University of Alberta

Mental Health and Chronic Medical Conditions: Schizophrenia, Its Treatment, Risk of Metabolic Complications, and Health Care Utilization

by

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ABSTRACT

Objective - To assess the relationship between schizophrenia and cardiovascular disease by evaluating metabolic risk associated with treatment for schizophrenia, prevalence of cardiovascular risk factors (CV-RF) and disease (CV-D), and health care utilization in people with schizophrenia compared to the non-schizophrenic population.

Methods – Four studies were completed to evaluate the dissertation objectives. A systematic review was completed to quantify the change in metabolic parameters associated with use of atypical antipsychotic agents. The second study utilized a period prevalence design to compare prevalence of CV-RF (diabetes, hypertension, dyslipidemia) and CV-D in people with and without schizophrenia using the administrative databases of Alberta Health and Wellness. General and cardiac specialist health care utilization was evaluated in people with schizophrenia using data from Alberta Health and Wellness. Lastly, results from the Canadian Community Health Survey were used to evaluate prevalence of CV-RF and CV-D while controlling for important lifestyle and demographic variables unavailable in the databases of Alberta Health and Wellness.

Results – Use of atypical agents, particularly clozapine, resulted in statistically significant weight gain and increases in total cholesterol and blood glucose compared to typical agents. Having schizophrenia was associated with a significantly higher prevalence of diabetes, obesity, smoking, and CV-D compared to people without schizophrenia. Individuals with schizophrenia visited a general practitioner and the emergency department more often, and were more

likely to be hospitalized than those without schizophrenia. Despite having a higher prevalence of coronary artery disease, individuals with schizophrenia were significantly less likely to visit a cardiologist or undergo revascularization compared to people with coronary artery disease who did not have schizophrenia. Conclusion – Individuals with schizophrenia have a considerable burden of cardiovascular disease compared to people without schizophrenia. This is likely a result of a number of factors, including medications used to treat schizophrenia, the increased prevalence of smoking and other unhealthy lifestyle factors, and the increased prevalence of cardiovascular risk factors in people with schizophrenia. Individuals with schizophrenia utilize the general health care system more frequently than their non-schizophrenic counterparts, therefore the opportunity exists for monitoring for and management of modifiable cardiovascular risk factors in this vulnerable population.

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Regarding the Chapter 5 study entitled "Diabetes, Cardiovascular Disease, and Health Care Use in People With and Without Schizophrenia", while the research and analysis are based on data from Statistics Canada, the opinions expressed to not represent the views of Statistics Canada.

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LIST OF ABBREVIATIONS

CAD – Coronary artery disease

CATIE – Clinical Antipsychotic Trials of Intervention Effectiveness

CCHS – Canadian Community Health Survey

CI – Confidence interval

CV-D – Cardiovascular disease

CV-RF – Cardiovascular risk factors

ED – Emergency department

EPS – Extrapyramidal symptoms

GP – General practitioner

HDL – High density lipoprotein

Kg - kilograms

LDL – Low density lipoprotein

mmHg – millimeters of mercury

Mmol/L – millimoles per litre

NCEP – National Cholesterol Education Program

NHANES – National Health and Nutrition Examination Survey

OR – Odds ratio

TG – Triglycerides

CHAPTER 1

Introduction

1.1 Introduction

1.1.1 Epidemiology, Cost, and Symptoms of Schizophrenia

Schizophrenia is a very debilitating mental illness associated with considerable morbidity and mortality (1). The lifetime prevalence of schizophrenic disorders is estimated to be 1.45 per 100 people (2). Although schizophrenia is less common than other chronic illnesses, the economic burden of schizophrenia is substantial in Canada, with the direct health care and non-health care costs estimated to be $2.02 billion in 2004, and the costs of lost productivity due to morbidity and premature mortality was estimated to be $4.83 billion in 2004 (3).

Schizophrenia is characterized by the development of positive and negative symptoms. Positive symptoms include hallucinations and delusions, whereas negative symptoms include anhedonia, avolition, affective flattening, alogia, and decreased attention (1). For the individual suffering from schizophrenia, the positive and negative symptoms result in a decreased ability for that person to function normally, and often increase risk of suicidality, victimization, substance abuse, unemployment, and homelessness (4). Effective treatment of the positive and negative symptoms is imperative for a person suffering from schizophrenia.

1.1.2 Schizophrenia: Association with Metabolic Dysregulation and Cardiovascular Disease (CV-D)

Not only is schizophrenia a debilitating disease due to its associated symptoms, it is also considered a risk factor for many chronic medical conditions. The Canadian Diabetes Association lists schizophrenia as a risk factor for diabetes, and observational studies have found the prevalence of diabetes to be 2 to 3 times higher in individuals with schizophrenia compared to the general population (5,6). A cohort study conducted by Dixon and colleagues is of particular importance because prevalence of diabetes was evaluated in a cohort of patients with schizophrenia in 1991, prior to the widespread exposure of atypical antipsychotic agents (6).

Metabolic syndrome encompasses a number of metabolic abnormalities including dysglycemia, visceral adiposity, dysregulation of plasma high-density lipoprotein (HDL) and triglycerides (TG), and increased blood pressure (7). Each abnormality is individually considered a risk factor for cardiovascular disease, and when two or more factors are present, the risk for cardiovascular disease is at least additive (7). Individuals with schizophrenia have a high prevalence of metabolic syndrome, which may contribute to their increased risk of cardiovascular disease. Baseline data from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Schizophrenia Trial demonstrated a 40.9% prevalence of metabolic syndrome (based on NCEP criteria) in people with schizophrenia included in the trial (8). In comparison, NHANES III data has measured the age-adjusted

prevalence of metabolic syndrome to be approximately 23.7% in the US population (9).

Given the increased risk of diabetes and metabolic syndrome in people with schizophrenia, it is not surprising that schizophrenia is a risk factor for cardiovascular morbidity and mortality (10-12). In a study conducted using the administrative databases of Saskatchewan Health, people with schizophrenia were 2.2 times more likely to die as a result of CV-D compared to matched comparison individuals without schizophrenia (10). The high prevalence of metabolic abnormalities and risk of CV-D emphasizes the importance of screening for and management of modifiable cardiovascular risk factors (CV-RF) in people with schizophrenia.

1.1.3 Atypical Antipsychotic Agents: Weight Gain and Metabolic Abnormalities

Although atypical antipsychotic agents are considered the first-line treatments for people with schizophrenia, especially in patients who are newly diagnosed with schizophrenia and have never received antipsychotic treatment (1), recent literature has demonstrated a number of concerning side effects associated with these agents. A number of experimental and observational studies have demonstrated a significant amount of weight gain and changes in lipid and blood glucose levels associated with atypical antipsychotic therapy (13-20). For example, results from the CATIE trial demonstrated that individuals randomized

to olanzapine gained an average of 4.3 kilograms, had a mean increase in A1C of 0.4%, and a mean increase in triglycerides of 0.46 mmol/L (13).

Use of atypical antipsychotic agents improve functional outcomes of people with schizophrenia, helping individuals who have been diagnosed with schizophrenia to function on a day-to-day basis (1). These medications, however, also seem to increase the risk of cardiovascular disease by increasing risk of obesity, dyslipidemia, and diabetes. Most importantly, the combination of schizophrenia and its treatment puts patients at an even greater risk for obesity, diabetes, dyslipidemia, metabolic syndrome, and CV-D.

1.1.4 Health Care Utilization in People With Schizophrenia

As a result of the increased risk of CV-RF associated with atypical antipsychotic agents, the American Psychiatric Association, American Diabetes Association, American Association of Clinical Endocrinologists, and North American Association for the Study of Obesity released a consensus statement on monitoring for metabolic abnormalities in people taking atypical antipsychotics in 2004 (21). Despite the publication of this document and other national and international guidelines for CV-RF monitoring in patients taking atypical antipsychotic agents, research has demonstrated little change in monitoring practices in people with schizophrenia (22-24). In addition, people with schizophrenia may be less likely to receive adequate treatment for metabolic abnormalities. Nasrallah and colleagues examined the proportions of individuals

treated for hypertension, dyslipidemia, and diabetes in the CATIE study population, and found that 88% of people with dyslipidemia and 62.4% of people with hypertension were not being treated (25).

One reason for the lack of change in monitoring practices and receipt of adequate treatment for metabolic abnormalities that has been suggested is that people with schizophrenia and other severe mental illnesses may have limited access to care and health care utilization (26). Although there is evidence demonstrating a reduced likelihood for treatment after a CV event compared to people without schizophrenia (27,28), there is little, if any, evidence available evaluating utilization of general health services in people with schizophrenia compared to the general population, an area where the monitoring for and management of CV-RF occurs for primary and secondary prevention of CV-D (26,29).

1.1.5 Schizophrenia, Metabolic Abnormalities, and Cardiovascular Disease: What the Literature is Lacking

Although existing literature has provided some insight into the burden of CV-RF and CV-D in people with schizophrenia, there are several important limitations to these data. Most studies have not been population-based, instead evaluating highly selected subgroups of people with schizophrenia that are drawn from registries and trials, limiting generalizability (8,11,30-32). Other studies did not use a non-schizophrenic concurrent comparison group, and as such, are unable to draw conclusions regarding whether prevalence of CV-D and CV-RF is truly

different in people with schizophrenia (25,30). Additionally, some population-based studies evaluating CV-RF and CV-D in people with and without schizophrenia are from periods prior to the widespread use of atypical antipsychotic agents, and are bereft of lifestyle and clinical data that may influence the association between schizophrenia and CV-D (6,10).

Although a number of reviews have been published evaluating the relationship between atypical antipsychotic use and change in metabolic parameters, the majority of this literature suffers from major limitations. Some reviews are narrative in nature or do not report methods for obtaining articles for the literature review (33-40), whereas other publications have only searched one database to identify literature (41-45) which may result in the omitting of important literature that is not indexed in the searched database (46). Other reviews were performed before widespread use of atypical antipsychotic agents and before the results of major antipsychotic trials were published (44,47-49)

In terms of health care utilization in schizophrenia, while a number of publications have demonstrated inadequate metabolic monitoring and inequities in cardiovascular care for people with schizophrenia or severe mental illness (22-24), few studies have evaluated primary health care use in this population, an area where the monitoring for and management of CV-RF occurs for primary and secondary prevention of CV-D (26,29).

1.2 Objectives

The objectives of this PhD thesis were to:

1. Quantify change in metabolic parameters, including weight, blood glucose, lipids, and blood pressure, as a result of treatment with atypical antipsychotics in people with schizophrenia, schizoaffective disorder, or schizophreniform disorder; and
2. Compare prevalence of cardiovascular risk factors (CV-RF) and cardiovascular disease (CV-D) in people with and without schizophrenia, while examining the potential impact of socio-demographic and lifestyle variables on this relationship; and
3. Compare general health care utilization including use of general practitioners (GP), emergency department (ED) encounters, hospitalizations, and self-reported unmet health care needs in people with and without schizophrenia; and
4. Compare access to specialist care for individuals with coronary artery disease (CAD) (internists, cardiologists) in people with and without schizophrenia.

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CHAPTER 2

The Impact of Atypical Antipsychotic Agents on the Development of Metabolic Abnormalities in People with Schizophrenia: A Systematic Review and Meta-Analysis of Randomised Trials (DRAFT)

2.1 Introduction

Schizophrenia is a serious mental illness characterized by the development of positive and negative symptoms (1). In addition to suffering from the debilitating symptoms of schizophrenia, individuals with schizophrenia have a greater prevalence of metabolic abnormalities, including diabetes and metabolic syndrome, and cardiovascular disease (CV-D) compared to people without mental illness (2-7). Individuals with schizophrenia and CV-D also have a higher risk of mortality compared to people with CV-D alone (7-9). The risk of metabolic abnormalities and CV-D seems to be present regardless of treatment status, as some of the publications evaluating the relationship between metabolic abnormalities and CV-D and schizophrenia were conducted during time periods prior to widespread atypical antipsychotic use (2,7,9).

Atypical antipsychotic agents are first-line therapy for treating schizophrenia and other psychotic disorders, particularly in individuals who are treatment naïve because they are associated with less dyskinesias compared to their older counterparts, the typical antipsychotic agents (1). Literature over the last decade, however, has identified a number of concerning side effects associated with

atypical antipsychotic agents. Based on observational and experimental study results, atypical agents seem to increase the risk of metabolic abnormalities such as hyperglycemia and dyslipidemia by causing weight gain, sedation, and decreased insulin sensitivity (10-17).

Although a number of reviews have been published evaluating the relationship between atypical antipsychotic use and change in metabolic parameters, the majority of this literature suffers from major limitations. Some reviews are narrative in nature or do not report methods for obtaining articles for the literature review or including studies in the review, making the reviews much more prone to bias (18-26). Other publications have only searched one database to identify literature (27-31), which may result in the omitting of important literature that is not indexed in the searched database (26). Other reviews were performed before widespread use of atypical antipsychotic agents, before the release of newer atypical agents such as paliperidone and ziprasidone, and before the results of major antipsychotic trials were published (30,32-34)

As a result of both having mental illness and using atypical antipsychotic agents to treat the symptoms of mental illness, patients with schizophrenia-related illnesses are at a high risk of metabolic abnormalities, and as a result, CV-D. In addition, the impact of atypical antiopsychotics on metabolic parameters has yet to be quantified using a comprehensive systematic review format. The objective of this systematic review was to quantify the change in metabolic parameters,

including weight, blood glucose, lipids, and blood pressure, as a result of atypical antipsychotic use compared to a different atypical antipsychotic agent, typical antipsychotic agents, or placebo in adults with schizophrenia, schizophreniform disorder, or schizoaffective disorder.

2.2 Methods

2.2.1 Study Eligibility Criteria

Randomised, controlled trials were eligible for the systematic review. No language, publication date, or publication status restrictions were imposed. Studies that evaluated adults (18 years of age and older) with a diagnosis of schizophrenia, schizophreniform disorder, or schizoaffective disorder based on DSM-III-R, DSM-IV, DSM-IV-TR, or ICD-10 diagnostic criteria were eligible for inclusion (35-38). Trials comparing monotherapy with an atypical antipsychotic agent of any dose (aripiprasole, clozapine, olanzapine, quetiapine, paliperidone, risperidone, or ziprasidone) to a different atypical antipsychotic agent of any dose, a typical antipsychotic agent of any dose, or placebo were eligible for inclusion in the systematic review.

The outcomes measures evaluated were:

1) Change in weight from baseline in kilograms;
2) Change in blood glucose (mmol/L) and A1C (%) from baseline;
3) Change in systolic and diastolic blood pressure (mmHg) from baseline; and

4) Change in lipids (mmol/L) (total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and/or triglycerides) from baseline.

2.2.2 Information Sources

Databases searched included: MEDLINE and MEDLINE In-Process and other non-indexed citations (1950 to present), EMBASE (1980 to present), PsycInfo (1987 to present), International Pharmaceutical Abstracts (1970 to present), PASCAL (1984 to present), Web of Science (1900 to present), Cochrane Database of Systematic Reviews (2010 Issue 1), and Cochrane Central Register of Controlled Trials (2010 Issue 1). The grey literature was searched using Proquest Dissertations and Theses (1716 to present) and OCLC PapersFirst (1993 to present).

Reference lists of relevant studies and reviews were also scanned for additional publications not identified by the search strategy.

The search was conducted in April 2010. **APPENDIX 2A** provides an example of the electronic database search strategy utilized for MEDLINE and MEDLINE In-Process and other non-indexed citations (1950 to present).

2.2.3 Study Selection

The titles and abstracts of the search results were initially screened by one reviewer (Lauren Bresee (LCB)) for relevancy. All relevant studies were assessed independently by two reviewers (LCB and John-Michael Gamble (JMG)) in an unblinded manner using a standardized assessment form. Disagreements were resolved by consensus. Agreement was measured using Cohen's kappa statistic (39).

2.2.4 Data Collection Process

A data collection form was developed by one reviewer (LCB) and piloted on five randomly selected included studies. We prespecified that two reviewers would independently extract data (LCB and JMG), but at the time of writing only one reviewer had completed data extraction. Disagreements will be resolved by consensus. Study authors were contacted for missing data, where appropriate.

2.2.5 Data Items

Data extracted from each study included study design; duration of the study; location of the study; number of locations if study was multisite; name, dose, timing and duration of intervention; name, dose, timing and duration of comparison; types of mental illness included in the study and method of diagnosis; demographic information of each study arm (sample size, mean age, male, female, number of participants completing trial, number of dropouts, number of lost to follow up), changes in metabolic parameters for each study

group (change in weight, blood glucose, A1C, systolic blood pressure, diastolic blood pressure, LDL, HDL, total cholesterol, TG); and source of study funding.

2.2.6 Risk of Bias in Individual Studies

The risk of bias in individual studies will be independently assessed by two reviewers (LCB and JMG) using the Jadad scale and Schulz approach to allocation concealment (40,41). At the time of writing only one reviewer had completed assessment of risk of bias in each study, and as such, risk of bias of individual studies is not presented in the results. Disagreements will be resolved by consensus.

2.2.7 Summary Measures

The meta-analyses were performed evaluating the weighted mean difference between treatment and control groups for all continuous parameters. A random effects model was used to produce the overall effect size and 95% confidence intervals (CI) for each comparison. The primary outcomes were changes in meatabolic parameters for atypical antipsychotics vs. placebo and typical antipsychotic agents. Weight was measured in kilograms (kg), blood glucose, LDL, HDL, total cholesterol, and triglycerides were measured in millimoles per litre (mmol/L), and blood pressure was measured in millimeters of mercury (mmHg). For studies with more than one atypical group, the average metabolic parameter change was entered into the meta-analysis to avoid unit of analysis errors.

2.2.8 Planned Methods of Analysis

Potential for heterogeneity was assessed in all meta-analyses using the I^2 statistic to measure percentage of total variation across studies that is due to between-study variation rather than chance (42). We planned to present all meta-analyses conducted with an I^2 statistic of less than 50%; meta-analyses with an I^2 statistic of ≥ 50% were classified as having high heterogeneity and as a result, studies were not combined to produce an overall effect size and confidence intervals (42).

2.2.9 Risk of Bias Across Studies

The potential for publication bias was assessed by examining funnel plots of the mean difference (x-axis) versus the standard error of the mean difference (y-axis) of the included studies for each outcome comparison. Each funnel plot was visually examined for asymmetry and the possibility of publication bias.

2.2.10 Additional Analyses

Sensitivity and subgroup analyses were prespecified. Sensitivity analyses were conducted evaluating sources of funding (industry funding vs. government funding), studies of less than 12 weeks duration (short-term), and studies that were conducted for 12 weeks or longer (medium to long-term duration) (43). Subgroup analyses were performed evaluating the impact of individual atypical antipsychotics on the change in metabolic parameters relative to placebo, typical antipsychotic therapy, and other atypical antipsychotics.

2.3 Results

2.3.1 Study Selection

FIGURE 2.1 demonstrates the study selection process for this systematic review. The combined search result produced 5,944 references, of these 2,788 were duplicates. After screening titles and abstracts, 303 complete manuscripts were reviewed for study inclusion. The measure of agreement was 0.57, indicating moderate agreement (39). Confusion regarding the inclusion of multiple studies using the same study group was the main reason for disagreement. A total of 49 studies were included, with 71 studies pending based on the need for additional information from the individual study authors at the time of writing.

2.3.2 Study Characteristics

All included studies at the time of writing were randomised trials published in English. Of the 49 included studies (10,11,14,44-89), 6 evaluated aripiprazole (51,60,65,67,69,75), 10 evaluated clozapine (14,46,49,55,56,70,72,74,78,84), 40 evaluated olanzapine (10,11,14,44-50,52-54,56-61,63-64,66,68-75,77,80-85,87-89), 13 evaluated quetiapine (10,46,58,60,62,63,68,72,73,76,81,82,88), 4 evaluated paliperidone (57,64,71,86), 25 evaluated risperidone (10,14,44-47,51-54,56,60,61,66,72,73,76,77,79-82,85,87,89), and 5 evaluated ziprasidone (10,50,63,78,81). Weight was the most common metabolic parameter measured in the included studies (measured in 94% of studies). Only two studies evaluated change in systolic blood pressure, and one evaluated change in diastolic blood

pressure. Thirty-three of the fifty studies were solely funded by industry (66%). **Table 2.1** summarizes the characteristics of the included studies.

2.3.3 Results of Individual Studies

Individual study results of changes in metabolic parameters are summarized in **Table 2.2**.

2.3.4 Synthesis of Results

The vast majority of planned comparisons could not be completed due to significant heterogeneity ($I^2 \geq 50\%$) associated with combining study results.

Atypical Antipsychotics Versus Placebo

Seven studies compared an atypical antipsychotic agent to placebo (48,57,62,64,71,76,86). An overall effect size of change in weight could not be produced because of significant heterogeneity ($I^2 = 78\%$), however, the atypical agents in the seven studies consistently increased weight, whereas the placebo group lost weight in four studies, gained weight in two studies, and neither gained nor lost weight in one study.

Change in LDL, HDL, and total cholesterol also could not be evaluated due to significant heterogeneity (56%, 64%, and 51%, respectively).

Mean change in blood glucose was no different between atypical antipsychotic agents and placebo (-0.0 mmol/L; 95% CI: -0.14 – 0.13) (**Figure 2.2**), whereas atypical antipsychotic agents were associated with a mean increase in triglycerides of 0.22mmol/L relative to placebo (95% CI: 0.11 – 0.34) (**Figure 2.3**).

Atypical Antipsychotics Versus Typical Antipsychotics

A total of twelve studies compared atypical agents to a typical agent (10,11,14,55,56,59,63,65,66,70,79,83). The most common typical agent comparison was haloperidol.

Mean change in weight could not be compared between atypical and typical agents due to significant heterogeneity (I^2 = 86%). Use of atypical agents was associated with a mean increase in blood glucose of 0.21 mmol/L (95% CI: 0.01 – 0.42) (**Figure 2.4**), and an increase in total cholesterol of 0.12 mmol/L (95% CI: 0.02 – 0.22) (**Figure 2.5**). No significant difference was seen in mean triglyceride change between atypicals and typicals (0.12 mmol/L; 95% CI: -0.06 – 0.30) (**Figure 2.6**).

2.3.5 Risk of Bias Across Studies

The funnel plots for each outcome were consistently symmetrical. This may be due to the fact that for all meta-analyses completed, there were less than ten

studies included and the studies were of similar size, which limits the capacity of the funnel plot to detect publication bias (91).

2.3.6 Additional Analyses

It was not possible to combine studies to perform the prespecified sensitivity analyses, including first episode illness vs. established disease, and study duration due to significant heterogeneity.

Subgroup Analyses: Individual Atypical Antipsychotic Agents

Of the six studies that evaluated aripiprazole, three measured weight change (51,60,67). These studies could not be combined to produce an overall effect size, however, due to significant heterogeneity (I^2 = 78%). Similarly, assessing change in blood glucose and HDL was not possible due to heterogeneity (58% and 83%, respectively). Use of aripiprazole was associated with a mean reduction in LDL of 0.19 mmol/L (95% CI: -0.21 - -0.17) (**Figure 2.7**), a mean reduction in total cholesterol of 0.31 mmol/L (95% CI: -0.34 - -0.29) (**Figure 2.8**), and a mean reduction in triglycerides of 0.37 mmol/L (95 CI: -0.48 - -0.26) (**Figure 2.9**) relative to a different atypical agent.

Clozapine was associated with a mean weight increase of 3.93 kg (95% CI: 2.82 – 5.03) relative to typical antipsychotic agents (**Figure 2.10**), but no difference was seen in mean weight change when compared to olanzapine (-0.15kg; 95% CI: -1.17 – 0.87) (**Figure 2.11**). In addition change in total cholesterol (0.12 mmol/L;

95% CI:-0.15 – 0.38) and triglycerides (0.27 mmol/L; 95% CI: -0.14 – 0.68) was no different between clozapine and olanzapine (**Figures 2.12 and 2.13**).

Olanzapine was associated with a mean increase in weight of 2.23 kg (95% CI: 1.84 – 2.62) relative to placebo (**Figure 2.14**). Change in weight between olanzapine and typical agents, a different atypical agent, and risperidone could not be estimated due to significant heterogeneity. Change in blood glucose relative to risperidone also could not be estimated due to heterogeneity (I^2 = 66%). Olanzapine was associated with a mean increase in blood glucose of 0.27 mmol/L (95% CI: 0.08 – 0.46), mean increase in total cholesterol of 0.22 mmol/L (95% CI: 0.13 – 0.32) and a mean increase in triglycerides of 0.18 mmol/L (95% CI: 0.02 – 0.35) compared to typical antipsychotic agents (**Figures 2.15, 2.16, 2.17**).

Quetiapine was associated with a mean change in weight of 1.04kg compared to placebo (95% CI: 0.52 – 1.56) (**Figure 2.18**). There was no difference in blood glucose change (0.09 mmol/L; 95% CI: -0.18 – 0.37) or total cholesterol change (0.13 mmol/L; 95% CI: -0.02 – 0.28) in people randomized to quetiapine compared to individuals who received typical agents (**Figures 2.19 and 2.20**). Use of quetiapine was associated with a mean increase in triglycerides of 0.1 mmol/L (95% CI: 0.07 – 0.13) relative to typical antipsychotics (**Figure 2.21**).

