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Epidemiological Assessment of Bipolar Disorder in Canada

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Epidemiological Assessment of Bipolar Disorder in Canada

by

Keltie McDonald

A THESIS
SUBMITTED TO THE FACULTY OF GRADUATE STUDIES
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Abstract

Objective: The original aim of this thesis was to estimate the prevalence of bipolar disorder (BD) including bipolar I (BDI) and bipolar II (BDII) disorder subtypes, in Canada in 2012 and to characterize persons with BD in terms of demographic features, health status, and mental health service utilization. During the course of this thesis, a third objective emerged which was to examine some indicators of validity of the World Mental Health version of the World Health Organization Composite International Diagnostic Interview (WMH-CIDI) classifications of BD.

Methods: Data were from the Canadian Community Health Survey-Mental Health (CCHS-MH; n=25,113) Interviews were based on the WMH-CIDI. The WMH-CIDI uses algorithms to determine the presence or absence of BD. Alternative classification methods were also considered. Using proportions and generalized linear modeling, I estimated prevalence of BD, examined agreement among different methods for classifying BD and described the epidemiology of BD according to the different classifications in terms of demographic features, health status and impact, and mental health service utilization.

Results: According the WMH-CIDI algorithm, the prevalence of BDI and BDII in Canada in 2012 was 0.87% (95% CI 0.67% to 1.07%) and 0.57% (95% CI 0.44% to 0.71%), respectively. I observed a lack of congruence between WMH-CIDI defined and self-reported BD, and few people taking lithium were positive for BD on the WMH-CIDI, which raises concern about the validity of the WMH-CIDI’s assessment of BD.

Conclusion: Prevalence estimates using the WMH-CIDI align with those reported in prior literature. However, existing algorithms used to diagnose BD in the WMH-CIDI appear to result in a large proportion of misclassification. Fully structured interviews may be inaccurate for
assessing BD. Future research should aim to develop and evaluate new methods of identifying BD in the general population.
Preface

This thesis includes two manuscripts. The first manuscript was published in the Canadian Journal of Psychiatry, the second manuscript was submitted to the Journal of Social Psychiatry and Psychiatric Epidemiology and is under review. The first author on both manuscripts was responsible for the data analyses, interpreting the results and the writing of the manuscripts, with support from the senior author and co-authors. All authors participated in the review of each work. With written permission from the publisher and co-authors, the manuscripts are included as chapters in this thesis.


Acknowledgements

I would like to sincerely thank everyone who assisted me in this process, both directly and indirectly. I would like to acknowledge all staff and faculty in the Department of Community Health Sciences. Foremost, thank you to my supervisor, Dr. Scott Patten, for your relentless support and invaluable mentorship. To my thesis supervisory committee, Drs. Andrew Bulloch, Anne Duffy, and Lauren Bresee, thank you for sharing your wisdom, and providing feedback and encouragement. To Jeanne Williams and Dina Lavorato, thank you for your assistance (and patience) with data analysis in the RDC. A special thanks to Maria McInerney and Stephanie Gill, my classmates and friends, for supporting me through the ups and downs of the journey and for making it a truly wonderful experience. Finally, I would like to express gratitude to my family for your unconditional support and for instilling in me the confidence and work ethic to pursue graduate studies and excellence in everything I do. Funding for this project was received from a grant from Hotchkiss Brain Institute, a Queen Elizabeth II/CIHR Scholarship and an Alberta Graduate Scholarship.
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Chapter One: INTRODUCTION
1.1 Overview of Research Project

Bipolar disorder (BD) is a severe neuropsychiatric disorder that typically onsets during adolescence and recurs or persists lifelong. Prevalence estimates for BD are very heterogeneous, but recent meta-analyses estimate the prevalence of BD between 0.7% and 2.0%.\(^1\)\(^-\)\(^4\) BD is associated with substantial morbidity. People with BD are at increased risk of other medical and psychiatric complicating conditions,\(^5\) impaired daily life functioning and disability, and decreased quality of life.\(^6\)

To date, research on the epidemiology of BD in Canada has been both infrequent and inadequate. In the absence of adequate epidemiological information, decision-making bodies suffer a lack of clear direction. Epidemiological information can inform decisions at all of the municipal, provincial and federal levels. For example, such decision-making bodies may include the City of Calgary, Alberta Health Services and Health Canada. At the municipal level, epidemiological prevalence data can inform city planning and service provisions in areas such as housing and supports such as police services. For example, population data provide a referent against which municipally supported populations can be compared, potentially supporting the identification of over- or under-served demographic groups. Epidemiological information is also useful for setting priorities that are relevant to municipal governments, which often form selective partnerships with charities and independent community agencies. At the provincial level delivery of services is often quantified using administrative data, which represent treated prevalence. The reach of formal health services (which in Canada are mostly provincially funded) and access to services cannot be assessed without accessing prevalence data that does not depend on treatment seeking.
The federal government also supports and sometimes operates health services for populations (e.g. the Armed Forces and First Nations) not covered by provincial health plans, which requires additional data. The federal government also has a role in health surveillance and, therefore, has an associated interest in national epidemiological data, identifying policy options and recommendations, and evaluating the impact of policy decisions.

Progress in community-level knowledge about BD in Canada has lagged for several reasons. Foremost, BD is often a difficult psychiatric illness to diagnose at the community level. Physicians usually require an extensive collection of information about the patient, their medical history and illness course, and differential diagnosis is often difficult owing to considerable overlap of BD symptoms with other psychiatric disorders. Furthermore, changing diagnostic criteria, evolving nosology of BD, and modifications to measurement tools limit comparability among studies.

Data from the most recent survey of mental health in a nationally representative sample in Canada, the 2012 Canadian Community Health Survey-Mental Health (CCHS-MH), were released in Fall 2013. The instrument used in this survey, the World Mental Health version of the World Health Organization Composite International Diagnostic Instrument (WMH-CIDI), was recently revised with the intent to produce more valid prevalence estimates of BD in general population samples. The release of these data seemed to provide a valuable opportunity to obtain updated epidemiological information about BD, which was originally the main purpose of this thesis.
1.2 Aim

The original purpose of this thesis was to obtain updated estimates of prevalence of BD in Canada, to differentiate bipolar I (BDI) and bipolar II (BDII) disorder for the first time in a nationally representative sample in Canada, and to describe persons with BD in terms of demographic features, health status, impact and mental health service utilization. Over the course of this thesis, in response to initial findings, a third objective emerged, which was to examine some indicators of validity of the instrument. Specifically, I assessed criterion validity of the WMH-CIDI classifications, by examining how closely a positive WMH-CIDI classification is associated with other criteria that also likely suggest the presence of BD.

1.3 Background

1.3.1 A Brief History of Bipolar Disorder

The concept of BD has a long history, but has only recently evolved into how we understand it today. The term *melancholia* dates prior to Hippocrates and derives from the assumption, at that time, that mental disorders originated from disruptions in bodily fluids and the brain. The origin of the term *mania* is less clear and has been associated with a number of different meanings throughout history. Among the earliest references were also in ancient Rome and Greece and have usually referred to forms of “non-normal” temperaments, typically increased excitement and agitation. There was a long interval between these historical descriptions and more modern concepts of BD (as cited in ⁹).
In the earliest years during the presence of asylums, mania referred generally to insanity. However, over the following century, an evolution of thinking about insanity occurred such that disorders of mood could be distinguished from other types of insanity. During the mid-19th century, Jean Pierre Falret and Jules Baillarger described a distinct set of disorders, which manifested as manic excitement and melancholia and an alternation from one to the other. Falret and Baillarger termed this disorder *folie circulaire* (circular insanity) and *folie à double forme*, respectively (as cited in ⁹, ¹⁰).

Around 1900, Emil Kraepelin established a broad division between two psychotic disorders of adulthood: *dementia praecox* (later renamed schizophrenia) and *manic-depressive psychosis* (later evolved into BD, but not as it is understand it today). The main determinant of the dichotomy was based on Kraepelin’s understanding of disease course and mental deterioration. While dementia praecox was a disorder of cognitive function where the patient never returned to normal, manic-depressive psychosis was characterized by a remitting course. Kraepelin incorporated Falret's *folie circulaire* into the latter manifestation as one of its many symptomatic forms (as cited in ⁹, ¹⁰).

Kraepelin’s manic-depression was a unitary concept that subsumed a range of mood disorders including both unipolar and BDs. While depression was dominated by lowered mood and slowed mental and physical activity, mania was dominated by elevated mood and accelerated mental and physical activity. Mixed states (introduced by Kraepelin’s colleague, Wilhelm Weygandt) occurred when domains of both depression and mania were present. Kraepelin described six
mixed states, which can be summarized into three major types: anxious depressive-mania, excited depression, and depression with flight of ideas (as cited in \textsuperscript{11}).

Kraepelin’s concept of manic-depression was highly influential and lasted for several decades. However, opposition to Kraepelin grew, particularly in Germany. Colleagues Karl Kleist and Karl Leonhard, described various affective disorders, which they assumed to be distinct entities. In one such description, Kleist coined the term \textit{bipolar} (as cited in \textsuperscript{9,10}).

In 1966, Jules Angst and Carlo Perris, independently, published papers from which they concluded that that unipolar disorders and BD are autonomous. Their work was followed and supported by a series of studies by other investigators. With the release of DSM-III in 1980, the dichotomy between unipolar depression and BD was officially recognized. In future versions of DSM, additional subgroups of BD were added including, hypomania, BDII, cyclothymia, and mixed episodes (as cited in \textsuperscript{9,10}).

\textit{1.3.2 Definition of Bipolar Disorder}

BD is a complex, genetically-based psychiatric disorder characterized by mood instability, manifesting through sustained episodes of disordered mood. Presently, there are two primary systems for classifying psychiatric disorders: The Diagnostic and Statistical Manual (DSM-5) \textsuperscript{12} and the International Classification of Diseases (ICD-10). \textsuperscript{13} Operational definitions for BD in this study are based on the DSM-IV \textsuperscript{14} criteria and classifications because the measurement instruments and algorithms employed in the study derive from the DSM-IV.
The DSM-IV \textsuperscript{14} recognizes several subtypes of BD including BDI and BDII, in addition to bipolar disorder not otherwise specified and cyclothymic disorder. Of primary interest in this study are BDI and BDII. In DSM-IV, a diagnosis of BDI requires at least one manic episode during the lifetime, defined by: (a) the experience of a distinct period of expansive, elevated or irritable mood; (b) a minimum episode duration of 7 days; (c) the presence of three or more of seven specified symptoms (or at least four if the mood is only irritable); (d) the episode is associated with a marked change in functioning that is observable by others or necessitates hospitalization or where psychotic symptoms are present; and (e) the mood disturbance is not better explained by the physiological effects of a substance. The diagnostic criteria for BDII require at least one hypomanic episode plus at least one major depressive episode during the lifetime. The primary distinction between mania and hypomania is that hypomania requires shorter duration of elevated mood, energy or agitation (4 days rather than 7), the mood disturbance is not severe enough to cause marked impairment in daily functioning and cannot include psychotic symptoms or require hospitalization. The clinical courses of BDI and BDII are often chronic, with multiple episodes of elevated, depressed or mixed mood. \textsuperscript{15} Although DSM-IV is used in this thesis, it is notable that DSM-5 \textsuperscript{12} is the current version of DSM. The primary change from the fourth to the fifth version related to the definition above includes an emphasis on changes in activity and energy as well as mood in criterion (a).

The WMH-CIDI is a fully structured diagnostic interview, meaning that the questions included in the interview are predetermined and fully scripted. In an attempt to achieve a high level of reliability, fully structured interviewing is rigid and does not allow deviations from the script;
therefore, the interviewer cannot provide clarification for a question nor can they ask follow up questions. The WMH-CIDI used in the CCHS-MH is based on DSM-IV diagnoses and operational definitions. However, there are notable nuances between the DSM criteria and the criteria included in the WMH-CIDI. First, the WMH-CIDI includes a requirement for increased energy that was not in the DSM-IV (however, it is in the DSM-5). Additionally, a criterion for a manic episode includes a duration of several days or longer (rather than 7 days, as in the DSM-IV and DSM-5), and a criterion for hypomanic episodes includes a duration of 14 or 7 days (rather than 4 days, as in the DSM-IV and DSM-5) depending on the severity of symptoms. Finally, the WMH-CIDI includes the concept of “super-symptoms” (that include becoming overly friendly, behaving inappropriately, getting involved in “foolish schemes”, getting into financial trouble, believing that they were someone else or connected to a famous person), which are extra to the requirements in the DSM-IV.

