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CANNABIS USE AND BIPOLAR DISORDER: BIPOLAR DISORDER CASE
IDENTIFICATION AND CANNABIS USE RISK ASSESSMENT

A Dissertation Presented

By

Patrick J. McCabe, MPH

Submitted to the Faculty of the

University of Massachusetts Graduate School of Biomedical Sciences, Worcester

in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

December 14th, 2011

CLINICAL AND POPULATION HEALTH RESEARCH

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IDENTIFICATION AND CANNABIS USE RISK ASSESSMENT

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ABSTRACT

Bipolar disorders (BD) are characterized by symptoms of grandiosity, decreased need for sleep, pressure to keep talking, flight of ideas, distractibility, increased goal-directed activities, psychomotor agitation, and excessive involvement in pleasurable activities. Those with a bipolar disorder have a high degree of psychiatric comorbidity including substance use disorders, and they also experience increased mortality. Despite the widespread recognition of BD as an important psychiatric condition, available population-based estimates for BD prevalence differs across data sources.

Cannabis is one of the most widely-used illicit substances. Evidence supports it as a risk factor for psychotic symptoms and disorders. Because populations with psychotic disorders and populations with bipolar disorder share genetic characteristics, cannabis may increase risk for bipolar disorders through the same pathways as it does with psychotic disorders. Limited and conflicting evidence regarding the association of cannabis use and bipolar disorder is currently available. This dissertation investigates cannabis use as a risk factor for incident manic symptoms and bipolar disorders in a large nationally representative longitudinal cohort.

The first aim of this dissertation is to evaluate the implications for manic, hypomanic and major depressive episode prevalence estimates arising from the different approaches to assessing DSM-IV criterion between two national surveys. Differences in the assessment of impairment strongly influence manic or hypomanic classification within the NESARC. Compared to multiple imputation estimates (19.7% [95% CI: 19.3-20.1]) which treat depressed mood and anhedonia as separate symptoms, symptom assessment in the NESARC substantially underestimates major depressive episode prevalence (16.9% [95% CI: 16.1-17.6]).

The second research objective examined self-reported cannabis use as a risk factor for incident manic symptoms, bipolar spectrum disorders (including manic and hypomanic episodes) and SCID-based recalibrated BD I and II. Cannabis use risk was assessed in the population as a whole and in sub-populations defined by age, substance abuse/dependence status, and family history. Among those reporting no lifetime major depressive or manic symptoms at baseline, self-reported past-year cannabis use was associated with increased odds of an incident week of extremely elevated or irritable mood accompanied by at least two manic episode criterion B symptoms (adj. OR 1.69, 95% CI: 1.08-2.65, $p=.02$) over the three year follow-up period. Among adults (ages 26 to 45) ≥ 1 reported use(s) of cannabis per week was associated with incident manic or hypomanic episodes (adjusted OR 2.52, 95% CI: 1.32-4.80, $p=.006$). Among those endorsing no major depressive symptoms, substance abuse/dependence, or anti-social traits in their first degree relatives, past year cannabis use is associated with increased

risk for incident bipolar spectrum disorders (adjusted OR 2.27, 95% CI: 1.01-5.10, $p=.05$) and CIDI recalibrated BD I and II (adjusted OR 5.49, 95% CI: 1.38-21.9, $p=.02$). Past year cannabis use risk for DSM-IV manic or hypomanic episodes among those aged 26 to 45 is concentrated in those with a baseline history of a substance use disorder (adj. OR 2.00, 95% CI: 1.10-3.66, $p=.02$) as compared to those with no such history (adj. OR 1.87, 95% CI: 0.49-7.21, $p=.36$).

The third research objective of this dissertation was a sensitivity analysis using externally-predicted categorized exposures and continuous cannabis use propensities. The sensitivity analysis found evidence of exposure misclassification. Exposures defined by external propensity scores had improved cross-sectional association with bipolar spectrum disorders compared to reported use when both were compared to an external standard. No significant risk estimates were found for categorized predicted cannabis use among groups that were previously found to have significant risk from reported exposure. However, among adults 18 to 45 years of age with no manic or major depressive symptoms at baseline, past year cannabis use propensity (as a log transformed continuous measure) was associated with incident manic or hypomanic episodes (adj. OR 1.49, 95% CI: 1.10-2.03, $p=.01$). Elevated risk for high cannabis use propensity (≥ 1 use/week in the past year) was also found in this same group (adj. OR 1.33, 95% CI: 1.03-1.72, $p=.03$). Among those with no reported history of depression, substance abuse/dependence, or anti-social traits among their first-degree relatives, propensity for past year cannabis use (adj. OR 1.61, 95% CI: 1.11-2.32, $p=.01$) and propensity for ≥ 1

use/week of cannabis in the past year (adj. OR 1.38, 95% CI: 1.03-1.85, $p=.03$) were associated with incident manic or hypomanic episodes. Among those without a substance use history at baseline, propensity for past year cannabis use (adj. OR 1.63, 95% CI: 1.33-1.55, $p<.001$) and propensity for ≥ 1 use/week of cannabis in the past year (adj. OR 1.54, 95% CI: 1.26-1.88, $p<.001$) were associated with incident manic or hypomanic episodes. Among those with a substance use history at baseline, propensity for past year cannabis use (adj. OR 1.26, 95% CI: 1.03-1.56, $p= .03$) was associated with incident manic or hypomanic episodes.

The findings of the first aim support the conclusion that the AUDADIS substantially under-estimated lifetime major depressive episode prevalence compared to an imputed estimate that treated anhedonia and depressed mood as separate and concurrent MDE symptoms. The operationalization of impairment for manic disorders in both the AUDADIS and CIDI strongly influences case identification, with the CIDI having suppressed manic and hypomanic prevalence estimates. Evidence was found supporting the conclusion that self-reported cannabis use is a significant risk factor for incident bipolar spectrum outcomes within subpopulations in a nationally representative cohort. A sensitivity analysis finds evidence that supports the conclusion that increasing cannabis use propensity is associated with increased risk of bipolar spectrum outcomes within population subgroups, with the greatest increased risk among those with the lowest innate risk. Under-reporting of illicit substance use is a major limitation in this dissertation; further study is needed with improved exposure measures.

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Chapter I Introduction

I A. Objective

The objective of this dissertation research is to explore cannabis use as a risk factor for bipolar disorder (BD) among a nationally-representative sample of U.S. adults. The National Comorbidity Survey Replication (NCS-R) and Epidemiological Catchment Area (ECA) studies found substantial role impairment among those who meet criteria for disorders across the bipolar disorder spectrum including those with sub-threshold BD.^{1,2} Evidence from a related disease state, psychosis, suggests that cannabis exposure may account for 8-50% of incident or recurrent disease episodes.³⁻⁵ However, limited and conflicting evidence exists for cannabis use as a risk factor for bipolar disorder.⁶⁻⁹ Only one prospective cohort study has addressed the association between cannabis and BD.⁷ This study found a significant association [OR 4.98 (95% CI: 1.80–13.81)]. The BD onset definition used in this study may have resulted in prevalent cases being included at baseline. However, this result is consistent with two prospective cohort studies which found cannabis as a risk factor for manic symptoms.^{6,9} These results on the other hand conflict with a population-wide retrospective cohort study which found a null association [OR 1.13 (95% CI: 0.82 to 1.57)] between cannabis use by age 18 and future affective psychosis hospitalization (predominately BD diagnoses).^{8,10} These divergent results point to a clear need to assess cannabis use (CU) as a risk factors for both BD and sub-threshold BD (manic symptoms, hypomanic episodes) in a large epidemiological sample.

I B. Background:

Bipolar disorders are characterized by symptoms of grandiosity, decreased need for sleep, pressure to keep talking, flight of ideas, distractibility, increased goal-directed activity, psychomotor agitation, and excessive involvement in pleasurable activities.¹¹ A diagnosis of Bipolar I is made if one or more manic episodes have occurred. A manic episode is a distinct period of abnormally and persistently elevated, expansive, or irritable mood, lasting at least 1 week, that includes three or more of the seven previously mentioned symptoms (four or more if the mood is only irritable) and is characterized by marked impairment in social functioning. A diagnosis of Bipolar II is made if both a Major Depressive Episode and a hypomanic episode have occurred but there is no history of BD-I, a manic episode, or psychosis. Hypomanic episodes share the same symptom criteria as manic episodes but are distinct from manic episodes in that they can last for as little as 4 days, do not have psychotic or delusional symptoms, and while they represent an unequivocal change in functioning that is uncharacteristic of the person when not symptomatic, they are not severe enough to cause marked social impairment. Population based estimates of the prevalence of bipolar disorder (I and II) range from about 1-6%.^{1, 2, 12-17} There is evidence of substantial role impairment in those with bipolar disorder even when the patient is euthymic.^{1, 2, 15, 18} Those with bipolar disorder have a high degree of psychiatric comorbidity including substance use disorders and also experience increased mortality.^{1, 15}

Available nationally representative, population-based estimates for BD prevalence in the US differ across data sources. The prevalence estimates for bipolar disorders, which are hierarchical with major depressive disorder, differ between the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) (4.4%; 95% CI: 4.3-4.6) and the National Comorbidity Survey-Replication (NCS-R) (3.9%; 95% CI: 3.4-4.4, unrecalibrated;¹⁷ and 2.1%; 95% CI: 1.7-2.4, recalibrated),¹ the other large, US population representative study of psychiatric disorders. Similarly, the prevalence of major depressive disorder in NESARC was 13.2% (95% CI: 13.0-13.4), compared to significantly higher rates of 16.6% (95% CI: 15.6-17.6)¹⁷ or 16.9% (95% CI 15.8-17.9, after re-calibration of bipolar disorders) in the NCS-R.¹⁹⁻²¹ It is important to understand and address differences in the reported prevalence estimates for mania, hypomania and MDE between the NESARC and the NCS-R in order to make more meaningful and valid risk estimates.

These differences are likely due in part to differences in the assessment approaches used. There are concerns regarding how best to assess BD prevalence specifically and mood disorders generally in population samples. Evidence from major epidemiological studies points to an inadequacy in the differentiation between diagnosis and treatment need.²² This concern has led to methods to re-adjust population based samples to improve concordance with clinical re-assessment samples through adjustments in impairment or disability measures, symptom threshold, and duration criteria.^{1, 20, 22}

I C. Study Population: the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC)

This dissertation will use National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) survey data from both wave 1 (n= 43,093, response rate 81.2%)²³,²⁴ and wave 2 (n= 34,653, cumulative response rate 70.2%).²⁵ The NESARC is a nationally representative sample of those over 18 years of age who were interviewed in a face-to-face household setting. The sample represents the adult, non-institutionalized, civilian population of the United States, including the District of Columbia and all 50 States. Residents in non-institutionalized, group-quarters housing, such as boarding houses, dormitories and shelters, were also included as well as military personnel living off base.²⁶ The NESARC is the largest nationally representative longitudinal survey to date that has assessed substance use and substance use disorders, mood disorders and anxiety disorders as well as family history of depression, alcohol or drug abuse, and anti-social behavior.

I C. 1 Alcohol Use Disorder and Associated Disabilities Interview Schedule (AUDADIS)

The NESARC represents an opportunity for researchers to better understand the impact of BD at the population level as well as risk factors for this condition, including cannabis use. However, a need exists to first accurately define and estimate the burden of BD in this survey. The NESARC used the National Institute on Alcohol Abuse and Alcoholism's (NIAAA) internally developed Alcohol Use Disorder and Associated Disabilities Interview Schedule (AUDADIS).^{27, 28} The AUDADIS is a structured

diagnostic interview designed for use by lay interviewers to generate diagnoses meeting DSM-IV criteria for alcohol and substance abuse and dependence as well as Axis I and Axis II disorders. The Axis I and Axis II disorders assessed by the AUDADIS included mood disorders (major depressive disorder, dysthymia, mania and hypomania), anxiety disorders (generalized anxiety, panic, social phobia and specific phobia) as well as seven personality disorders (paranoid, schizoid, avoidant, dependent, obsessive–compulsive, histrionic, and antisocial disorders). In wave 2 interviews, post traumatic stress disorder (PTSD) and childhood attention deficient hyperactive disorder (ADHD) were also assessed. The reliability of AUDADIS for alcohol and drug use disorder measures has been assessed in several test–retest studies in clinical and general population samples with good to excellent reliability for dependence but only fair to poor reliability for abuse diagnoses.^{27, 29-32} The test-retest reliabilities of the mood and anxiety disorder sections were fair to good.^{23, 29} Of the diagnoses of interest in this study only major depression was assessed in comparison with clinical diagnoses with good concordance ($k=0.73$).²⁹ No reliability or validity testing of the diagnosis outcomes of the High Mood section (mania/hypomania) of the AUDADIS are available, though dimensional symptom scales demonstrated fair reliability ($k=0.60$ (95% CI: 0.53- 0.64)).²³

I C. 2 AUDADIS and clinical significance

The issue of clinical significance arises in the High Mood section of the AUDADIS used in the NESARC to assess cases of mania and hypomania. A reasonable interpretation of how the AUDADIS operationalized the social functioning requirements of DSM-IV

mania criterion D may mean that up to 30% of those classified with mania in the study do not meet DSM- IV criterion D levels of social functioning impairment. A second potential source of discrepancy that has drawn less attention than the assessment of functional impairment is the operationalization of the symptom criteria in instruments used in major population based epidemiological surveys such as the NESARC. Preliminary evidence points to limitations in how major depressive symptoms were operationalized in AUDADIS, the diagnostic instrument of the NESARC. Large, well-executed, publicly-funded, population-based studies of psychiatric disorders play a critical role in providing service use and epidemiological evidence for researchers, clinicians and policy makers. The importance of these studies will only increase as genetic material is sampled from population representative samples.³³

Two major methodological differences between the NESARC and the NCS-R likely account for most of the difference in prevalence estimates observed. One difference is that the two surveys applied DSM-IV criteria differently in assessing mania, hypomania and major depressive episodes. The other major difference is that the NCS-R reported recalibrated BD estimates based on a clinical re-assessment.^{1,20} Briefly, the clinical re-assessment used the Structured Clinical Interview for DSM-IV (SCID)³⁴ on a sub-set of those with manic symptoms and from this sample overall BD estimates were made. As previously discussed, the AUDADIS instrument used in the NESARC applies DSM-IV mania criterion D social impairment in a manner that likely results in misclassification of respondent as manic who more appropriately should be identified as hypomanic. The

AUDADIS also does not operationalize elevated-mood-related hospitalization in those otherwise classified as hypomanic as grounds for re-classification as mania per DSM-IV criteria and as is done in the Composite International Diagnostic Interview (CIDI)^{35, 36} the diagnostic instrument used in the NCS-R. A comparison of how the two surveys assessed depressive symptoms may help to account for differences in MDE and BD-II case identification. DSM-IV major depression criterion A requires five (5) or more of nine (9) symptoms to have been present during the same 2-week period and at least one of the symptoms is either 1) depressed mood or 2) loss of interest or pleasure (anhedonia).¹¹ The NCS-R explicitly assessed depressed mood, anhedonia and the remaining seven symptom states for the same episode and requires a total of five of nine symptoms to meet criterion A.³⁷ The NESARC asked about lifetime depressed mood and lifetime anhedonia as stem questions for the remaining seven symptom states and further requires four of these seven symptoms to be endorsed for criterion A to be met.²⁸

The approach used in the NESARC results in depressed mood and anhedonia being treated as a single symptom state and as such, not being independently assessed within the same episode. This approach is not a problem for those who endorse only depressed mood or anhedonia as their endorsement of four or more of the remaining symptoms will be consistent with DSM-IV criterion A. For those endorsing both lifetime depressed mood and lifetime anhedonia a conflict with criterion A arises. Respondents to the NESARC major depression symptom module who endorse both lifetime depressed mood and anhedonia and only three other symptoms of the remaining seven, though having

endorsed five symptoms, are skipped out of the major depression module and not further assessed. As for the stem questions asked about lifetime symptoms of depressed mood and anhedonia, uncertainty exists as to whether these symptoms occurred in the same episode. This uncertainty of concurrency is the AUDADIS's developers rationale for requiring the endorsement of at least four of the remaining seven symptoms.³⁸ It is reasonable to suspect that a large proportion of the group endorsing both lifetime depressed mood and lifetime anhedonia and three other symptoms were referring to a concurrent presentation of depressed mood and anhedonia and would have met full criteria for major depression had these symptoms been assessed independently and these respondents were further assessed in the instrument for clinical significance and other criteria. Preliminary results by the author find 2.2 % (95% CI: 2.1-2.3, n=943) of the entire NESARC sample endorsed both depressed mood and anhedonia and only three other major depressive symptoms. This represents 9.8% (95% CI: 9.5-10.2) of all those endorsing five or more major depression symptoms (n=9760). A need exists to re-examine this group structurally overlooked by the AUDADIS. Examining the proportion of respondents meeting full criteria for a major depressive episode among those endorsing both depressed mood and anhedonia and endorsing an additional 4 to 7 symptoms and extrapolating this trend to 3 additional symptom endorsements (the un-assessed group), an estimated 75% ($R^2 = 0.998$) would have been classified as having a major depressive episode (MDE). This corresponds to an estimated 18.2% prevalence of MDE compared with an un-readjusted prevalence of 16.5% (95% CI: 16.3-16.8). This estimated readjustment shifts the NESARC MDE prevalence estimate closer to the NCS-

R estimate of 19.2% (95% CI: 18.2-20.2). About 8% of those in the 'un-assessed' MDE group who currently have hypomania without BD-II could be subject to reclassification as having BD-II (hypomania + MDE). An examination of how MDE among the structurally overlooked group impacts BD-II and sub-threshold BD case identification after the application of the re-calibration algorithm will be carried out.

I D. Cannabis use, psychosis and bipolar disorder

Longitudinal population based studies point to cannabis as a risk factor for psychosis.³⁹ Cannabis use is suspected of playing a role in psychosis through dopamine dysregulation.⁴⁰ Cannabis exposure may put carriers of the COMT Val(158)Met Val allele at a greater risk of psychosis.^{41,42} The clinical presentation of BD often has similar features to the clinical presentation of schizophrenia. Patients with BD often have psychotic symptoms and those with schizophrenic disorders often experience mania.⁴³ The two disorders may thus have a shared etiology. Twin studies have found genetic correlations between schizophrenia and BD.⁴⁴ Recently, the International Schizophrenia Consortium conducted a large, genome-wide association study and found evidence for a shared polygenic component to the risk of schizophrenia and BD.⁴⁵ Thus, cannabis use may similarly be a risk factor for BD as it is for psychotic disorders.

However, the limited evidence assessing cannabis use as a risk factor for bipolar disorder (BD) provides conflicting results.⁶⁻⁹ The one prospective cohort study to address the association between cannabis and BD,⁷ found a significant association [OR 4.98 (95%

CI: 1.80–13.81)] but the onset of BD was set at when the last symptom criteria were met rather than at the onset of the first affective episode. This BD onset definition risks misclassifying prevalent BD at baseline which may inflate risk estimates. The results of van Laar et al,⁷ are consistent with two prospective cohort studies, one using the same cohort,⁶. Both find associations between manic symptoms and cannabis use: the Netherlands Mental Health Survey and Incidence (NEMESIS) OR 2.70 (95% CI: 1.54–4.75)⁶ and the Early Developmental Stages of Psychopathology study (EDSP), OR 4.26 (95% CI: 1.42–12.76)⁹ The manic outcome in the Henquet et al NEMESIS study may have had too low a symptom threshold, with respondents needing to only endorse one symptom persisting for 2 days (their operationalization of DSM-III-R criteria) to be positive for mania. The EDSP study had a small sample size with only six cannabis exposed cases, raising questions of the power of their four leveled ordered logistic regression model to detect valid differences. The results from the NEMESIS and EDSP studies conflict with the Swedish Conscript cohort, a population-wide retrospective study (n=50,087) which found a null association [OR 1.13 (95% CI: 0.82 to 1.57)] between cannabis use by age 18 and future affective psychosis hospitalization (predominately BD diagnoses).^{8, 10} The examination of cannabis as a risk factor for manic symptoms and bipolar spectrum disorders in a large prospective epidemiological sample would contribute important evidence to the field.

I D.1 Cannabis Use and Bipolar Disorder: Substance Use Disorders and Family

History

In schizophrenia, cannabis abuse has been associated with earlier onset of the disorder.^{46,}

⁴⁷ In BD, a substance use disorder has been hypothesized to be an added insult that may manifest in a later BD.^{48, 49} Evidence from a first admission mania cohort finds that those with a pre-existing cannabis use disorders (CUD) had a significantly later age-at-onset of mania as compared to those without a CUD or those experiencing a CUD after the onset of BD [No CUD: age (SD) 18 (10), BD<= CUD: 16 (6), CUD < BD: 23 (6), $p = .002$].⁴⁸ Whether this result is merely the coincidence of the fact that the majority of CUD onset in the US population occurs by age 20⁵⁰ needs to be examined further with a longitudinal epidemiological sample such as the NESARC. One such approach is to investigate whether cannabis use status imparts different risk among those with histories of substance abuse/dependence and those without such histories, and to examine whether this risk is different for those at different developmental stages (ages 18-25 and those 26-45).

Alcohol and substance abuse are highly comorbid with BD⁵¹ and alcohol abuse and BD aggregate in families.⁵² A family history of alcohol or substance abuse, depression, or anti-social behavior may be indicative of underlying risk for BD.⁵³ Consequently, there exists a need to investigate whether cannabis use confers a greater risk for BD outcomes in individuals with alcohol or substance abuse histories as well as in those with family histories of depression, substance abuse and anti-social behavior.

I E. Bipolar Disorder Prevalence Estimates

To adequately investigate the relationship of cannabis use to BD using NESARC data it is necessary to understand differences in the reported prevalence estimates for mania, hypomania and major depressive episodes (MDE) between the NESARC and the NCS-R. The lifetime prevalence of BD-I (DSM-IV)¹¹ in NESARC wave 1 was 3.3% (95% CI: 3.2-3.4) and BD-II at 1.12% (95% CI: 1.05-1.18) with the NCS-R reporting prevalence estimates of BD-I and II twice, one estimate before a clinical recalibration algorithm was applied and one after its application. The NCS-R reported the lifetime prevalence of BD-I and BD-II as a group at 3.9% (95% CI: 3.4-4.4, un-recalibrated)¹⁷ and reported BD-I at 1.0% (95% CI: 0.7-1.3, recalibrated), BD-II at 1.1% (95% CI: 0.9-1.3, recalibrated) and a sub-threshold bipolar group at 2.4%.¹ The clinical re-calibration used in the NCS-R reduced the prevalence estimates for BD-I and BD-II by nearly a half. The prevalence of major depressive disorder (MDD) in NESARC was 13.2% (95% CI: 13.0-13.4), this compared to MDD of 16.6% (95% CI: 15.6-17.6)¹⁷ or 16.9% (95% CI 15.8-17.9, after recalibration of bipolar disorders)¹⁹⁻²¹ as seen in the NCS-R. The large differences in prevalence reported between these two nationally representative epidemiological samples point to differing methodological approaches, approaches that need to be understood and addressed. The difference in prevalence of MDD is explained in part by a higher rate of reported BD-I, BD-II and hypomania in the NESARC and possibly by differing methodological approaches by the two surveys in assessing DSM-IV mania, hypomania and MDE criteria. A comparison of how the two surveys assessed mania, hypomania and

MDE will aid future research on bipolar spectrum disorders using the NESARC dataset by improving the validity of case identification. This comparison is made in Chapter II.

I F. Cannabis use reporting and the NESARC

The exposure on which this dissertation focuses is self-reported cannabis use. Cannabis is a controlled substance under federal and state laws. Other researchers⁵⁴ examining the NESARC have found relatively low prevalence estimates for the reported use of illicit substances including cannabis. This may be due to features unique to the NESARC: specifically that the data was collected in face-to-face interviews by census workers (federal employees), rather than non-government contract researchers. This may have suppressed reports of cannabis use.⁵⁴ A goal of this dissertation is to assess whether cannabis use risk estimates differ if cannabis exposure classification conforms more closely with a less biased external exposure standard. In short, cannabis use propensities will be modeled using NCS-R effect estimates within the NESARC and from these propensities a categorized predicted cannabis use measure will be defined. Risk for bipolar outcomes associated with predicted cannabis use will be compared to reported cannabis use. The cannabis use propensities, as continuous measures, will also be assessed as risk factors for bipolar spectrum outcomes.

I G. Research Aims

As discussed, bipolar disorder is a serious psychiatric disorder. Cannabis may be a risk factor for bipolar disorder. The use of the NESARC represents an opportunity to examine cannabis use as a risk factor for bipolar disorder in a large longitudinal representative cohort and within potentially at-risk sub-populations. To these ends the specific aims of this investigation are:

Aim 1:

- 1) Evaluate implications for mania, hypomania and MDE prevalence estimates arising from the different approaches to assessing DSM-IV criterion between the Alcohol Use Disorder and Associated Disabilities Interview Schedule (AUDADIS)²⁸ used in the NESARC compared with the Composite International Diagnostic Interview (CIDI)^{35, 36} used in the NCS-R.
 - a. Identify approaches for reconciling criterion implementation differences between the two surveys with the goal of aligning the AUDADIS implementation more closely with the CIDI implementation.
 - b. Apply a clinically validated re-calibration algorithm used in the NCS-R¹⁹⁻²¹ to the NESARC dataset to more accurately identify cases of BD-I, BD-II and sub-threshold BD.
 - c. Conduct an imputation analysis to assess the impact of missing data/criterion information on prevalence estimates for major depressive episode and bipolar spectrum disorders.

Aim 2:

- 2) Examine cannabis use as a risk factor for incident (between NESARC wave 1 and wave 2) manic symptoms, bipolar spectrum disorders (DSM-IV¹¹ manic and hypomanic episodes) and CIDI recalibrated BD I and II as defined by approaches used in Aim 1:
 - a. In the total population and within strata of young adults (ages 18-25) and adults (ages 25-45) with and without histories alcohol or drug abuse/dependence.
 - b. Within strata defined by family history of depression, substance abuse or dependence and/or anti-social traits.
 - c. Examine cannabis use risk for BD outcomes among those reporting and those not reporting any lifetime depressive or manic symptoms at baseline.

Aim 3:

- 3) A sensitivity analysis will be conducted using external information from the NCS-R to produce propensity score models of cannabis use within the NESARC. Cannabis use propensity risk for incident bipolar outcomes will be assessed.
 - a. Categorized predicted exposure risk estimates will be compared to reported exposure estimates.
 - b. Cannabis use propensities will be assessed as risk factors for incident manic or hypomanic episodes in the population as a whole and among adults aged 18 to 45

- c. Risk will also be assessed within strata defined by family history and strata defined by substance use disorder history.

Chapter II Case Identification: NESARC/NCS-R Comparison, Reconciliation, Recalibration and Missing Criterion Information Assessment:

II A. Introduction

The specific aims of the research reported in this chapter include evaluating the implications for lifetime mania (BD-I), hypomania, bipolar-II (BD-II) and MDE prevalence estimates arising from the differences in approach to assessing DSM-IV criterion between the Alcohol Use Disorder and Associated Disabilities Interview Schedule (AUDADIS)²⁸ used in the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) and the Composite International Diagnostic Interview (CIDI)^{35, 36} used in the National Comorbidity Survey Replication (NCS-R). Approaches for reconciling criterion implementation differences between the two surveys will be identified. The goal is to align the AUDADIS implementation of DSM-IV criteria to more closely adhere to the CIDI implementation. After reconciling the two surveys criterion approaches, a clinically validated re-calibration algorithm used in the NCS-R¹⁹⁻²¹ will be applied to the NESARC dataset. The net result of this approach is to more accurately identify cases of BD I and BD II that rise to the level of treatment need. Lastly multiple imputation by chained equations (MICE)⁵⁵ will be applied to both surveys with the objective of assessing the impact of missing criterion information on BD-I, BD-II and sub-threshold BD prevalence estimates in the two surveys.

II B. The Surveys:

II B. 1 The National Epidemiologic Survey on Alcohol and Related Conditions

(NESARC):

The National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) was a three year longitudinal survey which fielded its first wave in 2001-2002 and the second wave in 2004-2005 assessing the same respondents.⁵⁶ The National Institute on Alcohol Abuse and Alcoholism (NIAAA), part of the National Institutes of Health sponsored the study and the U.S. Bureau of the Census carried out the field work using computer assisted personal interviewing (CAPI). The NESARC's main focus, as the survey's name implies, is alcohol use disorders and their related disabilities. The NESARC is a nationally representative sample of those 18 years of age or older who were interviewed in a household setting. The sample represents the adult non-institutionalized civilian population of the United States, including the District of Columbia and all 50 States. Residents in non-institutionalized group quarters housing, such as boarding houses, dormitories and shelters were also included as well as military personnel living off base.²⁶ The NESARC is the largest epidemiological survey in the US to date to have assessed substance use and substance use disorders, mood disorders and anxiety disorders as well as family history of depression, alcohol or drug abuse, and anti-social behavior.

The NESARC sampling frame for housing units (HUs) comes from a Bureau of the Census national survey called the Census 2000/2001 Supplementary Survey (C2SS) which was conducted between 2000 and 2001 and included approximately 78,300 households on a monthly basis.⁵⁶ Also included in the NESARC was a group quarters (GQ) frame. The group quarters sampling frame comes from the Census 2000 Group Quarters Inventory. The primary sampling units (PSUs) used in the NESARC mostly corresponds to the county-based PSUs found in the Census Bureau's Current Population Survey (CPS) with differences accounted for by changes in county definitions and Metropolitan Statistical Areas (MSA). The NESARC included samples from all of the PSU used in the C2SS but in order to maintain respondent confidentiality some PSUs were collapsed resulting in 435 PSUs.

The second stage of sampling for the NESARC consisted of within-PSU selection. The Census Bureau's Master Address File (MAF) was the primary source of the C2SS sample.⁵⁶ Information on race and ethnicity was collected as part of the C2SS and this was used to stratify housing units into three groups: Hispanic, non-Hispanic Black, and Other (non-Black, non-Hispanics). Hispanic, non-Hispanic Black HUs were then over-sampled. This over-sampling was done to improve the reliability of statistical analysis among each of these major race/ethnic subgroups within United States population. A HU equivalence was assigned to Group quarters units and these were then sampled together with the other HUs. Sampled HU or GQ entered the third stage of the NESARC sampling design.

Within each household selected in stage two a single individual was randomly selected from a list of persons residing in the household.⁵⁶ In GQs the census interviewers obtained a list of those residing at the location and interviewed persons based on their position on that list. Within households where young adults aged 18 to 24 years resided those 18 to 24 year olds were sampled at 2.25 times the rate of other household members. NESARC investigators over-sampled young adults in order to better assess adverse alcohol related outcomes in this population with an eye toward developing primary and secondary interventions.