When compared to olanzapine, use of paliperidone was associated with a mean weight loss of -0.90 kg (95% CI: -1.37 - -0.42) and a mean decrease in total

cholesterol of 0.3 mmol/L (95% CI: -0.42 - -0.18) (**Figures 2.22 and 2.23**). No difference was found between paliperidone and olanzapine for change in blood glucose, HDL, or LDL.

Risperidone was associated with a mean weight increase of 1.93 kg (95% CI: 1.09 – 2.76) when compared to typical agents (**Figure 2.24**). No difference was found between risperidone and typical agents in terms of change in blood glucose (-0.01 mmol/L; 95% CI: -0.36 – 0.34), total cholesterol (-0.01 mmol/L; 95% CI: -0.12 – 0.10), and triglycerides (-0.12 mmol/L; 95% CI: -0.37 – 0.12) (**Figures 2.25, 2.26, and 2.27**).

It was not possible to evaluate ziprasidone with typical antipsychotics or other atypical antipsychotic agents due to significant heterogeneity.

2.4 Discussion

In this comprehensive systematic review that included studies from a wide range of practice areas, we found that use of atypical antipsychotic agents was associated with a significant increase in blood glucose and total cholesterol compared to typical agents. In addition, our subgroup analyses found that individuals randomised to clozapine sustained a mean weight increase almost 4 kg relative to people randomised to a typical antipsychotic agent, whereas individuals who received paliperidone experienced significant weight loss and reduction in total cholesterol compared to people who received olanzapine. Subgroup analyses

must be interpreted with caution, however, and should only be used for hypothesis-generating purposes.

Evidence has demonstrated that atypical agents such as clozapine and olanzapine are more effective at treating symptoms of schizophrenia and less likely to cause dyskinesias compared to typical agents (10,72,91,92). Given the results of this systematic review and the baseline cardiovascular risk in someone with schizophrenia, the benefits of atypical antipsychotic treatment must be closely monitored and benefits weighed against the risk of metabolic abnormalities associated with these therapies.

Despite the comprehensive nature of this systematic review, there are a number of limitations that must be noted. Significant heterogeneity was a factor in limiting the presentation of prespecified comparisons. The heterogeneity associated with these combinations likely originates from a number of differing factors including medications, dosages of medications, age groups, proportions of males and females, and duration of study. In addition, we evaluated antipsychotic monotherapy, therefore the results do not apply to an individual taking more than one antipsychotic agent. Further, we included randomised controlled trials in our systematic review to ensure a balance of known and unknown risk factors for metabolic abnormalities between treatment and control groups. Randomised control trial populations, however, tend to differ from the general population in severity of illness, so the results of this systematic review may not be

generalizable to individuals with very severe mental illness. Lastly, there are currently a number of studies pending based on the need for additional information from study authors, and the addition of these studies to the systematic review may change parameter estimates.

2.5 Conclusions

Use of atypical antipsychotic agents in people with schizophrenia, schizophreniform disorder, and schizoaffective disorder increased blood glucose, and total cholesterol compared to people receiving typical antipsychotic agents. Given the baseline risk of cardiovascular disease in a patient with schizophrenia regardless of treatment, individuals should be closely and regularly monitored for changes in metabolic parameters upon initiation of atypical antipsychotic agents.

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Table 2.1. Characteristics of Included Studies

	Methods	Participants	Interventions	Outcomes	Notes
Ader 2008	Randomised, double-blind, multicentre, active control	Schizophrenia, schizoaffective, schizophreniform (DSM-IV)	Risperidone target 6mg/day Olanzapine target 20mg/day Risperidone group (n = 28) - mean age 39.8 +/- 7.6 - 22 men (78.6%) -6 women (21.4%) Olanzapine group (n = 31) - mean age 39.6 +/- 8.3 - 18 men (58.1%) - 13 women (41.9%)	Weight and blood glucose	24 week study Involved 7 sites in the USA 57.1% Loss to follow up in both groups Funded by industry (Ortho-McNeil Janssen) and NIH
Alvarez 2006	Randomised, open-label, multicentre, active control	Schizophrenia (DSM-IV) with prominent negative symptoms	Olanzapine mean 12.2mg/day (SD = 5.8) Risperidone mean 4.9mg/day (SD = 2.0) Olanzapine group (n = 124) - mean age 37 (SD = 10.6) - 85 men (68.5%) - 39 women (31.5%) - 37 dropouts (24.8%) Risperidone group (n = 123) - mean age 35.5 (SD = 10.6) - 94 men (76.4%) - 29 women (23.6%) - 47 dropouts (38.2%)	Weight	1 year study Involved 21 sites in Spain Funded by industry (Lilly)
Atmaca 2003	Randomised, active-control	Schizophrenia (DSM-IV)	Quetiapine mean 535.7mg +/- 110.5 Olanzapine mean 15.7mg +/- 4.8 Risperidone mean 6.7mg +/- 3.6 Clozapine mean 207.1mg +/- 62.4 Quetiapine group (n = 14) - mean age 30.1 +/- 8.4 - 6 men (42.9%) - 8 women (57.1%) - No dropouts Olanzapine group (n = 13) - mean age 29.6 +/- 8.1 - 6 men (46.2%) - 7 women (53.8%) - 1 dropout (7.7%) Risperidone group (n = 13) - mean age 27.9 +/- 7.8 - 7 men (53.8%) - 6 women (46.2%) - 1 dropout (7.7%) Clozapine group (n = 11) - mean age 31.3 +/- 7.2 - 5 men (45.5%) - 6 women (54.5%) - 1 dropout (9.1%)	Weight, triglycerides	6 week study Involved one centre in Turkey Internal funding
Baptista 2007	Randomised, active control, open-label	Severe schizophrenia (DSM-IV)	Olanzapine 10mg/day Risperidone 3mg/day Olanzapine group (n = 11) - age not reported - 2 men (18.2%) - 9 women (81.8%) - no dropouts Risperidone group (n = 11) - age not reported	Weight and glucose	15 days duration Funded by Janssen and a university grant

			- 8 men (72.7%) - 3 women (27.3%) - no dropouts		
Beasley 2003	Randomised, double-blind, placebo-controlled, multicentre	Schizophrenia, schizoaffective disorder (DSM-IV)	Olanzapine mean 13.4mg/day Placebo Olanzapine group (n = 224) - mean age 36.2 +/- 10.4 - 119 men (53.1%) - 105 women (46.9%) - 30 dropouts (13.4%) - no lost to follow up Placebo group (n = 102) - mean age 35.1 +/- 11.2 - 54 men (52.9%) - 48 women (47.1%) - 55 dropouts 53.9%) - 1 lost to follow up	Weight	Involved 19 sites in Croatia, Poland, Romania, Russia, USA, Yugoslavia Study was terminated early at 30 weeks (was supposed to be 52 weeks) Funded by industry (Eli Lilly)
Bitter 2004	Randomised, double-blind, active control, multicentre	Schizophrenia (DSM-IV) hospitalized patients	Olanzapine 5 – 25mg/day (mean 17.2mg +/- 4.8mg) Clozapine 100 – 500mg/day (mean 216.2mg +/- 107.9mg) - mean age of both study groups combined 37.6 years - 88 males in both study groups combined (59.9%) - 59 females in both study groups combined (40.1%) Olanzapine group (n = 75) - 17 dropouts (22.1%) - 13 loss to follow up (17.4%) Clozapine group (n = 72) - 20 dropouts (28%) - 12 lost to follow up (16.6%)	Weight	Involved 8 sites in Hungary and South Africa 18 weeks duration Funded by industry (Eli Lilly)
Breier 2005	Randomised, double-blind, active-control, multicentre	Schizophrenia (DSM-IV)	Olanzapine 10 – 20mg/day (mean 15.27mg/day (SD = 4.52)) Ziprasidone 40 – 160mg/day (mean 115.96mg/day (SD = 39.91)) Olanzapine group (n = 277) - mean age 40.1 (SD = 11.6) - 180 men (65%) - 97 women (35%) - 100 dropouts (36.1%) - 12 lost to follow up (4.3%) Ziprasidone group (n = 271) - mean age 38.2 (SD = 12.1) - 172 men (63.5%) - 99 women (36.5%) - 144 dropouts (53.1%) - 12 lost to follow up (4.4%)	Weight, glucose, total cholesterol, triglyceride, HDL, LDL	Involved 12 sites in Europe, North America, and South America Industry funded (Eli Lilly) 28 weeks duration
Chan 2007	Randomised, double-blind, active-control, multicentre	Schizophrenia or schizoaffective disorder (DSM-IV)	Aripiprazole 15mg/day Risperidone 6mg/day Aripiprazole group (n = 49) - mean age 35.2 +/- 10.9	Weight, glucose, total cholesterol	Involved 5 sites in Taiwan 4 week study duration Industry funded

			- 23 men (46.9%) - 26 women (53.1%) - 11 dropouts (22.4%) - 0 lost to follow up Risperidone group (n = 34) - mean age 35.1 +/- 8.6 - 22 men (64.7%) - 12 women (35.3%) - 10 dropouts (29.4%) - 0 lost to follow up		(Otsuka)
Chan 2010	Randomised, rater-blind, active control	Schizophrenia (DSM-IV) with neuroleptic-induced acute dystonia or parkinsonism (DSM-IV)	Olanzapine 2.5 – 20mg/day (mean 11.72mg/day +/- 4.87) Risperidone 0.5 – 6mg/day (mean 3.45mg/day +/- 1.54) Olanzapine group (n = 35) - mean age 40.8 (SD = 11.5) - 16 men (45.7%) - 19 women (54.3%) - 6 dropouts (17.1%) - 0 lost to follow up Risperidone group (n = 35) - mean age 41.1 (SD = 11.3) - 16 men (45.7%) - 19 women (54.3%) - 7 dropouts (20.0%) - 0 lost to follow up	Weight	Involved 1 site in Taiwan 8 weeks duration Funded by Department of Health – Taiwan and Taoyuan Mental Hospital Grant
Ciudad 2006	Randomised, open-label, active-control, multicentre	Schizophrenia (DSM-IV)	Olanzapine mean 12.2mg/day (SD = 5.8) Risperidone mean 4.9mg/day (SD = 2) Olanzapine group (n = 120) - mean age 37.3 (SD = 10.6) - 82 men (68.3%) - 38 women (31.7%) - 27 dropouts (22.5%) - 6 lost to follow up (5.0%) Risperidone group (n = 115) - mean age 35.6 (SD = 10.8) - 88 men (76.5%) - 27 women (23.5%) - 33 dropouts (28.7%) - 6 lost to follow up (5.2%)	Weight	Involved 21 centres in Spain 1 year duration Industry funded (Lilly)
Conley 2001	Randomised, double-blind, active-control, multicentre	Schizophrenia or schizoaffective disorder (DSM-IV)	Olanzapine 5 – 20mg/day (mean 12.4mg/day (SD = 4.6)) Risperidone 2 – 6 mg/day (mean 4.8mg/day (SD = 1.2)) Olanzapine group (n = 189) - mean age 38.9 (SD = 10.5) - 138 men (73.0%) - 51 women (27.0%) - 43 dropouts (22.8%) Risperidone group (n = 188) - mean age 41.0 (SD = 11.0) - 136 men (72.3%) - 52 women (27.7%)	Weight	Involved 41 sites in the USA 8 weeks duration Industry funded (Janssen Research Foundation)

			- 53 dropouts (28.2%)		
Covell 2004	Randomised, open-label, multicentre, active-control	Schizophrenia (chart diagnosis)	Clozapine First generation antpsychotics (FGA) Clozapine group (n = 138) - mean age 42 +/- 12 - 84 men (61%) - 54 women (39%) - 46 dropouts (33.3%) FGA group (n = 89) - mean age 40 +/- 11 - 54 men (61%) - 35 women (39%)	Weight	Reported as mutlicentre but number of sites not reported (all Connecticut State hospitals) 2 years duration Same study group as Essock (excluded) Funded by NIMH
Czobor 2002	Randomised, double-blind, active control, multicentre	Schizophrenia or schizoaffective disorder (DSM-IV), inpatients, treatment-resistant	Clozapine mean 526.6mg/day +/- 140.3 Olanzapine mean 30.4mg/day +/- 6.6 Risperidone mean 11.6mg/day +/- 3.2 Haloperidol mean 25.7mg/day +/- 5.7 91 patients (60.3%) completed trail out of entire group Clozapine group (n = 38) - mean age 42.6 +/-7.5 - 34 men (89%) - 4 women (11%) - at least 7 dropouts (18.4%) Olanzapine group (n = 38) - mean age 41.0 +/- 7.3 - 33 men (87%) - 5 women (13%) - at least 8 dropouts (21.1%) Risperidone group (n = 39) - mean age 42.9 +/- 9.7 - 33 men (85%) - 6 women (15%) - at least 6 dropouts (15.4%) Haloperidol group (n = 36) - mean age 37.3 +/- 11.0 - 28 men (78%) - 8 women (22%) - at least 11 dropouts (30.6%)	Weight	Included 4 sites – 2 in New York and 2 in North Carolina 14 weeks duration Funded by NIMH and Lilly (all drug companies provided meds)
Davidson 2007	Randomised, double-blind, placebo-controlled, multicentre	Schizophrenia (DSM-IV) for at least 1 year	Paliperidone ER 3mg/day Paliperidone ER 9mg/day Paliperidone ER 15mg/day Olanzapine 10mg/day Placebo Paliperidone ER 3mg/day group (n = 123) - mean age 36.3 (SD = 11.0) - 78 men (63%) - 45 women (37%) - 57 dropouts (45%) - 1 lost to follow up (0.8%) Paliperidone ER 9mg/day group (n = 123) - mean age 36.2 (SD = 10.9) - 79 men (64%) - 44 women (36%) - 47 dropouts (38%) - 0 lost to follow up	Weight, glucose, total cholesterol, triglyceride, LDL, HDL	Involved 74 sites in North America (31), Eastern Europe (17), Asia (12), Israel (5), Mexico (5), South Africa (4) 6 week duration Industry funded (Johnson & Johnson)

			Paliperidone ER 15mg/day group (n = 113) - mean age 37.6 (SD = 9.8) - 73 men (65%) - 40 women (35%) - 33 dropouts (29%) - 2 lost to follow up (1.8%) Olanzapine group (n = 126) - mean age 36.8 (SD = 10.6) - 96 men (76%) - 30 women (24%) - 40 dropouts (31%) - 3 lost to follow up (2.4%) Placebo group (n = 120) - mean age 37.3 (SD = 10.9) - 83 men (69%) - 37 women (31%) - 76 dropouts (62%) - 0 lost to follow up		
Deberdt 2008	Randomised, double-blind, active-control, multicentre	Schizophrenia or schizoaffective disorder (DSM-IV)	Olanzapine 7.5 – 20mg/day (mean 16.9mg/day) Quetiapine 300 – 800mg/day (mean 439.7mg/day) Olanzapine group (n = 68) - mean age 45.4 (SD = 9.4) - No report of men/women - 20 dropouts (29.4%) - lost to follow up not reported Quetiapine group (n = 65) - mean age 42.5 (SD = 11.5) - No report of men/women - 37 dropouts (56.9%) - lost to follow up not reported	Weight, glucose, A1C, total cholesterol, triglyceride, LDL, HDL	Involved 26 sites in the USA 24 weeks duration Industry funded (Eli Lilly)
Dossenbach 2004 Progress	Randomised, double-blind, active-control, multicentre	Schizophrenia (DSM-IV), hospitalized patients	Olanzapine 5 – 20mg/day (mean 14.8mg/day +/- 2.5) Fluphenazine 6 – 21mg/day (mean 11.7mg/day +/- 3.0) - mean age for both groups 35.4 +/- 10.4 Olanzapine group (n = 30) - 14 men (46.7%) - 16 women (53.3%) - no reports of dropouts or LTF Fluphenazine group (n = 30) - 14 men (46.7%) - 16 women (53.3%) - no reports of dropouts or LTF	Weight, systolic blood pressure	Involved 3 sites in Croatia 22 weeks duration Industry funded (Eli Lilly)
Hatta 2009	Randomised, rater-blinded, active-control, multicentre	Schizophrenia, schizoaffective disorder, acute schizophrenia-like psychotic disorder (IDC-10)	Risperidone 3 – 12mg/day (mean 7.2mg/day (SD = 3.1)) Olanzapine 10 – 20mg/day (mean 17.4mg/day (SD = 4.7)) Quetiapine 300 – 750mg/day (mean 579mg/day (SD = 210)) Aripiprazole 12 – 30mg/day)(mean	Weight, glucose, total cholesterol, triglyceride	Involved 15 sites in Japan 8 weeks duration Funded by the Japanese Government

			23.6mg/day (SD = 6.5) Risperidone group (n = 20) - mean age 41.1 (SD = 8.8) - 9 men (45%) - 11 women (55%) - 6 dropouts (30%) - 0 lost to follow up Olanzapine group (n = 17) - mean age 39.8 (SD = 10.8) - 12 men (71%) - 5 women (19%) - 2 dropouts (11.8%) - 0 lost to follow up Quetiapine group (n = 20) - mean age 39.8 (SD = 11.2) - 4 men (20%) - 16 women (80%) - 11 dropouts (55%) - 0 lost to follow up Aripiprazole group (n = 21) - mean age 42.1 (SD = 12.4) - 8 men (38%) - 13 women (62%) - 13 dropouts (61.9%) - 0 lost to follow up		
Jeste 2003	Randomised, double-blind, active-control, multicentre	Schizophrenia or schizoaffective disorder (DSM-IV) over the age of 60	Risperidone 1 – 3mg/day (mean 1.9mg/day (SD = 0.8)) Olanzapine 5 – 20mg/day (mean 11.1mg/day (SD = 5.4)) Risperidone group (n = 87) - mean age 70.9 (SD = 5.6) - 34 men (39.1%) - 53 women (60.9%) - 23 dropouts (26.4%) - 1 lost to follow up (1.1%) Olanzapine group (n = 88) - mean age 71.4 (SD = 5.6) - 28 men (31.8%) - 60 women (68.2%) - 17 dropouts (19.3%) - 0 lost to follow up	Weight	Involved 32 sites in USA (19), and 13 in Israel, Poland, Norway, the Netherlands, and Austria 8 week duration Industry funded (Johnson and Johnson)
Kahn 2007	Randomised, double-blind, placebo-controlled, multicentre	Acute schizophrenia (DSM-IV)	Quetiapine XR 400mg/day Quetiapine XR 600mg/day Quetiapine XR 800mg/day Quetiapine immediate release (IR) 400mg/day Placebo Quetiapine XR 400mg/day group (n = 113) - mean age 34.1 (SD = 9.6) - 79 men (70.3) - 34 women (29.7%) - 29 dropouts (25.7%) - 1 lost to follow up (0.9%) Quetiapine XR 600mg/day group (n = 113) - mean age 34.2 (SD = 9.9) - 62 men (55.0%) - 51 women (45.0%) - 20 dropouts (17.7%) - 1 lost to follow up (0.9%) Quetiapine XR 800mg/day group (n = 121)	Weight, glucose, A1C, total cholesterol, triglyceride, LDL, HDL	Involved 39 sites in Bulgaria, Greece, India, Indonesia, Phillipines, Russia, Romania, South Africa 6 week duration Industry funded (Astra Zeneca)

			- mean age 34.4 (SD = 10.3) - 72 men (59.8%) - 49 women (40.2%) - 28 dropouts (23.1%) - 3 lost to follow up (2.5%) Quetiapine IR 400mg/day group (n = 123) - mean age 34.4 (SD = 10.2) - 71 men (58.0%) - 48 women (42.0%) - 26 dropouts (21.1%) - 1 lost to follow up (0.9%) Placebo group (n = 118) - mean age 34.1 (SD = 12.1) - 69 men (58.3%) - 49 women (41.7%) - 32 dropouts (27.1%) - 1 lost to follow up (0.8%)		
Kahn 2008	Randomised, active-control, multicentre	First-episode schizophrenia, schizoaffective disorder, schizophreniform disorder (DSM-IV)	Olanzapine 5 – 20mg/day Quetiapine 200 – 750mg/day Ziprasidone 40 – 160mg/day Haloperidol 1 – 4 mg/day Olanzapine group (n = 105) - mean age 26.3 (SD = 5.9) - 67 men (64%) - 38 women (36%) - 23 dropouts (21.9%) - LTF not reported Quetiapine group (n = 104) - mean age 26.4 (SD = 5.7) - 68 men (65%) - 36 women (35%) - 34 dropouts (32.7%) - LTF not reported Haloperidol group (n = 103) - mean age 25.4 (SD = 5.6) - 64 men (62%) - 39 women (38%) - 35 dropouts (34.0%) - LTF not reported Ziprasidone group (n = 82) - mean age 26.7 (SD = 5.7) - 41 men (50%) - 41 women (50%) - 29 dropouts (35.4%) - LTF not reported	Weight, glucose, total cholesterol, triglyceride, LDL, HDL	Involved 50 sites in Europe and Israel 1 year duration Industry funded (Astra Zeneca, Pfizer, Sanofi) Also included an amisulpride arm
Kane 2007 Schizo Research	Randomised, double-blind, placebo-controlled, multicentre	Schizophrenia (DSM-IV) for at least 1 year and had to agree to 51andomize hospitalization for at least 14 days	Paliperidone ER 6mg/day Paliperidone ER 9mg/day Paliperidone ER 12mg/day Olanzapine 10mg/day Placebo Paliperidone 6mg group (n = 123) - mean age 37.0 (SD = 10.2) - 62 men (50.4%) - 61 women (49.6%) - 42 dropouts (34.1%) - 1 lost to follow up Paliperidone 9mg group (n = 122) - mean age 38.5 (SD =	Weight, glucose, total cholesterol, triglycerides, LDL, HDL	Involved 47 sites in Europe and 6 sites in India 6 week duration Industry funded (Johnson & Johnson)

			11.4) - 72 men (59%) - 50 women (41%) - 34 dropouts (27.9%) - 2 lost to follow up Paliperidone 12mg group (n = 129) - mean age 36.0 (SD = 10.6) - 68 men (53%) - 61 women (47%) - 29 dropouts (22.5%) - 0 lost to follow up Olanzapine group (n = 128) - mean age 36.3 (SD = 11.2) - 60 men (47%) - 68 women (53%) - 36 dropouts (28.1%) - 2 lost to follow up Placebo group (n = 126) - mean age 37.9 (SD = 10.9) - 66 men (52%) - 60 women (48%) - 67 dropouts (53.2%) - 2 lost to follow up		
Kasper 2006	Randomised, double-blind, active-control, multicentre	Acute relapse of schizophrenia (DSM-IV)	Aripiprazole mean 29.01mg/day Haloperidol mean 8.90mg/day Aripiprazole group (n = 861) - mean age 37.3 +/- 0.4 - 511 men (59%) - 350 women (41%) - 494 dropouts (57%) - LTF not reported Haloperidol group (n = 433) - mean age 36.8 +/- 0.5 - 247 men (57%) - 186 (43%) - 305 dropouts (70%) - LTF not reported	Weight	Involved 33 sites in the USA and 137 worldwide 52 weeks duration Industry funded (Bristol Myers Squibb and Otsuka)
Keefe 2006 Schizo Research	Randomised, double-blind, active-control, multicentre	Schizophrenia or schizoaffective disorder (DSM-IV)	Olanzapine 5 – 20mg/day (mean 12.3mg/day) Risperidone 2 – 10mg/day (mean 5.2mg/day) Haloperidol 2 – 19mg/day (mean 8.2mg/day) Olanzapine group (n = 159) - mean age 38.4 +/- 7.90 - 115 men (72.3%) - 44 women (27.7%) - 81 dropouts (59.7%) - 14 lost to follow up (8.8%) Risperidone group (n = 158) - mean age 39.5 +/- 8.25 - 111 men (70.3%) - 47 women (29.7%) - 92 dropouts (65.8%) - 12 lost to follow up (7.6%) Haloperidol group (n = 97)	Weight, glucose, total cholesterol, triglyceride	Involved sites in Canada and the USA (number not reported) 1 year duration Industry funded (Lilly)

