# CONTRIBUTIONS TO THE EPIDEMIOLOGY OF MOOD DISTURBANCES AND HEALTH DISPARITIES RESEARCH

By

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## ABSTRACT

My dissertation research project is centered around the concept of a depression spectrum among adolescents. I employed a study design that was in some ways similar to an epidemiological approach developed by Wade Hampton Frost in the 1930s for tuberculosis (TB) mortality research. My research assessed the experiences of individual birth cohorts, with cross-sectional snapshots that begin when each survivor of a birth cohort reaches the $12^{th}$-$13^{th}$ birthday interval with an end date just before the 18th birthday.

As an extension of our group's prior contributions to depression epidemiology, my dissertation project also examines health disparities in these mood disorder spectrum transitions (e.g., variations across the US Census 'race-ethnicity' subgroups).

The main results of my dissertation can be summarized as follows:

Study 1: In terms of female-to-male variation, studying US nationally representative samples of 12-17-year-olds male and female adolescents, I found a female excess occurrence of the DSM-IV-specified Major Depressive Disorder (MDD) once a Brief Depression Spell had occurred. In estimates for females and males together, among every 100 12-year-olds who experienced BDS, there were roughly five who had transitioned to the MDD experience. The corresponding estimate for 17-year-olds was roughly 40 MDD cases for every set of 100 BDS cases.

Study 2: My results highlight that disparity in adolescent mental health-related ethnic self-identification persists between Non-Hispanic Blacks and Non-Hispanic Whites. Additionally, younger aged Hispanics and non-Hispanic white adolescents were more likely to experience MDE, given a history of BDS.

Study 3: According to my meta-analysis approach, statistically robust and reproducible non-null estimates suggest a general age-associated excess occurrence of Brief Depressive Spells. More recently born cohorts are more likely to become cases of major depressive disorder once a brief depressive spell has already occurred.

For this dissertation, nonparticipation levels and self-reporting might be the most significant measurement issues. Whether recruitment of participants via social media or advertisements will yield increasingly definitive evidence on the epidemiology of mood disturbances is uncertain. The reliance on self-reports in mood disturbances field studies most likely will be a limitation that others will face in the future. It is necessary to ask people about

experiences such as Brief Depression Spells and Depression Syndromes because there now is no alternative to measurement of these facets of the Depression Spectrum.

This dissertation is dedicated to Emmanuel & Annette. I appreciate your continued support, understanding, and most of all love. I am grateful to you both for your dedicated partnership for success in my life.

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## LIST OF ABBREVIATIONS

ACASI - Audio Computer-Assisted Self-Interviewing

BDS – Brief Depressive Spell

CI – Confidence Intervals

DC – District of Columbia

DS – Depression Syndrome

DSM – Diagnostic and Statistical Manual

ESI – Ethnic Self-Identification

FI – Field Interviewer

MDD - Major Depressive Disorder

MDE – Major Depressive Episode

NSDUH – National Surveys on Drug Use and Health

OR – Odds Ratio

SAMHSA - Substance Abuse and Mental Health Services Administration

US – United States

WHO - World Health Organization

# CHAPTER 1 - INTRODUCTION

## 1.0 Overview of the Depression Spectrum Concept and Study Design

An important premise of this dissertation research project on adolescent depression is the concept of a depression spectrum. In the past three decades, Swiss psychiatrists Jules Angst and Barbara Hochstrasser, along with American psychiatric epidemiologist Kathleen Merikangas have published important epidemiologic evidence regarding 'brief depressive mood swings' (BDMS) and 'recurrent brief depression' (RBD) as syndromes that often appear between an adolescent's first 'brief depressive spell' of 1-3 days duration (BDS) and later more serious depressive illnesses in the form of 'Dysthymia,' 'Major Depressive Episode or Disorder' or 'Bipolar Disorder' and 'Manic-Depressive Psychoses.' Most of their evidence is from the longitudinal Zurich Cohort Study, with repeated measurements beginning in 1978 when the cohort participants were age 19 years (e.g., see Merikangas et al., 2003). This study will be discussed in greater detail in Chapter Two of this dissertation research report.

My dissertation research focused on the Brief Depression Spell and its more advanced depression spectrum elaboration. I employed a study design that was in some ways similar to an epidemiological approach developed by Wade Hampton Frost in the 1930s for tuberculosis (TB) mortality research, which is covered in Chapter Two. In brief, Frost developed cross-sectional snapshots of TB mortality for each 10-year interval cohort of births starting in 1880 and observed deaths at successive ages. From his work, the estimated diagonals of the cohort and year-specific tables show the experience of each birth cohort (Frost, 1939).

My research is somewhat more fine-grained in that I consider the experiences of individual birth cohorts, with cross-sectional snapshots that begin when each survivor of a birth cohort reaches the $12^{th}$-$13^{th}$ birthday interval with an end date just before the 18th birthday. To begin, please consider my starting point, with new infants born within a 12-month interval during either 1991 or 1992, who were first sampled and assessed in 2004 at age 12 years. In 2003, a new probability sample of survivors of that same 1991-1992 birth cohort was drawn and assessed for the first time, with no replacement sampling. The same drawing of a new sample (without replacement) from that same 1991-1992 cohort and a first-time assessment was repeated each year until 2009 when the birth cohort survivors were aged 17 years.

As described below in Chapter Three, this process of drawing a new sample without replacement clearly does not yield a person-centered longitudinal study with repeated measures

of individual participants. Rather, it is an epidemiologically based longitudinal study of survivors of each specific birth cohort. Just as Frost derived and studied cohort- and year-specific estimates to characterize the TB mortality experience of each set of cohort survivors across successive years and ages of life, my dissertation research project characterizes the mood disturbance experiences of each set of cohort survivors, year by year and age by age, across the adolescent years from age 12 to age 17. These epidemiological study design features will be made clearer in Chapter Three.

As an extension of our group's prior contributions to depression epidemiology, my dissertation project also examines health disparities in these mood disorder spectrum transitions (e.g., variations across the US Census 'race-ethnicity' subgroups).

1.1 Specific Aims

**Aim 1:** To compare and contrast age-specific epidemiological estimates for female and male adolescents with a prior history of BDS, estimating female-male differences in the post-BDS occurrence of a sustained (two-week) Depression Syndrome (DS), and then to compare and contrast the estimated occurrence of Major Depressive Episode (MDE) and Disorder (MDD) once both BDS+DS have occurred.[1]

**Aim 2.** Among cross-sectionally assessed survivors of each birth cohort, to estimate the age-specific Major Depressive Disorder (MDD) cumulative incidence proportion (CIP) among those survivors for whom there is an observed lifetime history of the Brief Depressive Spell (BDS), with attention to parameter variations across subgroups defined by self-identified Non-Hispanic Whites, Non-Hispanic Blacks, and Hispanic adolescents. This BDS→MDD conditional CIP estimate can be conceptualized as a conditional probability of MDD occurring among adolescents for whom the BDS experience already has occurred.

**Aim 3.** To estimate these same conditional MDD cumulative incidence proportions as experienced by BDS-affected adolescents during recent years of the 21st century in the US using the epidemiological mutoscope approach, conceptualized as an elaboration of Frost's approach. In contrast with the age-specific CIP estimates produced under Aim 2, my Aim 3 estimates are cohort-specific CIP estimates.

[1] My originally stated Aim 1 involves a minor revision. The original statement made it seem as if I might be studying the second occurrence of a Major Depressive Episode (MDE) based on my terminology of the 'next occurrence' of an episode. In this minor revision, I made it clearer that I am estimating how often an initial MDE has occurred after BDS+DS experiences have occurred.

For the rest of this dissertation, I will use these abbreviations across the depression spectrum. BDS is a brief depressive spell (1-3 days). DS is a sustained Depression Syndrome - defined in relation to an interval of at least two weeks duration of BDS-like experiences, but not necessarily with all of the syndrome features required for Major Depressive Episode or Disorder (MDE/MDD). As an elaboration of DS, MDD lasts at least two weeks, during which there is a running together of mood-related disturbances that meet diagnostic criteria specified in the American Psychiatric Association's Diagnostic and Statistical Manual, Fourth Edition (DSM-IV). Please note that DSM-5, the current diagnostic manual, was not published until May 2013, midway through the epidemiological surveys described below. For this reason, the estimates are based on DSM-IV diagnostic criteria for MDE and MDD.

In my dissertation research project, I am going to use the term 'risk factor' as it now is used conventionally in epidemiology research reports. When possible, I will try to draw a distinction between a 'prevalence correlate' (e.g., a mere cross-sectional association), a 'prevalence predictor' (e.g., an over-time predictor of prevalence from one point in time to a subsequent point in time), and a 'suspected causal influence' (e.g., an over-time covariate-adjusted predictor that might well exert a causal influence on an epidemiologically important outcome). To illustrate, when studying female-male variations or ethnicity-associated variations, it will be typical to think about these associations as correlates or predictors, but whether they qualify as causal influences will remain a topic for future research. In this dissertation research project, these covariates clearly are 'suspected' causal influences, but the evidence to demonstrate the causal influence cannot be discerned in this project.

## CHAPTER 2 - BACKGROUND AND SIGNIFICANCE

### 2.0 Overview of this Chapter

In Section 2.1, I will present an overview of the history of depression, mood disturbances, and depression spectrum research. Following that, I will give an overview of published epidemiological evidence organized by the 'five main rubrics of epidemiology' framework that Anthony and Van Etten (1998) advocated for psychiatric epidemiology and that has guided the structuring of literature review chapters over the past two decades. Accordingly, Section 2.2 offers information on depression epidemiology according to a global health perspective, using the rubric of 'Quantity' (How Many Are Affected?). The World Health Organization provides estimates for the global burden of MDD compared to other causes of morbidity and mortality. However, we have no estimates for all depression spectrum conditions, such as from Brief Depressive Spell to Major Depressive Episode/Major Depressive Disorder (MDE/MDD).

Under section 2.3, the topic 'Location' is discussed (Where are affected cases more or less likely to be found?) The topic is organized based on critical characteristics of the place, person, and time. The purpose of this section is not only to draw attention to male-female variations but also to what has been learned about variations across categories in the United States Census Bureau characterized as 'race-ethnicity' and 'mixed races,' which are reflective of a person's family heritage and ethnic self-identification at the time of the assessment. For this reason, in the rest of this dissertation research report, I will use terms such as family heritage and ethnic self-identification (ESI) as well as what the US political science experts call ‘race-ethnicity.’ The notion of race is difficult to sustain in epidemiological research today, even though it still has some meaning in political discourse.

Section 2.4 covers the rubric of ‘Causes’ (What accounts for some population members becoming cases while others are spared?). Behavioral genetics and genome-wide association studies (GWAS) are detailed in this section, with attention to population variability in the behavioral genetics ‘heritability’ estimates that is of some help. While often being extremely definitive, the GWAS method is not always as reliable as we might hope. Some of the leads have not been as replicable as we expected. Other suspected causes are mentioned, but epidemiology has not yet confirmed definitive evidence on the causes of mood disturbances. The topics of the transitions from Brief Depressive Spell (BDS) to Major Depressive Episode (MDE) have not yet been extensively studied under the rubric of 'Causes.' Therefore, this current dissertation project

might prove helpful. It provides estimates that can be used to make future research progress under the heading of causal determinants. In the absence of estimates of the type produced in this dissertation research project, it might not be easy to secure funding for any future, more definitive longitudinal studies on this facet of what causes the progression from BDS to MDE.

Section 2.5 discusses some probable mechanisms of the states and processes that lead to Brief Depressive Spells, onward toward a two-week sustained "Depression syndrome' (DS) involving depressed mood and/or depression-equivalents (e.g., anhedonia), onward towards MDE/MDD, and on into residual disabilities and handicaps and suicide fatality rates, the most prominent of which are suicides. Ultimately, this dissertation research project is intended to shed light on how often BDS experiences are followed by DS and MDE experiences. To that extent, this dissertation research project contributes to epidemiological evidence on this facet of potential pathways leading toward MDE, even though the evidence is based on cross-sectionally appended slices of the experiences across age, plus longitudinal cohort-specific experiences as each 'birth cohort' makes transitions during adolescence, age by age during successive years.

Under Section 2.6, 'Prevention and Control,' I offer a summary of evidence on 'What Can We Do?' Prevention refers to preventing the occurrence of a newly incident case, while control refers to reducing the duration or alleviating residual effects after the occurrence. My dissertation research focuses on the transition from a Brief Depressive Spell to Major Depressive Episode. Therefore, I will concentrate on 'secondary prevention' trial evidence in which the recruited participants already have experienced a Brief Depressive Spell. Consequently, the response variables of interest involve whether the BDS cases develop into cases of MDD with or without intervention, whether pharmacological, cognitive-behavioral, or some other alternative. Initially, the focus of this section will be on systematic reviews concerning these 'secondary prevention' measures. Still, I will also briefly discuss some primary prevention and other aspects of interventions that might eventually affect the BDS-to-MDE transition that is the focus of the dissertation.

Section 2.7 discusses some of the methodology innovations I will employ in my dissertation research. Here are three innovations I will examine. One of the innovations is the use of Bayesian credible intervals. As a comparison, I will present estimates from conventional 'frequentist' meta-analysis approaches and those 95% confidence intervals and estimates from Bayesian meta-analysis approaches with 95% credibility intervals, respectively. I will provide an

initial overview of how it can be worthwhile to compare and contrast these different 'compatibility' intervals within a single study, consistent with recommendations described by Gelman (unpublished essay, 2022; https://statmodeling.stat.columbia.edu/2022/04/05/confidence-intervals-compatability-intervals-uncertainty-intervals/ ).

As part of Section 2.7, I will discuss Frost's study of TB mortality to study the experiences of birth cohorts over time, which I adapted in my research on steps in the BDS-MDD transitions during the adolescent years of development – specifically as 12-year-olds progress and become 17-year-olds. Here I will reiterate that this is not a longitudinal study of individuals, each measured repeatedly over time. Instead, each year and age-specific sample has been drawn without replacement. This approach can be a strength because there is no chance of a reactive measurement that might occur when the same person must complete the same assessment two or more times. I will highlight this strength of the dissertation research design by describing how it is comparable to that of Frost's previous work on TB mortality, which he conducted at Johns Hopkins University as the first professor of epidemiology.

This section also covers my use of Hill function parameter estimates to explore potential differences in BDS-MDD health experiences across several different family heritage and ethnic self-identification subgroups and sexes within the US population as we look across age-specific estimates. The Hill functional analysis originated in toxicological, pharmacological, and pharmacodynamics research on dose-response relationships. In this case, I apply Hill's functional analysis to age-related variations (with increasing age being a substitute for an increasing drug dose) to study four Hill function parameters and ask whether their estimates vary across the subgroups. My dissertation research will have a more significant impact on public health research because I will be able to estimate four Hill function parameters as potential indicators of variations across health disparities subgroups and sexes when typically, only one or two parameters are evaluated in the published literature (e.g., just the prevalence proportions or incidence rates studied across subgroups).

In Section 2.8, I will describe what I believe will ultimately be the 'Significance' of this study if it is successful. I do not anticipate many immediately actionable directions for public health workers. However, the study will be significant in terms of its influence on the field (for example, concerning Bayesian credible intervals to supplement frequentist intervals and the

application of Hill functional analysis). Ultimately it will be the readers of my work who will decide the overall significance of this dissertation research project.

The primary epidemiological estimates in this dissertation research project are referred to as 'cumulative incidence proportions among survivors' (or sometimes 'CIPAS' or 'CIP') estimates. The pioneering epidemiologist Selwyn Collins was the first to estimate these proportions, which he sometimes called 'lifetime attack rates.' It is somewhat likely that this term is an adaptation of 'attack rate' concepts he learned when studying epidemiology at Johns Hopkins University School of Hygiene and Public Health with his epidemiology and biostatistics colleagues Wade Hampton Frost and Lowell Reed. Collins gained access to datasets compiled as part of his work in the US Public Health Service (USPHS), after the USPHS had completed multi-state and multi-site field surveys of the lifetime history of generally communicable disease experiences of school-attending adolescents during the later years of the 'Spanish Flu' Pandemic of 1917-1919. Although he acknowledged that these were not representative samples of any birth cohort due to the relatively high infant mortality rates, he appreciated that they were survey samples of survivors (i.e., those who had survived to the date of assessment). He considered the responses of the students to be highly valuable, especially when expressed graphically with the estimated lifetime attack rates on the y-axis and the age by which the student was assessed on the x-axis. In a forecast of this dissertation research project's Hill functional analysis, Collins learned to characterize the non-linear (generally sigmoidal) shape of his age-specific estimates by using the logistic ('catalytic') model he had learned from Reed. I describe Collins' approach and work in Chapter 3 of my dissertation research report. I drew inspiration for my dissertation research from his published articles in the 1920s, after he joined the US Public Health Service.

## 2.1 History

### 2.1.1 Pre-Epidemiology

Using my concept of the depression spectrum, a Brief Depressive Spell (BDS) can last 1-3 days (or more), a Depression syndrome (DS) must last at least two weeks, and a Major Depressive Episode (MDE) or Major Depressive Disorder (MDD) is a DS complicated by the combination of multiple mood-related disturbances within the same episode that lasts at least two weeks, with the appreciation that many adolescents who have experienced BDS do not achieve states of DS nor MDE/MDD. The history of written ideas about these conditions originates in the Old Testament and in Greek literature, mainly through anecdotal reports (for example,

Solomon's depression in the Bible; Homer's heroes' remorse in the Odyssey and Iliad) (King James Version, 2017, Ecc. 3; Kullmann, 1985). According to the Greek contributions attributed to Hippocrates, depression (melancholia in his time) is the result of an imbalance of humors caused specifically by an excess of black bile (Jouanna, 1984).

First published in 1621, Robert Burton's 'The Anatomy of Melancholy' is considered one of the earliest pieces in English on the topic of mood disturbances. Burton's work is generally quoted in the context of depression. However, he was also interested in anxiety. At that time, melancholia was not limited to depression but was also associated with anxiety. In general, melancholia can be diagnosed by examining several clinical pictures associated with negative affect and internalizing symptoms. Melancholia was characterized by the fact that the patient would remain quiet; an agitated patient was diagnosed with mania, in Greek, or furor, in Latin. In Burton's view, fear was intertwined with sorrow. As an example, the Greek hero Aeneas had a faithful follower named Fidus Achates (i.e., faithful) who faced misfortunes caused by fear (Virgil Aeneid, 6.158, etc.) (Burton, 1961). In Burton's words, "Sorrow's cousin-german is fear, or more accurately, she is fear's sister and constant companion -- an assistant and a principal agent." However, Burton observed that fear and sorrow can also occur independently. He discusses social phobia using examples from the Romans and the Greeks, saying "Tully (Cicero), the Roman orator, confessed to trembling at the beginning of his speech; Demosthenes, the Greek orator, confessed to trembling in front of Philippus". Burton's work has been influential because he provided a detailed clinical description of these melancholia-associated mood disturbances, as well as attempts to identify the causes of having too much black bile (Burton, reproduced 1961).

As a dissertation, this project cannot cover the entire history of melancholia and depression-related mood states. However, this section of the dissertation research offers an initial introduction to that history, establishing the context for more empirical and epidemiological investigations of this issue.

### 2.1.2 Epidemiological Evidence

The first identified epidemiological field surveys on the topic of mood disturbances were conducted before John Snow's investigations of cholera in 19th century London. The scientist responsible for these studies was Professor Frederick Holst. Initially, he estimated the Kingdom of Norway population according to a basic demographic census. He then branched out to

estimate melancholia, mania, dementia, and idiotia prevalence estimates according to case definitions that had originated in French psychiatry. It was a key informant survey, with each parish minister responsible for capturing information about every parishioner (church attender or not). Notes from these interviews were evaluated by a panel of alienists (psychiatrists of the time) and were used to sort members of the population into these four diagnostic categories (Holst, 1852; Fallati, 1839).

According to what I am aware of, the next formal epidemiological field survey of depression as a category of mental disturbances was conducted by psychiatrist Aaron J. Rosanoff in Nassau County, New York. Many have overlooked Rosanoff's work because he had eugenics concepts in mind when he was funded by a eugenics-focused social organization. He did, however, make clear case definitions for mood disturbances and conducted a near 100% census of Nassau County residents. Rosanoff used an innovative two-phase design with non-clinician assessors visiting each household to assess every household member, and then a clinician team to follow up for more formal diagnostic assessments of depression, mania, and other psychiatric categories of the time (Rosanoff, 1917; Anthony& Van Etten, 1998).

Charlotte Silverman's book ‘The Epidemiology of Depression’ presents a masterful overview of epidemiological research on depression. Her presentations covered research conducted from AJ Rosanoff's early 20th-century survey up until 1964 in an adult population survey conducted by Ivanys and colleagues in a district of Prague, Czechoslovakia. Among these contributions are the Depression-era Baltimore surveys conducted by Johns Hopkins researchers eventually led by psychiatrist Paul Lemkau, followed by his own surveys of Baltimore area residents in the 1950s. In these surveys, Lemkau and colleagues hybridized Holst's 2-phase procedure with non-clinician assessors, and then applied a more rigorous evaluation of the case records by a panel of psychiatrists.

From the 1950s through the 1990s, a series of local area population surveys were conducted in New Haven and other communities, including a five-site Epidemiologic Catchment Area (ECA) survey commissioned by the National Institute on Mental Health (NIMH). These surveys produced increasingly definitive evidence on the prevalence of Major Depression and related disorders (e.g., Dysthymia), as well as incidence estimates from a one-year follow-up of the baseline ECA survey participants (Eaton et al., 1989). According to many reviews of depression epidemiology, the subsequent estimates from the National Comorbidity Surveys

(NCS) of 1990-92 have replaced the earlier surveys largely because the sampling frame of the NCS was 48 lower states, whereas the ECA surveys covered only five sites. Yet, the early 1970s studies (in New Haven, Connecticut), and the 1980s ECA surveys (due to the over-time repeated measures prospective cohort design), merit special attention from those interested in depression epidemiology.

The Zurich Cohort Study (ZCS) is an important study in light of the depression spectrum concept, so before moving on to this chapter's sections on the five main rubrics of epidemiology, a few words on that study are appropriate. In brief, the ZCS was designed to investigate the prevalence of mental disorders and symptoms and functional somatic syndromes in the general population of the canton of Zurich, Switzerland. At the time of the study's inception in 1978, there was no standardized diagnostic interview for mental and functional somatic disorders. A new diagnostic interview (SPIKE) was thus developed to capture psychiatric symptoms and syndromes of both types (Angst et al., 1984). A total of 4547 subjects (men, 2201, and women, 2356) were recruited from the canton of Zurich in Switzerland for the Zurich Cohort Study.

ZCS is significant from a phenomenological point of view for its clarification of the depression spectrum concept and the identification of brief mood swings as an important feature of the epidemiology of Major Depression and related conditions (e.g., bipolar disorder). BMS (Brief Mood Swings) are sometimes transient and have been shown to be significant predictors of MDD and other severe mental disorders. When used in the vocabulary advocated by Eaton and colleagues (1995), a BMS may be viewed as either a precursor or part of the prodrome of MDDs or related mood disorders. Regardless of the point of view, it seems clear that BMS is a potentially modifiable predictor of a later DS or a later MDD onset.

In the later sections of this chapter, I will discuss the potential significance of the findings from this project within this context. Namely, I am seeking to investigate the progression from a BDS to an MDD and from BDS to DS. I have an appreciation that many young people have a BDS experience but never proceed to develop any DS or MDD experience or an MDD. There is a gap in epidemiological estimates of the positive predictive value when a BDS occurs. In some BDS cases, DS can occur, and then clinically significant MDD might occur later. It is interesting to note, however, that from a logical point of view there is never an MDD experience unless there is also a BDS experience and unless there is a DS experience. Thus, BDS has fundamental significance in research on mood disturbances and is arguably more fundamental than the Brief

Mood Swings identified by others, such as the work of Angst and Merikangas and their colleagues in Zurich Cohort Studies described below. This is because many individuals who experience a later MDD have not experienced a Brief Mood Swing. This is not true for BDS and DS. For MDD to occur, a prior BDS and DS must occur. Given the minimum two-week duration of a DS and the allowable 1–3-day duration of the BDS, and the overlap of the case definitions, it is not possible to have an MDD without first experiencing a BDS. Plus, it is not possible to have an MDD without a first DS experience, and it is not possible to have a DS experience without a first BDS experience. This aspect of the BDS, DS, and MDD phenomena deserves to be appreciated when the potential significance of this dissertation research project is considered.

2.2 Quantity: How Many in the Population Are Affected?

Although we do not yet have GBD Project estimates for Brief Depressive Spells or DS, we are fortunate to have estimates from the World Health Organization Global Burden of Disease (GBD) Project to help quantify the global burden of Major Depressive Disorder and related conditions. Worldwide, mental disorders represent one of the most significant burdens of disease.

The Global Burden of Disease Study 2019 (GBD 2019) shows that mental disorders remain among the top ten leading causes of burden, and there has been no sign of a reduction in the global burden since 1990. The estimated number of mental disorders in 1990 was 654.8 million, and in 2019, it is 970.1 million, representing a 48.1% increase from 1990 to 2019. However, from 1990 to 2019, there was no marked increase in the age-standardized prevalence of any mental disorder. The World Mental Health Survey estimates a lifetime prevalence of 10–15% for MDD (Bromet et al., 2011).

It is estimated that worldwide, mental illnesses accounted for 21.2% of years of healthy life lost due to disability (YLDs) in 2013, three times the disability associated with all infectious diseases (6.0% of YLDs), four times the disability associated with all injuries combined (5.0% of YLDs), eight times the disability associated with all cardiovascular and circulatory diseases (2.8% of YLDs), and 24 times the disability associated with all cancer (0·9% of YLDs). According to the GBD 2013 study, muscular-skeletal disorders contributed to 20.8% of YLDs.

Depressive disorders are extremely prevalent and severely disabling. The GBD 2019 estimated that major depressive disorder and dysthymia jointly accounted for 46.9 million

disability-adjusted life years (DALYs) globally in 2019, with each DALY equivalent to a healthy year of life lost to the disability caused by depressive disorders (Vos et al., 2020). When compared to a total of 369 diseases and injuries, depressive disorders were the 13th leading cause of overall burden, and the seventh leading cause of nonfatal burden, globally (Vos et al., 2020; Vigo et al., 2016)). The occurrence of depressive disorders was substantial across the lifespan, for both sexes, and across multiple locations globally.

In addition to the disability and mortality captured by the DALYs, depressive disorders also have a far-reaching impact. Caretakers, employers, and governments must manage the consequences of depressive disorders, including a reduction in productivity and a greater reliance on state welfare and health programs (Chisholm et al. 2016). Depressive disorders are also considered to be major determinants for fatal outcomes such as suicide (Moitra et al., 2021).

