (RC = Male)	0.88	1.02	0.68	1.06	0.87	1.03
Years of Schooling	0.83	1.01	0.84	1.01	0.38	1.01
Lifestyle Factor (Categorical, RC = No)	0.57	0.92	0.58	1.08	0.38	0.88
Study Group (RC = Schizophrenia)	< 0.001		< 0.001		< 0.001	
1st Degree Relatives	< 0.001	0.46*	< 0.001	0.45*	< 0.001	0.46*
Controls	< 0.001	0.30*	< 0.001	0.32*	< 0.001	0.30*

RC = Reference Category
(B) p = Significance for the regression coefficient associated with the independent variable
OR / Exp (B) = Odds Ratio derived from exponentiation of the regression coefficient.
*=Odds Ratios that do not include the null value ('1').

Age, race and study group membership were significant risk factors for diabetes in separate analyses for smoking, alcohol use and marijuana use. Patients with schizophrenia were assigned as the reference category for study group membership. Diabetes was associated with increasing age, African-American race and diagnosis of schizophrenia but not with sex, years of schooling or the presence of any of the factors. First degree relatives and controls had a lower

likelihood of having diabetes compared to patients with schizophrenia. The 95th percent Confidence Intervals for the corresponding odds ratio did not include the null value, 1. A stepwise regression with backwards elimination also confirmed that age, race and study group membership were the best risk factors for diabetes. Separate analyses within each study group also confirmed the significant associations between age and race with diabetes (data not shown). None of the lifestyle factors had any association with diabetes.

Multivariate analyses using severity and duration based measures of smoking, alcohol and marijuana use showed essentially similar results, but was restricted to the sample that included only those subjects in whom the lifestyle factor was present (data not shown). An additional multivariate analysis using all three lifestyle factors simultaneously along with socio-demographic factors also showed associations for age, race and study group membership only (data not shown). Results of multivariate analyses examining the associations for smoking, alcohol use and marijuana use with hypertension are presented in Table 17.

Table 17. Socio-Demographic and Lifestyle Factors Associated with Hypertension

	Smoking		Alcohol Use		Marijuana Use	
Independent Risk factors	**p**	**OR / Exp (B)**	**p**	**OR / Exp (B)**	**p**	**OR / Exp (B)**
Age (years)	< 0.001	1.05*	< 0.001	1.05*	< 0.001	1.05*
Race (RC = Caucasian)	< 0.001	6.18*	< 0.001	6.19*	< 0.001	6.16*
Sex (RC = Male)	0.96	0.99	0.82	0.97	0.94	1.00
Years of Schooling	0.047	1.05*	0.09	1.04	0.09	1.04
Lifestyle Factor (Categorical, RC = No)	0.30	1.15	0.26	1.15	0.78	0.96
Study Group (RC = Schizophrenia)	< 0.001		< 0.001		< 0.001	
1st Degree Relatives	< 0.001	0.18*	< 0.001	0.18*	< 0.001	0.18*
Controls	< 0.001	0.21*	< 0.001	0.19*	< 0.001	0.20*

RC = Reference Category
(B) p = Significance for the regression coefficient associated with the independent variable
OR / Exp (B) = Odds Ratio derived from exponentiation of the regression coefficient.
*=Odds Ratios that did not include the null value ('1').

Age, race, years of schooling, and study group membership were significant risk factors for hypertension for the analysis that included smoking as the lifestyle factor. Hypertension was associated with increasing age, African-American race, higher years of schooling and diagnosis of schizophrenia but not with sex, or any of the lifestyle factors. First degree relatives and controls had a lower likelihood of having hypertension as compared to patients with schizophrenia. Analyses for alcohol use and marijuana use also showed significant relations between hypertension and age, race and study group membership, but not for years of schooling. The strength of significant risk factors was confirmed in the reduced model using stepwise regression with backwards elimination (data not shown). Separate analyses within each study group and a simultaneous regression using all the lifestyle factors together also confirmed that none of the lifestyle factors had any association with hypertension (data not shown).