Although the DSM and ICD provide widely established systems for diagnosing BD, the nosology of BD is continually evolving and there exists low agreement among psychiatrists with divergent opinions regarding the breadth of the illness and criteria essential for its diagnosis. Minimum duration, stem criteria, and number of signs and symptoms are among the topics contributing to differing opinions. In particular, the emergence of “hard” and “soft” definitions of BD have developed into a topic of much debate. While some psychiatrists prefer a more stringent (hard) definition of BD that includes more severe and typical cases, others prefer a more inclusive (soft) definition that extends to a larger spectrum of BD cases and includes “minor” manifestations of mood instability (i.e. subthreshold cases). Zimmerman provides several possible negative implications for lowering the diagnostic threshold for BD associated
with both research and clinical practice. First, lowering the threshold for diagnosis is likely to lead to an increased false positive rate in diagnostic tests. If so, patients may be inappropriately prescribed mood stabilizers or other unnecessary medications leading to potentially significant adverse side effects. In addition, he points out that there is a general lack of adequate evidence for efficacy of mood stabilizers in treating subthreshold BD cases. Nevertheless, “softer” definitions of BD are emerging. For example, Akiskal and colleagues have recommended lowering the minimum symptom duration for hypomanic symptoms to 1-2 days from the 4 days specified in the DSM-5. These suggestions are owing to a body of literature based on epidemiological and clinical data interpreted as suggesting validity of definitions for hypomania that use a lower threshold than 4 days and possible clinical significance of subthreshold hypomanic symptoms, particularly when coupled with depression.

The evolution of BD nosology and persistent disagreement over its operational definition reflects, to some degree, conflict between different applications. For example, a definition that includes a broader spectrum of symptoms for BD may be useful in a clinical setting in order to account for atypical cases or patients with clinically significant adverse psychological symptoms possibly associated with BD who are likely to benefit from treatment, but may otherwise go untreated because their symptoms do not meet the requirements for formal diagnosis. On the other hand, an overly inclusive definition in population research may lead to a grossly elevated prevalence. Furthermore, atypical symptoms may represent a real illness much more often in a clinical setting than in the general population. The apparently widespread disagreement not only has clinical implications, but also implications for research. Epidemiological research relies on a valid, reliable and stable definition in order to minimize misclassification of the illness and to
enable comparisons between studies. This difficulty with BDs operational definition likely contributes to the heterogeneity observed in the epidemiologic literature for BD.

1.3.3 Prevalence of Bipolar Disorder

There exists substantial heterogeneity in prevalence estimates of BD in epidemiologic literature. In addition to inconsistencies in diagnostic approaches and operational definitions, different measurement instruments and study protocols may further contribute to the broad range of observed prevalence estimates.

A systematic review by Ferrari and colleagues was conducted to assess the quality and availability of global prevalence estimates of bipolar spectrum disorder. The authors also explored a number of potential sources of heterogeneity in prevalence estimates including differences in prevalence estimates by gender, response rate, combinations of BD definitions, and screening tools used to assess BD. The review included studies that used general population samples, produced point, 6 or 12-month prevalence estimates, and that defined BD (including BDI, BDII, cyclothymia, and BD-not otherwise specified) based on criteria from either the ICD or DSM. A total of 29 epidemiological studies from 20 different countries fit the well-defined inclusion criteria.

From these data, the estimated mean pooled point prevalence was 0.74% and 6 or 12-month prevalence was 0.84%. The range of prevalence estimates among all studies included in the systematic review was substantial; the range of point prevalence estimates was 0.0-3.7%, while 6
or 12-month prevalence estimates ranged 0.0-2.4%. This degree of heterogeneity is also apparent in the broader existing literature. For example, a study based on the World Mental Health Survey Initiative estimated a prevalence of 1-2% for BSD, whereas a study from the United States observed a prevalence of at least 5%. Interestingly, both studies used the same diagnostic instrument, the WMH-CIDI (the same as the instrument used in the CCHS-MH); however, the study from the United States computed prevalence using a softer definition of BD developed by the investigators. Nevertheless, the mean pooled prevalence estimates are somewhat lower than estimates observed in other prevalence studies not included in the systematic review. This may suggest that studies perceived as lower quality (i.e. those that did not meet the standards to be included in the systematic review) are overly inclusive, perhaps due to a lack of specificity of their diagnostic measures. On the other hand, prevalence estimates for males and females were similar, which has been consistently observed in other studies.

The review did not attempt to differentiate the subtypes of BD given its main objective, which was to estimate the pooled prevalence of bipolar spectrum disorder. Although, they did observe that, at the aggregate level, prevalence estimates were not significantly different regardless of the combinations of BD diagnoses included in the different studies. On the other hand, significant differences were observed depending on the diagnostic instrument used to assess BD. A possible explanation is that considerable differences in thresholds of diagnoses exist across diagnostic assessment instruments and may be a reflection of disparities in operational definitions of the bipolar spectrum. Furthermore, the review does not address problems that are pervasive in the broader literature. For example, the pooled estimates in the paper are based on point and 6-month prevalence, but a definitive diagnosis of BD is based on lifetime experiences of major mood
episodes (i.e. manic or hypomanic and major depressive). As a result, definitions of forms of prevalence other than lifetime may have varied meanings within the literature. While some investigators may define past year prevalence of BDI as the occurrence of a manic episode during the past 12-months, others may view it as the occurrence of any of a manic, hypomanic or major depressive episode as all may be indicative of active illness. This exemplifies one of the major challenges in BD research related to obtaining valid and consistent measurements of symptoms and diagnosis.

Prevalence estimates also differed as a function of overall response rates. Studies with poor (less than 60%) response rates had significantly lower prevalence estimates than those with average (60-79%) and excellent (80% or greater) response rates, while studies with average response rates had significantly higher prevalence than those with excellent response rates. The authors do not offer explanations for this finding, but it is reasonable to speculate that these differences may be due to varying selection probabilities of people with BD across the studies with poor, average and excellent response rates. For example, studies with excellent response rates may have targeted mainly healthy individuals that are more able to participate, thereby leading to fewer participants with BD and a lower observed prevalence. On the other hand, studies with average participation rates may have a more equal distribution of selection probabilities for the general population and people with BD, leading to a more accurate estimate of prevalence. Finally, studies with poor response rates may have had flawed sampling and selection procedures leading individuals who are ill at the time of the survey less likely to participate yielding a lower estimated prevalence. Population-based samples are often preferred over clinical samples because of their superior representativeness. However, unequal selection probabilities of people
with BD versus the general population may introduce bias. This highlights the importance of well-designed and well-executed studies when surveying the general population.

Prevalence estimates serve as a foundation for planning population health interventions, monitoring progress and setting priorities for resource allocation and research. For this reason, it is important to have prevalence estimates for BD that are specific to Canada. Unfortunately, Canadian information about the epidemiology of BD is limited. Only three studies have estimated prevalence of BD using community samples. Notably, all three studies were conducted over one decade ago, only one has examined data from a nationally representative sample of Canadians, and none have differentiated the BDI and BDII subtypes.

1.3.4 Prevalence of Bipolar Disorder in Canada

An early prevalence study used data from the Edmonton Survey of Psychiatric Disorders conducted between 1983-1986. The study utilized a two-stage sampling design, whereby addresses were selected from an electronic list of urban residential addresses in Edmonton, Alberta, followed by random selection of a single eligible respondent residing at that address. Eligible respondents were at least 18 years of age and usual occupants of the household (n=3,258). The overall response rate for the survey was 71.6%. Trained lay interviewers conducted assessments using version III of the Diagnostic Interview Schedule (DIS). From these data, the estimated 6-month prevalence of manic episode was 0.1% (SE=0.1%), and the lifetime prevalence was 0.6% (SE=0.1%).
The prevalence of affective disorders was also studied using data from the 1990-1991 Ontario Health Supplement, a provincial epidemiological survey of the prevalence of mental disorders. Respondents were urban (n=7107) and rural (n=2856) residents of Ontario ages 15 to 64 years. The overall response rate for the survey was 88.1%. Interviews were conducted using a modified CIDI (UM-CIDI). The estimated 12-month prevalence for BDI was similar for urban (0.6%, 95% CI 0.3% - 1.0%) and rural (0.4%, 95% CI 0.1% - 0.7%) groups. BDII was not examined in this study.

The most recent prevalence study in Canada used data from CCHS 1.2. This is the only study to date to estimate prevalence based on a nationally representative sample in Canada. The CCHS 1.2 was a national survey of the prevalence of mental disorders conducted in 2002 that also collected detailed information about health correlates and mental health service utilization. The overall response rate for this survey was 77%. The target population of this survey was Canadians ages 15 years and older living in the 10 provinces. From these data, the estimated prevalence of BDI was 2.20% (95% CI 1.94% - 2.37%).

It is interesting that the prevalence estimates for the Edmonton and Ontario community studies were very similar. It is notable that the DIS used in the Edmonton survey was a structured interview based on the third edition of the DSM, whereas the UM-CIDI used in the Ontario Health Supplement was based on the fourth edition (DSM-IV). The term bipolar disorder was first introduced in DSM-III, replacing the previous term manic depression, although the subtypes of BD were not included until the next version, DSM-IV. While there have been slight changes in the language used in the diagnostic criteria for BDI and explanations of differential diagnosis,
the duration and number of symptoms required for diagnosis has not changed across more recent versions of the DSM. The primary difference between the DIS and UM-CIDI is the placement of the screening questions. In the DIS, the screening questions were placed at the beginning of each section, whereas in the UM-CIDI, screening questions were placed at beginning of the questionnaire. This was done with the aim of preventing the possibility that respondents would learn to get out of answering many questions by answering “no” to the screening question. Despite the differences between the interviews used in the Edmonton and Ontario surveys, their prevalence estimates were comparable.

Analyses of the CCHS 1.2 observed a prevalence that is approximately 4-fold higher than the previous prevalence studies. The substantial increase in prevalence cannot be explained by random variation given that 95% confidence intervals for the estimates do not overlap. The UM-CIDI used in the Ontario study is also different than the CIDI used in CCHS 1.2. Importantly, it has been recognized that the version of the CIDI used in the CCHS 1.2 may overestimate the prevalence of BD and the CIDI has since been revised with the goal of producing more accurate estimates.²⁹,³⁰

Bulloch et al.³¹ estimated the treated prevalence of BD using data from the CCHS 1.2 and administrative data from a central repository of information for mental health services in the Calgary Zone. Estimates were limited to persons aged 18 years and older. The administrative data from the Calgary zone included visits with mental health services for the main reason of

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²⁹ The previous version of the CIDI used in the CCHS 1.2 is referred to as the CIDI, while the updated version used in the CCHS-MH is referred to as the WMH-CIDI.
BDI or BDII between 2002 and 2008. This excluded general practitioners or medical care unrelated to their condition. The CCHS 1.2 used the CIDI to derive a diagnosis of BD. Algorithms determined the presence of disorder based on symptoms reported by the respondent. Treated prevalence in the CCHS 1.2 included individuals who met the criteria for BDI using the CIDI and who also consulted with a psychiatrist during the 12-months preceding the interview. From the CCHS 1.2 the past year and lifetime treated prevalence among persons with BDI was 0.44% (95% CI 0.36% – 0.52%) and 1.17% (95% CI 1.02% – 1.33%), respectively. The estimated 7-year treated prevalence derived from the administrative data was 0.41% (95% CI 0.40% - 0.42%) for BDI and 0.12% (95% CI 0.11% - 0.13%) for BDII. Although both this study and the preceding study used data from the CCHS 1.2, they observed very different prevalence estimates (1.17% vs. 2.20%). This is because Bulloch et al. restricted their sample to respondents 18 years and older treated by a psychiatrist, while the former used all respondents to the survey.

1.4 Knowledge Gaps and Significance

Epidemiological knowledge of BD and other mental illnesses in Canada relies heavily on information collected from population surveys. Although the Public Health Agency of Canada has been monitoring physical illnesses using the Canadian Chronic Disease Surveillance System for many years, the system was only recently expanded (in 2010) to monitor mental illnesses including BD. Since the initiative is relatively new, the adequacy of the information collected is still unclear. The Surveillance System uses health administration data (e.g. records of physician billing, hospital discharge, etc.) and as such captures only the treated prevalence, which may be problematic for epidemiologic estimates given that BD is believed to be an undertreated
condition and, presently, many sources of administrative data in Canada cannot distinguish BD from major depressive disorder (due to a reliance on three digit ICD-9 codes, which are the same for both major depressive disorder and bipolar disorders). Therefore, it is important that large general population surveys are available to guide health policy and planning practices in Canada. Yet, only three general population surveys involving BD have been conducted. Moreover, all three surveys were conducted over one decade ago, only one examined a nationally representative sample of Canadians and none differentiated BDI and BDII. The lack of current epidemiologic information about BDI and the absence of information about BDII represent an important knowledge gap in Canada.