## 2.3 Location: Where Are Affected Cases More or Less Likely to Be Found?

### 2.3.1 Sex Differences (Binary Female-Male)

Studies have shown that women are more likely than men to suffer from Major Depressive Disorder as well as other conditions such as many forms of anxiety disorders. Based on epidemiological estimates over the past 100 years, the estimated prevalence and incidence of mental disorders differ greatly when females' experiences are contrasted with male experiences. (Laurence et al., 2022). To illustrate, there is a 1.5-to-3-times greater prevalence of major depression among women than among men (Bernaras, 2019). Additionally, women experience increased incidence of depression than men (Weissman, 1977 & 1993; Stalk et al., 2018). Researchers have found that these differences exist across all age groups (Sramek, 2022). According to the GBD 2019, anxiety disorders and depressive disorders were among the top ten causes of DALYs among females.

Women generally experience more severe symptoms. The fluctuating levels of estrogens and other hormones between puberty and menopause might be responsible for this phenomenon (Breslau et al., 2017, Deecher et al., 2008). As for MDD symptoms, they differ based on sex. Depression often occurs for longer or recurs more frequently in women than in men, and females can experience a lower quality of life and a younger onset age (Kornstein, 2020). Men with depression are more likely to engage in risk-taking behaviors, use alcohol or other drugs, and exhibit anger, whereas women with MDD report higher levels of daily stress, irritability, sleep problems, greater weight gain, anxiety, anhedonia, and physical symptoms (Martin et al., 2013).

Women tend to develop depression later in life (Arnold, 2003), and they experience mood swings and longer episodes of depression (Morgan et al., 2005; Rasgon et al., 2005).

There are some exceptions to a general rule that mood disorders tend to occur more often among females as compared with males. For example, women do not seem to differ appreciably in the occurrence of bipolar disorder (Baldassano et al., 2005; Diflorio and Jones, 2010a).
In spite of the important observed differences mentioned in this section, female-male variations are said to have been overlooked as variables when studying mental illnesses (Zucker and Beery, 2010). The neglect constrains our understanding of female-male variations of importance in prevention and clinical therapeutics directed toward Major Depression and related conditions.

2.3.2 US Census Race/Ethnicity and Ethnic Self-Identification

As noted previously in this dissertation report, political considerations and constituencies help to sustain the use of the terms 'race-ethnicity' in the work of the US Census. For science reports, the concept of 'ethnic self-identification' may be more useful. For convenience, I have used both terms in this report.

When considering epidemiological variations related to subgroup self-identification based on the US Census 'race-ethnicity' questions, the Epidemiologic Catchment Area Study found that estimates of the prevalence of major depression did not vary appreciably across racial and ethnic groups (Compton et al., 2006; Somervell et al., 1989). Researchers from the later Collaborative Psychiatric Epidemiology Surveys found that minorities—Asian, Hispanic, Afro-Caribbean, and African American (AA)—were appreciably less likely than non-Hispanic whites to meet MDD criteria (Budhwani et al., 2015), perhaps because the CPES samples included a larger number of minority group participants than was true for the ECA surveys.

Based on patient data from the National Ambulatory Medical Care Survey, Sclar et al. (2008) found that by 2003–2004 the proportion with diagnoses for MDD was similar for African Americans and Hispanics, but a much larger proportion of non-Hispanic White patients had received an MDD diagnosis. A number of other studies have also shown an apparent underdiagnosis of MDD among African Americans and Hispanics. A Veteran's Affairs (VA) poststroke depression (PSD) study found that AA and "all other" racial/ethnic groups (Asian, Asian American, Pacific Islander, North American Indian, and Alaskan Native) were less likely to be diagnosed with PSD than white non-Hispanics, even after adjusting for suspected confounding variables (Jia et al., 2010). Akincigil and colleagues (2012) found that among

elderly beneficiaries enrolled in Medicare, MDD diagnosis proportions were 6.4 % for non-Hispanic whites, 4.2 % for AA, 7.2 % for Hispanics, and 3.8 % for others. Following statistical adjustment for a range of covariates, AA were substantially less likely to receive a depression diagnosis from a health-care provider (adjusted odds ratio (AOR) = 0.53; 95% confidence interval (CI) = 0.41–0.69) as compared with non-Hispanic whites.

In a study of US Census race-ethnicity subgroups stratified by poverty and other indicators of social status, Riolo and colleagues (2005) found that persons living in poverty had MDD roughly 1.5 times more often than persons not living in poverty. However, MDD was associated with poverty only in non-Hispanic Whites ($p = .0023$). A lack of education (less than 8 years in school) was strongly associated with the prevalence of MDD only among Mexican Americans ($p < 0.0001$). Dysthymic Disorder (long-sustained low-grade depression-related experiences not meeting MDD criteria) seems to present a somewhat different epidemiological profile. For example, the estimated prevalence of dysthymic disorder in African Americans and Mexican Americans may be larger than in non-Hispanic Whites. This study's evidence disclosed that, after covariate adjustment for poverty, a lack of education was associated with dysthymic disorder in these subgroups. Substantial variations in dysthymic disorder also were found in subgroups defined by self-identified race/ethnicity, female sex, and educational attainment. Particularly, among non-Hispanic Whites, the estimated Dysthymic Disorder prevalence was inversely associated with educational attainment for both females and males. This inverse association was not found for Mexican American and African American subgroup members, for whom education was less prominent as an apparent source of variation in dysthymia prevalence and the education-dysthymia association varied for females and males in those subgroups (Woodward et al., 2012).

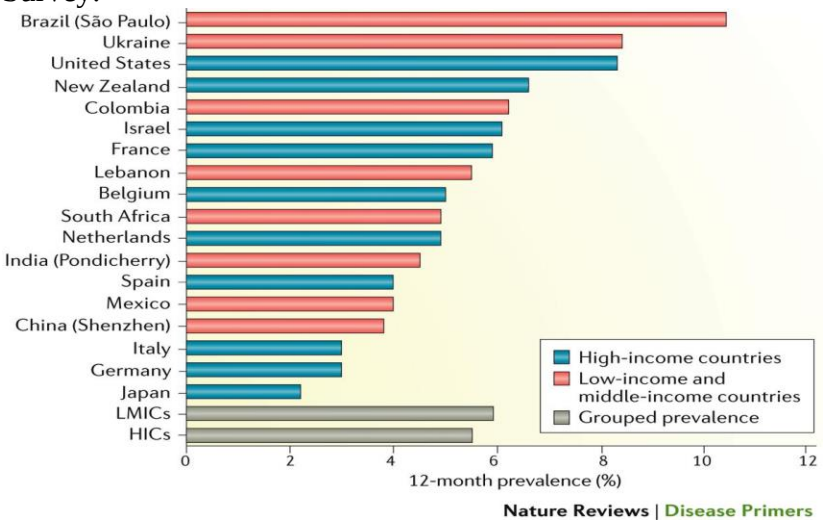
2.3.3 Geographical location

According to the WHO report, "Depression and Other Common Mental Disorders: Global Health Estimates," the prevalence of mental disorders is growing, especially in low- and middle-income countries. In the five years between 2005 and 2015, there was an estimated 18.4% increase in depression prevalence proportions worldwide. Moreover, depressive disorders accounted for the largest share of nonfatal health losses worldwide in 2015 (WHO, 2017).

Approximately 90,000 people in 18 countries across every continent were assessed for MDD using the DSM-IV criteria as described in a 2011 report from the World Mental Health

Survey (Bromet et al., 2011). According to Bromet et al. (2011), the mean 12-month prevalence of MDD was roughly 6%. In comparison with the 12-month prevalence of MDD, the MDD cumulative incidence was threefold higher, suggesting that one in six adults suffers from MDD. As noted by others, the estimates of cumulative incidence proportions among survivors might not serve well as a reliable metric when adults are studied. This estimator is affected by survivorship and attrition as well as recall bias and underreporting of MDD (Patten, 2009; Moffitt et al., 2010). Nonetheless, taken at face value, an estimated 20% of adults have experienced a Major Depressive Disorder experience during the accumulated lifetime of experience based on cross-sectional surveys such as the World Mental Health Surveys.

Figure 1. The Prevalence of Major Depressive Disorder by Country in the World Mental Health Survey.




This figure illustrates the 12-month prevalence of MDD by country in the WMH Survey, ranging from 2.2% in Japan to 10.4% in Brazil. The estimates varied considerably across countries to reflect both substantive and methodological factors. However, similarities were found in the 12-month prevalence of MDD in ten countries with high income (5.5%) and eight countries with low and middle income (5.9%), which stands as ecological evidence that MDD might not depend heavily upon a country's level of economic development. Additionally, Kessler and Bromet (2013) reported that the median age of onset, symptom profiles, severity, and primary sociodemographic correlates, such as sex, education and life events, for Major Depressive Disorder were comparable across countries. As a result of resources and treatments available, there were discrepancies between countries and cultures. In high-income countries,

50–60% of all people with severe MDD had received proper treatment, whereas fewer than 10% of people with MDD had received proper treatment in low-income countries (Wang et al., 2007).

## 2.4 Causes: What Accounts for Some Population Members Becoming Cases while Others are Spared?

### 2.4.1 Major Suspected Causes of MDD: Environmental Factors

Many factors may contribute to the development of MDD, but life experiences are the most studied among them. Among the suspected causal influence related to life events and changes are natural calamities, financial constraints, bullying, social seclusion, social stress, diagnosis of a serious medical disorder, death of loved ones, and childbirth (Kamran et al., 2022). During the COVID-19 pandemic and its associated constraints, mental health has been observed to suffer in many population subgroups. In a study conducted by Evans and colleagues (2021), the occurrence of symptoms of MDD increased markedly during the COVID-19 pandemic. The use of alcohol may be a contributing influence (Kamran et al., 2022). MDD occurrence also has been found to be associated with the use of certain medicines, such as beta-interferon, isotretinoin, and rimonabant (Zunszain, 2012; Soyka, 2008).

### 2.4.2 Major Suspected Causes: Genetic Factors and Heritability

Multifactorial disorders, such as MDD, are subject to environment-associated variations, but also seem to depend upon genetic variants (Kamran et al., 2022). In genetics, heritability refers to the degree to which a trait might depend upon genetic variants, with an environment thought to be held constant. Twin studies typically estimate heritability by comparing expected genetics and environmental characteristics via comparisons of mono- and dizygotic twins. Of course, heritability can be a population- and time-dependent phenomenon. The heritability of psychiatric disorders ranges from moderately to highly, though it is not known to what extent genetic variation is exclusive to each disorder or shared among them. According to twin studies and other similar studies, MDD has a moderately hereditary component (37%), with a plausible observed range between 26% and 49% (van Calker, 2021).

Overall, twin studies estimate heritability fairly similarly, but they rely on certain key assumptions, particularly the assumption of common environment between monozygotic and dizygotic twin pairs. The missing heritability reported by early genome-wide association studies (GWAS) led some studies to speculate that the disease's twin heritability might have been overestimated (Kamran et al., 2022). Despite this, there is an increasing body of literature on heritability estimation based on population-based registers or electronic health record (EHR)

data. Studying extended pedigrees based on recorded or inferred familial relationships, these estimates are similar to those from twin studies (Kamran et al., 2022). The estimated heritability of MDD for females seems to be larger than corresponding estimates for males. The majority of genetic risks, but not all, are shared by both sexes. MDD has a moderate heritability, which makes it useful to identify clinical subtypes that have a higher heritability. The early evidence showed recurrent MDD as a more heritable form of the disorder, but recent large-scale population-based studies have expanded the evidence to suggest that disorder subtypes based on the age of onset, comorbid anxiety disorder, severity, and postpartum depression are more heritable forms of MDD (Kendall et al., 2021).

### 2.4.3 Contribution of GWAS to Our Understanding of the Genetic Architecture of MDD

Gene-based association studies examine differences in the allelic frequency of genetic variants between groups of individuals who share similar ancestry yet differ phenotypically (e.g., MDD cases vs. controls). To date, the most studied genetic variants in GWAS are single nucleotide polymorphisms (SNPs), although genotyping arrays can also detect large copy number variants (CNVs) (Kamran et al., 2022). Based on genome-wide significance for all SNPs tested and independent replication evidence, GWAS identify SNPs that show appreciable associations with phenotypes of interest. There have been many remarkable discoveries in human genetics and genomics as a result of GWAS over the last 15 years. A number of successful applications of genetic and biochemical approaches have been reported (Uffelmann et al., 2021). Examples include understanding disease biology, estimating heritabilities, calculating genetic correlations between phenotypes, developing risk predictions based on genetic variables, assessing drug development programs, and inferring the causal relationship between risk factors and health outcomes. GWAS findings on MDD and its associated traits have proved more productive than earlier studies of candidate genes. There are now hundreds of loci reported in large-sample GWAS that are strongly and robustly associated with MDD and associated traits (Kamran et al., 2022). Whether these associations will prove to be replicable and causally important remains on the agenda for future research.

### 2.4.4 Exploring Causal Relationships

The genetic correlations between MDD and other disorders and traits might have heterogeneous origins not yet fully understood. Sleep quality may increase with MDD (because of the depression), or sleep quality may decrease with MDD (because of the depression).

Mendelian randomization (MR) studies can estimate causal relationships between genetically based traits (Davey, 2022) by taking SNPs associated with an exposure trait as genetic instruments and testing them for the causal effect of the exposure on a second trait. According to MR studies, MDD is associated with body mass index, years of education, and interleukin-6 levels. MR has also disclosed an apparent causal effect of MDD on smoking phenotypes (ever versus never smokers), metabolic syndrome and its components (waist circumference, hypertension, triglycerides, HDL cholesterol), coronary artery disease, stroke, and inflammatory bowel disease, together with bidirectional causal effects on schizophrenia, neuroticism, pain, osteoarthritis pain, insomnia, and atopic diseases (asthma, hay fever, and eczema) (Kamran et al., 2022). The latter bidirectional results help substantiate theories that MDD and these disorders and traits share biological bases. According to these MR findings, there is potential to target different phenotypes for MDD treatment. This approach might reduce comorbidities if MDD is addressed or prevented.

### 2.5 Mechanisms: What are the states and processes that lead to Brief Depressive Spells and onward toward MDD?

The focus of this dissertation research project is on the estimation of how often a Brief Depressive Spell might be followed by more clinically significant responses such as Major Depression, or its precursor state in the form of a subsyndromal two-week Depression Syndrome that can occur without allied clinical features required for MDD. Accordingly, the central contribution of this dissertation research project might fall under the category of mechanisms, as discussed in the overview of epidemiological evidence on the dissertation topic. Recent publications, however, have offered some suggestions as to how background conditions, circumstances, and processes might meander toward MDD and the sequelae of MDD such as suicide attempts or deaths, as well as residual disabilities, impairments, and handicaps that persist even in the absence of a case fatality. In this section, I will focus primarily on epidemiological evidence about these potential mediators and mechanisms, with the greatest emphasis on evidence that has been replicated at least once. For studies for which at least one replication study, I will not write about the speculative results.

Numerous pathophysiological mechanisms have been implicated in previous studies, under headings such as the biogenic amine hypothesis, the receptor hypothesis, neurotrophic factors, cytokine theory, and endocrine factors. A major challenge is that no single hypothesis

explains all aspects of MDD because multiple interrelated mechanisms are involved (Shadrina et al. 2018; Wang, 2021; Jesulola et al. 2018).

### 2.5.1 Pathophysiological mechanisms

A number of candidate biomarkers have been studied, but to date MDD seems to have no specific biomarkers that can be used for research or clinical purposes to confirm MDD diagnoses. When diagnosing MDD in the United States and in some other countries, a multifaceted approach is used that includes a psychiatric evaluation based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), a set of diagnostic criteria created by the American Psychiatric Association or based on the International Classification of Disease (ICD-10) (Guha, 2014).

When comes to depression and mood disturbances, the distinction between nomenclature versus classification is of central importance. As described by Morton Kramer (1980):

> It is essential to keep in mind that the ICD is a statistical classification of diseases, not a nomenclature of diseases. The distinction between these two is important. A nomenclature of disease is a list or catalog of approved terms for describing and recording clinical and pathological observations. To serve its full function it must be sufficiently extensive so that any pathological condition can be accurately recorded. As medical science advances, a nomenclature must expand to include the new terms necessary to record new observations.
>
> In contrast, a statistical classification indicates the relationship between diagnostic categories and must be confined to a limited number of categories that encompass the entire range of diseases and morbid conditions.

In this section on mechanisms, I rely heavily on a recently published review by Kamran (2022). In that review, the primary hypothesis about mediation and mechanisms are summarized in relation to a relatively small set of alternatives (and sometimes complementary explanations). In this section, I summarize what I learned by reading Kamran's work. I do not seek to defend these ideas. I offer them as lines of research that might help us understand what I see in my evidence about the epidemiological transition from BDS to DS and to MDE.

#### Biogenic Amine Hypothesis

Serotonin, dopamine, and noradrenergic neurons are abundant in the brain. In order for memory to work, behavior to be regulated, and mindfulness to take place, the prefrontal cortex has to be functioning, as it is controlled by norepinephrine through noradrenergic neurons. The dopaminergic system modulates reward and motivation, memory, and mindfulness, whereas the serotoninergic system innervates all areas of the brain (Girotti et al. 2018). Numerous behavioral symptoms (fatigue, low mood, psychomotor retardation, reduced motivation, and vigilance) have been linked to monoaminergic systems. In suicide cases, some studies reported significantly lower levels of serotonin in the brains of depressed patients. Reduced levels of norepinephrine (individually or in combination with dopamine) contribute to a wide range of depressive symptoms including aggression, sex, concentration, appetite, mindfulness, and motivation (Kamran et al., 2022).

### Receptor Hypothesis

A basic principle is that for every active biogenic amine or other endogenous agent in humans, there is a corresponding distribution of receptors through which that activity becomes possible. For this reason, a variety of theories about MDD mechanisms are based on inductive reasoning or empirical inferences based on the distribution of known receptor sites. Many studies have examined the role of specific receptors in the development and occurrence of depression (Kamran et al., 2022).

### The Cytokine Theory

Cytokines are inflammatory chemicals secreted by lymphoid cells in response to foreign pathogenic antigens. In some studies of MDD patients, altered immune functions may indicate the involvement of cytokines, sometimes in the context of chronic stress processes. Mixed evidence, some supportive and some not compatible, has come from the accumulating cytokine studies with a focus on MDD mechanisms (Kamran et al., 2022).

### Neurotrophic Factor Hypothesis

Stress hormone signaling, including cortisol, and neurotrophic factor signaling, including brain-derived neurotrophic factor (BDNF), are involved in the Neurotrophic Factor Hypothesis. Inflammatory factors in the brain and excessive neuronal activity have become central in research the pathophysiology of MDD. In some instances, the pathways involve inhibition of neurogenesis (formation of new neurons in the brain) over time (Kamran et al., 2022).

### Neuroplasticity/Neurogenesis Hypothesis

Multiple pathophysiological studies have produced evidence compatible with the hypothesis that deficient neurogenesis is important in the mechanisms underlying formation of MDD and related mood disturbances (e.g., disrupted metabolism of neurotropic factors such as BDNF; Shadrina et al., 2018). BDNF expression has been found to be dysregulated in the peripheral mononuclear cells of depressed patients, including DNA methylation of BDNF gene promoters. In addition, some studies indicate that MDD patients lose synaptic plasticity with possibly pathological morphological changes (Kamran et al., 2022). In depressed and suicidal patients, various studies have reported reduced levels of the neurotropic receptor tyrosine kinase 2 receptor TrkB and its genetic variant NTRK2 (Castrén, 2021). In antidepressant drugs, BDNF levels are increased, but the precise mechanism of how the drugs work is not known. Kamran et al. (2002) reported that the BDNF rs2049046 and rs11030094 are likely to influence response of antidepressant treatment in MDD patients (Kamran et al., 2022).

2.5.2 Therapeutic response as a source of evidence on mechanisms

Historically, as with other mental disorders, MDD and its treatment were based on magic and empirical environmental therapy before clinical therapeutics in psychiatry became formalized with a firm empirical base. By the 19$^{th}$ century some advances had been made, but rigorous efficacy and effectiveness studies were absent [e.g., treatment of neurosyphilis with mercury and other compounds; treatment of morphinism with cocaine; treatment of depression with Ashwagandha (Withania somnifera) and opiate-based compounds such as laudanum). The advent and refinement of randomized controlled trials in the mid-late 20th century accelerated research and development across what now is more than three ‘generations’ of antidepressant medicines and device-based therapeutic interventions such as electroconvulsive treatment and more recently transcranial magnetic stimulation. Some of the early advances followed the confirmation of monoaminergic hypotheses about serotonin (5-HT) and noradrenaline (NA). Ruiz and colleagues (2018) describe the evolution of more recent clinical therapeutics advances along these lines (Ruiz et al., 2018).

As an example of work in this area, one study conducted with antidepressants in the initial phase of depressive disorder demonstrated a relative efficacy of 23% after 6–8 weeks. However, 70% of the patients diagnosed with major depression did not achieve a response. This lack of a response has been associated with poor functional development (Ruiz et al., 2018). When an efficacious intervention seems to promote success in MDD therapeutic responses, the

evidence invites more ‘basic’ research on the mechanisms through which the interventions make a difference. From work along these lines, quite a few mechanisms of action of antidepressant drugs have been proposed, including the increase in brain-derived neurotropic factor (BDNF), which decreases when corticosterone is present.

Research into endogenous origins of MDD has led to the discovery of complex genetic, epigenetic, and psychosocial factors that seem to contribute to an endocrine, nervous, and immune system decompensation. In most instances, the onset of depression follows a stressful event in which half of the patients present elevated cortisol levels as well as dysfunction in the hypothalamic-pituitary-suprarenal axis (HHS); alterations in inflammatory and oxidative stress indicators; and in extreme cases, changes in brain morphology (Ruiz et al., 2018).

In summary, one of the potentially important contributions from research on mechanisms is to identify new target points for earlier and earlier interventions. As progress is made in understanding how often and under which conditions adolescents might progress from a Brief Depression Spell onward toward syndromes that require clinical attention, we should expect more informative epidemiological studies with contributions under the rubric of ‘Mechanisms.’

## 2.6 Prevention and Control: What can we do?

As I move on to the topic of prevention and control, I define prevention as the disruption of the processes leading to MDD, with prevention of newly incident MDD cases. In contrast, control involves either shortening of MDD episodes that have not been prevented or alleviating the MDD sequelae and accompanying difficulties when the episode persists. In this section, I will focus on systematic reviews, which include more than one or two studies about prevention and control. In this section, I will highlight studies that have attempted to disrupt the progression from a Brief Depressive Spell to Major Depressive Disorder (MDD).

Research on the prevention of depression in children and adolescents has made substantial progress over the last decade. According to recent meta-analyses, depression prevention programs, especially those conducted with targeted samples, consistently result in small but significant gains in preventing increases in depressive symptoms or depressive episodes (e.g., Merry et al., 2011; Sandler et al., 2014).

Tokgoz et al. performed a scoping review to provide a comprehensive overview of the field of digital health interventions for the treatment of depression. The synthesis included 65 studies in total. When categorizing the studies into prevention, early detection, therapy, and

relapse prevention, this team found that 52 studies focused primarily on therapy. Only one study focused on prevention, five on early detection, and seven on relapse prevention. Cognitive-behavioral therapy, acceptance and commitment therapy, and problem-solving therapy were the most common treatment approaches. When cognitive behavioral therapy was applied within the context of digital health interventions, robust effects were found. An increasingly dominant form of cognitive behavior therapy is often via web-based systems. Combining web-based and smartphone-based interventions is becoming more common.

Depression can be effectively treated with digital health interventions. The interventions focus on different areas of health care. Although most interventions can enhance depression treatment, determining which ones are appropriate can be difficult. Although cognitive-behavioral therapy through digital health interventions has shown good results in the treatment of depression, selection from among the several depression treatments remains very individualistic (Tokgoz et al., 2020).

Gladstone and colleagues (2021) found that college and university students across the United States are experiencing increases in depressive symptoms and clinical depression risks. Although college counseling centers try to address the problem through wellness outreach and psychoeducation, limited resources make it difficult for them to reach students who need help. By utilizing technology-based prevention programs, students who need mental health services can increase their reach and overcome barriers to access. The first chapter of the Gladstone manuscript describes the development of the Willow intervention, an adaptation of the CATCH-IT depression prevention intervention for use by students at a women's liberal arts college using a community participatory approach. The second part of their article presents data from a pilot study of Willow with 34 students (mean age = 19.82, SD = 1.19). Eighty-four percent of the participants completed the full intervention, and 29 (85%) logged onto Willow at least once. A majority of participants rated Willow positively for its acceptability, appropriateness, and feasibility. There was a reduction in depressive symptoms (95% CI (0.46–3.59)), anxiety symptoms (95% CI (0.41–3.14)), and rumination (95% CI (0.45–8.18)) after eight weeks of use. It was found that internet-based prevention interventions were acceptable, feasible, and potentially associated with lowered internalizing symptoms.

According to a study by Kanine and colleagues (2021), a depression prevention program, interpersonal psychotherapy-adolescent skills training (IPT-AST) was evaluated for fidelity,

feasibility, acceptance, and preliminary outcomes among African American children in urban pediatric primary care (PC). This open clinical trial involved 22 adolescents with elevated depressive symptoms. During good visits, adolescents were identified by filling out a screening questionnaire. Attendance at IPT-AST sessions and fidelity ratings were recorded. Adolescents and caregivers completed questionnaires about their attitudes toward the intervention and their symptoms and functioning pre-and post-intervention. Despite some difficulties recruiting participants, results showed high levels of fidelity, attendance, and acceptability. Caregivers and adolescents both noted improvement in their functioning. Self-reported depression, anxiety, and total mental health symptoms diminished marginally. Symptoms of mental health were reported by caregivers to have decreased.

Rigorous randomized controlled trials with evidence of reproducibility and multiple replicated samples of adolescents remain on the agenda for future research. After initial relatively small sample efficacy RCTs, it is important to conduct large sample RCTs with rigor and reproducibility features. In this fashion, epidemiologists can become more involved in the prevention and control of MDD and related conditions.

2.7 Potential Significance

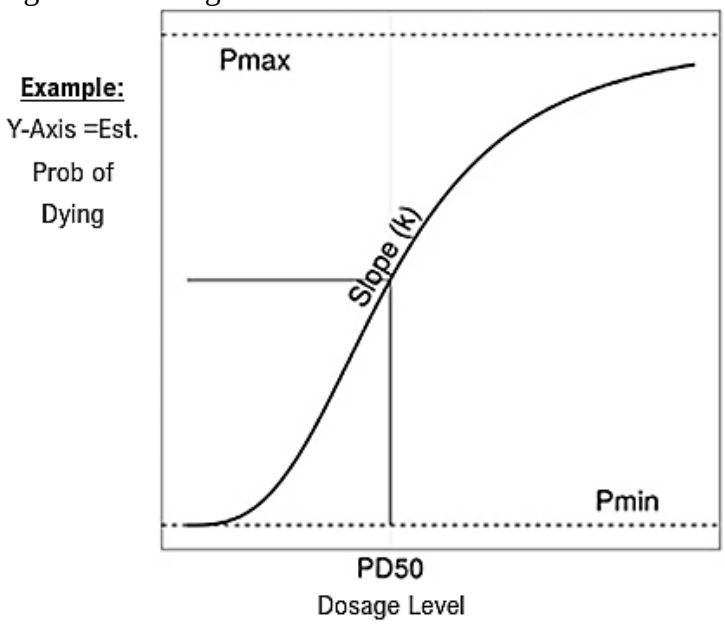
In recent years, studies on female-male ('sex as a biological variable') differences and on minority health disparities and inequities have gained prominence at the US National Institutes of Health. A separate NIH agency is dedicated to this concern; each center and institute participate in related program announcements.