The NESARC wave 1 sample has been weighted to be representative of the non-institutionalized adult (18 years of age and older) US population. The weighting of the NESARC sample is the product of seven individual weights.⁵⁶ These individual weights include the inverse probability of HU selection (base weight), a household non-interview, a within-household, a usually resided elsewhere, a person non-interview, and a first stage and second stage adjustment weight. The weighting of wave 2 of the NESARC was adjusted to represent the wave 1 population, minus any attrition between the two waves as the result of incapacitation/institutionalization, death, deportation/permanently leaving the US or military service during Wave 2 assessment.⁵⁷ This was accomplished by including weighting adjustments for non-response, psychiatric diagnoses and sociodemographic factors. This weighting readjustment resulted in there being no significant difference between wave 2 respondents and wave 2 respondents plus

wave 2 non-respondents on a number of baseline characteristics (age, gender, race-ethnicity, socioeconomic status or the presence of any mood, anxiety, lifetime substance or personality disorder).⁵⁷ Because of the complex sampling used in the NESARC, design effects need to be taken into account in the estimation of standard errors. Inaccurate variance estimates will result if statistics appropriate for simple random samples are applied to complex samples like the NESARC without taking the sampling design into account. The overall response rate for wave 1 (n= 43,093) was 81.2%^{23, 24} with n= 34,653 respondents participating in the 3-year follow up interview for a cumulative response rate 70.2% at wave 2.²⁵ All potential participants in the NESARC were informed in writing about the study.⁵⁸ This written information described the nature of the survey, the statistical uses of the study information, the voluntary nature of their participation, and the Federal laws in place that protect the confidentiality of survey participants. Only those respondents who received this written information and consented to be interviewed were included in the study. Full ethical review and approval of the NESARC study was received from the U.S. Office of Management and Budget and from the U.S. Census Bureau. A public use dataset of wave 1 is available for download on the internet from the National Archive²⁴ and both wave 1 and wave 2 data sets were requested and received from NESARC principal investigators. The use of these public use datasets has been deemed not to be human subject research and thus exempt from IRB approval by the University of Massachusetts Medical School's Research Subjects Office.

II B. 2 The National Comorbidity Survey Replication:

The National Comorbidity Survey Replication (NCS-R)⁵⁹ was conducted between February 2001 and April 2003, thus overlapping the time period of the NESARC's fielding. Face-to-face computer-assisted personal interviews (CAPI) of 9282 respondents were conducted by professional survey interviewers (not federal employees). The NCS-R used the World Health Organization (WHO) Composite International Diagnostic Interview (CIDI) to assess psychiatric disorders.³⁶ Previous versions of the CIDI had good to excellent kappa coefficients for most disorders in clinical and population samples though major depressive ($k=0.66$), bipolar I ($k=0.61$) and bipolar II ($k=0.59$) had only moderate test-retest reliability.⁶⁰ The CIDI used in the NCS-R was divided into two parts. Part 1 assessed core disorders including major depressive episode, manic and hypomanic episodes with Part 2 assessing services, consequences, and risk factors including substance use. Respondents were interviewed for part 2 if they met criteria or met sub-threshold criteria and sought treatment for any part 1 disorder, or reported planning or attempting suicide. A probability sub-sample selected those meeting sub-threshold criteria for any disorder, sought treatment, had suicidal ideation or used psychotropic medication. An additional probability sample of those not in the two previous groups were also selected and included in the part 2 interview. The NCS-R used a four-stage area probability sample using data from the 2000 census. The first stage involved primary sampling units based on metropolitan statistical areas, or counties defined by the census being selected by probabilities proportional to size (PPS). The resulting sample included 46 non-self-representative PSUs with 13 self-representative

units split into 26 pseudo-PSUs for a total of 84 PSUs. The second stage divided the PSUs into segments that had 50 to 100 housing units, these segments were selected by PPS. The third stage selected households within the selected segments. The final stage selected individuals within the household. The weighting of the NCS-R sample accounts for non-response to full participation by using information aggressively collected on non-responders by means of a short form. Respondents to both part 1 and part 2 are weighted to be representative of the non-institutionalized English-speaking adult (18 and older) household population of the contiguous 48 US states. Like the NESARC's AUDADIS, the NCS-R's CIDI was only administered in English. As with the NESARC, the NCS-R is a public use data set not considered human subject research and exempt from IRB approval.

II C. Methods: Approach

The methodological approach for the study in this chapter is as follows. First a determination of how DSM-IV criteria were applied in the two surveys was made. Differences between how the surveys applied DSM-IV criteria were identified. Identified DSM-IV criterion differences between the two surveys were 'reconciled', where possible, by using available information in the NESARC to recode individual NESARC criterion and sub-criterion related question responses to more closely adhere to the CIDI operational schema. So three separate series of estimates were made, one adhering to the NESARC/AUDADIS approach, the second being the reconciled NESARC/CIDI approach, and lastly the NCS-R/CIDI approach. The effect of applying each successive

DSM-IV criterion for mania, hypomania and MDE were examined within each of these three modeling approaches. The recalibration algorithm was then applied to the NESARC/CIDI and the NCS-R/CIDI models. Furthermore survey ‘skip-outs’ within the mania and MDE sections of the two surveys identified in the course of applying individual criterion, which created missing criterion and sub-criterion information were identified. This missing criterion information was coded as missing, and multiple imputation by chained equations (MICE)⁵⁵ was applied to NESARC/CIDI and the NCS-R/CIDI models to assess the impact of this missing criterion information on bipolar prevalence estimates.

II D. Survey Application of DSM-IV Criteria

II D. 1 Manic Episode Criterion

Both the NCS-R and the NESARC assessed mania, hypomania and major depressive episodes according to DSM-IV criteria. Published algorithms of how the psychiatric disorders were operationalized for the NCS-R have been published,²⁰ but algorithms of how the psychiatric disorders were operationalized in the NESARC have not.⁶¹

Determining the algorithms for the NESARC involved examination of the relevant research articles,^{16, 62} survey materials,²⁸ personal correspondence,^{38, 63} and/or inference from NESARC investigators constructed variables.

To define the cohorts of those meeting individual DSM-IV criterion for a manic episode for both the NESARC/AUDADIS and NESARC/CIDI approaches individual survey

responses from the High Mood section of the AUDADIS were used. Likewise with the NCS-R individual questions from the screening and manic section of the CIDI were used to operationalize individual manic episode criterion (Appendix A). DSM-IV manic episode criterion A is operationalized by the AUDADIS with the required endorsement of either a week or more of ‘extremely excited, elated or hyper mood’ such that other people were concerned about or thought was uncharacteristic of the respondent, or a week or more of irritable mood. The CIDI likewise requires a week or more of abnormally and persistently elevated, expansive, or irritable mood, but the CIDI also includes endorsing hospitalization as a means of meeting criterion A (i.e. hospitalization eliminates the requirement of a week or more of mood duration). Manic episode criterion B symptom questions (Table 2.1) for both the AUDADIS and the CIDI closely adhere to the DSM-IV and were assessed for the episode when the respondent’s mood was the most elevated or irritable. Both the AUDADIS and the CIDI require endorsement of at least three of the seven Criterion B symptoms for those endorsing elevated mood and at least four symptoms for those only endorsing irritable mood as prescribed by the DSM-IV. The AUDADIS does not systematically assess Mixed Episodes among all respondents and as such the requirement that the symptoms of a manic episode do not meet criteria for a Mixed Episode (i.e. criterion C) was not implemented. Similarly the CIDI does not operationalize criterion C. No differences between the NESARC/AUDADIS and NESARC/CIDI approaches are present for DSM-IV manic episode criterion A, B and C. Respondents to the NESARC who did not respond either ‘yes’ or ‘no’ to any of the manic episode or MDE stem questions (i.e. criterion A questions) were considered to have

Table 2.1: DSM-IV Manic and Hypomanic Symptoms by Corresponding Survey Symptom Questions

NCS-R	NESARC
Increase in goal-oriented activity (either socially, at work or school, or sexually) or psychomotor agitation	
1: Did you become so restless or fidgety that you paced up and down or couldn't stand still?	1: Feel so restless that you fidgeted, paced, or couldn't sit still? 2: Become so physically restless that it made you
2: Were you a lot more interested in sex than usual, or did you want to have sexual encounters with people you wouldn't ordinarily be interested in? 3: Did you become overly friendly or outgoing with people? 4: Did you try to do things that were impossible to do, like taking on large amounts of work? 5: Did you do anything else that wasn't usual for you - - like talking about things you would normally keep private, or acting in ways that you'd usually find embarrassing?	3: Become more sexually active than usual or have sex with people you normally wouldn't be interested in? 4: Become more active than usual, at work, at home, or in pursuing other interests?
More talkative than usual or pressure to keep talking	
6: Did you talk a lot more than usual or feel a need to keep talking all the time?	5: Find you were more talkative than usual? 6: Talk so fast that people had trouble understanding you or couldn't get a word in edgewise?
Distractibility	
7: Did you find it hard to keep your mind on what you were doing? 8: Did you constantly keep changing your plans or activities?	7: Have trouble concentrating because little things going on around you easily got you off track?
Flight of ideas or subjective experience that thoughts are racing	
9: Did your thoughts seem to jump from one thing to another or race through your head so fast you couldn't keep track of them?	8: Find that your thoughts raced so fast that it was hard to follow your own thoughts? 9: Find that your thoughts raced so fast that you couldn't keep track of them?
Decreased need for sleep	
10: Did you sleep far less than usual and still not get tired or sleepy?	10: Need much less sleep than usual?
Engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investment	
11: Did you get involved in foolish investments or schemes for making money? 12: Did you spend so much more money than usual that it caused you to have financial trouble? 13: Did you do reckless things like driving too fast, staying out all night, or having casual or unsafe sex?	11: Do anything unusual that could have gotten you into trouble - like buying things you couldn't afford or didn't need, making foolish decisions about money, or driving recklessly? 12: Do anything that you later regretted - like spending time with people you normally wouldn't be interested in?
Inflated self-esteem or grandiosity/delusional/psychotic	
14: Did you have a greatly exaggerated sense of self-confidence or believe you could do things you really couldn't do? 15: Did you have the idea that you were actually someone else, or that you had a special connection with a famous person that you really didn't have?	13: Feel that you were an unusually important person or that you had special gifts, powers, or abilities to do things that most other people couldn't do? 13A: Psychotic feature defined as presents of grandiosity (above question, for use in NESARC/CIDI approach) AND a history of psychotic diagnosis or episode.

refused these sections and were coded as missing. For the NCS-R refusal information was available and those who refused mania screening and/or stem questions were coded as missing.

II D. 2 Reconciling AUDADIS Manic Episode Criterion D with CIDI Approach:

The AUDADIS asks five questions to assess DSM-IV manic episode criterion D. DSM-IV manic episode criterion D requires that the mood disturbance be severe enough to cause marked social or occupational impairment or to necessitate hospitalization or have psychotic features. The questions (Appendix B, questions 7a1 to 7a5)²⁸ were asked specifically about the most elevated or irritable lifetime mood episode, the same episode for which criterion B symptoms were assessed. Respondents endorsing three or more manic symptoms were asked: 1) whether they were uncomfortable or upset by their manic symptoms ('uncomfortable with symptoms'), 2) did they have "any serious problems getting along with other people - like arguing with your friends, family, people at work or anyone else?" ('social impairment'), 3) "Did you have any serious problems doing things you were supposed to do - like working, doing your schoolwork, or taking care of your home or family?" ('occupational impairment'), 4) they were asked "Did you have trouble getting things done?" ('difficulty completing tasks'), and lastly 5) "Did you have any legal trouble - like being arrested, held at the police station or put in jail?" ('legal involvement'). The NESARC/AUDADIS approach requires the positive endorsement of any one of the five impairment questions to satisfy Criterion D.

In the CIDI criterion D, or impairment, is assessed among those who endorses 3 or more or the 15 criterion B symptom questions.²⁰ Only one question is asked to all the respondents endorsing 3 or more symptom questions. This question, M9, asks “How much did these episodes ever interfere with either your work, your social life, or your personal relationships – not at all, a little, some, a lot, or extremely?”⁶⁴ Those endorsing either ‘some’, ‘a lot’, or an ‘extreme’ amount of impairment continue further in the CIDI Mania section and are asked, among other things, more criterion D and criterion E questions. It is important to note at this juncture that those endorsing ‘not at all’ or ‘a little’ to question M9 are skipped out of the Mania section altogether. If criterion D was only being assessed with question M9 this would not be a problem but other questions capturing important and required DSM-IV criterion D features are not taken into account by the skip out at this question. Indeed the CIDI uses not only question M9 but other questions assessing impairment in the past 12 months (see Appendix A), hospitalization, seeing a mental health professional and psychotic features to operationalize criterion D. Questions asked after question M9 capture lifetime criterion D traits namely hospitalization and seeing a mental health professional. Criterion E is also assessed after M9 so those skipped out at M9 can not satisfy this criterion. Criterion E for manic episode (criterion F for hypomania) requires that the mood episode not be due to the direct physiological effects of substances or be the result of a general medical condition. The CIDI requires assessment of substance or illness induced mood episodes for criterion E to be coded as either present or absent. The CIDI uses questionnaire responses as a

screeners with clinicians evaluating freeform responses to determine if mood episodes were illness or substance induced. For the imputation analysis, hospitalization, seeing a mental health professional and criterion E are coded as missing among those that endorsing 'not at all' or 'a little' to question M9 and were skipped out of the mania section.

For the reconciled NESARC/CIDI model, criterion D was considered to have been met by the endorsement of either social or occupational impairment as described above, or the presence of psychotic features, or the endorsement of hospitalization, or seeing a mental health professional, or having had a mania related emergency room visit, or whether they were ever prescribed medication for mania. The CIDI does not ask about emergency room visits or prescriptions for mania but as these both involve seeing a mental health professional, a CIDI measure of impairment, and as such they were included in the reconciled NESARC/CIDI model. The AUDADIS impairment questions involving 'being uncomfortable with manic symptoms', 'having trouble getting things done' and 'legal involvement' were not considered sufficient, standing alone, to necessarily constitute impairment in the context of the CIDI approach or DSM-IV criterion D. The 'being uncomfortable or upset' question captures an ambiguous level of distress. Distress alone is not a part of DSM-IV criteria for mania. Distress could be considered impairing but the social and occupational impairment questions assess this trait. The 'having trouble getting things done' question is vague enough that it may misclassify some as being occupationally impaired who subsequently fail to endorse the 'occupational

impairment' question. Legal involvement was also not used as an impairment measure as it was not used in the CIDI and may also misclassify as manic some respondent who experienced legal involvement during a hypomanic episode (e.g. a traffic violation with outstanding warrants). As the AUDADIS grandiosity/delusional question (i.e Table 2.1, question 13) is not specific to delusional or psychotic features additional information was used to define psychotic features. All respondents to the NESARC were asked: "Did a doctor or other health professional EVER tell you that you had schizophrenia or a psychotic illness or episode?"²⁸ (coded 1=yes, 0=no). The psychotic feature trait for NESARC/CIDI modeling approach was defined as the endorsement of the grandiosity/delusional question and the psychotic illness or episode question. It should be noted that both the NESARC and the NCS-R do not apply hierarchy rules to their definitions of mania and bipolar disorder with respect to schizophrenia spectrum disorders (i.e. schizophrenia spectrum disorders were not used to exclude bipolar spectrum disorders).

II D. 3 AUDADIS DSM-IV Manic Episode Criterion E, Hypomanic Episode

Criterion F:

As previously mentioned the CIDI uses questionnaire responses to screen for illness or substance induced mood episodes and clinician evaluation of freeform responses to determine if the mood episodes meet manic episode criterion E (hypomanic episode criterion F). For the AUDADIS, questionnaire logic and variables constructed by NESARC investigators and included in the NESARC data file were used to infer how

substance and illness induced mood episodes were identified. A variable (nmandxlife) representing manic episode before the application of criterion E (mania meeting criterion A, B and D) was included in the data set. Variables indicating manic episodes with illness (dnmandxsni12 and dnmandxsni12) and substance use (nmandxsns12 and nmandxsns12) as a cause being ruled out in the last 12 months and prior to the last 12 months respectively were also included in the data set. From these variables one can identify which respondents the NESARC investigators identified as meeting lifetime manic episode criterion A, B and D as well those excluded for substance or illness induced mood episodes. The following approach was used to operationalize criterion E for both the NESARC/AUDADIS and NESARC/CIDI approaches. To fail to meet Criterion E respondents needed to have had all of their lifetime manic episodes either illness induced or substance induced. Episodes were considered illness induced if the respondent reported that a doctor or health professional told them that all of their episodes were related to a physical illness or medical condition (in both the past year and prior to the past year if applicable). To fail Criterion E for substance use a respondent would need to do all of the following: 1) report that all episodes followed substances use or withdrawal, 2) report stopping substance use or stopped experiencing withdrawal symptoms for at least a month and, 3) report manic symptoms did not continue after the cessation of substance use or withdrawal symptoms for all episodes (again, in both the past year and prior to the past year if applicable). These episodes can reasonably be explained better by substance use or withdrawal and as such fail to meet Criterion E. For

the NESARC/AUDADIS, NESARC/CIDI and the NCS-R/CIDI models a lifetime DSM-IV manic episode was defined as positive if respondents meet criterion A, B, D and E.

II D. 4 Survey Application of DSM-IV Hypomanic Episode Criterion

Both the AUDADIS and the CIDI assessed hypomanic episodes with the same set of questions that were used to assess manic episodes. DSM-IV hypomanic episode criterion A requires a distinct period of persistently elevated, expansive, or irritable mood, lasting at least 4 days. The AUDADIS does not assess mood episodes less than one week in duration. For the AUDADIS manic episode criterion A and hypomanic episode criterion A are the same. The CIDI operationalization of hypomanic episode criterion A includes mood episodes as short as four days. For both the AUDADIS and the CIDI hypomanic and manic symptom criterion (criterion B) are the same. DSM-IV hypomanic episode criterion C requires that the mood episode represent an unequivocal change in functioning. This unequivocal change in functioning is considered satisfied in the AUDADIS by the endorsement of any of the High Moods stem questions (Appendix B, questions 1, 2 or 3) the same question that constitute mania/hypomania criterion A. In the CIDI lifetime unequivocal change in functioning is effectively assessed by only one question, M9 (Appendix A), other questions assess functioning in the past 12 months and seeing a mental health professional is later used as an exclusion criterion (hypomania criterion E). For the CIDI question M9 endorsement of ‘some’ interference with work, social life, or personal relationships constitutes the unequivocal change in functioning requirements of hypomania criterion C (note that ‘a lot’ or an ‘extreme’ amount of

interference reported at M9 constitutes marked impairment, hypomanic episode criterion E). DSM-IV hypomanic episode criterion D that the mood disturbance and the unequivocal change in functioning be observed by others is not operationalized by either the AUDADIS or the CIDI.

DSM-IV hypomanic episode criterion E requires that the unequivocal change in functioning of criterion C not be severe enough to cause marked impairment in occupational or social functioning, require hospitalization or include psychotic features (i.e. does not meet the manic episode level of marked impairment, manic episode criterion D). For the NESARC/AUDADIS model endorsement of any of the AUDADIS manic episode impairment questions (Appendix B, questions 7a1 to 7a5) resulted in failure to meet hypomanic episode criterion E. For the NESARC/CIDI approach hypomanic episode criterion E was considered to have been met if all of the following were not endorsed: social or occupational impairment as described above, the presence of psychotic features, hospitalization, seeing a mental health professional, having had a mania related emergency room visit, and having been prescribed medication for mania. For the NCS-R/CIDI approach those meeting manic episode criterion D as described above fail to meet hypomanic episode criterion E (coded failure=0, meet hypomanic criterion A, B and C=1). Hypomanic criterion F (i.e. not illness or substance induced) is operationalized in the same way as manic episode criterion E as described above. For the NESARC/AUDADIS, NESARC/CIDI and the NCS-R/CIDI models DSM-IV hypomanic episode was defined as those respondents meeting criterion A, B, C, E and F.

Additionally in the NCS-R/CIDI hypomanic episode model those that meet criteria for a manic episode but for the condition that their episode lasted between 4 and 6 days (with no hospitalization) and as such did not meet criteria for a manic episode, are considered hypomanic in the CIDI schema.

II D. 5 Survey Application of DSM-IV Major Depressive Episode Criterion:

DSM-IV major depressive episode criterion A requires 5 or more of 9 symptoms to be present for at least 2 weeks and that at least one of the 5 or more symptoms is either depressed mood or anhedonia (i.e. loss of interest or pleasure). In the AUDADIS lifetime depressed mood and anhedonia are assessed by questions 1 and 2 of the Low Mood I section (Appendix C). The remaining other 7 symptoms (weight change, sleep disruption, psychomotor agitation or retardation, fatigue, feelings of worthlessness, loss of concentration and suicidality) are assessed with 19 separate questions. Examination of the Low Mood I section shows that after the symptom questions are asked 'Check Item 4.3' requires 4 of the previously mentioned 7 symptoms (not including depressed mood and/or anhedonia) to proceed further in the assessment of other major depressive episode criterion. Respondent endorsing both lifetime depressed mood and anhedonia and 3 of the remaining 7 symptoms for a total of 5 endorsed symptoms are skipped out of the major depressive episode section of the AUDADIS. This un-assessed group represents respondents who most probably meet MDE criterion A (but for the ambiguity of the concurrency of the depressed mood and anhedonia as the questions ask about lifetime occurrence) and are missing remaining DSM-IV criterion information. For the

imputation analysis relevant criterion questions (described in detail below) are coded as missing among this un-assessed group. Imputing responses to these missing criterion questions allows a probabilistic assessment of the impact of this group on MDE and Bipolar II prevalence estimates. In the CIDI implementation of MDE criterion A symptoms are assessed within the same mood episode and the 9 MDE symptoms are operationalized with 24 separate questions (Appendix D). MDE criterion A is satisfied in the NESARC/AUDADIS, NESARC/CIDI, and NCS-R/CIDI models when 5 or more symptoms are endorsed.

DSM-IV MDE criterion B, which requires that the symptoms not meet criteria for a Mixed Episode, was not implemented in either the NESARC or the NCS-R. DSM-IV MDE criterion C requires that the symptoms cause clinically significant distress or social or occupational impairment. The AUDADIS assessed MDE criterion C with 8 questions: 2 distress questions and 6 impairment questions (all yes/no questions, Appendix C questions 5 (1) - 5(8)). The CIDI assessed MDE criterion C with 9 questions: 4 distress related questions and 5 impairment questions (most on a 4 level Likert scale or 10 level visual analog scale, Appendix D). For the NESARC/CIDI implementation two changes were made to the NESARC/AUDADIS approach. First those reporting being uncomfortable or upset ("Were you uncomfortable or upset by your low mood or any of these other experiences?") but not reporting being very troubled ("Were you very troubled because of the way you felt at that time or did you often wish you could get better?") were not considered distressed as they were likely uncomfortable but not very

troubled by their symptoms, and as such not rising to a clinically significant level of distress. Secondly, those reporting being less active ("Did you find you did a lot less than usual or were less active?") but not endorsing "find(ing) you couldn't do the things you usually did or wanted to do?", were not considered impaired as their inactivity was likely not indicative of a clinically significant level of impairment. Both the AUDADIS and the CIDI applied the same approach to determining illness and substance induced exclusions (i.e. failing MDE criterion D) for MDE as was applied to mania criterion E and hypomania criterion F (reference above).

DSM-IV MDE criterion E requires the following: That bereavement not better account for symptoms, such that after the death of a loved one, the symptoms need to persist for longer than 2 months or be characterized by marked functional impairment, suicidal ideation, morbid preoccupation with worthlessness, psychomotor retardation, or psychotic symptoms.¹¹ The AUDADIS assesses bereavement but the CIDI does not. For the AUDADIS assessment of bereavement, questionnaire logic and variables constructed by NESARC investigators and included in the NESARC data file were used to infer how it was operationalized. A variable (majordeplife) representing lifetime MDE after exclusions for bereavement (MDE criterion E applied) but before the application of MDE criterion D (MDE criterion A, B and E) was included in the data set. As previously mentioned respondents meeting MDE criterion A and B can be identified from survey question responses. Those meeting MDE criterion A and B but not represented in the majordeplife variable were considered to be those identified as 'bereaved' by the

NESARC investigators. Variables indicating MDE with illness (dmajordepsni12 and dmajordepsnip12) and substance use (majordepsns12 and majordepsnsp12) as a cause being ruled out in the last 12 months and prior to the last 12 months respectively were also included in the data set which allow identification of those meeting MDE criterion D in the same manner as use for manic and hypomanic episodes. Comparing those identified as bereaved to individual survey responses one can infer a general approach to the operationalization of bereavement in the AUDADIS. The simplest operationalization that can be inferred relies on re-coded variables as found in the NESARC data set and is as follows: respondents that report one episode lasting less than 2 months needed to endorse that the episode began after someone close to them died. Respondent reporting more than one episode needed to endorse that all of their episodes that lasted “less than 2 months” only began after some one died. The NESARC/AUDADIS approach relies only on the positive endorsement of these bereavement responses to identify those excluded from a MDE diagnosis due to bereavement. The AUDADIS does not explicitly exclude those who earlier in the survey endorsed episodes of greater than 2 months (at least among those with more than one episode), or endorsed impairment, morbid preoccupation with worthlessness, suicidal ideation, psychomotor retardation, or psychotic symptoms (not assessed in either the AUDADIS or the CIDI MDE sections). For the NESARC/CIDI approach (or for this criterion it may be more apt to call the NESARC/DSM-IV approach as bereavement was not assessed in the CIDI) those not endorsing that their longest episode was 9 weeks or shorter in duration were ruled out for a bereavement exclusion. Additionally, in keeping with the DSM-IV, worthlessness,

suicidal ideation, psychomotor retardation and impairment (as defined above) were applied to rule out bereavement as an exclusion from a MDE diagnosis.

II E. National Comorbidity Survey-Replication Clinical Re-evaluation and Recalibration:

A recalibration algorithm for bipolar spectrum disorders based on CIDI diagnoses and individual CIDI questions has been published.²⁰ This recalibration algorithm reclassifies the CIDI diagnoses of BDI and BD II so as to increase these diagnoses' concordance with a weighted clinical reassessment sub-sample administered the lifetime non-patient version of the Structured Clinical Interview for DSM-IV (SCID).³⁴ This recalibration algorithm tightens up the criteria to meet BDI and BD II and creates a sub-bipolar group made up of those meeting the 'old' CIDI criteria for BDI or BD II but failing to meet the new definition. The algorithm creates a high threshold for meeting BDI, requiring the following conditions be met: 1) CIDI implemented DSM-IV criteria for mania, 2) endorse ≥ 6 of the 7 DSM-IV manic episode criterion B symptoms as well as 2 or more of the following 'super-symptoms': increased libido, being overly friendly or outgoing, involved in foolish investments, over spending leading to financial trouble or psychotic/delusional features. For the NESARC, foolish investments and over-spending are included in the same question (Table 2.1) the endorsement of which was considered to be equivalent to two 'super-symptoms'. The published algorithm states "at least 6 symptoms in the M7 series (DSM_MAN_OLD Criteria B1-B7)"²⁰ which other researchers⁶⁵ have interpreted to mean individual symptom questions in the M7 series as

opposed to endorsed DSM-IV criterion symptoms. Applying a threshold of 6 or more endorsed DSM-IV criterion symptoms results in Bipolar I case counts being in accord with published counts as included in public release data set. The algorithm is described in full in Appendix A. For Bipolar II the algorithm requires that the new definition of Bipolar I not be met and that the CIDI criteria for mania (pre-algorithm definition) be met and the respondent experienced a MDE, euphoria (elevated mood) and racing thoughts. Bipolar II is also met if the CIDI definition of bipolar II is met (hypomania plus a history of a MDE) and the hypomanic episode is at least 14 days long and at least 2 of the “super symptoms” are endorsed. Sub-threshold Bipolar Sub is defined as anyone left meeting the pre-algorithm CIDI definitions of mania and hypomania and not represented in the newly defined Bipolar I and Bipolar II groups.

II F. MICE: Multiple Imputation by Chained Equations

Multiple imputation (MI)⁶⁶ is a probabilistic approach for handling missing data. The fundamental approach to MI is to use the distribution of observed information (i.e. data) to predict a set of reasonable values for the missing information.⁶⁷ The predicted set of plausible values includes a random selection process to reflect their uncertainty. Multiple data sets containing these predicted values (e.g. ‘imputed’ data sets) with random variations are produced and then analyzed individually but in the same manner so as to produce a set of parameter estimates. The Stata user written program ICE was used to produce the multiple imputed data sets used in this study.⁶⁸⁻⁷² Lastly, these estimates are combined to produce the resulting overall estimate, variance and confidence intervals.

The Stata user written program MIM was used to produce the overall estimates for this study.⁷³ Rubin's rules are used to combine m number of estimates into an overall estimate.⁷⁴ Rubin's rules address both within-imputation uncertainty (one imputed data set's variability of the estimate) and between-imputation uncertainty (representing the variability due to the missing data).^{67, 74} Consider $\hat{\theta}_j$ is an estimate of interest (e.g. a mean) obtained from the j th imputed data set j and \mathbf{W}_j is the estimated variance of $\hat{\theta}_j$.

The average of the estimates is the combined estimate $\hat{\theta}$:⁶⁷

$$\hat{\theta} = \frac{1}{m} \sum_{j=1}^m \hat{\theta}_j \quad (1)$$

To obtain the total variance of $\hat{\theta}$ (i.e. $\text{var}(\hat{\theta})$) the within imputation variance

$\mathbf{W} = (1/m) \sum_{j=1}^m \mathbf{W}_j$ and the between imputation variance $\mathbf{B} = (1/(m-1)) \sum_{j=1}^m (\hat{\theta}_j - \hat{\theta})^2$ are combined:⁶⁷

$$\text{var}(\hat{\theta}) = \mathbf{W} + \left(1 + \frac{1}{m}\right) \mathbf{B} \quad (2)$$

Multiple imputation, as operationalized by the ICE procedure, uses multiple imputation by chained equations (MICE).⁵⁵ MICE involves the following general process:^{55, 67} first a variable with missing values, A1 say, is modeled (e.g. logit, ordinal or multinomial logistic regression, linear regression) with all other variables A2, . . . , Ak, but limited to data with the observed A1. Missing values in A1 are replaced by random draws from the

predicted distribution of A1. Then, A2 the next variable with missing data, is modeled with all the other variables A1, A3, . . . , Ak , restricted to individuals with the observed A2, but now also using the previously imputed values of A1. As with A1, missing values in A2 are replaced by random draws from the predicted distribution of A2. This procedure is repeated for all the variables with missing values. To produce a stable result this procedure is repeated several times (e.g. 10 or 20) to generate a single imputed data set. This whole procedure is repeated multiple times to produce multiple data sets. MI in general and MICE in particular assumes the missing data are missing at random (MAR- the probability of data being missing is not a function of unobserved information, conditional on the observed information). This assumption is not an unreasonable one in the context of this study. A considerable proportion of the missing criterion information in both the NESARC and the NCS-R is a by product of skip patterns within diagnostic sections. These skip patterns are based on observed characteristics so the missing data are less likely to be missing not at random (MNAR- data missing probability is dependent on the unobserved data, conditional on the observed information).