The ability to differentiate BDI and BDII subtypes in a nationally representative survey is significant. A major advantage of population surveys is the ability to capture and study individuals who use health services as well as those who do not seek help or those who are undiagnosed. Early recognition and prompt treatment of BD is important for preventing interference with social and occupational activities and other complications and improving prognosis. However, barriers to service utilization among persons with BD may be related to specific demographic characteristics and clinical features, and may be similar or different between the two BD subgroups. Furthermore, it is widely understood that the clinical course, prognosis and response to treatment differs between the subtypes. Among other differences, studies have shown that persons with BDI display more frequent comorbidity with substance abuse disorders and higher likelihood of hospitalization and suicide attempts, while persons with BDII display a greater number of affective episodes, more chronic depression and poorer return to baseline psychosocial functioning. However, generalizability of these finding may
be low because the majority of evidence is derived from small prospective cohort studies, which may not be representative of the distributions of these characteristics in the general population. Finally, BDII shares many clinical features with unipolar depression and individuals with BDII often seek treatment for depression rather than symptoms of positive polarity. Angst and colleagues suggests that patients often disregard hypomanic symptoms because they may be advantageous to their functioning rather than harmful. Therefore, individuals with BDII may be less often included in studies that use administrative data and, therefore, community samples hold an advantage of adding information that may otherwise be missed.

Among other goals, the CCHS-MH was intended to fill these knowledge gaps – to obtain updated epidemiological information about BD, differentiate BDI and BDII disorders in a nationally representative sample, and allow comparisons with data collected in the CCHS 1.2.

### 1.5 Canadian Community Health Survey – Mental Health

The target population of the CCHS-MH is all Canadian household residents ages 15 years and older living in the 10 provinces. All together it represents approximately 3% of the total population. Persons excluded from the survey were individuals living on reserve settlements, institutionalized individuals, and full-time members of the Canadian Forces. The survey employed a three-stage probability-sampling technique. In stage one, geographic areas, called clusters, were selected using the area frame designed for the Labour Force Survey. In the second stage, dwellings are systematically selected from a list of all dwellings in the cluster. In the final stage, a single eligible resident is selected from each dwelling using selection probabilities.
derived from the composition of the household. Clustering refers to the fact that individuals of a particular geographical area tend to be more alike than individuals randomly sampled from the population. When estimates are produced based on these data, clustering leads to unrealistically low variance estimates. In order for estimates based on these survey data to be more representative of the target population and to produce corrected variance estimates, survey weights must be incorporated into the calculations.

Survey weights for the CCHS-MH are provided by Statistics Canada, which are use to produce corrected estimates. A bootstrap re-sampling method is used to obtain the final point estimate and variance estimate. In this process, each individual included in the final sample is given a survey weight. Re-samples (with replacement) of n-1 respondents are selected and variance is estimated for each re-sample. The survey weight is recalculated for each re-sample and the final bootstrap weights are obtained. This process is repeated 500 times per respondent. Finally, the point estimate for each of the 500 samples is estimated and the standard deviation of these estimates is the bootstrap variance estimator. Using statistical packages, bootstrap variance estimators may be used to calculate the variances of frequencies, proportions, and linear regression.

1.6 Objectives

Despite recognition of the important impact of BD, advances in epidemiological knowledge of the condition have been hindered by unstable diagnostic conceptualizations. To further add to this issue, epidemiologic studies of BD in Canada are outdated and existing information is
inadequate and has been inconsistent. Given the difficulty in studying BD at the population level observed in the broader literature, it was recognized that studying BD in the CCHS-MH might involve similar challenges. Nevertheless, the use of the WMH-CIDI in the CCHS-MH provided the first opportunity to estimate the prevalence of BDI and BDII and to describe the subtypes separately, which would represent a major milestone in epidemiological description of the conditions. As a result, the original main objectives for this descriptive epidemiological research project were to:

1. obtain updated crude, age- and sex-specific lifetime prevalence estimates for each of BDI and BDII in 2012; and
2. characterize persons with BDI and BDII in terms of demographic features, health status and impact, and mental health service utilization.

Since this survey was the first in Canada to use the WMH-CIDI and in response to initial findings, some indicators of validity of the instrument’s classifications were also examined.

1.7 Thesis Outline

The literature review provided above is followed by two manuscripts and a conclusion. Chapter 1 provides an introduction to the research project, aims, and background literature. Chapters 2 and 3 are the main bodies of research, while chapter 4 provides a conclusion, discussing the results of the studies in context of existing knowledge, and making suggestions for future research.
Chapter Two: PREVALENCE OF BIPOLAR I AND II DISORDER IN CANADA
2.1 ABSTRACT

Objective: Current epidemiologic knowledge about BD in Canada is inadequate. To date, only three prevalence studies have been conducted; only one was based on a national sample, and none have distinguished between BDI and BDII. The objective of this study was to estimate the prevalence of BDI and II in Canada in 2012.

Method: Data were obtained from the CCHS-MH, a cross-sectional survey of a nationally representative sample of household residents ages 15 years and older (n=25,113). The survey response rate was 68.9%. Interviews were based on the WMH-CIDI. Prevalence was estimated using generalized linear modeling. Prevalence of self-reported BD and utilization of lithium were also estimated.

Results: The estimated lifetime prevalence of BDI and II (based on the WMH-CIDI) in Canada in 2012 was 0.87% (95% CI 0.67%–1.07%) and 0.57% (95% CI 0.44%–0.71%), respectively. Prevalence did not differ by sex. The estimated prevalence of self-reported BD was 0.87% (95% CI 0.65%-1.07%). There was a lack of congruence between WMH-CIDI defined and self-reported BD and few individuals taking lithium were positive for BD on the WMH-CIDI, which raises some concerns about the validity of the WMH-CIDI’s assessment of BD.

Conclusions: These prevalence estimates align with those reported in prior literature. However, caution should be exercised when interpreting general population studies that use WMH-CIDI defined BD due the possibility of misclassification.
2.2 Introduction

Prevalence estimates serve as a foundation for planning population health interventions, monitoring health system progress and setting research priorities. To date, only three general population studies of BD prevalence have been conducted in Canada and only one of these used a nationally representative sample. Two community-based studies, conducted in Edmonton and Ontario, obtained prevalence estimates for a manic episode, of 0.4% (lifetime) and 0.4% to 0.6% (12-month), respectively. More recently, a study using data from the 2002 Canadian Community Health Survey – Mental Health and Well-being (CCHS 1.2) estimated a lifetime prevalence of mania at 2.2%. However, it has since been suspected that the diagnostic tool used to diagnose BDI in the latter study may have overestimated the prevalence. Also, a substantial limitation of the previous studies is their inability to distinguish between BDI and BDII – no available Canadian estimates have made this distinction. The goal of this study was to employ newly calibrated algorithms to produce national estimates of BDI and BDII prevalence.

2.3 Method

2.3.1 Data Source

The CCHS-MH was a cross-sectional survey conducted by Statistics Canada. Detailed information about the survey is available from Statistics Canada. Information was collected from a nationally representative sample of household residents aged 15 years and older living in the 10 provinces (this target population covers approximately 97% of the Canadian general population).
population). Persons excluded from the survey were individuals living on reserve settlements, institutionalized individuals, and full-time members of the Canadian Forces. The survey employed a multi-stage probability-sampling technique. One person aged 15 years or older per sampled household was randomly selected to participate. Interviews were conducted by trained lay interviewers. The majority of interviews (87%) were conducted in person.

2.3.2 WMH-CIDI Classification

Interviews were based on the WMH-CIDI, 8 a fully structured interview intended to derive diagnoses of a number of mental disorders. Respondents answered a series of questions about possible symptoms of mania, hypomania and major depressive episode. Algorithms determined the presence or absence of BDI and BDII based on the answers received. The algorithms were updated through calibration adjustments based on clinical reappraisal studies intended to increase the accuracy of estimation. 8 These re-calibrated algorithms were used to derive a diagnosis according to operationalizations of DSM-IV 14 definitions and criteria. Respondents were classified as having BDI if they had ever experienced (a) at least six symptoms of mania; and (b) at least two “super-symptoms” (becoming overly friendly, behaving inappropriately, getting involved in “foolish schemes”, getting into financial trouble, believing that they were someone else or connected to a famous person). Respondents were classified as having BDII if they ever experienced (a) distinctly elevated mood lasting 7 days or longer, at least 3 symptoms of mania, euphoria or racing thoughts, and marked impairment in social or occupational functioning (or symptoms causing less severe impairment, but lasting at least 14 days); (b) at least one lifetime major depressive episode; and (c) did not meet the criteria for lifetime BDI. 30 Notably, the re-
calibrations do not completely align at the level of face validity with the DSM-IV diagnostic criteria. For example, the concept of “super-symptoms” and a 14 day duration are not present in DSM-IV (nor are they present in DSM-5). They represent adjustments intended to improve accuracy of prevalence estimation based on clinical calibration work. The interview used in the CCHS-MH is the same version as the one used in the clinical calibration study and was not modified by Statistics Canada.

2.3.3 Self-reported Bipolar Disorder

Respondents were asked about a list of conditions diagnosed by a health professional that had lasted or were expected to last more than six months. For self-reported BD, respondents were asked: “Do you have a mood disorder such as depression, bipolar disorder, mania or dysthymia?” Persons who answered yes were asked what disorder they were diagnosed with (more than one response was permitted).

2.3.4 Lithium Use

Medication use in the sample was collected as drug identification numbers for all psychotropic medications taken within the two days preceding the interview. Lithium was of particular interest in this study because lithium is a first-line of treatment for prophylaxis of BD, as recommended by current Canadian guidelines, and is likely to be used more exclusively than other mood stabilizers to treat BD.
2.3.5 Statistical Analysis

Data analysis was carried out at the Prairie Regional Data Centre at the University of Calgary using the statistical software, Stata 13.0. Crude and sex-specific prevalence were estimated as frequencies with associated 95% confidence intervals. The age-specific pattern was examined using generalized linear models of the binomial family with the log link function. An age-squared term was included in the model due to a better fit, based on comparing Akaike Information Criteria and Bayesian Information Criteria between models with and without the quadratic age term. Models were also assessed for an age-sex interaction using likelihood ratio tests and Wald tests. Analyses were carried out separately for WMH-CIDI classified BDI and BDII, self-reported BD, and lithium use. All analyses were weighted using the recommended procedures and replicate bootstrap weights provided by Statistics Canada in order to produce valid confidence intervals and results representative of the target population. For the remainder of the study, prevalence estimates for BD (WMH-CIDI classified and self-reported) refer to lifetime prevalence. In this case, lifetime prevalence is the most appropriate measurement choice because diagnostic criteria for BD relies on major mood episodes experienced at any time during the life course. In addition, the dynamic nature of the illness (persons may experience any of manic, hypomanic, mixed and/or depressive episodes in a given year) makes it difficult to define past year or point prevalence in such a way that effectively captures all persons with BD.
2.4 Results

The national response rate for the survey was 68.9% (n=25,113). Incomplete data prevented classification of some individuals into one or more subgroups of interest, the proportions of missing data were: WMH-CIDI BDI (0.39%), WMH-CIDI BDII (0.25%), self-reported BD (0.06%), and lithium use (0.82%).

The estimated prevalence of WMH-CIDI classified BDI and BDII in Canada in 2012 was 0.87% (95% CI 0.67% - 1.07%) and 0.57% (95% CI 0.44% - 0.71%), respectively. The estimated prevalence of self-reported BD was 0.87% (95% CI 0.65% - 1.07%), and the prevalence of lithium use in the sample was 0.14% (95% CI 0.08% - 0.20%). Sex-specific prevalence estimates were similar within each subgroup.

Generalized linear models including age as a quadratic term provided a better fit than those that assumed a linear association between age and log prevalence; therefore, analyses included the quadratic age function. Wald tests showed no evidence of an age by sex interaction or an age-squared by sex interaction for any of the WMH-CIDI classified BDI or BDII, self-reported BD or lithium models. Sex did not appear to modify nor confound the association between age and prevalence and, therefore, was not included in the final model. Age-specific prevalence for WMH-CIDI classified BDI and BDII and self-reported BD appear to increase with age until mid-30s, then subsequently decline. The prevalence of lithium use appears to increase steadily with age, then plateau at about 55 years of age. Figure 2.1 shows a plot of the fitted values with age.
for the generalized linear models estimating prevalence of each of WMH-CIDI classified BDI and BDII, self-reported BD, and lithium use.

Figure 2.1 Plot of the fitted values for the generalized linear model by age for each of: WMH-CIDI-classified BDI and BDII, self-reported BD, and lithium use in the sample.
Table 2.1 shows cross-tabulations of the WMH-CIDI defined BD I and BD II, self-reported BD and lithium use subgroups. Among those using lithium, most (74%) reported that they had been diagnosed with BD, consistent with expectation. However, the overlap of the other categories was low. For example, only 19% of those with WMH-CIDI defined BD I reported a diagnosis of BD, and of those who self-reported a BD diagnosis, only 19% were positive for BD I on the WMH-CIDI.