Research on 'Sex as a Biological Variable' clearly requires contrasts of epidemiological parameters for females versus males. For most disparities/inequities research, the contrasts involve subgroup variations in related parameters with the subgroups defined by US Census race-ethnicity categories. Examples of the parameters include disease incident or prevalence estimates or other estimated means for the subgroup (e.g., systolic or diastolic blood pressure values; body mass index values), or the equivalent statistical summaries for suspected causal influences (e.g., mean dietary sodium intake).

In my dissertation research project, I decided to use a Hill functional analysis approach to extend the coverage of subgroup comparisons to include four parameters of the sigmoidal Hill function as shown in the accompanying figure: (a) Pmin (the estimated value of a Y-axis probability at its low asymptote), (b) Pmax (the corresponding estimated value at its high

asymptote), (c) K, the estimated slope for values linking Pmin to Pmax across the middle range of X values, and (d) PD50, the estimated point on the X-axis where the Y value is at the midpoint (50th percentile) between the lower and upper asymptotes.

Figure 2. The Sigmoidal Hill Function.




As for many published Hill functional analyses in pharmacology and toxicology, parameter estimates are based on empirical dose-response values on the X-axis when the dose levels for a drug or toxic exposure are assigned at random as in a randomized controlled trial (RCT). The values on the Y-axis represent the estimated probability of some binary response such as death or survivorship (e.g., using PD50 as an analogy for LD50, the corresponding dose value when a lethal outcome occurs for 50% of the exposed). A Y-axis probability might also be representative of a medicine's effectiveness (e.g., depicted in ED50) or of some unwanted non-lethal 'side effect' of the medicine (e.g., another type of ED50).

The Hill function was introduced to me by a Neuropsychopharmacology paper that discussed how the likelihood of developing drug dependence can be affected by the number of days a drug is used after the onset of its use (Vsevolozhskaya & Anthony, 2017). They studied subgroups of newly incident drug users, drug subtype by drug subtype (e.g., alcohol, versus cannabis, versus cocaine, versus opioids). I adapt that approach to studying the depression disparities experienced by subgroups defined by sex and US Census 'race-ethnicity' classifications that map onto people's self-identification in relation to family heritage and ethnicity.

# CHAPTER 3 - MATERIALS & METHODS

## 3.0 Introduction

This chapter is organized into a basic set of sections for epidemiology research reports, beginning with the research design and population under study in conceptual terms (versus strictly operational or sampling terms). The cross-sectional design and multi-stage area probability sampling approaches are explained, with citations to several more detailed online monographs. A section on human subject protection procedures describes the consent of the participants, with a paragraph on implications for participation levels. The following areas focus on stories of participation. The final section of the chapter introduces the use of analysis weights that account for both selection probabilities and post-stratification adjustments to US Census distributions. Issues of variance estimation and the several approaches used to account for non-independence of observations in complex survey designs are also described.

The later paragraphs give an overview of the statistical approaches in the form of cross-classification and contingency table analyses, the analysis weights with post-stratification adjustment, functional analysis approaches (e.g., Hill functional analysis) and Bayesian inference approaches). Issues of variance estimation using Taylor series and the bootstrap are covered. A final section describes the analysis software used for this project and provides appropriate citations.

## 3.1 Research Design and Population Under Study

The United States National Surveys on Drug Use and Health (NSDUH) are cross-sectional surveys. The NSDUH samples of individuals are drawn without replacement (United States, National Survey on Drug Use and Health, 2019). The NSDUH surveys are designed to yield yearly nation-scale estimates about tobacco, alcohol, and other drugs (including non-medical use of prescription drugs), and mental health in the US.

Based on NSDUH, 2004-2020, this dissertation research project's study population consists of United States dwelling unit residents 12 years and older of the 50 states and the District of Columbia, excluding residents of institutional group quarters such as prisons and long-stay hospitals. This study population of non-institutionalized US residents has been sampled using multi-stage area probability sampling methods that start with state-level sampling frames. Institutionalized residents have been excluded for several logistical reasons. A few of these reasons include difficulty accessing extended hospital stay patients and incarcerated populations,

informed consent constraints, among other obstacles to institutional sample surveys of the type described in connection with the Epidemiologic Catchment Area (ECA) research on institutional and non-institutional populations in five United States metropolitan areas, which was conducted more than 25 years ago (United States, Substance Abuse and Mental Health Services Administration, 2016).

Nation-scale epidemiological surveys rarely include migrants and homeless people due to logistical difficulties when integrating data on these 'no conventional residence' population members. NSDUH is not a 'household survey.' Its sampling frame includes college dormitory and homeless shelter residents as well as residents of other non-institutional group quarters.

Each year, independent multi-stage probability samples are drawn by NSDUH staff, sampling each state and the District of Columbia. The state is the primary level of stratification. Within each state, equal state sampling regions (SSRs) are determined. Subsequently, census tracts are carefully chosen within each SSR, census block groups within each census tract, and area segments, which are a collection of census blocks within census block groups. Then, dwelling units are selected within each area segment, and lastly, one or more individuals from each dwelling unit are chosen for the interview (United States, 2019).

Starting in 2014, the NSDUH sample design made the sample sizes proportional to the state population sizes to improve the precision of estimates (National Survey on Drug Use and Health (U.S.), & United States, 2015). Before the redesign in 2014, the eight largest states had a target sample size of about 3,600, whereas the remaining states had target sizes of 900, respectively (National Survey on Drug Use and Health (U.S.), & United States, 2015). The 2014 sampling frame was centered on data from the 2006 to 2010 American Community Surveys (ACS) and the population projections from the 2010 census. By contrast, the sampling frame for the 2005-2013 surveys drew upon the 2000 census and its updates (National Survey on Drug Use and Health (U.S.), & United States, 2015; 2019). Year-specific participation levels are shown in a table later in this chapter.

The NSDUH sampling and assessment procedures make it possible to assess time sequences of events and processes not typically considered in cross-sectional survey analyses. The Standardized Assessment section of this chapter provides more information on these time sequences and their importance for this dissertation research project. The survey procedures and the sampling approach for data collection have been designed by statisticians, epidemiologists,

and other researchers employed by the US federal government. NSDUH has established data-sharing agreements and produced analysis-ready datasets, which have enabled this dissertation research project. A detailed methods report on sampling is available online: https://www.datafiles.samhsa.gov/studypublication/nsduh-2002-methodological-resource-book-mrb-nid14370).

### 3.2 Standardized Assessments

NSDUH conducts in-person interviews via Field Interviewers (FI) to foster a comfort level for respondents to talk about sensitive issues such as mental health and drug use. Privacy and confidentiality are fostered by use of audio computer-assisted self-interviewing techniques (ACASI). For anonymity, responses are not linked to names or identifiers (National Survey on Drug Use and Health (U.S.), & United States, 2017). Before the FI visits, letters are sent to sampled addresses. It is customary to have the FI speak with an adult occupant of the household (18 years old or older) as the screening respondent (National Survey on Drug Use and Health (United States, 2017).

Until Fall 2020, the FI recorded basic demographic data about all unit residents and characterized each sampled respondent via a hand-held computer, typically within the dwelling unit. Pandemic conditions in 2020 shifted Fall 2020 assessments to web-enabled approaches. The NSDUH selection process typically has generated adequate sample sizes for specified population age groups (National Survey on Drug Use and Health (United States, 2017). NSDUH assessments are offered in both English and Spanish, but not in other languages.

Table 1**.** U.S. National Surveys on Drug Use and Health, Overall Samples Sizes and Participation Levels, 2004-2020.

| Survey Year | Sample Surveyed | Public Use Sample | Weighted Screening Response Proportion | Weighted Interview Response Proportion | Overall Response Level[a] |
|---|---|---|---|---|---|
| 2004 | 67,760 | 55,602 | 91% | 77% | 70% |
| 2005 | 68,308 | 55,905 | 91% | 76% | 69% |
| 2006 | 67,802 | 55,279 | 91% | 74% | 67% |
| 2007 | 67,870 | 55,435 | 89% | 74% | 66% |
| 2008 | 68,736 | 55,739 | 89% | 74% | 66% |
| 2009 | 68,700 | 55,772 | 89% | 76% | 67% |
| 2010 | 68,487 | 57,873 | 89% | 75% | 66% |
| 2011 | 70,109 | 58,397 | 87% | 74% | 65% |
| 2012 | 68,309 | 55,268 | 86% | 73% | 63% |
| 2013 | 67,838 | 55,160 | 84% | 72% | 60% |
| 2014 | 67,901 | 55,271 | 82% | 71% | 58% |
| 2015 | 68,073 | 57,146 | 80% | 69% | 55% |
| 2016 | 67,942 | 56,897 | 78% | 68% | 53% |
| 2017 | 68,032 | 56,276 | 75% | 67% | 50% |
| 2018 | 67,791 | 56,313 | 73% | 67% | 49% |
| 2019 | 67,625 | 56,136 | 71% | 65% | 46% |
| 2020 | 36,284 | 32,893 | 68% | 63% | 43% |

[a]Participation level = Screening response rate % x Interview response rate %
Source: United States. Department of Health and Human Services. U.S. National Surveys on Drug Use and Health, Codebooks 2004-2020.

The initial letters are mailed with a Spanish version in predominantly Spanish-speaking districts. In cases where no English respondents are available, a certified Spanish-speaking FI visits the address. The interview is not conducted in instances where a sampled individual speaks neither English nor Spanish. The FI supervises the assessment session, which usually requires about one hour within the respondent's dwelling unit.

The NSDUH assessment includes two components: computer-assisted personal interviewing (CAPI) and the audio computer-assisted self-interview techniques (ACASI) (United States, 2017). The interviewer reads out questions to the respondents for the CAPI component and enters their answers into a computer. For the ACASI component, the respondent self-reads or listens to the questions on headphones and records responses on the computer without revealing the responses to the interviewer. The drug use module is self-reported and contains questions on alcohol, tobacco, marijuana, cocaine, crack cocaine, additional stimulants, heroin,

hallucinogens, and inhalants. The module on mental health follows the drug use questions. Other CAPI modules cover demographic data, household income, education, school enrollment, household composition, and health insurance.

Starting in 2004, NSDUH included depression modules, derived from the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) (American Psychiatric Association [APA], 1994). For this reason, this dissertation research project's estimates are based on the DSM-IV criteria for Major Depressive Episode (MDE). Adults aged 18 years or older and youths aged 12 to 17 were given somewhat different modules. The adult depression questions were derived from the depression section of NCS-R which used the depression and other modules from the World Health Organization (WHO) World Mental Health Survey Initiative Version of the Composite International Diagnostic Interview (WMH-CIDI) (Kessler & Üstün, 2004). Minimal revisions were made to the NCS-R questions to reduce their length and modify the questions for the ACASI format used in NSDUH.

For NSDUH, the lifetime history of experiencing a Major Depressive Episode is defined as having at least five or more of the following nine symptoms as occurring nearly every day in the same 2-week period and when at least one of the symptoms is a depressed mood or loss of interest or pleasure in daily activities: (1) depressed mood most of the day; (2) markedly diminished interest or pleasure in all or almost all activities most of the day; (3) significant weight loss when not sick or dieting, weight gain when not pregnant or growing, or decrease or increase in appetite; (4) insomnia or hypersomnia; (5) psychomotor agitation or retardation; (6) fatigue or loss of energy; (7) feelings of worthlessness; (8) diminished ability to think or concentrate or indecisiveness; and (9) recurrent thoughts of death or suicidal ideation (APA, 1994). Adults also complete the Sheehan Disability Scale (SDS), which measures impairment caused by depression. NSDUH's past year's MDE data is generated based on respondents who confirmed lifetime MDE. These respondents are asked whether in the past 12 months they experienced MDE symptoms for a period lasting two weeks or longer. The NSDUH depression approach makes no exclusions for MDE caused by medical illness, grief, or drug use disorders. This project's cumulative incidence proportions (given survival to the date of the assessment) are derived from responses in the NSDUH depression modules for adolescents aged 12-to-17-years-olds on the date of assessment, as depicted in the following flowchart.

Figure 3. The flow chart shows the process used to construct samples of adolescents who did and did not experience Brief Depressive Spells (lasting 1-3 days or more), and DSM-IV Major Depressive Episodes as defined in the text. Data from the United States National Surveys on Drug Use and Health. Ann Arbor, MI: Inter-university Consortium for Political and Social Research. Dataset: SDA/ NAHDAP/04596-0001)," United States, 2004-2020.

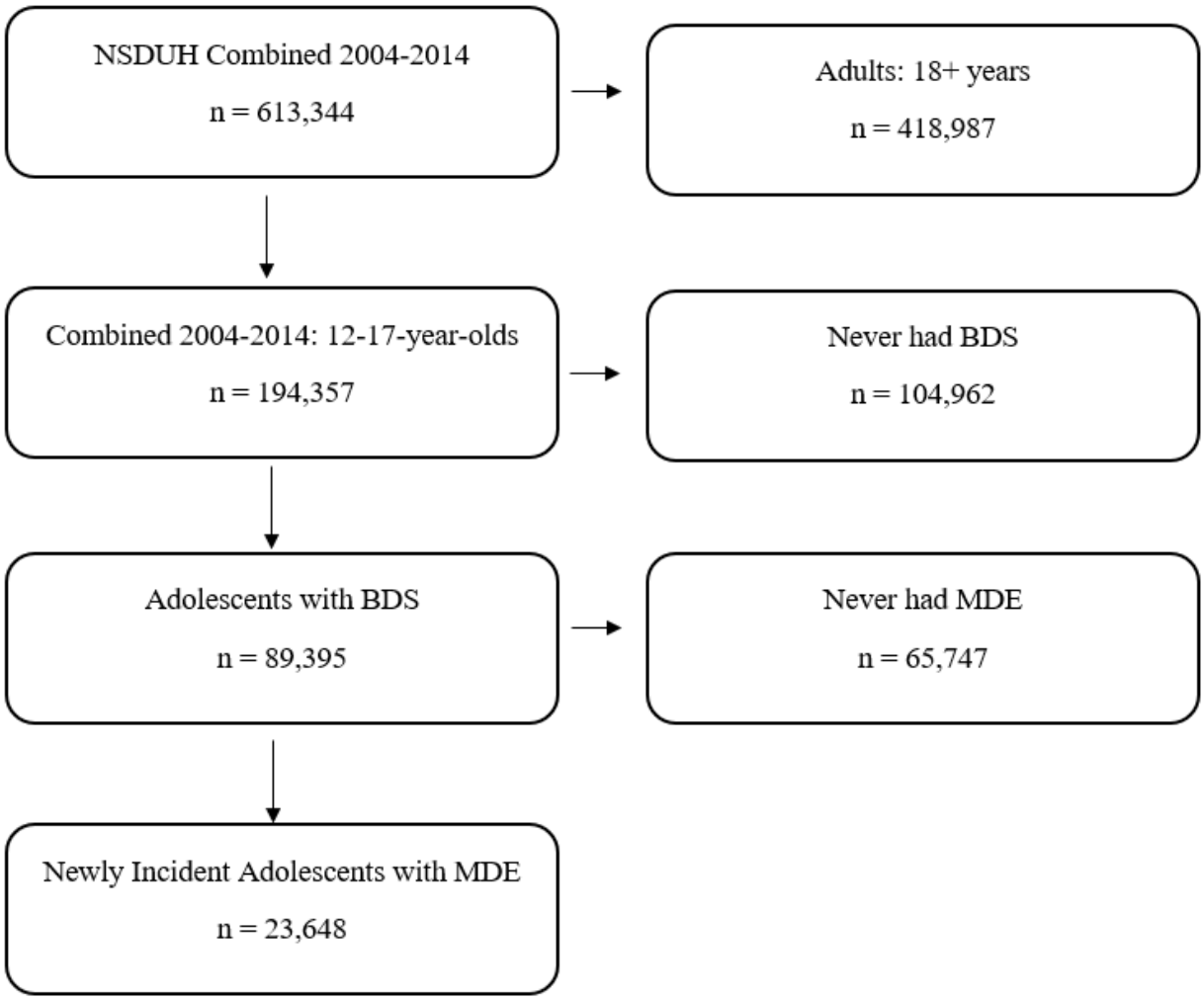
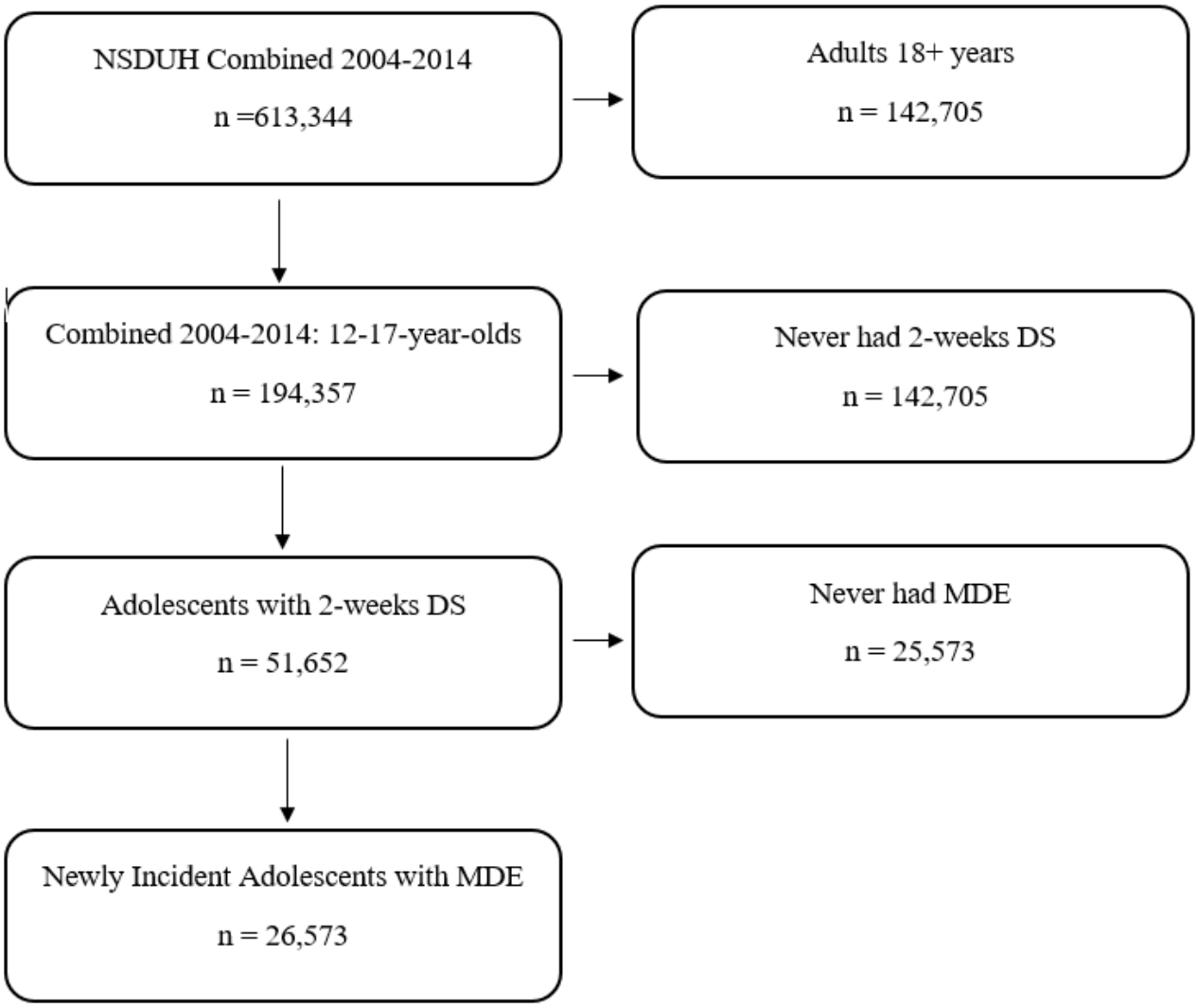


Figure 4. Flow chart showing the process used to construct samples of newly incident Major Depressive Episode cases given 2-weeks Depression Spell experiences among adolescent participants. Data from United States National Surveys on Drug Use and Health. Ann Arbor, MI: Inter-university Consortium for Political and Social Research. Dataset: SDA/ NAHDAP/04596-0001),” the United States, 2004-2014.




The SARS-COVID pandemic of 2020 deserves mention. The NSDUH field work proceeded as described above with an ACASI assessment of each sampled individual's dwelling unit during most of the first quarter of 2020. This assessment was done in the early stages of the pandemic. As of March 2020, the fieldwork approach was halted. Thereafter, during the final quarter of 2020, the fieldwork resumed, but the individual participants completed the assessment as a tablet-based computerized self-interview via an internet connection and cloud-based storage of the responses. The meta-analysis approaches described below indicate some degree of disruption of the time trends of estimates across the years from 2017 through 2020, but the meta-

analysis approach accommodates that methods variation as is the case for a conventional meta-analysis of different study designs and samples after completion by independent research teams and then reported in the literature for the aggregate meta-analysis. Details about the 2020 methods can be found in this online report (United States, 2020: https://www.samhsa.gov/data/report/nsduh-2020-methodological-resource-book-mrb).

### 3.3 Human Subjects Protection

FIs have been IRB trained on ethics, human subjects research, the IRB's role, and the role of FIs in protecting respondents' rights. Other applicable FI training includes the Confidential Information Protection and Statistical Efficiency Act (CIPSEA), records management training, and bilingual training for bilingual field interviewers. Field interviewers continue training to learn sampling procedures to protect sampling integrity, challenging field situations, screening, and interview procedures, answering interviewees' questions, and the overall quarterly review of project procedures and protocols after completing their first month of fieldwork.

All new FIs must pass certification and are trained to detect unlisted dwelling units, subsequently entered into the computer and selected for participation. In situations where FIs struggle to attain participation in a dwelling unit, refusal conversion procedures centered on the professional answering of questions, conversion letters, and the protocol to return to the dwelling unit at another time. The FI fieldwork is governed by institutional review board-approved protocols for recruitment and standardized computer-assisted self-interviews. The US Department of Health and Human Services Center for Behavioral Health Statistics and Quality commissioned the creation of the NSDUH open-access analysis files with de-identified data after applying disclosure analyses designed to prevent the re-identification of participants. Considering the open access and no contact with participants, the Michigan State University institutional review board ruled that plans to analyze these data qualified for the federal category "not human subjects research."

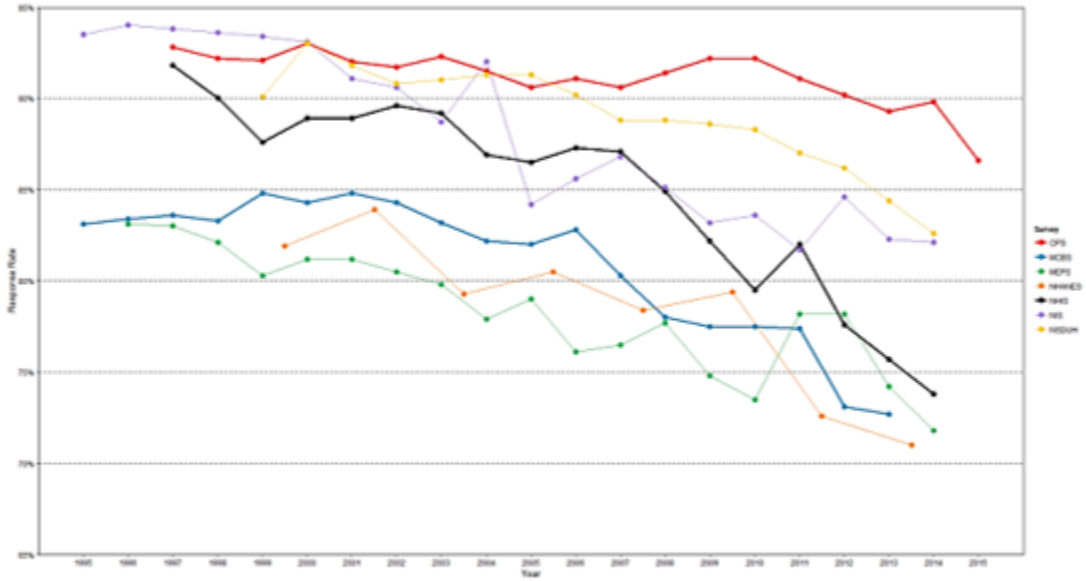
### 3.4 Participation Levels and Assessment Protocol

A monetary incentive (generally $30) has been awarded to respondents for participating in the NSDUH survey from 2002 through the most recently conducted surveys (e.g., United States, 2018). Concurrently, survey participation first increased, but there have been recent declines in participation levels, perhaps because the monetary value has not followed cost of living increases over the years. Expressed in the form of proportions but called 'rates,'

participation levels are expressed as functions of i) the household response rate, ii) the response rate of the individual selected by the screener, and iii) an unconditional response rate representing interviews in the second stage divided by the number of persons eligible to be interviewed if all households had been successfully screened (Czajka & Beyler, 2016). Screening response rates were calculated from the numerator of completed screenings and a denominator of total eligible dwelling units. However, ineligible respondents were subtracted from the total. Czajka & Beyler (2016) explained that the unconditional response rate is based on the product of the first two response rates. For example, if 92% of sample households were screened and 73% of the selected respondents were interviewed, the unconditional response rate would be (92×73)/100=67% (Czajka & Beyler, 2016). NSDUH conditional and unconditional response rates, as reported by Czajka & Beyler (2016), are replicated in Table 1. The table shows participation levels for the NSDUH ranging from 60%-75% from 2002 to 2014. Montgomery and colleagues (under review) updated these participation levels through 2020 and showed declining participation levels in recent years, with the SARS-COVID-2 pandemic disrupting participation markedly. Participation levels in 2020 are well below the 60%-70% levels seen in prior years (data not shown in the following table, which is based on 1999-2014 values).

NSDUH's declining participation levels are not unique to NSDUH. Federally funded national survey participation levels have been declining annually (Fig 3 and Table 1.). Of course, in research on depression-related conditions, the issue of non-response can be especially challenging if there are non-randomly missingness mechanisms such that individuals with a major depressive episode or brief depressive spell are more likely to refrain from participation. This topic is revisited in the Discussion section of this dissertation.

Figure 5. Declining Participation Levels in Federally Funded US National Surveys.



Source: Czajka, J. L., & Beyler, A. (2016). Background paper declining response rates in federal surveys: Trends and implications. *Mathematica policy research*, *1*, 1-86.

3.5 Statistical Analysis Approach

For the most part, this project required estimation of proportions and their standard errors, followed in some instances by interval estimation using complementary frequentist 95% confidence intervals and Bayesian credible intervals. The four-parameter Hill functional analysis approach also has been used, and meta-analysis approaches also have been used.