II F. 1 MICE and the NESARC:

MICE was applied to the NESARC data set to assess the impact of missing criterion information on the prevalence estimates of bipolar I (mania), bipolar II (hypomania and MDE), hypomania and MDE. Variables used for imputation included demographic variables, mania and major depressive episode related variables, and psychiatric comorbidity variables. The demographic variables have no missing values as the

NESARC investigators assigned or imputed any missing values in these variables.⁵⁶ The demographic variables included: gender (male=1, female=0), race/ethnicity (1=White, Not Hispanic or Latino, 2=Black, Not Hispanic or Latino, 3= American Indian/Alaska Native, Not Hispanic or Latino, 4= Asian/Native Hawaiian/Pacific Islander, Not Hispanic or Latino, 5=Hispanic or Latino), age cohort (1= 18-25, 2= 26-35, 3= 36-45, 4= 46 and older), educational status (1= less than High School, 2= High School or GED, 3= some college/Associate or Technical degree, 4= greater than or equal to a bachelor's degree), marital status (1=Married or living with someone as if married (not currently married or separated from another person), 2= Divorced or Separated, 3=Widowed, 4= Never Married), personal income quartiles in dollars (1= $\leq 8,800$, 2= 8,800 to $\leq 20,000$, 3= 20,000 to $\leq 36,000$, 4= $\geq 36,000$), urbanicity (1= Urban [metropolitan statistical area (MSA) , in central city], 2= Suburban [MSA, not in central city], 3= rural [not in MSA]), and census region (1= Northeast, 2= Midwest, 3= South, 4= West).

Manic episode related variables necessary to operationalized DSM-IV criteria and to apply the CIDI recalibration algorithm were included in MICE analysis. This included indicators of individual survey responses including indicators for the manic sections three stem questions (s5q1, s5q2 and s5q3) which were coded 1=yes and 0 =non-endorsement (i.e. 'no' or 'unknown') with those failing to explicitly endorse any of these three question (i.e. no 'yes' or 'no' responses) being coded as missing (e.g. complete absence of any 'yes' or 'no' responses for all three questions being interpreted as refusal of the whole manic section). All the other variables in the manic section are coded as missing if

all of these stem questions (i.e. s5q1, s5q2 and s5q3) are 'unknown' with subsequent 'unknown' responses for all other questions interpreted as non-endorsement and coded as 0. Other individual question indicators included survey questions s5q6a9, s5q6a11 and s5q6a12 which correspond to questions 3, 11 and 12 in Table 2.1 respectively. The seven DSM-IV manic episode criterion B symptoms were coded to separate indicators with the indicators for s5q6a11 and s5q6a12 used to passively impute (e.g. used to define) the excessive engagement in pleasurable activities symptom. An indicator for having three or more symptoms was passively imputed within the ICE procedure from the symptom count. This indicator was used to restrict the imputation models of the impairment (both NESARC/CIDI and NESARC/DSM-IV approaches), substance induced and illness induced variables to only respondents that logical would have been asked about these feature but for missing responses. The impairment, substance induced and illness induced variables, as well as the psychotic variable, conformed to the NESARC/CIDI coding scheme as described above. A separate impairment indicator conforming to the NESARC/DSM-IV schema described above was also included. The length of the manic episode is necessary to apply the CIDI recalibration algorithm, this was coded as (1= 1-2, 2= 3-17, 3= \geq 18 weeks) and were imputed by ordinal logistic regression. Log transformed age of mania onset use was also included and imputed by linear regression.

For MDE in the NESARC the depressed mood and anhedonia questions are the stem questions for the Low Mood I section and failure of respondents to provide a yes or no response to both of these question results in them being coded as missing. Depressed

mood and anhedonia as well as the remaining seven DSM-IV MDE symptoms were coded to separate dichotomous indicators. An indicator of endorsement of five or more symptoms was passively imputed within the ICE procedure by counting the number of endorsed symptoms. This indicator was used to restrict the imputation models of the impairment related, substance and illness induced variables, as described above, to only those who logically would be asked these criterion question under the assumption that all the symptoms were contemporaneous. Log transformed age of MDE onset use was also included and imputed by linear regression.

Other variables used in the MICE analysis included separate indicators for substance use variables: alcohol abuse (no dependence), alcohol dependence, cannabis abuse (no dependence), cannabis dependence, other substance abuse or dependence, other drug use and nicotine dependence. Other variables include the anxiety disorders variables panic disorder or agoraphobia, social phobia, specific phobia and generalized anxiety disorder. A separate indicator was coded for dysthymia. For those experiencing any illness induced anxiety disorders or dysthymia were coded to a variable to capture this effect. Likewise for those experiencing any substance induced anxiety disorders or dysthymia. Separate variables were coded for antisocial, paranoid, schizoid, avoidant, dependent, obsessive–compulsive and histrionic personality disorders. For the NESARC imputation using ICE all the above variables were considered for use in modeling ever other variable. All imputation variable models were assessed for high degrees of correlation of the predictive variables by running them as linear regress models and excluding

predictors with variance inflation factors (VIF) of 10 or more. This was done to address collinearity among the predictive variables within individual predictive models. The number of NESARC imputed data sets created and used in the analysis was n=100.^{67, 75} Individual criterion variables within each imputed data set were used to specify mania, hypomania, MDE, Bipolar I, II and sub-threshold Bipolar disorders. These estimates were aggregated using the MIM procedure.

II F. 2 MICE and the NCS-R:

In a similar fashion as the NESARC, the NCS-R imputation used demographic variables, mania and major depressive episode related variables, and psychiatric comorbidity variables. The demographic variables included: gender (male=1, female=0), race/ethnicity (1=White, Not Latino, 2=African Americans, Afro-Caribbean, 3= Mexican, all other Hispanics, 4= Asian, other), age cohort (1= 18-25, 2= 26-35, 3= 36-45, 4= 46 and older), educational status (1= less than 11 years, 2= 12 years, 3= 13 to 15 years, 4= 16 years or greater), marital status (1=Married or living with someone as if married, 2= Divorced or Separated or Widowed, 3= Never Married), and census region (1= Northeast, 2= Midwest, 3= South, 4= West).

The NCS-R manic episode variables included separate dichotomous indicators for elevated and irritable mood and seven indicators for each of the criterion B symptom and the psychotic feature as described above. All those explicitly refusing (refusal information is available in the NCS-R, unlike the NESARC) individual responses were

coded as missing, those endorsing dichotomous questions as 'don't know' were coded as 0. Stem question refusal was defined as refusing the manic screening question (M1) and refusing either the elevated mood (SC24) or the irritable mood questions (SC25). Episode length was coded to an ordered categorical indicator (1=4-6 days, 2=7-13 days, 3= 14 or more days) and modeled with ordinal logistic regression. Individual indicators for survey questions involving foolish investments/money making (M7K) and financial trouble/spending sprees (M7L) were coded to separate indicator variables. Those endorsing hypomania and mania criterion C, seeing a mental health professional, experiencing hospitalization or having a manic/hypomanic episode substance or illness induced were coded to separate indicators and considered missing if 'not at all' or 'a little' to question M9 were endorsed, individual question were refused or the stem questions were refused.

Psychiatric comorbidity related variables used in the imputation of the NCS-R data included the endorsement of MDE symptoms (depressed mood, anhedonia, weight loss/gain, insomnia, psychomotor retardation, fatigue, worthlessness, indecisiveness, suicidality, distress, impairment, duration and an illness or substance induced indicator). Other psychiatric comorbidity related variables included indicators for respondents meeting DSM-IV criteria for GAD, agoraphobia, social phobia, specific phobia and panic attack. The endorsement of being hospitalized for a mental health or substance related issue, suicidality (generally, outside the context of the MDE questions), the use of antipsychotic medication, stimulants, sedatives, tranquilizers and anti-depressives were

all coded to separate indicators. Individual psychiatric disorder variables were considered missing if the stem questions for their corresponding diagnostic section of the CIDI were refused. It should be noted that substance abuse and dependence in the NCS-R was assessed in part 2 of the survey, a sub-population, and as such these variables were not used in the full population imputation analysis.

The implementation of ICE with the NCS-R specified the prediction variables for individual imputed variables be significantly related ($p < 0.1$) and were selected by backwards stepwise selection. The number of imputed data sets created and used in the analysis was $n=50$.^{67, 75} As was done with the NESARC imputation, individual criterion variables within each imputed data set were used to specify mania, hypomania, MDE, Bipolar I, II and sub-threshold Bipolar disorders. These estimates were then aggregated using the MIM procedure.

II G. Results:

II G. 1 Manic episode

The results of applying successive DSM-IV manic episode criterion to the NESARC and NCS-R data sets are shown in Table 2.2. For the NESARC 2.3% ($n=1014$) of the respondents did not provide any valid (i.e. yes or no) responses to the manic diagnostic section stem questions. Subsequent manic and hypomanic episode and criterion prevalence estimates are based on a population of 42,079 respondents. For the NCS-R, only three respondents (0.04%) refused the manic stem questions with manic and

Table 2.2: Manic Episode Comparison

	NESARC AUDADIS		NESARC AUDADIS/CIDI		NCSS-R CIDI	
	n	Prevalence ⁱ % (95% CI)	n	Prevalence ⁱ % (95% CI)	n	Prevalence ⁱ % (95% CI)
Total Population	43,093		43,093		9282	
Valid stem question responses	42,079	97.7 (97.4-98.1)	42,079	97.7 (97.4-98.1)	9,279	99.96 (99.9 -1.00)
Meet criterion A	5148	12.5 (11.9-13.1)	5148	12.5 (11.9-13.1)	864	9.2 (8.5-10.0)
Meet criterion A and B						
Criterion C: Not operationalized	2591	6.2 (5.8-6.5)	2591	6.2 (5.8-6.5)	719	7.7 (7.0-8.3)
Meet criterion A,B and D	1551	3.7 (3.4-4.0)	1357	3.2 (3.0-3.5)	382	4.0 (3.5-4.5)
Criterion D Features Applied:						
Uncomfortable or upset		X				
Social impairment		X		X		X
Occupational impairment		X		X		X
Trouble getting things done		X				
Legal involvement		X				
Hospitalized for mania				X		X
Saw mental health professional				X		X
ER visit				X		
RX				X		
Psychotic features				X		X
Meet criterion A,B, D NOT E (illness or substance induced)	137	0.3 (0.2-0.4)	138	0.33 (0.25-0.40)	43	0.5 (0.3-0.6)
DSM-IV Manic Episode						
Meet criterion A,B, D and E	1414	3.4 (3.1-3.7)	1219	2.9 (2.7-3.1)	339	3.5 (3.1-4.0)

ⁱPrevalences from criterion A forward use valid stem question counts for the denominator

hypomanic episode and criterion prevalence estimates based on a population of 9,279 respondents. The application of criterion D (i.e. impairment criterion) is the only difference between the AUDADIS/NESARC and the AUDADIS/CIDI approaches. The 0.5% difference in prevalence of those meeting criterion A, B and D between the two approaches is significant ($p < 0.001$). Significant differences are also seen between the AUDADIS/CIDI and the NCS-R/CIDI approaches. Differences which remain relatively stable after the application of criterion A and B. It should be noted that the AUDADIS/NESARC results in $n=1414$ manic episode cases and that this differs from the number published¹⁶ by the NESARC investigators ($n=1411$). The three differing cases all failed to positively report the number of individual episodes they experienced and if their first episode occurred in the last 12 months (i.e. unknown responses) and were assessed for illness and substance induced episodes only for the period prior to the last 12 months. These three cases meet DSM-IV manic episode criterion A, B and D and reported that all of their episodes prior to the last 12 months were not either substance or illness induced and as such were considered to have meet DSM-IV criteria for a manic episode based of the best available information. The NESARC operationalization of manic episode criterion E required information from both time periods for those with an ambiguous number of episodes and onset.

II G. 2 Hypomanic episode

The results of applying successive DSM-IV hypomanic episode criterion are shown in Table 2.3. For the NESARC, as seen with mania, no differences between the AUDADIS/NESARC and the AUDADIS/CIDI approaches are seen until criterion E (not

meeting marked impairment, manic criterion D) is applied. The 0.4% difference in prevalence found between the two criterion approaches is significant ($p < 0.001$). This difference remains after applying the full hypomanic episode criteria (criterion A, B, C, E and F). Considerable differences are seen between the AUDADIS/CIDI and the NCS-R/CIDI approaches starting at criterion E (Table 2.3).

II G. 3 Major Depressive Episode

The results of applying successive DSM-IV major depressive episode criterion are shown in Table 2.4. For the NESARC 1.9% ($n=864$) of the respondents did not provide valid (i.e. yes or no) responses to any of the MDE section stem questions. The criterion prevalence estimates are based on those with at least one valid response ($n=42,229$). Remarkably only one respondent to the NCS-R refused themselves out of the MDE section. All three approaches produce similar criterion A and C prevalence estimates (Table 2.4) with the NESARC survey-question-based illness and substance induced estimates being higher than the NCS-R open form clinician reviewed method. The AUDADIS/NESARC approach identifies 1.6% ($n=713$) of the population as having experienced a MDE that was better explained by bereavement, which representing 8.8% (95% CI: 7.9-9.6) of all lifetime MDEs meeting criterion A, C and D. Comparing the AUDADIS/NESARC approach to bereavement with the strict DSM-IV approach shown in the AUDADIS/CIDI (DSM-IV) prevalence model shows that very few individuals ($n=15$) are excluded from a MDE due to bereavement. These represent only 1.7% (95% CI: 0.7-2.8) of the 690 that are identified by the bereavement question only approach

Table 2.3: Hypomanic Episode Comparison

	NESARC: AUDADIS		NESARC: DSM-IV/CIDI		NCS-R: CIDI	
	n	Prevalence* % (95% CI)	n	Prevalence* % (95% CI)	n	Prevalence* % (95% CI)
Total Population	43,093		43,093		9,282	
Valid stem question responses	42,079	97.7 (97.4-98.1)	42,079	97.7 (97.4-98.1)	9,279	99.96 (99.9 -1.00)
Meet criterion A	5148	12.5% (11.9-13.1)	5148	12.5% (11.9-13.1)	1654	17.8% (16.8-18.8)
Meet criterion A and B	2591	6.2% (5.8-6.5)	2591	6.2% (5.8-6.5)	978	10.6% (9.7-11.4)
Meet criterion A,B and C**	2591	6.2% (5.8-6.5)	2591	6.2% (5.8-6.5)	480	5.2% (4.6-5.7)
Meet criterion A,B,C and E	1040	2.5 (2.3-2.6)	1234	2.9% (2.7-3.1)	79	0.9% (0.7-1.2)
Criterion E, Does not include: Uncomfortable or upset		X				
Social impairment		X		X		X
Occupational impairment		X		X		X
Trouble getting things done		X				
Legal involvement		X				
Hospitalized for mania				X		X
Saw mental health professional				X		X
ER visit				X		
RX				X		
Psychotic features				X		X
Meet criterion A,B,C,E NOT F (illness or substance induced)	25	0.06% (0.03-0.09)	24	0.05% (0.02-0.07)	3	0.05% (0.0-0.1)
DSM-IV Hypomanic Episode	1015	2.4% (2.2-2.6)			76	0.9% (0.6-1.1)
Meet criterion A,B, C,E and F			1210	2.9% (2.7-3.1)	106***	1.2% (0.9-1.4)

*Prevalences from criterion A forward use valid stem question counts for the denominator

** Criterion D: Not operationalized

*** n=30 meet criteria for mania but for mood lasting between 4 and 6 days, considered hypomanic per CIDI

Table 2.4: Major Depressive Episode Comparison

	NESARC		NESARC		NCS-R	
	AUDADIS	AUDADIS/CIDI	AUDADIS/CIDI	CIDI		
	n	Prevalence	n	Prevalence	n	Prevalence
	% (95% CI)		% (95% CI)		% (95% CI)	
Total Population	43,093		43,093		9282	
Valid stem question responses	42,229	98.1 (97.8-98.4)	42,229	98.1 (97.8-98.4)	9281	99.99 (99.9-1.00)
Meet criterion A	9760	23.0 (22.1-23.9)	9760	23.0 (22.1-23.9)	1915	20.1% (19.1-21.0)
Meet criterion A and C						
Criterion B: Not operationalized	8604	20.3 (19.4-21.1)	8458	19.9 (19.1-20.8)	1887	19.8% (18.8-20.7)
Meet criterion A,C not D (illness or substance induced)	709	1.7 (1.5-1.8)	703	1.7 (1.5-1.8)	82	0.9% (0.7-1.0)
Meet criterion A,C,D not E						
Excluded for bereavement						Not operationalized
Bereavement Questions Only	713	1.6 (1.5-1.8)	690	1.6 (1.4-1.7)		
Episode(s) Not > 2 Months			585	1.3 (1.2-1.5)		
Worthlessness, Suicidal						
Ideation and Psychomotor			208	0.5 (0.4-0.6)		
Retardation			15	0.03 (0.01-0.05)		
Impairment						
DSM-IV Major Depressive Episode						
Meet criterion A,C,D and E	7124	16.9 (16.1-17.6)	7740	18.3 (17.6-19.1)		
Meet criterion A,C, and D			7755	18.3 (17.6-19.1)	1805	18.9% (17.9-19.9)

used in the AUDADIS/NESARC as described above. These 15 bereaved MDE excluded individuals also represent only 0.15% (95% CI: 0.06-0.25) of those meeting MDE criterion A, C and D.

II G. 4 Imputation Analysis

Table 2.5 summarizes the final prevalence estimates from the reconciled AUDADIS/CIDI and NCS-R/CIDI approaches and reports the estimates from the imputation analysis. Little difference is found in the AUDADIS/CIDI estimates for mania and hypomania before and after imputation. The AUDADIS/CIDI MDE estimate do not apply criterion E (bereavement) and includes a prevalence estimate of those who endorsed depressed mood, anhedonia and a total of five symptoms and skipped out of the AUDADIS MDE section (the un-assessed). The imputation prevalence estimate of this group is 75.3% a result consistent with the preliminary estimate of 75%. The proportion of those endorsing depressed mood, anhedonia and a total of five symptoms among those endorsing any MDE symptoms was 7.0% (95% CI: 6.5-7.5) for the NESARC and 6.1% (95% CI: 5.2-7.1) of the NCS-R. The remaining NESARC estimates are relatively unchanged or decrease slightly in the imputation analysis. The NCS-R imputation results on the other hand show considerable increases in the mania and hypomania prevalence estimates and subsequently the bipolar spectrum as a whole.

Table 2.5: Summary of Reconciled Models and Imputation Analysis

	NESARC		NCS-R	
	Imputation		Imputation	
	n=42079	n=43093	n=9279	n=9282
	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)
Manic Episode	2.9 (2.7-3.1)	2.9 (2.7-3.0)	3.5 (3.1-4.0)	4.4 (3.9-5.0)
Hypomania	2.9 (2.7-3.1)	2.8 (2.6-3.1)	1.2 (0.9-1.4)	2.0 (1.6-2.4)
Major Depressive Episode (n=42229)	18.3 (17.6-19.1)*	19.7 (19.3-20.1)*	18.9 (17.9-19.9)	18.9 (17.9-19.9)
*Bereavement criteria not applied				
MDE among 'Un-assessed' (n=943)	0	75.3 (69.5-81.1)		
CID/SCID Recalibration				
Bipolar I	0.8 (0.7-0.9)	0.8 (0.6-0.9)	1.0 (0.7-1.3)	1.3 (0.9-1.6)
Bipolar II	0.9 (0.7-1.0)	0.8 (0.7-0.9)	1.1 (0.8-1.3)	1.3 (1.0-1.5)
Sub-Bipolar	4.2 (3.9-4.5)	4.1 (3.8-4.4)	2.3 (1.9-2.8)	3.8 (3.1-4.5)

II H. Discussion:

The successive application of individual DSM-IV manic/hypomanic episode criteria demonstrates that a strict adherence to the DSM-IV/CIDI approach within the NESARC shifts cases from manic episodes to hypomanic episodes when social/occupational impairment criterion is applied. The bipolar spectrum prevalence, manic or hypomanic episodes, remains intact. Little difference in NESARC bipolar prevalence estimates between the pre and post imputation analysis were found. This suggests that the time consuming nature of an imputation analysis is not necessary for bipolar case identification in the NESARC. The prevalence estimate of MDE was significantly increased in the imputation analysis though this did not meaningfully impact bipolar II estimates. Substantial difference in NCS-R bipolar prevalence estimates between the pre- and post-imputation analysis were found.

The increased imputed prevalence estimates for mania and hypomania in the NCS-R is explained by the high proportion (38.5% 95% CI: 34.0-43.0) of those meeting DSM-IV manic episode criterion A and B who are precluded from a manic or hypomanic diagnosis by failing to be assessed for criterion E, hospitalization or mental health professional contact (skipped out at question M9). In addition, of those meeting manic episode criterion A and B and endorsing less than a little social or occupational impairment at question M9 (n=281), 4.1% (n=13) meet impairment criteria before imputation by way of endorsing psychotic features. Of these 13, 11 meet the recalibration symptom criteria for Bipolar I and when these 11 are added to in the Bipolar I prevalence estimate before

imputation a prevalence of 1.1% (95% CI: 0.8-1.4) is found. Imputed hospitalization or mental health professional contact is responsible for the bulk of the difference between this result (i.e. 1.1%) and the imputed estimate (i.e. 1.3%, Table 2.5). Imputed hospitalization or mental health professional contacts are also primarily responsible for the increase in the prevalence estimates of the bipolar spectrum as a whole (4.4% to 6.4%).

The major structural difference between the two surveys is that for the NESARC those endorsing three manic symptom were assessed for all remaining criteria whereas the NCS-R skipped-out those who only endorsed less than a little social or occupational impairment. Respondents with true mania may not endorse social or occupational impairment due to a lack of insight into the impairing nature of their disorder. Impaired insight has been observed to be greater among bipolar patients with pure manic episodes compared to mixed or depressed episodes.⁷⁶ Particularly relevant to the NCS-R result, evidence points to psychotic features in those with bipolar predicting poor insight.⁷⁷

Another important difference between the NESARC and the NCS-R is that psychotic features were explicitly assessed with a separate question in the NCS-R manic section where as the psychotic feature in the NESARC was conflated with grandiosity and for the NEASARC/CIDI implementation defined by information collected outside the manic diagnostic section (Table 2.1). Only 18.3% (95% CI: 13.2-23.5) of those meeting Bipolar I (pre-imputed re-calibrated) in the NESARC endorse the psychotic feature, as defined, where as 37.2% (95% CI: 25.0-49.4) do in the NCS-R (re-calibrated and including the 11

cases added in, as above). Important criterion information on psychotic features in the NESARC is clearly lost by the grandiosity and psychotic features being assessed by only one question and used as a symptom and not as a symptom *and* an impairment measure. These results demonstrate the dangers of skip-outs in a diagnostic instrument as well as the need to independently assess each criterion component individually.

Some limitations on the results merit mention. The assessment of impairment is difficult using self-reports particularly among those experiencing a manic/hypomanic episode. The use of census workers, federal government employees, may have limited the willingness participates in the NESARC to disclose information about psychiatric disorders and substance use (particularly illegal substances including cannabis) compared to the NCS-R. This may have suppressed the prevalence of bipolar disorder particularly among those with psychotic features who may have an underlying suspiciousness of government. The elevated mood episode duration of four days assessed by the CIDI may not be short enough and is certainly too long, at a week, in the AUDADIS,⁷⁸ this likely suppressed Bipolar II and hypomanic episodes in the NESARC compared to the NCS-R. The recalibration algorithm was developed from a small (n=40) sample of those endorsing the NCS-R manic section stem questions¹⁹ and CIDI case assignment used to develop the recalibration algorithm relied on missing information, as our imputation analysis demonstrates. The SCID, the validating standard of the clinical re-evaluation, is itself subject to case misidentification generally.⁷⁹ More specifically, those more appropriately classified as having schizoaffective disorder may have been missed in the

clinical re-evaluation as the SCID psychotic screen was not applied.⁸⁰ Though it should be noted that none of the 13 case w/ psychotic features described above were among the 40 clinical reassessed respondents.⁸¹ The assumption that missing criterion information is missing at random is reasonable but can not be known and differences in the number of available demographic and psychiatric comorbidity variables (i.e. substance use disorders) between the surveys may differentially affect the imputation results.

II I. Summary of Findings:

A strict application of a DSM-IV/CIDI approach to the assessment of impairment within the NESARC decreases prevalence estimates of manic episodes and correspondingly increases hypomanic episode estimates. Structural issues with the AUDADIS substantially under-estimate the prevalence of lifetime major depressive episode (16.9% [95% CI: 16.1-17.6]) compared to imputed estimates that do not conflate anhedonia and depressed mood (19.7% [95% CI: 19.3-20.1]). A skip-out within the CIDI used in the NCS-R prevented complete DSM-IV manic and hypomanic criterion information from being collected. Imputation of this missing information resulted in increased prevalence estimates for both manic (3.5% [95% CI: 3.1-4.0] increased to 4.4% [95% CI: 3.9-5.0]) and hypomanic (1.2% [95% CI: 0.9-1.4] increased to 2.0% [95% CI: 1.6-2.4]) episodes. The small differences between the imputed and un-imputed hypomania and bipolar prevalence estimates in the NESARC nullify the need to apply imputation for risk estimates in later aims.

II J. Conclusion:

The findings of this aim support the conclusion that the AUDADIS substantially underestimated lifetime major depressive episode prevalence compared to an imputed estimate that treated anhedonia and depressed mood as separate and concurrent MDE symptoms. The operationalization of impairment for manic disorders in both the AUDADIS and CIDI strongly influences case identification, with the CIDI operationalization suppressing manic and hypomanic prevalence estimates. Skip patterns within the survey instruments that violated the DSM-IV criterion structure or logic represent the primary deficiencies found. A practical finding of this aim was that imputed missing information did not meaningfully affect bipolar prevalence estimates within the NESARC.

The first aim of this dissertation demonstrated that the operationalization of DSM criteria is not always ideally implemented in nationally representative studies. The consequence of this is that psychiatric disorders, specifically manic, hypomanic and major depressive episodes, are subject to un-necessary misclassification in these major psychiatric epidemiological studies. Awareness of these shortcomings is needed among the research community that represents the consumers of these public use data sets.

Chapter III: Cannabis Use and Bipolar Disorder: Cannabis Use Risk Assessment

III A. Aim

The aim of the research reported in this chapter is to examine cannabis use as a risk factor for incident (between NESARC wave 1 and wave 2) manic symptoms, bipolar spectrum disorders (DSM-IV mania and hypomania) and CIDI recalibrated BD I and II as defined by approaches used in Aim 1. Cannabis use risk will be assessed in the total population and within strata of young adults (ages 18-25), adults (ages 26-45), older adults (ages >45) and among those with and without histories alcohol or drug abuse/dependence. Examination of risk among those both with and without histories alcohol or substance abuse/dependence by developmental age (young adults [ages 18-25] and adults [ages 26-45]) will be conducted. Also to be examined are groups that may be at increased risk because of baseline sub-threshold symptoms or family history of depression, anti-social behavior, alcohol or substance abuse/dependence.

III B. Background

Longitudinal studies point to cannabis as a risk factor for psychosis.^{5, 8, 41, 82-86} A meta-analysis of cannabis use and psychosis found that individuals having ever used cannabis were at increased risk of any psychotic outcomes (pooled adjusted OR: 1.41, 95% CI 1.20–1.65), and those using cannabis more frequently were at an even greater risk (OR:

2.09, 1.54–2.84).³⁹ Cannabis use is suspected of playing a role in psychosis through dopamine dysregulation.⁴⁰ Cannabis exposure may put carriers of the COMT Val(158)Met Val allele, which plays a role in dopamine regulation, at a greater risk of psychosis.^{41,42} Dopamine dysregulation is hypothesized to also play an important role in BD.⁸⁷

Recently a family study found that AKT1, which is involved in the phosphorylation of glycogen synthase kinase (GSK-3), may mediate psychosis through cannabinoid-regulated AKT1/GSK-3 signaling downstream of the dopamine D2 receptor.⁸⁸ The clinical presentation of BD often has similar features to the clinical presentation of schizophrenia. Patients with BD often have psychotic symptoms and those with schizophrenic disorders often experience mania.⁴³ Twin studies have found genetic correlations between schizophrenia and BD.⁴⁴ The International Schizophrenia Consortium conducted a large genome-wide association study and found evidence for a shared polygenic component to the risk of schizophrenia and BD.⁴⁵ Thus, cannabis exposure may increase risk for BD outcomes, possibly through dopamine dysregulation, by acting on the same genetic substrate as it does in psychosis.

However, the limited evidence assessing cannabis use as a risk factor for bipolar disorder (BD) provide conflicting results.⁶⁻⁹ A cohort study by van Laar et al,⁷ found a significant association between cannabis and DSMIII-R BD I and II [OR 4.98 (95% CI: 1.80–13.81)]. The onset definition of this study may have misclassified prevalent BD at

baseline which may have inflated the risk estimate. The results of van Laar et al,⁷ are consistent, however, with two prospective cohort studies, one also using the NEMESIS (Henquet et al),⁶ both found significant associations between manic symptoms and cannabis use [NEMESIS study OR 2.70 (95% CI: 1.54–4.75) and the EDSP study, OR 4.26 (95% CI: 1.42–12.76)⁹]. The manic symptom outcomes in the Henquet et al NEMESIS study had a low symptom duration threshold with respondents needing to only endorse one symptom persisting for 2 days (their operationalization of DSM-III-R criteria) to be positive. The EDSP study had a small sample size with only six cannabis exposed cases, raising questions about statistical power and violations of the assumption of parallel regression in their four level ordinal logistic regression model. The results from the NEMESIS and EDSP studies conflict with a result from the Swedish Conscript Cohort (n=50,087) which found a null association [OR 1.13 (95% CI: 0.82 to 1.57)] between cannabis use by age 18 and future affective psychosis hospitalization (predominately BD diagnoses).^{8, 10} The conflicting results are likely partially explained by the more severe outcome (hospitalization) in the Swedish Conscript Cohort compared to the symptom level and the not-necessarily-hospitalized DSM-III-R BD I and II outcomes of the NEMESIS and EDSP studies. No study to date has assessed cannabis use as a risk factor for DSM-IV BD with a sample as large as the NESARC, nor has any study examined risk among those with no reported lifetime manic or major depressive symptoms at baseline.