4.5 DISCUSSION

This study compared the associations between lifestyle factors such as smoking, alcohol, and marijuana use and diabetes and hypertension in patients with schizophrenia, their 1st degree relatives, and contemporaneously enrolled healthy controls. Higher rates for diabetes and hypertension in patients with schizophrenia in this sample have previously been reported (Brar, Paper 2). This study also found higher rates of smoking, alcohol and marijuana in patients with schizophrenia compared with healthy controls. The National Survey on Drug Use and Health (NSDUH), an annual survey commissioned by the Substance Abuse and Mental Health Services Administration (SAMHSA), found that the rates of (current) smoking steadily decreased from 26% to 23% in the period between 2002 to 2010 (NSDUH, 2012). The rates of smoking in the

control group in the study are two-fold higher than NSDUH rates as the study sample included current and past smokers. The rates of smoking in patients with schizophrenia were three-fold higher than the rates in the NSDUH survey. The NSDUH survey also showed that approximately half (51.8%) of all individuals surveyed were current drinkers. These rates are higher than the rates observed among healthy controls in the study sample (38.3%) as only those subjects who "*drank at least once a week for six months or more*" were classified as alcohol drinkers. In the study sample, the rate of alcohol use in patients with schizophrenia was approximately 35% higher than the rates in controls. The rates for lifetime use of marijuana in the NSDUH survey range from 43% in 18 year old subjects to 56% in subjects who were in their mid fifties. These are in close approximation to the lifetime rates observed among controls in the study sample (54.8%). The rates of marijuana use in patients with schizophrenia were approximately 25% higher than the rates in controls in the study sample. The rates of smoking and marijuana use in patients with schizophrenia were also significantly higher than the rates in their 1st degree relatives. The rates for alcohol use however did not differ significantly between patients and their 1st degree relatives. The lack of differences may have resulted from commonly inherited genetic variants by patients with schizophrenia and their 1st degree relatives that are linked to alcohol use (Ribbe et al., 2011). Studies in twins have shown that individuals with schizophrenia and alcoholism have a genetic predisposition to the development of both disorders (Kendler, 1985).

Smoking and alcohol use were not associated with diabetes in any of the study groups or in the combined sample. However, an inverse association between marijuana use and diabetes was found in the unadjusted analysis that did not correct for socio-demographic factors. This inverse association was not observed in any single study group but only in the combined sample

that corrected for study group membership. It is important to note that this association was not observed after adjusting for socio-demographic factors in the multivariate model.

An inverse association between marijuana use and diabetes was reported in a recent study that examined the NHANES-III (Rajavashisth et al., 2012). The authors argued that cannabinoids, bioactive components of marijuana, have demonstrable anti-inflammatory properties that may decrease the incidence of diabetes through their action on prostaglandins and COX-2 (Partignani et al., 2005). In animal models, cannabinoids have been shown to have a beneficial effect against atherosclerosis and complications of diabetes (Rajesh et al., 2007). This inverse association merits further investigation and replication in an independent sample.

Alcohol use was not associated with hypertension in any of the study groups or in the combined sample. Marijuana use showed an inverse association with hypertension in 1st degree relatives, but not in the other study groups, or in the combined sample, or in the multivariate model. An explanation for this inverse association is not readily available. It could have spuriously emerged from a type-1 error as the analyses were not corrected for multiple comparisons. Smoking was associated with a higher likelihood of hypertension in patients with schizophrenia, and in the combined sample that corrected for study group membership but not in the multivariate model. An association between smoking and hypertension has been shown earlier (Rosen et al., 2006). Furthermore, it is not surprising that this association was also observed in patients with schizophrenia as this sample is known to smoke heavily and draw higher levels of nicotine from cigarettes (de Leon et al., 1995).