			- mean age 39.8 +/- 8.32 - 69 men (71.1%) - 28 women (28.9%) - 63 dropouts (72.2%) - 7 lost to follow up (7.2%)		
Kerwin 2007	Randomised, open-label, active-control, multicentre	Schizophrenia (DSM-IV) who required a medication change due to side effects or inadequate control of symptoms from current medication	Aripiprazole 10 – 30mg/day Standard of care (SOC) group – olanzapine, quetiapine, or risperidone Aripiprazole group (n = 284) - mean age 38.1 (SE = 10.8) - 169 men (59.5%) - 115 women (40,5%) - 114 dropouts (40.1%) - 6 lost to follow up (2.1%) SOC group (n = 271) - mean age 38.3 (SE = 11.1) - 163 men (60.1%) - 108 women (39.9%) - 99 dropouts (36.5%) - 6 lost to follow up (2.2%)	Weight, glucose, total cholesterol, triglyceride, LDL, HDL	Involved 98 sites in 12 European countries 26 weeks duration Industry funded (Bristol Myers Squibb and Otsuka)
Kinon 2006	Randomised, double-blind, active-control, multicentre	Schizophrenia or schizoaffective disorder (DSM-IV) with prominent negative symptoms	Olanzapine 10 – 20mg/day (mean 15.6mg/day +/- 4.3) Quetiapine 300 – 700mg/day (mean 455.8 +/- 156.3) Olanzapine group (n = 171) - mean age 41.67 +/- 9.53 - 114 men (66.7%) - 57 women (33.3%) - 69 dropouts (40.4%) - 12 lost to follow up (7.0%) Quetiapine group (n = 175) - mean age 40.45 +/- 9.61 - 114 men (65.1%) - 61 women (34.9%) - 100 dropouts (57.2%) - 9 lost to follow up (5.1%)	Weight	Reported at multicentre, but number and location of sites not reported 6 months duration Industry funded (Eli Lilly)
Kinon 2008	Randomised, double-blind, active-control, multicentre	Schizophrenia, schizoaffective disorder, schizophreniform disorder (DSM-IV), acutely ill requiring at least 5 days hospitalization	Olanzapine 15 – 30mg/day (mean 19.26mg/day (SD = 5.46)) Aripiprazole 20mg/day (mean 19.97mg/day (SD = 0.27)) Olanzapine group (n = 306) - mean age 39.5 (SD = 9.37) - 228 men (74.5%) - 78 women (25.5%) - 72 dropouts (23.5%) - LTF not reported Aripiprazole group (n = 298) - mean age 39.0 (SD = 9.63) - 207 men (69.5%) - 91 women (30.5%) - 61 dropouts (20.5%) - LTF not reported	Weight, triglyceride	Involved 44 sites in the USA 5 days duration Industry funded (Eli Lilly)
Krakowski 2009	Randomised, double-blind, active-control,	Schizophrenia or schizoaffective	Clozapine 500mg/day (200 – 800mg/day) Olanzapine 20mg/day (10	Weight, glucose, total	Involved 2 sites in New York state 12 weeks duration

	multicentre	disorder (DSM-IV), aggressive inpatients and were hospitalized for the trial	– 30mg/day) Haloperidol 20mg/day (10 – 30mg/day) Clozapine group (n = 34) - mean age 35.2 (SD = 11.8) - 29 men (85.3%) - 5 women (14.7%) - 0 dropouts or LTF Olanzapine group (n = 31) - mean age 35.4 (SD = 9.9) - 24 men (77.4%) - 7 women (22.6%) - 0 dropouts or LTF Haloperidol group (n = 28) - mean age 31.3 (SD = 9.7) - 24 men (85.7%) - 4 women (14.3%) - 0 dropouts or LTF	cholesterol, triglyceride	Funded by NIMH (meds provided by Eli Lilly and Novartis)
Lieberman 2003 Am J Psych	Randomised, double-blind, active-control, multicentre	First-episode schizophrenia, schizophreniform disorder, schizoaffective disorder (DSM-IV) with < 16 cumulative weeks of antipsychotic treatment	Olanzapine mean 9.1mg/day Haloperidol mean 4.4mg/day Olanzapine group (n = 131) - mean age 23.5 (SD = 4.6) - 104 men (79.4%) - 27 women (20.6%) - 42 dropouts (32%) - LTFs not reported Haloperidol group (n = 132) - mean age 24 (SD = 4.9) - 111 men (84.1%) - 21 women (15.9%) - 61 dropouts (46%) - LTFs not reported	Weight, glucose, total cholesterol	Involved 14 sites in North America and Europe 12 week duration Funded by industry (Lilly) and NIMH grants
Lieberman 2005	Randomised, double-blind, active control, multicentre	Schizophrenia (DSM-IV)	Olanzapine 7.5 – 30mg/day (mean 20.1mg/day) Quetiapine 200 – 800mg/day (mean 543.4mg/day) Risperidone 1.5 – 6mg/day mean 3.9mg/day) Perphenazine 8 – 32mg/day (mean 20.8mg/day) Ziprasidone 40 – 160mg/day (mean 112.8mg/day) Olanzapine group (n = 336) - mean age 40.8 +/- 10.8 - 244 men (73%) - 92 women (27%) - 210 dropouts (64%) - LTFs not reported Perphenazine group (n = 261) - mean age 40.0 +/- 11.1 - 199 men (76%) - 62 women (24%) - 192 dropouts (75%) - LTFs not reported Quetiapine group (n = 337) - mean age 40.9 +/- 11.2 - 255 men (76%) - 82 women (24%) - 269 dropouts (82%)	Weight, glucose, A1C, total cholesterol, triglycerides	Involved 57 sites in the USA 18 month study Funded by NIMH Patients with tardive dyskinesia could not receive perphenazine (Phase 1A)

			- LTFs not reported Risperidone group (n = 341) - mean age 40.6 +/- 11.3 - 253 men (74%) - 88 women (26%) - 245 dropouts (74%) - LTFs not reported Ziprasidone group (n = 185) - mean age 40.1 +/- 11.0 - 129 men (70%) - 56 women (30%) - 145 dropouts (79%) - LTFs not reported		
Lindenmayer 2003	Randomised, double-blind, active-control, multicentre	Schizophrenia, schizoaffective disorder, hospitalized throughout trial	Clozapine mean 443.7mg/day (SD = 120.2) Olanzapine mean 20.1mg/day (SD = 1.2) Risperidone 8.5mg/day (SD = 2.2) Haloperidol 20mg/day (SD = 0) - overall mean age 40.33 (SD = 9.4) Clozapine group (n = 28) - 25 men (89.3%) - 3 women (10.7%) - 11 dropouts (39.3%) - 0 lost to follow up Olanzapine group (n = 26) - 22 men (84.6%) - 4 women (15.4%) - 4 dropouts (15.4%) - 0 lost to follow up Risperidone group (n = 22) - 18 men (81.8%) - 4 women (18.2%) - 8 dropouts (36.4%) - 0 lost to follow up Haloperidol group (n = 25) - 20 men (80%) - 5 women (20%) - 5 dropouts (20%) - 0 lost to follow up	Glucose, total cholesterol	Same study group as Czobor/Volavka Involved 4 sites in New York and North Carolina 14 week duration Funded by NIMH and Eli Lilly, companies provided meds
Marder 2007	Randomised, double-blind, placebo-controlled, multicentre	Acute episode of schizophrenia (DSM-IV), diagnosis for at least 1 year, agreed to voluntary hospitalization for at least 14 days	Paliperidone ER 6mg/day Paliperidone ER 12mg/day Olanzapine 10mg/day Placebo Paliperidone 6mg group (n = 112) - mean age 42.1 (SD = 10.2) - 76 men (68%) - 36 women (32%) - 53 dropouts (47%) - 8 lost to follow up (7%) Paliperidone 12mg group (n = 112) - mean age 41.4 (SD = 10.7) - 77 men (69%) - 35 women (31%) - 48 dropouts (43%) - 10 lost to follow up (9%) Olanzapine group (n = 110) - mean age 40.5 (SD = 11.0)	Weight, glucose, total cholesterol, triglyceride, LDL, HDL	Involved 74 sites in the USA 6 weeks duration Industry funded (Johnson & Johnson)

			- 88 men (80%) - 22 women (20%) - 54 dropouts (50%) - 6 lost to follow up (5%) Placebo group (n = 110) - mean age 42.3 (SD = 10.7) - 86 men (78%) - 24 women (22%) - 69 dropouts (62%) - 4 lost to follow up (4%)		
McEvoy 2006	Randomised, open-label, active-control, multicentre	Schizophrenia (DSM-IV) that had discontinued treatment in Phase 1 CATIE due to inadequate efficacy	Clozapine mean 332.1mg/day (SD = 156.9) Olanzapine mean 23.4mg/day (SD = 7.9) Quetiapine mean 642.9mg/day (SD = 195) Risperidone mean 4.8mg/day (SD = 1.3) Clozapine group (n = 49) - mean age 39.4 (SD = 9.9) - 40 men (82%) - 9 women (18%) - 25 dropouts (51.0%) Olanzapine group (n = 19) - mean age 44.3 (SD = 10.5) - 18 men (95%) - 1 woman (5%) - 12 dropouts (63.2%) Quetiapine group (n = 15) - mean age 37.1 (SD = 11.8) - 12 men (80%) - 3 women (20%) - 13 dropouts (86.7%) Risperidone group (n = 16) - mean age 37.7 (SD = 9.3) - 10 men (63%) - 6 women (37%) - 12 dropouts (75%)	Weight, glucose, A1C, total cholesterol, triglyceride	Phase 2 efficacy of CATIE trial Open-label clozapine or double-blind atypical therapy Involved 57 sites in the USA Funded by NIMH
McEvoy 2007	Randomised, double-blind, active-control, multicentre	Schizophrenia, schizophreniform disorder, or schizoaffective disorder (DSM-IV) – first episode illness, continuously ill for at least 1 month but no more than 5 years, without therapy for longer than 16 weeks	Olanzapine 2.5 – 20mg/day (mean 11.7mg/day (SD = 5.3)) Quetiapine 100 – 800mg/day (mean 506mg/day (SD = 215)) Risperidone 0.5 – 4mg/day (mean 2.4mg/day (SD = 1.0)) Olanzapine group (n = 133) - mean age 24.7 (SD = 5.8) - 101 men (75.9%) - 32 women (24.1%) - 91 dropouts (68.4%) - 0 lost to follow up Quetiapine group (n = 134) - mean age 25.0 (SD = 6.1) - 92 men (68.6%) - 42 women (31.3%) - 95 dropouts (70.9%) - 0 lost to follow up Risperidone group (n = 133) - mean age 23.9 (SD = 5.5) - 99 men (74.4%) - 34 women (25,6%) - 95 dropouts (71.4%)	Weight, glucose, systolic blood pressure, diastolic blood pressure, total cholesterol, triglyceride, HDL	Sites not reported 52 weeks duration Industry funded (Astra Zeneca)

			- 0 lost to follow up		
Naber 2005	Randomised, double-blind, active-control, multicentre	Schizophrenia (DSM-IV), failed to respond to at least one antipsychotic previously, no clozapine or olanzapine in previous 3 months	Clozapine 100 – 400mg/day (mean 209mg/day +/- 91) Olanzapine 5 – 25mg/day (mean 16.2mg/day +/- 4.8) Clozapine group (n = 57) - mean age 35.2 +/- 10.8 - 35 men (61%) - 22 women (39%) - 22 dropouts (38.6%) - 13 lost to follow up (22.8%) Olanzapine group (n = 57) - mean age 32.9 +/- 10.4 - 34 men (60%) - 23 women (40%) - 22 dropouts (38.6%) - 14 lost to follow up (24.6%)	Weight, glucose	Involved 8 sites in Germany 26 weeks duration Industry funded (Lilly Deutschland)
Newcomer 2008	Randomised, double-blind, active-control, multicentre	Schizophrenia or schizoaffective disorder (DSM-IV-TR); must have received olanzapine monotherapy 10 – 20mg/day for 1 – 24 months immediately prioir to screening; BMI >= 27kg/m^2	Aripiprazole 5 – 30mg/day (mean 16mg/day) Olanzapine 10 – 40mg/day (mean 15.9mg/day) Aripiprazole group (n = 88) - mean age 39.7 +/- 10.1 - 50 men (56.8%) - 38 women (43.2%) - 26 dropouts (29.5%) - 6 lost to follow up (6.8%) Olanzapine group (n = 85) - mean age 38.7 +/- 10.1 - 61 men (71.8%) - 24 women (28.2%) - 16 dropouts (18.8%) - 6 lost to follow up (7.0%)	Weight, glucose, total cholesterol, triglyceride, LDL, HDL	Reported as multicentre, but number and location of sites not reported 16 weeks duration Industry funded (Bristol Myers Squibb and Otsuka)
Potkin 2006	Randomised, double-blind, placebo-controlled, multicentre	Schizophrenia or schizoaffective disorder (DSM-IV), acute exacerbation requiring hospitalization	Risperidone 1 – 6mg/day (mean 4.37mg/day +/- 0.94) Quetiapine 50 – 800mg/day (mean 556.4 +/- 141.9) Placebo Risperidone group (n = 153) - mean age 34.7 (SD = 9.6) - 105 men (69%) - 48 women (31%) - 22 dropouts (15%) - 5 lost to follow up (3%) Quetiapine group (n = 156) - mean age 34.2 (SD = 9.8) - 100 men (64%) - 56 women (36%) - 31 dropouts (20%) - 10 lost to follow up (6%) Placebo group (n = 73) - mean age 36.1 (SD = 9.8) - 46 men (63%) - 27 women (37%) - 17 dropouts (23%) - 11 lost to follow up (15%)	Weight	Involved 30 sites in the USA, Romania, India 6 week study duration Industry funded (Janssen)
Ritchie 2003	Randomised, open-label, active-control, multicentre	Elderly patients (over the age of 60) with schizophrenia who were	Olanzapine 5 – 20mg/day (mean 9.9mg/day (SD = 4.2)) Risperidone 0.5 – 6mg/day (mean 1.7mg/day (SD =	Weight	Involved 8 sites in Australia 4 weeks duration Industry funded (Eli Lilly)

		taking typical antipsychotic agents	1.2)) Olanzapine group (n = 34) - mean age 69.5 (SD = 7.3) - 10 men (29.4%) - 24 women (71.6%) - 4 dropouts (11.8%) - 0 lost to follow up Risperidone group (n = 32) - mean age 69.7 (SD = 4.8) - 9 men (28.1%) - 23 women (71.9%) - 10 dropouts (31.3%) - 0 lost to follow up		
Sacchetti 2009	Randomised, double-blind, active-control, multicentre	Schizophrenia (DSM-IV) with resistance or intolerance to at least 3 acute cycles with different antipsychotic treatments in the previous 5 years	Clozapine 200 – 600mg/day (mean 346mg/day +/- 61) Ziprasidone 80 – 160mg/day (mean 130mg/day +/- 24) Clozapine group (n = 73) - mean age 38.3 +/- 11.2 - 49 men (67.1%) - 24 women (32.9%) - 28 dropouts (38.4%) - LTFs not reported Ziprasidone group (n = 73) - mean age 41.6 +/- 10.2 - 52 men (71.2%) - 21 women (28.8%) - 28 dropouts (38.4%)	Weight, glucose, total cholesterol, triglyceride, LDL, HDL	Involved 23 sites in Italy 18 weeks duration Industry funded (Pfizer)
Schooler 2005	Randomised, double-blind, active-control, multicentre	First-episode schizophrenia, schizoaffective disorder, or schizophreniform disorder (DSM-IV) – no more than 1 year; no more than 2 hospitalizations, < 12 weeks cumulative exposure to antipsychotics	Risperidone mean 3.3mg/day Haloperidol mean 2.9mg/day Risperidone group (n = 278) - mean age 25.2 (SD = 6.84) - 196 men (70.5%) - 82 women (29.5%) - 97 dropouts (34.9%) - 20 lost to follow up (7.2%) Haloperidol group (n = 277) - mean age 25.7 (SD = 6.87) - 200 men (72.2%) - 77 women (27.8%) - 85 dropouts (30.7%) - 16 lost to follow up (5.8%)	Weight	Involved 11 countries, number of sites not reported Industry funded (Johnson & Johnson)
Smith 2009	Randomised, open-label, active-control, single	Hospitalized patients with schizophrenia or schizoaffective disorder (DSM-IV)	Olanzapine 5 – 40mg/day (mean 25.2mg/day (SD = 10.1)) Risperidone 2 – 10mg/day (mean 6.1mg/day (SD = 1.8)) Olanzapine group (n = 23) - mean age 41.22 +/- 7.27 - 23 men (100%) - 3 dropouts (13%) - 0 lost to follow up Risperidone group (n = 23) - mean age 42.52 +/- 9.10 - 22 men (95.7%) - 1 woman (4.3%) - 3 dropouts (13%) - 0 lost to follow up	Glucose, A1C	5 months duration Industry funded (Eli Lilly)

Stroup 2006	Randomised, double-blind, active-control, multicentre	Individuals in phase 1 (schizophrenia DSM-IV) who discontinued treatment due to intolerability	Olanzapine mean 20.5mg/day Quetiapine mean 565.2mg/day Risperidone mean 4.1mg/day Ziprasidone mean 115.9mg/day Authors do not report LTFs Olanzapine group (n = 108) - mean age 40.0 (SD = 11.6) - 73 men (68%) - 35 women (32%) - 44 dropouts (67%) Risperidone group (n = 104) - mean age 41.8 (SD = 11.0) - 72 men (69%) - 31 women (31%) - 44 dropouts (64%) Quetiapine group (n = 95) - mean age 40.1 (SD = 10.6) - 67 men (71%) - 28 women (29%) - 53 dropouts (84%) Ziprasidone group (n = 137) - mean age 41.3 (SD = 10.8) - 96 men (70%) - 41 women (30%) - 104 dropouts (77%)	Weight, glucose, A1C, total cholesterol, triglyceride	Phase 2 (tolerability) of CATIE trial Involved 57 sites in the USA 6 months duration Funded by NIMH
Stroup 2007	Randomised, double-blind, active-control, multicentre	Participants from CATIE phase 1 who were 59andomized to perphenazine and discontinued (schizophrenia DSM-IV)	Olanzapine 7.5 – 30mg/day (mean 20.7mg/day) Quetiapine 200 – 800mg/day (mean 586.1mg/day) Risperidone 1.5 – 6mg/day (mean 3.7mg/day) Olanzapine group (n = 39) - mean age 39.9 (SD = 10.4) - 29 men (74%) - 10 women (26%) - 23 dropouts (61%) - LTFs not reported Quetiapine group (n = 38) - mean age 40.7 (SD = 11.4) - 30 men (79%) - 8 women (21%) - 22 dropouts (58%) - LTFs not reported Risperidone group (n = 38) - mean age 42.0 (SD = 10.3) - 29 men (76%) - 9 women (24%) - 32 dropouts (84%) - LTFs not reported	Weight, glucose, A1C, total cholesterol, triglyceride	Phase 1B of the CATIE trial Involved 57 sites in the USA 18 months duration Funded by NIMH
Tollefson 1997	Randomised, double-blind, active-control, multicentre	Schizophrenia, schizoaffective disorder, schizophreniform disorder	Olanzapine 5 – 20mg/day (mean 13.2mg/day (SD = 5.8)) Haloperidol 5 – 20mg/day (mean 11.8mg/day (SD =	Weight	Involved 174 sites in Europe and North America 6 weeks duration Funding not stated,

		(DSM-III-R)	5.6)) Olanzapine group (n = 1336) - mean age 38.7 (SD = 11.6) - male and female not reported - 433 dropouts (32.4%) - 15 lost to follow up (1.1%) Haloperidol group (n = 660) - mean age 38.3 (SD = 11.1) - male and female not reported - 340 dropouts (51.5%) - 11 lost to follow up (1.7%)		but 1st author from Lilly
Tollefson 2001	Randomised, double-blind, active-control, multicentre	Schizophrenia (DSM-IV); previous treatment with olanzapine or clozapine or olanzapine non-responders were excluded; patients were resistant to at least 2 different antipsychotics from different classes given for at least 6 weeks at a therapeutic dose	Olanzapine 15 – 25mg/day (mean 20.5mg/day (SD = 2.8)) Clozapine 200 – 600mg/day (mean 303.6mg/day (SD = 108.7)) - both groups mean age = 38.6 (SD = 10.6) Olanzapine group (n = 90) - 61 men (67.8%) - 29 women (32.2%) - 34 dropouts (37.8%) - 2 lost to follow up (2.2%) Clozapine group (n = 90) - 54 men (60.0%) - 36 women (40.0%) - 35 dropouts (38.9%) - 2 lost to follow up (2.2%)	Weight	Involved 41 investigators from Belgium, Denmark, Finland, France, Germany, Italy, Norway, Portugal, South Africa, Spain, Sweden, Switzerland, Great Britain, Ireland 18 weeks duration Industry funded (Eli Lilly)
Tran 1997	Randomised, double-blind, active-control, multicentre	Schizophrenia, schizoaffective disorder, schizophreniform disorder (DSM-IV); patients excluded if they failed to show a response to at least 3 antipsychotics in 3 chemical classes at therapeutic doses for at least 6 weeks	Olanzapine 10 – 20mg/day (mean 17.2mg/day +/- 3.6) Risperidone 4 – 12mg/day (mean 7.2mg/day +/- 2.7) - mean age for both groups 36.21 +/- 10.73 - 220 men in both groups (64.9%) - 117 women in both groups (35.1%) Olanzapine group (n = 172) - 68 dropouts (39.5%) - 6 lost to follow up (3.5%) Risperidone group (n = 167) - 82 dropouts (49.1%) - 5 lost to follow up (3.0%)	Weight	Involved 35 sites from Belgium, France, Germany, the Netherlands, South Africa, Spain, Switzerland, UK, USA 28 weeks duration Industry funded (Eli Lilly)
Tzimos 2008	Randomised, double-blind, placebo-controlled, multicentre	Schizophrenia (DSM-IV) for at least 1 year, experiencing an acute episode; elderly patients (65 years and older)	Paliperidone ER 3 – 12mg/day (mean 9.0mg/day) Placebo Paliperidone group (n = 76) - mean age 70 (SD = 5.0) - 56 men (74%) - 20 women (26%) - 12 dropouts (16%) - 0 lost to follow up Placebo group (n = 38) - mean age 69 (SD = 3.3)	Weight	Involved 21 sites in South Africa, Czech Republic, Greece, Russia, Slovakia, Ukraine 6 weeks duration Industry funded (Johnson & Johnson)

			- 27 men (71%) - 11 women (29%) - 12 dropouts (32%) - 0 lost to follow up		
Van Bruggen 2003	Randomised, active-control	First or second episode schizophrenia, schizoaffective disorder, schizophreniform disorder (DSM-IV)	Olanzapine 5 – 30mg/day Risperidone 1 – 8mg/day Olanzapine group (n = 18) - mean age 21.0 (SD = 2.8) - 13 men (72%) - 5 women (28%) - dropouts and LTFs not reported Risperidone group (n = 26) - mean age 20.6 (SD = 3.0) - 22 men (85%) - 4 women (15%) - 2 dropouts (7.8%) - LTFs not reported	Weight	Involved 1 site in Amsterdam 6 – 10 weeks duration Funded by the Dutch Health Research Council and Eli Lilly
Voruganti 2007	Randomised, rater-blind, active-control, multicentre	Schizophrenia (DSM-IV), originally taking a typical antipsychotic and were in need of a switch to an atypical antipsychotic	Olanzapine mean 17.2mg/day (SD = 2.5) Quetiapine 612.8mg/day (SD = 122.6) - dropouts and LTFs not reported for either group Olanzapine group (n = 42) - mean age 41.33 (SD = 13.61) - 35 men (83%) - 7 women (17%) Quetiapine group (n = 43) - mean age 38.72 (SD = 14.37) - 28 men (65%) - 15 women (35%)	Weight	Reported as multicentre, but location and number of sites not reported 12 months duration Funded by Astra Zeneca, McMaster University, and St. Joseph's Hospital, Hamilton
Wang 2006	Randomised, double-blind, active-control, multicentre	Schizophrenia (DSM-IV), on stable typical antipsychotic therapy for at least 2 years with a reason for switching (previous atypical use – excluded)	Risperidone mean 5.3mg/day Olanzapine mean 13.8mg/day - mean age both groups 47.0 (SD = 9.3) Risperidone group (n = 19) - 8 men (42.1%) - 11 women (57.9%) - 8 dropouts (42.1%) - 0 lost to follow up Olanzapine group (n = 17) - 9 men (52.9%) - 8 women (47.1%) - 5 dropouts (29.4%) - 0 lost to follow up	Weight	Involved 2 centres in the USA 22 weeks duration Industry funded (Janssen)