Cannabis abuse has been associated with earlier onset of schizophrenia with the interpretation that cannabis use precipitates or accelerates the onset in those at risk.^{46, 47} In BD a similar observation has been made whereby onset after a substance use disorder, cannabis or alcohol, has been hypothesized to be an added insult, or diathesis, that may manifest BD.^{48, 49} To examine whether cannabis use status imparts different risk among those with histories of substance abuse/dependence and those without such histories, a stratified analysis will be used. Examining cannabis exposure risk within groups defined by age and substance abuse/dependence status may provide evidence from a population sample that supports the diathesis hypothesis.

III C. Methods

III C. 1 Sample

The National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) is the largest national epidemiologic survey to date to assess for a wide range of mental illnesses and co-occurring mental health and substance use disorders using the Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM-IV). The survey was conducted in two waves (2001-2002 and 2004-2005) of face-to-face interviews with non-institutionalized respondents, including those living in dormitories, boarding houses, shelters, and off-base military housing (Chen et al, 2006); prisons, jails and hospitals were not sampled. Both waves are adjusted to be representative of the adult non-institutionalized U.S. population (18 years of age and older) (Grant et al, 2003; Grant et

al, 2004), wave 1 had a response rate of 81.2% (n= 43,093)^{23, 24} and wave 2 (n= 34,653) had a cumulative response rate of 70.2%.²⁵

III C. 2 Diagnostic Measures

The Alcohol Use Disorder and Associated Disabilities Interview Schedule–DSM-IV Version (AUDADIS),²⁸ a structured diagnostic interview designed for use by lay interviewers, was administered at wave 1 to determine lifetime and recent (past 12 months) diagnoses of major Axis I and Axis II disorders, including dysthymia, bipolar disorder, anxiety disorders (agoraphobia, panic disorder, social phobia, specific phobia and generalized anxiety disorder), antisocial personality disorder (ASPD), conduct disorder (with no subsequent ASPD), other personality disorders (paranoid, schizoid, avoidant, dependent, obsessive–compulsive and histrionic), and substance abuse or dependence (including alcohol, marijuana, cocaine, opioids, hallucinogens, methamphetamine, or other illicit drugs). A modified version of the AUDADIS for the assessment of DSM-IV disorders within the intervening 3-years period between wave 1 and wave 2 was used to identify incident bipolar spectrum outcomes. This same wave 2 interview assessed, adverse events, post traumatic stress disorder (PTSD) and childhood attention deficit hyperactivity disorder (ADHD). The three primary outcomes of this study are incident manic symptoms, incident bipolar spectrum disorders (DSM-IV manic and hypomanic episodes) and CIDI recalibrated BD I and II outcomes. Incident manic/hypomanic symptoms were defined as the endorsement of any stem questions in the manic/hypomanic sections of the AUDADIS, which involved the endorsement of a

week or more of extremely elevated or irritable mood. The diagnostic operationalization of manic and hypomanic episodes in both wave 1 and wave 2 in this cannabis use risk analysis conform to the NESARC/CIDI approach (w/no imputation) defined in Aim 1 (Chapter 2). The primary difference between manic and hypomanic episodes case identification in this analysis and those reported by the NESARC investigators is how social and occupational impairment are operationalized (manic episode criterion D and hypomanic episode criterion E, see Aim1 for details). The diagnostic operationalization of CIDI recalibrated BD I and II outcomes are described in detail in Aim 1. Lifetime DSM-IV disorders at wave 1 and collected in the wave 1 interview were coded for use in multivariate models as potential confounders of the association of cannabis and BD. Most of these disorders have been reported to be associated with both cannabis use and BD.^{16, 50} The DSM-IV diagnostic measures used in this analysis include: alcohol abuse, alcohol dependence, nicotine (tobacco) dependence, other drug (sedatives, tranquilizers, cocaine, opioids, hallucinogens, amphetamine, inhalants, heroin or other drugs used without a prescription) abuse and a separate indicator for other drug dependence, lifetime dysthymia, agoraphobia or panic disorder, social phobia, specific phobia, generalized anxiety disorder (GAD), conduct disorder (with no ASPD), ASPD, and other personality disorders as delineated above. Post traumatic stress disorder (PTSD) and childhood (<18 years of age) attention deficit-hyperactivity disorder (ADHD) were assessed at wave 2 interview for disorder onset before the wave 1 interview. DSM-IV disorders were dichotomously coded (0= not endorsed, 1= endorsed) with respondents being coded as missing if they failed to either positively or negatively endorse all the stem questions

from the corresponding disorder's diagnostic section in the AUDADIS. Aggregated dichotomous indicators of the presents of any substance use disorder and any non-substance use psychiatric comorbidity were created for use in the analysis of lower count strata.

III C. 3 Exposure Measures

Cannabis use was coded in several ways. Ever having used cannabis (ever used), lifetime use prior to past year (distal use) and use within past year at wave 1 (proximal use) were dichotomously coded (0= not endorsed, 1= endorsed). To assess a dose response, cannabis use was further categorized into five use groups (no reported use, ≥ 1 use/week in the last 12 months, < 1 use/week in the last 12 months, ≥ 1 use/week before the last 12 months, and < 1 use/week before the last 12 months). All cannabis exposures were assessed at the wave 1 (baseline) interview and represents cannabis use within one year of the baseline interview or any time prior to the past years of the baseline interview. Those not positively or negatively endorsing ever using cannabis are coded as missing.

III C. 4 Family History Score

Alcohol and substance abuse are highly comorbid with BD⁵¹ and alcohol abuse and BD aggregate in families.⁵² Evidence suggests substance use disorders, depression and antisocial traits are concentrated in families of those with early-onset BD.⁵³ To capture potential familial/genetic risk for BD a proxy measure was constructed, a family history

density score. The family history density score represents the density⁸⁹ of first-degree relatives (parents, full brothers and sisters, sons and daughters) identified by the respondent as experiencing either major depression, alcohol abuse, substance abuse, or anti-social behavior. The crude family history density score is constructed by counting all reported major depression, alcohol abuse, substance abuse, and anti-social behavior among the respondents first-degree relatives and dividing this by four and then by the number of first-degree relatives. The score can range from 0 to 1. A score of 1 means all first degree relative reported being positive for all four traits (alcohol abuse, depression, substance abuse and antisocial behaviors) with lower scores representing decreasing concentration of these traits. The non-zero crude family history density scores have a log-normal distribution. A three level categorical variable was created from the crude family history density scores: family history density score=1 if the crude score equaled zero, family history density score=2 for those in the lowest median of those with non-zero densities (mean 0.058, median 0.063, range 0.008 – 0.1) and family history density score=3 for those in the highest median of those with non-zero densities (mean 0.241, median 0.2, range 0.102 – 1.0).

III C. 5 Other Measures

A history of traumatic events early in life (e.g.. abuse, neglect) has been associated with later major depression, psychosis and substance abuse.^{90,91} A dichotomous indicator of early life adverse events was coded as positive if the respondent endorsed experiencing any of the following before age 13: being in a war zone, being a refugee, experiencing a

life threatening illness, natural disaster, molested, abused, neglected, were in physical fights, injured in a fight, kidnapped, stalked, mugged, yourself or someone close to you directly effected by terrorism, unexpectedly witness severe injury/killing/dead body, someone very close with life threatening illness/injury or traumatic event, or other traumatic event. Other substance use (sedatives, tranquilizers, cocaine, opioids, hallucinogens, amphetamine, inhalants, heroin or other drugs used without a prescription) was coded to a dichotomous indicator (0= not endorsed, 1= endorsed). Respondents endorsing lifetime use of cigarettes <100 times, cigars or pipes <50 times and the use of oral tobacco products <20 times were coded as no/low tobacco users (0=not no/low users, 1= no/low users). Baseline norms based mental health score from the Short Form-12 version 2 (SF-12v2)⁹² were categorized into quartiles (Table 2.2) with increasing quartiles associated with increasing norms based mental health.

III C. 6 Demographic Measures

Demographic measures included: gender (male=1, female=0), age cohort (1= 18 to 25, 2=26 to 35, 3=36 to 45, and 4 =46 and older), self reported race/ethnicity (white=1, black=2, Hispanic or Latino=3, American Indian/Alaska native=4, and Asian/Hawaiian/Pacific Islander=5) for the sub-group analyses race/ethnicity groups 4 and 5 were collapsed into one group, personal income (\$) quartiles (1= <=8800, 2= 8801 to <= 20000, 3= 20001 to <=36000, 4= >=36001), education status (1= < high school, 2=high school or GED, 3= some college or an Associate Degree, 4= >= Bachelor's Degree), urbanicity (1= urban, in central city of Metropolitan Statistical Area [MSA],

2=suburban, in MSA but not in central city, 3= rural, not in a MSA), census region (1= Northwest, 2= Midwest, 3= South, 4= West), and marital status (1=married or living with someone as if married, 2= divorced or separated, 3= widowed, 4= never married).

III D. Data Analysis

The demographic characteristics (counts, weighted means) of the cohort as a whole and by cannabis use status will be reported. Descriptive statistics (counts, proportions) and measures of association (odds ratios) of baseline covariates with ever reporting using cannabis in the wave 1 interview and incident bipolar spectrum disorders will also be reported. Separate logistic regression models were constructed to assess cannabis use as a risk factor for incident manic symptoms, DSM-IV bipolar spectrum outcomes as well as for the more strictly defined CIDI recalibrated BD I and II outcomes. The onset of bipolar outcomes was defined for the primary analysis as the age at which the first bipolar symptoms (DSM-IV manic, hypomanic or MDE symptoms) were reported. To avoid including prevalent emergent BD in our analytical cohort respondents reporting manic, hypomanic or MDE symptoms at baseline were excluded from the primary analysis. Subsequent stratified analyses include those with manic, hypomanic or MDE symptoms at baseline but control for the presents of these symptoms. All analysis excluded any respondents who reported at wave 1 ever having a medical professional say they had schizophrenia or a psychotic illness or episode. With the exception of counts all reported statistics are probability weighted to be representative of the U.S. population. Variances were estimated by Taylor series linearization with single primary sampling

unit strata centered at the overall mean. All of the analyses were performed using STATA statistical software.⁹³

III D. 1 Nested Models

The primary analysis consist of a series of nested logistic regression models that assess cannabis use as a risk factor in the population as a whole for three incident manic episode related outcomes; any manic symptoms, bipolar spectrum disorders and CIDI recalibrated BD I and II. The first model (Model 1) assesses the association of ever using cannabis and incident BD outcomes, the second model (Model 2) stratifies ever use into proximal (within past year of baseline interview) and distal use (prior to past year use). The third model (Model 3) added demographic factors to Model 2 to adjust risk estimates by age, gender, race/ethnicity, education level, marital status, urbanicity and region. It should be noted that urbanicity may modify cannabis use risk for psychosis⁹⁴ and geographical region,⁹⁵ specifically increasing latitude, has been associated with increased risk for schizophrenia. Thus, urbanicity and region maybe risk factors for bipolar disorder. Model 4 adds histories of substance use disorders (alcohol, cannabis, other drugs and nicotine), other illicit drug use and smoking to Model 3 to control for potential confounding of cannabis use with other substance use.

Model 3: $\text{logit}(p)=\ln\{p/(1-p)\}=\beta_0 + \beta_1\text{proximal cannabis} + \beta_2\text{distal cannabis} + [\beta_3\text{gender}+ \beta_4\text{age} + \dots + \beta_i\text{west region}]$

Model 5 added the family history density score and childhood adverse events to Model 4 to control for possible genetic or environmental exposures associated with these measures. The final model (Model 6) added indicators for lifetime and baseline mental health at wave 1: SF-12v2 mental health norm-based score and baseline history of psychiatric comorbidities including dysthymia, PTSD, agoraphobia or panic disorder, social phobia, specific phobia, generalized anxiety disorder (GAD), conduct disorder with out antisocial personality disorder (ASPD), ASPD, childhood attention deficit hyperactivity disorder (ADHD) and other personality disorders (avoidant, dependent, obsessive-compulsive, paranoid, schizoid and histrionic). The psychiatric comorbidity measures in Model 6 and the family history density score and childhood adversity measures in Model 5 represent or are proxies for possible underlying factors that may cause both bipolar disorder and cannabis use. Covariate dichotomous and categorical variables are only included in any of the models if they have a minimum cell count of 3. The collinearity of covariates in all reported models was examined by assessing the variance inflation factor (VIF) of a weighted linear regression model of the dependent variable using all the independent variables. A VIF of 10 or greater is indicative of collinearity. No covariates with a VIF of >5 are included in any of the models. The variables for each of the nested models are added as a group as described.

III D. 2 Symptom Threshold Analysis

To assess cannabis use risk for sub-bipolar spectrum disorder outcomes of increasing symptom concentration, three models with outcomes with an increasing number of manic

episode criterion B symptoms were constructed. The three outcomes assessed were all among those reporting no manic, hypomanic or MDE symptoms at wave 1 and represent incident events between the wave1 and wave 2 interviews. The sub-bipolar spectrum disorder outcomes all included a week or more of incident elevated or irritable mood and were defined as follows: 1) at least 1 incident criterion B symptom (n=1009), 2) 2 or more incident criterion B symptoms (n=771), and 3) at least 3 criterion B symptoms (n=532). All the covariates described above were included in the adjusted models of all three outcomes.

III D. 3 Lifetime Manic/Hypomanic or MDE Symptoms at Baseline

Respondents with any lifetime manic or MDE symptoms at baseline, the population excluded from the primary nested model analysis, were analyzed as a separate strata for bipolar spectrum disorder and CIDI recalibrated BD I and II outcomes. The model of incident bipolar spectrum disorders excluded those meeting lifetime criteria for bipolar spectrum disorders (DSM-IV manic and hypomanic episodes) at wave 1. The model of incident CIDI recalibrated BD I and II excluded those meeting lifetime criteria CIDI recalibrated BD I and II at wave 1. All the covariates described above were included in the adjusted model of bipolar spectrum outcomes with the model of CIDI recalibrated BD I and II including adjustment for any (non- CIDI recalibrated BD I and II) lifetime bipolar spectrum disorders at baseline.

III D. 4 Sub-group Analyses

Sub-group analyses were conducted within populations stratified by age cohort, family history score groups, substance abuse/dependence status and within strata stratified by substance abuse/dependence status and age cohort. With the exception of the age cohort analysis all the subgroup analyses were restricted to respondents aged 18 to 45. This restriction was done so that there would be increased power to detect an effect between proximal cannabis use and incident bipolar spectrum outcomes as older respondents report current cannabis use infrequently. These analyses may provide evidence for effect modification across these domains.

III D. 5 Age Cohorts

The association of cannabis use (specified as a five level or three level exposure variable) with incident bipolar spectrum disorders by age cohorts (ages 18 to 25, 26 to 45, and 46 and older) was assessed. For this analysis those with lifetime baseline manic/hypomanic or MDE symptoms but not meeting criteria for a DSM-IV manic or hypomanic episode were included. A dichotomous indicator of the presents of any lifetime baseline manic/hypomanic or MDE symptoms (0= no symptoms, 1= symptoms) was created and included in adjusted models along with the other covariates included in the primary nested bipolar spectrum disorder model (Model 6). The number of covariates included in a logistic regression model can be relatively large (< 4 events per predictor variable) with little bias particularly if the sample size is large, sparse cell sizes are addressed,

collinearity is minimal and the goal of the analysis is the assessment of potential confounding.⁹⁶

III D. 6 Family History Strata

The examination of proximal and distal cannabis use as a risk factor for bipolar spectrum disorders and CIDI recalibrated BD I and II across strata defined by family history score groups was conducted. Separate models for both the bipolar outcomes were evaluated for each of the three family history score groups: 1) among those reporting no family history, 2) among those in the lowest family history score median, and 3) those in the highest family history score median. The logistic regression models included all of the covariates described above with the exception that aggregated substance abuse/dependence and psychiatric comorbidity indicators were used. The proportion of incident BD outcomes within each stratum will also be reported.

III D. 7 Substance Abuse or Dependence Strata

Two substance abuse or dependence strata were defined: those endorsing any lifetime substance abuse/dependence (alcohol, cannabis or other drugs) or having nicotine dependence at wave 1 and those not endorsing any such abuse or dependence. The odds of incident DSM-IV manic or hypomanic events among those reporting proximal and distal cannabis use was assessed within these substance abuse or dependence strata. To assess whether developmental stage influences risk, both substance abuse/dependence

stratum were further stratified by age (18 to 25 years of age [young adults], and 26 to 45 [adults]) and cannabis use risk was likewise assessed within these (four) groups. A dose response analysis using the five level cannabis use measure was done among the lifetime substance abuse/dependence strata by age.

III E. Results

The demographic characteristics of the cohort are shown in Table 3.1. Table 3.2 reports the counts and proportions of substance use, substance use disorders, psychiatric comorbidities, and other measures and their association with ever having used cannabis and incident DSM-IV manic or hypomanic episodes. Only respondents reporting no lifetime manic or MDE symptoms at wave 1 are included in Table 3.2. This exclusion of those with manic or MDE symptoms for the primary nested model analysis, the analytical population on which Table 3.2 reports, leaves some covariates with relatively low representation (i.e. other drug dependence and dysthymia). Separating those with only conduct disorder from those with ASPD (which requires both a history of conduct disorder and adult ASPD) also finds those reporting only conduct disorder with relatively low representation. Most of these covariates and/or potential confounders are both positively (odds ratios greater than 1) and significantly associated with both cannabis use and incident bipolar spectrum outcomes. Notably alcohol abuse only (not including those with dependence) is crudely associated with reduced risk for manic or hypomanic outcomes whereas alcohol dependence is associated with increased risk. Increasing family history scores are associated with increasing likelihood of reporting ever using

Table 3.1: Demographic Characteristics of Wave 2 Respondents with Available Cannabis Use Information by Cannabis Use Status

	All (N=34446) N (% ^b)	No Reported Cannabis Use ^a (N=27534) N (% ^b)	Reported Cannabis Use ^a (N=6912) N (% ^b)
Male gender	14469 (47.9)	10838 (45.2)	3631 (58.1)
Age:			
18-25	4410 (14.7)	3221 (13.5)	1189 (19.6)
26-35	6385 (18.4)	4764 (17.1)	1621 (23.4)
36-45	7472 (21.3)	5315 (18.9)	2157 (30.6)
46 and older	16179 (45.5)	14234 (50.6)	1945 (26.4)
Race/Ethnicity			
White	20047 (70.9)	15426 (69.2)	4621 (77.3)
Black	6533 (11.0)	5468 (11.4)	1065 (9.6)
Hispanic or Latino	6325 (11.6)	5387 (12.5)	938 (7.9)
American Indian/Alaska Native	576 (2.2)	395 (1.9)	181 (3.3)
Asian/Hawaiian/Pacific Islander	965 (4.3)	858 (4.9)	107 (2.0)
Personal Income Quartiles (\$)			
<=8,800	4410 (24.2)	3221 (25.3)	1189 (20.3)
8,801 to <=20,000	6385 (24.9)	4764 (25.7)	1621 (21.8)
20,001 to <=36,000	7472 (23.2)	5315 (23.1)	2157 (23.8)
>=36,001	16179 (27.7)	14234 (26.0)	1945 (34.0)
Education			
<High School	5711 (14.7)	5016 (15.9)	695 (10.1)
High School or GED	9893 (29.0)	8163 (30.1)	1730 (25.1)
Some College/Associate Degree	10414 (30.7)	7921 (29.3)	2493 (36.0)
>=Bachelor's Degree	8428 (25.6)	6434 (24.8)	1994 (28.8)
Urbanicity			
Urban	11594 (28.9)	9138 (28.4)	2456 (30.7)
Suburban	16302 (50.6)	12966 (50.4)	3336 (51.3)
Rural	6550 (20.5)	5430 (21.2)	1120 (17.9)
Census Region			
Northeast	6409 (19.7)	5117 (19.7)	1292 (19.5)
Midwest	7499 (23.1)	5857 (22.9)	1642 (24.2)
South	12741 (35.2)	10727 (36.7)	2014 (29.4)
West	7797 (22.0)	5833 (20.7)	1964 (26.9)
Marital Status			
Married/Living with someone	18330 (63.2)	14834 (64.2)	3496 (59.2)
Divorced/Separated	5472 (10.4)	4113 (9.6)	1359 (13.6)
Widowed	3043 (6.1)	2943 (7.4)	100 (1.1)
Never Married	7601 (20.4)	5644 (18.8)	1957 (26.1)

^a All demographic groups significantly difference by cannabis use status ($p < 0.001$)

^b Weighted percent

Table 3.2: Association of Baseline Substance Use and Psychiatric Comorbidities with Cannabis use and Incident Bipolar

	All (N=20,434) ^a		Cannabis use ever (N=3167)		Manic or Hypomanic Episode (N=411)		
	N (%) ^b	N (%) ^c	OR (95% CI)	P-value	N (%) ^d	OR (95% CI)	P-value
Alcohol Abuse (not dependent)	3370 (17.4)	1176 (36.6)	3.69 (3.29-4.13)	<.001	50 (10.8)	0.57 (0.39-0.84)	.006
Alcohol Dependence	1481 (8.1)	781 (27.0)	7.97 (6.92-9.18)	<.001	55 (15.2)	2.06 (1.46-2.91)	<.001
Nicotine Dependence	2347 (12.5)	871 (29.5)	4.18 (3.71-4.72)	<.001	90 (22.7)	2.10 (1.51-2.91)	<.001
No/Low Tobacco Use Lifetime	11875 (56.4)	1101 (33.6)	0.33 (0.29-0.36)	<.001	215 (52.3)	0.85 (0.67-1.07)	0.16
Other Drug Use	1698 (8.8)	1351 (43.4)	38.3 (32.8-44.7)	<.001	61 (15.4)	1.92 (1.33-2.77)	<.001
Other Drug Dependence	110 (0.6)	98 (3.0)	29.6 (15.1-58.2)	<.001	3 (0.6)	1.06 (0.27-4.15)	.94
Family History Density Score							
No Family History	11146 (55.1)	1222 (38.9)	Ref.		198 (48.6)	Ref.	
Lowest Median	5669 (27.3)	880 (27.4)	1.50 (1.31-1.72)	<.001	106 (25.1)	1.04 (0.77-1.41)	.85
Highest Median	3619 (17.6)	1065 (33.8)	3.52 (3.10-3.99)	<.001	107 (26.3)	1.72 (1.28-2.30)	<.001
Childhood Adverse Event	5431 (26.8)	1207 (38.1)	1.89 (1.67-2.14)	<.001	200 (51.5)	2.98 (2.37-3.76)	<.001
Dysthymia	58 (0.3)	15 (0.5)	2.24 (0.94-5.35)	0.07	3 (0.7)	2.77 (0.7-11.0)	.15
Post Traumatic Stress Disorder	440 (4.0)	176 (5.1)	1.38 (1.13-1.70)	.003	89 (18.1)	5.72 (4.23-7.73)	<.001
Agoraphobia or Panic Disorder	438 (2.1)	109 (3.2)	1.69 (1.29-2.20)	<.001	16 (3.7)	1.79 (1.01-3.15)	.05
Social Phobia	451 (2.3)	109 (3.5)	1.79 (1.36-2.34)	<.001	11 (2.1)	0.92 (0.45-1.88)	.82
Specific Phobia	1252 (5.7)	262 (8.2)	1.62 (1.33-1.97)	<.001	38 (8.5)	1.56 (1.03-2.34)	.04
Generalized Anxiety Disorder	197 (0.8)	53 (1.3)	1.79 (1.24-2.58)	.002	15 (2.3)	2.96 (1.62-5.43)	.001
Conduct Disorder (No ASPD)	131 (0.7)	41 (1.3)	2.29 (1.49-3.52)	<.001	6 (1.3)	1.91 (0.78-4.70)	0.16
Antisocial Personality Disorder	330 (1.8)	207 (6.8)	9.3 (6.9-12.5)	<.001	21 (5.0)	3.03 (1.84-4.99)	<.001
Childhood ADHD	260 (1.4)	87 (2.7)	2.46 (1.77-3.43)	<.001	39 (11.3)	10.4 (6.81-16.0)	<.001
Other Personality Disorders	1390 (6.6)	303 (9.4)	1.60 (1.37-1.87)	<.001	73 (15.6)	2.59 (1.85-3.61)	<.001
Norrs Based Mental Health							
Quartile 1: 15.8 - 46.3	5075 (23.7)	829 (25.0)	Ref.		153 (36.6)	Ref.	
Quartile 2: >46.3 - <=52.3	4188 (20.7)	887 (28.3)	1.39 (1.23-1.56)	<.001	70 (18.5)	0.59 (0.40-0.87)	.008
Quartile 3: >52.3 - <=58.4	6053 (31.0)	996 (32.6)	0.99 (0.88-1.13)	.94	99 (24.7)	0.51 (0.36-0.73)	<.001
Quartile 4: >58.4 - <=64.5	5118 (24.6)	455 (14.0)	0.49 (0.42-0.57)	<.001	89 (20.1)	0.52 (0.38-0.71)	<.001

^a Excluding any lifetime major depressive or manic/hypomanic episode symptoms at wave 1 and missing information on listed covariates

^b Covariate count and weighted percent

^c Cannabis use count and weighted percent of total cannabis use count by covariate

^d Incident manic/hypomanic episode count and weighted percent of total incident manic/hypomanic episode count by covariate

cannabis. Respondents in the highest median, but not those in the lowest median, of the family history score are at increased risk for bipolar spectrum outcomes compared to those reporting no family history.

III E. 1 Nested Models

Table 3.3 reports the result of the primary nested model analysis for incident manic symptoms and incident DSM-IV manic and hypomanic episodes. Table 3.3 (cont.) reports the result of the nested model analysis for incident CIDI recalibrated BD I and II episodes. Models of all three outcomes find statistically significant ($p < .05$) un-adjusted risk concentrated in past year cannabis use (proximal use, Model B). The odds of incident manic symptoms associated with proximal cannabis use is attenuated slightly by the adjustment for other substance use and substance use disorders but remains significant in the fully adjusted model (Model F, OR 1.67, 95% CI: 1.12-2.48, $p = .01$). For incident bipolar spectrum disorders proximal use, but not distal use, remained significant after control for demographic characteristics but no longer remained significant after adjustment for other substance use and substance use disorders (Table 3.3). Like incident bipolar spectrum disorders the CIDI recalibrated BD I and II outcomes saw proximal use, but not distal use, remained significant after control for demographic characteristics but no longer remained significant after adjustment for other substance use and substance use disorders [Table 3.3 (cont.)].