As stated earlier, multivariate analyses that included socio-demographic factors failed to show associations between any of the lifestyle factors and diabetes or hypertension. Several reasons could account for the lack of relationship between lifestyle factors and diabetes or

hypertension. The model does not include information on atypical antipsychotic use or adiposity that may account for major factors responsible for the development of diabetes or hypertension. Furthermore, it is possible that the multivariate models examined may have been over-fitted with too many independent factors. However, this was not the case as step-wise regression with both 'forward selection' and 'backwards elimination' failed to show any associations with any of the lifestyle factors. It is also possible that the effect size, i.e. the proportion of variance explained by another variable or set of variables (in this case, age and race) is so large that the addition of other risk factors, for example lifestyle factors, does little to improve the model. Lack of associations between lifestyle factors and diabetes and hypertension may also have resulted from the characteristic of the variable used for the analyses. For example, alcohol has a known U-shaped relationship with cardiovascular diseases. Low to moderate levels of alcohol consumption are beneficial (cardio-protective), whereas heavy use is detrimental. The categorical variable used in the analyses essentially combined all levels of alcohol consumption, thus reducing its sensitivity.

The weaknesses of the study include the cross-sectional nature of the data that precludes examination of causality and characterization of diabetes and hypertension by self-report that can result in under-estimation of the outcome (Elliott and Huizinga, 1989). Furthermore, as mentioned earlier, patients with schizophrenia and non-psychiatric controls who had alcohol or substance abuse and/or dependence were excluded from enrollment in the genetic studies, whereas 1st degree relatives of probands were not. This differential truncation of alcohol and marijuana use data for two of the three groups used for this study is likely to have affected the internal validity of the findings. Another important weakness of this study is the lack of validity of selected items chosen for characterizing alcohol and marijuana use. The psychometric

properties of the items chosen from DIGS for this study have not been established. Lastly, as mentioned earlier, the study does not address other important mediators that may explain the relationship if any, between lifestyle factors and diabetes and hypertension. For example, obesity or atypical antipsychotic use may mediate the response between alcohol use and diabetes, but in the absence of body weight and medication use data, this could not be examined. The strengths of this study include uniformity of data collection, diagnostic case ascertainment, contemporaneously recruited controls, and a large and heterogeneous sample.

These limitations notwithstanding, the high rates of smoking, alcohol and marijuana use observed in this sample should provide caution to healthcare providers for allocating services for the management of these risk factors. Smoking, alcohol and marijuana use in patients with schizophrenia are associated with a wide range of poor clinical and social outcomes (Drake et al., 1989; Drake et al., 1990). Although associations of these lifestyle factors with diabetes and hypertension were not found, other associations, such as smoking with chronic pulmonary obstructive disease in patients with schizophrenia, are well-established (Oud and Meyboom-deJong, 2009). Addressing these lifestyle risk factors proactively will go a long way in meeting the goals for the SAMHSA "10 X 10 Wellness Campaign" to increase life expectancy by 10 years in 10 years (10 X 10) for people with mental illness.

4.6 LITERATURE CITED

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5.0 GENERAL DISCUSSION

Medical comorbidities such as cardiovascular diseases, diabetes, pulmonary and infectious diseases are implicated in the shortened lifespan in patients with severe mental illnesses like schizophrenia and related disorders, such as schizoaffective disorder and psychotic disorder, not otherwise specified. Much of the research in this area has focused on assessing the prevalence of obesity and obesity-related illnesses in patients with schizophrenia with respect to treatment with psychotropic antipsychotic medications. There is however a paucity of systematic research on other factors, namely socio-demographic and lifestyle factors, which may also contribute to the development of these comorbidities in these patients. Furthermore, it is not known how the risk afforded by these factors may be modified by the genetic predisposition associated with several medical comorbidities. Specifically, it is not known how shared genetic and environmental factors within families of patients with schizophrenia, for example common socio-demographic factors, may modify the genetic predisposition for the development of medical illnesses. It is also not known whether the risk for developing medical comorbidities in patients with schizophrenia is higher than the risk in their first degree relatives who do not have a mental illness.