**Table 2.1 Cross-tabulations of the WMH-CIDI BD I and BD II, self-reported BD and lithium use subgroups.**

<table>
<thead>
<tr>
<th>Denominator</th>
<th>Bipolar I WMH-CIDI</th>
<th>Bipolar II WMH-CIDI</th>
<th>Self-reported bipolar</th>
<th>Lithium use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bipolar I WMH-CIDI</td>
<td>–</td>
<td>–</td>
<td>0.19 (0.10, 0.28)</td>
<td>0.03 (0.00, 0.07)</td>
</tr>
<tr>
<td>Bipolar II WMH-CIDI</td>
<td>–</td>
<td>–</td>
<td>0.13 (0.04, 0.21)</td>
<td>0.03 (0.00, 0.07)</td>
</tr>
<tr>
<td>Self-reported bipolar</td>
<td>0.19 (0.09, 0.29)</td>
<td>0.08 (0.03, 0.14)</td>
<td>–</td>
<td>0.14 (0.07, 0.21)</td>
</tr>
<tr>
<td>Lithium use</td>
<td>0.20 (0.03, 0.37)</td>
<td>0.11 (0.00, 0.26)</td>
<td>0.74 (0.57, 0.92)</td>
<td>–</td>
</tr>
</tbody>
</table>

* Estimates are weighted.
2.5 Discussion

The estimated prevalence of WMH-CIDI classified BDI and BDII in Canada in 2012 was 0.87% and 0.57% respectively. The estimated prevalence of self-reported BD was 0.87%. This study provides the first prevalence estimates for BDI and BDII, separately, in a nationally representative sample in Canada.

Although WMH-CIDI-classified and self-reported BD appear to provide prevalence estimates that align with that in the literature, the two measurement methods do not appear to capture the same group of individuals. Of those who self-reported BD, very few met the WMH-CIDI criteria for BDI (19%) or BDII (8%). This suggests that misclassification of individuals may have occurred.

Lithium was used in this study as an additional referent for BD classifications. Lithium is likely to be prescribed primarily for treatment of BD (and quite infrequently for other purposes including suicide prevention, recurrent major depression and antidepressant augmentation). The proportion of lithium users that self-reported BD (74%) is consistent with this expectation, but this frequency was considerably higher than the proportion of lithium users that met the WMH-CIDI criteria for either BDI (20%) or BDII (11%). Of course, the lack of agreement between these different measures may also be due to poor recognition and under-treatment of BD. In the absence of a gold standard, it is unclear to what extent misclassification occurred in each subgroup.
An additional indication that misclassification has occurred arises from the observation that both WMH-CIDI defined subgroups showed a parabolic pattern of change in prevalence with age, with a distinct decline in prevalence from mid- to late-adulthood. This is not concordant with the trend that would be expected for a lifelong, recurrent condition in the absence of a cohort effect or an extremely strong effect of BD on mortality. This is also in contrast to results of a systematic review that found age-specific lifetime prevalence remained relatively steady across ages 18 to 64 years. The age-specific trends observed in this study may be occurring for a number of reasons. It could, theoretically, be explained to some extent by a reduced life expectancy among persons with BD, but it is unlikely that early mortality could fully explain the marked decline. Another potential explanation could be a cohort effect, with diagnoses made more frequently in more recent birth cohorts, but this explanation is also unlikely because prevalence was not unexpectedly high even in younger ages. Finally, the trend may be explained by recall bias. Studies of other mood disorders such as depression have observed similar declines with age when using lifetime prevalence, which has led to a greater emphasis on 12-month prevalence in the more recent literature. Unfortunately, types of prevalence other than lifetime to study BD may be unsuitable because definitions of BD depend on major mood episodes that occur during the life course. Specifically, the lifetime occurrence of a manic (or hypomanic) episode determines the definitive diagnosis of BD. However, in any given year there may only be episodes of manic/hypomanic or depressive polarity. For example, persons may only have a major depressive episode during the past year, and yet have a diagnosis BDI due to a previous manic episode. The apparent flaws of lifetime prevalence and its vulnerability to recall bias coupled with the need to focus on lifetime prevalence may contribute to the discrepancy in WMH-CIDI classifications.
These findings appear to contrast with a study of validity of the WMH-CIDI in relation to standardized clinical assessments in the World Health Organization World Mental Health Survey Initiative. The study showed good concordance between the WMH-CIDI and Structured Clinical Interview for DSM-IV (SCID) diagnoses of BDI and BDII in clinical reappraisal sample, with sensitivity and specificity of approximately 87% and 97%, respectively. However, a specificity of 97% implies a false positive rate of 3% and this is not consistent with the observed prevalence of <1%, even if the sensitivity is zero. Even much higher specificity would result in a high proportion of WMH-CIDI positive subjects being false positive, which, combined with suboptimal sensitivity could explain these results.

It is possible that fully structured interviews are inadequate for accurate diagnosis of BD in the general population. Notably, earlier versions of the WMH-CIDI included diagnostic modules for psychotic disorders, but the modules were excluded from later versions of the instrument because their outputs were invalid. For example, false positive rates for psychotic symptoms such as delusions and hallucinations were found to be quite high, possibly due to misunderstanding of the interview questions, lack of insight, drug-induced states, or religious beliefs. Cross-validation studies repeatedly showed poor agreement with clinical diagnoses within the National Comorbidity Survey and Epidemiologic Catchment Area studies. This may be due to the inability of a rigid, fully structured interview to assess such subtle disturbances and to collect the extensive contextual information required for accurate diagnosis. Similar problems may apply to the measurement of BDI and BDII in the general population using fully structured interviews. For example, it may be difficult for a fully-structured diagnostic interview to distinguish a normative adolescent experience from hypomanic symptoms.
In Canada, mental health policy and planning still relies heavily on information collected from population surveys. If the measurement tools used in these surveys are not valid sources information, then more resources must be allocated to developing infrastructure for surveillance through administrative data. In 2010, the Public Health Agency of Canada expanded the Canadian Chronic Disease surveillance system to monitor mental illnesses including BD. Since this is a relatively new initiative, the quality of information collected is yet to be determined. However, additional surveillance using health administration data does not solve all problems, since BD is believed to be an undertreated condition and physician billing and hospital discharge data reflect only the treated prevalence.

2.6 Conclusion

Prevalence research lays the framework for understanding burden of disease in the population. Many countries still rely heavily on population surveys for collecting public health information and surveillance. The WMH-CIDI is one of the most widely used instruments internationally. Findings in the current study raise questions about the validity of the WMH-CIDI for measurement of BDI and BDII, and by extension, our understanding of the epidemiology of BD to date. In light of the results of this study, it is recommended that future and past studies that use the WMH-CIDI be interpreted with caution.
Chapter Three: ASSESSMENT OF BIPOLAR DISORDER IN THE GENERAL POPULATION: TIME FOR A NEW APPROACH?
3.1 Abstract

**Purpose:** BD is usually identified in population surveys using algorithms applied to data collected by fully structured diagnostic interviews. However, this approach may be inaccurate for identifying BD. Psychiatric diagnosis often requires an understanding of clinical course and family history, which are difficult to assess using such algorithms. However, surveys typically collect data additional to the structured interview. We aimed to explore whether supplementation of the algorithms with additional survey information improves the apparent accuracy of the diagnostic classifications.

**Methods:** The CCHS-MH was a nationally representative survey of Canadians ages 15 and older (n=25,113). Psychiatric illnesses were identified in the survey using the WMH-CIDI. Due to concerns about the accuracy of WMH-CIDI algorithms, we developed a case definition for BD using additional survey information from outside of the WMH-CIDI. Using the WMH-CIDI algorithm and case definition, we estimated prevalence and described demographic features and health status indicators of BD. All analyses were weighted using procedures recommended by Statistics Canada.

**Results:** The estimated prevalence of BD was 1.44% (95% CI 1.20-1.68) and 0.48% (95% CI 0.37-0.59) using the WMH-CIDI algorithms and case definition, respectively. Although both methods appeared to capture severely ill individuals, there was low congruence between them.

**Conclusion:** Applying a case definition approach to identify BD in population survey data appears to have improved specificity relative to standard algorithms, but lowered sensitivity. Fully structured interviews may be inaccurate for assessing BD. Future research should aim to develop and evaluate new methods of identifying BD in the general population.
3.2 Introduction

BD is associated with substantial morbidity and mortality. As a result of the impact of BD, it is important to study the epidemiology of this illness in order to understand surveillance activities, set priorities for resource allocation and support other research activities. However, the methods for identifying BD at the population level must be valid in order to be informative.

The CCHS-MH provided an important opportunity to gain updated information about the prevalence of BD in Canada. The CCHS-MH used the WMH-CIDI to identify people with BD including BDI and BDII using calibrated algorithms produced by the WMH-CIDI developers. However, recent analyses demonstrated strikingly low congruence between the WMH-CIDI classified BD and self-reported diagnosis of BD or lithium utilization in the CCHS-MH. Among respondents who self-reported having ever been diagnosed with BD by a health professional, only 19% were classified on the WMH-CIDI as having BDI and only 8% were classified as having BDII. Furthermore, among respondents using lithium, only 20% and 11% were classified as having BDI or BDII by the WMH-CIDI, respectively, while 74% reported a professional diagnosis of BD. Since lithium is most specifically prescribed for mood stabilization and prevention of recurrence in BD, it is difficult to reconcile these findings under the assumption that the WMH-CIDI was providing valid diagnostic data. Although plausible prevalence estimates for BD were produced from both self-reported and WMH-CIDI classifications, these findings suggest that the recalibrated algorithms for BDI and BDII in the WMH-CIDI result in considerable misclassification. This is disconcerting given that the WMH-CIDI is commonly used in population-level surveys around the world.
It is increasingly acknowledged that emphasis on cross-sectional assessment and fully structured interviews are insufficient to accurately classify some psychiatric disorders including BD. For example, early fully structured diagnostic interviews included modules for psychotic disorders, but the modules were excluded from later versions of the instruments because their outputs were considered invalid. These problems with fully structured interviews may also apply to the diagnosis of BD in the general population. Rigid, fully structured interviews may be unable to detect the pathological mood and cognitive disturbances necessary for accurate diagnosis. Major psychiatric disorders share overlapping symptoms (depression, anxiety, suicidal thoughts, psychotic symptoms) and, in terms of mood dysregulation, overlap with personality disorders and normative mood swings. Additionally, psychiatric diagnosis often requires an understanding of family history, clinical course of the illness, and history of treatment response, which are difficult to assess through structured interviews in cross-sectional surveys. Given the apparent issues with fully structured diagnostic interviews, alternative approaches need to be considered.

An alternative analytical approach employs case definitions that are a set of criteria established for the purpose of deciding whether a person has a particular disease based on previously recorded information. Case definitions are frequently used for studying illnesses in administrative data sets and often incorporate a variety of information sources such as physician, hospital and prescription claims, self-reported diagnoses, and medical records to identify cases. Varying the components within a case definition has been used as a method of controlling sensitivity and specificity of the definitions. One example of this approach is the development of case definitions for vascular comorbidities in multiple sclerosis (MS). Several case definitions were generated by varying numbers of physician, hospital, and prescription claims.
required in order to identify patients with diabetes, hypertension, and hyperlipidemia in MS. The diagnostic validity of each case definition was assessed using sensitivity, specificity, and positive and negative predictive values. For example, one or more hospital code and one or more physician code over a one-year period produced a definition with 64% sensitivity and 99% specificity, whereas one or more hospital code(s) and two more physician codes over one year decreased the sensitivity considerably with only a minor improvement in specificity.

Although the case definition method has not been used in large population surveys in psychiatric epidemiology, the same principles may apply. This would involve treating the algorithm-defined WMH-CIDI diagnosis as one of several pieces of information in assigning a diagnosis rather than treating the WMH-CIDI as a stand-alone measurement instrument.

We aimed to (1) address some of the measurement problems by supplementing the existing algorithms for BD with survey data in addition to that from the WMH-CIDI; a case definition approach similar to that used in analyses of administrative databases; and (2) apply the WMH-CIDI algorithm and selected case definitions to generate descriptive epidemiological estimates in terms of selected demographic features, health status and mental health service utilization variables. To our knowledge, this is the first published attempt to apply the concept of a case definition to mental health survey data.
3.3 Methods

Data were from the CCHS-MH, a cross-sectional survey conducted by Statistics Canada between January 2 and December 31, 2012. The target population of the survey included Canadian household residents aged 15 years and older. People were excluded from the survey if they were living on reserves and other Aboriginal settlements, full-time members of the Canadian Forces or institutionalized. Sampling was based on a complex multi-stage design. Most interviews (87%) were conducted in person. Diagnoses of specific psychiatric illnesses in the CCHS-MH were based on the WMH-CIDI. Extensive information was also collected about demographic features, health and well-being, and medication and health service utilization.