Table 3.3: Successive Adjusted Models of Cannabis Use Risk and Incident Manic Outcomes

Models	Cannabis Use	OR	95% CI	P-value	Variables in Model
Incident Manic Symptoms^a					
Model A n=21235	Ever Used	1.66	1.41 - 1.97	<.001	Ever Used
Model B n=21235	Proximal Distal	3.07 1.41	2.28 - 4.14 1.17 - 1.69	<.001 <.001	Proximal and distal cannabis use
Model C n=21235	Proximal Distal	2.13 1.39	1.54 - 2.94 1.15 - 1.67	<.001 .001	Model B plus gender, age group, race, education, urbanicity, region, income and marital status
Model D n=21208	Proximal Distal	1.68 1.21	1.11 - 2.55 0.97 - 1.53	.02 .10	Model C plus alcohol abuse, alcohol dependence, no/low tobacco use, nicotine dependence, other drug use, drug abuse and drug dependence
Model E n=20858	Proximal Distal	1.64 1.13	1.09 - 2.49 0.89 - 1.43	.02 .30	Model D plus family history density score category, childhood events
Model F n=20434	Proximal Distal	1.67 1.16	1.12 - 2.48 0.92 - 1.48	.01 .21	Model E plus Baseline norms based mental health score, history of dysthymia, agoraphobia or panic disorder, social phobia, specific phobia, GAD, conduct disorder(no ASPD), ASPD, PTSD, childhood ADHD and any personality disorder
Incident Bipolar Spectrum Disorders^b					
Model A n=21235	Ever Used	1.67	1.26 - 2.21	.001	Ever Used
Model B n=21235	Proximal Distal	3.63 1.29	2.37 - 5.57 0.94 - 1.77	<.001 .11	Proximal and distal cannabis use
Model C n=21235	Proximal Distal	2.33 1.33	1.47 - 3.70 0.96 - 1.83	.001 .09	Model B plus gender, age group, race, education, urbanicity, region, income and marital status
Model D n=21208	Proximal Distal	1.59 1.09	0.91 - 2.78 0.77 - 1.55	.11 .62	Model C plus alcohol abuse, alcohol dependence, no/low tobacco use, nicotine dependence, other drug use, drug abuse and drug dependence
Model E n=20858	Proximal Distal	1.48 0.92	0.84 - 2.59 0.64 - 1.34	.17 .68	Model D plus family history density score category, childhood events
Model F n=20434	Proximal Distal	1.48 0.96	0.83 - 2.65 0.64 - 1.42	.18 .82	Model E plus Baseline norms based mental health score, history of dysthymia, agoraphobia or panic disorder, social phobia, specific phobia, GAD, conduct disorder(no ASPD), ASPD, PTSD, childhood ADHD and any personality disorder

^a Incident extremely elevated of irritable mood for >=week, w/no lifetime MDE symptoms or extremely elevated of irritable moods for >= week at wave 1

^b Incident DSM-IV manic and hypomanic episodes, no lifetime MDE symptoms or extremely elevated of irritable moods for a week or more at wave 1

Table 3.3 (cont.): Successive Models of Cannabis Use Risk for Incident CIDI Recalibrated Bipolar I and II Outcomes

Models	Cannabis Use	Incident CIDI Recalibrated Bipolar I and II Outcomes ^a			
		OR	95% CI	P-value	Variables in Model
Model A n=21740	Ever Used	1.63	1.00 – 2.68	.052	Ever Used
Model B n=21740	Proximal Distal	4.17 1.14	1.99 – 8.75 0.61 – 2.10	<.001 .68	Proximal and distal cannabis use
Model C n=21740	Proximal Distal	2.95 1.27	1.32 – 6.56 0.68 – 2.36	.009 .44	Model B plus gender, age group, race, education, urbanicity, region, income and marital status
Model D n=21713	Proximal Distal	2.06 1.04	0.69 – 6.15 0.46 – 2.35	.19 .92	Model C plus alcohol abuse, alcohol dependence, no/low tobacco use, nicotine dependence, other drug use, drug abuse and drug dependence
Model E n=20858	Proximal Distal	1.48 0.92	0.84 – 2.59 0.64 – 1.34	.17 .68	Model D plus family history density score category, childhood events
Model F n=20534	Proximal Distal	1.44 0.86	0.44 – 4.65 0.35 – 2.11	.54 .75	Model E plus Baseline norms based mental health score, agoraphobia or panic disorder, social phobia, specific phobia, GAD, conduct disorder (no ASPD), ASPD, PTSD, childhood ADHD and any personality disorder

^aNo lifetime MDE symptoms or extremely elevated of irritable moods for a week or more at wave 1

III E. 2 Symptom Threshold Analysis

The results of the symptom threshold analysis are found in Table 3.4. For all respondents with no lifetime manic or MDE symptoms at wave 1 past year cannabis use, but not use prior to the past year, is associated with increased odds of an incident week of extremely

Table 3.4: Cannabis Use Risk and Incident Manic Symptom Threshold

Incident Elevated and/or Irritable Mood Plus at Least One Criterion B Symptom (n=1003)^a

(N= 20434)	OR ^b	95% CI	P-value
No Reported use	Ref.		
Proximal Use	1.94	1.29 – 2.93	.002
Distal Use	1.20	0.94 – 1.55	.14

Incident Elevated and/or Irritable Mood Plus at Least Two Criterion B Symptoms (n=768)^a

(N= 20434)	OR ^b	95% CI	P-value
No Reported use	Ref.		
Proximal Use	1.69	1.08 – 2.65	.02
Distal Use	1.09	0.81 – 1.47	.56

Incident Elevated and/or Irritable Mood Plus at Least Three Criterion B Symptoms (n=529)^a

(N= 20434)	OR ^b	95% CI	P-value
No Reported use	Ref.		
Proximal Use	1.33	0.75 – 2.36	.32
Distal Use	1.12	0.77 – 1.62	.55

^a Excluding any lifetime manic or major depressive episode symptoms at wave 1

^b Adjusted for gender, age group, race, education, urbanicity, region, income, marital status, alcohol abuse, alcohol dependence, tobacco use and dependence, other drug use, abuse and dependence, family history score, childhood events, history of dysthymia, agoraphobia or panic disorder, social phobia, specific phobia, generalized anxiety disorder, conduct disorder, ASPD, PTSD, childhood ADHD, other personality disorders and baseline norms based mental health score

Table 3.5: Cannabis Use Risk for Various Manic Outcomes Among those with Any Reported Lifetime Manic or Major Depressive Episode Symptoms at Baseline

Incident Bipolar Spectrum Disorders (DSM-IV Manic or Hypomanic Episode, n=528)^a			
(N= 10153)	OR ^b	95% CI	P-value
No Reported use	Ref.		
Proximal Use	1.11	0.67 – 1.84	.69
Distal Use	1.10	0.78 – 1.56	.57
Use groups:			
No Reported use	Ref.		
>= 1 use per week last 12 months	1.22	0.63 – 2.34	.55
< 1 use per week last 12 months	1.03	0.56 – 1.88	.93
>= 1 use per week before last 12 months	1.11	0.70 – 1.76	.65
<1 use per week before last 12 months	1.10	0.75 – 1.60	.62
Incident CIDI Recalibrated Bipolar I and Bipolar II (n=317)^a			
(N= 11374)	OR ^c	95% CI	P-value
No Reported use	Ref.		
Proximal Use	1.31	0.73 – 2.37	.37
Distal Use	1.16	0.79 – 1.71	.45
Use groups:			
No reported use	Ref.		
>= 1 use per week last 12 months	1.52	0.68 – 3.36	.30
< 1 use per week last 12 months	1.11	0.55 – 2.28	.69
>= 1 use per week before last 12 months	1.09	0.63 – 1.89	.75
<1 use per week before last 12 months	1.15	0.74 – 1.78	.53

^a Excluding corresponding wave 1 outcomes

^b Adjusted for gender, age group, race, education, urbanicity, region, income, marital status, alcohol abuse, alcohol dependence, tobacco use and dependence, other drug use, abuse and dependence, family history score, childhood events, history of dysthymia, agoraphobia or panic disorder, social phobia, specific phobia, generalized anxiety disorder, conduct disorder, ASPD, PTSD, childhood ADHD, other personality disorders and baseline norms based mental health score

^c Same as ^b but including baseline history of DSM-IV mania and hypomania

elevated or irritable mood accompanied by at least one manic episode criterion B symptom (adjusted OR 1.94, 95% CI: 1.29-2.93, $p=.002$). Past year use of cannabis was also associated with increased odds of an incident week of extremely elevated or irritable mood accompanied by at least two manic episode criterion B symptoms (adjusted OR 1.69, 95% CI: 1.08-2.65, $p=.02$). Proximal cannabis use was not however significantly associated with an incident week of extremely elevated or irritable accompanied by at least three manic episode criterion B symptoms (adjusted OR 1.33, 95% CI: 0.75-2.36, $p=.32$).

III E. 3 Lifetime Manic/Hypomanic or MDE Symptoms at Baseline

Table 3.5 reports the odds of incident manic outcomes, DSM-IV manic and hypomanic episodes and CIDI recalibrated BD I and II, with proximal and distal cannabis use and with cannabis use categorized into five-levels. Among those reporting any manic or MDE symptoms at baseline cannabis use is not a significant risk factor for incident manic outcomes (Table 3.5).

III E. 4 Results from Sub-group Analyses: Age Cohorts

Table 3.6 reports the adjusted associations of cannabis exposure with incident bipolar spectrum disorders by age cohorts (ages 18 to 25, 26 to 45, and >46). Compared to those reporting never using cannabis no level of cannabis use was associated with incident bipolar spectrum disorders among the young adults (Table 3.6). Among adults (ages 26 to 45) ≥ 1 use of cannabis per week was associated with incident bipolar spectrum

disorders (adjusted OR 2.52, 95% CI: 1.32-4.80, $p=.006$). Curiously members of the same age cohort reporting historic low levels of cannabis use (< 1 use per week before last 12 months at baseline) also experience significantly increased risk of incident bipolar spectrum outcomes (adjusted OR 1.47, 95% CI: 1.01-2.12, $p=.05$). Low numbers of

Table 3.6: Cannabis Use Risk for Incident Bipolar Spectrum Disorders by Age Cohort

	OR	95% CI	P-value
Age 18 to 25 (N= 3729): Incident Bipolar Spectrum Disorders (n=211)^a			
No Reported use	Ref. ^b		
≥ 1 use per week last 12 months	0.88	0.35 – 2.17	.77
< 1 use per week last 12 months	1.43	0.64 – 3.21	.38
≥ 1 use per week before last 12 months	1.06	0.46 – 2.43	.89
< 1 use per week before last 12 months	0.91	0.43 – 1.91	.80
Age 26 to 45 (N= 12196): Incident Bipolar Spectrum Disorders (n=451)^a			
No reported use	Ref. ^c		
≥ 1 use per week last 12 months	2.52	1.32 – 4.80	.006
< 1 use per week last 12 months	1.71	0.93 – 3.49	.08
≥ 1 use per week before last 12 months	1.34	0.88 – 2.27	.15
< 1 use per week before last 12 months	1.47	1.01 – 2.12	.05
Age 46 and older (N= 15296): Incident Bipolar Spectrum Disorders (n=296)^a			
No reported use	Ref. ^d		
Proximal	0.71	0.20 – 2.53	.59
Distal	0.76	0.43 – 1.36	.36

^a Excluding respondents with lifetime manic or hypomanic episodes

^b Adjusted for lifetime manic or MDE symptoms at baseline, gender, age group, race, education, urbanicity, region, income, marital status, alcohol abuse, alcohol dependence, tobacco use and dependence, other drug use, abuse and dependence, family history score, childhood events, history of dysthymia, agoraphobia or panic disorder, social phobia, specific phobia, generalized anxiety disorder, conduct disorder, ASPD, PTSD, childhood ADHD, other personality disorders and baseline norms based mental health score

^c Same covariates as ^b plus marital status

^d Adjusted for baseline manic or MDE symptoms, gender, substance abuse or dependence, other drug use, psychiatric comorbidities, and baseline norms based mental health score

incident bipolar spectrum disorder and reported uses of cannabis ≥ 1 use of per week restricted cannabis use risk assessment among those older than 46 years of age to past year and prior to past year use. For the older adults both proximal and distal use had odds ratios for incident bipolar spectrum disorders of less than one.

III E. 5 Family History Score Strata

The analysis of cannabis use risk by family history score strata is reported in Table 3.7. Respondents reporting no alcohol or substance abuse or dependency, major depression or anti-social traits in their first degree relatives are at increased risk for incident bipolar spectrum disorders (adjusted OR 2.27, 95% CI: 1.01-5.10, $p=.05$) and CIDI recalibrated BD I and II (adjusted OR 5.49, 95% CI: 1.38-21.9, $p=.02$) if they endorsed proximal cannabis use. Respondents reporting family history traits such that they entered into the lowest median of those with any positive family history reports were at non-significant reduced risk for incident bipolar outcomes for both proximal and distal cannabis use endorsement (Table 3.7). Cannabis use is not significantly associated with incident outcomes among those respondents in the highest median of those with any positive family history reports.

III E. 6 Substance Abuse or Dependence Strata

The association of past year and prior to past year cannabis use and incident manic or hypomanic episodes among those with and without a history of substance abuse or

Table 3.7: Reported Cannabis Use Risk for Bipolar Outcomes Among Those Aged 18 to 45 by Family History Density Score Group

Baseline Use Groups:	Bipolar Spectrum Disorders ^a				CID1 recalibrated BDI and II ^b				
	n	Outcome % (95% CI)	OR ^c	95% CI	n	Outcome % (95% CI)	OR ^d	95% CI	P-value
No Reported Family History^c									
No Reported use	238	3.0 (2.5-3.4)	Ref.	N=7460	80	1.0 (0.7-1.2)	Ref.	N= 7797	
Proximal Use			2.27	1.01 – 5.10			5.49	1.38 – 21.9	.02
Distal Use			1.41	0.86– 2.30			1.35	0.53 – 3.47	.53
Low Median Family History^c									
No Reported use	156	3.8 (3.1-4.6)	Ref.	N=3876	71	1.6 (1.1-2.1)	Ref.	N=4039	
Proximal Use			0.39	0.13 – 1.15			0.31	0.06 – 1.46	.13
Distal Use			0.76	0.40 – 1.44			0.39	0.15 – 1.02	.06
High Median Family History^d									
No Reported use	294	6.4 (5.5-7.3)	Ref.	N=4790	185	3.6 (3.0-4.2)	Ref.	N= 5351	
Proximal Use			1.53	0.88 – 2.68			1.20	0.59 – 2.40	.61
Distal Use			1.13	0.76 – 1.67			1.09	0.66 – 1.78	.74

^a Excluding those with wave 1 manic or hypomanic episodes

^b Excluding those with wave 1 CID1 recalibrated BD I and II

^c Adjusted for lifetime manic or MDE symptoms at baseline, gender, age group, race, education, urbanicity, region, income, substance abuse or dependence, tobacco status, other drug use, childhood events, history of a psychiatric comorbidity, and baseline norms based mental health score

^d Adjusted for same covariates at ^c and wave 1 bipolar spectrum disorder

dependence (nicotine dependence or alcohol, cannabis or other substance abuse or dependence) are reported in Table 3.8A. Neither proximal nor distal cannabis use are not significantly associated with bipolar spectrum disorder outcomes in either group. Table 3.8B shows risk estimates for those with and without substance abuse or dependence stratified into young adult (18 to 25 years of age) and adult (26 to 45 years of age) cohorts. Proximal cannabis use risk in those with substance abuse/dependence histories is concentrated in those aged 26 to 45 (adjusted OR 2.00, 95% CI: 1.10-3.66, $p=.02$) with a null result for the young adult cohort with substance abuse/dependence histories (adjusted OR 1.13, 95% CI: 0.49-2.61, $p=.77$). Cannabis use prior to the past year is not associated with incident manic or hypomanic episodes among both age cohorts with substance abuse/dependence histories. Both proximal and distal cannabis use are not significantly associated with bipolar spectrum disorder outcomes among both young adults and adults without a history of substance abuse/dependence. Table 3.8C reports cannabis use risk across the five-level exposure categories among the adults with substance abuse/dependence histories. Limited power (low cell counts) among the other substance abuse/dependence age cohort sub-strata groups restricted the analysis of cannabis use risk across the five-level exposure categories to the adults (26 to 45 years of age) with substance abuse/dependence histories. Those with substance abuse/dependence at baseline and reported the highest level of cannabis use (≥ 1 use per week) at baseline are at significantly increased adjusted risk of incident bipolar spectrum outcomes at wave 2 (adjusted OR 2.52, 95% CI: 1.22-5.21, $p=.01$). This high cannabis use group is also at an elevated though not statistically significant risk for the CIDI recalibrated BD I and II

Table 3.8A: Cannabis Use Risk for Bipolar Spectrum Outcomes^a among those Aged 18 to 45 with and without any Substance Abuse or Dependence at Baseline

	No History of Substance Abuse or Dependence N= 9987			History of Substance Abuse or Dependence ^b N= 6361		
	OR ^c	95% CI	P-value	OR ^d	95% CI	P-value
	Baseline Use Groups:					
No Reported use	Ref.			Ref.		
Proximal Use	1.86	0.71 – 4.88	.21	1.49	0.91– 2.43	.11
Distal Use	0.78	0.45 – 1.37	.39	1.42	0.98 – 2.07	.07

^a Excluding any wave 1 manic or hypomanic episodes

^b Lifetime history of alcohol, cannabis, illicit substance, tobacco or RX drug abuse or dependence at wave 1

^c Adjusted for baseline manic or MDE symptoms, gender, education, urbanicity, region, low/no tobacco use, other drug use, family history score, childhood events, psychiatric comorbidities, baseline norms based mental health score

^d Same as ^b and including alcohol, other drug abuse, dependence, and tobacco dependence

Table 3.8B: Cannabis Use Risk for Bipolar Spectrum Outcomes^a among Young Adults (18 to 25) and Adults (26 to 45) with and without Lifetime Substance Abuse or Dependence at Baseline

	Those aged 18 to 25			Those aged 26 to 45		
	OR ^b	95% CI	P-value	OR ^b	95% CI	P-value
	Baseline Use Groups:					
	w/History of Substance Abuse or Dependence^c					
	N= 1284			N= 5078		
No Reported use	Ref.			Ref.		
Proximal Use	1.13	0.49 – 2.61	.77	2.00	1.10 – 3.66	.02
Distal Use	1.59	0.76 – 3.33	.21	1.34	0.88 – 2.03	.17
	No History of Substance Abuse or Dependence					
	N=2524			N=7405		
No Reported use	Ref.			Ref.		
Proximal Use	1.36	0.41 – 4.53	.61	1.87	0.49 – 7.21	.36
Distal Use	0.45	0.15 – 1.32	.14	1.03	0.56 – 1.89	.93

^a Incident manic or hypomanic episodes excluding any wave 1 manic or hypomanic episodes

^b Adjusted for baseline manic or MDE symptoms, gender, race, education, urbanicity, region, alcohol abuse, alcohol dependence, tobacco use and dependence, other drug use and abuse, family history score, childhood events, psychiatric comorbidities, and baseline norms based mental health score

^c Lifetime history of alcohol, cannabis, illicit substance, tobacco or RX drug abuse or dependence at wave 1

Table 3.8C: Cannabis Use Risk for Bipolar Outcomes among those Aged 26 to 45 with Lifetime Substance Abuse or Dependence at Baseline^a

	Bipolar Spectrum Outcomes ^b			CIDI recalibrated BD I and II ^c		
	OR ^d	N= 5078 95% CI	P-value	OR ^e	N= 5421 95% CI	P-value
Baseline Use Groups:						
No Reported use	Ref.			Ref.		
>= 1 use/week past year	2.52	1.22 – 5.21	.01	2.39	0.87 – 6.62	.09
< 1 use/week past year	1.55	0.75 – 3.18	.23	1.15	0.40 – 3.28	.80
>=1 use/week prior to past year	1.24	0.73 – 2.08	.42	1.21	0.58 – 2.50	.61
<1 use/week prior to past year	1.39	0.90 – 2.15	.14	1.56	0.84 – 2.89	.16

^aLifetime history of alcohol, cannabis, illicit substance, tobacco or RX drug abuse or dependence at wave 1

^bExcluding any wave 1 manic or hypomanic episodes

^cExcluding any wave 1 CIDI recalibrated bipolar I or II

^dAdjusted for baseline manic or MDE symptoms, gender, race, education, urbanicity, region, alcohol abuse, alcohol dependence, tobacco use status and dependence, other drug use and abuse, family history score, childhood events, psychiatric comorbidities, and baseline norms based mental health score

^eSame as ^b plus bipolar spectrum disorders at wave 1

outcomes (adjusted OR 2.39, 95% CI: 0.87-6.62, p=.09). The other cannabis exposure groups do not have significant associations with incident bipolar outcomes (Table 3.8C).

III F. Comments

The strong association of the listed potential confounders in Table 3.2 with both cannabis use and incident bipolar spectrum disorders is considerable. The accumulative effect of these covariates is seen in the comparison of the corresponding Model C with Model F in the three series of nested models of Table 3.3. The percent change in the proximal cannabis use coefficient (standardized for a unit variance in the independent and dependent variables) between Model C with Model F in the incident manic symptom models was 34%, 56% for the incident bipolar spectrum disorder series, and 69% for the CIDI recalibrated series. Proximal cannabis remained a significant risk factor for incident manic symptom but not for bipolar spectrum disorders. Collectively other substance use (abuse/dependence), childhood factors, family history, and preexisting

psychiatric liability explain a substantial portion of the association between past year cannabis use and incident bipolar spectrum disorder outcomes. Though care was made to include all relevant potential confounding factors the possibility that uncontrolled confounding exists can not be dismissed and the large percentage changes in effect estimates coefficients only underscore this point. Specifically uncontrolled confounding in the form of unmeasured genetic predisposition for both cannabis use and bipolar spectrum disorders that is not captured in the family history score groups can not be ruled out.

The risk estimates reported in Table 3.3 are for events over a relatively short three year period among those with no lifetime manic or major depressive episode symptoms at baseline. The power to detect increased risk in this relatively low risk population (incident manic or hypomanic episodes 1.9%, 95% CI: 1.7- 2.2) may be limited. The symptom threshold analysis (Table 3.4) provides evidence that proximal cannabis use is associated with incident sub-DSM-IV disorder level manic outcomes, specifically for manic symptom events featuring a week or more of extremely elevated or irritable mood with two or more manic episode criterion B symptoms. This result should be interpreted with some caution as only respondents endorsing three or more manic episode criterion B symptoms were asked whether their episode was substance induced or not. Indeed all of the symptom level estimates do not exclude substance induced events unlike the disorder level outcomes (manic and hypomanic episode, CIDI recalibrated BD I and II). Among those with two or more manic episode criterion B symptoms in the analysis reported in

Table 3.4 (n=768) n=50 report proximal cannabis use. These proximal cannabis users were more likely (OR 1.87, 95% CI: 0.97-3.64, p=.06) to report racing thoughts or finding it hard to follow their own thoughts as compared to the non-proximal cannabis users, suggesting the possible role of cannabis's acute psychotropic effects.

Unlike the population assessed in the primary nested model analyses the cohort with lifetime manic or major depressive episode symptoms at wave 1 were at relatively high risk. The cohort with lifetime manic or major depressive episode symptoms at baseline experienced 5.1% (95% CI: 4.6-5.7) incident manic or hypomanic episodes over the three year follow-up period (Table 3.5). Reported cannabis use was not associated with bipolar spectrum disorders in this at-risk population. This result does not support an interaction between depressive or manic symptoms and cannabis use. Even among those age 18 to 45 with manic symptoms at baseline (n=1471), who are at very high risk with 11.7% (95% CI: 9.5-13.9) experiencing incident manic or hypomanic episodes between wave 1 and wave 2, are not at significantly higher risk because of proximal cannabis use (OR 1.64, 95% CI: 0.87-3.09, p=.12, age group and gender adjusted). Similar results were seen among those with major depressive episode symptom (results not shown). These results suggest the possibility that the pathway in which cannabis may confer risk is 'already in use' or has reached a threshold in these symptomatic respondents such that the effect of an additional cannabis 'insult' is limited if present at all.

The age cohort sub-group analysis is informative in that we see that the older adult cohort is at reduced risk for incident outcomes related to reported cannabis use status (Table 3.6). This result is not so surprising in that this older group includes those that have been selected based on their long history of not experiencing a manic or hypomanic episode while being exposed to cannabis, i.e. if cannabis exposure does have an adverse effect it would have likely already removed at-risk individuals from the risk pool. The result that adults (26 to 45 years of age) but not young adults (18 to 25 years of age) are at increased risk from proximal cannabis use may point to developmental differences, greater accumulative exposure in the 26 to 45 year olds or other characteristics of this age group such as substance abuse and dependence (discussed later) that maybe driving risk. It should be noted that the increased risk in those 26 to 45 years of age using cannabis at the highest use level remained when those with symptoms of mania and major depression were excluded (adj. OR 2.82, 95% CI: 1.12 – 7.07, $p=.03$). The increased, though not necessarily significant, risk across all exposure groups for the 26 to 45 year olds suggest that prior to past year use is also be a risk factor in this age group. The significant odds of incident bipolar spectrum disorders among those reporting <1 use per week prior to the past 12 month could also be the result of under-reporting of current use, where respondent may feel more comfortable reporting prior to past year use while actually being a current user.

The results from the family history score stratified analysis offer challenges for interpretation (Table 3.7). Characteristic of the family history score itself likely

contribute to the divergent risk estimates between those with no reported family history and those in the lowest median of those with family history reports. Increasing age (OR 1.04, 95% CI: 1.03-1.04, $p < .0001$) and increasing family size (OR 1.15, 95% CI: 1.13-1.18, $p < .0001$) are strongly associated with inclusion in the lowest median family history group compared to the no reported history group. Being older and having a larger family increase the time and number of people at risk for the traits the family history score captures, increasing the likelihood of inclusion. Both age (OR 0.92, 95% CI: 0.91-0.93, $p < .0001$) and family size (OR 0.82, 95% CI: 0.79- 0.86, $p < .0001$) are also associated with a reduced risk of proximal cannabis use. One interpretation of the results for the first two family history strata is that the process of creating the no versus low family history groups preferentially placed older high-risk non-cannabis using respondents into the lowest median family history group as opposed to the no family history group, possibly lowering risk estimate in the former and increasing them in the latter group. In a post hoc analysis a group defined by combining the no reported family history group with the lowest median group finds proximal cannabis use is no longer a significantly associated with incident bipolar spectrum disorders (OR 1.27, 95% CI: 0.65 – 2.49, $p = .48$) or CIDI recalibrated BD I and II (OR 1.38, 95% CI: 0.40 – 4.77, $p = .60$). An alternative interpretation of the elevated risk in the no reported history group is that the environmental exposures like cannabis maybe more easily detected in a group with low inherent risk and the risk estimates are unbiased. In the present analysis it is not possible to disentangle the family history scores identification of a low risk population (no

reported history) from its possible selection effects (selection of higher risk non-proximal cannabis using respondents out of the no reported family history group).

Evidence that certain age groups with substance abuse or dependence are at increased risk from cannabis exposure is found in these data (Table 3.8B). The result that risk for bipolar spectrum disorders among those with a history of substance abuse or dependence is concentrated in those aged 26 to 45 (Table 3.8B, 3.8C) is consistent with observations in other bipolar cohorts.^{48,49} The result does not constitute a significant multiplicative interaction however (interaction $p=0.25$) and represents a modest increase in risk. In these other bipolar cohorts alcohol or cannabis dependence over an extended period preceded a bipolar onset. Cannabis exposure may function as a component cause of mania and increase risk among those with a substance abuse/dependence history, particularly among those with longer histories of abuse/dependence, such as is likely the case in our 26 to 45 year old cohort. Excluding those with cannabis abuse or dependence from the significant risk estimate in reported in Table 3.8B saw only marginally changes in the effect estimates for the high use group (OR 1.89; 95% CI : 1.07 – 3.34, $p=.03$) suggesting cannabis use, not raising to the level of abuse or dependence, is driving risk in this population.

An important feature of the NESARC cohort is the relatively low reported prevalence of lifetime cannabis use. Nationally representative prevalence estimates published by the

National Institute on Drug Abuse (NIDA) point to considerably higher cannabis use rates than seen in the NESARC for the year 2001, with 18 to 28 year olds reporting past years use at 29.2% and lifetime use at 55.7%.⁹⁷ Gruzca et al⁵⁴ compared substance use and substance use disorder prevalence estimates between the NESARC and the 2002 National Survey on Drug Use and Health (NSDUH). The NSDUH found lifetime and past year cannabis use prevalence estimates to be 2.1 and 2.6 times those reported in the NESARC respectively but with no significant difference between the surveys for past year cannabis use disorders ($p=.32$).⁵⁴ The association of ever using cannabis and the use of other drugs with bipolar spectrum disorders reported in Table 2.2 may be inflated as the suppression of substance use reporting in the NESARC was disproportionately among those not reporting poly-substance use.⁵⁴ All illicit substance use prevalence estimates are lower in the NESARC as compared to the NSDUH. Gruzca et al suggest that the use of computerized self-administration methods (ACASI) by the NSDUH, which allows respondents to anonymously enter sensitive information, may in part account for the differences in the prevalence estimates. The NESARC, by contrast, collected information in a face to face interview using census workers, federal employees, which may have suppressed reports of illegal substance use. Misclassification of cannabis use most certainly exists in the NESARC data. If the suppression of self-reported cannabis use in the NESARC is uniform (with false positive rates approximately null), and misclassification is non-differential with respect to incident manic outcome status, effect estimates will be biased toward the null assuming classification is independent of other errors.⁹⁸ The possibility of differential misclassification exists particularly if those with

greater underlying risk (i.e. poly-substance users, more comorbid disorders, etc.) preferential report cannabis use. Aim 3 of this dissertation is a sensitivity analysis that uses external predicted probabilities of cannabis exposure from the National Comorbidity Survey Replication to assess the influence of hypothetically un-suppressed cannabis use reporting on risk estimates.

III G. Limitations

Certain limitation of the research reported above need to be acknowledged. As previously discussed the self-reported exposure of this study is of an illegal substance. There is likely misclassification of exposure which may undermine the validity of the risk estimates. The likely suppression of reports of other illicit substance use may have limited the adequate control of confounding. The proxy measures of underlying genetic risk and childhood histories (i.e. family history scores and childhood adverse events) are likely weak proxies, leaving open the possibility of uncontrolled confounding via inadequate or unmeasured underlying risk. The NESARC sample does not include institutional settings which likely disproportionately include cannabis exposed individuals on the bipolar spectrum, potentially biasing estimates toward the null. The statistical power of some of the analyses was low. Collectively these limitations need to be considered when interpreting the risk estimates.

III H. Strengths

In spite of the noted limitations this study has some important strengths. This study used the largest longitudinal nationally representative sample available. The large sample size allowed the assessment of cannabis use risk within the population as a whole and in sub-populations defined by symptoms, age cohort, family history and substance abuse or dependence. Substance use was systematically excluded as the acute cause of the incident manic or hypomanic episodes. The multivariate adjusted models of risk estimates used a large number of relevant demographic characteristics, substance use/abuse/dependence, individual and family history, and psychiatric comorbidity measures to adjust risk estimates and control for potential confounding. Estimates within strata defined by substance abuse or dependence are likely to have less biased cannabis use reporting (i.e. demonstrated willingness to report substance use, abuse or dependence).

III I. Summary of Findings

Among those reporting no lifetime major depressive or manic symptoms at baseline self-reported past-year cannabis use was associated with increased odds of an incident week of extremely elevated or irritable mood accompanied by at least two manic episode criterion B symptoms (adj. OR 1.69, 95% CI: 1.08-2.65, $p=.02$) over a three year follow-up period. Among adults (ages 26 to 45) ≥ 1 use of cannabis of per week was associated with incident manic or hypomanic episodes (adjusted OR 2.52, 95% CI: 1.32-4.80, $p=.006$). This elevated risk among those aged 26 to 45 remained even when those with

lifetime major depressive or manic symptoms at baseline were excluded (adj. OR 2.82, 95% CI: 1.12 – 7.07, $p=.03$). Risk for DSM-IV manic or hypomanic episodes among those aged 26 to 45 using cannabis in the past year is concentrated in those with a baseline history of a substance use disorder (adj. OR 2.00, 95% CI: 1.10-3.66, $p=.02$) compared to those with no such histories (adj. OR 1.87, 95% CI: 0.49-7.21, $p=.36$).

Among those endorsing no major depressive symptoms, substance abuse/dependence or anti-social traits in their first degree relatives past year cannabis use is associated with increased risk for incident bipolar spectrum disorders (adjusted OR 2.27, 95% CI: 1.01-5.10, $p=.05$) and CIDI recalibrated BD I and II (adjusted OR 5.49, 95% CI: 1.38-21.9, $p=.02$).

III J. Conclusions

This aim finds evidence supporting the conclusion that self-reported cannabis use is a significant risk factor for incident bipolar spectrum outcomes within subpopulations in a nationally representative cohort. Specifically adults (aged 18 to 45) reporting cannabis use at a high level (≥ 1 use/week) experience the greatest increase in risk. The evidence points to the underlying liability of a history of a substance use disorder among those aged 26 to 45 as a contributor to this elevated risk. Equally as important is that the evidence supports the conclusion that cannabis use is *not* a significant risk factor for incident bipolar outcome within populations that are at elevated risk for bipolar outcomes because of a baseline history of MDE or manic symptoms or family history factors. In

contrast, the evidence suggests those at low innate risk because of family history have increased cannabis use risk for bipolar disorder outcomes.

Future research needs to explore what specific characteristics of those with substance use disorders drives their increased risk for bipolar spectrum disorders associated with cannabis use. Additionally relevant genetic and environmental factors that increase risk for bipolar spectrum disorders need to be identified in population representative samples. Improved measures of the underlying risk for bipolar spectrum disorders will improve the identification of those most at risk for bipolar spectrum disorders as the result of cannabis exposure.