In this context, sampling error is introduced because NSDUH is not based on a 100% census of the population. NSDUH multi-stage area probability sampling means that methods such as the Taylor series and bootstrap re-sampling are required to estimate variances, standard errors, and intervals. These approaches deal with non-independent observations within sampled dwelling units and geopolitical units for the multi-stage area probability sampling. Analysis weights take into account the inverse probabilities of selection, as well as post-stratification adjustments that try to deal with the variability of non-participation across subgroups. The NSDUH research team seeks to improve estimates via (1) adjustment of household weights for non-response at the screener level; (2) post-stratification of household weights to meet population controls for various household-level demographics by state; (3) adjustment of household weights for extremes; (4) post-stratification of selected person weights; (5) adjustment of responding person weights for non-response at the questionnaire level; (6) post-stratification of responding person weights; (7) adjustment of responding person weights for extremes.

To be clear, the NSDUH's multi-stage sampling approach mentioned earlier imposes some limitations on the standard formulae for variances estimation (described further in section 3.6.3) which do not necessarily hold. This is because individuals sampled within a census block or within a dwelling unit tend to be more similar to one another than individuals drawn at random from a national registry (i.e., the non-independent observation problem). The research approach in this dissertation has taken this into account and has been adapted to address these interdependent observations, primarily with the use of the Taylor series (delta) approach for variance estimation.

## 3.6 Estimation Approaches

This section of Chapter 3 provides an overview of the specific statistical analysis approaches I used in my dissertation project. I have already discussed how analysis-weighted estimates must be used to account for variation in the sample selection probabilities at each stage of multistage area probability sampling. The analysis weights also included post-stratification adjustments to bring subgroup counts into line with the most recent US Census data for subgroups defined by sex, age, race, and ethnicities as reported by the US Census Bureau. The purpose of this section is to explain how the cumulative incidence proportions are estimated, taking into account cohort-specific, age-specific, and year-specific variations. Additionally, I describe the epidemiological mutoscope approach that can be utilized to study the experiences of individual birth cohorts. By using the four-parameter Hill function, I examine the health disparities among census race-ethnicity subgroups in a way that can identify health disparities and lead efforts to achieve health equity and social justice in the future. In the next section, I describe the ways in which I use Bayesian credible intervals to complement the more conventional 95% confidence intervals.

### 3.6.1 Cumulative Incidence Proportions Among Survivors (CIPAS, sometimes shortened as CIP)

Selwyn D. Collins was a pioneering statistician who worked for the US Public Health Service (USPHS) from 1920 through 1959. He was a part of a USPHS research team organized by Edgar Sydenstricker. Social scientist Edgar Sydenstricker helped Joseph Goldberger conduct the cotton mill village surveys, which led to the discovery that pellagra was caused by a restricted diet. During the end of the Spanish flu epidemic, Collins' USPHS research involved analyses of morbidity records collected during cross-sectional surveys of school-attending youths whose schools had been sampled for the Child Hygiene investigations conducted by the USPHS.

Characterizing the lifetime history statistics on diseases such as diphtheria and scarlet fever as ‘attack rates,’ Collins concluded that age-specific estimates based on the lifetime histories described in survey questionnaire reports could provide a useful representation of the experiences of subgroups based on the life histories of the surviving school-attending youths. In his study, Collins used a logistic function sigmoid curve model to estimate the extent to which the CIPAS estimates might rise from relatively low levels in the youngest school children up to an upper asymptote at the highest age group, along with a slope parameter estimate to characterize the "rise over run" increases across the age subgroups in between the oldest and the youngest students. I was shown these early epidemiological studies conducted by Collins by my doctoral advisor while taking the course 'Historical Roots of Epidemiology'. I then decided to write about them in a poster presentation. On the basis of that unpublished work, this dissertation research project was constructed (Gregoire & Anthony, unpublished poster presentation, 2021).

My pre-dissertation work inspired me to apply similar estimation and functional analysis techniques to this dissertation's novel approach to studying teen depression experiences. Rather than using Collins' attack rate terminology, or lifetime prevalence (as explained below and by Streiner et al, 2009), I chose to use the term cumulative incidence proportion among survivors (also referred to as CIPAS and CIP). By including ‘among survivors,’ the study acknowledges a potential source of error when adults are asked about their lifetime morbidity histories. In countries with relatively low infant mortality rates this source of error appears to be rather small for conditions such as depression.

To calculate age-specific estimates of CIPAS for communicable diseases, Collins created a ratio with the numerator being the number of students of that age who had already experienced the communicable disease and the denominator being all students of that same age. Social scientists who were unaware of epidemiology's distinction between prevalence and incidence used the term 'lifetime prevalence' for that ratio in their community field survey research in the 1950s and 1960s, which led Johns Hopkins epidemiologist-psychiatrist Ernest M. Gruenberg to characterize 'lifetime prevalence' as a "gimmick". Gruenberg (1963) was not the first to criticize the concept of lifetime prevalence. Prior critiques had been offered by the biostatistician James Doull, his student Morton Kramer, and also by the famous child psychiatrist-epidemiologist Rema Lapouse, now primarily recognized because there is an annual ‘Rema Lapouse Award’

granted by the American Public Health Association to recognize lifetime achievements in psychiatric epidemiology and the prevention and control of mental disorders.

Aside from the criticisms, which mostly apply to conditions with relatively high case fatality rates and are affected by left truncation and censoring issues well known in 'time-to-event' survival analysis research, the CIPAS estimate's value has been demonstrated in a series of epidemiological studies and investigations of the 'force of morbidity' and 'infection'. These studies have been based on cross-sectionally derived serostatus evidence when epidemiologists try to estimate infectious disease parameters from field survey estimates of antibody levels in populations. This dissertation research project on depression, substitutes the individual's lifetime history of: (a) the first Brief Depressive Spell (BDS), lasting 1-3 days at minimum, (b) the first 'Depression Spell' (DS) lasting two weeks at minimum but without requiring the full syndrome of major depression, and (c) the DSM-IV Major Depressive Episode or Disorder (MDE, MDD), lasting two weeks at minimum and also with the sustained two-week duration requirements for the allied clinical features of MDE that have been described in an earlier sections of this dissertation report. In place of serostatus assays of antibody persistence and level, this project is based on what the teens report about their experiences of BDS, DS, and MDE up to and as of the date of the NSDUH survey assessment.

As for my age-specific BDS CIPAS estimates, computed from 2004 to 2020, my numerator is the analysis weighted number of participants who have experienced a BDS at that age, and the denominator is all participants at that age; similar to what Collins estimated for his set of communicable diseases based on the 1917-19 Child Hygiene surveys conducted by the USPHS. I derive these estimates for each subgroup under study, as denominated by the US Census race-ethnicity categories for which there were a sufficient number of NSDUH participants to provide reasonably precise estimates, and for males and females separately as well.

Regarding the transition from BDS to DS, the denominators are teens who experienced BDS, and the numerators are those who experienced DS. Accordingly, the transition from BDS to MDE/MDD is reflected in the number of MDE/MDD lifetime history cases as observed among those who had experienced a BDS (which by definition must occur as a 1–3-day experience before the MDE/MDD experiences of the two-week syndrome can occur). Set theory clarifies the temporal sequencing issue such that a person who qualifies as a DSM-IV MDE case

must also qualify as a member of the subset defined by a two-week DS, and must also qualify as a member of the subset defined by a one-to-three-day BDS. As will be shown in this report's estimates, there are many BDS cases who do not progress to MDE, and there are many DS cases who do not progress to MDE.

As shown in the next chapter, these CIPAS estimates have been produced year-by-year and age-by-age for all US study population members age 12-to-17-years-old on the date of the NSDUH survey assessment. Additionally, they have been produced for the US Census race-ethnicity subgroups. They also have been produced for males versus females. Lastly, they have been developed for birth cohorts studied over time, according to Wade Hampton Frost's cohort research on tuberculosis mortality described in Chapter 2 and adapted to the 'epidemiological mutoscope' approach developed by my doctoral advisor and his research fellows and trainees over the past decade (e.g., Seedall & Anthony, 2015; Cheng et al., 2016).

Each mutoscope shows the experience of a cohort over time, as displayed in the diagonals of the tables that list the age of the participants in the columns and the year of assessment in the rows. For this project, the diagonal trace of each cohort's experience provides a cohort-wise view of the epidemiological trajectory of depression. For example, the BDS's MDE CIPAS estimate for 12-year-olds in 2004 then is followed by the next CIPAS estimate for 13-year-olds in 2005 and then by the next CIPAS estimate for 14-year-olds in 2006, and so on, down each diagonal of the epidemiological mutoscope table.

This dissertation takes advantage of the differences between successive age-specific estimates to derive approximations of the incidence of communicable diseases based on the lifetime histories of the students, age by age, just as Collins' work involved using successive age-specific estimates to evaluate communicable diseases. The estimated slope of the Hill function described in Chapter 2 is an estimate of the difference at the inflection point of the Hill curve (i.e., at the point of the PD50 parameter estimate).

### 3.6.2 Meta-Analysis

In addition to estimating CIPAS stratified by age, year, and US Census subgroups as described above, I then produced age-specific meta-analysis summaries. In this work, I started with the conventional frequentist 95% confidence intervals and point estimates, treating each year's sample from NSDUH as a newly completed and independent replication sample, given

that NSDUH samples are drawn without replacement of individuals. These meta-analysis estimates based on the software described below are shown in the next chapter.

With the assistance of my guidance committee member, Dr. Olga A.Vsevolozhskaya, I extended those frequentist interval estimates in the direction of Bayesian inference, and I generated Bayesian credible intervals. With the help of my advisors, I learned how to use the R software functions that specify a conjugate prior with a beta-binomial likelihood specification such that the beta prior becomes a beta posterior. This is a useful approach because the conjugate prior reduces Bayesian updating computations and means that the so-called hyperparameters of the prior distribution are modified without the computational intensity of computing integrals. I ensured that the estimated proportion could be ranged between 0.0 and 1.0 when specifying that first prior (for the 2004 posterior estimate).

Dr. Vsevolozhskaya showed me how to create bounds for the Bayesian credible interval by specifying an expected range within which the estimate should fall. Once the posterior estimate for 2004 and its 95% credibility interval were derived, these results became an informative prior for estimation of the meta-analysis summary estimate that combined 2004 and 2005 data. That posterior estimate, based on the prior and the 2005 data, then became the prior for the next step, which called upon the NSDUH 2006 estimate as data, and produced the next posterior estimate. And so on, until the final posterior estimate and a Bayesian credible interval had been derived, based on all of the steps between 2004 and 2020. The final meta-analysis summary estimates are shown in my Results chapter.

The complementary frequentist 95% confidence intervals are also shown in the Results chapter. In general, it can be seen that the frequentist approach and the Bayesian approach yield point estimates that are not appreciably different from one another. Based on the same inputs of NSDUH analysis-weighted point estimates and Taylor series standard errors, the Bayesian credible intervals tend to be narrower than the corresponding frequentist 95% confidence intervals.

Professor Andrew Gelman of Columbia University's Department of Statistics discussed recently with Professor Sander Greenland of UCLA's Department of Epidemiology and Statistics that the terms 'confidence interval' and 'credibility interval' may not serve as well as the more-direct term 'compatibility interval.' That is, the point of departure for frequentist inference is to think of and to approach the point estimate as a fixed population parameter with bounds that

generally either are or are not compatible with a null specification. (Here, I specified alpha equal to 0.05 so that the resulting interval bounds are interpretable as 95% intervals.

In this dissertation, the null hypothesis might be whether adolescents experiencing BDS have a zero chance of developing MDE. Additionally, for subgroup analyses, whether the difference between the two estimated proportions is equal to zero. In essence, the inference task is to judge whether the 95% interval is or is not compatible with the null. This is given the idea that the true value of the population parameter is zero. (In my work, it is not possible for the fixed population parameter to be less than zero, but it might equal zero.) The inference from the 95% interval allows for the possibility that the fixed population parameter value might fall outside of the interval (be 'incompatible with' that interval) five percent of the time but cannot state or draw any inference about whether the observed interval does or does not trap the true population parameter value five percent of the time.

Bayesian inference, on the other hand, specifies the proportion as a random variable along with the likelihood function distribution. It derives the posterior estimate and its 95% interval based on the conjugate beta prior for a binomial distribution. In the case of the specifications being correct, we can conclude that the 95% interval will include the true 'random' population parameter value somewhere between the intervals. Though it may not be the precise posterior point estimate, the bounds should include the true population parameter.

As such, both the frequentist 95% interval and the Bayesian 95% credibility interval can be said to be 'compatibility' intervals with respect to the fixed variable interpretation of the population parameter value (according to the frequentist approach) and with respect to the random variable interpretation of the population parameter value (according to the Bayesian approach). Presentation of both the frequentist 95% CI and the Bayesian 95% CRINT gives the reader a choice. In my estimates, the Bayesian 95% CRINT has the advantage of being generally narrower than the corresponding frequentist 95% CI, such that the 'zone of incompatible values' is more constrained.

### 3.6.3 Variance Estimation

The complex NSDUH sampling design generally motivates the use of Taylor series linearization (TSL) as a calculus-based approximation of variances and standard errors (SE) of the estimated parameters. All variance and SE estimates for the parameters reported in this study are based on TSL approaches unless some other approaches are stated as an alternative. One

alternative involves bootstrap re-sampling to derive frequentist 95% confidence bounds, especially appropriate for parameters such as medians.

### 3.6.4 Frequentist Confidence Intervals

The logic of a frequentist confidence interval (CI) starts by specifying the parameter as if it qualifies as a 'fixed' parameter in the domain specified by Fisher, Pearson, and other early frequentists. Estimation and inference proceed accordingly, whether the CI is based on the TSL variance estimates, or whether the CI are based on alternative approaches such as bootstrap re-sampling.

### 3.6.5 Bayesian Credible Intervals

Whereas frequentist 95% CI treats the population parameter value as a 'fixed variable,' the Bayesian approach treats the population parameter point estimate as a 'random variable.' A set of published and unpublished articles and books have helped me think through the inference contrasts of frequentist 95% CI versus the Bayesian Credible Intervals (CRINT), most recently some articles and blog posts by Columbia Professor Andrew Gelman (2022).

### 3.6.6 Hill functional analysis

The Hill function was introduced in pharmacology, toxicology, and the study of drug-receptor interactions in the early 20th century. In this epidemiology research project, I do not seek to infer drug-receptor mechanisms by using the Hill function. Rather than focusing on standard epidemiological estimates of prevalence proportions and incidence rates, I seek to broaden our understanding of how female-male and US Census race-ethnicity health disparities might be disclosed by analyzing all four parameters of the model-based Hill function. In Chapter 2 of this dissertation, the four parameters of the Hill function are described. As part of my research, I fitted the Hill function to the age-specific CIPAS estimates for the various subgroups mentioned above.

My biostatistics advisor O.A. Vsevolozhskaya taught me to use R-Studio and her R scripts to fit the Hill function to the age-specific estimates and to obtain confidence intervals for the Hill function parameters. This frequentist interval estimation approach involved a weighted residual bootstrap procedure to repeatedly generate datasets based on the fitted nonlinear regression model. In this instance, more than **B**=999 bootstrap datasets were created. The weighted residual bootstrap was implemented as follows:

**Step 1.** Fit a model to the original sample of observations weighted by the inverse of their variance to account for heteroskedasticity. Obtain the fitted values as

$\hat{y}_i = f(x_i, \hat{B})$

**Step 2.** Get the residuals:

$\epsilon_i = y_i - \hat{y}_i$

**Step 3.** Construct the standardized residuals:

$\tilde{\eta}_i = \epsilon_i / \hat{\sigma}(x_i)$

**Step 4.** Resample with replacement, to get

$\tilde{\eta}_1, \ldots, \tilde{\eta}_n$

**Step 5.** Set

$\tilde{y}i = f(x_i, \hat{B}) + \hat{\sigma}(x_i)\, \tilde{\eta}_i$

**Step 6.** Regress the bootstrap values $y_i$ on $x_i$ (as in Step 1.) to obtain

$\hat{B}^*$

**Step 7.** Repeat Steps 4-6 **B > 999** times.

The confidence intervals are obtained based on the percentiles in the empirical distribution of the bootstrap parameter estimates:

$\hat{B}^*$

This procedure was implemented using the function weighted_nls Boot.

As described by Vsevolozhskaya & Anthony (2017), the Hill functional analysis makes it possible to derive non-linear interpolations of the empirical estimates [e.g., here, the estimated proportion transitioning into a Major Depression Episode (MDE) after an adolescent's Brief Depression Spell (BDS) for age values in between the 12th birthday and the 18th birthday]. Hence, the PD50 parameter of the Hill function (analogous to an LD50 or ED50 in a pharmacological or toxicological study of dose-response relationships) can have a value just under 13 (e.g., 12.9) or otherwise fall in between the ordinal values of age in years from 12 to 17 for the adolescent participants in the NSDUH community samples. Vsevolozhskaya & Anthony (2017) go on to explain the parametric Hill equation as:

Figure 6. The Hill Equation.

$$y_i = (P_{\max} - P_{\min}) \times \frac{1}{1 + \left(\frac{PD_{50}}{x_i}\right)^k} + P_{\min} + \epsilon_i,$$

In my project, $y_i$ is the empirical proportion of adolescents assessed at a stated age value who have experienced MDE given that a BDS had occurred (either during the same MDE experience or in some prior time interval). Here, $x_i$ is the age of the NSDUH adolescent population under study for subject I as i = 1, …, n. The $\epsilon_i$ values are assumed to be independent and normally distributed with constant variance $\sigma^2$.

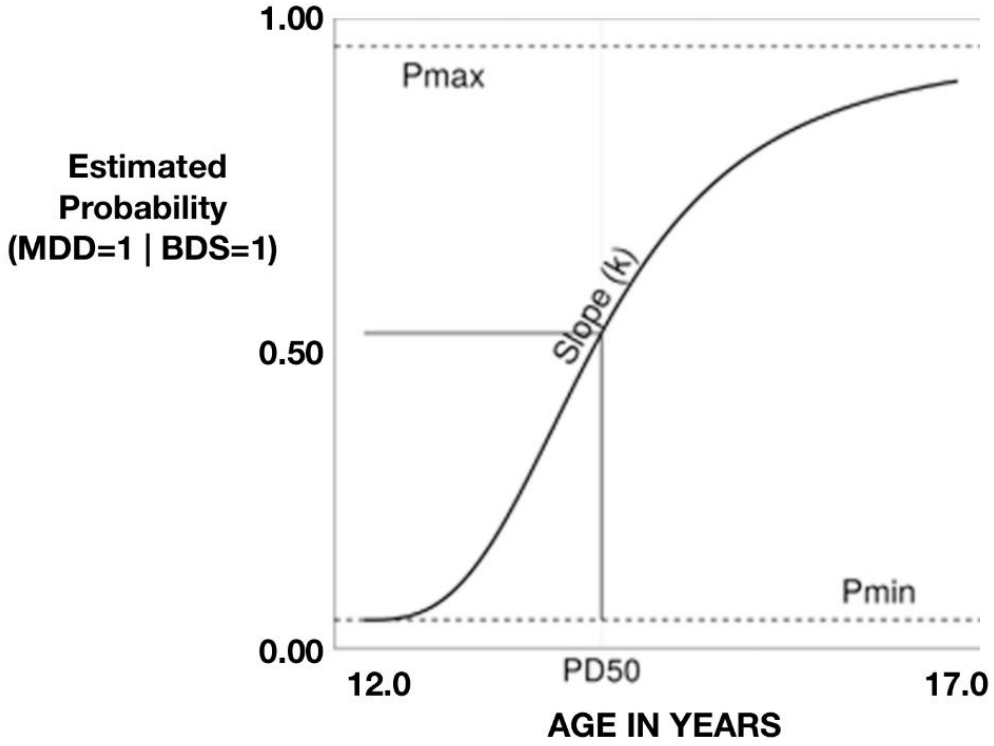
Vsevolozhskaya & Anthony (2017) also explain that Pmin, Pmax, PD50, and k are four Hill function parameters requiring estimation. As they state: "An iterative estimation process requires users to supply plausible starting parameter values, supplied here as “eye-balled” empirical point estimates" (Vsevolozhskaya & Anthony, 2017).

The four parameters that control the particular shape of each sigmoid Hill function can be given the following epidemiological interpretations. (Please note that the corresponding statements can be made for the transition from BDS+DS to MDE.)

1. Pmin is the estimated age-specific proportion experiencing MDE among the adolescents who had experienced a BDS at or before entry to the adolescent years (e.g., age 12);
2. Pmax is the estimated age-specific proportion who experienced MDE (conditional on BDS=1) among the adolescents who remain in adolescence (e.g., here, before the 18th birthday);
3. PD50 stands for the number of years of adolescence after which the proportion experiencing MDE, given BDS=1, is halfway between Pmin and Pmax, and finally
4. k is the rate of transitioning from BDS to MDE across the range from P min to P max, evaluated at the age indicated by the PD50 estimate (i.e., an inflection point estimated via this functional analysis approach).

A graphical representation of these parameters is shown in Fig 6.61. It is my adaptation of a figure that first appeared in Vsevolozhskaya & Anthony (2016).

Figure 7. A graphical representation of the Hill Function parameters.




3.7 Software

Throughout this dissertation project, I used Stata and its 'svy' commands for complex analysis and estimation of survey sample data, as well as 'metan' commands for meta-analysis. I also became proficient in the use of ‘R’ commands and R-Studio for the work and estimates completed with the assistance of my advisory team, and in particular with Dr. Vsevolozhskaya and our colleague Dr. Xiaoran Tong, who guided me to at least a basic level of mastery of their creative software innovations.

# CHAPTER 4 - RESULTS (AIM 1)

## 4.0 Chapter Overview

For the first section of this chapter, I organized my presentation of results in the form of a journal article outline. My idea is that this approach might accelerate submission of my first peer-reviewed journal article based on Aim 1. One or more separate articles might be produced for each aim.

## 4.1 Focus on Female-Male Variations

### 4.1.1. Restatement of Aim 1

Exactly as stated in my Introductory Chapter, the aim of the first study in my dissertation research project is as follows:

Aim1: To compare and contrast age-specific epidemiological estimates for female and male adolescents with a prior history of BDS, estimating female-male differences in the post-BDS occurrence of a sustained (two-week) Depression Syndrome (DS), and then to compare and contrast the estimated occurrence of Major Depressive Episode (MDE) once both BDS+DS have occurred.

In Chapter 2, I provided background information based on a scholarly review of prior theory and evidence on the research aims and estimates to be presented in this section. I motivated the study of progressions beyond a brief depressive spell as an elaboration of the well-established conceptual model devised by Angst, Merikangas, and their collaborators. Drawing primarily upon their longitudinal epidemiology studies of adolescents in Switzerland, they identified relatively short-lived mood swings as predictors of later formation of more clinically significant affective syndromes including Major Depressive Episode.

Methods in my work are derived from the work of Selwyn Collins in the 1920s. Collins was presented with compiled data from US Public Health Service-sponsored surveys of school-attending youths in a small set of US communities such as Hagerstown and Baltimore in Maryland. In these surveys, questionnaires were used to ask the students about their lifetime histories of diseases, with a primary focus on communicable diseases such as scarlet fever. Collins plotted the age-specific cumulative incidence proportions (his 'attack rates') in accordance with the reported data. He then produced smoothed estimates with a focus on estimated slopes of the basic logistic model he learned while working at Johns Hopkins

University. After transforming the model-based predicted odds, Collins estimated each condition's age-specific occurrence, using the term "attack rate" to describe it.

The basis of my work comes from early Collins epidemiological studies of age-specific disease occurrence among US community residents during adolescence without limiting the study to school-attending youth. My research, which included community-dwelling samples of adolescents (excluding those in institutionalized institutions), derived corresponding age-related cumulative incidence proportions for transitions from Brief Depression Spell (BDS) to Major Depression Episode (MDE), as defined in the American Psychiatric Association's Diagnostic and Statistical Manual (DSM-IV). I also derived corresponding proportions for the transition into MDD after the occurrence of a Depression Syndrome, defined to involve a two-week sustained Depression syndrome with two weeks of sustained depression or a depression-equivalent (e.g., anhedonia). That is, the BDS might or might not be followed by a two-week Depression Syndrome (DS) that falls short of Major Depressive Episode criteria. In some cases, the experience of a BDS followed by a DS is followed by a Major Depressive Episode (MDE) or Disorder (MDD). As previously mentioned, MDE and MDD are interchangeable acronyms. They refer to a sustained Depression Syndrome (DS) lasting at least two weeks, but during the DS experience there is an additional set of MDE-related clinical experiences. The range of this set of allied clinical experiences, each sustained for two weeks or more, is extensive and might involve pathological guilt, neurocognitive manifestations of MDE (e.g., trouble concentrating), neurovegetative manifestations (e.g., sleep or appetite disturbances), and death or suicide-related thoughts or behaviors (e.g., suicide attempt).

Thus, when an adolescent experiences MDE/MDD, they join a group that requires a DS as well as a BDS in sequence before the MDE takes place. However, as shown in this study’s estimates, not all BDS-affected adolescents progress to MDE, and not all DS+BDS-affected adolescents progress to MDE/MDD. This dissertation research project’s estimates of these epidemiological parameters are especially novel features of the work and have not previously been seen in published articles on this topic.

This dissertation can be considered a step forward from the earlier works of Angst and colleagues. This is because the point of departure is not the mood swing episode that is central in their concept of the depression spectrum. Rather, the point of departure is the Brief Depressive Spell possibly lasting an entire day or two, but without the mood swing component (e.g.,

oscillation from low-high or low-high-low or high-low mood). The BDS might be regarded as a relatively normal aspect of life experience during adolescence. However, as recently discovered by Quinlan and colleagues (Quinlan et al., 2019) and as confirmed in this dissertation research project, a BDS occurs less often than might be expected. For almost all subgroups under study here, the estimated unconditional BDS cumulative incidence proportion based on lifetime histories remains well below the 50% value across the child-adolescent age span from 12 years through 17 years. As described below, BDS might be regarded as a target condition for 'targeted preventive interventions' intended to disrupt progression from BDS toward the more advanced forms of sustained Depression syndromes and toward clinically diagnosable Major Depressive Episodes. As noted in the Discussion of these findings, the same 'targeted intervention' implication also emerges when this dissertation research's findings on the transition into MDD after a two-week sustained spell of depression or depression-equivalents (i.e., the Depression syndrome) are considered.

In terms of methods, this dissertation research project also shifts from the ‘smoothing’ model used by Collins in his 1920s work with its basic logistic model – i.e., a model used to ‘smooth’ the age-specific estimates, condition by condition. I turned to the four-parameter Hill functional analysis approach and estimated all four Hill function parameters (Pmin, Pmax, the slope k, and the PD50 parameter) to enable female-male comparisons of all four Hill function estimates.

## 4.2 Materials and Methods

I provided a detailed overview of study methods in Chapter 3. In brief, the population under study encompassed all community-dwelling adolescents ages 12 through 17 years, with a multi-stage area probability sampling frame that included college dormitories, homeless shelters, and other non-institutional group quarters as well as household dwelling units. The only exclusions from the survey sampling frame were the relatively small numbers of adolescents living in institutions such as long-stay psychiatric hospitals, and the small numbers with residence within the boundaries of US military bases.