Table 2.2 Results of Individual Studies

	Weight change - kg (SD)	Glucose Change - mmol/L (SD)	A1C Change - % (SD)	SBP Change - mmHg (SD)	DBP Change - mmHg (SD)	LDL Change - mmol/L	HDL Change - mmol/L (SD)	TC Change - mmol/L (SD)	TG Change - mmol/L (SD)
Ader 2008 Olanzapine Risperidone	 4.3 (6.8) 2.1 (6.0)	NR	NR	NR	NR	NR	NR	NR	NR
Alvarez 2006 Olanzapine Risperidone	 3.8 (6.1) 2.1 (6)	NR	NR	NR	NR	NR	NR	NR	NR
Atmaca 2003 Clozapine Olanzapine Quetiapine Risperidone	 6.52 (3.41) 8.92 (3.13) 4.41 (2.21) 0.54 (0.72)	NR	NR	NR	NR	NR	NR	NR	 0.41 (0.06) 0.35 (0.11) 0.13 (0.05) 0.04 (0.02)
Baptista 2007 Olanzapine Risperidone	 0.53 (0.86) 0.75 (0.98)	 -0.24 (0.7) 0.49 (0.61)	NR	NR	NR	NR	NR	NR	NR
Beasley 2003 Olanzapine Placebo	 0.16 (2.8) -1.97 (2.8)	NR	NR	NR	NR	NR	NR	NR	NR
Bitter 2004 Clozapine Olanzapine	 4.1 (5.6) 3.3 (5.3)	NR	NR	NR	NR	NR	NR	NR	NR
Breier 2005 Olanzapine Ziprasidone	 3.06 (6.9) -1.12 (4.7)	 0.28 (1.7) -0.01 (1.2)	NR	NR	NR	 0.02 (0.8) -0.27 (0.7)	 -0.06 (0.3) 0.02 (0.25)	 0.08 (0.95) -0.33 (0.8)	 0.39 (1.2) -0.24 (1.1)
Chan 2007 Aripiprazole Risperidone	 0.9 (2.2) 1.5 (2.5)	 0.23 (1.8) -0.15 (1.5)	NR	NR	NR	NR	NR	 -0.08 (1.4) 0.5 (0.7)	NR
Chan 2010 Olanzapine Risperidone	 1.61 (3.1) 1.17 (3.2)	NR	NR	NR	NR	NR	NR	NR	NR
Ciudad 2006 Olanzapine Risperidone	 3.8 (6.1) 2.1 (6.0)	NR	NR	NR	NR	NR	NR	NR	NR
Conley 2001 Olanzapine Risperidone	 3.3 (5.1) 1.5 (3.5)	NR	NR	NR	NR	NR	NR	NR	NR
Covell 2004 Clozapine FGA	 5.9 (8.5) 2.3 (6.7)	NR	NR	NR	NR	NR	NR	NR	NR
Czobor 2002 Clozapine Haloperidol Olanzapine Risperidone	 4.2 (4.7) 0.2 (0.2) 5.4 (4.6) 2.3 (2.8)	NR	NR	NR	NR	NR	NR	NR	NR
Davidson 2007 Paliperidone 3 Paliperidone 9 Paliperidone 15 Olanzapine Placebo	 0.6 (2.77) 1.5 (3.14) 1.9 (3.63) 2.2 (3.94) -0.8 (4.24)	 0 (1.59) 0.1 (1.22) 0 (0.87) 0 (1.24) 0 (1.59)	NR	NR	NR	 0 (0.71) 0 (0.81) -0.1 (0.75) 0.2 (0.67) -0.2 (0.74)	 0 (0.26) 0 (0.18) 0.1 (0.26) 0 (0.35) 0 (0.23)	 -0.1 (0.79) -0.1 (0.85) 0 (0.80) 0.3 (0.74) -0.2 (0.81)	 -0.2 (0.94) -0.1 (0.88) 0 (0.74) 0.3 (0.74) -0.2 (1.09)
Deberdt 2008 Olanzapine Quetiapine	 0.99 (5.82) -0.82 (5.3)	 -0.01 (1.5) -0.06 (1.1)	 0.07 (0.5) -0.03 (0.4)	NR	NR	 -0.14 (0.8) -0.07 (0.5)	 -0.03 (0.2) -0.02 (0.2)	 -0.2 (0.9) -0.11 (0.7)	 -0.11 (0.98) 0.07 (0.9)
Dossenbach 2004 Fluphenazine Olanzapine	 0.04 (3.21) 5.15 (6.41)	NR	NR	 -4.3 (15) 5.7 (17.0)	NR	NR	NR	NR	NR
Hatta 2009 Aripiprazole Olanzapine Quetiapine Risperidone	 -0.5 (2.8) 1.1 (3.8) 1.2 (3.2) -0.8 (2.5)	 0.23 (0.73) -0.18 (0.6) -0.29 (0.8) 0.07 (0.87)	NR	NR	NR	NR	NR	 0.01 (0.94) 0.22 (0.94) 0.22 (0.78) 0.05 (1.34)	 -0.04 (0.6) 0.19 (0.93) 0.05 (0.73) 0.23 (0.63)
Jeste 2003 Olanzapine Risperidone	 1.4 (4.1) 0.6 (2.2)	NR	NR	NR	NR	NR	NR	NR	NR
Kahn 2007 Quet XR 400 Quet XR 600	 1.09 (2.44) 1.80 (3.1)	 -0.04 (1.0)	 0.03 (0.26)	NR	NR	 0.07 (0.67) 0.22 (0.74)	 0.01 (0.23)	 0.17 (0.85) 0.25 (0.93)	 0.17 (0.92)

Quet XR 800 Quet IR 400 Placebo	1.54 (2.47) 1.4 (2.49) 0.48 (3.23)	0.09 (0.81) -0.08 (0.8) -0.08 (0.8) 0.02 (0.94)	-0.01 (0.3) 0.07 (0.3) -0.01 (0.3) -0.02 (0.3)			0.04 (0.76) 0.25 (0.66) -0.1 (0.66)	-0.02 (0.3) -0.01 (0.3) 0 (0.28) -0.01 (0.2)	0.17 (0.85) 0.36 (0.82) -0.15 (0.8)	0.15 (1.12) 0.31 (1.11) 0.32 (0.85) -0.11 (0.8)
Kahn 2008 Haloperidol Olanzapine Quetiapine Ziprasidone	7.3 (8.1) 13.9 (1.7) 10.5 (1.8) 4.8 (1.9)	0.4 (2.03) 0.5 (1.02) 0.5 (1.02) 0.2 (1.81)	NR	NR	NR	0.5 (2.03) 0.7 (1.02) 0.7 (1.02) 0.3 (1.02)	-0.1 (1.01) -0.1 (0.1) -0.1 (1.01) -0.1 (0.1)	0.5 (3.04) 0.8 (1.02) 0.6 (1.02) 0.4 (1.81)	0.2 (1.0) 0.3 (1.0) 0.3 (1.0) 0.1 (1.81)
Kane 2007 Paliperidone 6 Paliperidone 9 Paliperidone 12 Olanzapine Placebo	0.2 (2.4) 0.6 (2.7) 0.9 (3.3) 1.3 (2.8) -0.7 (2.4)	0 (0.96) 0.1 (1.01) 0.1 (0.93) 0 (0.89) 0.1 (1.0)	NR	NR	NR	0 (0.7) -0.2 (0.8) -0.1 (0.7) 0.1 (0.7) 0 (0.7)	0 (0.2) 0 (0.2) 0.1 (0.2) 0 (0.2) 0.1 (0.2)	-0.1 (0.8) -0.2 (0.9) -0.2 (0.8) 0.2 (0.8) -0.1 (0.8)	-0.2 (0.9) -0.1 (0.7) -0.3 (0.8) 0.1 (1.2) -0.3 (0.7)
Kasper 2006 Aripiprazole Haloperidol	1.05 (5.87) 0.39 (5.83)	NR	NR	NR	NR	NR	NR	NR	NR
Keefe 2006 Haloperidol Olanzapine Risperidone	-2.34 (4.8) 3.0 (7.87) 0.81 (6.26)	0.03 (3.18) 0.07 (1.90) 0.32 (2.38)	NR	NR	NR	NR	NR	-0.1 (0.63) 0.09 (0.7) -0.06 (0.7)	-0.25 (1.3) -0.03 (2.0) -0.38 (2.5)
Kerwin 2007 Aripiprazole SOC	-1.3 (6.42) 1.4 (5.01)	0.01 (0.08) 0.18 (0.08)	NR	NR	NR	-0.35 (0.6) -0.15 (0.6)	0.05 (0.18) 0.01 (0.18)	-0.53 (0.3) -0.2 (0.29)	-0.52 (1.0) -0.15 (1.0)
Kinon 2006 Olanzapine Quetiapine	1.03 (5.78) 0.39 (4.74)	NR	NR	NR	NR	NR	NR	NR	NR
Kinon 2008 Aripiprazole Olanzapine	NR	0.32 (1.22) 0.57 (1.14)	NR	NR	NR	NR	NR	NR	0.09 (0.82) 0.49 (1.09)
Krakowski 2009 Clozapine Haloperidol Olanzapine	2.36 (7.1) -2.0 (4.7) 3.59 (4.2)	1.09 (3.3) -0.04 (0.4) -0.01 (1.0)	NR	NR	NR	NR	NR	0.29 (0.99) -0.17 (0.6) 0.03 (0.9)	0.64 (1.89) 0.08 (0.74) 0.12 (0.63)
Lieberman 2003 Haloperidol Olanzapine	2.64 (4.54) 7.30 (6.13)	-0.19 (1.3) 0.27 (1.9)	NR	NR	NR	NR	NR	0.25 (0.87) 0.45 (0.71)	NR
Lieberman 2005 Olanzapine Perphenazine Quetiapine Risperidone Ziprasidone	4.3 (7.5) -0.91 (8.1) 0.5 (7.5) 0.4 (7.5) -0.73 (6.8)	0.83 (2.85) 0.29 (1.8) 0.38 (2.6) 0.37 (2.1) 0.13 (2.95)	0.41 (1.65) 0.1 (0.97) 0.05 (0.92) 0.08 (0.74) -0.1 (1.9)	NR	NR	NR	NR	0.25 (1.0) 0.01 (0.96) 0.14 (1.0) -0.05 (0.9) -0.24 (1.8)	0.48 (1.74) 0.09 (2.1) 0.22 (2.2) -0.03 (1.3) -0.2 (1.44)
Lindenmayer 2003 Clozapine Haloperidol Olanzapine Risperidone	NR	0.24 (0.95) 0.59 (1.4) 0.79 (1.42) 0.15 (0.68)	NR	NR	NR	NR	NR	0.42 (1.02) -0.11 (1.4) 0.52 (0.69) 0.24 (0.95)	NR
Marder 2007 Olanzapine Paliperidone 6 Paliperidone 12 Placebo	2.7 (4.4) 1.0 (3.9) 2.0 (3.5) 0.4 (3.6)	0.5 (1.7) 0 (1.3) 0.4 (1.2) 0.1 (1.5)	NR	NR	NR	0.1 (0.7) 0 (0.8) 0 (0.7) -0.1 (0.7)	0 (0.2) 0 (0.2) 0 (0.2) 0 (0.2)	0.2 (0.9) 0 (0.9) -0.1 (0.8) -0.2 (0.8)	0.1 (1.1) -0.1 (0.9) -0.1 (0.8) -0.2 (1.0)
McEvoy 2006 Clozapine Olanzapine Quetiapine Risperidone	0.6 (8.9) 2.8 (14.5) 0.5 (9.0) 1.8 (5.1)	0.73 (1.87) 1.31 (3.68) -1.29 (3.6) 1.79 (7.4)	0.1 (0.91) 0.13 (0.57) -0.1 (0.58) 0.1 (0.48)	NR	NR	NR	NR	0.19 (0.83) 0.01 (0.89) -0.34 (0.7) -0.23 (0.8)	0.59 (1.64) -0.12 (1.65) -0.06 (1.47) 0.23 (1.67)

McEvoy 2007 Olanzapine Quetiapine Risperidone	11.1 (9.2) 5.68 (9.1) 6.6 (9.1)	0.48 (1.02) 0.34 (1.07) 0.27 (1.09)	NR	8.5 (14.1) 7.5 (14.0) 2.7 (14.6)	4.8 (9.5) 4.1 (9.5) 1.8 (9.9)		-0.17 (0.3) -0.09 (0.3) -0.07 (0.3)	0.41 (1.28) 0.65 (1.34) 0.29 (1.39)	0.75 (1.68) 0.77 (1.75) 0.22 (1.81)
Naber 2005 Clozapine Olanzapine	5.0 (6.8) 3.5 (5.9)	0.6 0 SDs not reported	NR	NR	NR	NR	NR	NR	NR
Newcomer 2008 Aripiprazole Olanzapine	-1.8 1.41 SDs not reported	0.09 (0.1) 0.28 (0.1)	NR	NR	NR	-0.33 (0.1) -0.14 (0.1)	0.02 (0.02) -0.06 (0)	-0.48 (0.1) -0.17 (0.1)	-0.30 0.12 SDs not reported
Potkin 2006 Quetiapine Risperidone Placebo	1.6 (2.8) 1.6 (2.3) 0.5 (2.5)	NR	NR	NR	NR	NR	NR	NR	NR
Ritchie 2003 Olanzapine Risperidone	2.8 (1.8) 2.1 (1.4)	NR	NR	NR	NR	NR	NR	NR	NR
Sacchetti 2009 Clozapine Ziprasidone	0.8 (4.6) -2.6 (4.7)	0.33 0 SDs not reported	NR	NR	NR	0.10 -0.16 SDs not reported	0.05 0.21 SDs not reported	0.05 -0.13 SDs not reported	0.11 -0.17 SDs not reported
Schooler 2005 Haloperidol Risperidone	6.5 (8.86) 7.5 (9.29)	NR	NR	NR	NR	NR	NR	NR	NR
Smith 2009 Olanzapine Risperidone	NR	0.41 (0.83) 0.13 (0.82)	-0.02 (0.5) 0.14 (0.5)	NR	NR	NR	NR	NR	NR
Stroup 2006 Olanzapine Quetapine Risperidone Ziprasidone	3.73 (2.83) 0.18 (2.66) -0.64 (1.85) -2.16 (2.7)	0.82 (2.3) -0.01 (2.3) 0.47 (2.44) -0.06 (2.5)	0.52 (3.11) 0.23 (2.73) 0.10 (1.63) 0.09 (0.70)	NR	NR	NR	NR	0.46 (0.89) 0.12 (0.96) -0.07 (1.0) -0.32 (1.1)	0.79 (2.31) 0.18 (1.85) -0.31 (1.6) -0.33 (1.4)
Stroup 2007 Olanzapine Quetiapine Risperidone	5.4 (6.0) 0.91 (5.6) 1.3 (2.8)	1.43 (3.3) 0.18 (1.1) -0.02 (1.5)	1.34 (2.5) 0.06 (0.74) -0.09 (0.6)	NR	NR	NR	NR	0.54 (0.84) 0.03 (0.78) 0.11 (0.84)	1.21 (3.07) 0.29 (1.18) 0.08 (0.77)
Tollefson 1997 Haloperidol Olanzapine	0.02 (2.79) 1.88 (3.54)	NR	NR	NR	NR	NR	NR	NR	NR
Tollefson 2001 Clozapine Olanzapine	2.3 (2.9) 1.8 (5.0)	NR	NR	NR	NR	NR	NR	NR	NR
Tran 1997 Olanzapine Risperidone	4.1 (5.9) 2.3 (4.8)	NR	NR	NR	NR	NR	NR	NR	NR
Tzimos 2008 Paliperidone Placebo	0 (2.1) 0 (2.3)	NR	NR	NR	NR	NR	NR	NR	NR
Van Bruggen 2003 Olanzapine Risperidone	3.6 (3.8) 4.5 (5.2)	NR	NR	NR	NR	NR	NR	NR	NR
Voruganti 2007 Olanzapine Quetiapine	7.24 (2.43) 2.84 (1.72)	NR	NR	NR	NR	NR	NR	NR	NR
Wang 2006 Olanzapine Risperidone	3.5 (4.4) 1.5 (2.8)	NR	NR	NR	NR	NR	NR	NR	NR

NR = not reported; FGA = first-generation antipsychotic; SD = standard deviation; SOC = standard of care

Figure 2.1. Flow Diagram of Study Selection

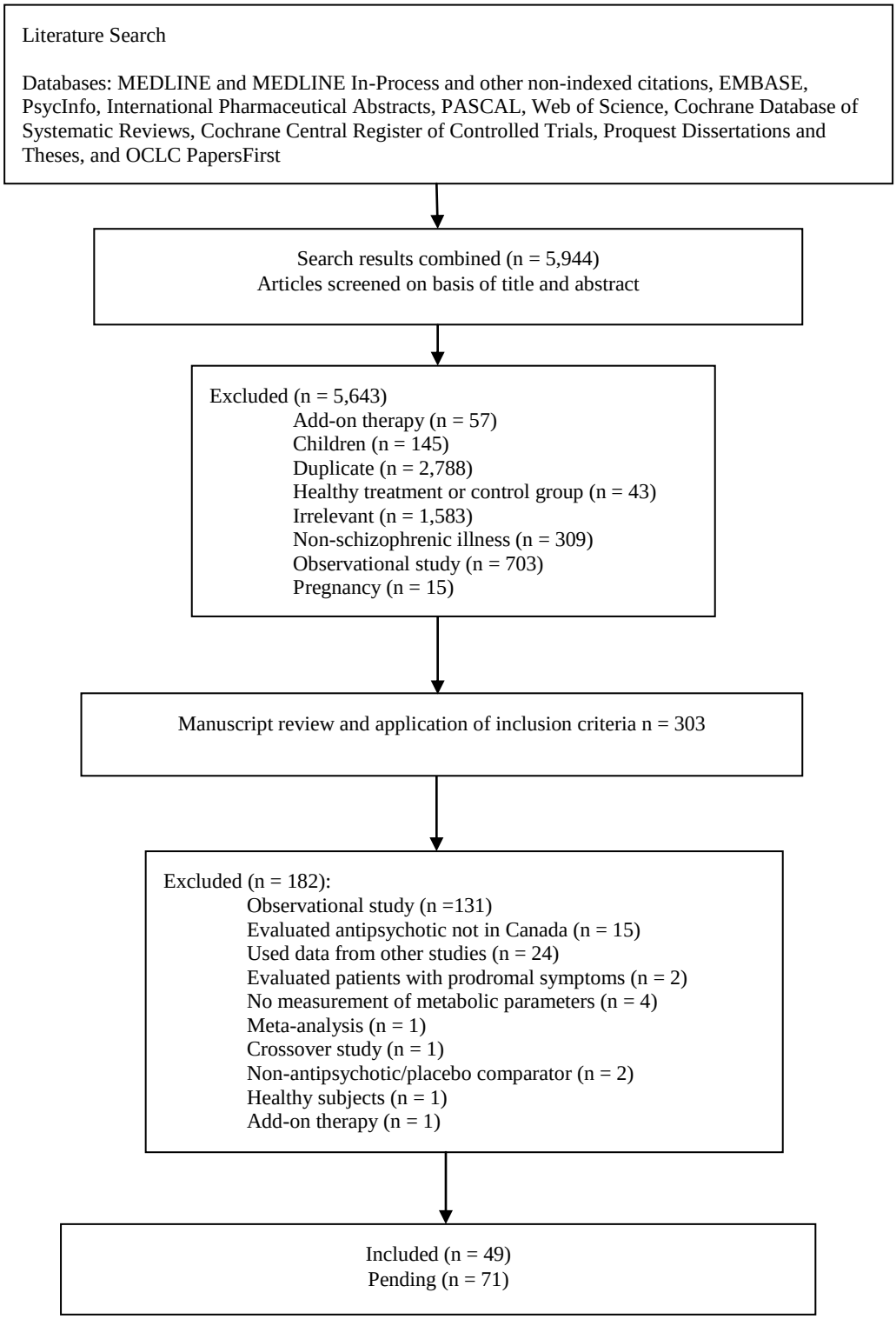


Figure 2.2 Change in Blood Glucose: Atypical Antipsychotics vs. Placebo

Study or Subgroup	Atypical Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Davidson 2007	0.03	1.23	121	0	1.59	120	15.1%	0.03 [-0.33, 0.39]
Kahn 2007	-0.03	0.83	118	0.02	0.94	118	38.0%	-0.05 [-0.28, 0.18]
Kane 2007 Schizo Research	0.05	0.95	126	0.1	1	126	33.6%	-0.05 [-0.29, 0.19]
Marder 2007	0.3	1.4	111	0.1	1.5	110	13.3%	0.20 [-0.18, 0.58]
Total (95% CI)			**476**			**474**	**100.0%**	**-0.00 [-0.14, 0.13]**

Heterogeneity: Tau² = 0.00; Chi² = 1.43, df = 3 (P = 0.70); I² = 0%
Test for overall effect: Z = 0.07 (P = 0.95)

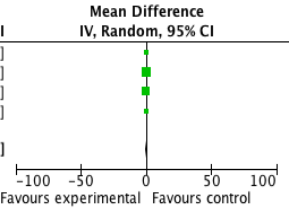


Figure 2.3 Change in Triglycerides: Atypical Antipsychotics vs. Placebo

Study or Subgroup	Atypical Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Davidson 2007	0	0.83	121	-0.2	1.09	120	21.8%	0.20 [-0.04, 0.44]
Kahn 2007	0.24	1	118	-0.11	0.78	118	25.0%	0.35 [0.12, 0.58]
Kane 2007 Schizo Research	-0.125	0.9	126	-0.3	0.7	126	33.0%	0.17 [-0.02, 0.37]
Marder 2007	-0.033	0.93	111	-0.2	1	110	20.2%	0.17 [-0.09, 0.42]
Total (95% CI)			**476**			**474**	**100.0%**	**0.22 [0.11, 0.34]**

Heterogeneity: Tau² = 0.00; Chi² = 1.63, df = 3 (P = 0.65); I² = 0%
Test for overall effect: Z = 3.81 (P = 0.0001)

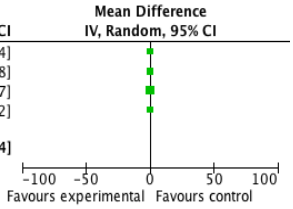


Figure 2.4 Change in Blood Glucose: Atypical Antipsychotics vs. Typical Antipsychotics

Study or Subgroup	Atypical Mean	SD	Total	Typical Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Kahn 2008	0.4	1.31	97	0.4	2.03	103	18.8%	0.00 [-0.47, 0.47]
Keefe 2006 Schizo Researc	0.32	2.38	159	0.033	3.18	97	7.8%	0.29 [-0.45, 1.02]
Krakowski 2009	0.54	2.16	33	-0.044	0.39	28	7.4%	0.58 [-0.17, 1.33]
Lieberman 2003 Am J Psych	0.27	1.9	131	-0.19	1.27	132	27.3%	0.46 [0.07, 0.85]
Lieberman 2005	0.43	2.69	300	0.29	1.8	261	29.7%	0.14 [-0.23, 0.51]
Lindenmayer 2003	0.396	1.01	25	0.59	1.4	25	9.1%	-0.19 [-0.87, 0.48]
Total (95% CI)			**745**			**646**	**100.0%**	**0.21 [0.01, 0.42]**

Heterogeneity: Tau² = 0.00; Chi² = 4.83, df = 5 (P = 0.44); I² = 0%
Test for overall effect: Z = 2.06 (P = 0.04)

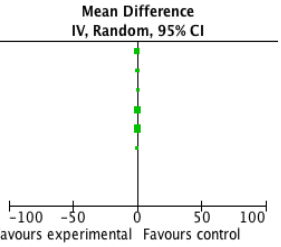


Figure 2.5 Change in Total Cholesterol: Atypical Antipsychotics vs. Typical Antipsychotics

Study or Subgroup	Atypical Mean	SD	Total	Typical Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Kahn 2008	0.6	1.31	97	0.5	3.04	103	2.4%	0.10 [-0.54, 0.74]
Keefe 2006 Schizo Researc	0	0.73	159	-0.096	0.63	97	34.0%	0.10 [-0.07, 0.27]
Krakowski 2009	0.13	0.94	33	-0.17	0.64	28	6.1%	0.30 [-0.10, 0.70]
Lieberman 2003 Am J Psych	0.45	0.71	131	0.25	0.87	132	26.4%	0.20 [0.01, 0.39]
Lieberman 2005	0.023	1.26	300	0.013	0.96	261	28.7%	0.01 [-0.17, 0.19]
Lindenmayer 2003	0.39	0.89	25	-0.11	1.4	25	2.3%	0.50 [-0.15, 1.15]
Total (95% CI)			**745**			**646**	**100.0%**	**0.12 [0.02, 0.22]**

Heterogeneity: Tau² = 0.00; Chi² = 4.21, df = 5 (P = 0.52); I² = 0%
Test for overall effect: Z = 2.40 (P = 0.02)

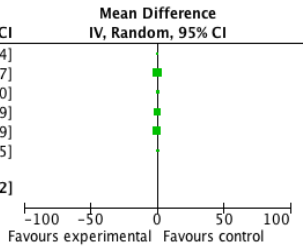


Figure 2.6 Change in Triglycerides: Atypical Antipsychotics vs. Typical Antipsychotics

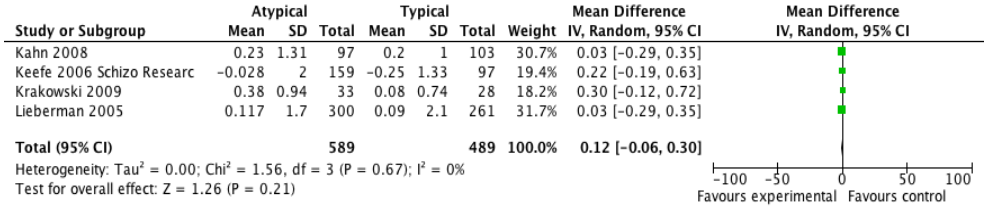


Figure 2.7 Change in LDL: Aripiprazole vs. Other Atypical Antipsychotics

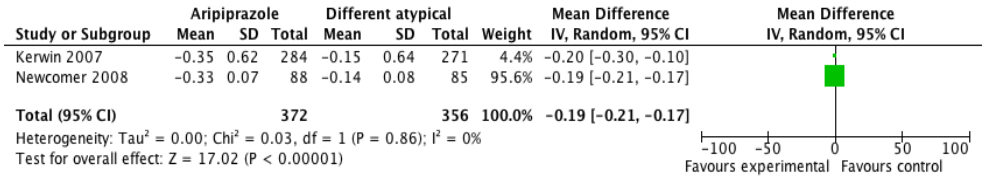


Figure 2.8 Change in Total Cholesterol: Aripiprazole vs. Other Atypical Antipsychotics