Chapter IV:

IV A. Introduction

A major limitation of the Aim 2 analysis was the low reported prevalence of cannabis use in the NESARC. The National Institute on Drug Abuse (NIDA) Monitoring the Future report⁹⁷ and the 2002 National Survey on Drug Use and Health (NSDUH)⁵⁴ both point to considerable higher cannabis use rates than seen in the NESARC for the year 2001 to 2002. Both NIDA's Monitoring the Future and the NSDUH's main purpose was the collection of substance use information. The NESARC's main focus was on alcohol and related conditions which included the assessment of a wide range of psychiatric comorbidities. The National Comorbidity Survey Replication (NCS-R) also examined a wide range of psychiatric comorbidities in a similar manner and during the same time period as the NESARC.⁵⁹ The reported lifetime use of cannabis among adults (aged ≥ 18) was very similar between the NCS-R at 42.7 % (SE 1.0)⁹⁹ and the NSDUH at 42.8 % (41.9 - 43.7).⁵⁴

The NCS-R represents a very similar population to that of the NESARC. The reported cannabis use prevalence estimates of the NCS-R are in keeping with other estimates that employed anonymous reporting. These features make the NCS-R a good population to make external estimates of cannabis use probabilities within the NESARC. Using

identical measures from both surveys predicted probabilities (i.e. propensity scores) of ever using cannabis, use within the past year and high use in the past year (≥ 1 use/week) can be estimated in the NESARC using effect estimates from the NCS-R. The NCS-R will function as the external standard. These predicted probabilities could be used as proxies for NCS-R-like exposures within the NESARC. The use of externally estimated exposures will serve as a vehicle to conduct a sensitivity analysis. This sensitivity analysis will address the question of how would cannabis use risk estimates might differ in the NESARC if cannabis use reporting conformed more closely to our hypothetically un-suppressed NCS-R use reports.

IV B. Sensitivity Analysis Methods

IV B. 1 The surveys sample populations

The NESARC and the NCS-R represent very similar populations but as their sampling frames differed in some respects, differences between the two samples exist. As previously described the main differences between the two surveys is that the sampling frame for the NESARC included all 50 states and group quarters such as boarding houses, dormitories and shelters where as the NCS-R sampling frame included the lower 48 states and did not include group quarters. In the NCS-R students living in dormitories from a family in a sampled household were eligible to be sampled. To assess the demographic differences between the two surveys standardized differences in the prevalence of individual characteristics were determined. Cohen's d is a measure of

effect size and is defined as the difference between two means divided by their pooled standard deviation.¹⁰⁰ Standardized mean differences between the surveys demographic characteristics are reported as one hundred times Cohen's d. Cohen's d is a measure of effect size between two independent means with increasing absolute values representing increasing effect sizes. A rule of thumb for interpreting the standardized mean differences defined here is that absolute values of about 20 represent small effect sizes, 50 medium effect sizes and 80 large effect sizes.¹⁰¹ The pooled standard deviations were calculated by concatenating the two datasets while retaining the data structure (primary sampling units, strata) of the individual surveys. The pooled standard deviations represent simple random sample estimates based on the total number of observations of both surveys that has taken the design of both surveys into account.

IV B. 2 Exposure Measures

In the NCS-R cannabis use was assessed in part 2 or the long form of the survey.⁵⁹ Part 2 respondents were asked about past 30-day, past year and lifetime substance use, including cannabis use. Part 2 respondents to the NCS-R were weighted to be representative of the household population of the 48 contiguous US states. Reports of ever using cannabis, <1 use/week in the past year, and ≥ 1 use/week in the past year were dichotomously coded (1= reported use, 0=not reported). These same measures are also found in the NESARC and were coded accordingly.

IV B. 3 Demographic Measures

Demographic measures in the two surveys were assessed in very similar ways and captured identical traits. The following demographic measures were found and coded in the same manner in both survey data sets: gender (male=1, female=0), age cohort (1= 18 to 25, 2=26 to 35, 3=36 to 45, and 4 =46 and older), race/ethnicity (white=1, black=2, Hispanic or Latino=3, and Other =4), Household income (\$) quartiles (1= <=23000, 2= 23000 to <= 47000, 3= 47001 to <=80500, 4= >=80500), education status (1= < high school, 2=high school or GED, 3= some college or an Associate Degree, 4= >= Bachelor's Degree), census region (1= Northwest, 2= Midwest, 3= South, 4= West), marital status (1=married or living with someone as if married, 2= divorced or separated or widowed, 3= never married), and native birth status (1=native born, 0= not native born).

IV B. 4 Analytical Approach

Three separate models were constructed using the NCS-R data. These models are propensity score models using external data.¹⁰² All the demographic variables listed above were used as predictive variables in three models of 1) ever using cannabis, 2) past 12 month use and 3) >=1 use/week in the past 12 months. The propensity score models only included independent variables that were nearly identically assessed and captured the same trait between the two surveys. Enough differences existed between how the two surveys assessed other substance use and applied DSM-IV criteria for substance use and non-substance use disorders to preclude the use of these measures in the propensity

models. Therefore the independent variables used in the cannabis use propensity score models were restricted to the demographic variables listed above. The propensity score models discrimination characteristics within the NCS-R were assessed by the area under the receiver operator characteristic curve (AUC).

Coefficients from each NCS-R cannabis use model were used to generate predicted probabilities within the NESARC dataset (predicted probabilities = $1/[1 + e^{-(\beta_{0,NCS-R} + \text{male} * \beta_{\text{male},NCS-R} + \dots + \text{native born} * \beta_{\text{native born},NCS-R})}]$). Effect estimates from the NCS-R were used, in other words, to generate a propensity score within the NESARC. The mean predicted probabilities of the three exposure models within the NESARC represent an estimation of the prevalence of the given exposure (i.e. a perfectly predicted exposure would have probabilities of 1 and 0, the mean of which would be its prevalence). The mean predicted values from the NESARC were examined for their consistency with prevalence estimates from the NCS-R taking into consideration meaningful differences that may exist between the two samples.

IV B. 5 Categorizing Predicted Exposures

Risk estimates of continuous predictors of exposure (i.e. propensity score) can be hard to interpret and compare to risk estimates from dichotomous or categorical exposures (i.e. our reported use exposures). To facilitate comparison of the predicted exposures and the reported exposures cut points were established to classify the predicted probabilities into categorical variables. After inspection and satisfaction that the mean predicted

probabilities of the three exposure prediction models were reasonable, cut points at the mean predicted probability (i.e. the estimated prevalence) were imposed. In other words, for a mean predicted probability of say .40, the highest 40% of the predicted probability would be code 1 and the lowest 60% coded as 0. The high use level (≥ 1 use/week in the past 12 months) was defined as: the highest predicted probability from the high use propensity model while maintaining the total prevalence at the mean predicted probability (i.e. the cut point) of the high use propensity score model. The past year use level was defined as including: respondents already classified as high use (in past year) or respondents with the highest predicted probability from the past year use model while maintaining the total prevalence at the mean predicted probability of the past year cannabis use propensity model. Similarly the ever using cannabis level was defined as including: respondents already classified in the past year group or respondents with the highest predicted probability from the ever use model while maintaining the total prevalence at the mean predicted probability of the ever used cannabis propensity model. These three indicators were used to define the four level categorized predicted probability variable: 1) those with no use, 2) ≥ 1 use/week in the past 12 months, 3) <1 use/week past 12 month and 4) prior to past 12 month use. Also separate dichotomous indicators for predicted proximal and predicted distal cannabis use were also specified.

IV B. 6 Assessment of propensity score based classified exposure variable

Standardized mean differences between NCS-R cannabis use prevalence estimates and the NESARC reported and predicted cannabis use estimates will be reported. To assess

how well the above describes classification schemas improved classification within our domain of interest, standardized mean differences between the NCS-R and the NESARC for reported and predicted cannabis use by bipolar spectrum disorder status (cross-sectional prevalence of DSM-IV manic or hypomanic episodes from wave 1 of the NESARC and the NCS-R) will be compared. An improvement in the balance between the NCS-R and the NESARC on the cross-sectional relationship between cannabis use status and bipolar outcomes will provide a measure of support for the validity of the exposure classifications.

IV B. 7 Sensitivity Analysis

Reported cannabis use and predicted cannabis use risk estimates will be compared among groups with significant effect estimates reported in Chapter 3 (i.e. incident manic symptoms, among adults age 26 to 45, by family history status and by substance use disorder status). These analyses will provide evidence as to how sensitive risk estimates in the NESARC are to improved hypothetically less biased 'NCS-R-like' reporting. Continuous predicted probabilities or their log transformed values will also be included in multivariate models of incident bipolar spectrum outcomes in the NESARC. These analyses will provide evidence as to whether cannabis use propensity is associated with risk for bipolar spectrum outcomes.

Table 4.1: Demographic Variable Balance Between the NCSR and the NESARC

	NCSR	NESARC	Mean	Pooled	Standardized
	Mean	Mean	Difference	Std. Dev.	Mean Difference ¹
Male gender	0.47	0.48	-0.01	0.50	-1.9
Age:					
18-25	0.17	0.15	0.02	0.36	6.3
26-35	0.16	0.19	-0.02	0.39	-5.7
36-45	0.21	0.21	0.00	0.41	-0.9
46 and older	0.46	0.45	0.00	0.50	0.7
Race/Ethnicity:					
White	0.73	0.71	0.02	0.45	4.1
Black	0.12	0.11	0.01	0.31	4.1
Hispanic or Latino	0.11	0.12	0.00	0.32	-1.5
Other	0.04	0.06	-0.03	0.25	-10.9
Household Income Quartiles (\$)					
<=23000	0.27	0.27	0.00	0.44	-0.3
>23000 to <=47000	0.23	0.30	-0.07	0.46	-14.5
>47000 to <=80500	0.25	0.26	-0.01	0.44	-2.4
>80500	0.25	0.18	0.08	0.38	20.5
Education:					
<High School	0.17	0.16	0.01	0.36	3.1
High School or GED	0.33	0.29	0.03	0.46	7.0
Some College	0.28	0.30	-0.03	0.46	-5.7
>=Bachelor's Degree	0.23	0.25	-0.02	0.43	-4.0
Region:					
Northeast	0.19	0.20	-0.01	0.40	-2.1
Midwest	0.24	0.23	0.00	0.42	0.9
South	0.36	0.35	0.00	0.48	0.8
West	0.22	0.22	0.00	0.41	0.3
Marital Status:					
Married/living with someone	0.56	0.62	-0.06	0.49	-11.7
Divorced/Separated/Widowed	0.21	0.17	0.03	0.38	8.8
Never Married	0.23	0.21	0.02	0.41	5.7
Native Born	0.92	0.85	0.07	0.35	18.9

¹Standardized mean difference equals 100 times the difference in means divided by the pooled sample standard deviation

IV C. Results

Table 4.1 shows the balance of the means of the demographic characteristics between the two surveys. There is good balance between the two surveys with two notable exceptions, the NESARC has a lower proportion of those in the highest income group and also has fewer respondents reporting being native born. The prediction models have fair to good discrimination characteristic (Table 4.2). Table 4.3 shows the mean predicted probabilities of the three models. The models predict slightly lower prevalence

Table 4.2: Cannabis Use Propensity Models

	Cannabis Use Ever			Cannabis in Past 12 Months			High Use in Past 12 Months >= 1 use/week		
	OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value
(N=5672)									
Male gender	1.94	1.59 - 2.37	<.001	2.45	1.92 - 3.12	<.001	3.03	2.18 - 4.23	<.001
Age:									
18-25	1.14	0.84 - 1.53	0.39	0.66	0.47 - 0.93	0.02	0.67	0.42 - 1.06	0.09
26-35	1.21	0.91 - 1.62	0.19	0.33	0.24 - 0.46	<.001	0.46	0.30 - 0.72	0.001
36-45	0.27	0.20 - 0.37	<.001	0.11	0.08 - 0.16	<.001	0.11	0.06 - 0.20	<.001
46 and older									
Race/Ethnicity									
White	0.99	0.75 - 1.31	0.96	1.18	0.76 - 1.81	0.45	1.31	0.88 - 1.96	0.18
Black	0.81	0.58 - 1.12	0.20	0.91	0.49 - 1.71	0.77	0.65	0.33 - 1.26	0.20
Hispanic or Latino	0.88	0.54 - 1.46	0.62	1.25	0.69 - 2.26	0.46	1.68	0.92 - 3.08	0.09
Other									
Household Income Quartiles (\$)									
<=23000	1.12	0.87 - 1.44	0.37	0.89	0.61 - 1.30	0.54	1.06	0.71 - 1.57	0.78
>23000 to <=47000	1.42	1.12 - 1.79	<.001	0.91	0.60 - 1.37	0.65	1.12	0.70 - 1.79	0.62
>47000 to <=80500	1.77	1.36 - 2.32	<.001	0.99	0.63 - 1.55	0.97	0.99	0.65 - 1.49	0.94
>80500									
Education									
<High School	0.99	0.77 - 1.26	0.92	0.89	0.58 - 1.36	0.58	0.61	0.40 - 0.94	0.03
High School or GED	1.09	0.86 - 1.37	0.49	1.17	0.81 - 1.68	0.39	0.61	0.38 - 0.99	0.05
Some College	1.07	0.78 - 1.45	0.67	0.86	0.55 - 1.34	0.49	0.27	0.16 - 0.47	<.001
>=Bachelor's Degree									
Census Region									
Northeast	0.70	0.53 - 0.93	0.02	0.65	0.43 - 0.97	0.04	0.69	0.35 - 1.34	0.26
Midwest	0.51	0.39 - 0.66	<.001	0.40	0.26 - 0.63	<.001	0.42	0.20 - 0.88	0.02
South	1.33	1.05 - 1.69	0.02	0.92	0.62 - 1.36	0.66	1.07	0.57 - 2.04	0.82
West									
Marital Status									
Married/Living with someone	1.45	1.15 - 1.83	<.001	1.91	1.29 - 2.82	<.001	1.73	1.04 - 2.89	0.04
Divorced/Separated/Widowed	1.04	0.78 - 1.40	0.76	1.99	1.42 - 2.80	<.001	2.05	1.22 - 3.44	0.008
Never Married									
Native Born	4.33	2.89 - 6.47	<.001	3.74	1.96 - 7.16	<.001	5.08	1.96 - 13.14	0.001
	AUC	95% CI		AUC	95% CI		AUC	95% CI	
	0.72	0.71 - 0.73		0.78	0.76 - 0.80		0.80	0.78 - 0.83	

estimates (i.e. mean predicted probability) across all three models as compared to the NCS-R. The performance of the prediction models and the classification schema are presented in Table 4.4. The standardized differences of the reported use groups in the cohort as a whole were all >20 with the exception of the past year high use group (17.2). In the cohort as a whole there are small differences in the means between the reported and predicted classification groups. Within groups defined by cross-sectional bipolar spectrum disorder status the reclassification schema improved the concordance (i.e. lowered standardized differences) between the NCS-R and the NESARC for the predicted exposure groups. Reported use is more strongly associated with bipolar outcome in the NESARC than in the NCS-R (lower standardized differences), particularly for the high use group.

Table 4.3: Cannabis Use Prevalence and Mean Predicted Cannabis Use Probabilities Using NCS-R Demographics to Predict Baseline NESARC Cannabis Use

	NCS-R		NESARC		NESARC	
	Reported Use		Reported Use		Mean Predicted Probability	
	%	95% CI	%	95% CI	%	95% CI
Cannabis Use Groups:						
Ever Used	42.5	40.4 – 44.6	20.7	19.7 – 21.7	40.2	39.1 – 41.2
Any use past year	9.5	8.5 – 10.4	4.1	3.8 – 4.4	8.7	8.3 – 9.0
>= 1 use/week past year	3.9	3.3 – 4.6	1.7	1.5 – 1.9	3.5	3.4 – 3.7

Table 4.4: Balance of Cannabis Use between the NCSR and Wave 1 of the NESARC

	NCSR		NESARC		Standardized Mean Differences ¹	
	Reported		Predicted		Reported	Predicted
	Mean	Mean	Mean	Mean		
Whole Cohort	(n=5669)	(n=41996)	(n=42013)			
No use	0.575	0.793	0.605	-53.7	-6.0	
>= 1 use/week past year	0.039	0.017	0.036	17.2	2.0	
< 1 use/week past year	0.055	0.024	0.050	20.5	2.3	
Prior to past year use	0.330	0.166	0.309	44.1	4.5	
Bipolar Spectrum Disorder	(n=431)	(n=2427)	(n=2425)			
No use	0.370	0.578	0.488	-41.3	-23.2	
>= 1 use/week past year	0.100	0.072	0.088	10.8	4.0	
< 1 use/week past year	0.106	0.063	0.072	17.8	12.9	
Prior to past year use	0.423	0.287	0.351	29.5	14.8	
No Bipolar Spectrum Disorder	(n= 5238)	(n=39569)	(n= 39588)			
No use	0.585	0.805	0.611	-55.5	-5.4	
>= 1 use/week past year	0.036	0.014	0.033	19.6	2.2	
< 1 use/week past year	0.053	0.022	0.049	21.4	1.7	
Prior to past year use	0.326	0.160	0.307	45.3	4.1	

¹Standardized mean difference equals 100 times the difference in means divided by the pooled sample standard deviation

IV C. 1 Risk Estimates with Predicted Exposure Groups

Tables 4.5 to 4.7 report the predicted cannabis use risk estimates in comparison with the reported estimates. Of the significant risk estimates for reported cannabis use in Chapter 3, none are found to be significant for categorized predicted use. Only for incident manic symptoms outcomes did predicted cannabis use risk approaches significance (adjusted OR 1.54, 95% CI: 0.99-2.38, p=.054).

Table 4.5: Reported and Predicted Cannabis Use Risk for Incident Manic Symptoms

Baseline Use Groups:	Reported Cannabis Use			Predicted Cannabis Use		
	OR ^b	95% CI	P-value	OR ^b	95% CI	P-value
Incident Manic Symptoms^a						
	N=20434			N= 20424		
No Reported use	Ref. ^b			Ref. ^b		
>= 1 use/week past 12 months	2.23	1.27 – 3.39	.006	1.54	0.99 – 2.38	.054
< 1 use/week last 12 months	1.37	0.83 – 2.26	.21	0.86	0.57 – 1.28	.44
Prior to past 12 month use	1.17	0.92 – 1.49	.19	1.11	0.87 – 1.40	.39

^a Excluding those with manic or major depressive episode symptoms at wave 1

^b Adjusted for gender, age group, race, education, urbanicity, region, income and marital status, alcohol abuse, alcohol dependence, no/low level tobacco use, nicotine dependence, other drug use, drug abuse and drug dependence, family history density score category, childhood events, baseline norms based mental health score, history of dysthymia, agoraphobia or panic disorder, social phobia, specific phobia, GAD, conduct disorder(no ASPD), ASPD, PTSD, childhood ADHD and any personality disorder

Table 4.6: Reported and Predicted Cannabis Use Risk for Bipolar Spectrum Disorders among those aged 26 to 45 and among those aged 26 to 45 with Substance Use Disorder Histories

Baseline Use Groups:	Reported Cannabis Use			Predicted Cannabis Use		
	OR ^b	95% CI	P-value	OR ^b	95% CI	P-value
All Those Age 26 to 45 : Incident Bipolar Spectrum Disorders^a						
	N=12196			N=12189		
No Reported use	Ref. ^b			Ref. ^b		
>= 1 use/ week last 12 months	2.50	1.30 – 4.80	.007	1.60	0.67 – 3.80	.28
< 1 use/week last 12 months	1.88	0.98 – 3.64	.06	0.77	0.33 – 1.83	.56
Use prior to last 12 months	1.43	1.01 – 2.03	.05	0.91	0.68 – 1.21	.50

Those Age 26 to 45 w/Substance Use Disorder Histories: Incident Bipolar Spectrum Disorders^a

Baseline Use Groups:	Reported Cannabis Use			Predicted Cannabis Use		
	OR ^b	95% CI	P-value	OR ^b	95% CI	P-value
Those Age 26 to 45 w/Substance Use Disorder Histories: Incident Bipolar Spectrum Disorders^a						
	N=5078			N=5077		
No Reported use	Ref. ^c			Ref. ^c		
>= 1 use/ week last 12 months	2.57	1.25 – 5.28	.01	2.04	0.71 – 5.89	.18
< 1 use/week last 12 months	1.57	0.76 – 3.35	.22	0.74	0.23 – 2.40	.61
Use prior to last 12 months	1.33	0.88 – 2.02	.17	0.99	0.60 – 1.63	.97

^a Excluding any wave 1 manic or hypomanic episodes

^b Adjusted for lifetime manic or MDE symptoms at baseline, gender, age group, race, education, urbanicity, region, income, alcohol abuse, alcohol dependence, tobacco use and dependence, other drug use, abuse and dependence, family history score, childhood events, history of dysthymia, agoraphobia or panic disorder, social phobia, specific phobia, generalized anxiety disorder, conduct disorder, ASPD, PTSD, childhood ADHD, other personality disorders and baseline norms based mental health score

^c Adjusted for same variables as ^b less income, other drug dependence and psychiatric comorbidities aggregated into one indicator

Table 4.7: Reported and Predicted Cannabis Use Risk for Bipolar Spectrum Disorders Among those with No Reported Family History Aged 18 to 45

Baseline Use Groups:	Reported Cannabis Use			Predicted Cannabis Use		
	OR	95% CI	P-value	OR	95% CI	P-value
Incident Bipolar Spectrum Disorders^a						
		N=7640			N= 7635	
No Reported use	Ref. ^b			Ref. ^b		
Proximal	2.27	1.01 – 5.10	.05	1.55	0.96 – 2.50	.08
Distal	1.41	0.86 – 2.30	.17	1.02	0.63 – 1.66	.94
Incident CIDI Recalibrated Bipolar I and II^c						
		N=7792			N=7792	
No Reported use	Ref. ^d			Ref. ^d		
Proximal	5.49	1.38 – 21.9	.02	1.03	0.67 – 3.80	.93
Distal	1.35	0.53 – 3.47	.53	1.19	0.33 – 1.83	.64

^a Excluding those with wave 1 manic or hypomanic episodes

^b Adjusted for lifetime manic or MDE symptoms at baseline, gender, age group, race, education, urbanicity, region, income, substance abuse or dependence, tobacco use, other drug use, childhood events, history of a psychiatric comorbidity, and baseline norms based mental health score

^c Excluding those with wave 1 CIDI recalibrated BD I and II

^d Adjusted for same covariates at ^b and wave 1 bipolar spectrum disorder

IV C. 2 Risk Estimates with Cannabis Use Propensities

Table 4.8 shows the odds of bipolar spectrum outcomes per unit of predicted probability for the three predicted exposures. Propensity for ever using cannabis was not significantly associated with bipolar spectrum outcomes, a unit change in the log transformed continuous probability of past year use and ≥ 1 use/week in the past year were significantly associated with bipolar spectrum outcomes among adults aged 18 to 45. Table 4.9 reports risk for incident bipolar spectrum outcomes for individual cannabis use propensities by family history strata. Cannabis use propensities for past year and high use in the past year are both significantly associated with bipolar spectrum outcomes

Table 4.8: Odds of Bipolar Spectrum Disorders among those aged 18 to 45 Associated with Cannabis Use Propensity

Each cannabis use propensity in separate model:	Odds Bipolar Spectrum Disorders at Wave 2 ^a			
	N	OR ^b	95% CI	P-value
Ever Used	10708	1.60	0.43 – 5.91	.48
Past 12 months ^c	10792	1.49	1.10 – 2.03	.01
>= 1 use/week past 12 months ^c	10792	1.33	1.03 – 1.72	.03

^a Manic or hypomanic episode excluding those with any reported manic or depressive symptoms at wave 1

^b Adjusted for gender, education, urbanicity, region, income, alcohol abuse, alcohol dependence, tobacco use and dependence, other drug use and abuse, family history score, agoraphobia or panic disorder, social phobia, specific phobia, conduct disorder, ASPD, other personality disorders, ADHD, PTSD, childhood adverse events and baseline norms based mental health score

^c Log transformed

Table 4.9: Odds of Bipolar Spectrum Disorders Associated with Cannabis use Propensities among those aged 18 to 45 by Family History Score Groups

Cannabis Use Propensities	Odds Bipolar Spectrum Disorders at Wave 2 ^a			
	N	OR ^b	95% CI	P-value
With No Reported Family History				
Ever Used	7635	3.71	0.88 – 15.6	.07
Past 12 months ^c	7640	1.61	1.11 – 2.32	.01
>= 1 use/week past 12 months ^c	7640	1.38	1.03 – 1.85	.03
Lowest Median Family History Score				
Ever Used	3876	0.28	0.04 – 1.97	.20
Past 12 months ^c	3876	1.40	0.88 – 2.22	.15
>= 1 use/week past 12 months ^c	3876	1.26	0.85 – 1.88	.25
Highest Median Family History Score				
Ever Used	4785	1.07	0.21 – 5.63	.93
Past 12 months ^c	4790	0.92	0.67 – 1.25	.59
>= 1 use/week past 12 months ^c	4790	0.94	0.72 – 1.22	.62

^a Excluding any wave 1 manic or hypomanic episodes

^b Adjusted for baseline manic or MDE symptoms, gender, education, urbanicity, region, low/no tobacco use, other drug use, substance use disorder, family history score, childhood events, psychiatric comorbidities, baseline norms based mental health score

^c Log transformed cannabis use propensity

Table 4.10: Odds of Bipolar Spectrum Disorders Associated with Cannabis use Propensities among those aged 18 to 45 with and without Substance Use Disorder Histories

Cannabis Use Propensities	Odds Bipolar Spectrum Disorders at Wave 2 ^a			
	N	OR	95% CI	P-value
With No Substance Use Disorder History at Baseline ^b				
Ever Used	9920	0.57	0.21 – 1.55	.27
Past 12 months ^c	9929	1.63	1.33 – 2.00	<.001
>= 1 use/week past 12 months ^c	9929	1.54	1.26 – 1.88	<.001
With a Substance Use Disorder History at Baseline ^d				
Ever Used	6361	0.76	0.16 – 3.62	.72
Past 12 months ^c	6362	1.26	1.03 – 1.56	.03
>= 1 use/week past 12 months ^c	6362	1.21	0.97 – 1.50	.09

^a Excluding any wave 1 manic or hypomanic episodes

^b Adjusted for baseline manic or MDE symptoms, gender, education, urbanicity, region, low/no tobacco use, other drug use, family history score, childhood events, psychiatric comorbidities, baseline norms based mental health score

^c Log transformed cannabis use propensity

^d Same as ^b and including alcohol and other drug abuse, dependence, and tobacco dependence

for those in the no reported family history group. Cannabis use propensities are not associated with incident outcomes among those in the lowest or highest median family history groups. Among those with no reported substance use disorders at baseline, propensities for past year and high use in the past year are both significantly associated with bipolar spectrum outcomes (Table 4.10). A significant effect estimate was also found for past year cannabis use propensity for those reporting a lifetime substance use disorder at wave one.

IV C. Comments

NCS-R represents a good choice for an external study to generate a propensity score within the NESARC.¹⁰³ The measures used in the propensity models were the same in both studies and the validation measure, bipolar spectrum disorders were assessed in a similar manner (within the context of some differences seen in Aim 1). The differences between the study populations reasonably account for the differences in the prevalence of exposure reported in the NCS-R and those predicted in the NESARC. The greater proportion of native born and higher income respondents in the NCS-R (Table 4.1), both of whom report ever using cannabis at proportionally higher rates, likely accounts for the lower mean predicted probabilities (prevalence estimates) of cannabis use estimated in the NESARC. The disproportionately higher reporting of cannabis use (lower relative standardized mean differences, Table 4.4) among those with bipolar spectrum disorders at wave 1 in the NESARC points to differential reporting of cannabis use by cross-sectional bipolar spectrum status as compared to the NCS-R external standard.

The improvement in the proportions of the predicted exposure group, compared to reported use, across bipolar spectrum status provides support for these propensity score derived exposure measures as being reasonable proxies for ‘NCS-R-like’ exposures, the goal of the re-classification schemas (Table 4.4). The propensity score derived exposure measures may be reasonable proxies for un-suppressed cannabis use reporting, it still is however an undesired substitute for a well measured exposure with little

misclassification. Absent a well measured exposure with little misclassification propensity score derived measures of exposure represent a reasonable alternative.

The propensity scores as continuous measures point to any past year cannabis use and ≥ 1 use/week of cannabis in the past year as significant risk factors for incident manic and/or hypomanic episodes among those 18 to 45 years of age. Risk associated with propensity for cannabis use in the past year or high use in the past year is concentrated in those at relatively low risk for incident manic outcomes: those with no reported family history and those with no history of substance use disorders. The inefficiencies incurred by introducing cut points for the categorized predicted exposures may explain their lack of replicating this result. Also, inefficiencies in the propensity model themselves may have also contributed (i.e. no substance use/abuse/dependence or family history measures) to the result that propensity for high cannabis use was not a significant risk in the substance use disorder strata (Table 4.10). The significant increased risk for bipolar spectrum disorders seen for past year cannabis use propensities within relatively low risk groups suggests the possibility that those with lower innate risk (i.e. genetic load) may be more susceptible to cannabis exposure and/or said risk maybe more efficiently detected.

IV D. Limitations

The propensity score models only rely on demographic variables and their discrimination characteristics were not ideal. Other non-illicit substance use measures such as tobacco and alcohol use/abuse differed between the surveys preventing their inclusion in the

predictive models of cannabis exposure. The validation standard, NCS-R bipolar spectrum disorders, was not assessed in the exact same manner in both surveys as described in Aim 1. The external data set was only cross-sectional preventing validation of our exposure and outcome in the longitudinal context. Correction for lost to follow-up is incorporated into wave 2 weights and as such can not be directly assessed in the context of our particular exposure and outcome. As in Aim 2 characteristics of the family history score may have influenced risk estimates in the no family history and lowest median family strata.