This dissertation evaluated the association between socio-demographic and lifestyle factors with diabetes and hypertension in patients with schizophrenia, their non-psychiatric first degree relatives, and contemporaneously recruited non-psychiatric controls. The dissertation

also included a systematic review of published studies that examined the associations between socio-demographic and lifestyle factors and diabetes and hypertension in patients with schizophrenia and related disorders. The systematic review was carried out using established methodology. A cross-sectional study using pooled data derived from the Diagnostic Interview for Genetic Studies (DIGS) was examined. The data for these analyses were derived from four large NIMH-funded genetic studies in patients with schizophrenia. These studies investigated the genetic basis for schizophrenia by enrolling patients with schizophrenia and related disorders, their affected (psychiatric) and unaffected (non-psychiatric) first degree relatives, and unrelated non-psychiatric controls from the same geographic areas. The DIGS was used to obtain socio-demographic and clinical information for diagnostic formulation of all study participants including the proband, or index case (patient with schizophrenia), their psychiatrically ill and non-psychiatric first degree relatives, and unrelated non-psychiatric controls. In addition to psychopathology, the DIGS also elicited information about medical comorbidities. This uniform methodology facilitated the pooling of data in order to examine factors associated with medical comorbidities in all groups of interest. The associations between socio-demographic and lifestyle factors and diabetes and hypertension were compared in patients with schizophrenia, their non-psychiatric first degree relatives, and unrelated non-psychiatric controls.

5.1 SUMMARY OF FINDINGS

The systematic review based on 26 studies showed a strong effect of age and African-American race on the prevalence of diabetes. Age was also associated with the metabolic syndrome, although the effect of race was equivocal. Sex was an effect modifier for diabetes and the

metabolic syndrome in some, but not all, studies with higher rates in females. Studies of hypertension were too few to reach meaningful conclusions. Other social and lifestyle factors were either rarely or never examined, which prohibited an assessment of attributable risk.

The first cross-sectional study showed higher rates of diabetes and hypertension in patients with schizophrenia compared with unrelated non-psychiatric controls. While the rates of hypertension in patients with schizophrenia were also higher than the rates in their 1st degree relatives, the rates of diabetes did not differ between these two groups. Multivariate models that included age, race, sex, years of schooling, marital status, occupational status, and living arrangement as independent risk factors showed that only age and race were significant risk factors for diabetes and hypertension. The higher risks for diabetes and hypertension in patients with schizophrenia compared to their 1st degree relatives and unrelated non-psychiatric controls were also confirmed in the multivariate analyses.

The second cross-sectional study showed higher rates of smoking, alcohol and marijuana use in patients with schizophrenia compared with unrelated non-psychiatric controls. The rates of smoking and marijuana use in patients were also higher than the rates in their 1st degree relatives. Multivariate analyses that included age, race, sex and years of schooling failed to show any significant associations for smoking, alcohol or marijuana use with diabetes or hypertension.

Only established non-modifiable factors, namely age and race, were confirmed as risk factors for diabetes and hypertension in the systematic review and cross-sectional study. The analyses confirmed the high rates of diabetes and hypertension in patients with schizophrenia and the high rates of lifestyle factors, namely smoking, alcohol and marijuana use, in this population. However, the attributable risk of other socio-demographic factors and lifestyle

factors (smoking, alcohol and marijuana use) on the prevalence of diabetes or hypertension was not demonstrated.

The dissertation confirms the need for developing services for minority, mainly African-American, patients with schizophrenia in order to reduce the disease burden and mortality associated with co-morbid diabetes and hypertension. The strong association with age also emphasizes the need for preventative services for patients early in the course of schizophrenia who have not yet developed diabetes or hypertension.

5.2 FUTURE DIRECTIONS

The associations of diabetes and hypertension with increasing age and African-American race underscore the need for primary prevention of these disorders in an already disadvantaged population. It is important for clinicians and other care providers to have a heightened awareness of the risk for diabetes and hypertension in minority race patients. Interventions, both pharmacological and behavioral, must be instituted in this vulnerable group of patients early in the course of the psychiatric illness before diabetes and hypertension develop.

The bivariate associations between lifestyle factors, such as smoking, alcohol and marijuana use, and diabetes and hypertension deserve an independent examination. These associations could be examined in national administrative and claims databases, or in studies that have enrolled large numbers of patients with schizophrenia. Secondary data analyses examining the association between lifestyle factors and diabetes and hypertension in the CATIE (Comparative Antipsychotic Trial of Intervention Effectiveness) study would be an ideal starting point.

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