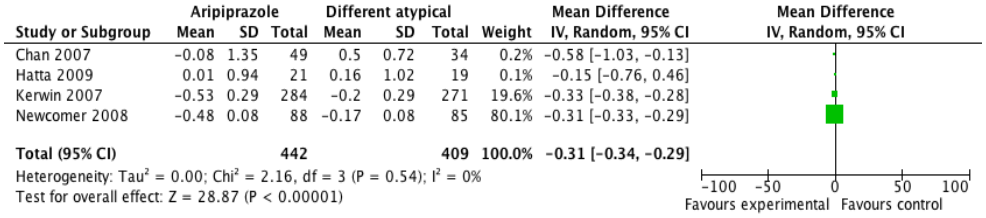


Figure 2.9 Change in Triglycerides: Aripiprazole vs. Other Atypical Antipsychotics

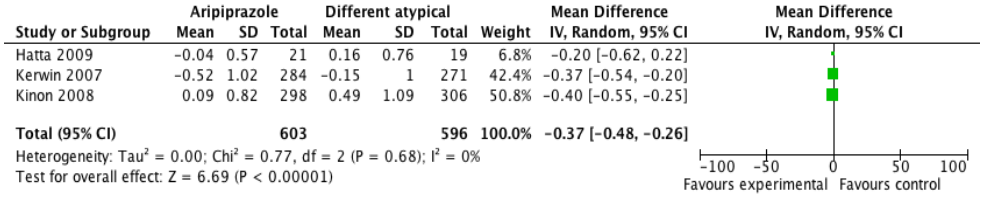


Figure 2.10 Change in Weight: Clozapine vs. Typical Antipsychotics

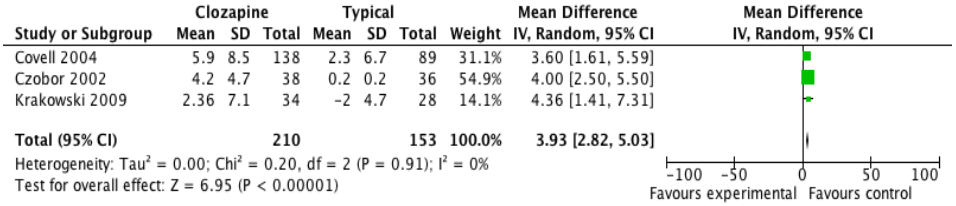


Figure 2.11 Change in Weight: Clozapine vs. Olanzapine

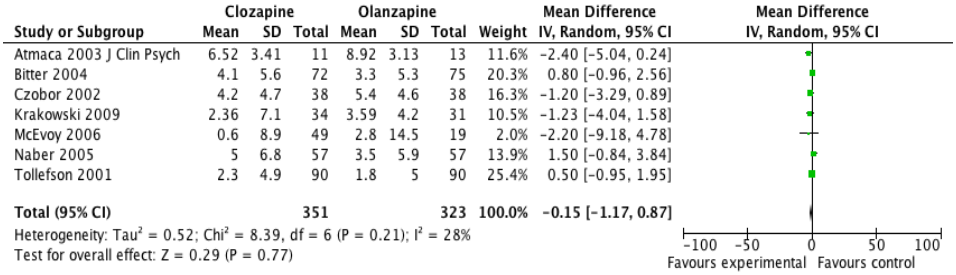


Figure 2.12 Change in Total Cholesterol: Clozapine vs. Olanzapine

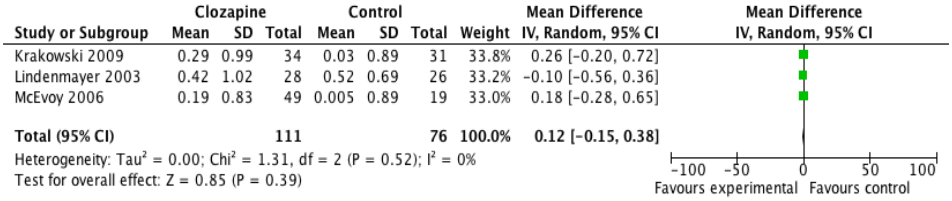


Figure 2.13 Change in Triglycerides: Clozapine vs. Olanzapine

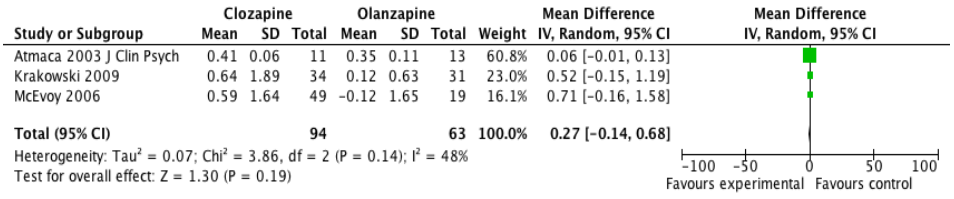


Figure 2.14 Change in Weight: Olanzapine vs. Placebo

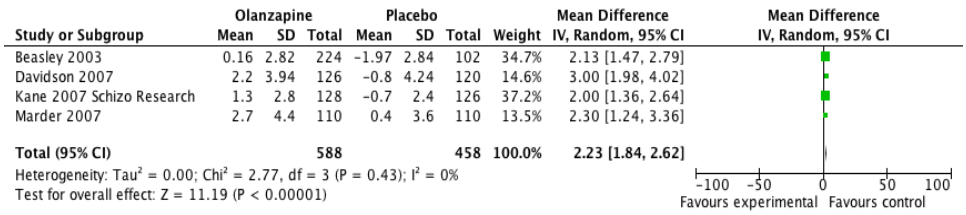


Figure 2.15 Change in Blood Glucose: Olanzapine vs. Typical Antipsychotics

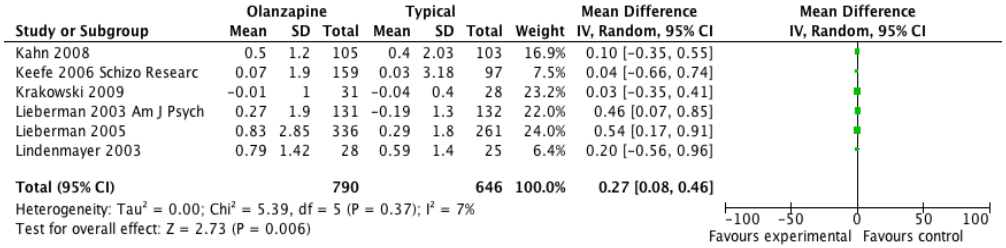


Figure 2.16 Change in Total Cholesterol: Olanzapine vs. Typical Antipsychotics

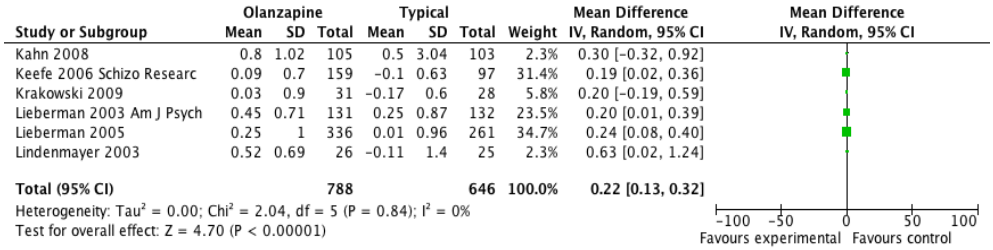


Figure 2.17 Change in Triglycerides: Olanzapine vs. Typical Antipsychotics

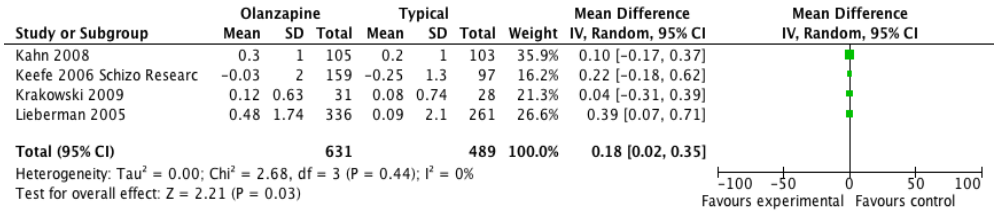


Figure 2.18 Change in Weight: Quetiapine vs. Placebo

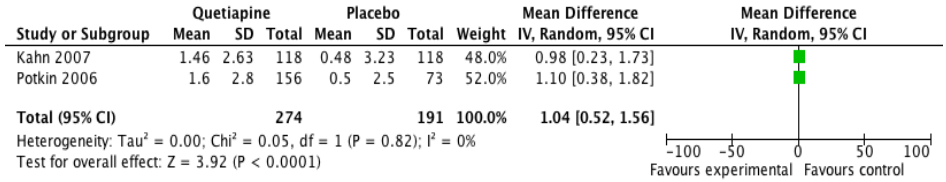


Figure 2.19 Change in Blood Glucose: Quetiapine vs. Typical Antipsychotics

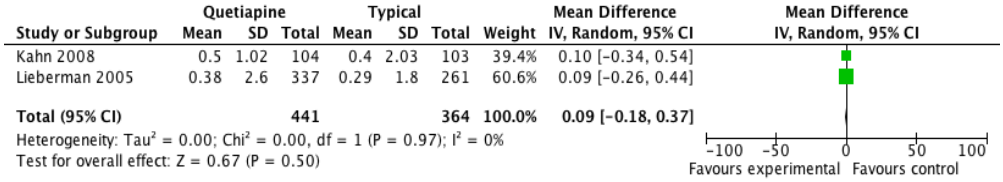


Figure 2.20 Change in Total Cholesterol: Quetiapine vs. Typical Antipsychotics

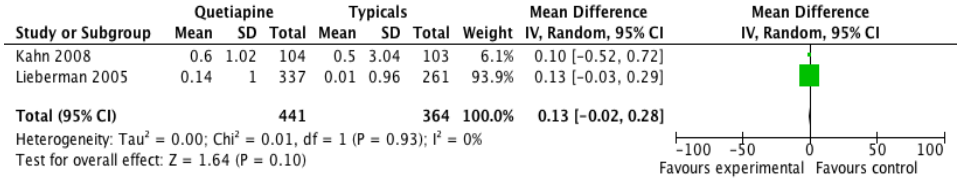


Figure 2.21 Change in Triglycerides: Quetiapine vs. Typical Antipsychotics

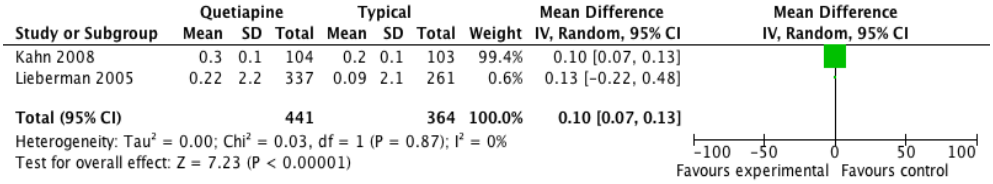


Figure 2.22 Change in Weight: Paliperidone vs. Olanzapine

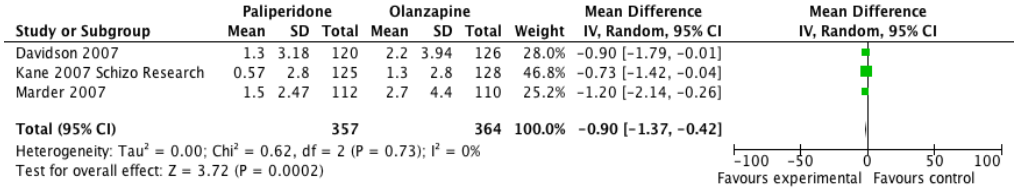


Figure 2.23 Change in Total Cholesterol: Paliperidone vs. Olanzapine

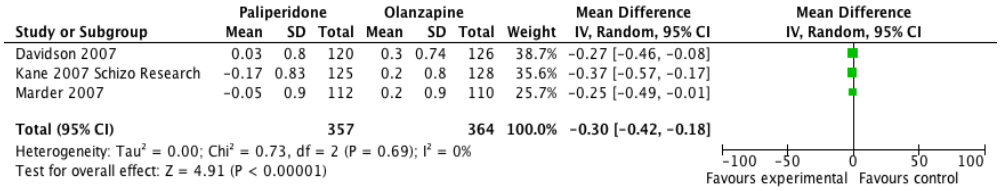


Figure 2.24 Change in Weight: Risperidone vs. Typical Antipsychotics

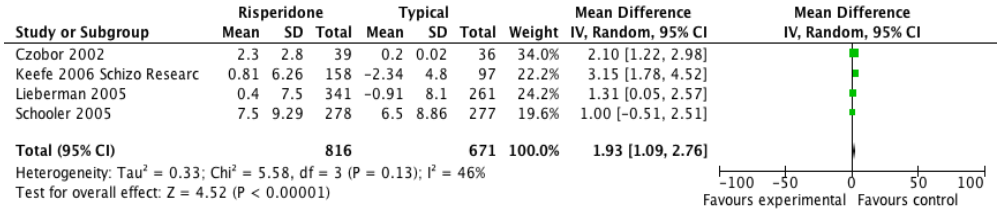


Figure 2.25 Change in Blood Glucose: Risperidone vs. Typical Antipsychotics

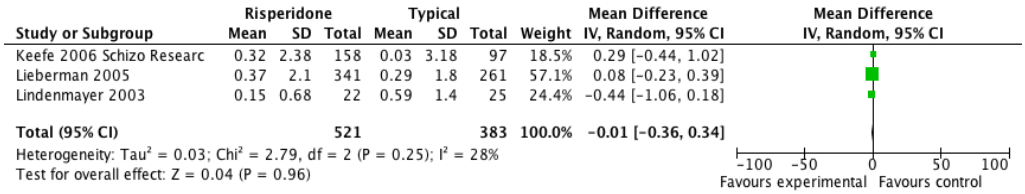


Figure 2.26 Change in Total Cholesterol: Risperidone vs. Typical Antipsychotics

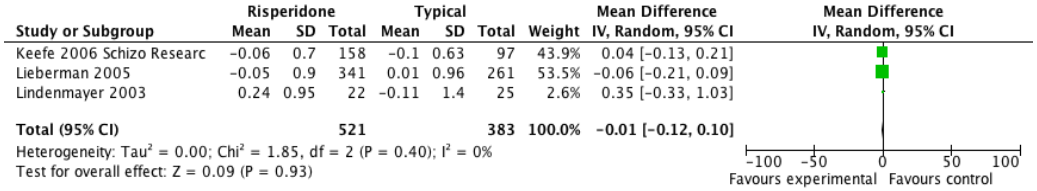
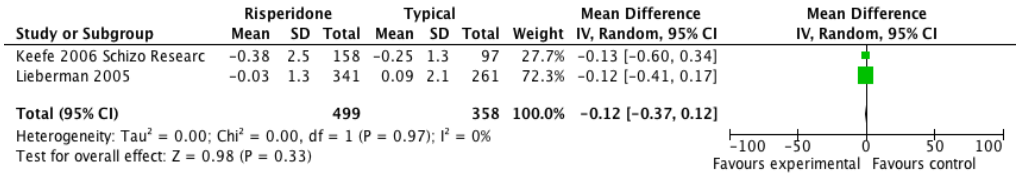


Figure 2.27 Change in Triglycerides: Risperidone vs. Typical Antipsychotics



CHAPTER 3

Prevalence of Cardiovascular Risk Factors and Disease in People with Schizophrenia: A Population-Based Study

Bresee LC, Majumdar SR, Patten SB, Johnson JA. Schizophrenia Research 2010;117;75-82

3.1 Introduction

Schizophrenia is a debilitating mental illness with a lifetime prevalence of 1%, and it is characterized by the development of symptoms that are both positive (i.e., paranoid delusions) and negative (i.e., anhedonia or social withdrawal) (1-3). In addition, schizophrenia is considered a risk factor for many chronic medical conditions such as diabetes (4,5). Observational studies have found the prevalence of diabetes to be 2 to 3 times higher in individuals with schizophrenia compared to the general population (4,5). Baseline data from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Schizophrenia Trial demonstrated a 41% prevalence of metabolic syndrome in trial participants (6). In comparison, NHANES III data estimated the age-adjusted prevalence of metabolic syndrome to be approximately 24% in the US population (7).

Morbidity and mortality due to cardiovascular disease (CV-D) also appears to be greater in people with schizophrenia, with a more than doubling of the risk of CV-related mortality (8). Prevalence of heart failure (HF), arrhythmia, and stroke are also higher in people with schizophrenia than control populations (8). Despite increased cardiovascular morbidity and mortality, people with severe mental

illness are less likely to receive medically necessary procedures including coronary artery bypass grafting (CABG) or percutaneous coronary interventions (PCI) compared to the non-mentally ill population (9). In addition, people with schizophrenia tend to have low rates of diagnosis and treatment for dyslipidemia (88% untreated), diabetes (30% untreated), and hypertension (62% untreated) in people with schizophrenia (10).

Although existing literature has provided some insight into the burden of cardiovascular risk factors (CV-RF) and CV-D in people with schizophrenia, there are several important limitations to these data. Most studies have not been population-based, instead evaluating highly selected subgroups of people with schizophrenia, such as randomized trial participants or hospital inpatients, limiting generalizability (11,12). Other studies did not use a non-schizophrenic concurrent comparison group, and as such, are unable to draw conclusions regarding whether prevalence of CV-D and treatment of CV-RF is truly greater in people with schizophrenia (10,11). Additionally, some population-based studies evaluating CV-RF and CV-D in people with and without schizophrenia are from periods prior to the widespread use of atypical antipsychotic agents (5,8), agents that themselves might increase the risk of CV-RF and CV-D as a result of weight gain and development of type 2 diabetes and dyslipidemia (13-15). Lastly, population-based studies conducted during the time frame where atypical antipsychotic agents were first-line therapy suffer from limitations. For example, a study using data from the Canadian province of Ontario used emergency departments and

hospitalizations only (16). Similarly, studies from the United States and Denmark used hospitalization data only, limiting the generalizability and likely excluding those with less severe schizophrenia (17,18).

We therefore undertook a study of the prevalence of CV-RF and CV-D in people with schizophrenia compared to the non-schizophrenic population in a large, population-based cohort in the era of atypical antipsychotic drug use. Our objectives were to evaluate and compare prevalence of CV-RF and CV-D in people with and without schizophrenia, while examining the potential impact of socio-demographic variables on this relationship.

3.2 Methods

3.2.1 Study Design

A period prevalence design was used. Data from the administrative databases of Alberta Health and Wellness from January 1, 1995 to December 31, 2006 were used to establish the study cohort. Individuals aged 20 years and older were included in this study.

3.2.2 Databases of Alberta Health and Wellness

Alberta is a Canadian province with a population of approximately 3.3 million people (19). Medically necessary access to physicians and hospitals within Alberta is universally provided as a result of the Canada Health Act, meaning that access to physicians and hospitals is not refused based on health insurance status,

although a modest needs-based health insurance premium is paid by individuals or families in Alberta. Health insurance premiums were partially subsidized for individuals of First Nations status, those qualifying for social assistance, and individuals receiving supports for independence. The need for, and receipt of, health care subsidies represents a robust measure of lower socio-economic status within the Canadian health care system.

Alberta Health and Wellness databases include information on all individuals within the province of Alberta eligible for Alberta health care coverage. The Alberta Health and Wellness databases utilized in the study included the Discharge Abstract Database, Alberta Physician Claims Data, and the Ambulatory Care Classification System. These databases provide de-identified information on demographics, hospitalizations, emergency room visits, physician visits, diagnostic and procedural codes, and mortality (20,21). Diagnostic and procedural codes were based on International Classification of Disease, 9th revision and 10th Canadian revision codes (ICD-9-CM and ICD-10-CA).

3.2.3 Identification of Schizophrenia

Individuals with schizophrenia were identified based on physician claims and hospital discharge data (ICD-9-CM 295.X or ICD-10-CA F20.X). Rawson and colleagues previously validated the use of ICD-9 codes from a neighboring Canadian jurisdiction, and found a 93.9% concordance between hospital discharge data and a 61.8% concordance between the physician service claims and

hospitalization in terms of diagnosis of schizophrenia (ICD-9-CM code 295) (22). Individuals with prevalent schizophrenia were identified from January 1, 1995 until December 31, 2006. Persons who did not meet the criteria for schizophrenia formed the non-schizophrenic cohort, and were used as the comparison group for the analysis.

3.2.4 Identification of Cardiovascular Risk Factors (CV-RF)

CV-RF were identified through ICD-9-CM and ICD-10-CA codes. Identification of diabetes was based on the established case definition of the National Diabetes Surveillance System (NDSS), having two or more physician service claims for diabetes within a two year period, or one hospitalization with a diabetes code as the primary, secondary, or other diagnosis (20,23,24). Hypertension was identified based on the validated algorithm created by Tu and colleagues, which utilized two physician billing codes for hypertension over a three year period (25). Prevalence of dyslipidemia was based upon previously validated criteria (8,20). Prevalence of CV-RF was assessed from January 1, 1995 to December 31, 2006. **Appendix 3A** provides detailed information for identification of CV-RF.

3.2.5 Identification of Cardiovascular Disease (CV-D)

Identification of acute coronary syndrome (ACS), ischemic heart disease including past myocardial infarction (IHD), arrhythmia, heart failure (HF), and stroke were based upon previously validated criteria (8,20). CV-D was defined as a diagnosis of any of these conditions. Prevalence of ACS, IHD, arrhythmia, HF,

stroke, and CV-D was assessed from January 1, 1995 to December 31, 2006. **Appendix 3A** provides detailed information for identification of CV-D.

3.2.6 Statistical Analysis

Each cohort was described in terms of age, sex, socio-economic status (SES) (based on receipt of health care subsidies), and number of general practitioner (GP) visits in the year of entry into the cohort. The number of GP visits in the year of identification was used to control for the possibility of surveillance bias, since greater exposure to primary care physicians might increase the likelihood of having a CV-RF or CV-D identified (26). Individuals with multiple claims for CV-RF or CV-D were only counted once in each respective analysis.

Multivariate logistic regression was used to calculate odds ratios (OR) and 95% confidence intervals (CI) to compare the prevalence of CV-RF and CV-D in the schizophrenic and non-schizophrenic cohorts while adjusting for potential confounding variables including age, sex, socio-economic status, and GP visits. Variables were assessed for multicollinearity and clinically relevant two-way interactions with schizophrenia (i.e., age, sex, health care premium subsidy status, and each year in the study cohort) were considered. Statistically significant interaction terms ($p<0.1$) were evaluated using stratified analyses. In the presence of significant interaction, multivariable analyses were performed within the stratified analyses only. All analyses were completed using SPSS Version 15.0 (SPSS Inc., Chicago, Illinois).

3.2.7 Ethics Approval

Permission to conduct this study was granted from the University of Alberta Health Research Ethics Board, in Edmonton, Alberta, Canada.

3.3 Results

Individuals with schizophrenia (n = 28,755, 1%) were older (mean age: 47.6 years vs. 45.3 years) and more likely to have lower SES (59% received health care subsidies vs. 21%) than non-schizophrenic individuals (n = 2,281,636) (**Table 3.1**). People with schizophrenia were also significantly more likely to have visited a GP seven or more times in their year of cohort identification (45% vs. 19%) (**Table 3.1**). We found no significant change in prevalence of CV-RF or CV-D over time (data not presented), and therefore time was not included in the analysis. In part due to the large sample size, a number of statistically significant interaction terms were present. As a result, we present only unadjusted aggregate data (**Table 3.2**) and stratified multivariable analyses (**Table 3.3**).

3.3.1 Cardiovascular Risk Factors

In terms of CV-RF, diabetes was almost twice as common in those with schizophrenia than those without (10% vs. 6%) while other risk factors were similarly distributed (**Table 3.2**). It also appeared that patients with schizophrenia were more likely to have multiple risk factors compared with the non-schizophrenic controls (**Table 3.2**). **Figure 3.1** demonstrates the differing prevalence of diabetes in men and women with and without schizophrenia

according to 10-year age bands. Women with schizophrenia had a higher prevalence of diabetes compared to men without schizophrenia across all age groups.

3.3.2 Prevalence of Established Cardiovascular Disease

Prevalence of ACS, IHD, arrhythmia, HF, and stroke were each greater in those with schizophrenia than those without (**Table 3.2**). Of note, the prevalence (collectively) of all CV-D was far greater in the schizophrenic cohort (27% vs. 17%, OR: 1.76; 95% CI: 1.72 – 1.81) (**Table 3.2**). **Figure 3.2** illustrates the prevalence of CV-D in males and females with and without schizophrenia according to 10-year age bands. Similar to the relationship with diabetes, men with schizophrenia had the highest prevalence of CV-D in the older age groups, and women with schizophrenia had a higher prevalence of CV-D compared to men without schizophrenia, and this association was consistent across all age groups.

3.3.3 Potential Role of Age, Sex, and Socioeconomic Status

Age and sex were found to be significant effect modifiers of the relationship between diabetes and CV-D and schizophrenia. Results of the stratified analyses are presented in **Table 3.3**.