3.3.1 WMH-CIDI Classified Bipolar Disorder

The WMH-CIDI contains several different modules to collect detailed information about possible mental health problems including manic, hypomanic and major depressive episode(s). Entrance into the mania/hypomania module is contingent on endorsement of at least one of two screening questions that ask if respondents have ever experienced a period of several days or longer in which they have felt (a) irritable and grouchy and/or (b) more excited and full of energy than usual. For persons who screened into and completed the mania/hypomania module, algorithms are used to determine the presence or absence of BD using the respondents answers to symptom-specific questions. The WMH-CIDI algorithms are intended to derive a possible diagnosis according to operationalizations of DSM-IV definitions and criteria. The 2012 algorithms for WMH-CIDI defined BD I and BDII are available in a previous report and
represent a modification of earlier definitions (these were employed in a 2002 national survey in Canada). It is notable that the 2012 algorithms were developed through clinical calibration adjustments intended to improve the accuracy of estimation in relation to the diagnoses made by the Structured Clinical Interview for DSM-IV (SCID). These changes were made by the WMH-CIDI development team due to a perception that the earlier 2002 algorithms over-estimated prevalence. However, the 2012 algorithms do not align completely with the DSM diagnostic criteria at the level of content validity (how well a measure represents every single component of a construct). For example, the 2012 algorithms include a minimum of 7 or 14 days duration of hypomania depending on the severity of the symptoms, whereas DSM-IV (and the 2002 algorithms) included a minimum duration of 4 days. The CCHS-MH used the published WMH-CIDI instrument, which was not modified by Statistics Canada. More detailed information about the 2002 and 2012 algorithms can be found online.

3.3.2 Case Definitions for Bipolar Disorder

We developed three candidate case definitions for BD intended to have a range of sensitivity and specificity by altering their components. The basic strategy was to increase sensitivity among those respondents reporting few symptoms but having convincing ancillary evidence (e.g. assessed by a psychiatrist and reporting a diagnosis) to improve specificity by requiring such evidence when symptoms were present. The components of the three candidate case definitions were selected from the mania/hypomania, depression, mental health service utilization, and medication use modules in the CCHS-MH. The components were: the initial screening questions for mania and hypomania modules, diagnosis of BDI and BDII based on the 2002 algorithms,
self-reported diagnoses of BD or mania, consultations with a psychiatrist and use of a mood stabilizer. The 2002 algorithms were used in this study because the 2002 algorithms align more closely to the DSM-IV criteria at the level of content validity than the 2012 algorithms. The 2002 algorithms may result in higher prevalence estimates and rather than modifying symptom patterns as was done with the recalibrated algorithms, the intention was to use additional information from outside the WMH-CIDI modules in order to improve the specificity of the symptom patterns. The candidate case definitions were evaluated based on prevalence estimates and validity in the context of the broader literature and in order to select a single definition to be used in the descriptive epidemiologic portion of the study. Full details of the case definition development and selection are available in Appendix A.

3.3.3 Epidemiologic Parameters

Demographic features. The interview included a comprehensive demographics and general information module including self-reported age, sex, marital status, highest education level of the respondent, employment status, personal income, and immigration status.

Health status. Perceived life stress was evaluated using the item: “Thinking about the amount of stress in your life, would you say that most days are…?”. Possible responses ranged from “not stressful at all” to “extremely stressful”. Disability was assessed using the World Health Organization’s Disability Assessment Schedule (WHODAS 2.0) and distress was assessed using the 6-item Kessler Distress Scale (K6).
3.3.4 Statistical Analysis

Data analysis was conducted at the Prairie Regional Data Centre on the University of Calgary main campus using STATA 13. Crude and sex-specific prevalence were estimated as frequencies with 95% confidence intervals. Age-specific prevalence was estimated using a generalized linear model of the binomial family with a log link function. Age-specific prevalence models were assessed for an age-sex interaction using Wald tests. All models were assessed for non-linear trends; Akaike Information Criteria and Bayesian Information Criteria were compared between models with and without an age-squared term. The age-squared term was included in all models due to a better fit. Demographic features and health status parameters were estimated as proportions and/or means with 95% confidence intervals. All analyses were weighted using the recommended procedures and replicate bootstrap weights provided by Statistics Canada. The weights are applied to produce results that are more representative of the target population and to produce corrected variance estimates.

3.4 Results

The national-level survey response rate was 68.9%, yielding a final sample size of 25,113 respondents.

The estimated prevalence of the inclusive, moderately inclusive and stringent case definition was 3.31% (95% CI 2.94% - 3.68%), 0.48% (95% CI 0.37% - 0.59%), and 0.22% (95% CI 0.15% - 0.29%), respectively. Prevalence estimates for males and females were not significantly different.
for any of the case definitions. All three age-specific prevalence patterns showed a gradual increase in prevalence to early to mid-adulthood, followed by a decline. Of the three case definitions, the moderately inclusive case definition appeared to have the highest criterion validity primarily based on the age-specific prevalence trend. As a result, the moderately inclusive case definition was selected to carry out the descriptive epidemiologic portion of the study (more detailed results are available in Appendix A).

The proportions of missing data for the subgroups were: 2002 CIDI algorithm (0.51%), 2012 WMH-CIDI algorithm (0.17%) and BD case definition (0.65%).

The estimated crude prevalence of BD according to the 2002 CIDI and 2012 WMH-CIDI algorithms were 2.62% (95% CI 2.30 - 2.93) and 1.44% (95% CI 1.20 - 1.68), respectively. According to the selected case definition, the estimated prevalence of BD was 0.48% (95% CI 0.37 - 0.59). The prevalence estimate for males was not different from that of females for any of the CIDI algorithms or the case definition.

The pattern of change in estimated prevalence with age is shown in Figure 3.1. The 2002 and 2012 CIDI algorithms showed similar non-linear pattern with increasing prevalence with age until approximately 25 to 35 years, followed by a decline. The case definition showed a less dramatic change in estimated prevalence with age, with peak prevalence at approximately 35 to 45 years.
Figure 3.1 Predicted age-specific prevalence of bipolar disorder using each of the 2002 CIDI algorithm, 2012 WMH-CIDI algorithm, and case definition.
Among those positive for BD using the 2002 CIDI algorithm, 54.33% (95% CI 48.06% - 60.59%) met the 2012 WMH-CIDI criteria, and 13.01% (95% CI 9.25% - 16.76%) met the case definition for BD. Among those positive using the 2012 WMH-CIDI algorithm, 98.20% (95% CI 96.72% - 99.68%) were positive using the 2002 CIDI algorithm and 17.39% (95% CI 11.49 - 23.28) were positive using the case definition. Finally, for those with BD using the case definition, 71.12% (95% CI 61.55% - 80.66%) met the 2002 CIDI algorithm, and 52.45% (95% CI 40.74 - 64.15) met the 2012 WMH-CIDI algorithm.

Demographic features of the case definition and WMH-CIDI defined samples are shown in Table 3.1. The mean age of persons with BD for the case definition group (42.60, 95% CI 38.29 - 46.90) was slightly higher than that of the WMH-CIDI algorithm group (38.68, 95% CI 36.47 - 40.89). The percentage of males and females within the case definition group were somewhat different (39.09%, 95% CI 27.81 - 50.36 vs. 60.91%, 95% CI 49.63 - 72.19), whereas BD occurred with similar frequency according to the WMH-CIDI algorithm (51.10%, 95% CI 43.20 - 59.01 vs. 48.90% 95% CI 40.99 - 56.80). Persons with BD were more often unemployed according the case definition (68.32%, 95% CI 58.19 - 78.44) compared with the WMH-CIDI algorithm (39.5%, 95% CI 31.68 - 47.45). Compared with the entire survey sample, the proportions of persons with BD were considerably higher in the lowest income ranges (Figure 3.2).
Table 3.1 Demographic features of those with and without BD according to the case definition and the WMH-CIDI algorithm.

<table>
<thead>
<tr>
<th></th>
<th>Case Definition</th>
<th>WMH-CIDI Algorithm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% (95% CI)</td>
<td></td>
</tr>
<tr>
<td>Age (mean)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BD</td>
<td>42.60 (38.29-46.90)</td>
<td>45.67 (45.54-45.80)</td>
</tr>
<tr>
<td>No BD</td>
<td>38.68 (36.47-40.89)</td>
<td>38.68 (36.47-40.89)</td>
</tr>
<tr>
<td>WMH-CIDI Algorithm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BD</td>
<td>45.75 (45.61-45.88)</td>
<td>45.75 (45.61-45.88)</td>
</tr>
<tr>
<td>No BD</td>
<td>49.27 (49.15-49.40)</td>
<td>49.27 (49.15-49.40)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>39.09 (27.81-50.36)</td>
<td>49.35 (49.24-49.45)</td>
</tr>
<tr>
<td>Female</td>
<td>60.91 (49.63-72.19)</td>
<td>50.65 (50.54-50.76)</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married/CL</td>
<td>40.32 (27.55-53.09)</td>
<td>50.65 (50.54-50.76)</td>
</tr>
<tr>
<td>Divorced/Separated/Widowed</td>
<td>24.79 (15.66-33.92)</td>
<td>12.85 (12.20-13.50)</td>
</tr>
<tr>
<td>Single</td>
<td>34.89 (24.37-45.40)</td>
<td>26.84 (26.13-27.54)</td>
</tr>
<tr>
<td>Employment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full-time</td>
<td>21.95 (13.12-30.78)</td>
<td>56.73 (55.69-57.77)</td>
</tr>
<tr>
<td>Part-time</td>
<td>9.73 (3.07-16.37)</td>
<td>11.89 (11.25-12.52)</td>
</tr>
<tr>
<td>Not Employed&lt;76 years and not employed during the past week</td>
<td>68.32 (58.19-78.44)</td>
<td>31.39 (30.46-32.31)</td>
</tr>
<tr>
<td>Education&lt;76 years and not employed during the past week</td>
<td>39.56 (31.68-47.45)</td>
<td>31.59 (30.66-32.53)</td>
</tr>
<tr>
<td>&lt; HS diploma</td>
<td>25.56 (11.91-39.21)</td>
<td>18.00 (17.23-18.77)</td>
</tr>
<tr>
<td>HS diploma</td>
<td>16.22 (8.12-24.33)</td>
<td>15.75 (15.00-16.51)</td>
</tr>
<tr>
<td>PS degree or higher</td>
<td>58.22 (44.89-71.54)</td>
<td>66.25 (65.20-67.30)</td>
</tr>
<tr>
<td>Immigrant</td>
<td>% Yes</td>
<td></td>
</tr>
<tr>
<td>% Yes</td>
<td>6.80 (2.16-11.45)</td>
<td>25.25 (23.99-26.51)</td>
</tr>
</tbody>
</table>

* Unless otherwise specified
b <76 years and not employed during the past week
c HS=High school, PS=Post-secondary
d Not born in Canada
Figure 3.2 Percent of respondents per personal income range for each of the case definition and WMH-CIDI defined subgroups as well as the total sample.
As expected, the health status of those with BD is considerably poorer than persons without BD. Among those who met the case definition, only 41.49% (95% CI 30.17 - 52.81) reported good, very good, or excellent mental health, and for the WMH-CIDI algorithm 54.35% (95% CI 46.12 - 62.58) reported similarly. On the other hand, 92.23% (95% CI 91.69% - 92.77%) of total sample reported good, very good or excellent mental health. Furthermore, 39.22% (95% CI 26.05 - 52.60) perceived life to be quite a bit or extremely stressful, while 48.65% (95% CI 39.98 - 57.33) of the WMH-CIDI algorithm group reported similarly. In the total sample, only 20.62% (95% CI 19.67% - 21.56%) reported life to be quite a bit or extremely stressful. Mean distress scores, measured by the K6, were approximately 3-fold higher in those with BD according to the case definition (8.92, 95% CI 7.98 - 9.86) and WMH-CIDI algorithm (9.66, 95% CI 8.72 - 10.60) compared with the total population (3.04, 95% CI 2.96 - 3.12). Mean global disability scores, measured by the WHODAS 2.0 were also high: Case definition 23.56 (95% CI 19.51 - 27.61) and WMH-CIDI algorithm 18.90 (95% CI 15.80 - 22.00). According to population norms produced by the scale developers, these summary scores are higher than 89.6% and 93% of the general population. 58, 59

3.5 Discussion

The estimated crude prevalence of BD was 2.62% (95% CI 2.30 - 2.93) using the 2002 CIDI algorithm, 1.44% (95% CI 1.20 - 1.68) using the 2012 WMH-CIDI algorithm, and 0.48% (95% CI 0.37 - 0.59) using a case definition that was selected from among three alternatives. BD was roughly similar in its prevalence frequencies in males and females using both the CIDI algorithms and case definition.
It is expected that the prevalence observed based on the 2012 algorithm is lower than that observed based on the 2002 algorithm. The 2002 CIDI algorithm was believed to produce prevalence estimates that were too high and the algorithm was recalibrated based on clinical reappraisal studies in order to produce more accurate classifications. It appears that the recalibrations were successful at lowering the estimated prevalence and bring it more in line with the 1% - 2% typically observed as intended. ¹

Although the recalibrations seemed to produce more valid prevalence estimates, it is believed that there are problems with the recalibrated algorithm that seem to indicate inaccuracy in the classifications of respondents. ⁵⁰ Using the case definition, we sought to explore whether combining the estimates with other data from the survey may improve classification of subjects. By including the supplementary information into the requirements of the case definition, we observed an age-specific prevalence pattern that was perhaps more realistic than the 2002 and 2012 CIDI estimates in the sense that is showed a lesser decline of prevalence with age. However, the prevalence was lower than expected. This likely reflects the additional specificity from the requirement for treatment (a self-reported BD diagnosis by a health professional or past year consultation with a psychiatrist) built into the definition. As a result, the case definition will miss those respondents who are untreated (and likely over-represented in the younger BD population due to lower treatment rates in the early course of the illness). This would limit the utility of the definition in surveys, which ideally should capture treated and untreated cases. Unfortunately, the inclusive case definition that did not include treatment information was highly non-specific, and therefore, not further used in this study.
Despite including quite different respondents, both the case definition and WMH-CIDI algorithm appeared to capture severely ill and negatively impacted individuals. Persons identified as having BD compared to those without BD were more often single, not employed, and had lower income. Furthermore, individuals identified as having BD perceived more life stress and reported more distress and disability than those without BD. Together these may indicate that WMH-CIDI items in the survey measure stress-related symptoms or maladjustment, but that is not necessarily related to having BD.