As was true for the field survey work of the USPHS and analyses completed by Collins roughly 100 years ago, this dissertation research project is based on a survey of adolescents conducted with federal government sponsorship. It is known as the US National Survey on Drug Use and Health (NSDUH). For the NSDUH, all 50 states and the District of Columbia are

included in the sampling frame. For the NSDUH, a new sample of dwelling units and participants was drawn each year from 2002 to the present, with an audio computer-assisted self-interview (ACASI) module on depression-related experiences added in 2004 to the prior coverage of drug use and other health topics. Each year from 2004 through 2019, roughly 15,000-17,000 adolescents in the 12-17 age range participated after individual assent and parent consent protocols that had been approved by a cognizant institutional review board (IRB). The Michigan State University IRB reviewed my dissertation research protocol and judged it to qualify for the federal 'not human subjects research' category due to the de-identification of participants and no contact with human subjects during my project. It should be noted that the estimates from 2020 are based on a somewhat smaller number of adolescent participants due to the pandemic circumstances (United States, 2020).

During each of these years, the federal government has commissioned the creation of a detailed online methods report (e.g., https://www.samhsa.gov/data/report/2020-nsduh-annual-national-report). The report describes the study sample, the ACASI protocol, and each standardized assessment item. Montgomery and colleagues have prepared a summary overview of these details for all years from 2002 through 2022 (Montgomery et al., under review). My dissertation thesis has supplementary appendix material that includes extracted information from these online reports and from the report prepared by Montgomery and colleagues, with a specific focus on adolescents and on the depression module items.

For this section of my dissertation's Results chapter, I produced age- and year-specific analysis-weighted proportions. The analysis weights have two primary input values: (1) the inverse of the participant's probability of selection, and (2) a post-stratification adjustment factor (PSAF) that is intended to bring the NSDUH distributions into balance with the distributions found in the US Census age-, sex-, and race-ethnicity reports for each year. In this way, the NSDUH seeks to yield estimates that are nationally representative of the US population each year. As such, the primary focus of estimation is one that regards the US population parameter as a 'fixed' value for which the sample derives a realization. Accordingly, almost all prior NSDUH reports with estimates and confidence interval estimation are based on the frequentist tradition of Pearson and Fisher, with the parameter regarded as a fixed value, and the resulting 95% confidence interval (CI) is designed to trap that value. However, the frequentist confidence interval does not allow us to make any statement such as 'There is a 95% chance that the

confidence interval includes the true population parameter value.' Conceptualized in this way, even if each year's sample were to be re-drawn and re-assessed a large (perhaps approaching an infinite) number of times, the resulting 95% CI might not trap the fixed true population parameter value in 5% of these replications.

Except when noted explicitly, the variance estimation approach has been based on Taylor series linearization after a logarithmic transformation of the proportion being estimated, and with back-transformation for tabular and visualization displays of the resulting population parameter estimates and what Greenland, Gelman, and others have started to describe as 'compatibility intervals' (Gelman, 2022). The Taylor series approach helps deal with non-independent observations that arise with the NSDUH multi-stage area probability sampling. For example, when a US census block group is sampled, and multiple dwelling units or participants are sampled within those units, the characteristics of two participants drawn at random from within each block group or unit will tend to be more similar than two participants drawn at random from the total population. This departure from the independence assumption of simple random sampling (SRS) from a total list of a country's residents tends to create a 'survey design effect' such that variances based on the multi-stage area probability sampling approach can be too small relative to the variances based on the SRS approach. (Sometimes the 'design effect' yields a 'too large' variance. However, in most published estimates, the design effect results in compatibility intervals that are smaller than the SRS counterparts.)

For my dissertation research project, I show the 95% CI based on the frequentist approach, but I also show a Bayesian alternative 95% 'credibility interval' (CRINT). The point of departure for the Bayesian 95% CRINT is one that regards the population value as a 'random' variable as opposed to one that has a 'fixed' value. The resulting Bayesian 95% CRINT is one that should always trap the population parameter value. That is, based on *certeris paribus* principles ('all else held constant), the Bayesian 95% compatibility interval has a 95% chance of trapping the true population parameter's value. Other details about the Bayesian approach are presented in Chapter 3 of this dissertation.

As noted, Gelman (2022), building upon concepts introduced by Sander Greenland, argues that these two types of intervals might best be regarded as 'compatibility' or non-compatibility intervals. In this instance, one might conceptualize an expectation that none of the BDS experiences are followed by progression toward the more durable Depression Syndromes or

onward to the Major Depressive Episode (MDE). That is, the true population parameter might be expected to be zero, and under this null hypothesis, the inferences concern whether the intervals do or do not trap the null value. The Bayesian approach has an additional nuance, in that an initial prior can be specified to be non-null with a suitable distribution specified (e.g., in this study, the beta-binomial distribution), and with a set of plausible boundary conditions such as the range anticipated for the Bayesian CRINT. Then, each year's data are combined with Bayes' approach to yield a posterior point estimate and its accompanying CRINT.

For this work, after the specification of the Bayesian conjugate prior to the beta-binomial specification and a plausible set of boundary conditions, the 2004 estimate has been taken as data. Then, a posterior estimate and CRINT have been devised with the beta-binomial conjugate prior specified for the posterior distribution. The resulting estimate from 2004 and CRINT from 2004 become the prior for evaluation against the estimate from 2005. The result is a meta-analytic summary estimate based on the initial prior specification plus the data from 2004, the posterior from 2004, and the posterior from 2005. Iteratively, for my dissertation research project, I repeated this process, year by year, so that the meta-analysis summary includes a Bayesian point estimate as well as a 95% CRINT based on these iterations across all years of the NSDUH from 2004 through 2020.

In contrast, the frequentist meta-analysis started with the 2004 estimate and its frequentist 95% CI (no prior). Then, with the standard meta-analysis approach, the 2004 estimate and the 2005 estimate contribute to a meta-analysis summary estimate based solely on the 2004 and 2005 estimates. Then, 2004, 2005, and 2006 estimates are meta-analyzed to yield the next meta-analysis estimate and 95% CI based solely on those three years of data. And so on, through 2020 so the meta-analysis summary estimate in 2020 is based on all estimates from 2004 through 2020. Please note that the resulting 95% CI has the standard frequentist interpretation with the population parameter treated as 'fixed' whereas the Bayesian approach is based on the concept of a 'random' variable.

After downloading from the NSDUH public use datasets, I conducted the data analyses using Stata and R software. The visualizations of the age- and year-specific estimates, the frequentist 95% CI, and the Bayesian 95% CRINT are from R software provided by Drs. Vsevolozhskaya and Tong. The Hill function parameter estimates are based on R software provided by Dr. Vsevolozhskaya, as described in Chapter 3.

4.3 Results

Section 4.1 Description of The Unweighted Sample

Tables 2A through 2C provide a description of the unweighted sample of adolescents. The columns display participant age on the date of assessment. The rows display the year of assessment. Tables 2B and C provide unweighted sample descriptions for females versus males and for US Census 'race-ethnicity subgroups, respectively (also termed 'ethnic self-identification and abbreviated as ESI).

The female-male distribution was more or less evenly distributed between males and females (51% versus 49%). With respect to ESI, more than half of the participants self-identified as non-Hispanic white (57%). Just under one in seven self-identified as non-Hispanic Black (13%), about one in five self-identified as Hispanic (19%), one in 33 self-identified as Asian (3.4%) and the remainder self-identified as non-Hispanic in the other ESI subgroups, too infrequently to specify in the more fine-grained subgroups (e.g., Native Hawaiian).

Table 2. Adolescent participant characteristics in aggregate, all years. (Data from the US National Surveys on Drug Use and Health, 2004-2020).

| | **Unweighted 'n'** | **Analysis-weighted Distribution (%)** | **Analysis-Weighted 95% CI** |
|---|---|---|---|
| 12 | 41,166 | 15.3 | [14.7-15.2] |
| 13 | 44,454 | 16.6 | [16.3-16.9] |
| 14 | 44,838 | 16.7 | [16.4-17.0] |
| 15 | 46,134 | 17.2 | [16.9-17.5] |
| 16 | 46,536 | 17.3 | [17.0-17.6] |
| 17 | 45,212 | 16.8 | [16.5-17.1] |
| **B. Sex** | | | |
| Male | 136,920 | 51.0 | [50.7-51.3] |
| Female | 131,420 | 49.0 | [48.7-49.3] |
| **C. US Census Race/Ethnicity (ESI)** | | | |
| Non-Hispanic White | 153,986 | 57.4 | [57.1-57.7] |
| Non-Hispanic Black | 36,206 | 13.5 | [13.2-13.8] |
| Hispanic | 51,082 | 19.0 | [18.7-19.3] |
| Non-Hispanic Asian | 9,218 | 3.4 | [3.1-3.7] |
| Non-Hispanic Other | 17,848 | 6.6 | [6.3-6.9] |

Section 4.2. Unconditional Cumulative Incidence Proportions for Brief Depressive Spells

In order to place my conditional cumulative incidence proportions (CIP) into context, I will start by presenting estimated age-specific and sex-specific unconditional CIP for the Brief Depressive Spell experience. Throughout this section, the tables and figures convey the point

estimates, the frequentist 95% CI, and the Bayesian 95% CRINT. Hill function parameter estimates also are presented.

Table 3. Estimated Female Cumulative Incidence Proportion For Brief Depressive Spell: Age-Specific Meta-Analysis Summary Estimates and Compatibility Intervals. Data from the US National Surveys on Drug Use and Health, 2004-2020.

| Age | Frequentist p-hat | Frequentist 95% CI | Bayesian p-hat | Bayesian 95% CRINT |
|---|---|---|---|---|
| 12 | 41.7 | 40.3, 43.0 | 41.6 | 40.7, 42.7 |
| 13 | 49.8 | 48.4, 51.2 | 49.6 | 48.6, 50.6 |
| 14 | 55.1 | 53.2, 57.0 | 54.7 | 53.8, 55.8 |
| 15 | 59.6 | 58.4, 60.9 | 59.4 | 58.7, 60.3 |
| 16 | 59.4 | 58.1, 60.7 | 59.3 | 58.5, 60.1 |
| 17 | 58.8 | 56.8, 60.8 | 58.4 | 57.5, 59.1 |

Table 4. Estimated Male Cumulative Incidence Proportion For Brief Depressive Spell: Age-Specific Meta-Analysis Summary Estimates and Compatibility Intervals. Data from the US National Surveys on Drug Use and Health, 2004-2020.

| Age | Frequentist p-hat | Frequentist 95% CI | Bayesian p-hat | Bayesian 95% CRINT |
|---|---|---|---|---|
| 12 | 32.1 | 30.0, 34.3 | 33.2 | 32.2, 34.0 |
| 13 | 33.6 | 32.3, 34.9 | 33.7 | 32.9, 34.7 |
| 14 | 36.1 | 34.9, 37.2 | 36.0 | 35.3, 36.7 |
| 15 | 39.2 | 37.9, 40.5 | 39.4 | 38.6, 40.1 |
| 16 | 40.5 | 39.3, 41.8 | 40.5 | 39.7, 41.3 |
| 17 | 41.8 | 40.9, 42.6 | 41.8 | 40.9, 42.5 |

These estimates help to clarify the female excess occurrence of BDS as well as a pattern of age-associated increases in CIP estimates. To draw inferences about female-male variations, I studied the overlap of the intervals in place of formal hypothesis-testing about departures from the null (e.g., whether the females and males might be considered as exchangeable samples of an underlying population). I will discuss whether and when the compatibility intervals do or do not overlap.

First, pertaining to the female frequentist 95% CI, Table 3 makes it possible to see that at age 12 years, the meta-analysis summary estimate across the years from 2004 through 2020 indicates that 41%-42% of females had experienced a brief depressive spell. There is an age-associated shift upward from the age 12-years summary estimate of 41.7% to an age 13 years estimate of 49.8%, then to an age 14 years estimate of 55.1%, followed by an age 15 years estimate of 59.6% . The corresponding 95% CIs for the 12-year-olds, 13-year-olds, 14-year-olds, and 15-year-olds are, respectively: (16.7%, 21.8%), and (24.2%, 29.9%). That is, virtually no overlap of

these frequentist 95% CI, suggesting an age-specific increase in BDS among females from age 12 years to age 15 years respectively. Among the 15-year-olds, and 16-year-olds there was an overlap in the CI. Similar results were also seen among the 16-to-17-year-olds.

Secondly, as for the corresponding female Bayesian credible intervals, the age-specific estimates for 12-year-olds have a credible interval of (40.7%, 42.7%) versus the credible interval for 13-year-olds of (48.6%, 50.6%), versus the credible interval for 14-year-olds of (53.8%, 55.8%), versus the credible interval for 15-year-olds of (58.7%, 60.3%) again with no overlap of the intervals. Among the 15-year-olds, and 16-year-olds there was an overlap in the CI. Similar results were also seen among the 16-to-17-year-olds.

The contrast of estimates for females versus males yields evidence not compatible with equal CIP. Note, as examples, how the Bayesian 95% credibility intervals and the frequentist 95% CI respectively fail to overlap in the comparison of males versus females in all of the age-specific estimates during adolescence. That is, the evidence suggests that females, age by age, are more likely to experience BDS.

Since the evidence from the frequentist approach is not as convincing as the evidence from the Bayesian approach, I created a table (Table 5 that shows the Bayesian 95% credibility intervals for BDS each of the sex subgroups under study.

Table 5. Estimated BDS Cumulative Incidence Proportions For Male And Female With Bayesian Credible Intervals.

| | **BDS: Bayesian Credible Interval** | |
|---|---|---|
| **Age** | **Male** | **Female** |
| 12 | **33.2%** (32.2,34.0) | **41.6%** (40.7,42.7) |
| 13 | **33.7** (32.9,34.7) | **49.6** (48.6,50.6) |
| 14 | **36.0** (35.3,36.7) | **54.7** (53.8,55.8) |
| 15 | **39.4** (38.6,40.1) | **59.4** (58.7,60.3) |
| 16 | **40.5** (39.7,41.3) | **59.3** (58.5,60.1) |
| 17 | **41.8** (40.9,42.5) | **58.4** (57.5,59.1) |

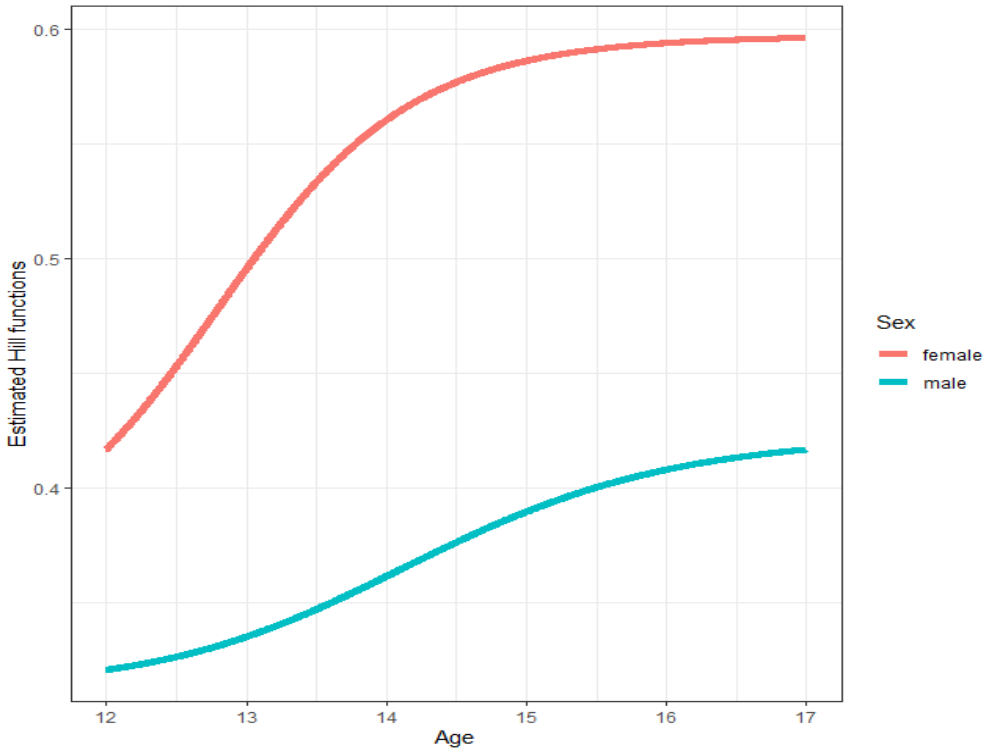
Section 4.2.1 Hill Function Model Parameter Estimates for Females and for Males

The contrast of Hill parameter estimates for BDS among males versus females sheds light on the estimated unconditional CIP when these subgroups are compared. Note, as examples, how the Pmax and PD50 confidence intervals fail to overlap in the comparison of females versus males. That is, the evidence suggests differences for the point of inflection (PD50) and in the Pmax estimates. As explained in Chapter 3, the PD50 parameter is an estimate of the age at which the BDS CIP is halfway between Pmin and Pmax. Numerically, that female age estimate is slightly larger than the corresponding male estimate. The Pmax estimate suggests that the oldest female adolescents in this population have a BDS CIP of 58%-62%; the corresponding male estimate is 41%-43%. Fig 5 displays the sigmoidal Hill function graphs for females and males.

Table 6. The Four Parameters Estimated With Hill Functions [$P_{min}$, $P_{max}$, PD50, and the Hill Slope (K)] For Females And for Males From 2004-2020. Data From The US National Surveys On Drug Use And Health, 2004-2020.

| | **Males** | | **Females** | |
|---|---|---|---|---|
| **Hill Function Parameters** | Hill Function Estimate | Hill Function 95% CI | Hill Function Estimate | Hill Function 95% CI |
| **$P_{min}$** | 0.31 | 0.30, 0.33 | 0.37 | 0.24, 0.50 |
| **$P_{max}$** | 0.42 | 0.41, 0.43 | 0.60 | 0.58, 0.62 |
| **K** | 15.50 | 9.74, 21.25 | 19.30 | 1.95, 36.66 |
| **PD50** | 14.23 | 13.94, 14.51 | 12.86 | 11.98,13.75 |

Figure 8. Hill equation fit depicting the male to female differences in adolescents with a prior history of BDS. These curves were fitted with R software with the min and max variables constrained to the minimum and maximum values in the data. Data from the US National Surveys on Drug Use and Health, 2004-2020. (Table 6 show no 95% CI overlap for PD50 and Pmax.).




In the next sections, to fulfill Aim 1, I condition on the BDS experience for an estimate of the occurrence of Depression syndrome (DS) given the prior BDS experience. I then present corresponding conditional CIP for the occurrence of Major Depressive Episode (MDE) given the prior experience of BDS followed by DS.

Section 4.3 Female-Male CIP Estimates For Experiencing A Depression syndrome After A Brief Depressive Spell.

As in the prior section, I will present the point estimates, the compatibility intervals, and the Hill function estimates. Here the focus is on the occurrence of a two-week sustained Depression syndrome given prior occurrence of BDS. With respect to the female frequentist 95% CI, Table 7 makes it possible to see that at age 12 years, the meta-analysis summary estimates across the years from 2004 through 2020 shift upward from an age 12-years summary estimate of 52.8% to an age 13 years estimate of 60.0%. The corresponding 95% CIs for the 12-year-olds and the 13-year-olds are, respectively: (49.1%, 56.4%), and (56.8%, 63.2%). That is, virtually no overlap of these frequentist 95% CI, suggesting an age-specific increase in the occurrence of

sustained (two weeks) Depression Syndrome following a Brief Depressive Spell among females from age 12 years to age 13 years respectively. Among the older aged adolescents, there were overlaps in the CI. Regarding the male frequentist 95% CI, Table 8 overlaps were noted between all the age groups. Secondly, as for the corresponding female Bayesian credible intervals, overlaps were only seen among the 15-to-16-year-olds and 16-to-17-year-olds. Conversely for males, overlaps were seen among the 14-year-olds and older adolescents.

The contrast of estimates for females versus males yields a new discovery of larger conditional CIP for females. No compatibility interval overlaps were noted between the age-specific estimates. Since the evidence from the frequentist approach is not as convincing as the evidence from the Bayesian approach, I created a table (Table 9) that shows the Bayesian 95% credibility intervals for DS|BDS for the sex subgroups under study.

Table 7. Female: Estimated Cumulative Incidence Proportion For Depression syndrome Given A Prior Brief Depressive Spell (Age-Specific Meta-Analysis Summary Estimates And Compatibility Intervals). Data From The US National Surveys On Drug Use And Health, 2004-2020.

| Age | Frequentist p-hat | Frequentist 95% CI | Bayesian p-hat | Bayesian 95% CRINT |
|---|---|---|---|---|
| 12 | 52.8 | 49.1, 56.4 | 51.4 | 50.0, 52.8 |
| 13 | 60.0 | 56.8, 63.2 | 58.7 | 57.5, 59.9 |
| 14 | 64.7 | 61.6, 67.7 | 63.6 | 62.5, 64.7 |
| 15 | 69.6 | 66.3, 72.6 | 68.7 | 67.6, 69.7 |
| 16 | 68.7 | 66.4, 70.8 | 67.9 | 66.7, 68.8 |
| 17 | 70.6 | 67.1, 73.8 | 69.1 | 68.1, 70.2 |

Table 8. Male: Estimated Cumulative Incidence Proportion For Depression syndrome Given A Prior Brief Depressive Spell (Age-Specific Meta-Analysis Summary Estimates And Compatibility Intervals). Data From The US National Surveys On Drug Use And Health, 2004-2020.

| Age | Frequentist p-hat | Frequentist 95% CI | Bayesian p-hat | Bayesian 95% CRINT |
|---|---|---|---|---|
| 12 | 43.3 | 40.5, 46.2 | 42.6 | 41.1, 44.2 |
| 13 | 46.9 | 43.8, 50.1 | 46.2 | 44.8, 47.6 |
| 14 | 49.4 | 46.7, 52.0 | 49.1 | 47.6, 50.4 |
| 15 | 53.0 | 51.1, 54.9 | 52.7 | 51.4, 54.2 |
| 16 | 56.0 | 53.1, 58.9 | 55.0 | 53.8, 56.2 |
| 17 | 57.8 | 54.6, 60.9 | 56.7 | 55.6, 57.9 |

Table 9. Estimated Conditional Cumulative Incidence Proportions (%) For The Occurrence Of DS, Given Prior BDS For Males And Females, With Bayesian Credible Intervals.

| | **DS, given BDS=1: Bayesian Credible Interval** | |
|---|---|---|
| **Age** | **Male** | **Female** |
| 12 | **42.6%** | **51.4%** |
| | (41.1, 44.2) | (50.0, 52.8) |
| 13 | **46.2** | **58.7** |
| | (44.8, 47.6) | (57.5, 59.9) |
| 14 | **49.1** | **63.6** |
| | (47.6, 50.40 | (62.5, 64.7) |
| 15 | **52.7** | **68.7** |
| | (51.4, 54.2) | (67.6, 69.7) |
| 16 | **55.0** | **67.9** |
| | (53.8, 56.2) | (66.7, 68.8) |
| 17 | **56.7** | **69.1** |
| | (55.6, 57.9) | (68.1, 70.2) |

Section 4.3.1 Hill Function Model Parameter Estimates for Females and for Males

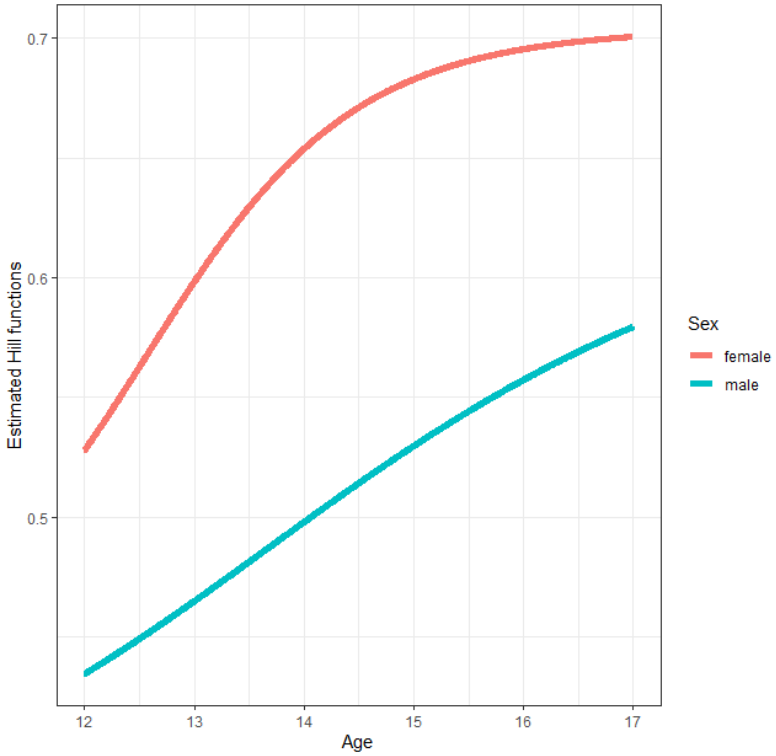
The contrast of Hill parameter estimates for DS|BDS among males versus females sheds light on the estimated conditional CIP when males and females are compared. Here the confidence intervals for all four Hill parameters overlap between males and females respectively. Numerically, that female age estimate is slightly larger than the corresponding male estimate. However, the Hill parameters between males and females suggest that there is no difference in the occurrence of Depression syndrome given a prior history of Brief Depressive Spells.

Table 10. The Four Parameters Estimated With Hill Functions [$P_{min}$, $P_{max}$, PD50, and the Hill Slope (K)] for Females and for Males From 2004-2020. Data From The US National Surveys On Drug Use And Health, 2004-2020.

| | **Males** | | **Females** | |
|---|---|---|---|---|
| **Hill Function Parameters** | Hill Function Estimate | Hill Function 95% CI | Hill Function Estimate | Hill Function 95% CI |
| **$P_{min}$** | 0.37 | 0.00, 0.41 | 0.45 | 0.00, 0.53 |
| **$P_{max}$** | 0.64 | 0.60, 1.00 | 0.70 | 0.69, 0.74 |
| **k** | 6.72 | 1.84, 10.76 | 14.37 | 6.94, 26.60 |
| **PD50** | 14.26 | 12.18, 16.06 | 12.71 | 10.43, 13.37 |

Fig 6 displays the sigmoidal Hill function graphs for females and males. (Please note that all 95% CI in Table 10 show overlap, compatible with null hypothesis of female-male difference in the BSD➔DS sequence.)

Figure 9. Hill Equation Fit Depicting The Male To Female Differences In Adolescents With A Sustained (Two Weeks) Depression Syndrome And A Prior History Of BDS. Data From The US National Surveys On Drug Use And Health, 2004-2020.




Section 4.4 Female-Male CIP Estimates For Experiencing A Major Depressive Episode Given Prior Occurrence Of The Depression syndrome And The Brief Depressive Spell.