IV E. Summary of Findings

No risk estimates for categorized predicted exposures were found to be significant among estimates that were significant for reported exposures. However, among adults 18 to 45 years of age with no manic or major depressive symptoms at baseline, past year cannabis use propensity (as a log transformed continuous measure) was associated with incident manic or hypomanic episodes (adj. OR 1.49, 95% CI: 1.10-2.03, $p=.01$). Elevated risk for high cannabis use propensity (≥ 1 use/week in the past year) was also found in this same group (adj. OR 1.33, 95% CI: 1.03-1.72, $p=.03$). Among those with no reported history of depression, alcohol or substance abuse/dependence, or anti-social traits among their first-degree relatives, propensity for past year cannabis use (adj. OR 1.61, 95% CI: 1.11-2.32, $p=.01$) and propensity for ≥ 1 use/week in the past year (adj. OR 1.38, 95% CI: 1.03-1.85, $p=.03$) was associated incident manic or hypomanic episodes. Among those without a substance use disorder history at baseline, propensity for past year

cannabis use (adj. OR 1.63, 95% CI: 1.33-1.55, $p < .001$) and propensity for ≥ 1 use/week in the past year (adj. OR 1.54, 95% CI: 1.26-1.88, $p < .001$) were associated incident manic or hypomanic episodes. Among those with a substance use disorder history at baseline, propensity for past year cannabis use (adj. OR 1.26, 95% CI: 1.03-1.56, $p = .03$) was associated incident manic or hypomanic episodes.

IV F. Conclusions

A sensitivity analysis was conducted that compared predicted cannabis exposure risk estimates for incident bipolar spectrum outcomes to risk estimates based on reported cannabis exposures. Evidence from categorized predicted exposures does not support a significant association ($p < .05$) between cannabis use and bipolar outcomes. However, evidence from the continuous propensity measures is largely in accord with the results from Aim 2. Specifically the evidence supports the conclusion that any or high cannabis use levels in the past year predicts bipolar spectrum disorders in adults age 18 to 45, those with no reported family history and those with a substance use history. The sensitivity analysis provided additional evidence supporting the conclusion that those at low inherent risk for bipolar disorders, namely those without a substance use history, are at increased risk from cannabis exposure. Risk estimates from cannabis use propensities based on an external data source largely support risk estimate based on reported use. Future research in this area will benefit from better exposure measurement.

Chapter V:

V A. Implications

V A. 1 Public use data sets: Caution

Evidence from the first aim of this dissertation supports the use of caution among researcher using public use data sets. Such caution should be applied even more strenuously when such public use data set do not publish algorithms for their constructed variables (e.g. diagnoses) as is true for the NESARC. The publication of such algorithms however does not guarantee that the operationalization of diagnostic criteria is ideal, as was demonstrated with manic and hypomanic episodes in the NCS-R. The current version of the CIDI retains the features described in Aim 1.¹⁰⁴ The latest version of the AUDADIS (AUDADIS-V)¹⁰⁵ still does not explicitly assesses anhedonia and depressed mood within the same mood episode, it dose however ask additional screening questions to those endorsing as few as four major depressive episode symptoms (including anhedonia or depressed mood) before they are skipped out of the major depressive episode section.

V A. 2 Practical considerations from Aim 1

Practical considerations result from the findings of Aim1. Studies with a focus on major depressive episode should consider the implications of symptom assessment when using

NESARC data. The ‘un-assessed’ MDE group of Aim 1 endorsed a total of only five MDE symptoms of which only four are known to be within the same episode. One might be tempted to infer that this group is ‘less severe’ than those with more symptoms mitigating their misclassification. However nearly a quarter of this ‘un-assessed’ group (22.3%, 95% CI: 18.9-25.7) endorsed having thoughts of death or suicide demonstrating that this group misclassification should not be ignored. The finding that very few lifetime major depressive episodes are excluded for bereavement meeting DSM-IV criteria suggests that bereavement related major depressive episodes are not qualitatively different from non-bereavement related episodes. This result is evidence in support of the decision to eliminate the bereavement exclusion in the DSM-V.^{106, 107}

The impact of the assessment of impairment in manic/hypomanic episodes within the AUDADIS should also be considered when using NESARC data. Estimates of Bipolar I prevalence using all of the impairment indices of the AUDADIS are clearly inflated (Table 2.2) compared to a CIDI-type assessment. The shifting of manic episode cases to hypomanic episodes was not a major issue in this dissertation’s analyses of cannabis use risk as bipolar spectrum outcomes (manic or hypomanic episodes) were assessed. It should be recognized however that the assessment of impairment is difficult and those not endorsing impairment may lack insight. Making the distinction between a manic episode and a hypomanic episode based on self-reports is inherently an imprecise enterprise. For instance about a fifth (20.6% 95% CI: 15.1-26.1) of those meeting manic episode criteria in the AUDADIS approach but not in the AUDADIS/CIDI approach

(n=295) endorsed six or more symptoms suggesting they may indeed have been impaired in spite of their failure to endorse any of the impairment measures.

V A. 3 Implications for CIDI

The CIDI operationalization of manic episode impairment criterion would benefit from assessing hospitalization or mental health professional contact before respondents are skipped out. Also the CIDI would be also be improved by flagging those endorsing psychotic/delusional features and collecting complete criterion information on them.

Psychosis is a difficult trait to assess in a population based self-reported symptom setting^{108, 109} it may however be less difficult to attain accurate self-reports of elevated or irritable mood related hospitalization or mental health professional contact. These changes are reasonable to consider as the CIDI transitions from assessing diagnoses according to the DSM-IV to those meeting DSM-V criteria.

Among those 18 to 45 years of age propensity for cannabis use with in the past year and propensity for greater than one use of cannabis per week in the past year are associated with incident manic or hypomanic episodes (Table 4.8). These results are all the more compelling in that all those reporting a week or more of extremely elevated or irritable mood or two weeks or more of anhedonia or depressed mood were excluded from the analyses. Risk from cannabis is concentrated in those aged 26 to 45 with histories of substance use disorders. This result supports a hypothesis that cannabis may precipitate the onset of a bipolar spectrum disorder in those with a demonstrated liability for

substance abuse or dependence.^{48, 49} Future research in this area exploring factors that may further explain this increased risk is needed (i.e. kind, duration and severity of substance use disorders). The result that those aged 18 to 45 reporting no family history suggests that either: 1) those at relatively low risk may be more susceptible to cannabis exposure and/or 2) that the detection of increased risk within a low risk population maybe more efficient. Future population based research also needs to better identify those with genetic risk for bipolar disorders and substance use disorders in order to better identify those most at risk from cannabis exposure.

The results of Aim 2 reported in Chapter 3 need to be considered in the light of the evidence of differential reporting of cannabis use. In Chapter 4 it was found that NESARC respondents on the bipolar spectrum at baseline reported cannabis use less differently from the external standard (lower standardized mean differences) than those not on the bipolar spectrum (Table 4.4). This finding points to those with more psychiatric involvement being more likely to report cannabis use. This is consistent with the observation of Grucza et al⁵⁴ that the prevalence of substance use disorders including cannabis use disorders in the NESARC did not differ from the NSDUH whereas reported cannabis use in the NESARC was half that of the NSDUH (i.e. use not to the level of a substance use disorder was less likely to be reported). If one assumes that cannabis use reporting in the NCS-R is un-biased, the improved cross-sectional association with bipolar spectrum disorders of predicted use compared to reported use serves to provide a measure of validation for the propensity models as reasonable proxies for un-biased

cannabis use reporting. The risk estimates based on the propensity scores represent the best metric to assess whether cannabis use is a significant risk factor for bipolar spectrum disorders absent well measured exposures; as the propensity scores are not burdened with the added inefficiencies of cut-points that the categorized predicted exposure introduces. The assumption that cannabis use reporting in the NCS-R has low misclassification however may not be a reasonable one. The validity of risk estimates in this dissertation may be undermined by under-reporting of both cannabis exposure and other illicit substances that may confound the relationship between cannabis and bipolar disorder. Reasonable efforts were made to address cannabis under-reporting though the use of external cannabis propensity scores but potential uncontrolled confounding introduced by other illicit substance use under-reporting remains.

Future population based research on cannabis needs to find approaches to address the issue of illicit drug use under-reporting. It may be that using federal government employee should not be the first choice when recruiting those to conduct face-to-face interviews. The true gold standard for cannabis exposure is a biological measure of exposure. However those reluctant to accurately report their cannabis use may be equally reluctant to participate in research where biological samples are collected and tested for the metabolites of illegal substances. Future studies should consider the use of anonymous reporting approaches such as computerized self-administration and the use of Certificates of Confidentiality. Certificates of Confidentiality allow investigators to refuse to disclose information on research participants in any criminal, civil,

administrative, legislative, or other proceeding, whether at the local level, state, or federal level.¹¹⁰ This may make participants feel more at ease about disclosing illegal activities including the use of illicit substances such as cannabis, knowing that such disclosures are unlikely to put them in legal if not social jeopardy.

V B. Conclusion

Consumers of public use study data need to recognize possible deficiencies that may unfortunately be found in these important resources. In the data sets used in this dissertation a considerable proportion of those meeting or with a high likelihood of meeting DSM mood disorder criteria are not being identified and/or assessed appropriately. Future survey instruments need to validate that their operationalization of diagnostic criteria does not violate criterion structure.

Evidence is found that self-reported or propensity for any or elevated cannabis use in the past year is associated with incident manic or hypomanic episodes within sub-populations in a nationally representative sample. Risk from cannabis is concentrated in those aged 26 to 45 with histories of substance use disorders, a result consistent with observations in clinical manic cohorts. A novel finding of this dissertation is that cannabis use propensity risk is also concentrated in those at inherently low risk for incident bipolar outcomes via family history characteristics and not having a history of a substance use disorder. This result merits further investigation with improved measures of underlying risk. The use of self-reported cannabis use is a weakness in this dissertation. Future

studies should employ biological measures of exposure, anonymous reporting and/or Certificates of Confidentiality to improve measures of cannabis and other illicit substance use.

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Appendix A: Page 1

Revised NCSR algorithm for Bipolar Spectrum

We re-calibrated bipolar disorder using our clinical data in the United States and significantly improved the concordance of the CIDI and the SCID (validity statistics are attached). To do this we worked with several experts in the bipolar field. They told us that the cidi was over-estimating bipolar I disorder. Therefore we went back to the raw data and looked for patterns in the data to arrive at new, more restrictive definitions of bipolar I, II, and created a new variable called bipolar sub-threshold. We tested these new definitions by using the validity statistics to see how well these did in predicting the clinical dx in the clinical sample. The best definition was as follows:

WMH CAPI

Manic Episode(Old Version) – DSM-IV Criteria(DSM_MAN_OLD)

A. Part 1 AND Part 2

Part 1. A distinct period of abnormally and persistently elevated, expansive, or irritable mood.

SC24 = Yes(1) OR SC25a = Yes(1)

Part 2. A distinct period of abnormally and persistently elevated, expansive, or irritable mood lasting at least 1 week(or any duration if hospitalization is necessary).

(M3b >= 1 week) OR (M3d >= 1 week) OR (M6b >= 1 week) OR (M6d >= 1week) OR
(0 < M20 < 998)OR (M22 >= 1 week) OR M48 is Yes(1)

B. During the mood disturbance, three(or more) of the following symptoms have persisted(four if the mood is only irritable) and have been present to a significant degree:

Mood is only irritable: SC25a is Yes(1) and (SC24 is NOT Yes(1))

1. inflated self-esteem or grandiosity

M7n is Yes(1) OR M7o is Yes(1)

2. decreased need for sleep(e.g., feels rested after only 3 hours of sleep)

M7j is Yes(1)

3. more talkative than usual or pressure to keep talking

M7f is Yes(1)

4. flight of ideas or subjective experience that thoughts are racing

M7i is Yes(1)

5. distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli)

M7g is Yes(1) OR M7h is Yes(1)

6. increase in goal-oriented activity(either socially, at work or school, or sexually) or psychomotor agitation.

M7a is Yes(1) OR M7b is Yes(1) OR M7c is Yes(1) OR M7e is Yes(1)

7. excessive involvement in pleasurable activities that have a high potential for painful consequences(e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments)

M7k is Yes(1) OR M7l is Yes(1) OR M7m is Yes(1)

Appendix A: Page 2

WMH CAPI

Manic Episode(Old Version) – DSM-IV Criteria(DSM_MAN_OLD)

C. The symptoms do not meet criteria for a Mixed Episode

Not Operationalized

D. Part 1 OR Part 2 OR Part 3

Part 1. The mood disturbance is sufficiently severe to cause marked impairment in occupational functioning or in usual social activities or relationships with others.

M9 is (4,5) OR M9a is (1,2) OR (at least 1 of M27a-M2d is between 7 and 10) OR
(5 <= M29 < 365) OR M33 is Yes(1)

Part 2. The mood disturbance is sufficiently severe to necessitate hospitalization to prevent harm to self.

M48 is Yes(1)

Part 3. There are psychotic features

M7o is Yes(1)

E. The symptoms are not due to the direct physiological effects of a substance(e.g., a drug of abuse, a medication, or other treatment) or a general medical condition (e.g. hyperthyroidism)

NOT(M10b is Yes(1)) AND M10a is(1,5,8,9)

NOTE: M10b is used as an initial screener only. All open ended items are reviewed by a clinician to determine organic exclusion.

WMH CAPI Bipolar I Old

DSM_MAN_OLD is Yes(1)

Appendix A: Page 3

WMH CAPI

Hypomanic Episode(Old version) – DSM-IV Criteria(DSM_HYP_OLD)

A. Part 1 AND Part 2

Part 1. A distinct period of abnormally and persistently elevated, expansive, or irritable mood.

SC24 is Yes(1) OR SC25a is Yes(1)

Part 2. A distinct period of abnormally and persistently elevated, expansive, or irritable mood lasting at least 4 days, that is clearly different from the usual nondepressed mood.

SC24 is Yes(1) OR (M3b \geq 4 days) OR (M3d \geq 4 days) OR (M6b \geq 4 days) OR (M6d \geq 4 days)
OR
(0 < M20 < 998) OR (M22 \geq 4 days)

B. During the mood disturbance, three(or more) of the following symptoms have persisted(four if the mood is only irritable) and have been present to a significant degree:

Mood is only irritable: SC25a is Yes(1) and (SC24 is NOT Yes(1))

1. inflated self-esteem or grandiosity

M7n is Yes(1) OR M7o is Yes(1)

2. decreased need for sleep(e.g., feels rested after only 3 hours of sleep)

M7j is Yes(1)

3. more talkative than usual or pressure to keep talking

M7f is Yes(1)

4. flight of ideas or subjective experience that thoughts are racing

M7i is Yes(1)

5. distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli)

M7g is Yes(1) OR M7h is Yes(1)

6. increase in goal-oriented activity(either socially, at work or school, or sexually) or psychomotor agitation.

M7a is Yes(1) OR M7b is Yes(1) OR M7c is Yes(1) OR M7e is Yes(1)

7. excessive involvement in pleasurable activities that have a high potential for painful consequences(e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments)

M7k is Yes(1) OR M7l is Yes(1) OR M7m is Yes(1)

C. The episode is associated with an unequivocal change in functioning that is uncharacteristic of the person when not symptomatic.

M9 is (3,4,5) OR M9a is (1,2,3) OR (at least 1 of M27a-M2d is between 4 and 10) OR
($2 \leq M29 \leq 365$) OR M33 is Yes(1).

D. The disturbance in mood and the change in functioning are observable by others.

Not Operationalized

Appendix A: Page 4

WMH CAPI

Hypomanic Episode(Old version) – DSM-IV Criteria(DSM_HYP_OLD)

E. Part 1 AND Part 2 AND Part 3.

Note: By strict DSM criteria, those people who meet all criteria for mania but have a duration of 4 to 6 days without hospitalization are excluded from a diagnosis of hypomania. (See mania criterion A,D and hypomania criterion E). We have defined these people as meeting hypomania. This is implemented by suppressing Criterion E for those with a duration of 4 to 6 days and without hospitalization.

Part 1. The mood disturbance is not severe enough to cause marked impairment in occupational functioning or in usual social activities or relationships with others.

NOT (M9 is (4,5) OR M9a is (1,2) OR (at least 1 of M27a-M27d is between 7 and 10) OR
(5 <= M29 < 365) OR M33 is Yes(1))

Part 2. The mood disturbance is not severe enough to necessitate hospitalization to prevent harm to self.

M48 is No(5)

Part 3. There are no psychotic features

M7o is No(5)

F. The symptoms are not due to the direct physiological effects of a substance(e.g., a drug of abuse, a medication, or other treatment) or a general medical condition (e.g. hyperthyroidism)

NOT(M10b is Yes(1) AND M10a is(1,5,8,9))

NOTE: M10b is used as an initial screener only. All open ended items are reviewed by a clinician to determine organic exclusion.

Appendix A: Page 5**WMH CAPI Bipolar II Old**

A. Presence (or history) of one or more Major Depressive Episodes

dsm_mde is Yes(1)

B. Presence (or history) of at least one Hypomanic Episode

dsm_hyp_old is Yes(1)

C. There has never been a Manic Episode or Mixed Episode

dsm_man_old is NOT Yes(1)

E. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

M9 is (3,4,5) OR M9a is (1,2,3) OR (at least 1 of M27a-M2d is between 4 and 10) OR (5 <= M29 <= 365) OR M33 is Yes(1)

Appendix A: Page 6

WMH CAPI

Recalibrated Bipolar I/II/Sub, Mania, Hypomania, Sub-Hypomania

Bipolar I

dsm_man_old is Yes (1) AND at least 6 symptoms in the M7 series(DSM_MAN_OLD Criteria B1-B7) AND at least two of the following symptoms: M7b, M7c, M7k, M7l, M7o is 1(yes)

Bipolar II

NOT Bipolar I AND

(Bipolar I Old is Yes (1) AND dsm_mde = 1 AND M1 = 1 AND M7i = 1)

Note: These are the people who meet criteria for our old bipolar I definition (mania) but no longer meet criteria with the new definition, and have a major depressive episode and euphoria and racing thoughts

OR

(Bipolar II Old is Yes(1) AND

(M3b >= 14 days OR M3d >= 14 days OR M6b >= 14 days OR M6d >= 14 days or M20 >= 14 days OR M22 >= 14 days) AND

at least 2 of the following symptoms (M7b,M7c,M7k,M7l,M7o))

Note: This is our old definition of bipolar II (in *italicized* text) tightened up to include a duration of at least 14 days and at least 2 of the “super” symptoms in terms of concordance

Bipolar Sub

Note: anyone left with old mania/hypomania who did not meet criteria for bipolar I and bipolar II above

Not Bipolar I or Bipolar II as defined above AND (dsm_man_old is Yes(1) OR dsm_hyp_old is Yes(1))

Mania (dsm_man)


Bipolar I is Yes(1)

Hypomania (dsm_hyp)

Bipolar II is Yes(1) OR (Bipolar Sub is Yes(1) AND dsm_man_old is Yes(1))

Sub-Hypomania (dsm_hypsub)

Bipolar Sub is Yes(1) AND (Bipolar II Old is Yes(1) OR dsm_hyp_old is Yes(1))


Appendix B:		Section 5 - HIGH MOOD	
 Statement		Now I'd like to ask you about OTHER moods and related experiences you may have had.	
1.	In your ENTIRE LIFE, have you ever had a time lasting at least 1 week when you felt so extremely excited, elated or hyper that other people thought you weren't your normal self?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No	
2.	In your ENTIRE LIFE, have you ever had a time lasting at least 1 week when you felt so extremely excited, elated or hyper that other people were concerned about you?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No	
3.	In your ENTIRE LIFE, have you ever had a time lasting at least 1 week when you were so irritable or easily annoyed that you would shout at people, throw or break things, or start fights or arguments?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No	
CHECK ITEM 5.1	Is at least 1 item marked "Yes" in 1 - 3?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No - <i>SKIP to Section 6, page 82</i>	
6a. The next few questions are about experiences many people have had when they felt extremely (excited, elated or hyper/irritable or easily annoyed). During that time when (you were the most excited, elated or hyper/you felt the most irritable or easily annoyed), did you . . . (<i>Repeat entire phrase frequently</i>)		b.	
(1)	Need much less sleep than usual?	1 <input type="checkbox"/> Yes - <i>Mark Box E1</i> 2 <input type="checkbox"/> No - <i>Go to next experience</i>	Box 1 <input type="checkbox"/> E1
(2)	Find you were more talkative than usual?	1 <input type="checkbox"/> Yes - <i>Mark Box E2</i> 2 <input type="checkbox"/> No - <i>Go to next experience</i>	Box 1 <input type="checkbox"/> E2
(3)	Talk so fast that people had trouble understanding you or couldn't get a word in edgewise?	1 <input type="checkbox"/> Yes - <i>Mark Box E2</i> 2 <input type="checkbox"/> No - <i>Go to next experience</i>	
(4)	Have trouble concentrating because little things going on around you easily got you off track?	1 <input type="checkbox"/> Yes - <i>Mark Box E3</i> 2 <input type="checkbox"/> No - <i>Go to next experience</i>	Box 1 <input type="checkbox"/> E3
(5)	Find that your thoughts raced so fast that you couldn't keep track of them?	1 <input type="checkbox"/> Yes - <i>Mark Box E4</i> 2 <input type="checkbox"/> No - <i>Go to next experience</i>	Box 1 <input type="checkbox"/> E4
(6)	Find that your thoughts raced so fast that it was hard to follow your own thoughts?	1 <input type="checkbox"/> Yes - <i>Mark Box E4</i> 2 <input type="checkbox"/> No - <i>Go to next experience</i>	
(7)	Feel so restless that you fidgeted, paced, or couldn't sit still?	1 <input type="checkbox"/> Yes - <i>Mark Box E5</i> 2 <input type="checkbox"/> No - <i>Go to next experience</i>	Box 1 <input type="checkbox"/> E5
(8)	Become more active than usual, at work, at home, or in pursuing other interests?	1 <input type="checkbox"/> Yes - <i>Mark Box E5</i> 2 <input type="checkbox"/> No - <i>Go to next experience</i>	
(9)	Become more sexually active than usual or have sex with people you normally wouldn't be interested in?	1 <input type="checkbox"/> Yes - <i>Mark Box E5</i> 2 <input type="checkbox"/> No - <i>Go to next experience</i>	
(10)	Become so physically restless that it made you uncomfortable?	1 <input type="checkbox"/> Yes - <i>Mark Box E5</i> 2 <input type="checkbox"/> No - <i>Go to next experience, page 77</i>	

Section 5 - HIGH MOOD (Continued)	
10a. How old were you the MOST RECENT time when you felt extremely (excited, elated or hyper/irritable or easily annoyed) and you also had some of those other experiences?	____ Age
CHECK ITEM 5.6A Is respondent's age in 10a within 1 year of his/her present age or is present age or 10a unknown?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No - <i>SKIP to 11a</i>
10b. Did this MOST RECENT time BEGIN to happen during the last 12 months?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No
11a. How long did this MOST RECENT time last when you felt extremely (excited, elated or hyper/irritable or easily annoyed)? <i>(Must be at least 1 week)</i>	____ Week(s) OR ____ Month(s) OR ____ Year(s)
b. Since this MOST RECENT time BEGAN, have there been at least 2 months when your mood was back to normal AND you DIDN'T have ANY of the OTHER experiences you mentioned?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No - <i>SKIP to 11d</i>
CHECK ITEM 5.6B Is 10b marked "Yes"?	1 <input type="checkbox"/> Yes - <i>SKIP to 11d</i> 2 <input type="checkbox"/> No
11c. Did this MOST RECENT time when your mood was back to normal BEGIN to happen in the last 12 months?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No
d. In your ENTIRE LIFE, what was the LONGEST time that you've had when you felt extremely (excited, elated or hyper/irritable or easily annoyed)? <i>(Must be at least 1 week)</i>	____ Week(s) OR ____ Month(s) OR ____ Year(s) } <i>SKIP to Check Item 5.7</i>
e. How long did that time last when you felt extremely (excited, elated or hyper/irritable or easily annoyed)? <i>(Must be at least 1 week)</i>	____ Week(s) OR ____ Month(s) OR ____ Year(s)
f. Since that time BEGAN, have there been at least 2 months when your mood was back to normal AND you DIDN'T have ANY of the OTHER experiences that you mentioned?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No - <i>SKIP to Check Item 5.7</i>
CHECK ITEM 5.6C Is 8c marked "Yes"?	1 <input type="checkbox"/> Yes - <i>SKIP to Check Item 5.7</i> 2 <input type="checkbox"/> No
11g. Did this time when your mood was back to normal BEGIN to happen in the last 12 months?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No
CHECK ITEM 5.7 Refer to Check Item 2.0, Section 2A, page 9. Is respondent a lifetime abstainer of alcohol?	1 <input type="checkbox"/> Yes - <i>SKIP to 14</i> 2 <input type="checkbox"/> No
12. Did (that time/ANY of those times) when you felt extremely (excited, elated or hyper/irritable or easily annoyed) BEGIN to happen AFTER you were drinking heavily or a lot more than usual?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No - <i>SKIP to 14</i>
13. Did (that time/ANY of those times) when you felt extremely (excited, elated or hyper/irritable or easily annoyed) BEGIN to happen DURING a period when you were experiencing the bad aftereffects of drinking?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No
14. Did (that time/ANY of those times) when you felt extremely (excited, elated or hyper/irritable or easily annoyed) BEGIN to happen AFTER using a medicine or drug?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No - <i>SKIP to Check Item 5.8</i>
15. Did (that time/ANY of those times) when you felt extremely (excited, elated or hyper/irritable or easily annoyed) BEGIN to happen DURING a period when you were experiencing the bad aftereffects of a medicine or drug?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No
CHECK ITEM 5.8 Is at least 1 item marked "Yes" in 12, 13, 14 OR 15?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No - <i>SKIP to 17, page 80</i>
CHECK ITEM 5.9 Is Check Item 5.5 marked "No"?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No - <i>SKIP to Check Item 5.10A, page 79</i>

Section 5 - HIGH MOOD (Continued)	
16a. During that time, did you STOP (drinking heavily/using any medicines or drugs/experiencing the bad aftereffects of drinking/medicines or drugs) for at least 1 month?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No - <i>SKIP to 17, page 80</i>
b. Did you CONTINUE to feel extremely (excited, elated or hyper/irritable or easily annoyed) for at least 1 month AFTER you STOPPED (drinking heavily/using any medicines or drugs/experiencing the bad aftereffects of drinking/medicines or drugs)?	1 <input type="checkbox"/> Yes } <i>SKIP to 17, page 80</i> 2 <input type="checkbox"/> No }
CHECK ITEM 5.10A Is 8c marked "Yes" or 10b marked "Yes" or 11c marked "Yes" or 11b marked "No"?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No - <i>SKIP to Check Item 5.10B</i>
16c. Did ANY of the times when you felt extremely (excited, elated or hyper/irritable or easily annoyed) in the last 12 months BEGIN to happen (after drinking heavily/using a medicine or drug/when you were experiencing the bad aftereffects of drinking/medicines or drugs)?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No - <i>SKIP to Check Item 5.10B</i>
d. Did they ALL BEGIN to happen (after drinking heavily/using a medicine or drug/when you were experiencing the bad aftereffects of drinking/medicines or drugs)?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No
e. During ANY of those times in the last 12 months when you felt extremely (excited, elated or hyper/irritable or easily annoyed) after (drinking heavily/using a medicine or drug), did you STOP (drinking heavily/using any medicines or drugs/ experiencing the bad aftereffects of drinking/medicines or drugs) for at least 1 month?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No - <i>SKIP to Check Item 5.10B</i>
f. During ALL of those times, did you STOP (drinking heavily/using any medicines or drugs/experiencing the bad aftereffects of drinking/medicines or drugs) for at least 1 month?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No
g. Did you CONTINUE to feel extremely (excited, elated or hyper/irritable or easily annoyed) for at least 1 month AFTER ANY of those times in the last 12 months when you STOPPED (drinking heavily/using any medicines or drugs/experiencing the bad aftereffects of drinking/medicines or drugs)?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No - <i>SKIP to Check Item 5.10B</i>
h. Did you CONTINUE to feel extremely (excited, elated or hyper/irritable or easily annoyed) for at least 1 month after ALL of those times?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No
CHECK ITEM 5.10B Is 8c marked "Yes"?	1 <input type="checkbox"/> Yes - <i>SKIP to 17, page 80</i> 2 <input type="checkbox"/> No
16i. Did ANY of the times when you felt extremely (excited, elated or hyper/irritable or easily annoyed) BEFORE 12 months ago BEGIN to happen (after drinking heavily/using a medicine or drug/when you were experiencing the bad aftereffects of drinking/medicines or drugs)?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No - <i>SKIP to 17, page 80</i>
j. Did they ALL BEGIN to happen (after drinking heavily/using a medicine or drug/when you were experiencing the bad aftereffects of drinking/medicines or drugs)?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No
k. During ANY of those times BEFORE 12 months ago when you felt extremely (excited, elated or hyper/irritable or easily annoyed) after (drinking heavily/using a medicine or drug), did you STOP (drinking heavily/using any medicines or drugs/ experiencing the bad aftereffects of drinking/medicines or drugs) for at least 1 month?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No - <i>SKIP to 17, page 80</i>
l. During ALL of those times, did you STOP (drinking heavily/using any medicines or drugs/experiencing the bad aftereffects of drinking/medicines or drugs) for at least 1 month?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No
m. Did you CONTINUE to feel extremely (excited, elated or hyper/irritable or easily annoyed) for at least 1 month AFTER ANY of those times BEFORE 12 months ago when you STOPPED (drinking heavily/using any medicines or drugs/experiencing the bad aftereffects of drinking/medicines or drugs)?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No - <i>SKIP to 17, page 80</i>