The current epidemiologic information provided by the WMH-CIDI is potentially inaccurate and should be used with caution in public health and clinical practice. The WMH-CIDI algorithm appears to have problems that are difficult to solve, or at least were not easily solved by the case definition approach. It is possible that fully structured interviews are not capable of accurately identifying BD in general population samples. As a result, new approaches to studying psychiatric disorders such as BD at the population level need to be explored. For example, prospective cohort studies that utilize semi-structured interviews by trained clinicians may be a promising alternative. Although these types of approaches are often more highly demanding of time and resources, semi-structured interviews would still allow good reliability while clinicians highly experienced with diagnosing BD and other psychiatric disorders would be able to capture a longitudinal assessment of mood changes and symptoms. Primary care databases may be another suitable option. Population-based administrative databases like The Health Improvement Network (THIN) in the United Kingdom (UK), or hospitalization, medication use or physician billing data, or some combination of such sources may ultimately be the best strategy of studying the epidemiology of this condition.
Chapter Four: CONCLUSION
**4.1 Summary of Main Findings**

The original aim of this thesis was two-fold: (1) to estimate the prevalence of BDI and BDII in Canada in 2012; and (2) to characterize persons with BD in terms of demographic features, health status, and mental health service utilization. I also examined some indicators of validity of the WMH-CIDI classifications of BD. Manuscript one estimated the prevalence of BD in 2012 and examined the agreement of several different methods of classifying BD in the CCHS-MH.

Since it was observed that WMH-CIDI did not appear to produce entirely valid classifications of BD, manuscript two examined the appropriateness of using a case definition approach as an alternative to the WMH-CIDI algorithms for studying the epidemiology of BD.

The objective of manuscript one was to estimate the prevalence of BDI and BDII in Canada in 2012. Using diagnoses obtained from the WMH-CIDI algorithms, the estimated lifetime prevalence of BDI in 2012 in Canada was 0.87% (95% CI 0.67% - 1.07%) and BDII was 0.57% (95% CI 0.44% - 0.71%). Prevalence did not differ by sex. The estimated prevalence of self-reported BD was 0.87% (95% CI 0.65% - 1.07%). There was, however, a lack of agreement between WMH-CIDI defined and self-reported BD. Furthermore, few individuals using lithium at the time of the survey were positive for BD on the WMH-CIDI. Together, these raise concerns about the validity of the WMH-CIDI’s assessment of BD.

The purpose of manuscript two was to investigate whether a case definition approach using additional survey information from outside of the WMH-CIDI could be used as an alternative to the conventional WMH-CIDI algorithms in order to address problems of misclassification of
persons with respect to BD diagnosis. I developed a case definition for BD by supplementing the existing WMH-CIDI algorithm with additional survey information in order to improve specificity. The estimated prevalence of BD using the case definition was substantially lower than that produced by the WMH-CIDI, suggesting that the case definition was more specific. There was little agreement between the WMH-CIDI and case definition classifications, yet both appeared to include highly ill and impacted individuals. The case definition did not appear to adequately address problems of misclassification; it appears that fully structured diagnostic interviews may be unable to accurately distinguish the differences between BD and other types of severe psychiatric disturbances.

4.2 Challenges and Limitations of Studying the Epidemiology of Bipolar Disorder in General Population Samples

This thesis revealed several limitations and challenges to studying BD at the population level. Foremost, the widespread lack of consensus regarding essential criteria for a diagnosis of BD and the difficulty of achieving the correct diagnosis in BD hinders the ability to research BD in population surveys. In addition, lifetime prevalence may be an inappropriate measure for quantifying BD in the population using fully structured interviews, yet it is an essential aspect of the diagnostic concept. Fully structured diagnostic interviews appear to be an inadequate method for identifying BD.
4.2.1 Existing Issues Associated with Diagnosing Bipolar Disorder

The foundation of epidemiological research is a valid and reliable operational definition of the subject under study. As with most psychiatric conditions, there is no recognized biological marker for BD. Unlike diagnosing medical conditions, which typically involves identifying biological markers, diagnosis of psychiatric conditions including BD rely primarily on personal reports of symptoms and the expertise of the consulting physician. This is likely one reason that the nosology of BD is in constant evolution and there is pervasive disagreement over the criteria essential for diagnosis of the condition. Regardless of the criteria for diagnosing BD, it is a difficult condition to diagnose and achieving the definitive diagnosis often takes a long time. This is likely in part because mood episodes in the early course of BD are often of depressive polarity, but it is not until the individual experiences their first manic or hypomanic episode that BD can be accurately diagnosed. Furthermore, in clinical settings, many people with BD seek treatment for depression rather than symptoms of positive polarity. As a result, an individual’s diagnosis may change several times before the correct diagnosis is made. This is one reason that using self-reported professional diagnosis of BD alone in population surveys may also lead to misclassification. I attempted to address problems of possible insensitivity of self-reported classifications and nonspecificity of the current algorithms by combining the approaches in our case definition. Unfortunately, this did not appear to meaningfully improve the validity of the results. Given the widespread difficulties defining and diagnosing BD, it is not surprising that we also encountered obstacles estimating the prevalence of BD.
4.2.2 Lifetime Prevalence may not be an Appropriate Measure

The lifetime prevalence of BD refers to the proportion of a population having met criteria for BD at any point during their life up to the time of assessment. Given that BD is a persistent, lifelong illness, the pattern of change in prevalence with age may be expected to increase through teenage years to early-adulthood followed by a period of stabilization. This pattern is expected because prevalence is the product of the incidence and duration of the disorder, therefore, once all new cases of the disorder have presented (i.e. there are no new cases), the prevalence of the disorder should stabilize. However, using the CCHS-MH data, we observed a parabolic trend of age-specific prevalence such that prevalence increases to mid-adulthood, followed by a substantial decline with age. This unexpected pattern is interpreted as suggesting substantial misclassification of subjects with respect to BD diagnosis.

It is notable that the parabolic trend of change in prevalence with age could, theoretically, be explained by recall bias, a cohort effect or early mortality. Similar trends have been observed in the literature including other psychiatric disorders such as depression and anxiety, and in recent years have most often been attributed to recall bias. Recall bias refers to systematic error in a measurement due to a differential accuracy of recall by participants. It is possible that in this survey individuals of older ages were less likely to recall past major mood episodes (which may have occurred many years prior to the interview) and, therefore, were less likely than younger respondents to be classified by the WMH-CIDI as positive for BD. However, it is unlikely that the magnitude of recall bias is enough to explain the observed substantial decline in prevalence with age given the persistent and chronic nature of BD. Whereas people with depression can go
many years without episode recurrent or using treatment, individuals with BD often require long-term maintenance treatment by medication, therefore forgetting is less likely in those with BD.

It is also possible that a cohort effect has contributed to a differential observed prevalence of BD across the age range. Individuals born during a similar time often share various characteristics and these characteristics may change across future generations (i.e. cohorts). For example, BD may have been rather infrequent in earlier generations, but may have grown increasingly common in more recent cohorts. This type of trend in change of prevalence with age would appear visually similar to that observed in studies one and two. However, given the strong genetic component of BD it seems unlikely that this explanation would be valid for WMH-CIDI diagnosed BD. On the other hand, it is plausible that such a phenomenon explains the trend in self-reported BD prevalence. For example, investigators have observed increased frequency of diagnosis of BD, and decreasing frequency of schizophrenia.\textsuperscript{63, 64} It is suggested that the pattern reflects that physician are increasingly favouring a diagnosis of BD over other psychotic disorders.

Finally, the trend could also be explained, partly, by early mortality among individuals with BD. In a large national cohort study conducted in Sweden it was observed that people with BD had approximately 2-fold increased mortality and died approximately 9 years earlier compared with the rest of the population. Among the most common causes of mortality among those with BD were cardiovascular disease, diabetes, respiratory problems, unintentional injuries, and suicide.\textsuperscript{40} However, it is unlikely that early mortality alone could fully explain the substantial decline in prevalence with age that was observed.
Lifetime prevalence relies on retrospective reports of mood symptoms and diagnoses, and may be particularly susceptible to cohort effects, differential mortality or declining age-specific incidence as well as recall bias. The pattern of age-specific prevalence was not unexpectedly high among younger ages and there was a dramatic decrease in prevalence with age starting in middle-adulthood, together, suggesting that the prevalence of BD in this thesis may have been an underestimate. To minimize these forms of bias, intervals such as annual or 6-months prevalence or other measures such as cumulative incidence are typically preferred. Unfortunately, using types of prevalence other than lifetime to study BD may be impractical.

Current methods of diagnosing BD depend on the occurrence of major mood episodes across the life course. The lifetime occurrence of a manic (or hypomanic) episode determines the definitive diagnosis of BD, but persons may experience episodes of any of manic, hypomanic or depressive polarity in any given year. Therefore, the apparent flaws of lifetime prevalence may be less easily addressed for the study of BD compared with other psychiatric disorders. To address these issues, prospective studies that utilize incidence may be better methods for studying BD in the future. Alternatively, more sensitive interviews for past episodes may be required.

4.2.3 Fully Structured Diagnostic Interviews May Be Inadequate

The studies included in this thesis suggest that fully structured interviews, particularly the WMH-CIDI, may be inadequate for accurately diagnosing BD and, therefore, studying BD in the general population. The limited overlap between WMH-CIDI defined diagnosis, self-reported professional diagnosis and lithium use observed in manuscript one raises concern about the
validity of the WMH-CIDI module for BD. Despite the clear advantages of using fully structured interviews for large-scale epidemiological surveys, they may not be an appropriate measure for all disorders. Schizophrenia is a previous case-in-point for this possibility.

Fully structured interviews are often advantageous for several reasons. They are believed to improve inter-subject and inter-rater reliability. They are also believed to be more efficient; the introduction of fully structured interviews into research allowed for large-scale epidemiological studies to be carried out in relatively short amounts of time and with lesser financial costs. Trained lay interviewers could conduct the interviews rather than highly trained clinicians with limited availability for research. However, if the results are invalid, the process is no longer efficient because the cost of carrying out the research is much greater than the knowledge gained. Diagnosing BD is challenging even in clinical practice, and rigid, fully structured interviews may be unable to accurately assess the mood disturbances and symptoms necessary for diagnosing BD. Given the difficulty of ascertaining a correct diagnosis of BD, it is essential for clinicians to take into account key contextual information such as frequency and type(s) of past mood episodes, as well as family history. Although the survey collected an abundance of information about each respondent, surveys designed for use in the general population do not usually collect the essential contextual information to yield an accurate diagnosis. While acknowledging this, I aimed to improve the WMH-CIDI algorithms for BD in manuscript two by supplementing them with survey information from outside of the WMH-CIDI. Unfortunately, this did not produce a clear improvement. However, a case definition approach taken in future surveys may still be worthwhile if plans are made, a priori, to collect essential contextual information not included in the CCHS-MH such as family and medical history as well as past mood episodes.
Furthermore, in the community it may sometimes be difficult to distinguish some symptoms of BD from normative experiences. For example, in schizophrenia research, measures of psychotic symptoms such as delusions and hallucinations have previously been found to have quite high false positive rates, possibly due to misunderstanding of the interview questions, lack of insight, drug-induced states, or religious beliefs.\textsuperscript{45,46} As a result of the apparently high false positive rate, diagnostic modules for schizophrenia were removed from later versions of the CIDI owing to apparently invalid outputs. Similar problems with misclassification may also be occurring in the BD module. For example, episodes of euphoria that merely represent periods of positive affect may be mistakenly recorded as pathological episodes by fully structured interviews. This may be not only a result of nonspecific questions, but also related to the interview process used in fully structured interviews. In these types of interviews, interviewers are provided with a script that they are to read exactly without deviation or probes. Although this approach likely maximizes reliability, respondents may be unable to get clarification if they do not fully understand a question and may lead to invalid responses.\textsuperscript{16,57}

Epidemiological information about BD should remain focused on accurately identifying persons with BD in the general population. Investigating the most valid and reliable method of diagnosing BD in the general population is highly important. Until such valid diagnoses can be obtained, descriptions of persons with BD to be used to inform public health policies and initiatives may be misrepresentative.
4.3 Clinical and Public Health Implications

A primary purpose of descriptive epidemiology is to characterize trends in health states, evaluate whether programs or policies are effective and economical, and inform priorities and changes when needed.