With respect to the female frequentist 95% CI, Table 11 makes it possible to see that at age 12 years, the meta-analysis summary estimates across the years from 2004 through 2020 shift upward from an age 12-years summary estimate of 45.7% to an age 13 years estimate of 57.3%. The corresponding 95% CIs for the 12-year-olds and the 13-year-olds are, respectively: (41.8%, 49.6%), and (54.0%, 60.4%). That is, there is no overlap of these frequentist 95% CI, suggesting an age-specific increase in the occurrence of a Major Depressive Episode given DS+BDS among females from age 12 years to age 13 years respectively. Among the older aged adolescents, there were overlaps in the CI. Regarding the male frequentist 95% CI, Table 12 overlaps were noted between all the age groups. Secondly, as for the corresponding female and male the Bayesian credible intervals, overlaps were only seen among the 16-to-17-year-olds. The contrast of estimates for females versus males yields a new discovery of larger proportions when these two subgroups are compared. No overlaps were noted between the age-specific estimates between the sexes. Since the evidence from the frequentist approach is not as

convincing as the evidence from the Bayesian approach, I created a table (Table 13) that shows the Bayesian 95% credibility intervals for MDE|(DS+BDS) for the sex subgroups under study. (These 95% CRINT in Table 13 do not overlap, suggesting non-compatibility of evidence relative to a null specification about female-male variations for (BDS+DS)□MDE sequences.)

Table 11. Female: Estimated Cumulative Incidence Proportion For A History Of Major Depressive Episodes Following The Occurrence Of A Brief Depressive Spell And A Sustained (Two Weeks) Depression Syndrome. Data From The US National Surveys On Drug Use And Health, 2004-2020.

| Age | Frequentist p-hat | Frequentist 95% CI | Bayesian p-hat | Bayesian 95% CRINT |
|---|---|---|---|---|
| 12 | 45.7 | 41.8, 49.6 | 44.9 | 43.0, 47.0 |
| 13 | 57.3 | 54.0, 60.4 | 56.9 | 55.4, 58.5 |
| 14 | 61.0 | 58.5, 63.5 | 60.9 | 59.3, 62.3 |
| 15 | 65.1 | 61.6, 68.4 | 64.3 | 63.1, 65.7 |
| 16 | 67.9 | 65.7, 70.0 | 67.5 | 66.2, 68.7 |
| 17 | 68.1 | 65.0, 68.1 | 67.3 | 66.0, 68.5 |

Table 12. Male: Estimated Cumulative Incidence Proportion For A History Of Major Depressive Episodes Following The Occurrence Of A Brief Depressive Spell And A Sustained (Two Weeks) Depression Syndrome. Data From The US National Surveys On Drug Use And Health, 2004-2020.

| Age | Frequentist p-hat | Frequentist 95% CI | Bayesian p-hat | Bayesian 95% CRINT |
|---|---|---|---|---|
| 12 | 30.6 | 28.3, 33.0 | 30.6 | 28.5, 32.9 |
| 13 | 36.0 | 33.5, 38.6 | 36.0 | 33.8, 38.2 |
| 14 | 40.7 | 38.3, 43.2 | 40.7 | 38.8, 42.7 |
| 15 | 46.6 | 42.5, 50.8 | 46.3 | 44.2, 48.2 |
| 16 | 48.4 | 45.7, 51.2 | 48.4 | 46.6, 50.2 |
| 17 | 53.5 | 50.8, 56.0 | 53.2 | 51.4, 55.0 |

Table 13. Shows The Male And Female Bayesian Credible Interval % Among Adolescents With A Prior History Of Major Depressive Episodes Following The Occurrence Of A Brief Depressive Spell And A Sustained (Two Weeks) Depression Syndrome.

| MDE\|BDS +DS: Bayesian Credible Interval | | |
|---|---|---|
| **Age** | **Male** | **Female** |
| 12 | **30.6%** (28.5,32.9) | **44.9%** (43.0,47.0) |
| 13 | **36.0** (33.8,38.2) | **56.9** (55.4,58.5) |
| 14 | **40.7** (38.8,42.7) | **60.9** (59.3,62.3) |
| 15 | **46.3** (44.2,48.2) | **64.3** (63.1,65.7) |
| 16 | **48.4** (46.6,50.2) | **67.5** (66.2,68.7) |
| 17 | **53.2** (51.4,55.0) | **67.3** (66.0,68.5) |

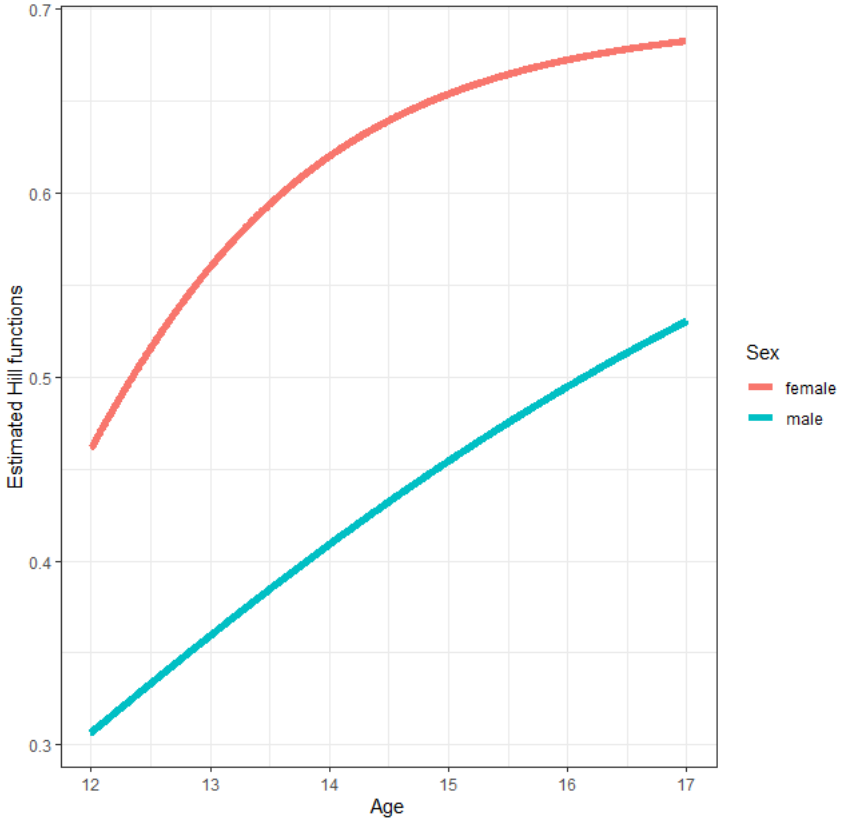
Section 4.4.2 Hill Function Model Parameter Estimates for Females and for Males

The contrast of Hill parameter estimates for MDE(DS+BDS) among males versus females sheds light on the estimated conditional CIP when males and females are compared. Here the confidence intervals for all four Hill parameters overlap between males and females respectively. Numerically, that female age estimate is slightly larger than the corresponding male estimate. However, 95% CI for each Hill parameter (female vs. male) suggest compatibility with the null hypothesis of no female-male differences in these parameter estimates for how often MDE occurs once a prior BDS and DS have occurred.

Table 14. The four parameters estimated with Hill functions [$P_{min}$, $P_{max}$, PD50, and the Hill slope (K)] for females and for males who had experienced MDE, given prior occurrence of a sustained (two weeks) Depression Syndrome and a prior history of BDS. Data from the US National Surveys on Drug Use and Health, 2004-2020.

| | **Males** | | **Females** | |
|---|---|---|---|---|
| **Hill Function Parameters** | Hill Function Estimate | Hill Function 95% CI | Hill Function Estimate | Hill Function 95% CI |
| **$P_{min}$** | 0.03 | 0.00, 0.26 | 0.08 | 0.00, 0.43 |
| **$P_{max}$** | 0.69 | 0.56, 1.00 | 0.70 | 0.67, 0.72 |
| **K** | 4.27 | 2.74, 9.09 | 10.42 | 7.36, 18.81 |
| **PD50** | 13.81 | 12.41, 16.21 | 11.41 | 10.92, 13.06 |

Figure 10. Hill equation fit depicting the male to female differences in adolescents with a major depressive episode and prior history of sustained (two weeks) Depression Syndrome and BDS. Data from the US National Surveys on Drug Use and Health, 2004-2020.



# CHAPTER 5 - RESULTS (AIM 2)

## 5.0 Focus on Minority Health Disparities and ESI Sub-Group Variations.

## 5.1 Introduction

The main aim for this chapter of my dissertation research project was stated as follows: Aim 2: Among cross-sectionally assessed survivors of each birth cohort, to estimate the age-specific Major Depressive Disorder (MDD) cumulative incidence proportion (CIP) among those survivors for whom there is an observed lifetime history of the Brief Depressive Spell (BDS), with attention to parameter variations across subgroups defined by self-identified Non-Hispanic Whites, Non-Hispanic Blacks, and Hispanic adolescents. This BDS□MDD conditional CIP estimate can be conceptualized as a conditional probability of MDD occurring among adolescents for whom the BDS experience already has occurred.

In Chapter 2, I motivated the rationale for studying minority health disparities and Ethnic Self-Identification (ESI) variations in the conditional cumulative incidence proportion for Major Depression (MDD), given prior experience with a Brief Depression Spell (BDS), and for conditional cumulative incidence proportion for MDD, given prior experience with a two-week sustained spell of depression or depression-equivalents. In Chapter 4, I provided a display of my general research approach that starts with age- and year-specific point estimates, and then continues to meta-analysis summary estimates in two forms: (a) frequentist point estimates and 95% CI for the population parameters considered as 'fixed' and (b) Bayesian point estimates and 95% CRINT for the population parameters considered as 'random.' In this section, I take the same approach to the study of minority health disparities. I also provide Hill function estimates based on the four-parameter Hill functional analysis approaches described in prior sections of this dissertation monograph.

A novel feature of this dissertation research approach to minority health disparities involves the application of Hill function parameter comparisons. In general, study of minority health disparities has been restricted to estimation of prevalence or incidence proportions and their subgroup variations. On occasion, slope estimates have been studied as they might vary from subgroup to subgroup.

In my work, I decided to study age-associated conditional probabilities of transitioning into Major Depressive Disorder (MDD), given that prior experiences with mood disturbances of lesser clinical significance have occurred, such as a Brief Depression Spell (BDS) that might

predominate one or two days of an adolescent's life, but that might otherwise be transient. With the Hill function approach, it is possible to compare and contrast minority health disparities in relation to four parameters: Pmin, Pmax, the slope k, and PD50 (analogous to an LD50 or an ED50 in a pharmacological or toxicological experiment).

As described in earlier sections of this dissertation, the background and conceptualization of this dissertation research builds on pioneering epidemiological surveys of school-attending adolescents that the US Public Health Service completed during the years of the Spanish Flu Pandemic before 1920 (Collins, 1930). It also builds on the pioneering conceptualization of stage transitions from brief mood swings to more formally diagnosed affective disorders, with empirical estimates from longitudinal studies of adolescents growing up in Switzerland, with Angst and Merikangas as major contributors (e.g., Angst et. al., 1990; Angst et al., 1997).

## 5.2 Methods

The methods for this part of the dissertation research project are identical to those described in Section 4.2 with one exception. Namely, the NSDUH ACASI assessment asked participants to self-identify as Hispanic or non-Hispanic, and then asked them to self-identify membership in one or more US Census categories of 'race-ethnicity.' The result is an 'ethnic self-identification' variable.

Here, due to small numbers of adolescents self-identifying with relatively rare subgroups (e.g., Native Hawaiian), my estimates for minority health disparities are focused on the Hispanic subgroup versus these alternatives: (a) non-Hispanic White and (b) non-Hispanic Black/African-American. The unweighted sample numbers for other non-Hispanic subgroups proved to be too small for statistically precise estimates.

## 5.3 Results

In Section 4.1, I provided unweighted numbers of sample participants by the primary ESI subgroups. Readers are referred to Table 2 for these numbers. The first column of Table 15 shows estimated conditional cumulative incidence proportions that convey how often 12-year-old non-Hispanic White adolescents experienced a Major Depressive Disorder (MDD) after first experiencing a Brief Depression Spell (BDS). The rows in that column depict the year-specific estimates I derived. The final rows show a frequentist meta-analysis summary estimate of just under one MDD case for every 20 BDS cases (18.4%), with a 95% CI of 15.9% to 22.2%. The

corresponding Bayesian point estimate is not appreciably different at 18.0% and its 95% CRINT is 17.0%, 19.2%.

Given the age-associated increases shown for all adolescents in Chapter 4, it might be expected that there would be a corresponding age-associated increase for non-Hispanic White adolescents. Table 15 confirms this expectation. (Unremarkably, the same pattern of general age-associated increases can be seen for the other ESI subgroups in later tables of this section.) The contrast of estimates for non-Hispanic Whites versus non-Hispanic Black/African-Americans yields a new discovery of variation in BDS□MDD transition proportions when these subgroups are compared. Note, as an example, how the Bayesian 95% credibility intervals fail to overlap in the comparison of non-Hispanic Whites versus non-Hispanic Black/African-Americans in most of the age-specific estimates during adolescence. That is, the evidence suggests that non-Hispanic White adolescents, age by age, might be more likely than non-Hispanic Black/African-Americans to make the transition from the Brief Depression Spell onward toward Major Depression as defined in the DSM-IV.

It is important to note that the largest unweighted sample sizes are available for non-Hispanic White adolescents. Whereas the overlap of the frequentist 95% CI might leave the reader with an impression that there is not much in the way of age-by-age increases in the proportions who experience MDD after experiencing BDS. The Bayesian compatibility intervals show no overlap whatsoever as we look across the meta-analysis summary CRINT estimated using the Bayesian approach in the age-specific estimates from age 12 years until age 16 years. Viewed with the Bayesian perspective, there is evidence compatible with the non-null expectation of age-associated increases as we look across the years from age 12 to age 16. To illustrate, consider the Bayesian point estimate of 18.0% for adolescents at age 12 years who had experienced a BDS and then transitioned to a Major Depressive Episode and Disorder. The Bayesian 95% CRINT for that age 12 estimate is 17.0% to 19.2%. The next age group, assessed at age 13 years, has a Bayesian point estimate of 25.5% and the CRINT of 24.5% to 26.6% does not overlap with the CRINT for the 12-year-olds. Non-overlapping CRINT also can be seen all the way along the age dimension until we reach the contrast of the 16-year-old and 17-year-old subgroups. Robustly increasing estimates with non-overlapping CRINT can be seen across the comparison of estimates from age 12 years to age 16 years. The CRINT for 16-year-old is 37.5% to 39.7%, with a slight overlap when compared with the corresponding CRINT values for 17-

year-olds: 39.6% to 41.9%. It seems that during the earliest years of adolescence, roughly one in five non-Hispanic White adolescents who experience a Brief Depressive Episode have experienced a Major Depressive Episode. This proportion seems to grow during the subsequent four years of adolescence, reaches a value of 38.6% at age 16 years (95% CRINT = 37.5%, 39.7%) and then stops its ascent by age 17 years when the point estimate is more than double the value observed at age 12 years (CRINT = 39.6%, 41.9%).

A congruent age-specific pattern of increasing point estimates, age by age, can be seen in the Bayesian estimates for adolescents who self-identified as non-Hispanic Black/African-American (Table 16) and for those who self-identified as Hispanic (Table 17). Non-overlapping CRINT are seen for 12- and 13-year-olds in these tables. Thereafter, it seems that roughly one in three adolescents in the non-Hispanic Black/African-American subgroup made the transition from a BDS to an MDE, without the mid-adolescent increases seen for non-Hispanic White adolescents. For the self-identified Hispanic adolescents, the estimates in mid-adolescence are not much different from what can be seen for the non-Hispanic Whites. In those middle years of adolescence, it seems that the BDS□MDE transition has occurred for approximately 40 individuals among 100 BDS-affected adolescents who self-identify as either Hispanic (Table 17) or non-Hispanic White (Table 15). Because the evidence from the frequentist approach is not as convincing as the evidence from the Bayesian approach, I created a table that shows the Bayesian 95% credibility intervals for each of the three ESI subgroups under study. This table appears after the more detailed tables for each subgroup. The extra table clarifies the age-specific differences as well as the separation of ESI subgroups. It provides insight into the potential minority health disparities in depression epidemiology that is worthy of future consideration in research and public health practice.

Table 15. Non-Hispanic Whites: Estimated Age-Specific & Year-Pair-Specific Estimates for the Probability of Transitioning into a Major Depressive Episode after a Brief Depressive Spell During Adolescence, 2004-2020. (Data from the US National Surveys on Drug Use and Health, 2004-2020, Public Use Datasets).

| **Estimated Conditional Cumulative Incidence Proportions (%)** | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Year-Pairs** | **Age in years:** | **12** | **13** | **14** | **15** | **16** | **17** |
| 2004 | | 16.3 | 22.9 | 24.4 | 30.1 | 35.4 | 34.9 |
| 2005 | | 19.3 | 20.3 | 25.1 | 28.9 | 36.0 | 33.3 |
| 2006 | | 12.1 | 22.8 | 23.6 | 31.8 | 32.1 | 32.9 |
| 2007 | | 11.3 | 19.3 | 25.5 | 31.0 | 36.7 | 38.1 |
| 2008 | | 15.2 | 23.7 | 26.1 | 27.6 | 36.5 | 35.7 |
| 2009 | | 16.1 | 22.9 | 27.0 | 31.9 | 33.5 | 33.8 |
| 2010 | | 13.8 | 23.3 | 30.6 | 31.3 | 34.5 | 38.2 |
| 2011 | | 16.8 | 24.8 | 28.6 | 31.1 | 35.1 | 37.1 |
| 2012 | | 13.9 | 26.4 | 29.9 | 36.7 | 39.7 | 38.7 |
| 2013 | | 15.3 | 22.5 | 36.6 | 38.7 | 38.6 | 41.4 |
| 2014 | | 23.8 | 29.0 | 36.5 | 43.8 | 41.3 | 43.6 |
| 2015 | | 17.2 | 32.7 | 40.6 | 44.5 | 41.1 | 45.8 |
| 2016 | | 21.9 | 33.7 | 38.8 | 45.3 | 53.5 | 52.2 |
| 2017 | | 24.0 | 27.4 | 35.9 | 42.3 | 45.7 | 51.0 |
| 2018 | | 29.6 | 37.4 | 41.0 | 49.8 | 47.7 | 54.8 |
| 2019 | | 29.2 | 32.8 | 43.8 | 48.6 | 48.5 | 51.2 |
| 2020 | | 30.2 | 36.3 | 44.6 | 57.7 | 50.7 | 49.0 |
| **Cumulative Incidence Proportions (%): Frequentist Meta-Analysis Summary Estimates** | | **18.4** | **26.3** | **32.4** | **37.8** | **39.4** | **41.6** |
| Frequentist 95% Confidence Intervals | | 15.9,22.2 | 20.0,26.0 | 25.1,30.3 | 29.0,37.4 | 29.4,36.4 | 29.3,38.2 |
| **Bayesian Meta-Analysis Summary Estimates (%)** | | **18.0** | **25.5** | **32.3** | **36.0** | **38.6** | **40.7** |
| Bayesian Credible Intervals % | | 17.0,19.2 | 24.5,26.6 | 31.3, 33.4 | 34.9,37.1 | 37.5, 39.7 | 39.6, 41.9 |

Table 16. Non-Hispanic Black/African-American Subgroup: Estimated Age-Specific & Year-Pair-Specific Estimates for the Probability of Transitioning into a Major Depressive Episode after a Brief Depressive Spell During Adolescence, 2004-2020. (Data from the US National Surveys on Drug Use and Health, 2004-2020, Public Use Datasets).

| | **Estimated Conditional Cumulative Incidence Proportions (%)** | | | | | |
|---|---|---|---|---|---|---|
| **Year-Pairs** | **Age in years:** | **12** | **13** | **14** | **15** | **16** | **17** |
| 2004 | | 12.4 | 22.8 | 31.3 | 26.4 | 29.7 | 21.5 |
| 2005 | | 12.5 | 21.6 | 25.7 | 24.8 | 22.9 | 32.0 |
| 2006 | | 21.1 | 15.9 | 22.6 | 27.0 | 24.0 | 21.7 |
| 2007 | | 20.3 | 20.0 | 29.4 | 28.1 | 36.3 | 23.9 |
| 2008 | | 22.7 | 19.0 | 26.2 | 26.4 | 27.5 | 31.7 |
| 2009 | | 9.4 | 15.6 | 26.5 | 30.3 | 31.5 | 36.2 |
| 2010 | | 16.2 | 16.8 | 21.8 | 23.3 | 32.5 | 24.5 |
| 2011 | | 14.4 | 19.2 | 24.8 | 29.7 | 32.9 | 30.9 |
| 2012 | | 27.4 | 25.4 | 18.8 | 38.6 | 35.5 | 29.2 |
| 2013 | | 13.5 | 25.3 | 30.0 | 31.0 | 22.8 | 30.1 |
| 2014 | | 22.8 | 30.3 | 25.2 | 31.6 | 35.3 | 41.6 |
| 2015 | | 20.0 | 21.7 | 35.7 | 42.1 | 27.3 | 36.1 |
| 2016 | | 22.5 | 26.3 | 29.5 | 29.8 | 44.0 | 39.9 |
| 2017 | | 9.9 | 30.1 | 27.8 | 40.5 | 39.5 | 43.7 |
| 2018 | | 35.3 | 31.6 | 34.4 | 44.9 | 41.6 | 36.9 |
| 2019 | | 29.9 | 35.0 | 41.2 | 37.6 | 47.9 | 43.8 |
| 2020 | | 18.9 | 7.4 | 28.8 | 67.8 | 37.7 | 69.3 |
| **Cumulative Incidence Proportions (%): Frequentist Meta-Analysis Summary Estimates** | | **18.8** | **22.8** | **27.6** | **33.0** | **32.8** | **33.6** |
| Frequentist 95% Confidence Intervals | | 15.9,22.2 | 20.0,26.0 | 25.1,30.3 | 29.0,37.4 | 29.4,36.4 | 29.3,38.2 |
| **Bayesian Meta-Analysis Summary Estimates (%)** | | **18.9** | **23.4** | **27.5** | **32.3** | **32.5** | **32.9** |
| Bayesian Credible Intervals % | | 17.0,20.9 | 21.5,25.5 | 25.5,29.7 | 30.2,34.7 | 30.3,34.5 | 30.7,35.3 |

Table 17. Hispanic Subgroup: Estimated Age-Specific & Year-Pair-Specific Estimates for the Probability of Transitioning into a Major Depressive Episode after a Brief Depressive Spell During Adolescence, 2004-2020. (Data from the US National Surveys on Drug Use and Health, 2004-2020, Public Use Datasets).

| | **Estimated Conditional Cumulative Incidence Proportions (%)** | | | | | |
|---|---|---|---|---|---|---|
| **Year-Pairs** | **Age in years:** | **12** | **13** | **14** | **15** | **16** | **17** |
| 2004 | | 16.9 | 17.7 | 31.2 | 33.1 | 31.3 | 51.0 |
| 2005 | | 13.5 | 24.7 | 27.0 | 34.6 | 34.8 | 39.2 |
| 2006 | | 14.3 | 21.3 | 24.9 | 27.2 | 41.2 | 33.0 |
| 2007 | | 11.6 | 26.6 | 17.3 | 26.5 | 33.2 | 33.5 |
| 2008 | | 14.6 | 21.9 | 27.5 | 31.0 | 30.8 | 27.1 |
| 2009 | | 19.3 | 19.7 | 26.9 | 28.7 | 24.6 | 38.6 |
| 2010 | | 22.8 | 22.0 | 29.8 | 42.4 | 32.0 | 30.0 |
| 2011 | | 13.0 | 20.8 | 32.3 | 33.4 | 34.2 | 33.9 |
| 2012 | | 16.6 | 33.5 | 37.2 | 34.0 | 40.5 | 34.3 |
| 2013 | | 19.9 | 40.5 | 34.1 | 34.5 | 42.8 | 38.9 |
| 2014 | | 26.9 | 28.2 | 35.5 | 42.4 | 41.2 | 44.4 |
| 2015 | | 22.4 | 46.0 | 27.8 | 42.2 | 43.8 | 48.7 |
| 2016 | | 24.2 | 33.3 | 36.4 | 38.7 | 50.4 | 46.5 |
| 2017 | | 23.1 | 36.5 | 32.7 | 45.9 | 46.8 | 53.8 |
| 2018 | | 28.9 | 33.9 | 43.8 | 45.2 | 48.9 | 52.2 |
| 2019 | | 30.8 | 48.7 | 45.8 | 47.0 | 52.6 | 56.7 |
| 2020 | | 36.2 | 42.0 | 35.2 | 46.1 | 53.7 | 69.5 |
| **Cumulative Incidence Proportions (%): Frequentist Meta-Analysis Summary Estimates** | | **20.1** | **29.8** | **31.9** | **37.0** | **39.6** | **42.2** |
| Frequentist 95% Confidence Intervals | | 17.3,23.3 | 25.4,34.6 | 28.6,35.4 | 33.8,40.3 | 35.6,43.8 | 37.5,47.0 |
| **Bayesian Meta-Analysis Summary Estimates (%)** | | **20.5** | **30.8** | **32.4** | **37.1** | **39.5** | **42.5** |
| Bayesian Credible Intervals % | | 18.7,22.6 | 32.9,28.8 | 30.5,34.3 | 35.3,39.0 | 37.5,41.7 | 40.5,44.4 |

In Table 15, it is possible to see the estimates for a non-Hispanic White subgroup, for whom the upper Bayesian 95% credibility intervals are shown as 20.9% for 12-year-olds, 25.5% for 13-year-olds, 20.7% for 14-year-olds, 34.7% for 15-year-olds, 34.5% fo16-year-olds, and 35.3% fo17-year-olds. Please note that the Bayesian 95% credible interval for 12-years-olds is not appreciably different for the non-Hispanic Black/African-American subgroup at that age. There is a substantial overlap of those interval estimates. Now consider the interval estimates for

13-year-olds. I found no appreciable variation for non-Hispanic Whites versus non-Hispanic Black/African-Americans at age 13 (Table 15 and Table 16), but the Hispanic 13-year-olds appeared to be more likely to make that transition from BDS to MDD as indicated by a lower 95% bound of the credibility interval for the other two subgroups being considered Table 17).

At age 14 years, I discovered a minority health disparity with a smaller estimate for the non-Hispanic White subgroup of adolescents as compared with the other two subgroups. The same was true for the 15-year-olds, the 16-year-olds, and the 17-year-olds. It is noteworthy that the only appreciable difference between the Hispanic adolescent subgroup and the non-Hispanic Black/African-American subgroup can be seen at age 17 years. Otherwise, there is overlap of the Bayesian CRINT in that comparison across the years from age 12 to age 16.

In the following summary display of the Bayesian 95% CRINT, I highlighted the lower BDS□MDE transition proportion estimates for non-Hispanic White adolescents at age 14 through 17 years. Before that age, no appreciable variations in the proportion can be seen.