Section 5 - HIGH MOOD (Continued)	
16n. Did you CONTINUE to feel extremely (excited, elated or hyper/irritable or easily annoyed) for at least 1 month after ALL of those times?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No
17. Did you EVER go to any kind of counselor, therapist, doctor, psychologist or any person like that to calm down or feel better when you felt extremely (excited, elated or hyper/irritable or easily annoyed)?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No
18a. Were you a patient in the hospital for at least 1 night because you felt extremely (excited, elated or hyper/irritable or easily annoyed)?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No
b. Did you EVER go to an emergency room for help at any time when you felt extremely (excited, elated or hyper/irritable or easily annoyed)?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No
19. Did a doctor EVER prescribe any medicines or drugs to help you calm down or feel better?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No
CHECK ITEM 5.11 Is at least 1 item marked "Yes" in 17 - 19?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No - <i>SKIP to Check Item 5.11A</i>
20a. About how old were you the FIRST time you went anywhere or saw anyone to get help for feeling extremely (excited, elated or hyper/irritable or easily annoyed)?	_____ Age
b. How old were you the MOST RECENT time you went anywhere or saw anyone to get help for feeling extremely (excited, elated or hyper/irritable or easily annoyed)?	_____ Age OR 0 <input type="checkbox"/> Happened only once
CHECK ITEM 5.11A Refer to Check Item 2.0, Section 2A, page 9. Is the respondent a lifetime abstainer of alcohol?	1 <input type="checkbox"/> Yes - <i>SKIP to Check Item 5.11B</i> 2 <input type="checkbox"/> No
21a. Did you EVER drink alcohol to calm down or to feel better when you felt extremely (excited, elated or hyper/irritable or easily annoyed)?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No - <i>SKIP to Check Item 5.11B</i>
b. Did this happen during the last 12 months?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No - <i>SKIP to Check Item 5.11B</i>
c. Did this happen before 12 months ago, that is, before last (Month one year ago)?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No
CHECK ITEM 5.11B Refer to Check Item 3.10, Section 3B, page 39. Is the respondent a lifetime non-drug user?	1 <input type="checkbox"/> Yes - <i>SKIP to Check Item 5.12</i> 2 <input type="checkbox"/> No
22a. Did you EVER take any medicines or drugs ON YOUR OWN, that is, without a prescription, in greater amounts, or more often or longer than prescribed, to help calm down or feel better when you felt extremely (excited, elated or hyper/irritable or easily annoyed)?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No - <i>SKIP to Check Item 5.12</i>
b. Did this happen during the last 12 months?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No - <i>SKIP to Check Item 5.12</i>
c. Did this happen before 12 months ago, that is, before last (Month one year ago)?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No
CHECK ITEM 5.12 Is Check Item 5.5 marked "No"?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No - <i>SKIP to Check Item 5.13A</i>
23a. Did that time when you felt extremely (excited, elated or hyper/irritable or easily annoyed) BEGIN to happen DURING a time when you were physically ill or getting over being ill?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No - <i>SKIP to 24a, page 81</i>
b. Did a doctor or other health professional tell you that this time was related to your physical illness or medical condition?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No } <i>SKIP to 24a, page 81</i>
CHECK ITEM 5.13A Is 8c marked "Yes" or 10b marked "Yes" or 11c marked "Yes" or 11b marked "No"?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No - <i>SKIP to Check Item 5.13B, page 81</i>

Section 5 - HIGH MOOD (Continued)	
23c. Did ANY of the times when you felt extremely (excited, elated or hyper/irritable or easily annoyed) in the last 12 months BEGIN to happen DURING a time when you were physically ill or getting over being physically ill?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No - <i>SKIP to Check Item 5.13B</i>
d. Did ALL of those times when you felt extremely (excited, elated or hyper/irritable or easily annoyed) in the last 12 months ONLY BEGIN to happen DURING times when you were physically ill or getting over being physically ill?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No - <i>SKIP to 23f</i>
e. Did a doctor or other health professional tell you that ALL of the times like this were related to your physical illness or medical condition?	1 <input type="checkbox"/> Yes - <i>SKIP to Check Item 5.13B</i> 2 <input type="checkbox"/> No
f. Did a doctor or other health professional tell you that ANY of the times like this were related to your physical illness or medical condition?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No
CHECK ITEM 5.13B Is 8c marked "Yes"?	1 <input type="checkbox"/> Yes - <i>SKIP to 24a</i> 2 <input type="checkbox"/> No
23g. Did ANY of the times BEFORE 12 months ago when you felt extremely (excited, elated or hyper/irritable easily annoyed) BEGIN to happen DURING a time when you were physically ill or getting over being physically ill?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No - <i>SKIP to 24a</i>
h. Did ALL of those times BEFORE 12 months ago when you felt extremely (excited, elated or hyper/irritable or easily annoyed) ONLY BEGIN to happen DURING times when you were physically ill or getting over being physically ill?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No - <i>SKIP to 23j</i>
i. Did a doctor or other health professional tell you that ALL of the times like this were related to your physical illness or medical condition?	1 <input type="checkbox"/> Yes - <i>SKIP to 24a</i> 2 <input type="checkbox"/> No
j. Did a doctor or other health professional tell you that ANY of the times like this were related to your physical illness or medical condition?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No
24a. During (that time/ANY of those times) when you felt extremely (excited, elated, or hyper/irritable or easily annoyed), did you ever have a period lasting at least 1 week when you went back and forth between feeling extremely (excited, elated or hyper/irritable or easily annoyed) and feeling sad, blue, depressed or down or not caring about things or enjoying things?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No - <i>SKIP to Section 6, page 82</i>
b. During ALL of those times, did you have periods lasting at least 1 week when you went back and forth between feeling (excited, elated or hyper/irritable or easily annoyed) and feeling sad, blue, depressed or down or not caring about things or enjoying things?	1 <input type="checkbox"/> Yes } <i>Go to Section 6, page 82</i> 2 <input type="checkbox"/> No }

Appendix C:		Section 4A - LOW MOOD I	
Statement I 		Now I'd like to ask you some questions about moods and related experiences that many people have had.	
1.	In your ENTIRE LIFE, have you ever had a time when you felt sad, blue, depressed, or down most of the time for at least 2 weeks?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No	
2.	In your ENTIRE LIFE, have you ever had a time, lasting at least 2 weeks, when you didn't care about the things that you usually cared about, or when you didn't enjoy the things you usually enjoyed?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No	
CHECK ITEM 4.1	Is "Yes" marked in 1 OR 2?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No - SKIP to Section 4B, page 68	
4a.	The next few questions are about experiences many people have had when they (felt sad, blue, depressed, or down/didn't care about things or enjoy things). During that time when (your mood was at it's lowest/you enjoyed or cared the least about things), did you . . . <i>(Repeat entire phrase frequently)</i>		b.
(1)	Lose at least 2 pounds a week for several weeks or at least 10 pounds altogether within a month, other than when you were physically ill or dieting?	1 <input type="checkbox"/> Yes - Mark Box C1 2 <input type="checkbox"/> No - Go to next experience	Box 1 <input type="checkbox"/> C1
(2)	Lose your appetite nearly every day for at least 2 weeks?	1 <input type="checkbox"/> Yes - Mark Box C1 2 <input type="checkbox"/> No - Go to next experience	
(3)	Gain at least 2 pounds a week for several weeks or at least 10 pounds altogether within a month (other than when you were growing or pregnant)?	1 <input type="checkbox"/> Yes - Mark Box C1 2 <input type="checkbox"/> No - Go to next experience	
(4)	Find that you wanted to eat a lot more than usual for no special reason, most days for at least 2 weeks?	1 <input type="checkbox"/> Yes - Mark Box C1 2 <input type="checkbox"/> No - Go to next experience	
(5)	Have trouble falling asleep nearly every day for at least 2 weeks?	1 <input type="checkbox"/> Yes - Mark Box C2 2 <input type="checkbox"/> No - Go to next experience	Box 1 <input type="checkbox"/> C2
(6)	Wake up too early nearly every day for at least 2 weeks?	1 <input type="checkbox"/> Yes - Mark Box C2 2 <input type="checkbox"/> No - Go to next experience	
(7)	Sleep more than usual nearly every day for at least 2 weeks?	1 <input type="checkbox"/> Yes - Mark Box C2 2 <input type="checkbox"/> No - Go to next experience	
(8)	Feel tired nearly all the time or get tired easily most days for at least 2 weeks, even though you weren't doing more than usual?	1 <input type="checkbox"/> Yes - Mark Box C3 2 <input type="checkbox"/> No - Go to next experience, page 62	Box 1 <input type="checkbox"/> C3

Appendix C:		Section 4A - LOW MOOD I (Continued)	
4a. During that time when (your mood was at it's lowest/you enjoyed or cared the least about things), did you . . . <i>(Repeat entire phrase frequently)</i>		b.	
(9) Move or talk MUCH more slowly than usual, most days for at least 2 weeks?	1 <input type="checkbox"/> Yes - <i>Mark Box C4</i> 2 <input type="checkbox"/> No - <i>Go to next experience</i>	Box 1 <input type="checkbox"/> C4	
(10) Become so restless that you fidgeted or paced most of the time for at least 2 weeks?	1 <input type="checkbox"/> Yes - <i>Mark Box C4</i> 2 <input type="checkbox"/> No - <i>Go to next experience</i>		
(11) Become so restless that you felt uncomfortable for at least 2 weeks?	1 <input type="checkbox"/> Yes - <i>Mark Box C4</i> 2 <input type="checkbox"/> No - <i>Go to next experience</i>		
(12) Feel worthless nearly all the time for at least 2 weeks?	1 <input type="checkbox"/> Yes - <i>Mark Box C5</i> 2 <input type="checkbox"/> No - <i>Go to next experience</i>	Box 1 <input type="checkbox"/> C5	
(13) Feel guilty about things you normally wouldn't feel guilty about, most of the time for at least 2 weeks?	1 <input type="checkbox"/> Yes - <i>Mark Box C5</i> 2 <input type="checkbox"/> No - <i>Go to next experience</i>		
(14) Have trouble concentrating or keeping your mind on things, most days for at least 2 weeks?	1 <input type="checkbox"/> Yes - <i>Mark Box C6</i> 2 <input type="checkbox"/> No - <i>Go to next experience</i>	Box 1 <input type="checkbox"/> C6	
(15) Find it harder than usual to make decisions, most of the time for at least 2 weeks?	1 <input type="checkbox"/> Yes - <i>Mark Box C6</i> 2 <input type="checkbox"/> No - <i>Go to next experience</i>		
(16) Attempt suicide?	1 <input type="checkbox"/> Yes - <i>Mark Box C7</i> 2 <input type="checkbox"/> No - <i>Go to next experience</i>	Box 1 <input type="checkbox"/> C7	
(17) Think about committing suicide?	1 <input type="checkbox"/> Yes - <i>Mark Box C7</i> 2 <input type="checkbox"/> No - <i>Go to next experience</i>		
(18) Feel like you wanted to die?	1 <input type="checkbox"/> Yes - <i>Mark Box C7</i> 2 <input type="checkbox"/> No - <i>Go to next experience</i>		
(19) Think a lot about your own death?	1 <input type="checkbox"/> Yes - <i>Mark Box C7</i> 2 <input type="checkbox"/> No - <i>Go to Check Item 4.3</i>		
CHECK ITEM 4.3	Are at least 4 Boxes marked for C1-C7 in column b, pages 61 - 62?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No - <i>SKIP to Section 4B, page 68</i>	
5. Now I'd like to ask you about some other things that might have happened to you during that time when (your mood was at its lowest/you enjoyed or cared the least about things) for at least 2 weeks and you had some of the other experiences you mentioned at the same time. During that time...			
(1) Were you uncomfortable or upset by your low mood or any of these other experiences?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No		
(2) Did you have arguments or friction with friends, family, people at work or anyone else?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No		
(3) Were you very troubled because of the way you felt at that time or did you often wish you could get better?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No		

Appendix C: Section 4A - LOW MOOD I (Continued)	
5. During that time when (your mood was at its lowest/you enjoyed or cared the least about things)...	
(4) Did you have any trouble doing things you were supposed to do - like working, doing your schoolwork, or taking care of your home or family?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No
(5) During that time, did you spend more time than usual by yourself, because you didn't want to be around people as much as usual?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No
(6) Did you find you couldn't do the things you usually did or wanted to do?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No
(7) Did you find you did a lot less than usual or were less active?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No
(8) Did you depend a lot more on people to take care of every day things for you or to give you a lot of reassurance or attention?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No
6a. About how old were you the FIRST time you BEGAN (to feel sad, blue, depressed or down/not to care about things or enjoy things) for at least 2 weeks and when you also had some of the other experiences you just mentioned? <i>Refer to other experiences marked "Yes" in 4a(1)-(19) and 5(1)-(8), pages 61 - 63, if necessary.</i>	_____ Age
CHECK ITEM 4.4 Is respondent's age in 6a within 1 year of his/her present age or is present age or 6a unknown?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No - SKIP to 7
6b. Did this FIRST time BEGIN to happen during the last 12 months?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No
7. In your ENTIRE LIFE, how many SEPARATE times lasting at least 2 weeks were there when you (felt sad, blue, depressed, or down/didn't care about things or enjoy things) and when you also had some of the other experiences you mentioned? By separate times, I mean times separated by at least 2 months when your mood was much improved or back to normal and you DIDN'T have ANY of the other experiences you mentioned.	_____ Number
CHECK ITEM 4.5 Is number entered in 7, 2 or more or unknown?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No - SKIP to 9e, page 64
8a. How old were you the MOST RECENT time you BEGAN (to feel sad, blue, depressed or down/not to care about things or enjoy things) for at least 2 weeks and when you also had some of these other experiences?	_____ Age
CHECK ITEM 4.6A Is respondent's age in 8a within 1 year of his/her present age or is present age or 8a unknown?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No - SKIP to 9a
8b. Did this MOST RECENT time BEGIN to happen during the last 12 months?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No
9a. How long did this MOST RECENT time last when you (felt sad, blue, depressed or down/didn't care about things or enjoy things)? <i>(Must be at least 2 weeks.)</i>	_____ Week(s) OR _____ Month(s) OR _____ Year(s)
b. Since this MOST RECENT time BEGAN, have there been at least 2 months when your mood was much improved or back to normal AND when you DIDN'T have ANY of the OTHER experiences you mentioned?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No - SKIP 9d
CHECK ITEM 4.6B Is "Yes" marked in 8b?	1 <input type="checkbox"/> Yes - SKIP to 9d 2 <input type="checkbox"/> No
9c. Did this MOST RECENT time when your mood was much improved BEGIN to happen in the last 12 months?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No
d. In your ENTIRE LIFE, what was the LONGEST time that you've had when you (felt sad, blue, depressed, or down/didn't care about things or enjoy things)? <i>(Must be at least 2 weeks.)</i>	_____ Week(s) OR _____ Month(s) OR _____ Year(s) } SKIP to Check Item 4.7, page 64

Appendix C:		Section 4A - LOW MOOD I (Continued)	
9e.	How long did that time last when you (felt sad, blue, depressed or down/didn't care about things or enjoy things)? <i>(Must be at least 2 weeks.)</i>	____ Week(s) OR ____ Month(s) OR ____ Year(s)	
f.	Since that time BEGAN, have there been at least 2 months when your mood was much improved or back to normal AND you DIDN'T have ANY of the OTHER experiences you mentioned?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No - SKIP to Check Item 4.7	
CHECK ITEM 4.6C	Is "Yes" marked in 6b?	1 <input type="checkbox"/> Yes - SKIP to Check Item 4.7 2 <input type="checkbox"/> No	
9g.	Did this time when your mood was much improved BEGIN to happen in the last 12 months?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No	
CHECK ITEM 4.7	Is Check Item 4.5 marked "No"?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No - SKIP to Check Item 4.8A	
CHECK ITEM 4.8	Is number marked in 9e, 2 months or more or is Follow-up probe 9ep coded "Yes"?	1 <input type="checkbox"/> Yes - SKIP to Check Item 4.10 2 <input type="checkbox"/> No	
10a.	Did that time when you (felt sad, blue, depressed or down/didn't care about things or enjoy things) BEGIN to happen just after someone close to you died?	1 <input type="checkbox"/> Yes } 2 <input type="checkbox"/> No } SKIP to Check Item 4.10	
CHECK ITEM 4.8A	Is number in 9d, less than 2 months or is Follow-up probe 9dp coded "No"?	1 <input type="checkbox"/> Yes - SKIP to Check Item 4.9A 2 <input type="checkbox"/> No	
10b.	Did ALL of those times when you (felt sad, blue, depressed or down/didn't care about things or enjoy things) last for at least 2 months?	1 <input type="checkbox"/> Yes - SKIP to Check Item 4.10 2 <input type="checkbox"/> No	
CHECK ITEM 4.9A	Is 6b marked "Yes" or 8b marked "Yes" or 9c marked "Yes" or 9b marked "No"?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No - SKIP to Check Item 4.9B	
10c.	Think about the times in the last 12 months when you (felt sad, blue, depressed or down/didn't care about things or enjoy things) for LESS than 2 months. Did ANY of those times BEGIN to happen just after someone close to you died?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No - SKIP to Check Item 4.9B 0 <input type="checkbox"/> No times lasting less than 2 months in the past 12 months - SKIP to Check Item 4.9B	
d.	Did ALL of those times ONLY BEGIN to happen just after someone close to you died?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No	
CHECK ITEM 4.9B	Is 6b marked "Yes"?	1 <input type="checkbox"/> Yes - SKIP to Check Item 4.10 2 <input type="checkbox"/> No	
10e.	Think about the times BEFORE 12 months ago when you (felt sad, blue, depressed or down/didn't care about things or enjoy things) for LESS than 2 months. Did ANY of those times BEGIN to happen just after someone close to you died?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No - SKIP to Check Item 4.10 0 <input type="checkbox"/> No times lasting less than 2 months before 12 months ago - SKIP to Check Item 4.10	
f.	Did ALL of those times ONLY BEGIN to happen just after someone close to you died?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No	
CHECK ITEM 4.10	Refer to Check Item 2.0, Section 2A, page 9. Is the respondent a lifetime abstainer of alcohol?	1 <input type="checkbox"/> Yes - SKIP to 13 2 <input type="checkbox"/> No	
11.	Did (that time/ANY of those times) when you (felt sad, blue, depressed or down/didn't care about things or enjoy things) BEGIN to happen AFTER you were drinking heavily or a lot more than usual?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No - SKIP to 13	
12.	Did (that time/ANY of those times) when you (felt sad, blue, depressed or down/didn't care about things or enjoy things) BEGIN to happen DURING a period when you were experiencing the bad aftereffects of drinking?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No	
13.	Did (that time/ANY of those times) when you (felt sad, blue, depressed or down/didn't care about things or enjoy things) BEGIN to happen AFTER using a medicine or drug?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No - SKIP to Check Item 4.11, page 65	

Appendix C:		Section 4A - LOW MOOD I (Continued)	
14.	Did (that time/ANY of those times) when you (felt sad, blue, depressed or down/didn't care about things or enjoy things) BEGIN to happen DURING a period when you were experiencing the bad aftereffects of a medicine or drug?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No	
CHECK ITEM 4.11	Is at least 1 item marked "Yes" in 11, 12, 13 OR 14?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No - <i>SKIP to 16, page 66</i>	
CHECK ITEM 4.12	Is Check Item 4.5 marked "No"?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No - <i>SKIP to Check Item 4.13A</i>	
15a.	During that time, did you STOP (drinking heavily/using any medicines or drugs/experiencing the bad aftereffects of drinking/medicines or drugs) for at least 1 month?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No - <i>SKIP to 16, page 66</i>	
b.	Did you CONTINUE (to feel sad, blue, depressed or down/not to care about things or enjoy things) for at least 1 month AFTER you STOPPED (drinking heavily/using any medicines or drugs/experiencing the bad aftereffects of drinking/medicines or drugs)?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No } <i>SKIP to 16, page 66</i>	
CHECK ITEM 4.13A	Is 6b marked "Yes" or 8b marked "Yes" or 9c marked "Yes" or 9b marked "No"?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No - <i>SKIP to Check Item 4.13B</i>	
15c.	Did ANY of the times when you (felt sad, blue, depressed or down/didn't care about things or enjoy things) in the last 12 months BEGIN to happen (after drinking heavily/using a medicine or drug/when you were experiencing the bad aftereffects of drinking/medicines or drugs)?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No - <i>SKIP to Check Item 4.13B</i>	
d.	Did they ALL BEGIN to happen (after drinking heavily/using a medicine or drug/when you were experiencing the bad aftereffects of drinking/medicines or drugs)?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No	
e.	During ANY of those times in the last 12 months when you (felt sad, blue, depressed or down/didn't care about things or enjoy things) (after drinking heavily/using a medicine or drug), did you STOP (drinking heavily/using any medicines or drugs/ experiencing the bad aftereffects of drinking/medicines or drugs) for at least 1 month?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No - <i>SKIP to Check Item 4.13B</i>	
f.	During ALL of those times, did you STOP (drinking heavily/using any medicines or drugs/experiencing the bad aftereffects of drinking/medicines or drugs) for at least 1 month?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No	
g.	Did you CONTINUE (to feel sad, blue, depressed or down/not to care about things or enjoy things) for at least 1 month AFTER ANY of those times in the last 12 months when you STOPPED (drinking heavily/using any medicines or drugs/experiencing the bad aftereffects of drinking/medicines or drugs)?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No - <i>SKIP to Check Item 4.13B</i>	
h.	Did you CONTINUE (to feel sad, blue, depressed or down/not to care about things or enjoy things) for at least 1 month AFTER ALL of those times?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No	
CHECK ITEM 4.13B	Is 6b marked "Yes"?	1 <input type="checkbox"/> Yes - <i>SKIP to 16, page 66</i> 2 <input type="checkbox"/> No	
15i.	Did ANY of the times when you (felt sad, blue, depressed or down/didn't care about things or enjoy things) BEFORE 12 months ago BEGIN to happen (after drinking heavily/using a medicine or drug/when you were experiencing the bad aftereffects of drinking/medicines or drugs)?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No - <i>SKIP to 16, page 66</i>	
j.	Did they ALL BEGIN to happen (after drinking heavily/using a medicine or drug/when you were experiencing the bad aftereffects of drinking/medicines or drugs)?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No	
k.	During ANY of those times BEFORE 12 months ago when you (felt sad, blue, depressed or down/didn't care about things or enjoy things) (after drinking heavily/using a medicine or drug) did you STOP (drinking heavily/ using any medicines or drugs/ experiencing the bad aftereffects of drinking/medicines or drugs) for at least 1 month?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No - <i>SKIP to 16, page 66</i>	

Appendix C:		Section 4A - LOW MOOD I (Continued)	
15l.	During ALL of those times, did you STOP (drinking heavily/using any medicines or drugs/experiencing the bad aftereffects of drinking/medicines or drugs) for at least 1 month?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No	
m.	Did you CONTINUE (to feel sad, blue, depressed or down/not to care about things or enjoy things) for at least 1 month AFTER ANY of those times BEFORE 12 months ago when you STOPPED (drinking heavily/using any medicines or drugs/experiencing the bad aftereffects of drinking/medicines or drugs)?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No - SKIP to 16	
n.	Did you CONTINUE (to feel sad, blue, depressed or down/not to care about things or enjoy things) for at least 1 month AFTER ALL of those times?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No	
16.	Did you EVER go to any kind of counselor, therapist, doctor, psychologist or any person like that to help improve your mood or make you feel better?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No	
17a.	Were you a patient in a hospital for at least one night because you (felt sad, blue, depressed or down/didn't care about things or enjoy things)?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No	
b.	Did you EVER go to an emergency room for help during any time when you (felt sad, blue, depressed or down/didn't care about things or enjoy things)?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No	
18.	Did a doctor EVER prescribe any medicines or drugs to improve your mood or to make you feel better?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No	
CHECK ITEM 4.14	Is at least 1 item marked "Yes" in 16-18? Did respondent ever seek help for their low mood?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No - SKIP to Check Item 4.14A	
19a.	About how old were you the FIRST TIME you went anywhere or saw anyone to get help for (feeling sad, blue, depressed or down/not caring about things or enjoying things)?	_____ Age	
b.	How old were you the MOST RECENT time you went anywhere or saw anyone to get help for (feeling sad, blue, depressed or down/not caring about things or enjoying things)?	_____ Age OR 0 <input type="checkbox"/> Happened only once	
CHECK ITEM 4.14A	Refer to Check Item 2.0, Section 2A, page 9. Is respondent a lifetime abstainer of alcohol?	1 <input type="checkbox"/> Yes - SKIP to Check Item 4.14B 2 <input type="checkbox"/> No	
20a.	Did you EVER drink alcohol to improve your mood or to make yourself feel better when you (felt sad, blue, depressed, or down/didn't care about things or enjoy things) for at least two weeks?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No - SKIP to Check Item 4.14B	
b.	Did this happen during the last 12 months?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No - SKIP to Check Item 4.14B	
c.	Did this happen before 12 months ago, that is, before last (Month one year ago)?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No	
CHECK ITEM 4.14B	Refer to Check Item 3.10, Section 3B, page 39. Is respondent a lifetime non-drug user?	1 <input type="checkbox"/> Yes - SKIP to Check Item 4.15, page 67 2 <input type="checkbox"/> No	
21a.	Did you EVER take any medicines or drugs ON YOUR OWN, that is, without a prescription, in greater amounts or more often or longer than prescribed to help improve your mood or to make yourself feel better when you (felt sad, blue, depressed, or down/didn't care about things or enjoy things)?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No - SKIP to Check Item 4.15, page 67	
b.	Did this happen during the last 12 months?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No - SKIP to Check Item 4.15, page 67	

Appendix C: Section 4A - LOW MOOD I (Continued)	
21c. Did this happen before 12 months ago, that is, before last (<i>Month one year ago</i>)?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No
CHECK ITEM 4.15 Is Check Item 4.5 marked "No"?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No - <i>SKIP to Check Item 4.16A</i>
22a. Did that time when you (felt sad, blue, depressed or down/didn't care about things or enjoy things) BEGIN to happen DURING a time when you were physically ill or getting over being physically ill?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No - <i>SKIP to Section 4B, page 68</i>
b. Did a doctor or other health professional tell you that this time was related to your physical illness or medical condition?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No } <i>SKIP to Section 4B, page 68</i>
CHECK ITEM 4.16A Is 6b marked "Yes" or 8b marked "Yes" or 9c marked "Yes" or 9b marked "No"?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No - <i>SKIP to Check Item 4.16B</i>
22c. Did ANY of the times when you (felt sad, blue, depressed or down/didn't care about things or enjoy things) in the last 12 months BEGIN to happen DURING a time when you were physically ill or getting over being physically ill?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No - <i>SKIP to Check Item 4.16B</i>
d. Did ALL of those times when you (felt sad, blue, depressed or down/didn't care about things or enjoy things) in the last 12 months ONLY BEGIN to happen DURING times when you were physically ill or getting over being physically ill?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No - <i>SKIP to 22f</i>
e. Did a doctor or other health professional tell you that ALL the times like this were related to your physical illness or medical condition?	1 <input type="checkbox"/> Yes - <i>SKIP to Check Item 4.16B</i> 2 <input type="checkbox"/> No
f. Did a doctor or other health professional tell you that ANY of the times like this were related to your physical illness or medical condition?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No
CHECK ITEM 4.16B Is 6b marked "Yes"?	1 <input type="checkbox"/> Yes - <i>SKIP to Section 4B, page 68</i> 2 <input type="checkbox"/> No
22g. Did ANY of the times BEFORE 12 months ago when you (felt sad, blue, depressed or down/didn't care about things or enjoy things) BEGIN to happen DURING a time when you were physically ill or getting over being physically ill?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No - <i>SKIP to Section 4B, page 68</i>
h. Did ALL of those times BEFORE 12 months ago when you (felt sad, blue, depressed or down/didn't care about things or enjoy things) ONLY BEGIN to happen DURING times when you were physically ill or getting over being physically ill?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No - <i>SKIP to 22j</i>
i. Did a doctor or other health professional tell you that ALL of the times like this were related to your physical illness or medical condition?	1 <input type="checkbox"/> Yes - <i>SKIP to Section 4B, page 68</i> 2 <input type="checkbox"/> No
j. Did a doctor or other health professional tell you that ANY of the times like this were related to your physical illness or medical condition?	1 <input type="checkbox"/> Yes 2 <input type="checkbox"/> No } <i>Go to Section 4B, page 68</i>

Appendix D: Page 1

WMH CAPI

DSM-IV Major Depressive Episode

A. Five(or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure. **Note: DSM-IV states that children and adolescents may be “irritable rather than sad”. This is not operationalized when examining adults who report symptoms from childhood.**

Part 1 AND Part 2.

Part 1. Symptoms have been present during the same 2 week period and at least one of the symptoms is either(1) depressed mood or (2) loss of interest or pleasure.

(D22b \geq 2 weeks OR D22d \geq 2 weeks OR D39 \geq 2 weeks) AND
(D24a is Yes(1) OR D24b is Yes(1) OR D24c is Yes(1) OR D24d is Yes(1) OR D24e is Yes(1) OR D24f is Yes(1))

Part 2. At least five of the following symptoms must be present and represent a change from previous functioning:

Note: “change from previous functioning” is implicit in the item corresponding to each symptom (e.g. “more than usual”, “less than usual”).

1. depressed mood most of the day, nearly every day, as indicated by either subjective report(e.g., feels sad or empty) or observation made by others.

D24a is Yes(1) OR D24b is Yes(1) OR D24c is Yes(1) OR D24d is Yes(1)

2. markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day(as indicated by either subjective account or observation made by others)

D24e is Yes(1) OR D24f is Yes(1)

3. significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day.

D26a is Yes(1) OR (D26f \geq 10 lbs) OR D26b is Yes(1) OR (D26d \geq 10 lbs)

4. insomnia or hypersomnia nearly every day.

D26g is Yes(1) OR D26h is Yes(1)

5. psychomotor agitation or retardation nearly every day(observable by others, not merely subjective feelings of restlessness or being slowed down).

D26m is Yes(1) OR D26o is Yes(1)

6. fatigue or loss of energy nearly every day.

D26j is Yes(1)

7. feelings of worthlessness or excessive or inappropriate guilt(which may be delusional) nearly every day(not merely self-reproach or guilt about being sick)

D26v is Yes(1)

8. diminished ability to think or concentrate, or indecisiveness, nearly every day(either by subjective account or as observed by others)

D26p is Yes(1) OR D26r is Yes(1) OR D26s is Yes(1)

Appendix D: Page 2**WMH CAPI****DSM-IV Major Depressive Episode**

A. Part 2.

9. recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

D26aa is Yes(1) OR D26bb is Yes(1) OR D26cc is Yes(1) OR D26dd is Yes(1) OR D26ee is Yes(1)

B. The symptoms do not meet criteria for a Mixed Episode

Not operationalized.

C. Part 1 OR Part 2.

Part 1. The symptoms cause clinically significant distress.

D17 is (2,3,4) OR D18 is (1,2) OR D19 is (1,2,3) OR D24b is Yes(1)

Part 2. The symptoms cause clinically significant impairment in social, occupational, or other important areas of functioning.

D28 is (3,4,5) OR D28a is (1,2,3) OR (At least 1 value of D66a-D66d is between 4 and 10)

D. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication), or are not due to a general medical condition. **NOTE: D29b is used as an initial screener only. All open ended items are reviewed by a clinician to determine organic exclusion.**

NOT(D29b is Yes(1)) AND D29a is (1,5,8,9)

E. Part 1 OR Part 2 OR Part 3

Part 1. The symptoms are not better accounted for by Bereavement.

Not operationalized.

Part 2. If the symptoms are associated with bereavement, they persist for longer than two months

Not operationalized

Part 3. If the symptoms are associated with bereavement, they are characterized by (a) marked functional impairment, (b) morbid preoccupation with worthlessness, (c) suicidal ideation, (d) psychotic symptoms, or (e) psychomotor retardation. At least one of a-e must be present.

Not operationalized

NOTE: D23 was deleted from the instrument therefore the bereavement criteria could not be operationalized.