In studies one and two, I quantified the burden of disease from BD in Canada. Knowledge of the prevalence of BD in the population may be useful for policy makers and inform more effective resource allocation. Persons with BD, particularly those with an additional co-occurring condition are high users of health services. Adequate treatment for BD typically requires ongoing use of prescription medications and consultations with a psychiatrist. Prolonged untreated BD frequently leads to recurrence, poorer health status and hospitalization. Therefore, early identification and adequate treatment through ongoing clinical monitoring of persons with BD, may ultimately lead to reduced impact of the illness on the individual and society, as well as make the health care system more resource and cost efficient. Unfortunately, the results of studies one and two suggest that there may be, currently, no accurate method for assessing these things at the level of the general population.

Although the WMH-CIDI algorithm appears to be calibrated reasonably well for aggregate estimates of prevalence, the apparent misclassification of individuals is likely to distort any assessment of associations. In order to explore this, a series of calculations were performed using a hypothetical sample. For example, a 2x2 table was calculated based on the following parameters: (a) the prevalence of a hypothetical exposure in the total sample is 5.0%; (b) 1.0% of
those with BD are not exposed; and (c) the prevalence ratio (PR) of the exposure is 2.0. Using the sensitivity (87%) and specificity (99%) observed in a study of validity of the WMH-CIDI in relation to the SCID 43 an expected 2x2 table can be calculated which represents the extent of misclassification. Applying the imperfect sensitivity and specificity leads to an expected value for the estimated prevalence of 1.9%, while the true prevalence based on the parameters is 1.1%. In addition, the expected value for the PR is 1.5, which is lower than the assumed true value of this parameter of 2.0 used in the calculation. It is not surprising that the PR is lower after taking misclassification into account given the diluting effect of non-differential misclassification bias.

Here, the misclassification of disease status is non-differential since the same sensitivity and specificity is applied to the exposed and non-exposed subjects. It is notable that during these hypothetical calculations, changes in sensitivity made very little to no impact on the expected prevalence ratio and expected prevalence. This suggests that specificity is more highly important classification probability to consider in the development of a valid measurement tool (see Appendix B for sample 2x2 tables and calculations).

The findings in this thesis raise questions about the validity of the WMH-CIDI for measurement of BD, and by extension, our understanding of the epidemiology of BD to date. Epidemiologic research provides the framework for understanding burden of disease in the population. Many countries, including Canada, still rely heavily on population surveys for collecting public health information and surveillance. The WMH-CIDI is one of the most widely used instruments internationally. If the measurement tools used in these surveys are not valid sources of information for some disorders, then public health policy, planning and research priorities suffer from a lack of clear direction. Furthermore, using invalid information to guide actions may even
be harmful owing to ineffective allocation of resources and misdirection of public health policy and research priorities. Major deficits remain in the understanding of BD epidemiology in Canada, and some re-evaluation of international knowledge based on research using the WMH-CIDI may be required.

4.4 Directions for Future Research

Based on the findings in this thesis, it appears that fully structured interviews, even with supplementary information, seem unlikely to accurately capture the BD diagnosis. As a result, existing knowledge about BD at the population level remains inadequate. Future investigations must focus on identifying efficient and valid methods for diagnosing BD at the population level. In addition, future investigations should seek to identify the extent of validity of the existing information and, in turn, how appropriate using that information is for guiding public policy.

New approaches to studying BD at the population level need to be explored. Before valid research can be undertaken to study BD, a precise, stable, valid and reliable definition of BD is essential. These approaches must consider including familial and developmental information as well as the longitudinal course of the illness. Given the strong genetic linkage of BD, it is highly important to consider family history. Family history is among the strongest risk factors for BD. For example, a population-based cohort of persons born in Denmark was to assess the risks of receiving a diagnosis of BD among other psychiatric disorders in offspring of parents having been admitted to a psychiatric facility and received diagnoses of schizophrenia, BD, or unipolar depression. The study showed that the risk of BD was 0.48% in offspring with neither parent
ever having been admitted to a psychiatric facility, 4.4% with only one parent ever admitted, and
24.9% in offspring with both parent ever admitted. Although clinical course is likely highly
variable between people, developmental trajectories should be considered, as there are several
markers that may suggest increased risk of BD. For example, it has been observed that
individuals at high risk of developing BD are also at higher risk of comorbid conditions such as
anxiety and sleep disorders compared with controls and the early course often includes recurrent
episodes of depressive polarity. Furthermore, the diagnostic tool must be able to distinguish
mood dysregulation of BD from mood swings associated with other psychiatric disorders and
normal experience. For example, Duffy and Carlson assert that adolescent boys with ADHD
often have an inflated positive view of themselves, but these ideas may be more of a reflection of
poor judgment and difficulty reading social cues than grandiosity, an important symptom in
mania. Using these principles, it may be possibly to develop fully structured instruments that
produce more valid classifications.

Administrative databases that include medical history, physician billing and prescription codes
may also help to address some of these issues. The Public Health Agency of Canada expanded
the Canadian Chronic Disease surveillance system in 2010 to monitor mental disorders including
BD. However, this surveillance system is still unable to distinguish the BD subtypes, and the
adequacy of information collected is yet to be determined. Surveillance using Canadian health
administration data will not solve all problems because physician billing and hospital discharge
data reflect only the treated prevalence and diagnostic codes recorded in some provinces are
flawed. For example, most provinces use ICD-9 codes for outpatient billing, which are recorded
to three digits and cannot distinguish BD from major depressive disorder. Administrative data
may also be helpful for studying the change in prevalence with age. Given the high risk for early mortality among persons with BD, it may be worthwhile to examine this in greater detail with the aim of elucidating explanations for the unexpected trend of change in prevalence that was observed in this study (and frequently observed in other epidemiological research).

In lieu of adequate Canadian administrative data, databases from other nations may provide good alternatives. One example of an alternative is THIN, a primary care database of electronic medication records from the UK, covering 6.2% of the UK population. The database includes longitudinal information on patients including demographics, therapy, consultation and additional health data such as prescriptions. The database is a powerful source for studying a wide range of medical and psychiatric illnesses. Although mindful of the associated challenges, it may be a worthwhile endeavour for Canada to allocate more resources to further develop infrastructure with better record linkage for surveillance through administrative data as it can be used for a variety of essential activities, not only monitoring BD. Of course, this type of approach will not solve all problems given that administrative databases can only assess treated prevalence, and BD is often believed to be an undertreated condition. Furthermore, variables such as family history may or may not be assessed accurately in such data sources. Finally, THIN exists only in the UK and nothing like it yet exists in Canada.

To address shortcomings of community surveys that use fully structured interviews and studies of administrative databases, a better method may be to combine the two approaches. Although this alternative is likely more expensive and less efficient, it may help to reduce misclassification owing to inadequate information and problems with rigid interview designs, thereby ultimately
improving efficiency. For example, a possible option may be to carry out surveys with a two-stage design that utilizes a highly sensitive screening section, followed by a rigorous and highly detailed interview and records review of those who screen positive. A highly sensitive screening section would allow large samples to be assessed without requiring resources to rigorously assess the entire sample. The smaller subset that endorses the screening questions could then be assessed using a protocol designed to collect extensive information through clinician interviews, a records review, family interview and perhaps consensus review of all data to form an opinion about the diagnosis. The multiple “checks and balances” in the process may allow for more accurate classification, thereby reducing bias.

4.5 Conclusion

This thesis has identified several challenges and limitations of assessing BD in the general population. Descriptive epidemiology including prevalence research is essential for understanding the burden of disease in the population, and therefore, guiding public health planning and resource allocation. Although updated information about the prevalence of BD in Canada is presented in this thesis, caution is encouraged for users of this information. This thesis has identified possible misclassification of BD by the WMH-CIDI, which is a widely used instrument internationally. In conclusion, knowledge about the epidemiology of BD appears to remain inadequate and future work should prioritize accurate methods for classifying persons with BD in the general population.
REFERENCES


APPENDIX A: CHAPTER 2 SUPPLEMENTARY MATERIALS

A.1. Case Definition Components

_Screening Questions._ Initial screening questions were considered to account for the possibility that persons who truly have BD may or may not screen into the mania module for any number of reasons (avoidance of stigmatization, lack of personal insight, etc.). Inclusion of individuals who did not screen into the mania module (and therefore did not have symptom-level data) was considered essential in order to allow for inclusion of possible false negatives.

_WMH-CIDI classified BD based on the 2002 algorithms._ In concordance with DSM-IV, the presence of a lifetime manic episode is defined in the 2002 algorithm as: (a) a distinct period of abnormally and persistently elevated, expansive or irritable mood lasting at least one week; (b) at least three of seven symptoms (or 4 or more if mood is only irritable) were present during the mood disturbance (inflated self-esteem or grandiosity, decreased need for sleep, more talkative than usual, flight of ideas or racing thoughts, distractibility, increased goal-oriented activity or psychomotor agitation, excessive involvement in pleasurable, but risky activities); and (c) marked impairment in normal daily activities or occupational/social functioning or if mood disturbance includes psychotic features or severe enough to require hospitalization. The algorithm for a hypomanic episode is similar to that of a manic episode except that hypomania requires: (a) a minimum symptom duration of 4 days (rather than 7); (b) the mood disturbance is not severe enough to cause marked impairment in normal daily activities or occupational/social functioning and did not include psychotic symptoms or lead hospitalization. The algorithm for
major depressive episode requires: (a) depressed mood or loss of interest or pleasure lasting at least two weeks; (b) at least five symptoms that represent a distinct change in functioning; (c) symptoms cause clinically significant distress or impairment in social/occupational functioning; and (d) symptoms are not better accounted for by bereavement or the symptoms are characterized by a marked functional impairment preoccupation with worthlessness, suicidal ideation or psychomotor retardation. 7,14 The BD algorithms are based on content of the WMH-CIDI, while the remaining information was taken from survey content that was not part of the WMH-CIDI.

A.1.1. Self-reported Bipolar Disorder or Mania
Respondents self-reported if they have ever been diagnosed by a health professional with BD and/or mania. Although misdiagnosis may occur in a clinical setting, persons with BD are presumably much more likely to receive, accept and report such a diagnosis than persons without BD.

A.1.2. Consultation with a psychiatrist
Consultation with a psychiatrist included any self-reported visits during the past year to address his/her mental health problems. Although some persons with BD may be seeing health professionals other than psychiatrists such as a general practitioner or psychologist, consultation with a psychiatrist was chosen as a candidate element of case definitions because the severity of the illness often warrants treatment by a specialist.
Medication use. Respondents were asked about all medications taken for mental health symptoms during the 2 days preceding the interview. Lithium and anticonvulsants were included as mood stabilizers in the stringent case definition. We chose to include lithium and anticonvulsants taken as mood stabilizers in the medication use component because they are recommended pharmacological treatment for BD\textsuperscript{38} and with the aim to include as many persons as possible using evidence-based treatment for BD, while minimizing medications possibly used for other indications.

It was not considered realistic to identify definitions that could distinguish between BDI and BDII due to a lack of information collected in the survey that was capable of supporting such distinctions. Therefore, all three case definitions are intended to represent an aggregate of BDI and BDII. In order to address the highly branched nature of the survey, some case definitions allow persons to meet the definition of a case regardless of their endorsement to the screening questions if they also meet specific other criteria. Figure 1A shows the combination of components that comprise each case definition.
Figure 1A Components of each of the highly inclusive, moderately inclusive, and stringent case definitions developed to identify bipolar disorder in the Canadian Community Health Survey-Mental Health.