Presence of diabetes was significantly greater in women with schizophrenia across all age groups. The largest discrepancy in women with and without

schizophrenia was in the 20 – 29 year old age group, although the absolute difference in prevalence of diabetes was small (2.4% vs. 0.8%, OR: 2.49; 1.78 – 3.49). The relationship between diabetes and schizophrenia, while still statistically significant, grew weaker in the older age groups (women aged 60 and older OR: 1.20; 1.11 – 1.31). Only men with schizophrenia aged 30 to 49 were significantly more likely to have prevalent diabetes compared with their non-schizophrenic counterparts (men 30 – 39 years OR: 1.57; 1.30 – 1.91, 40 – 49 years OR: 1.19; 1.05 – 1.36). The prevalence of diabetes in women with schizophrenia was greater than the prevalence of diabetes for men without schizophrenia, and this was consistent across all age groups (**Table 3.3**).

CV-D was consistently more prevalent in people with schizophrenia, but the strength of the association decreased with increasing age for both males and females (**Table 3.3**). Males and females aged 20 – 29 with schizophrenia had the largest discrepancy in prevalence of CV-D compared to their non-schizophrenic counterparts (men 7.1% vs. 2.7%, OR: 2.17; 1.86 – 2.53; women 8.7% vs. 3.5%, OR: 2.29; 1.91 – 2.76). Similar to the relationship with diabetes, women with schizophrenia had a higher prevalence of CV-D compared to men without schizophrenia (**Table 3.3**). Complete stratified analyses for other CV-RF and CV-D variables are presented in **Appendix 3B**.

3.4 Discussion

In this large population-based study, individuals with schizophrenia were found to have a greater prevalence of diabetes and established cardiovascular disease than people without schizophrenia. These findings seem to suggest a 'metabolic aging' associated with the diagnosis of schizophrenia, such that those with schizophrenia develop CV-RF and CV-D at much younger ages than those without schizophrenia. We also found that women with schizophrenia always had a higher prevalence of diabetes and CV-D compared to men without schizophrenia, and that this association was consistent across all age groups. This susceptibility among women suggests that a diagnosis of schizophrenia negates the protective effect of female sex on developing CV-D (27).

Our results confirm the results of previous publications evaluating the relationship between CV-RF, CV-D and schizophrenia (5,8,11,12,16-18), while providing more detailed information on the effect of age and sex on this relationship. Recent publications from Canada (16), the United States (18), and Denmark (17) have demonstrated an increased incidence and prevalence of cardiovascular morbidity and mortality in the era of first-line atypical antipsychotic therapy, but were only able to look at hospitalization or emergency department visits. In addition to hospitalization and emergency department data, we were able to utilize physician visit data to evaluate our study objectives, which likely provides insight into the relationship between CV-RF and schizophrenia in those with less severe

schizophrenia who are not admitted to hospital. As a result, we believe our results to be more generalizable to the entire schizophrenic population.

The prevalence of CHF, stroke, and CV-D in aggregate was significantly higher in people with schizophrenia. This may be due to a number of factors. Although individuals with schizophrenia visited a GP more frequently than their non-schizophrenic counterparts, evidence suggests that schizophrenic individuals are not being adequately screened for risk factors like dyslipidemia and hypertension (28-30). Alternatively, differences in lifestyle factors such as smoking status, body mass index, diet, and exercise may be contributing to the increased prevalence of CV-D in people with schizophrenia. Smoking is significantly more common in people with schizophrenia, and active smoking is associated with both an increased risk of diabetes and CV-D in general (31). Likewise, poor diet and physical inactivity are common in those with schizophrenia and are also risk factors for CV-D (32,33). Finally, a number of therapies used to treat schizophrenia, such as the atypical antipsychotic agents, are associated with weight gain, dyslipidemia, and type 2 diabetes, which all increase risk of CV-D (13-15).

Strengths of this study include the population-based design, the recency of the data, the use of physician visit, emergency department, and hospitalization data, and use of a non-schizophrenic comparison group. As with most studies which utilize administrative data, our study is not without limitations. First, given we

utilized physician billing codes, ambulatory care data, and hospitalization discharge information to identify CV-RF and CV-D, the potential for misclassification of illness exists. As a result, the potential for a negative bias exists if the misclassification of the outcome variables was more likely to occur in the schizophrenic population. Second, we did not have access to clinical information such as smoking status, body mass index, blood pressure, or glycemic control, and were therefore unable to evaluate the impact of clinical and lifestyle parameters on the prevalence of CV-RF and CV-D, parameters that may explain the increased prevalence of CV-D in people with schizophrenia. In addition, provincial coverage of medication is not universally provided to all Albertans, and as a result we were unable to compare use of medications for the management cardiovascular risk or for the treatment of schizophrenia and the impact these agents may have on prevalence of CV-RF and CV-D. Lastly, it must be noted that because we had a very large sample size to conduct our study, the likelihood of seeing a statistical difference in people with and without schizophrenia was increase, although the strength of association, particularly in older age groups, was small.

3.5 Conclusions

In our large population-based study, people with schizophrenia had a higher prevalence of CV-RF (driven mostly by diabetes) and established CV-D than those without schizophrenia. The prevalence of CV-RF and CV-D varied somewhat by age, sex, and socioeconomic status. Based on our results,

aggressive monitoring for CV-RF should probably start at the time of diagnosis of schizophrenia, particularly in women, as the cardiovascular protective effect of female sex seems to be negated. Furthermore, attention to healthy weight, physical activity, and smoking cessation may be even more important (and harder to achieve) in the schizophrenic population than the general populace.

3.6 References

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Table 3.1. Descriptive Information for People With and Without Schizophrenia

	Schizophrenia (n = 28,755; 1.2%)	No Schizophrenia (n = 2,281,636; 98.8%)	Unadjusted Comparison
Male	14,596 (50.8%)	1,128,788 (49.5%)	OR: 1.05; 95% CI: 1.03 – 1.08
Age (mean;S.D.;min – max)	47.6;16.7; 20 - 107	45.3;16.6; 20 - 109	Mean diff.: 2.35 years $p < 0.001$
Low Socioeconomic Status (based on health care subsidies)	16,938 (58.9%)	468,215 (20.5%)	OR: 5.55 95% CI: 5.42 – 5.69
Number of General Practitioner Visits Year of Identification			
0 visits	4,960 (17.2%)	705,778 (30.9%)	OR: 0.47; 0.45 – 0.48
1 – 2 visits	4,205 (14.6%)	541,893 (23.8%)	OR: 0.55; 0.53 – 0.57
3 – 6 visits	6,721 (23.4%)	599,066 (26.3%)	OR: 0.86; 0.83 – 0.88
7 or more visits	12,869 (44.8%)	434,899 (19.1%)	OR: 3.44; 3.36 – 3.52

Table 3.2. Prevalence of Cardiovascular Risk Factors and Cardiovascular Disease in Schizophrenia and No Schizophrenia Populations

	Schizophrenia (n = 28,755)	No Schizophrenia (n = 2,281,636)	Unadjusted Comparisons (OR; 95% CI)
Diabetes	2,952 (10.3%)	126,817 (5.6%)	1.94; 1.87 – 2.02
Hypertension	6,529 (22.7%)	480,949 (21.1%)	1.10; 1.07 – 1.13
Dyslipidemia	6,605 (23.0%)	478,668 (21.0%)	1.12; 1.09 – 1.16
Number of CV-RF			
0	17,054 (59.3%)	1,484,968 (65.1%)	0.78; 0.76 – 0.80
1	7,965 (27.7%)	543,107 (23.8%)	1.23; 1.20 – 1.26
2	3,087 (10.7%)	217,356 (9.5%)	1.14; 1.10 – 1.19
3	649 (2.3%)	36,205 (1.6%)	1.43; 1.32 – 1.55
Acute coronary syndrome	629 (2.2%)	45,912 (2.0%)	1.09; 1.01 – 1.18
Heart failure	2,155 (7.5%)	86,122 (3.8%)	2.07; 1.98 – 2.16
Stroke	2,559 (8.9%)	98,315 (4.3%)	2.17; 2.08 – 2.26
MI/IHD/Arrhythmia	5,590 (19.4%)	312,837 (13.7%)	1.52; 1.48 – 1.56
Cardiovascular Disease (CV-D)*	7,615 (26.5%)	387,312 (17.0%)	1.76; 1.72 – 1.81

* CV-D defined as any of the following: ACS, IHD, arrhythmia, HF, or stroke

Table 3.3. Comparison Between People With and Without Schizophrenia: Stratified Analyses of Diabetes and Cardiovascular Disease

	Male		Comparison (aOR; 95% CI)	Female		Comparison (aOR; 95% CI)
	Schizophrenia	No Schizophrenia		Schizophrenia	No Schizophrenia	
Diabetes						
Age 20 – 29	26 (1.0%)	1,339 (0.6%)	1.18; 0.79 – 1.76	36 (2.4%)	1,762 (0.8%)	**2.49; 1.78 – 3.49**
Age 30 – 39	122 (3.8%)	3,164 (1.4%)	**1.57; 1.30 – 1.91**	140 (5.8%)	5,585 (2.4%)	**1.72; 1.44 – 2.04**
Age 40 – 49	277 (7.2%)	8,766 (3.3%)	**1.19; 1.05 – 1.36**	329 (9.3%)	10,654 (4.0%)	**1.58; 1.40 – 1.78**
Age 50 – 59	335 (13.6%)	16,060 (8.4%)	1.03; 0.91 – 1.16	392 (14.4%)	12,420 (6.7%)	**1.34; 1.20 – 1.50**
Age 60 – 69	247 (21.8%)	16,598 (15.4%)	1.08; 0.93 – 1.25	291 (18.3%)	12,197 (11.2%)	**1.21; 1.06 – 1.38**
Age 70 and older	279 (22.8%)	18,762 (18.8%)	1.06; 0.92 – 1.21	478 (20.0%)	19,510 (14.8%)	**1.20; 1.08 – 1.33**
CV-D						
Age 20 – 29	190 (7.1%)	6,270 (2.7%)	**2.17; 1.86 – 2.53**	128 (8.7%)	7,896 (3.5%)	**2.29; 1.91 – 2.76**
Age 30 – 39	381 (11.8%)	13,047 (5.6%)	**1.62; 1.44 – 1.81**	339 (13.9%)	15,214 (6.6%)	**1.87; 1.66 – 2.11**
Age 40 – 49	734 (19.0%)	29,439 (11.0%)	**1.38; 1.27 – 1.50**	650 (18.3%)	28,057 (10.6%)	**1.46; 1.34 – 1.60**
Age 50 – 59	784 (31.9%)	41,748 (21.7%)	**1.19; 1.09 – 1.30**	768 (28.2%)	34,446 (18.5%)	**1.24; 1.13 – 1.35**
Age 60 – 69	579 (51.2%)	41,620 (38.5%)	**1.24; 1.11 – 1.41**	648 (40.8%)	34,023 (31.3%)	**1.17; 1.06 – 1.30**
Age 70 and older	859 (70.2%)	61,655 (61.9%)	**1.20; 1.06 – 1.36**	1,555 (65.0%)	73,897 (55.9%)	**1.23; 1.13 – 1.34**

Figure 3.1. Prevalence of Diabetes in People With and Without Schizophrenia

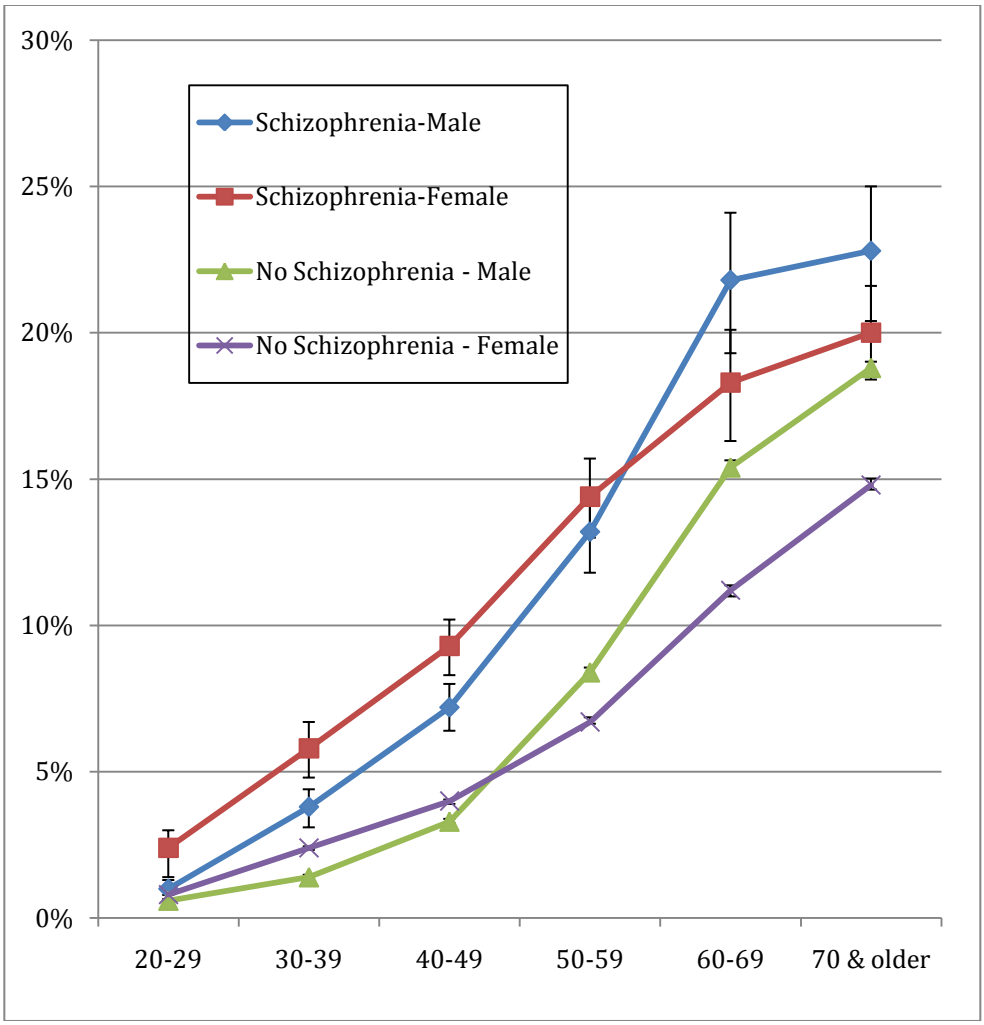
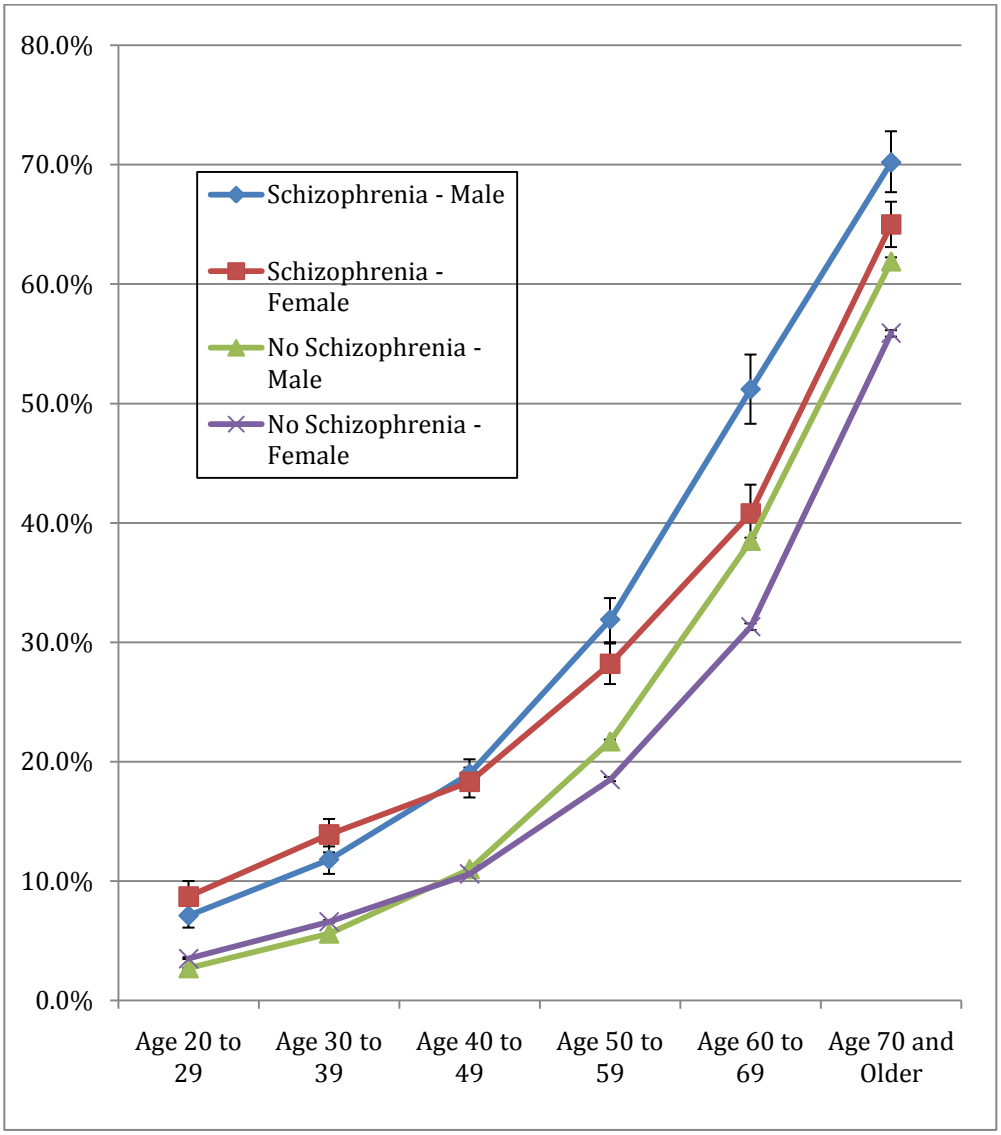


Figure 3.2. Prevalence of CV-D in People With and Without Schizophrenia



CHAPTER 4

Comparison of General Health Services and Specialized Cardiac Care in People with and without Schizophrenia

Submitted to: Psychiatric Services

4.1 Introduction

Not only is schizophrenia a debilitating disease due to its associated positive and negative symptoms (1,2), it is also considered a risk factor for many chronic medical conditions. Observational studies have found the prevalence of diabetes to be 2 to 3 times higher in individuals with schizophrenia compared to the general population (3-5). We previously reported a large population-based study showing that the prevalence of cardiovascular disease (CV-D) was significantly higher in people with schizophrenia (27%) compared to non-schizophrenic controls (17%) (5).

Despite the increased cardiovascular morbidity and mortality, research has demonstrated people with severe mental illness are less likely to receive medically necessary procedures for CV-D compared to those without schizophrenia (6-8). For example, data from the CATIE study recognized that people with schizophrenia were inadequately identified and treated for diabetes, hypertension, and dyslipidemia (6). In addition, Kisely and colleagues confirmed that individuals with severe mental illness were significantly less likely to receive revascularization procedures compared to the non-mentally ill population (7). Lastly, national and international guidelines for monitoring for cardiovascular risk

factors (CV-RF) and CV-D are available in people with severe mental illness, particularly for individuals taking atypical antipsychotic agents, but these guidelines have had little impact on clinical care of those with mental illness to date (9-11).

Given the increased risk of cardiovascular morbidity and mortality in people with schizophrenia, the opportunity to access care is vital for primary and secondary prevention of cardiovascular disease in this population (9). Access to a general practitioner (GP) and specialist care, where indicated, is necessary for monitoring for and management of cardiovascular risk (9,12). While a number of studies have demonstrated inequities in cardiovascular care for people with schizophrenia or severe mental illness (6-11), little is known about access to primary and specialist care in this population. It has been suggested that people with schizophrenia have substantially limited access to primary health care (9). Copeland and colleagues investigated trajectories of primary care use by people over the age of 50 and found that increasing use was associated with improved survival, but increasing use was least common in people with schizophrenia (13).

People with schizophrenia thus appear to have unmet health care needs. This could be a result of not enough health care in general, or a suboptimal mix of primary and non-psychiatric specialist care. Either or both situations would likely result in missed opportunities for monitoring and management of cardiovascular risk factors and disease. The first step towards addressing potential unmet health

care needs would be to examine population-levels of general and specialty health care use. Therefore, the purpose of this project was to evaluate health care utilization and the potential opportunities for care in people with schizophrenia compared to the non-schizophrenic population, with a focus on cardiovascular risk factors and established coronary artery disease (CAD). We specifically examined use of specialized cardiac care services (visits to cardiologists and internists and coronary revascularization procedures) because of previous work demonstrating that, all else equal, those with schizophrenia are older and carry a greater burden of cardiovascular disease and risk factors. Our objectives were:

1. To evaluate and compare general health care utilization including use of GP, emergency department (ED) encounters, and hospitalizations in people with and without schizophrenia; and
2. To evaluate and compare access to specialist care for individuals with CAD (internists, cardiologists) in people with and without schizophrenia.

4.2 Methods

4.2.1 Study Design

A period prevalence study design was utilized to evaluate the study objectives. Data from the administrative databases of Alberta Health and Wellness from January 1, 1995 to December 31, 2006 were used to create the study cohort. Individuals aged 20 years and older were included in this study.

4.2.2 Databases of Alberta Health and Wellness

Alberta is a Canadian province with a population of approximately 3.3 million people in 2006 (14). Medically necessary access to physicians and hospitals within Alberta is universally provided as a result of the Canada Health Act, although a modest needs-based health insurance premium is paid by individuals or families in Alberta. Health insurance premiums were partially subsidized for individuals of First Nations status, those qualifying for social assistance, and individuals receiving supports for independence. The need for, and receipt of, health care subsidies represents a robust measure of lower socio-economic status within Alberta (15).

Alberta Health and Wellness databases utilized in the study included the Discharge Abstract Database, Alberta Physician Claims Data, the Ambulatory Care Classification System, and Vital Statistics. These databases provide de-identified information on demographics, hospitalizations, emergency department encounters, physician encounters, diagnostic and procedural codes, and mortality (16). Diagnostic and procedural codes were based on International Classification of Disease, 9^{th} revision and 10^{th} revision codes (ICD-9-CM and ICD-10-CA). The ICD-10-CA is a modified version of the ICD-10, and was developed by the Canadian Institute for Health Information to capture morbidity in a Canadian context (17). Alberta Health and Wellness databases include information on all individuals within the province of Alberta eligible for Alberta Health care

coverage. Essentially all Albertans (99.5%) were covered by the Alberta Health Care Insurance Plan based on 2006 Canadian census data (14,18).

4.2.3 Identification of Schizophrenia

Individuals with schizophrenia were identified based on physician claims and hospital discharge data (ICD-9-CM 295.X or ICD-10-CA F20.X). Rawson and colleagues previously validated the use of ICD-9 codes in the Saskatchewan Health databases, and found a 93.9% concordance between hospital discharge data and a 61.8% concordance between the physician service claim and hospitalization in terms of diagnosis of schizophrenia (ICD-9-CM code 295) (19). Individuals with prevalent schizophrenia were identified from January 1, 1995 until December 31, 2006. Persons who did not meet the criteria for schizophrenia created the non-schizophrenic cohort, and were used as the comparison group for the analysis.

4.2.4 General Practitioner (GP), Emergency Department (ED), and Hospital Encounters

Access to health care in general was measured by examining GP visits, ED encounters, and hospitalizations. We considered primary, urgent, and emergent health care use and hospitalizations regardless of the reason for the encounter as a broad measure of access to general health care services. Although visits to the GP, ED, or hospitalizations may have been for psychiatric illness in people with schizophrenia, we evaluated utilization of health care services in general to

identify whether the opportunity for identification and management of cardiovascular disease exists in people with schizophrenia. Information for GP visits and hospitalizations was collected from January 1, 1995 to December 31, 2006, and from January 1, 1998 to December 31, 2006 for ED visits.

4.2.5 Identification of Coronary Artery Disease (CAD), Specialist Care, Revascularization Procedures, and Sensitivity Analysis

Prevalence of CAD was identified through ICD-9-CM and ICD-10-CA codes. CAD was defined as a diagnosis of acute coronary syndrome, ischemic heart disease, past myocardial infarction, or arrhythmia, and was based upon previously published criteria (16,20).

Access to specialist care was evaluated in people CAD by comparing access to internists and cardiologists between people with and without schizophrenia. General internists are consultant-based specialists within Canada that specifically manage diabetes and CV-D, and were therefore included in the specialist category (21). Revascularization was identified using procedure codes for percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG) from Alberta Physician Claims Data. Prevalence of CAD and revascularization was measured from January 1, 1995 to December 31, 2006. **Appendix 4A** provides detailed information for identification of CAD and revascularization procedures.

We conducted a sensitivity analysis by evaluating a non-procedure-based specialty to distinguish access to specialist care overall vs. access to those who undertake expensive procedures. We completed this analysis by comparing access to specialist care, including internists and endocrinologists, in those with diabetes. Identification of diabetes was based on the established case definition of the National Diabetes Surveillance System (NDSS), having two or more physician service claims for diabetes within a two year period, or one or more hospitalizations with a diabetes code as the primary, secondary, or other diagnosis (16,22,23), from which we calculated prevalence of diabetes from January 1, 1995 to December 31, 2006.