Table 18. Age-specific ESI Summary Display of the Bayesian 95% Credible Intervals.

| | | | **Age** | | | |
|---|---|---|---|---|---|---|
| **ESI** | **12** | **13** | **14** | **15** | **16** | **17** |
| Non-Hispanic White | 17.0,20.9 | 21.5,25.5 | 25.5,29.7 | 30.2,34.7 | 30.3,34.5 | 30.7,35.3 |
| Non-Hispanic Black | 17.0,19.2 | 24.5,26.6 | 31.3,33.4 | 34.9,37.1 | 37.5,39.7 | 39.6,41.9 |
| Hispanics | 18.7,22.6 | 28.8,32.9 | 30.5,34.3 | 35.3,39.0 | 37.5,41.7 | 40.5,44.4 |

5.3.1 Comparison of Hill Function parameter variation across US Ethnic Self Identification subgroups

The contrast of Hill parameter estimates for MDE|BDS among US Ethnic Self Identification subgroups sheds light on the estimated conditional CIP when these subgroups are compared. Note, as examples, how the Pmax confidence intervals fail to overlap in the comparison of Non-Hispanic Blacks versus Non-Hispanic Whites. That is, the evidence suggests differences for the point of inflection (PD50) in the estimates. As explained in Chapter 3, the PD50 parameter is an estimate of the age at which the MDE|BDS CIP is halfway between Pmin and Pmax. Numerically, that Non-Hispanic Whites and Hispanics estimate is slightly larger than the Non-Hispanic Blacks estimate. The Non-Hispanic White Pmax estimate suggests that the

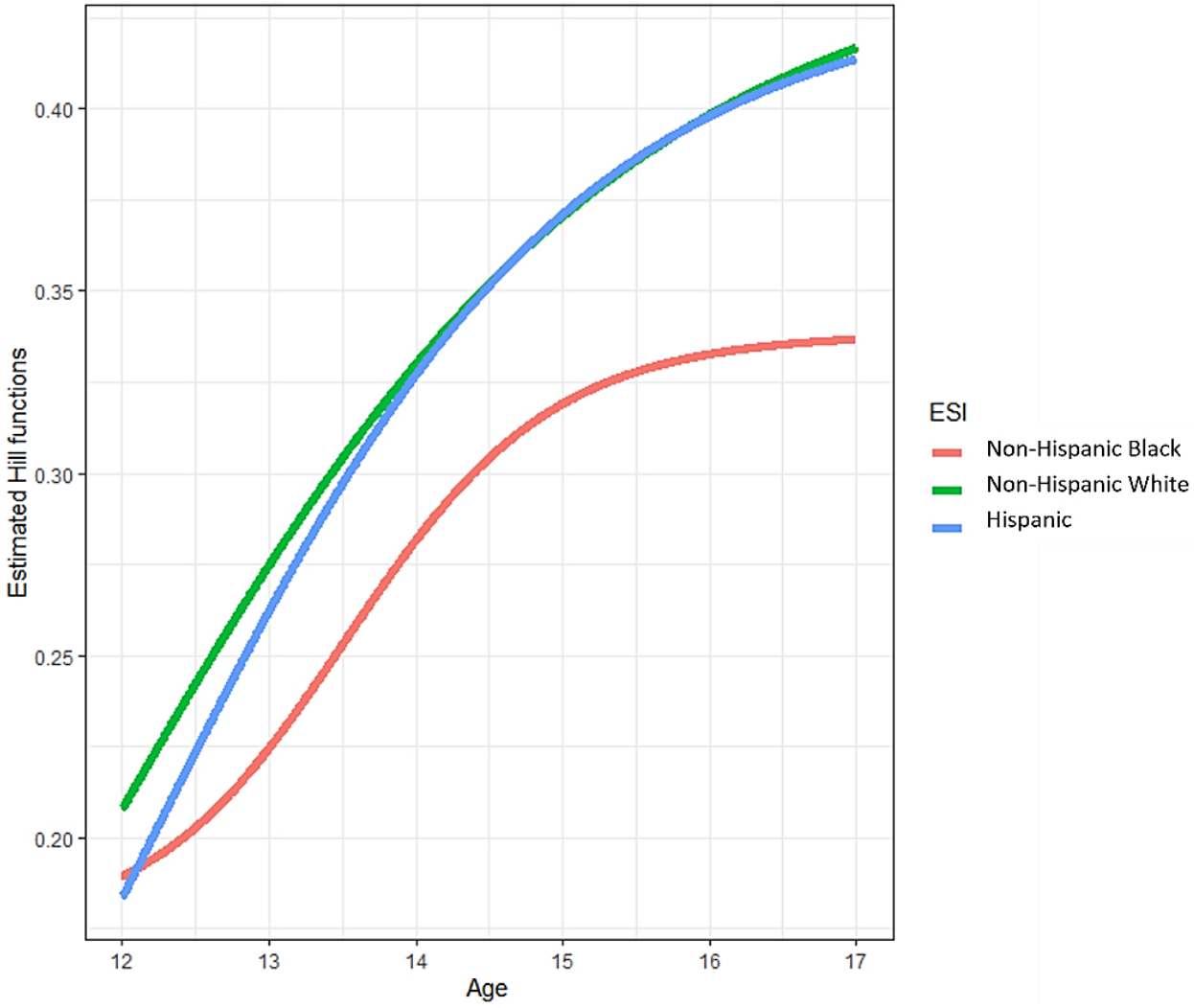
oldest adolescents in this population have a MDE|BDS CIP of 40%-47%; the corresponding Non-Hispanic Black estimate is 32%-36%.

The Hill Function four-parameter estimations are depicted in Table 18 for four groups of self-identified US Census race/ethnicity subgroups of adolescents.

Table 18. The four parameters estimated with Hill functions ($P_{min}$, $P_{max}$, PD50, and the Hill slope (K) for US Ethnic Self Identification subgroups with Major Depressive Episode after a Brief Depressive Spell during adolescence from 2004-2020. Data from the US National Surveys on Drug Use and Health, 2004-2020.

| **Hill Function Parameters** | **Non-Hispanic Whites** Hill Function Estimate (95% CI) | **Non-Hispanic Blacks** Hill Function Estimate (95% CI) | **Hispanics** Hill Function Estimate (95% CI) | **All ESI** Hill Function Estimate (95% CI) |
|---|---|---|---|---|
| **$P_{min}$** | 0.01 (0.00, 0.28) | 0.18 (0.14, 0.22) | 0.00 (0.00, 1.62) | 0.26 (0.25, 0.28) |
| **$P_{max}$** | 0.44 (0.40, 0.47) | 0.34 (0.32, 0.36) | 0.45 (0.22, 0.68) | 0.40 (0.38, 0.42) |
| **K** | 9.42 (3.65, 15.18) | 19.97 (6.90, 33.05) | 7.46 (0.00, 31.25) | 25.46 (10.92, 40.00) |
| **PD50** | 12.52 (10.99, 14.04) | 13.58 (13.12, 14.04) | 12.27 (1.86, 22.68) | 14.35 (14.02, 14.69) |

Figure 11. Hill equation fit depicting the US Ethnic Self Identification subgroups differences in adolescents with a major depressive episode and prior history Brief Depressive Spell. Data from the US National Surveys on Drug Use and Health, 2004-2020.



# CHAPTER 6 - RESULTS (AIM 3)

## 6.0 Focus on Cohort Experiences

## 6.1 Introduction

As stated in Chapter 1, the third aim for my dissertation research project is: To estimate the conditional MDE cumulative incidence proportions as experienced by BDS-affected adolescents during recent years of the 21st century in the US using the epidemiological mutoscope approach, conceptualized as an elaboration of Frost's cohort-specific approach in his posthumously published tuberculosis mortality rate research. In contrast with the age-specific CIP estimates produced under Aim 2, my Aim 3 estimates are cohort-specific CIP estimates.

## 6.2 Methods

The populations under study, sampling plans, participation levels, and standardized assessment protocols for this aim are described in Chapter 3. The analysis approach required estimation of age- and year-specific conditional cumulative incidence proportions that reflect the occurrence of Major Depressive Episodes among adolescents who previously had experienced a Brief Depressive Spell. This set of estimates reflects the experience of individual birth cohorts as they might or might not make the BDS➔MDE transition.

The study of cohort-specific experiences is of crucial importance in epidemiological research of this type. As Frost's work showed, the cohort-wise view of morbidity and mortality estimates can give an impression of the epidemiology of the condition that is not the same as the age-specific view of the same estimates. This set of cohort-wise estimates for adolescent depression will clarify whether the cohort-specific estimates have a pattern that is congruent with the pattern previously seen in the dissertation research project's age-specific estimates. In addition, the cohort-wise estimates will help us understand whether the previously disclosed age-specific patterns might have cohort-specific origins. That is, the study of age-specific patterns of cumulative incidence proportions can make it seem that there are age-specific increases in the estimates when in fact the increases are artifacts of cohort variations in morbidity experiences. A note about the concept of 'birth cohort' is needed in this context. For privacy protection reasons, NSDUH gathers birth date information but releases only the age of the participant at assessment when it provides public use datasets. An approximation of the 'birth cohort' membership can be made by subtracting the age at assessment from the year of assessment. For example, a 12-year-old in the 2004 dataset will be a member of the 1991-1992 birth cohorts (via

the arithmetic operation of 2004-12=1992). To be sure, there is a bit of crude numeracy in this approach to identifying a birth cohort. I gauge that roughly one-half of those age 12 years when assessed in 2004 will have been born in 1991 and the complement in 1992. (Consider 12-year-olds assessed in January 2004. Some might have had a January 1992 birthday, but many would have been born in 1991. In this fashion, the NSDUH estimates for 'birth cohorts' might be regarded as approximations of what might be found if the NSDUH datasets disclosed the actual birth year.

6.3 Results

Table 20. shows the mutoscopic orientation of year-specific and age-specific cumulative incidence proportions that reflect the BD→MDE transition. Consistent with the concept devised by Herman Casler when he patented his 19th century mechanical mutoscope, the mutoscopic view of a cohort's experiences involves linking cross-sectional snapshots of the experience of an individual cohort, with each snapshot taken across successive intervals (here, a year-by-year interval) in order to put on display a more dynamic view of the cohort's experiences. Think of a snapshot of a bird in a cage, followed by a succession of snapshots as the cage door is opened, and the bird flies out of the cage. By 'flipping' those snapshots across the successive images, Casler's mechanical mutoscope provided a view of the bird flying out of the cage before the motion picture mechanisms were developed. Here, the snapshots are the year-specific and age-specific estimates from the NSDUH, arranged for each birth cohort so that the forward progress of the cohort's experience can be seen.

In the following tables, the diagonals are highlighted because these diagonal cells portray the experiences of individual cohorts (as defined in Chapter 3). The CIP estimates displayed in Table 20 were used to construct estimates for successive birth cohorts. These estimates enabled me to compare cohort experiences over time, and to inspect their congruence with corresponding age-specific patterns for MDE given a prior history of BDS (Table 21).

Table 19. Age-Specific & Year-Pair-Specific Estimates For The Cumulative Incidence Proportion Of Adolescents Who Experienced A Brief Depressive Spell And Then Transitioned Into A Major Depressive Episode, 2004-2020. (Data From The United States National Surveys On Drug Use And Health, PDAS Public Use Datasets).

| **Age** | **12** | **13** | **14** | **15** | **16** | **17** |
|---|---|---|---|---|---|---|
| **Year** | CIP of MDE \| BDS=1 Estimated for All Adolescents (%) | | | | | |
| **2004** | 15.8 | 22.1 | 27.1 | 30.0 | 33.0 | 35.9 |
| **2005** | 17.7 | 21.0 | 25.8 | 28.5 | 33.5 | 33.9 |
| **2006** | 14.6 | 21.6 | 23.6 | 30.2 | 33.0 | 31.5 |
| **2007** | 12.7 | 21.0 | 24.2 | 29.2 | 36.2 | 35.2 |
| **2008** | 16.5 | 23.5 | 26.0 | 28.9 | 33.6 | 33.6 |
| **2009** | 15.8 | 20.8 | 27.2 | 30.9 | 31.0 | 34.6 |
| **2010** | 16.0 | 22.2 | 28.9 | 32.4 | 33.7 | 34.6 |
| **2011** | 15.3 | 22.6 | 28.8 | 31.5 | 34.6 | 35.9 |
| **2012** | 16.6 | 27.6 | 30.8 | 35.9 | 38.3 | 36.2 |
| **2013** | 16.4 | 28.4 | 34.8 | 36.2 | 38.2 | 39.1 |
| **2014** | 23.8 | 28.3 | 34.9 | 40.9 | 41.2 | 43.2 |
| **2015** | 19.2 | 35.2 | 35.2 | 43.9 | 40.7 | 43.4 |
| **2016** | 22.5 | 32.6 | 36.8 | 40.9 | 45.1 | 49.9 |
| **2017** | 21.5 | 30.0 | 32.8 | 43.7 | 44.7 | 49.8 |
| **2018** | 30.9 | 36.4 | 40.2 | 48.4 | 47.4 | 51.8 |
| **2019** | 29.9 | 37.9 | 43.4 | 48.1 | 48.6 | 52.9 |
| **2020** | 32.3 | 36.3 | 38.2 | 56.6 | 50.7 | 56.5 |
| **Meta-analysis** | **19.1** | **27.0** | **31.4** | **37.1** | **38.7** | **40.7** |
| **Confidence Interval** | 16.7,21.8 | 24.2,29.9 | 28.7,34.2 | 33.2,41.0 | 35.9.41.6 | 37.0,44.6 |
| **Bayesian** | **18.5** | **26.4** | **40.0** | **36.0** | **38.2** | **40.0** |
| **Credible Intervals** | 17.7,19.4 | 25.5,27.4 | 39.2,40.7 | 35.3,36.7 | 37.5,39.0 | 39.2,40.7 |

Table 19 puts on display my estimated age- and year-specific BDS➔MDE transition proportion for all adolescents in the NSDUH study population across the year range from 2004 through 2020. First, consider the frequentist 95% CI and the narrower Bayesian 95% CRINT for 12-year-olds, irrespective of cohort membership. The smallest bound is 16.7% and the largest bound is 21.8%. Until 2016, all of the year-specific estimates fall within these bounds. After that year, there is an upward shift, consistent with separately made unconditional population prevalence estimates reported by Keyes and other depression epidemiologists (Keyes, 2021). However, no other depression epidemiologists have studied the BDS➔MDE transitions I estimated in this dissertation research project. As noted later in this dissertation research report, the published evidence that suggests increased prevalence of MDE among adolescents during

these years of the 21st century might be traced back to an increased proportion transitioning from BDS to MDE, versus an alternative of an increased age-specific incidence of BDS and depression in general.

Next, consider the column of estimates for 17-year-olds with a lower bound of 37% and an upper bound of just under 45%, The year-specific point estimates for 17-year-olds do not exceed the upper bound of 45% until 2018, when more than 50% of the BDS-affected adolescents transition to MDE. This extraordinary value greater than 50% can be seen in each of the years from 2018 through 2020, with some ambiguity in 2020 due to the COVID-related shift in assessment methods of the NSDUH field work, as described in Chapter 3.

Of greater importance to this dissertation research project is the general tendency of the cohort-specific experiences, year by year, to be congruent with the age-specific increasing estimates shown in the prior sections of this chapter. It is difficult to contradict the thesis advanced in this project – namely, that over the course of the adolescent years under study there is a general tendency for BDS to be followed by MDE, and that this tendency seems to increase age by age, whether age is studied cross-sectionally in repeated national samples, or whether age is studied dynamically over time in the experience of successive 'birth cohorts,' subject to limitations already mentioned.

## 6.4 Unanticipated Results

Although not required in my statement of specific aims for this dissertation research project, I decided to use a differencing approach that Collins used to study the age-specific 'incidence' of communicable diseases in the Spanish Flu Pandemic era surveys of school-attending adolescents in the United States. Collins considered the use of calculus and the integrals but decided upon the alternative approach of taking differences. I wondered what I would find if I were to use Collins' differencing approach in the study of the cohort experiences of adolescents who had experienced Brief Depressive Spells in the 21st century. The next table shows what I found when I took the differences, which serve as crude approximations of the age-specific shifts in the incidence of Major Depressive Episodes given that an adolescent already has experienced a Brief Depressive Spell.

I have not yet had time to produce the Bayesian CRINT and estimates, but the frequentist point estimates and age-specific 95% CI are shown in Table 21. My meta-analysis summary estimates suggest relatively stable BDS□MDE proportions during each year of adolescence.

That is, the frequentist 95% CI overlap age by age, across a range of point estimates from just under five percent (meta-analysis summary estimate when 15-year-olds become 16-year-olds) to a larger value of just under 10 percent (meta-analysis summary estimate when 12-year-olds become 13-year-olds). After rounding, the mode for this set of estimates is about six percent. That is, in this dissertation study of the BDS□MDE transition during the adolescent years of community-dwelling adolescents, we observe estimated CIP increases of roughly six percent (1 in 16) year by year across these years of adolescence. This estimated CIP mode of about six percent serves as a point estimate that we can try to understand and to reduce in future epidemiological investigations of adolescent experiences with depression.

To be clear, this final set of estimates pertain to the transition from BDS to MDE. The six percent approximation for the mode is not based solely on the cross-sectionally derived cumulative incidence proportion. It is based on the difference of successive CIP estimates, exactly as Collins derived his age-specific communicable disease ‘attack rates’ from the cumulative incidence proportions he had derived from the pre-1920 USPHS Child Hygiene field surveys of school-attending youths. In future studies, these differencing-based estimates can be refined by making use of the calculus, but I have not completed this work as part of my dissertation research project.

Table 20. Estimating The Age-Specific Incidence of Major Depressive Episodes Among Adolescents Who Had Experienced A Brief Depressive Spell in the United States, 2004-2020. Data from U.S. National Surveys on Drug Use and Health, PDAS datasets).

| **Birth Cohort** | **13-12** | **14-13** | **15-14** | **16-15** | **17-16** |
|---|---|---|---|---|---|
| **Year** | Estimated Differenced Cumulative Incidence Proportions for MDE given BDS=1 for All Non-Institutionalized Adolescents Age 12-17 Years in the United States. | | | | |
| **1992** | 5.2 | 2.6 | 5.6 | 4.4 | 1 |
| **1993** | **3.9** | 2.6 | 4.7 | 2.1 | 3.6 |
| **1994** | 6.4 | **5.0** | 4.9 | 2.8 | 2.2 |
| **1995** | 10.8 | 3.7 | **5.2** | 2.2 | 1.6 |
| **1996** | 4.3 | 8.1 | 2.6 | **6.8** | 0.8 |
| **1997** | 6.4 | 6.6 | 7.1 | 2.3 | **5.0** |
| **1998** | 6.6 | 8.2 | 5.4 | 5 | 2.2 |
| **1999** | 12.3 | 7.2 | 6.1 | -0.2 | 9.2 |
| **2000** | 11.8 | 6.5 | 9 | 1.2 | 4.7 |
| **2001** | 11.9 | 6.9 | 5.7 | 3.8 | 7.1 |
| **2002** | 11.4 | 1.6 | 6.9 | 3.7 | 5.5 |
| **2003** | 13.4 | 0.2 | 15.6 | 0.2 | 7.9 |
| **Meta-analysis summary estimate** | **9.6** | **6.5** | **6.9** | **4.5** | **6.2** |
| **95% Confidence Interval** | 8.0, 11.5 | 5.0, 8.3 | 5.1, 9.2 | 3.1, 6.6 | 4.5, 8.5 |

# CHAPTER 7 - DISCUSSION

## 7.0 Overview of this chapter

This chapter discusses the most significant findings and results from each study presented here. My goal with this discussion is to explain the results in light of the prior literature and the theoretical concepts introduced in the background chapter. I wish to highlight the many strengths of each research study while also acknowledging the research's limitations, a problem that every scientific researcher encounters at one time or another. In the next chapter (Chapter 8), I discuss what conclusions I can draw from the research, including any implications for future research and public health practice.

As has been previously mentioned in the results section, I decided that it would be best to start with a two-group comparison of female versus male empirical estimates as manifest in cumulative incidence proportions among survivors (CIPAS, CIP).

## 7.1 Female-Male Variations (Aim 1)

The age- and year-specific contingency table estimates, with summary estimates from frequentist and Bayesian meta-analysis approaches, have extended the pioneering work of Collins on communicable diseases and the work of Angst, Merikangas, and colleagues on brief mood swings and the occurrence of later affective syndromes. Here, studying US nationally representative samples of 12-17-year-olds male and female adolescents, my first finding of note extends the established line of research on female excess occurrence of depression syndromes. In my Bayesian estimation approach, I found that among every 1000 US female adolescents, an evaluation at age 12 years might show as few as 407 who already had experienced a Brief Depressive Spell and as many as 427 per 1000; the Bayesian point estimate was 416 per 1000. By comparison, the corresponding Bayesian estimates for males at age 12 year ranged from 322 per 1000 to 340 per 1000, with a point estimate of 332 per 1000. (The corresponding frequentist point estimates here, and later in the dissertation, did not vary appreciably from the Bayesian point estimates. However, the estimated Bayesian 95% credibility intervals tended to be more precise than the corresponding frequentist 95% confidence intervals.)

Evaluated during the 12 months before the 18$^{th}$ birthday, at age 17 years, the Bayesian point estimates for female and male adolescents in the US were 584 BDS cases and 418 BDS cases per 1000, respectively. Interval bounds at this age were 575 to 591 per 1000 for females versus 409 to 425 per 1000 for males when evaluated at age 17 years.

If we think about the female excess in Brief Depressive Spell experiences in terms of males 'catching up' with females, the males do not 'catch up' with the earliest adolescent female BDS cumulative incidence proportions until the males reach age 17 years — i.e., a lag time interval of about five years before the BDS CIP estimate for males reaches the values seen for females at age 12 years.

Estimating the age-specific BDS CIP variations in relation to the four Hill function parameters, my dissertation evidence was compatible with the null hypothesis of no female-male variation for the Pmin parameter (e.g., evaluated at the lowest age value) and for the 'k' slope parameter (i.e., the CIP difference evaluated at the inflection point corresponding with PD50). However, there was a female excess in the PD50 parameter and in the Pmax parameter, as signaled by the age-specific estimates just mentioned. Namely, with respect to the PD50 parameter, the females reached the halfway mark between Pmin and Pmax just before the 13$^{th}$ birthday (PD50 = 12.86 years; 95% CI = 11.98, 13.75), whereas the males did not reach that halfway mark until just after the 14$^{th}$ birthday (PD50 = 14.23 years; 95% CI = 13.94, 14.51). The BDS Pmax estimate for the females was 60% (95% CI = 58%, 62%); the corresponding BDS Pmax estimates for males was 42% (95% CI = 41%, 43%).

Upon viewing these findings of my dissertation research, some observers might note the long line of epidemiological studies about 'sex as a biological variable' and the female excess occurrence of depression syndromes and ask 'What else is new?' My response draws attention to the mixed findings of prior studies with epidemiologically credible samples of females and males, including the Zurich Longitudinal Study findings that prompted Professor Angst and his colleagues to make the following assertion: "… the results suggest that the female preponderance of depression in community studies may be largely attributable to the prevalence of more threshold-level manifestations and the increased frequency of comorbidity of depression and anxiety among female subjects (Angst et al., 1997).

It is possible that the unconditional BDS estimates from this dissertation research challenges the idea that the female excess does not emerge in sub-threshold stages of the depression spectrum. With the strengths of multiple replications, nationally representative samples, and standardized assessments, the estimates of this study are not compatible with the idea that the female excess in mood disturbances does not emerge until a threshold has been

crossed — unless that threshold is defined to be shorter than the minimum one-day duration of the BDS as researched in the NSDUH depression module.

As described in relation to the other post-BDS sequences investigated in this dissertation, this dissertation's research findings draw attention to these other facets of a possible early emergence of a female excess before the threshold is crossed and the affected adolescent becomes a case of Major Depression. Here, I draw attention to what my dissertation evidence shows about the transition from BDS to a more sustained (two-week) Depression Syndrome (DS), also a 'sub-threshold' sequence if the threshold is set at the occurrence of the first 'Major Depressive Episode.'

Again, we might reflect back on the idea that the female excess occurrence of mood disturbances might not be manifest until after an MDD threshold transition has occurred. The evidence from this dissertation research suggests otherwise, with perhaps an earlier emergence of a female excess along the depression spectrum — earlier than the previously described delay of the female excess until later in the process (i.e., after the affected adolescent becomes a case of Major Depression).

I found a female excess occurrence of the DSM-IV-specified Major Depressive Disorder (MDD) once a Brief Depression Spell had occurred. In estimates for females and males together, among every 100 12-year-olds who experienced BDS, there were roughly five who had transitioned to the MDD experience. The corresponding estimate for 17-year-olds was roughly 40 MDD cases for every set of 100 BDS cases.

In contrast, among females, the corresponding estimates for 12-year-olds were substantially larger. Roughly 40-42 MDD cases for every 100 females who had experienced BDS and almost 60 MDD cases for every 100 females who had experienced BDS. The estimates for males, age by age, were substantially smaller. These findings from the dissertation research project extend what has been found in prior studies that generally disclosed that females have higher levels of major depression and depressive symptoms when compared with males (Salk et al., 2018). In this work, there is methods novelty in the use of both Bayesian credible intervals and frequentist confidence intervals to quantify the variations and their compatibility with or against the null hypotheses being considered.

Using the Hill function to assess the female-male differences, I found estimates of Pmax and PD50 estimates that were greater for females than males. In addition, the females had an

estimated steeper slope (k = 19.3) with a respective point of inflection occurring at approximately 12.9 years of age. By contrast, the males had a shallower estimated slope (k = 15.5), with a respective point of inflection occurring at 14.2 years of age. The Hill function estimates confirm that females affected by BDS experience MDD earlier than males affected by BDS, and at a greater rate.

One possible negative consequence of emphasizing the preponderance of young women with depression is that depression might become a female-stereotyped disorder. Such a stereotype can be harmful to both males and females. The stereotype might lead to over-diagnosis of brief depressive spells and major depression in females, whereas manifestations of mood disturbance might be overlooked or neglected in male adolescents. It is crucial that depressive symptoms are not overlooked in males, particularly because gender biases in diagnosis have been documented (Hartung & Widiger, 1998). Males may be less likely to develop depression than women; however, this does not mean that depressed males are not distressed and impaired.

7.2 Minority Health Disparities and ESI Sub-Group Variations.

Several prior studies have suggested that African American individuals have lower rates of depression compared with White individuals. These NSDUH findings indicate that the CIP of depression differs slightly by ESI.

In this study, I estimated the age-specific and year-specific cumulative incidence proportions (among survivors) for having become a case of DSM-IV major depressive episode after a brief depressive spell experience. I described the parameter variations across subgroups defined by self-identified Non-Hispanic Whites, Non-Hispanic Blacks, and Hispanic adolescents. The guiding hypothesis originated with a parsimonious theory based on the null. Accordingly, my forecast was for no subgroup variation in any of the estimated parameters. I used both frequentist 95% confidence intervals (CI) and Bayesian 95% credible intervals (CRINT) to make the subgroup comparison. with the four parameters estimated with Hill functions (Pmin, Pmax, PD50, and the slope).

To summarize the pattern of estimates for Non-Hispanic Black adolescents, age 12 to 17 years old at the time of the NSDUH assessment, the Bayesian approach suggests age-specific increments in the estimated proportion of BDS-affected adolescents who have made a later transition and have qualified as cases of DSM-IV Major Depressive Episode cases. The estimates

from the frequentist approach suggest a less robust shift in the age-specific estimates, with no clear pattern of age-by-age shifts except in the age-specific estimates for 12-year-olds versus 13-year-olds.