**Highly Inclusive Case Definition:**
(a) mania or hypomania + major depressive episode; OR
(b) self-reported diagnosis

**Moderately Inclusive Case Definition:**
(a) mania or hypomania & MDE + self-reported diagnosis; OR
(b) screen positive + no mania/hypomania & MDE + self-reported diagnosis + consultation with psychiatrist; OR
(c) screen negative + self-reported diagnosis + consultation with psychiatrist

**Stringent Case Definition:**
(a) mania or hypomania & MDE + self-reported diagnosis + consultation with psychiatrist; OR
(b) screen positive + no mania/hypomania & MDE + self-reported diagnosis + consultation with psychiatrist + use of mood stabilizer; OR
(c) screen negative + self-reported diagnosis + consultation with psychiatrist + use of mood stabilizer
A.2. Case Definition Selection

A.2.1. Method

The three candidate case definitions were assessed, initially, by examining prevalence estimates. The case definition that produced the most plausible estimates was selected and used to carry the descriptive epidemiologic portion of the study. Plausibility was based on knowledge from an extensive review of the literature resulting in the following guidelines: (a) crude prevalence estimate between 0.7% and 2.0%; \(^1\-^4\) (b) similar prevalence in males and females; \(^1\) and (c) an age-specific prevalence trend that fits with the typical age of onset of the disorder. \(^60\) These estimates were used to select a single case definition that appeared to be most valid based on existing knowledge of BD. Crude and sex-specific prevalence were estimated as frequencies with 95% confidence intervals. Age-specific prevalence was estimated using a generalized linear model of the binomial family with a log link function. Age-specific prevalence models were assessed for an age-sex interaction using Wald tests.

A.2.2. Results

The proportions of missing data for the subgroups were: inclusive case definition (0%), moderately inclusive case definition (0.65%) and stringent case definition (1.34%).

The estimated prevalence of the inclusive, moderately inclusive and stringent case definition was 3.31% (95% CI 2.94% - 3.68%), 0.48% (95% CI 0.37% - 0.59%) 0.22% (95% CI 0.15% -
0.29%), and 0.22% (95% CI 0.15% - 0.29%), respectively. Prevalence estimates for males and females were not significantly different for any of the case definitions.

All three age-specific prevalence patterns showed a gradual increase in prevalence to early to mid-adulthood, followed by a decline (Figure 2A). The increase was much more dramatic for the highly inclusive case definition and WMH-CIDI subgroup. Peak prevalence was near 25 years for the moderately inclusive case definition versus approximately 45-50 years for the highly inclusive and stringent case definitions as well as the WMH-CIDI algorithm.

Figure 2A Predicted age-specific prevalence of bipolar disorder using each of the highly inclusive, moderately inclusive, and stringent case definitions.
Of the three case definitions, the moderately inclusive case definition appeared to have the highest face validity. The crude prevalence estimate aligned quite closely with that observed in a recent systematic review. BD is a lifelong disorder that typically onsets in adolescence or early-adulthood, therefore, we would expect the age-specific prevalence to increase with age to approximately age 30 (when the majority of individuals with BD have experienced their first manic or hypomanic and major depressive episode) and then plateau. The decline in prevalence with age for the highly inclusive case definition was substantially more dramatic than could likely be explained by mortality. The stringent case definition produced an age-specific prevalence that gradually increased with age, but did not fit the expectations for a disorder that onsets in early adulthood. The age-specific prevalence for the moderately inclusive case definition appeared to peak at approximately 30 years of age and only a moderate decline with age. As a result, the moderately inclusive case definition was selected to carry out the descriptive epidemiologic portion of the study.
APPENDIX B: MISCLASSIFICATION EXAMPLE

Table 1B Actual 2x2 table based on the assumptions that the prevalence of the exposure in the total sample is 5%, prevalence of bipolar disorder among the unexposed is 1% and that the prevalence ratio of the exposure is 2.0.

<table>
<thead>
<tr>
<th></th>
<th>Bipolar Disorder</th>
<th>No Bipolar Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposed</td>
<td>25</td>
<td>1225</td>
</tr>
<tr>
<td>Not Exposed</td>
<td>237.5</td>
<td>23512.5</td>
</tr>
</tbody>
</table>

Applying a sensitivity of 87% and specificity of 99%, we can calculate the expected values for the observed table:

Table 2B Observed 2x2 table based on the actual 2x2 table and the following probabilities of classification: sensitivity of 87% and specificity of 99%.

<table>
<thead>
<tr>
<th></th>
<th>Bipolar Disorder</th>
<th>No Bipolar Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposed</td>
<td>34</td>
<td>1216</td>
</tr>
<tr>
<td>Not Exposed</td>
<td>441.75</td>
<td>23308.25</td>
</tr>
</tbody>
</table>

Using table 2B we can calculate the expected value for the prevalence of bipolar disorder and the expected value for the prevalence ratio of exposure:

Expected value for Prevalence:

\[
\frac{(34 + 441.75)}{25000} \times 100 = 1.9\%
\]

Expected value for Prevalence Ratio:

\[
\frac{\frac{34}{34+1216}}{\frac{441.75}{447.75 + 23308.25}} \times 100 = 1.5
\]
APPENDIX C: STUDENT CONTRIBUTIONS

As the primary author, Keltie McDonald contributed significantly to the manuscripts included in this thesis.

For manuscript one, Keltie planned and completed the data analysis, interpreted the results, and wrote the first draft of the manuscript. The senior author and co-authors provided suggestions throughout the process and contributed to the intellectual content of the work during review of the document.

For manuscript two, Keltie completed the majority of the work independently. With input from the senior author, Keltie developed the case definitions. Keltie planned and completed the analysis and wrote the first draft. Along with the senior author and co-authors, Keltie interpreted the results and contributed to review of the final document.
APPENDIX D: PERMISSION FROM PUBLISHER FOR PAPER 1

RE: Permission to Use Paper in Thesis

Dear Ms McDonald:

Please accept this email as permission to use your coauthored article, Prevalence of Bipolar I and II Disorder in Canada, as part of your thesis. I have attached a PDF of the article, which will become open access on TheCJP.ca six months after publication. If there is anything else you need, please just let me know; I would be happy to help.

Thank you for publishing with The Canadian Journal of Psychiatry.
Virginia

Virginia StDenis

From: Keltie Claire McDonald
Sent: Thursday, February 12, 2015 6:51 PM
To: CJP
Subject: Permission to Use Paper in Thesis

To whom it may concern,

I am the primary author of the paper entitled: “Prevalence of Bipolar I and II Disorder in Canada”, which is set for publication in the March 2015 issue of CJP. I am currently an MSc student at University of Calgary, and the manuscript is to be a component of my thesis. I would like to request permission to include this paper within my thesis. Please advise if this is possible and how to proceed.

Thank you in advance,
Keltie

Keltie McDonald
APPENDIX E: PERMISSION FROM CO-AUTHORS FOR PAPER 1

RE: Permission to Use Paper#1 in Thesis

Andrew G.M. Bulloch
Sun 2/15/2015 11:37 AM
To: Keltie Claire McDonald

You have my permission Keltie

Andy

Andrew G.M. Bulloch, PhD

From: Keltie Claire McDonald
Sent: February-14-15 8:04 PM
To: Scott B. Patten; Andrew G.M. Bulloch; Anne C. Duffy; Lauren Bresee; Jeanne Williams; Dina Lavorato
Subject: Permission to Use Paper#1 in Thesis

Hi Everyone,

I am currently preparing my thesis document and I require your permission to include the manuscript "Prevalence of Bipolar I and II Disorders in Canada" (to be printed in the March, 2015 issue of CJP) in my thesis.

In addition, you should know that I will need to sign a form to grant a non-exclusive license to Library and Archives Canada. This is a departmental regulation/requirement.

Please respond by replying to this email at your earliest convenience.

Thank you,

Keltie
Hi Keltie,

You have my permission.

Thanks,

Lauren

---

From: Keltie Claire McDonald  
Sent: Saturday, February 14, 2015 8:04 PM  
To: Scott B. Patten; Andrew G.M. Bulloch; Anne C. Duffy; Lauren Bresee; Jeanne Williams; Dina Lavorato  
Subject: Permission to Use Paper#1 in Thesis

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Please respond by replying to this email at your earliest convenience.

Thank you,

Keltie
Re: Permission to Use Paper#1 in Thesis

Anne Duffy
Sun 2/15/2015 10:44 AM
Inbox
To: Keltie Claire McDonald

Dear Keltie
Thank you I agree and consent yt Anne

Sent from my iPhone

---
From: Keltie Claire McDonald
Sent: Saturday, February 14, 2015 8:04 PM
To: Scott B. Patten; Andrew G.M. Bulloch; Anne C. Duffy; Lauren Bresee; Jeanne Williams; Dina Lavorato
Subject: Permission to Use Paper#1 in Thesis

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Thank you,

Keltie

Keltie McDonald
Re: Permission to Use Paper#1 in Thesis

Jeanne Williams  
Tue 2/17/2015 11:33 AM  
Inbox  
To: Keltie Claire McDonald

Yes, you have my permission.  
Jeanne

On Feb 14, 2015, at 8:04 PM, "Keltie Claire McDonald" wrote:

Hi Everyone,

I am currently preparing my thesis document and I require your permission to include the manuscript "Prevalence of Bipolar I and II Disorders in Canada" (to be printed in the March, 2015 issue of CJP) in my thesis.

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Please respond by replying to this email at your earliest convenience.

Thank you,

Keltie
Hi Keltie,
Yes, you have my permission to include the below mentioned manuscript in your thesis.
Thanks,
Dina

From: Keltie Claire McDonald
Sent: Saturday, February 14, 2015 8:04 PM
To: Scott B. Patten; Andrew G.M. Bulloch; Anne C. Duffy; Lauren Bresee; Jeanne Williams; Dina Lavorato
Subject: Permission to Use Paper#1 in Thesis

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Thank you,

Keltie
Re: Permission to Use Paper#1 in Thesis
Scott B. Patten
Sat 2/14/2015 9:58 PM
Inbox
To: Keltie Claire McDonald

I agree.

Scott

**********

From: Keltie Claire McDonald
Sent: Saturday, February 14, 2015 8:04 PM
To: Scott B. Patten; Andrew G.M. Bulloch; Anne C. Duffy; Lauren Bresee; Jeanne Williams; Dina Lavorato
Subject: Permission to Use Paper#1 in Thesis

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Please respond by replying to this email at your earliest convenience.

Thank you,

Keltie
RE: Permission to Use Paper#2 in Thesis

Andrew G.M. Bulloch
Sun 2/15/2015 11:37 AM
Inbox
To: Keltie Claire McDonald

You have my permission Keltie

Andy

From: Keltie Claire McDonald
Sent: February-14-15 8:08 PM
To: Scott B. Patten; Andrew G.M. Bulloch; Jeanne Williams; Dina Lavorato; Anne C. Duffy; Lauren Bresee
Subject: Permission to Use Paper#2 in Thesis

Hi Everyone,

I apologize for the repeat email. Please respond to this email separately as this is for a different paper.

I am currently preparing my thesis document and I require your permission to include the manuscript "Assessment of Bipolar Disorder in the General Population: Time for a New Approach?" in my thesis.

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Please respond by replying to this email at your earliest convenience.

Thank you,

Keltie
RE: Permission to Use Paper#2 in Thesis

Lauren Bresee
Mon 2/16/2015 9:44 AM
Inbox
To: Keltie Claire McDonald
Cc: Scott B. Patten

Hi Keltie,

You have my permission.

Thanks,

Lauren

From: Keltie Claire McDonald
Sent: Saturday, February 14, 2015 8:08 PM
To: Scott B. Patten; Andrew G.M. Bulloch; Jeanne Williams; Dina Lavorato; Anne C. Duffy; Lauren Bresee
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Thank you,

Keltie
Re: Permission to Use Paper#2 in Thesis

Jeanne Williams

Tue 2/17/2015 11:21 AM

Inbox

To: Keltie Claire McDonald

Of course you have my permission.

Jeanne

-------------------

On Feb 14, 2015, at 8:08 PM, "Keltie Claire McDonald" wrote:

Hi Everyone,
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Please respond by replying to this email at your earliest convenience.

Thank you,

Keltie
RE: Permission to Use Paper#2 in Thesis

Dina Lavorato
Wed 2/18/2015 9:52 AM
Inbox
To: Keltie Claire McDonald

Hi Keltie,
You have my permission to include the below mentioned manuscript in your thesis.
Thanks,
Dina

From: Keltie Claire McDonald
Sent: Saturday, February 14, 2015 8:08 PM
To: Scott B. Patten; Andrew G.M. Bulloch; Jeanne Williams; Dina Lavorato; Anne C. Duffy; Lauren Bresee
Subject: Permission to Use Paper#2 in Thesis

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Please respond by replying to this email at your earliest convenience.

Thank you,

Keltie
Re: Permission to Use Paper#2 in Thesis

Scott B. Patten  
Sat 2/14/2015 9:57 PM  
Inbox  
To: Keltie Claire McDonald <kcmcdona@ucalgary.ca>;

I agree.
Scott

From: Keltie Claire McDonald  
Sent: Saturday, February 14, 2015 8:08 PM  
To: Scott B. Patten; Andrew G.M. Bulloch; Jeanne Williams; Dina Lavorato; Anne C. Duffy; Lauren Bresee  
Subject: Permission to Use Paper#2 in Thesis

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