4.2.6 Statistical Analysis

Each cohort was described in terms of age, sex, receipt of health care subsidies (as a marker for socioeconomic status (15)), and urban or rural dwelling. Urban or rural dwelling was identified using the postal code for each individual. Postal codes with a "0" in the second position of a postal code indicate areas that are serviced by rural route mail delivery by Canada Post (24). Individuals with the second digit '0' in the Forward Sortation Area were classified as living in a rural dwelling (24). All other individuals were classified as residing in an urban dwelling (24).

GP encounters, ED encounters, and hospitalizations were compared based on any use (yes/no), and on level of use (high/low) based on a median split of the mean

annual visits for the entire study group. Mean annual visits were calculated for each individual by dividing the total number of visits from January 1, 1995 until December 31, 2006 by the number of years in the cohort. Specialist access and revascularization was compared between groups as a binary variable.

Multivariate logistic regression was used to compare the schizophrenic and non-schizophrenic cohorts in terms of binary variables while adjusting for variables that could potentially influence utilization of health care, including age, sex, socioeconomic status, urban vs. rural dwelling, and diabetes and CAD for the general medical access models. All analyses were completed using SPSS Version 15.0 (SPSS Inc., Chicago, Illinois).

4.2.7 Ethics Approval

Permission to conduct this study was granted from the University of Alberta Health Research Ethics Board Panel B.

4.3 Results

Individuals with schizophrenia (n = 28,755; 1.2%) were older (mean age: 48 years vs. 45 years), and were more likely to have received subsidized health care funding (59% vs. 21%) compared to the non-schizophrenic cohort (n = 2,281,636) (**Table 4.1**). Those with schizophrenia were more likely to have diabetes (10% vs. 6%) and CAD (20% vs. 14%) compared to those without schizophrenia.

People with schizophrenia were more likely to access the health care system in general (**Table 4.2**). Seventy-six percent of people with schizophrenia had four or more GP encounters per year compared to 47% of people without schizophrenia (adjusted OR: 3.60; 95% CI: 3.49 – 3.71). Likewise, people with schizophrenia were more likely to be hospitalized at least once per year (10% vs. 1%; aOR: 7.88; 7.54 – 8.23) and visit an emergency department one or more times per year (34% vs. 13%; aOR: 3.47; 3.38 – 3.56) (**Table 4.2**).

Despite having an increased prevalence of cardiovascular risk factors and disease, individuals with schizophrenia were less likely to receive specialized cardiac care compared to people without schizophrenia. Cardiologist encounters (50% vs. 59%; aOR: 0.76; 0.72 – 0.80) and CABG/PCI (6% vs. 12%; aOR: 0.55; 0.49 – 0.61) were significantly less likely in the schizophrenic cohort, whereas internist encounters were more common in people with schizophrenia (89% vs. 84%; aOR: 1.64; 1.51 – 1.79) (**Table 4.3**).

In contrast, differences were much smaller for use of less procedure-based specialty care. For individuals with diabetes, there was no difference in endocrinologist encounters (7% vs. 8%; aOR: 0.93; 0.81 – 1.08) compared to the non-schizophrenic cohort (**Table 4.4**). Similarly to CAD, people with schizophrenia and diabetes were more likely to see an internist compared to the non-schizophrenic cohort (89% vs. 83%; aOR: 1.67; 1.48 – 1.88).

4.4 Discussion

Although previous research has demonstrated a discrepancy between cardiovascular care for people with schizophrenia compared to individuals without schizophrenia (6-11), little research has been done to evaluate why this inconsistency exists. In this large population-based study, we were able to examine access to general and specialist care in people with schizophrenia, and compare access to people without schizophrenia, while taking into consideration important factors that may impact access to care, including socio-economic status and urban or rural dwelling. Schizophrenic individuals were significantly more likely to access the general health care system, including GP encounters, hospitalizations, and ED encounters, compared to the non-schizophrenic population, indicating that opportunities exist for the monitoring for and management of cardiovascular abnormalities in people with schizophrenia.

Despite the demonstrated use of medical care in general in our jurisdiction, individuals with schizophrenia and CAD had significantly less access to cardiologist compared to people with CAD who did not have a diagnosis of schizophrenia. Given the decreased access to cardiologists, it is not surprising we found that prevalence of revascularization was much lower in the schizophrenic population with CAD. Our results replicate similar findings by others that demonstrated a decreased likelihood of invasive cardiac procedures in those with severe mental illness (7,8). We did find, however, that individuals with schizophrenia and diabetes or CAD were more likely to visit an internist

compared to those without schizophrenia. In addition, when looking at a less procedure-based specialty, we found no difference in access to endocrinologists for individuals with diabetes, with or without schizophrenia. Further research is needed to investigate why people with schizophrenia and CAD in particular are not receiving specialist cardiac care to the same extent as their non-schizophrenic counterparts.

Strengths of this study include the population-based nature, utilizing the population of the province of Alberta aged 20 years and older, and the ability to adjust for important potentially mediating variables that play a part in the relationship between schizophrenia and health care utilization, including socioeconomic status and urban or rural dwelling. Based on this, the results are highly generalizable to the general schizophrenic population. Lastly, we conducted a sensitivity analysis evaluating non-procedure-based specialist care in people with and without schizophrenia. As with most studies which utilize administrative data to answer questions, however, our study is not without limitations. The potential for misclassification of illness exists due to use of physician billing codes to identify disease. In addition, although we were able to evaluate the frequency of visits to primary, urgent, and specialist care, we were unable to assess the reasons for each visit. Lastly, we used a period-prevalence study design to examine the study objectives, therefore the possibility of survival bias exists (25).

4.5 Conclusions

Individuals with schizophrenia and CAD were significantly less likely to receive specialist cardiac care compared to their non-schizophrenic counterparts. Despite suggestions to the contrary, however, we found that people with schizophrenia accessed the general health care system more often than the non-schizophrenic population, demonstrating the opportunity for monitoring for and management of cardiovascular disease exists in this vulnerable population.

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Table 4.1. Descriptive Information of People With and Without Schizophrenia

	Schizophrenia (n = 28,755; 1.2%)	No Schizophrenia (n = 2,281,636; 98.8%)
Male	14,596 (50.8%)	1,128,788 (49.5%)
Age (mean;S.D.;min – max)	47.6 years; 16.7; 20 - 107	45.3 years; 16.6; 20 - 109
Receipt of Health Care Subsidies	16,938 (58.9%)	468,215 (20.5%)
Urban Dwelling	24,554 (85.4%)	1,898,234 (83.2%)
Mean Annual Psychiatrist Visits (S.D.; min – max)	10.5 visits (17.2; 0 – 312)	0.16 visits (1.50; 0 – 237)
Diabetes	2,952 (10.3%)	126,817 (5.6%)
CAD	5,673 (19.7%)	318,145 (13.9%)

Table 4.2. Physician Encounters, Emergency Room Encounters, and Hospitalizations

	Schizophrenia (n = 28,755; 1.2%)	No Schizophrenia (n = 2,281,636; 98.2%)	Adjusted OR; 95% CI
Any GP Encounter	28,691 (99.8%)	2,244,086 (98.4%)	7.57; 5.92 – 9.69
≥ 4 Yearly GP Encounters	21,732 (75.6%)	1,065,262 (46.7%)	3.60; 3.49 – 3.71
Any ER Encounter	25,748 (89.5%)	1,571,347 (68.9%)	3.57; 3.44 – 3.71
≥ 1 yearly ER Encounters	9,810 (34.1%)	287,251 (12.6%)	3.47; 3.38 – 3.56
Any hospitalization	22,683 (78.9%)	921,899 (40.4%)	5.67; 5.50 – 5.84
≥ 1 yearly hospitalizations	2,929 (10.2%)	24,726 (1.1%)	7.88; 7.54 – 8.23

Table 4.3. Procedures and Access to Specialist Care in Individuals with Established Coronary Artery Disease

	Schizophrenia (n = 5,673; 19.7%)	No Schizophrenia (n = 318,145; 13.9%)	Adjusted OR; 95% CI
Cardiologist	2,856 (50.3%)	186,143 (58.5%)	0.76; 0.72– 0.80
CABG or PCI	350 (6.2%)	37,882 (11.9%)	0.55; 0.49 – 0.61
Internist	5,035 (88.8%)	266,197 (83.7%)	1.64; 1.51 – 1.79

Table 4.4. Access to Specialist Care in People with Diabetes

	Schizophrenia (n = 2,952; 10.3%)	No Schizophrenia (n = 126,817; 5.6%)	Adjusted OR; 95% CI
Endocrinologist	210 (7.1%)	9,657 (7.6%)	0.93; 0.81 – 1.08
Internist	2,631 (89.1%)	105,753 (83.4%)	1.67; 1.48 – 1.88

CHAPTER 5

Diabetes, Cardiovascular Disease, and Health Care Use in People with and without Schizophrenia

Bresee LC, Majumdar SR, Patten SB, Johnson JA. European Psychiatry 2010;doi:10.1016/j.eurpsy.2010.05.003.

5.1 Introduction

Schizophrenia is a debilitating illness due to its early onset of associated persistent symptoms such as anhedonia, hallucinations, and delusions (1). In addition to the associated symptoms of schizophrenia, recent publications have demonstrated an increased risk for and prevalence of cardiovascular risk factors (CV-RF) and disease (CV-D) in people with schizophrenia (2-9). Compared with the general population, individuals with schizophrenia have been found to have a higher prevalence of type 2 diabetes, obesity, and metabolic syndrome (2-7) and a greater incidence of (and mortality from) CV-D (2,3,8,9).

Despite the increased risk of CV morbidity and mortality, individuals with schizophrenia are less likely to receive adequate metabolic screening and medical intervention compared to individuals without mental illness (10-15). Kisely and colleagues demonstrated that people with severe mental illness are less likely to receive percutaneous coronary interventions (PCI) compared with non-mentally ill counterparts (10). Individuals with schizophrenia are less likely to receive reperfusion therapy, beta-blockers, and angiotensin-converting enzyme inhibitors after myocardial infarction compared to those without a psychiatric disorder (11).

Low rates of treatment for CV-RF such as diabetes, hypertension, and dyslipidemia, have been identified in people with schizophrenia (12). Lastly, the European Psychiatric Association, European Association for the Study of Diabetes, and European Society of Cardiology released a position statement emphasizing the lack of monitoring for CV risk and CV-D in patients with severe mental illness, despite the availability of clinical practice guidelines (2).

The available literature assessing CV-RF and CV-D in schizophrenia has primarily been drawn from two potentially biased sources. Studies have either used population-based administrative data that is bereft of socioeconomic and clinical data (3,6,8) or have used highly selected and relatively small clinical cohorts that are drawn from registries and trials and that are not likely to be generalizable (5,7). The few population-based studies evaluating the prevalence of CV-RF and CV-D are from time periods before widespread use of atypical antipsychotic agents (4,5,8), medications that may themselves increase development of CV-D through weight gain, type 2 diabetes, and dyslipidemia (16-18). Lastly, while a number of publications have demonstrated inadequate metabolic monitoring and treatment of CV-RF in people with mental illness (2, 10-15), few studies have evaluated primary health care use in this population, an area where the monitoring for and management of CV-RF occurs for primary and secondary prevention of CV-D (2,19).

The objectives of this study were to describe and compare in people with and without schizophrenia their self-reported:

1. Prevalence of modifiable CV-RF, including diabetes, smoking status, overweight and obesity, and hypertension;
2. Prevalence of CV-D, including heart disease and stroke; and
3. Health care use, including access to a regular medical doctor, hospitalizations, number of visits with a regular medical doctor in a 12 month period, access to specialist care, and unmet health care needs.

5.2 Methods

5.2.1 Canadian Community Health Survey, Cycle 3.1

The master file of the Canadian Community Health Survey (CCHS) cycle 3.1 was used to evaluate the study objectives. The CCHS 3.1 was a nationally representative cross-sectional survey conducted in 2005. The survey collected information related to self-reported health determinants, health status, and health care use for the Canadian population (20). Individuals living on Indian Reserves or Crown land, full-time members of the Canadian Forces, individuals residing in institutions, and residents residing in certain remote regions were not eligible for the survey (20).

Trained interviewers gathered information for the CCHS using computer-assisted interviewing methods. Approximately half of the interviews were conducted in person and half conducted over the telephone (20). The CCHS cycle 3.1 sampling

frame covered approximately 98% of the Canadian population aged 12 years and older, and the response rate was 78.9% (21).

5.2.2 Study Design

A cross-sectional study design was utilized to address the study objectives. Individuals aged 18 years and older were selected for the analysis. People with schizophrenia were identified and compared to individuals without schizophrenia. Previous research conducted with the CCHS has demonstrated the prevalence of schizophrenia or other psychosis to be consistent with published literature evaluating the epidemiology of schizophrenia (22). For example, the lifetime prevalence of schizophrenia or other psychosis in that study was 0.9% (34), similar to population based estimates from elsewhere, with 1-year prevalence estimated to be 0.34 per 100 (95% CI: 0.22 – 0.50), and lifetime prevalence of schizophrenia estimated at 0.55 per 100 (95% CI: 0.37 – 0.80) (23). It must be noted that we excluded individuals under the age of 18 years from our study and only evaluated a diagnosis of schizophrenia, whereas other studies have included all age groups and other types of psychoses (22,23), which may influence our prevalence estimate.

5.2.3 Identification of Cardiovascular Risk Factors (CV-RF) and Cardiovascular Disease (CV-D)

Survey participants were asked whether they had a number of different chronic medical conditions that were diagnosed by a health professional (20). The CV-RF

evaluated in the survey included body mass index (BMI), from which we evaluated overweight (BMI of 25.0 to 29.9 kg/m^2) and obesity (BMI ≥ 30.0 kg/m^2) (24), smoking status (daily or occasional smoking), hypertension (defined as a diagnosis of high blood pressure or if the respondent took medication for high blood pressure in the past month), and a diagnosis of diabetes. CV-D was defined as being diagnosed with heart disease by a health professional, or the respondent reporting that he or she suffered from the effect of a stroke.

5.2.4 Health Care Use

Health care use was evaluated in people with and without schizophrenia by comparing whether the respondent reported having a regular medical doctor, and whether they had been an overnight patient in a hospital or nursing home in the past 12 months (20). Number of visits to the regular medical doctor, other doctor, and number of nights as an overnight patient in the previous 12 months were also compared in people with and without schizophrenia (20). Unmet health care needs were evaluated based on whether there was a time in the past 12 months the respondent felt that he or she needed health care but did not receive it (20).

5.2.5 Statistical Analysis

The weighted prevalence of each descriptive variable was calculated and compared between people with and without schizophrenia. Odds ratios (OR) and 95% confidence intervals (CI) were calculated using logistic regression analysis to compare prevalence of CV-RF, CV-D, and health care use, while controlling

for differences in sociodemographic and lifestyle variables in people with and without schizophrenia. Individuals with missing data were excluded from the analysis (20). For the CV-RF and CV-D models, we completed "under-adjusted" analyses typical of data drawn from administrative databases, and fully adjusted analyses including important lifestyle and sociodemographic variables.

Important sociodemographic and lifestyle variables that were used in our models included: age, sex, marital status (married/common law or single/separated/divorced/widowed), annual household income (annual household income less than $20,000 CAD or ≥ $20,000 CAD, the before-tax low-income cut-off for 2005 (25)) education (did not finish high school, high school graduate, post-secondary attendance), alcohol use in the previous 12 months, and regular or occasional physical activity. The total number of chronic conditions, not including schizophrenia or cardiovascular conditions, was used in the models as a marker for comorbidity (26). **Appendix 5A** lists the chronic medical conditions included in the calculation of this variable. Additional variables included in the CV-RF and CV-D models were smoking status, overweight, and obesity. For the health care use models, additional variables included urban residence and access to a regular medical doctor. Variables were selected for inclusion in logistic regression models based on a review of the literature, clinical relevance, and statistical significance for each model ($p < 0.25$ for univariate comparisons, and $p < 0.1$ for retention in the model) (27).

The CCHS utilized a complex survey design with stratification and multiple stages of selection (20). As a result, sampling weights and bootstrap variance estimates were used to account for the multistage cluster survey design (20) to produce weighted prevalence estimates and 95% confidence intervals (CI).

Data for this study were obtained from the CCHS 3.1 master file maintained at the University of Calgary Prairie Regional Research Data Centre in Calgary, Canada. Analyses were completed using Stata 9 (StataCorp LP, College Station, Texas).

5.3 Results

A total of 399 people were identified with schizophrenia, and were compared to 120,044 without schizophrenia; this represents a population-level prevalence of 0.3%. Individuals with schizophrenia were more likely to be male (62% vs. 49%), unmarried (72% vs. 35%), and have an annual household income of less than $20,000 (40% vs. 10%) (**Table 5.1**).

In terms of lifestyle factors, people with schizophrenia were less likely to drink alcohol in the previous 12 months (55% vs. 82%) or engage in regular or occasional physical activity (70% vs. 82%) (**Table 5.1**).

5.3.1 Cardiovascular Risk Factors (CV-RF)

Individuals with schizophrenia were more likely to report diabetes (12% vs. 5%, OR 2.40; 95% CI: 1.40 – 4.12), obesity (35% vs. 16%, OR: 2.88; 95% CI: 2.00 –

4.16), and current smoking (44% vs. 23%, OR: 2.59; 95% CI: 1.89 – 3.54) (**Table 5.2**). We initially adjusted for variables commonly available in administrative database studies, including age, sex, and number of physician visits, and the difference in prevalence between people with and without schizophrenia for diabetes remained significant (adjusted OR: 2.12; 95% CI: 1.23 – 3.68). After adjusting for sociodemographic and lifestyle variables, there was, however, no longer a significant difference in prevalence of diabetes seen between people with and without schizophrenia (adjusted OR: 0.86; 95% CI: 0.49 – 1.51) (**Table 5.3**).

5.3.2 Cardiovascular Disease (CV-D)

CV-D (heart disease or stroke) was reported to a similar degree by people with and without schizophrenia (7% vs. 6%) (**Table 5.3**).

5.3.3 Health Care Use

No statistically significant difference was found between individuals with and without schizophrenia in terms of access to a regular medical doctor (86.7% vs. 85.7%) (**Table 5.4**). Individuals with schizophrenia, however, were more likely to have 3 or more consults with a regular medical doctor in the previous 12 months (62.7% vs. 38.8%) and 2 or more visits with another medical doctor in the previous 12 months (55.0% vs. 15.1%) (**Table 5.4**). In both unadjusted and adjusted analyses, individuals with schizophrenia were significantly more likely to be an overnight patient in the previous 12 months (21.9% vs. 8.0%). Just

under one-quarter (22%) of people with schizophrenia reported having unmet health care needs, compared to 12% of people without schizophrenia (**Table 5.4**).

5.4 Discussion

In this nationally representative sample, we found that individuals with schizophrenia had a considerably greater burden of potentially modifiable lifestyle factors including smoking, obesity, and diabetes when compared with the general population. Many previous studies have not evaluated the impact of risk factors such as income, education, marital status, alcohol use, and physical activity, factors that may play important roles in the complex pathway towards development of diabetes and CV-D (28-34). The relative patterns and prevalence of these various risk factors seemed to explain the greater (under-adjusted) prevalence of diabetes and established cardiovascular disease seen in this study and previously reported by others in people with schizophrenia (2-9). Indeed, in models that controlled for these modifiable risk factors, there was no independent association between schizophrenia and diabetes or CV-D. These results clearly highlight the need to move away from a "mental health-centric" treatment focus for patients with schizophrenia, and provide patient-centered care that emphasizes both physical and mental health.

In terms of health care use, we found no reported difference in those with and without schizophrenia for a regular medical doctor or unmet health care needs. This result is very important as the literature suggests people with severe mental

illness have limited access to general health care (2). Individuals with schizophrenia were more likely to be an overnight patient in the previous 12 months, and visited their regular medical doctor and another medical doctor more frequently than those without schizophrenia. These results demonstrate that individuals with schizophrenia are accessing the primary health care system, and regardless of the reason for accessing the system, the opportunity to provide CV-RF and CV-D monitoring and management exists in patients with schizophrenia (2,19).

As with most studies that utilize survey data, a number of limitations must be noted. The CCHS was a cross-sectional survey, therefore the possibility of survival bias exists (35), a possibility compounded by our exclusion of people residing in institutions (20). Nevertheless, the prevalence of CV-RF in our study is similar to what has been reported in the literature (2-4,8). It must be noted that the prevalence of schizophrenia in our survey data was lower than other studies reporting prevalence of schizophrenia (23). This could partially be explained by survival bias, and also by the exclusion of people residing in institutions, which limits the generalizablilty of the results to individuals with less severe schizophrenia (20). The accuracy of self-reported diagnoses is also an issue. The CCHS asks participants about "long-term conditions" which are expected to last or have already lasted 6 months or more and that have been diagnosed by a health professional (20). As a result, very recently diagnosed conditions are not captured. Also, the wording of some questions may create confusion for survey

participants and influence the results of our study, and it is possible that respondents with schizophrenia might be at greater risk of inaccurate answers. For example, participants are asked "Do you have a regular medical doctor?". This question may be confusing to individuals who have regular access to a specialist physician, such as a psychiatrist. In addition, despite being able to evaluate physician and hospital encounters, we were unable to investigate the reasons for the encounters. We do not feel this minimizes the conclusions of our study, however, as we were evaluating the opportunity for monitoring for and management of cardiovascular risk and disease in this population. Lastly, we did not have access to information regarding atypical antipsychotic use, and were therefore unable to evaluate the contribution of medication to metabolic risk in those with schizophrenia.

5.5 Conclusions

Individuals with schizophrenia had a higher prevalence of modifiable CV-RF including smoking, obesity, and diabetes compared to the general population in this nationally representative survey. Our data suggests substantial opportunities exist to manage modifiable risk factors and prevent the onset of diabetes and cardiovascular disease in this vulnerable population.

5.6 References

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Table 5.1. Demographic and Lifestyle Variables for Respondents With and Without Schizophrenia

	Schizophrenia (n = 399; 0.3%)	No Schizophrenia (n = 120,044; 97.7%)	Unadjusted OR; 95% CI
Proxy completion of survey	15.0 % 95% CI: 9.1 – 20.8	1.8 % 95% CI: 1.7 – 1.9	9.62; 5.94 – 15.60
Age			
18 – 29 years	10.9% 95% CI: 7.3 – 14.5	21.0% 95% CI: 20.9 – 21.1	0.46; 0.31 – 0.68
30 – 39 years	22.8% 95% CI: 17.0 – 28.6	17.7% 95% CI: 17.5 – 18.0	1.37; 0.99 – 1.91
40 – 49 years	27.8% 95% CI: 20.1 – 35.4	21.7% 95% CI: 21.3 – 22.0	1.39; 0.95 – 2.04
50 – 59 years	25.0% 95% CI: 18.1 – 31.9	17.2% 95% CI: 16.9 – 17.4	1.61; 1.11 – 2.33
60 years and older	13.5% 95% CI: 8.0 – 19.1	22.4% 95% CI: 22.2 – 22.6	0.54; 0.34 – 0.88
Sex (male)	62.1% 95% CI: 54.6 – 69.6	49.0% 95% CI: 48.9 – 49.0	1.71; 1.24 – 2.35
Resides in urban location	80.1% 95% CI: 73.6 – 86.5	82.2% 95% CI: 81.8 – 82.5	0.87; 0.57 – 1.33
Marital status (married or common law)	27.5% 95% CI: 20.3 – 34.7	65.0% 95% CI: 64.6 – 65.3	0.20; 0.14 – 0.29
Annual household income < $20,000	39.6 % 95% CI: 31.8 – 47.4	9.8 % 95% CI: 9.5 – 10.0	6.06; 4.36 – 8.41
Alcohol use in past 12 months	55.4 % 95% CI: 47.7 – 63.2	81.5 % 95% CI: 81.1 – 81.8	0.28; 0.21 – 0.39
Regular or occasional	70.0 %	81.7 %	

physical activity	95% CI: 62.0 – 78.0	95% CI: 81.3 – 82.0	0.52; 0.36 – 0.77
Education			
Did not finish high school	35.5 % 95% CI: 28.0 – 42.9	16.7 % 95% CI: 16.4 – 17.0	2.75; 1.98 – 3.82
High school graduate	21.0 % 95% CI: 14.0 – 27.9	16.5 % 95% CI: 16.2 – 16.9	1.34; 0.87 – 2.05
Post-secondary attendance	43.6 % 95% CI: 35.6 – 51.5	66.8% 95% CI: 66.4 – 67.2	0.38; 0.28 – 0.53

Table 5.2. Prevalence of Cardiovascular Risk and Cardiovascular Disease in Respondents With and Without Schizophrenia

	Schizophrenia (n = 399, 0.3%)	No Schizophrenia (n = 120,044, 97.7%)	Unadjusted OR; 95% CI
Diabetes	11.9 % 95% CI: 6.6 – 17.2	5.3 % 95% CI: 5.2 – 5.5	2.40; 1.40 – 4.12
Hypertension	27.7 % 95% CI: 20.8 – 34.6	21.4 % 95% CI: 21.1 – 21.7	1.41; 0.99 – 2.00
Overweight (BMI 25.0-29.9 kg/m^2)	27.9 % 95% CI: 21.3 – 34.5	34.1% 95% CI: 33.7 – 34.6	0.75; 0.53 – 1.04
Obesity (BMI $\geq$ 30.0 kg/m^2)	34.8 % 95% CI: 26.7 – 43.0	15.6 % 95% CI: 15.3 – 16.0	2.88; 2.00 – 4.16
Smoker – daily or occasional	43.8 % 95% CI: 36.1 – 51.4	23.1 % 95% CI: 22.8 – 23.5	2.59; 1.89 – 3.54
Heart Disease	5.7 % 95% CI: 3.1 – 8.2	5.2 % 95% CI: 5.0 – 5.4	1.10; 0.67 – 1.79
Suffers from effects of a Stroke	1.1 % 95% CI: 0.3 – 1.9	1.2 % 95% CI: 1.1 – 1.3	0.90; 0.36 – 2.23
Cardiovascular Disease (CVD)[a]	6.6 % 95% CI: 3.9 – 9.3	6.0 % 95% CI: 5.8 – 6.1	1.11; 0.71 – 1.73

[a]CVD defined as self report of either heart disease or suffers from the effects of a stroke.

Table 5.3. Adjusted Cardiovascular Risk and Cardiovascular Disease Models

	Age, Sex, and GP Visits OR; 95% CI	Full Model OR; 95% CI
Diabetes	2.12; 1.23 – 3.68	0.86; 0.49 – 1.51[a]
Hypertension	1.31; 0.91 – 1.89	0.94; 0.59 – 1.48[a]
Heart Disease	1.10; 0.65 – 1.86	0.77; 0.43 – 1.38[b]
Stroke	0.92; 0.35 – 2.41	0.37; 0.08 – 1.75[b]
CV-D	1.12; 0.68 – 1.83	0.66; 0.33 – 1.32[b]

[a]Adjusted for sex, age, marital status, income, education, alcohol use, physical activity, body mass index, and total number of chronic medical conditions

[b]Adjusted for sex, age, marital status, income, education, alcohol use, physical activity, body mass index, diabetes, hypertension, and total chronic medical conditions

Table 5.4. Health Care Use in Respondents With and Without Schizophrenia

	Schizophrenia (n = 399, 0.3%)	No Schizophrenia (n = 120,044, 97.7%)	Unadjusted OR; 95% CI	Adjusted OR; 95% CI
Regular medical doctor	86.7 % 95% CI: 81.4 – 91.9	85.7 % 95% CI: 85.4 – 85.9	1.09; 0.69 – 1.73	1.23; 0.65 – 2.35[a]
3 or more consults with regular MD in past 12 months	62.7 % 95% CI: 55.1 – 70.4	38.8% 95% CI: 38.4 – 39.2	2.66; 1.91 – 3.69	1.94; 1.25 – 3.02[a]
Overnight patient in the past 12 months	21.9 % 95% CI: 16.1 – 27.6	8.0 % 95% CI: 7.8 – 8.2	3.22; 2.31 – 4.49	2.37; 1.51 – 3.74[b]
4 or more nights as a patient in the past 12 months	69.7 % 95% CI: 57.3 – 82.0	44.5 % 95% CI: 43.1 – 45.8	2.87; 1.57 – 5.26	2.82; 1.26 – 6.34[b]
2 or more visits with other medical doctors in past 12 months	55.0 % 95% CI: 48.0 – 62.0	15.1 % 95% CI: 14.8 – 15.4	6.88; 5.18 – 9.15	7.79; 5.09 – 11.91[a]
Unmet health care needs	22.0 % 95% CI: 15.1 – 28.8	11.8 % 95% CI: 11.5 – 12.1	2.10; 1.39 – 3.17	1.27; 0.81 – 1.98[c]

[a]Adjusted for sex, age, urban dwelling, marital status, income, education, alcohol use, physical activity, smoking status, body mass index, diabetes, hypertension, cardiovascular disease, and total number of chronic conditions

[b]Adjusted for above variables and regular medical doctor

[c]Adjusted for sex, age, income, education, physical activity, smoking status, cardiovascular disease, and total number of chronic medical conditions

CHAPTER 6

General Discussion and Conclusions

6.1 Discussion

Schizophrenia and cardiovascular disease (CV-D) are two serious medical conditions, each associated with considerable morbidity and mortality. Previous literature has demonstrated a relationship between these illnesses, and individuals with schizophrenia are more likely to die as a result of CV-D compared to their non-schizophrenic counterparts (1,2). The aim of this dissertation was to further clarify the association between schizophrenia and CV-D and provide insight into the mechanisms behind this relationship. To address this aim, a series of four studies were conducted, using three different data sources, including a systematic review of published literature, responses from the Canadian Community Health Survey (CCHS) and the administrative health records for Albertans, available through Alberta Health and Wellness.

Based on the results of this dissertation, individuals with schizophrenia have a greater burden of CV-D compared to their non-schizophrenic counterparts, and this relationship is consistent between males and females across all age groups. The greater burden of CV-D in people with schizophrenia is likely due to a number a factors: the medications used to treat schizophrenia, particularly the atypical antipsychotic agents (3,4), the increased prevalence of cardiovascular risk factors such as diabetes, hypertension, and obesity (5,6), and the increased prevalence of negative lifestyle factors such as cigarette smoking and reduced

physical activity (6). In addition, we found that people with schizophrenia consistently had a lower socioeconomic status compared to people without schizophrenia, and socioeconomic status plays a major role in morbidity and mortality independent of important negative lifestyle factors such as smoking and reduced physical activity (6-8).

While a number of studies have demonstrated an increased prevalence of diabetes and CV-D in people with schizophrenia compared to people without schizophrenia (5,9-11), the majority of studies were unable to evaluate the role of important mediating variables in this relationship, such as body mass index (12,13), smoking status (12,14), alcohol use (12,15), marital status (16), and socioeconomic status (8). We utilized data from the CCHS cycle 3.1 (17) to evaluate the relationship between diabetes, cardiovascular disease, and schizophrenia. Results from the CCHS demonstrated that, compared to respondents without schizophrenia, people with schizophrenia were more likely to smoke daily (43.8% vs. 23.1%), more likely to be obese (34.8% vs. 15.6%), less likely to engage in regular or occasional physical activity (70.0% vs. 81.7%), less likely to be married (27.5% vs. 65.0%), and more likely to have an annual household income of less than $20,000 (39.6% vs. 9.8%) (6). After adjusting for variables typically available in administrative database studies (age, sex, and number of general practitioner visits), we found an independent association between schizophrenia and diabetes (OR: 2.12; 95% CI: 1.23 - 3.68) (6). When we accounted for variables not available in typical administrative database

studies, however, including body mass index, smoking status, marital status, physical activity, education, household income, and alcohol use, the relationship between schizophrenia and diabetes was no longer significant (OR: 0.86; 95% CI: 0.49 - 1.51) (6). The results of this study suggest that having schizophrenia is not an independent risk factor for developing diabetes, rather, the prevalence of other important risk factors for diabetes such as smoking status and body mass index is higher in those with schizophrenia, resulting in a higher prevalence of diabetes. As many of the risk factors for diabetes and CV-D that are elevated in people with schizophrenia are modifiable risk factors (frequency of physical activity, smoking status, and body mass index, for example), our results suggest that the opportunity for prevention of CV-D and diabetes exists in people with schizophrenia. More research is needed to identify implementation strategies for programs to modify risk factors for diabetes and CV-D in this population.

Through two separate data sources, with one source being provincial administrative data and the second source a national self-report survey, we found that people with schizophrenia utilize the general health care system more frequently than people without schizophrenia. Tables 4.2 and 5.4 demonstrate that people with schizophrenia were significantly more likely to visit a general practitioner and be hospitalized compared to people without schizophrenia. We believe this information is novel as there is very little literature available on the access to primary care in people with schizophrenia. In fact, the recent European Psychiatric Association, European Association for the Study of Diabetes, and

European Society of Cardiology position statement on diabetes and cardiovascular disease in people with severe mental illness states: "Patients may have limited access to general healthcare with less opportunity for cardiovascular risk screening and prevention than would be expected in a non-psychiatric population" (9). Our results indicate that there are opportunities for screening for and prevention of cardiovascular disease in this vulnerable population. However, it must be noted that the focus of these visits may be overtaken by mental health needs, with limited time spent on assessment of cardiovascular risk. Given the increased prevalence of modifiable cardiovascular risk factors (5,6) and the frequent utilization of primary health care by people with schizophrenia, more research is needed to ensure cardiovascular risk assessment and management is occurring each time a person with schizophrenia accesses the primary health care system.

In terms of utilization of specialist care in people with established disease, we found that despite having a higher prevalence of coronary artery disease, individuals with schizophrenia were significantly less likely to see a cardiologist or undergo revascularization compared to people without schizophrenia. To evaluate whether this finding was consistent across other medical specialties, we conducted a sensitivity analysis to investigate the utilization of endocrinologists in people with diabetes and found no difference in people with and without schizophrenia. Our results confirm results of similar studies that have identified reduced utilization of cardiac revascularization in people with severe mental

illness (18,19). The reasons for reduced utilization of cardiologists and revascularization procedures in this population, however, are unclear, especially given the equal utilization of endocrinologists in people with diabetes, with and without schizophrenia. Postulated reasons include: inability or unwillingness to provide informed consent to see a cardiologist on the part of the patient or legal guardian; unwillingness on the part of the general practitioner or other physician to refer the patient to a cardiologist; differences in cardiovascular anatomy that result in contraindications to revascularization in patients with schizophrenia; or concerns about adherence to therapy and lifestyle modification following revascularization in the schizophrenic population. The reasons for the reduced utilization of cardiologists and coronary revascularization in people with schizophrenia needs to be further investigated.

Despite the availability of national and international guidelines for monitoring for and management of CV-D in patients with schizophrenia and other severe mental illnesses, evidence demonstrates that the uptake of these guidelines has been minimal (20-22). This could be a result of confusion as to who is responsible for monitoring patients with mental illness, whether it be the general practitioner or the psychiatrist, or confusion due to differences in guidelines that are currently available for management of cardiovascular risk in people with mental illness. For example, the position statement by the American Diabetes Association, American Psychiatric Association, and American Association of Clinical Endocrinologists (23) recommends that a person on an atypical antipsychotic

agent should have their fasting lipids monitored at baseline, 12 weeks, and if normal, every 5 years thereafter, whereas the European Psychiatric Association, European Association for the Study of Diabetes, and European Society of Cardiologists guidelines recommend fasting lipids at baseline, 6 weeks, 12 weeks, and then annually (9). It is apparent that policy needs to be established to clearly assign responsibility for metabolic monitoring. Also, consistent recommendations need to be developed to minimize the confusion associated with monitoring for and management of cardiovascular risk.

Given the complex care needs for someone with schizophrenia, "The Patient-Centered Medical Home" concept is an option as a means to provide comprehensive care that needs to be evaluated in this population. "The Patient-Centered Medical Home" was originally developed in pediatrics, and subsequently in primary care to better facilitate communication among patients and providers to effectively manage chronic disease (24), and has been suggested as an option to improve the coordination of care in people with severe mental illness (25). The development of "The Patient-Centered Medical Home" in psychiatry is in its infancy, however, and research is not currently available to identify whether "The Patient-Centered Medical Home" care model results in improved patient outcomes (25). Research is needed to identify whether "The Patient-Centered Medical Home" concept will help improve the monitoring for and management of CV-D in patients with schizophrenia.

As with all research that is observational in nature, there are a number of limitations to consider. We utilized a cross-sectional, period-prevalence design for three of our studies, and this study design is subject to survival bias (26). As such, our study results may not be generalizable to the most severely ill people with schizophrenia. In addition, there is risk of misclassification bias in our studies that utilized administrative and survey data, as we were reliant upon physician diagnoses, procedure codes, and self-report of disease states to identify schizophrenia, cardiovascular risk factors, and CV-D. Also, the administrative databases of Alberta Health and Wellness do not contain clinical information such as body mass index, blood pressure, or smoking status, therefore we were unable to control for these variables in our analyses.

In terms of limitations of our systematic review, we chose to include randomised controlled trials (RCT) to ensure a balance of known and unknown risk factors for metabolic abnormalities between the treatment and control groups. RCT study groups, however, tend to be highly specialized groups of individuals based on stringent inclusion and exclusion criteria, therefore the results of our systematic review may not be generalizable to the entire schizophrenic population. In addition, we only examined the metabolic changes as a result of antipsychotic monotherapy, and for that reason our results are not applicable to individuals taking more than one antipsychotic concurrently.

In terms of future research based on the results of this dissertation, more work will be completed on the systematic review as information is received from individual study authors. In addition, as part of my post-doctoral fellowship, I plan to conduct a study evaluating mortality, receipt of evidence-based therapies, and achievement of treatment targets (low density lipoprotein, total cholesterol, and for those with diabetes, A1c) in people hospitalized with a first cardiovascular event, with and without mental illness using the databases of the Alberta Kidney Disease Network (27).

6.2 Conclusions

Individuals with schizophrenia have a considerable burden of cardiovascular disease compared to people without schizophrenia. This is likely a result of a number of factors, including medications used to treat schizophrenia, the increased prevalence of smoking and other unhealthy lifestyle factors, and the increased prevalence of obesity, diabetes, and hypertension in people with schizophrenia. We also found that individuals with schizophrenia utilize the general health care system more frequently than their non-schizophrenic counterparts, therefore providing the opportunity for management of modifiable cardiovascular risk factors in this vulnerable population. Nonetheless, given the negative outcomes in this difficult to treat population, more effective policies or practice guidelines need to be established to assign responsibility for metabolic monitoring to ensure regular screening and follow-up occurs in people with schizophrenia.

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APPENDIX 2A: MEDLINE and MEDLINE In-Process and other non-indexed citations (1950 to present) Electronic Search Strategy

1. exp Schizophrenia/

2. exp Psychotic Disorders/

3. Schizophreniform.mp.

4. schizoaffective.mp.

5. or/1-4

6. Antipsychotic Agents/

7. atypical.ti,ab.

8. novel.ti,ab.

9. second generation.ti,ab.

10. or/7-9

11. 6 and 10

12. exp Clozapine/

13. olanzapine.mp.

14. quetiapine.mp.

15. exp Risperidone/

16. ziprasidone.mp.

17. aripiprazole.mp.

18. paliperidone.mp.

19. or/11-18

20. 5 and 19

21. exp Weight gain/

22. exp body weight/

23. exp overweight/

24. exp obesity/

25. exp hypertension/

26. exp blood pressure/

27. exp dyslipidemias/

28. exp hyperlipidemias/

29. exp hypercholesterolemia/

30. exp lipids/

31. exp triglycerides/

32. exp lipoproteins, LDL/

33. exp cholesterol, LDL/

34. exp lipoproteins, HDL/

35. exp cholesterol, HDL/

36. exp Hemoglobin A, glycosylated/

37. exp glucose intolerance/

38. exp blood glucose/

39. exp hyperglycemia/

40. Diabetes Mellitus, Type 2/

41. ((diabet* or DM) adj5 ("type 2" or "type ii" or non insulin dependent or matur* onset or late onset)).ti,ab.

42. (diabet* not (juvenile or "type 1" or "type i")).ti.

43. (diabetes adj5 (complication* or education)).mp.

44. (niddm or mody or T2DM).ti,ab.

45. (diabet* not gestational).ti.

46. diabetes mellitus/

47. or/21-46

48. 20 and 47

49. limit 48 to (humans and "all adult (19 plus years)")

50. limit 49 to (classical article or clinical conference or clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or randomized controlled trial)

APPENDIX 3A: Identification of Cardiovascular Risk Factors and Cardiovascular Disease

Acute Coronary Syndrome[1]

From Discharge Abstracts Database

- Acute MI: ICD-9-CM of 410.X; ICD-10-CA of 121.X – 122.X
- Unstable Angina: ICD-9-CM of 411.X, 413.X; ICD-10-CA of 120.X, 124.X

Heart Failure[1]

From Discharge Abstracts Database, Alberta Physician Claims Data, Ambulatory Care Classification System

- Heart Failure: ICD-9-CM of 428.X; ICD-10-CA of 150.X

Old MI/IHD/Arrhythmia[2]

From Discharge Abstracts Database, Alberta Physician Claims Data, Ambulatory Care Classification System

- Old MI: ICD-9-CM of 412.X, ICD-10-CA of 125.2
- Ischemic Heart Disease: ICD-9-CM of 414; ICD-10-CA of 125.1, 125.5, 125.6, 125.8, 125.9
- Arrhythmia: ICD-9-CM of 426.X – 427.X; ICD-10-CA of 147.X – 149.X

Stroke[1]

From Discharge Abstracts Database, Alberta Physician Claims Data, Ambulatory Care Classification System

- Stroke: ICD-9-CM of 430.X – 438.X; ICD-10-CA of 160.X – 169.X, G45.X

Hypertension[2]

From Discharge Abstracts Database, Alberta Physician Claims Data, Ambulatory Care Classification System

- Hypertension: ICD-9-CM of 401.X – 405.X; ICD-10-CA of I10, I11.X, I12.X, I13.X

Dyslipidemia[2]

From Discharge Abstracts Database, Alberta Physician Claims Data, Ambulatory Care Classification System

- Dyslipidemia: ICD-9-CM of 272.X; ICD-10-CA of E78.X

References

1. Alberta Diabetes Surveillance System Alberta Diabetes Atlas 2007.
2. Curkendall SM, Mo J, Glasser DB, Stang MR, Jones JK. Cardiovascular disease in patients with schizophrenia in Saskatchewan, Canada. J Clin Psychiatry 2004;65:715-720.

APPENDIX 3B: Additional Stratified Analyses Based on Significant Socio-economic Status (Receipt of Healthcare Subsidies) and Schizophrenia Interaction

	Subsidy		Comparison (aOR; 95% CI)	No Subsidy		Comparison (aOR; 95% CI)
	Schizophrenia	**No Schizophrenia**		**Schizophrenia**	**No Schizophrenia**	
Hypertension						
Age 20 – 29	59 (2.8%)	1,479 (1.7%)	**1.47; 1.12 – 1.91**	44 (2.2%)	5,845 (1.6%)	1.21; 0.89 – 1.63
Age 30 – 39	271 (8.6%)	3,967 (5.9%)	**1.28; 1.13 – 1.46**	170 (6.8%)	20,778 (5.3%)	1.12; 0.96 – 1.31
Age 40 – 49	674 (16.0%)	9,086 (14.5%)	0.95; 0.87 – 1.03	474 (14.8%)	60,994 (13.0%)	0.96; 0.87 – 1.06
Age 50 – 59	807 (28.0%)	15,529 (33.9%)	**0.65; 0.60 – 0.71**	746 (32.5%)	97,866 (29.4%)	0.91; 0.83 – 1.00
Age 60 – 69	788 (44.7%)	37,540 (55.5%)	**0.54; 0.49 – 0.59**	446 (46.7%)	70,650 (47.4%)	**0.77; 0.68 – 0.89**
Age 70 and older	1,583 (56.6%)	97,838 (70.0%)	**0.46; 0.43 – 0.50**	467 (57.0%)	59,377 (64.5%)	**0.59; 0.51 – 0.68**
Dyslipidemia						
Male						
Age 20 – 29	163 (11.9%)	1,222 (3.6%)	**3.25; 2.72 – 3.88**	75 (5.7%)	7,743 (3.9%)	1.10; 0.87 – 1.40
Age 30 – 39	344 (18.6%)	3,244 (11.5%)	**1.51; 1.34 – 1.71**	185 (13.4%)	25,550 (12.6%)	0.92; 0.78 – 1.07
Age 40 – 49	602 (25.6%)	5,361 (19.3%)	**1.30; 1.17 – 1.43**	382 (25.2%)	57,782 (24.1%)	**0.88; 0.78 – 0.99**
Age 50 – 59	425 (29.3%)	6,065 (30.2%)	**0.86; 0.77 – 0.97**	374 (37.1%)	63,366 (36.8%)	**0.83; 0.73 – 0.95**
Age 60 – 69	234 (32.9%)	11,238 (40.9%)	**0.64; 0.54 – 0.75**	168 (40.0%)	36,457 (45.3%)	**0.70; 0.57 – 0.85**
Age 70 and older	201 (22.3%)	18,282 (34.0%)	**0.52; 0.44 – 0.61**	94 (29.2%)	17,804 (38.8%)	**0.59; 0.47 – 0.76**
Female						
Age 20 – 29	67 (8.9%)	1,887 (3.7%)	**2.29; 1.77 – 2.96**	47 (6.5%)	7,821 (4.4%)	**1.36; 1.01 – 1.84**
Age 30 – 39	194 (14.8%)	3,214 (8.2%)	**1.80; 1.54 – 2.10**	158 (14.0%)	16,821 (8.8%)	**1.55; 1.31 – 1.83**
Age 40 – 49	432 (23.1%)	5,545 (15.9%)	**1.44; 1.29 – 1.61**	368 (21.9%)	37,631 (16.3%)	**1.28; 1.14 – 1.43**
Age 50 – 59	459 (32.0%)	8,523 (33.1%)	**0.87; 0.77 – 0.97**	466 (36.1%)	50,890 (31.6%)	1.07; 0.95 – 1.20
Age 60 – 69	372 (35.4%)	17,799 (44.4%)	**0.63; 0.55 – 0.72**	229 (42.8%)	29,288 (42.7%)	0.89; 0.75 – 1.06
Age 70 and older	425 (22.4%)	28,343 (33.0%)	**0.56; 0.51 – 0.63**	141 (28.3%)	16,792 (36.4%)	**0.65; 0.53 – 0.79**
ACS						
Male	207 (2.4%)	11,018 (5.7%)	**0.59; 0.51 – 0.68**	149 (2.5%)	19,470 (2.1%)	1.06; 0.90 – 1.25
Female	208 (2.5%)	9,056 (3.3%)	**0.79; 0.69 – 0.91**	65 (1.1%)	6,368 (0.7%)	0.97; 0.76 – 1.25
Stroke						

Age 20 – 29	34 (1.6%)	640 (0.8%)	**1.97; 1.39 – 2.80**	31 (1.5%)	1,793 (0.5%)	**2.78; 1.93 – 3.98**
Age 30 – 39	91 (2.9%)	1,123 (1.7%)	**1.41; 1.13 – 1.76**	59 (2.4%)	3,692 (0.9%)	**2.08; 1.60 – 2.71**
Age 40 – 49	224 (5.3%)	1,866 (3.0%)	**1.47; 1.27 – 1.70**	127 (4.0%)	7,616 (1.6%)	**2.00; 1.67 – 2.39**
Age 50 – 59	256 (8.9%)	2,965 (6.5%)	**1.18; 1.03 – 1.35**	176 (7.7%)	11,397 (3.4%)	**1.84; 1.57 – 2.15**
Age 60 – 69	290 (16.4%)	7210 (10.7%)	**1.44; 1.27 – 1.64**	156 (16.3%)	10,919 (7.3%)	**2.11; 1.77 – 2.51**
Age 70 and older	848 (30.3%)	31,211 (22.3%)	**1.39; 1.28 – 1.50**	267 (32.6%)	17,883 (19.4%)	**1.77; 1.52 – 2.05**

APPENDIX 4A: Identification of Coronary Artery Disease and Revascularization Procedures

Acute Coronary Syndrome[1]

From Discharge Abstracts Database

- Acute MI: ICD-9-CM of 410.X; ICD-10-CA of 121.X – 122.X
- Unstable Angina: ICD-9-CM of 411.X, 413.X; ICD-10-CA of 120.X, 124.X

Prior MI, Ischemic Heart Disease, and Arrhythmia

From Discharge Abstracts Database, Alberta Physician Claims Data, Ambulatory Care Classification System

- Prior MI: ICD-9-CM of 412.X, ICD-10-CA of 125.2
- Ischemic Heart Disease: ICD-9-CM of 414; ICD-10-CA of 125.1, 125.5, 125.6, 125.8, 125.9
- Arrhythmia: ICD-9-CM of 426.X – 427.X; ICD-10-CA of 147.X – 149.X

Procedures[1]

From Alberta Physician Claims Data

- Percutaneous Coronary Intervention (PCI): 51.59A, 51.59C, 51.59D, 51.59E, 51.59F
- Coronary Artery Bypass Graft (CABG): 48.12, 48.12A, 48.13, 48.13A, 48.14, 48.14A, 48.15A, 48.15B, 48.15C, 48.15D, 48.15E, 48.15F

References

1. Alberta Diabetes Surveillance System Alberta Diabetes Atlas 2007.

2. Curkendall SM, Mo J, Glasser DB, Stang MR, Jones JK. Cardiovascular disease in patients with schizophrenia in Saskatchewan, Canada. J Clin Psychiatry 2004;65:715-720.

APPENDIX 5A: Chronic Medical Conditions From the Canadian Community Health Survey Cycle 3.1

Chronic Medical Conditions

Food allergies

Allergies other than food allergies

Asthma

Chronic bronchitis

Emphysema

Fibromyalgia

Arthritis or rheumatism

Back problems excluding fibromyalgia and arthritis

Migraine headaches

Epilepsy

Cancer

Stomach or intestinal ulcers

Urinary incontinence

Bowel disorder/ Crohn's disease or colitis

Alzheimer's disease or other dementia

Cataracts

Glaucoma

Thyroid condition

Chronic fatigue syndrome

Suffers from multiple chemical sensitivities

Mood disorder

Anxiety disorder

Autism or any other developmental disorder

Attention deficit disorder, no hyperactivity (ADD)

Attention deficit hyperactivity disorder (ADHD)

Eating disorder such as anorexia or bulimia