With respect to the significance of the differences between pairs of racial/ethnic subgroup variations using the four parameters estimated with Hill functions; comparing NHW with NHB significant differences were observed in Pmax. When comparing the Pmin Hill parameter there were no significant differences noted among the three subgroups.

My results highlight that disparity in adolescent mental health related ESI persists between Non-Hispanic Blacks and Non-Hispanic Whites. Additionally, I found that younger aged Hispanics and non-Hispanic white adolescents were more likely to report MDE, given a history of BDS. A study done by Alexander et al. in 2009 stated that Caucasian youths were 1.55 times as likely as Hispanic youths to receive adequate mental health care.

Furthermore, their study stated that when individuals from racial or ethnic minority groups engage in mental services, they are more likely to make only a small number of visits to their providers than non-Hispanic whites (Alexander et al. 2009). Several factors contribute to higher MDE rates in racial groups. Researchers found that adolescent mental health is significantly related to ethnic identity, including ethnic identity exploration and affirmation (Fisher et al., 2014).

My results, like prior research, found that non-Hispanic Black adolescents had significantly lower MDE rates than their non-Hispanic White counterparts, which may be attributable to the underreporting of MDE and BDS in non-Hispanic Black adolescents. Cultural and social context shapes one's view of mental illness and thus influences one's interpretation of related symptoms. For example, non-Hispanic Black adolescents were found to be more likely to use their own types of expression (e.g., somatic complaints) to express their depressive symptoms (Lu et al., 2017). Furthermore, minority adolescents may also suffer from unexamined or unrecognized MDE due to a lack of sensitivity to ethnocultural differences in measurement instruments (Choi, 2002).

The most recent systematic review synthesized the multi-dimensional barriers, including individual, family, and sociocultural risk factors that hinder minority adolescents from seeking services from mental health professionals (Lu et al., 2021). Notably, cultural differences and unmatched ethnic backgrounds between minority adolescents and mental health practitioners

may lead to frequent mistrust of professionals and poor-quality therapeutic relationships that increase minority adolescents' reluctance to seek mental health services (Kwan et al., 2018) and lowers their adherence to mental health treatment protocols. For many years, the need to improve mental health practitioners' cultural competence in providing services has been acknowledged.

The current study is limited in its reliance on self-reports of depressive symptoms that may differ from clinical evaluations and could be subject to recall bias. This study utilized repeated cross-sectional data and it remains possible that the surveyed populations differed over time, though the NSDUH's high response rate, consistent sampling design, and use of survey weights safeguard against this possibility.

Other limitations that deserve consideration include: (a) my assumption of no appreciable variation in the female-male, ESI subgroup, and cohort-specific analyses with respect to details such as right-censoring, (b) new paragraphs will be added on each of these details, as well as the corresponding implications for future research such as time-to-event survival analyses that can reduce the degree of reliance upon this assumption about right-censoring (e.g., at age 17 for those with BDS+DS who had not yet experienced MDE, but who might do so at age 18 or in some later year).

Some strengths of this research include having large sample sizes that yield statistically precise estimates even when modest-level associations are observed, plus the strengths of a nationally representative sample that helps to promote the external validity of these results, as well as standardized computer-assisted assessment methods to maximize validity and reliability of the study measurements. That is, computer-assisted self-interviewing methods may have helped ensure more honest, more complete, and perhaps more accurate responses to questions on sensitive topics such as drug use and mood disturbances such as depression spells. These are important strengths in a cross-sectional survey that is unburdened by the uncertainties that come with sample attrition during longitudinal follow-up studies on relationships of this type.

### 7.3 Mutoscope Approach to Estimation of Cohort-Wise Experiences

In this study, I estimated the conditional MDE cumulative incidence proportions as experienced by BDS-affected adolescents during recent years of the 21$^{st}$ century in the US using the epidemiological mutoscope approach, conceptualized as an elaboration of Frost's approach. In contrast with the age-specific CIP estimates produced under Aims 1 and 2, Aim 3 estimates are cohort-specific CIP estimates.

For this part of my dissertation research, I downloaded NSDUH PDAS datasets and completed analyses with the dimensions of the problem specified about the year of assessment (a t-dimension), the modal birth year of each cohort (an x-dimension), and the estimated occurrence of BDS or MDE or each transition from BDS to MDE by the date when the NSDUH assessment had occurred (a y-dimension).

This data structure was conceptualized as a Yit matrix, where i=0 refers to the experience of a specific birth cohort (or set of adjacent birth cohorts, e.g., 1991-92, explained above), as observed when the birth cohort members had survived to the point of the age 12 birthday (or beyond). The mutoscope view is gained when successive cross-sectional panel surveys of population experience are repeated with new samples or panels, survey year by survey year.

In terms of my dissertation research's third aim, I used a frequentist approach relative to a null hypothesis. Guided by depression prevalence trends in recent journal articles, I expected the more recently born cohorts to be more likely to become MDD cases once BDS has already occurred.

Estimation of incidence was calculated by taking age- and cohort-specific differences in cumulative MDD 'lifetime attack rates' in successive years, conditional on prior mood disturbances (BDS, DS), using the Collins' approach from the 1920s. The main prior contributors to this line of research include Wade Hampton Frost and James C Anthony, and their contributions already have been described in Chapter 2 of this dissertation research report. This research study provides an initial exploration, via the novel "mutoscope" approach, of MDE experienced by prior BDS-affected adolescents during recent years of the 21$^{st}$ century.

# CHAPTER 8 - CONCLUSION

## 8.0 Overview of this chapter

In the final chapter (Chapter 8), I discuss what can be concluded from the research, particularly any implications for future research and possibly for public health practice.

## 8.1 Conclusion

The main conclusions of my dissertation research project can be summarized as follows:

1. According to my meta-analysis approach, statistically robust and reproducible non-null estimates suggest a general age-associated excess occurrence of Brief Depressive Spells.
2. In addition, many US adolescents experience Major Depressive Disorder after they have experienced one or more Brief Depression Spells, also with a female excess generally seen in this project's estimated proportions for the occurrence of Major Depressive Disorder after the experience of (a) Brief Depressive Spell, and later two weeks sustained Depression syndrome (sustained depression and depression-like conditions such as anhedonia). Here, also, the estimates are statistically robust non-null estimates (i.e., with values not compatible with each null hypothesis).
3. The same can be said of the three primary US Ethnic Self Identification (ESI) subgroups under study, with the Hill functional analysis harnessed for the first time to aid in the estimation of minority health disparities that involve adolescent mood disturbances and the progression to Major Depression. Readers are referred to the Results and Discussion chapters for the detailed contrasts between the experiences of the several ESI adolescent subgroups for which I was able to produce estimates.
4. My use of Wade Hampton Frost's cohort-specific approach provides evidence that helps to disconfirm a null hypothesis of no age-associated occurrence of Major Depression after adolescents had experienced shorter and less complex mood disturbances. The cohort-specific estimates in successive years of assessment are not longitudinal at the individual level, but the cohort-level estimates do not seem to be compatible with any hypothesis of stability as the cohort moves forward, birthday by birthday, across the adolescent years under study. Instead, the residual impression is that the cohorts are experiencing an age-associated increase in the estimated cumulative incidence proportions as each cohort transitions from age 12 to age 13 to age 14 and onward.

## 8.2 Public health practices

With outreach and early identification, as well as targeted Major Depressive Disorder (MDD) preventive interventions in these practice sectors, the findings from this dissertation research project have some potential implications for clinical practice and for public health practice. However, it is true that pragmatic action steps and directives for public health tactics do not always emerge from each and every epidemiology dissertation research project.

As described in Chapter 2, I suggest that public health work might be improved with a greater attention to the depression spectrum concept introduced by Angst, Merikangas, and others, and extended here to encompass Brief Depression Spells. Given the several subgroup disparities in these dissertation estimates, future public health action steps and tactics might be organized in relation to (a) whether the Brief Depressive Spell (BDS) occurs in the first place, and whether BDS can be prevented, (b) whether and when the BDS cascades forward to become a two-week sustained Depression Spell (DS). If disrupted, this state-transition might dampen subsequent occurrence of the Major Depressive Episode because an MDE cannot occur unless a BDS plus DS sequence has occurred. In addition, (c) once sustained DS has occurred, an intervention might disrupt the transition from DS to MDE case status. Chapter 2 describes some cognitive-behavioral therapeutic interventions, sometimes with web-based applications, that might be applied in new secondary prevention initiatives to reduce the occurrence of MDD once BDS or DS have occurred.

## 8.3 Directions for future research

The direction of future research should include prospective and longitudinal investigations, possibly with randomized controlled trials integrated into otherwise observational studies. Thus, in an era of smartphones and web-based clinical therapeutics, it should be possible to embed randomized trials within observational studies. Given convincing evidence that BDS and DS+BDS have elevated non-null positive predictive values that help signal the excess occurrence of subsequent MDD, we should embed an RCT of these non-toxic or low toxicity interventions within observational longitudinal studies, as opposed to the Tuskegee-type tradition of discovering an underlying pathological process that might be disrupted by an intervention. Moreover, if BDS and DS can predict MDD, then how is it ethical to discover an adolescent with BDS or DS and proceed to not offer an intervention that might disrupt the subsequent progression to MDD?

With or without decisions that there is an ethical mandate to offer an intervention when an adolescent experiences a BDS or DS, future directions for research should include the development and testing of novel intervention modalities that might disrupt the progression to Major Depression once Brief Depression Spells or Depression Syndromes have occurred. Utilization of EMA (ecological momentary assessment) or ESM (experience sampling methods) to detect when the BDS progresses from Day 1 to Day 2 should be possible. For example, a smartphone daily monitoring app might be used to monitor BDS, and when BDS occurs, the app might deliver a text message or some other disruptive intervention to prevent the BDS progression that otherwise might result in later DS or MDE.

As alternatives to RCT, there now are non-RCT adaptive interventions and SMART intervention designs that can be applied as an extension of current large-sample epidemiology observational studies. The estimates from this dissertation research project should be useful to intervention researchers who seek funding support for future interventional investigations along these lines.

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## APPENDIX A: CHAPTER 4

Table 21. Estimated Female Cumulative Incidence Proportion For Brief Depressive Spell: Age-Specific and Year-Specific Meta-Analysis Summary Estimates and Compatibility Intervals. Data from the US National Surveys on Drug Use and Health, 2004-2020.

| Estimated Unconditional Cumulative Incidence Proportions (%) | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Year-Pairs** | **Age in years:** | **12** | **13** | **14** | **15** | **16** | **17** |
| **2004** | | 45.4 | 51.9 | 59.2 | 60.5 | 60.0 | 61.0 |
| **2005** | | 45.3 | 51.9 | 54.0 | 59.9 | 62.4 | 61.2 |
| **2006** | | 44.0 | 51.0 | 55.5 | 58.5 | 58.6 | 58.4 |
| **2007** | | 41.0 | 49.4 | 49.3 | 55.4 | 58.7 | 56.3 |
| **2008** | | 41.9 | 47.4 | 53.2 | 59.3 | 55.9 | 55.2 |
| **2009** | | 39.2 | 48.5 | 56.1 | 58.2 | 55.5 | 58.3 |
| **2010** | | 38.1 | 44.8 | 47.6 | 56.8 | 55.1 | 50.1 |
| **2011** | | 38.0 | 43.5 | 50.0 | 55.5 | 56.3 | 54.2 |
| **2012** | | 40.6 | 52.3 | 51.8 | 59.1 | 58.3 | 55.5 |
| **2013** | | 41.3 | 49.8 | 56.4 | 60.1 | 58.7 | 57.2 |
| **2014** | | 43.7 | 51.2 | 57.7 | 58.1 | 61.1 | 59.1 |
| **2015** | | 43.4 | 49.8 | 57.3 | 60.9 | 59.8 | 58.9 |
| **2016** | | 39.6 | 48.7 | 55.3 | 60.0 | 61.9 | 60.0 |
| **2017** | | 36.0 | 49.4 | 54.2 | 64.4 | 61.2 | 63.6 |
| **2018** | | 42.5 | 50.6 | 57.2 | 63.5 | 62.3 | 66.3 |
| **2019** | | 45.2 | 51.9 | 62.3 | 62.3 | 62.2 | 64.2 |
| **2020** | | 45.8 | 64.6 | 62.9 | 68.3 | 69.8 | 62.3 |
| **Cumulative Incidence Proportion (%): Frequentist Meta-Analysis Summary Estimate & CI.** | | 41.7<br>40.3,43.0 | 49.8<br>48.4,51.2 | 55.1<br>53.2,57.0 | 59.6<br>58.4,60.9 | 59.4<br>58.1,60.7 | 58.8<br>56.8, 60.8 |
| **Cumulative Incidence Proportion (%): Bayesian Meta-Analysis Summary & CRINT** | | 41.6<br>40.7,42.7 | 49.6<br>48.6,50.6 | 54.7<br>53.8,55.8 | 59.4<br>58.7,60.3 | 59.3<br>58.5,60.1 | 58.4<br>57.5,59.1 |

Table 21 (cont'd)

| **(B) 95% confidence intervals for estimates in (A)** | | | | | | |
|---|---|---|---|---|---|---|
| **2004** | 41.9,48.9 | 48.7,55.1 | 55.4,62.8 | 57.4,63.6 | 57.1,62.9 | 57.5,64.4 |
| **2005** | 41.9,48.7 | 48.0,55.8 | 50.6,57.4 | 56.6,63.0 | 59.4,65.2 | 58.0,64.3 |
| **2006** | 41.0,47.1 | 47.6,54.3 | 52.1,58.9 | 55.9,61.1 | 54.8,62.3 | 55.4,61.3 |
| **2007** | 36.9,45.3 | 46.0,52.7 | 45.7,52.9 | 52.3,58.6 | 55.2,62.2 | 52.6,59.8 |
| **2008** | 38.1,45.7 | 43.9,51.0 | 49.7,56.7 | 55.7,62.9 | 52.6,59.3 | 51.9,58.4 |
| **2009** | 36.1,42.4 | 44.2,52.8 | 52.9,59.2 | 55.3,61.0 | 52.1,58.9 | 54.4,62.0 |
| **2010** | 34.7,41.6 | 41.4,48.2 | 44.2,50.9 | 53.1,60.3 | 51.6,58.6 | 46.5,53.8 |
| **2011** | 35.0,41.1 | 39.9,47.2 | 46.2,53.7 | 51.8,59.1 | 53.2,59.5 | 51.0,57.4 |
| **2012** | 36.8,44.6 | 48.6,55.9 | 48.3,55.2 | 55.2,62.9 | 55.1,61.5 | 52.5,58.4 |
| **2013** | 37.5,45.2 | 46.6,53.1 | 52.6,60.0 | 56.8,63.2 | 55.4,61.9 | 54.2,60.2 |
| **2014** | 40.0,47.5 | 46.9,55.5 | 53.5,61.7 | 54.0,62.0 | 57.1,64.9 | 54.6,63.4 |
| **2015** | 38.7,48.2 | 45.4,54.2 | 53.9,60.7 | 57.6,64.1 | 55.9,63.7 | 54.8,62.9 |
| **2016** | 36.0,43.3 | 45.3,52.1 | 51.3,59.3 | 56.6,63.2 | 58.5,65.2 | 54.6,65.2 |
| **2017** | 31.6,40.7 | 45.4,53.4 | 50.4,58.0 | 60.8,67.7 | 57.7,64.6 | 60.2,67.0 |
| **2018** | 38.8,46.2 | 45.9,55.3 | 53.3,61.1 | 58.8,67.9 | 58.2,66.3 | 62.5,69.9 |
| **2019** | 40.5,50.0 | 48.1,55.6 | 58.5,66.0 | 57.5,66.9 | 58.6,65.7 | 60.6,67.6 |
| **2020** | 37.9,53.8 | 56.3,72.1 | 55.3,70.0 | 62.0,74.0 | 61.6,76.8 | 54.3,69.7 |
| **Frequentist meta-analysis summary estimate 95% CI** | 40.3,43.0 | 48.4,51.2 | 53.2,57.0 | 58.4,60.9 | 58.1,60.7 | 56.8,60.8 |
| **Bayesian meta-analysis summary estimate 95% CRINT** | 40.7,42.7 | 48.6,50.6 | 53.8,55.8 | 58.7,60.3 | 58.5,60.1 | 57.5,59.1 |
| **(C) Standard errors for estimates in (A)** | | | | | | |
| **2004** | 1.8 | 1.6 | 1.9 | 1.6 | 1.5 | 1.8 |
| **2005** | 1.8 | 2.0 | 1.7 | 1.6 | 1.5 | 1.6 |
| **2006** | 1.6 | 1.7 | 1.7 | 1.3 | 1.9 | 1.5 |
| **2007** | 2.2 | 1.7 | 1.8 | 1.6 | 1.8 | 1.9 |
| **2008** | 1.9 | 1.8 | 1.8 | 1.8 | 1.7 | 1.6 |
| **2009** | 1.6 | 2.2 | 1.6 | 1.5 | 1.7 | 1.9 |
| **2010** | 1.8 | 1.7 | 1.7 | 1.8 | 1.8 | 1.9 |
| **2011** | 1.6 | 1.9 | 1.9 | 1.9 | 1.6 | 1.6 |
| **2012** | 2.0 | 1.9 | 1.8 | 2.0 | 1.6 | 1.5 |
| **2013** | 2.0 | 1.7 | 1.9 | 1.7 | 1.7 | 1.6 |
| **2014** | 1.9 | 2.2 | 2.1 | 2.1 | 2.0 | 2.3 |
| **2015** | 2.4 | 2.3 | 1.7 | 1.7 | 2.0 | 2.1 |
| **2016** | 1.9 | 1.7 | 2.1 | 1.7 | 1.7 | 2.7 |
| **2017** | 2.3 | 2.0 | 1.9 | 1.8 | 1.8 | 1.7 |
| **2018** | 1.9 | 2.4 | 2.0 | 2.3 | 2.1 | 1.9 |
| **2019** | 2.4 | 1.9 | 1.9 | 2.4 | 1.8 | 1.8 |
| **2020** | 4.1 | 4.1 | 3.8 | 3.1 | 3.9 | 4.0 |

Table 22. Estimated Male Cumulative Incidence Proportion For Brief Depressive Spell: Age-Specific and Year-Specific Meta-Analysis Summary Estimates and Compatibility Intervals. Data from the US National Surveys on Drug Use and Health, 2004-2020.

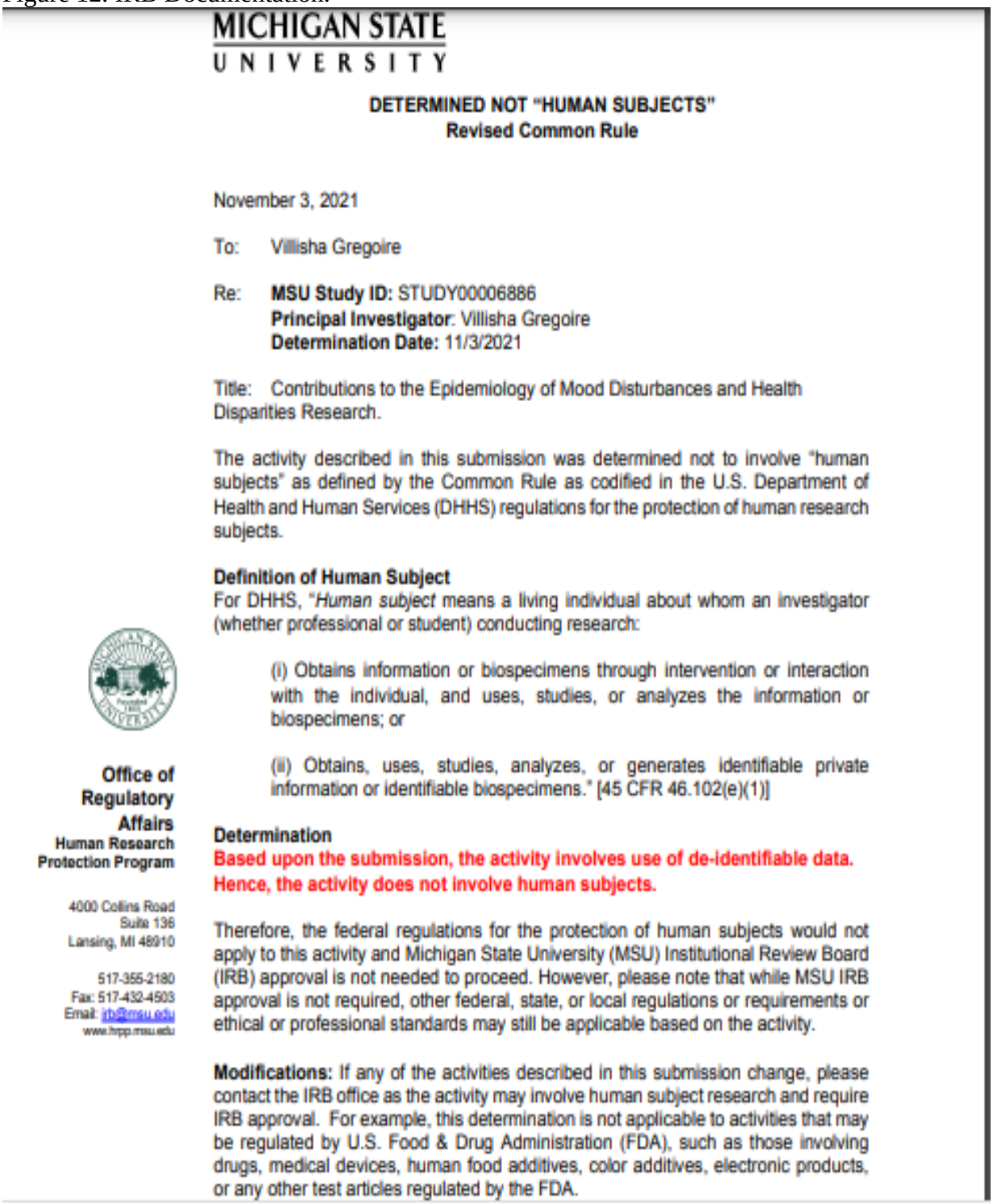
| Estimated Unconditional Cumulative Incidence Proportions (%) | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Year-Pairs** | **Age in years:** | **12** | **13** | **14** | **15** | **16** | **17** |
| **2004** | | 38.0 | 37.0 | 39.9 | 46.0 | 43.7 | 43.4 |
| **2005** | | 39.6 | 37.9 | 40.0 | 41.6 | 43.0 | 44.7 |
| **2006** | | 40.1 | 36.9 | 38.0 | 39.5 | 39.5 | 42.5 |
| **2007** | | 34.6 | 34.7 | 36.7 | 42.1 | 36.7 | 41.5 |
| **2008** | | 35.4 | 35.3 | 38.7 | 38.0 | 41.5 | 40.3 |
| **2009** | | 33.1 | 33.4 | 34.9 | 41.6 | 41.6 | 41.6 |
| **2010** | | 31.2 | 31.9 | 33.3 | 39.5 | 39.2 | 43.1 |
| **2011** | | 30.2 | 31.8 | 35.4 | 38.0 | 40.8 | 39.0 |
| **2012** | | 32.6 | 30.7 | 33.6 | 36.4 | 35.3 | 40.8 |
| **2013** | | 31.2 | 30.9 | 36.6 | 38.2 | 39.4 | 41.2 |
| **2014** | | 30.2 | 34.8 | 33.3 | 36.4 | 37.7 | 42.8 |
| **2015** | | 30.9 | 32.0 | 35.5 | 38.8 | 42.4 | 40.0 |
| **2016** | | 31.5 | 29.4 | 33.0 | 37.7 | 38.7 | 40.6 |
| **2017** | | 26.5 | 29.3 | 36.5 | 39.3 | 40.3 | 41.1 |
| **2018** | | 24.3 | 34.2 | 34.8 | 35.7 | 43.4 | 40.7 |
| **2019** | | 30.5 | 35.5 | 36.1 | 37.1 | 43.6 | 45.2 |
| **2020** | | 22.7 | 33.4 | 41.4 | 40.0 | 45.2 | 43.3 |
| **Cumulative Incidence Proportion (%): Frequentist Meta-Analysis Summary Estimate & CI.** | | 32.1<br>30.0,34.3 | 33.6<br>32.3,34.9 | 36.1<br>34.9,37.2 | 39.2<br>37.9,40.5 | 40.5<br>39.3,41.8 | 41.8<br>40.9,42.6 |
| **Cumulative Incidence Proportion (%): Bayesian Meta-Analysis Summary & CRINT** | | 33.2<br>32.2,34.0 | 33.7<br>32.9,34.7 | 36.0<br>35.3,36.7 | 39.4<br>38.6,40.1 | 40.5<br>39.7,41.3 | 41.8<br>40.9,42.5 |

Table 22 (cont'd)

| **(B) 95 confidence intervals for estimates in (A)** | | | | | | |
|---|---|---|---|---|---|---|
| **2004** | 34.9,41.1 | 34.0,40.1 | 36.3,43.6 | 43.0,48.9 | 40.3,47.2 | 40.2,46.7 |
| **2005** | 35.7,43.5 | 34.3,41.7 | 36.8,43.3 | 38.6,44.7 | 39.6,46.5 | 41.6,47.9 |
| **2006** | 37.5,42.7 | 33.7,40.3 | 34.7,41.4 | 36.2,42.8 | 36.1,43.0 | 39.5,45.6 |
| **2007** | 31.0,38.4 | 31.5,38.1 | 33.2,40.3 | 38.9,45.4 | 33.6,39.9 | 38.1,45.0 |
| **2008** | 31.1,40.0 | 32.2,38.4 | 35.5,41.9 | 34.9,41.2 | 38.2,44.8 | 37.8,42.8 |
| **2009** | 29.6,36.7 | 30.2,36.8 | 32.6,37.2 | 38.5,44.8 | 38.0,45.2 | 38.2,45.1 |
| **2010** | 27.7,34.9 | 28.7,35.2 | 30.0,36.7 | 36.1,42.9 | 36.2,42.3 | 40.3,46.0 |
| **2011** | 27.1,33.4 | 28.8,35.0 | 32.4,38.5 | 34.9,41.2 | 38.0,43.7 | 35.8,42.3 |
| **2012** | 28.7,36.7 | 27.4,34.1 | 30.8,36.5 | 33.2,39.7 | 31.9,38.8 | 38.0,43.6 |
| **2013** | 28.0,34.6 | 27.2,34.8 | 33.5,39.9 | 35.3,41.1 | 35.9,42.9 | 37.2,45.3 |
| **2014** | 26.9,33.6 | 31.3,38.5 | 30.4,36.3 | 32.8,40.1 | 34.0,41.5 | 38.9,46.7 |
| **2015** | 27.3,34.6 | 28.2,36.0 | 32.4,38.8 | 35.1,42.6 | 38.7,46.2 | 36.2,44.0 |
| **2016** | 27.9,35.4 | 26.0,33.0 | 29.7,36.5 | 34.6,40.9 | 34.6,42.9 | 37.0,44.4 |
| **2017** | 23.2,30.1 | 25.4,33.6 | 32.5,40.7 | 35.8,42.8 | 37.0,43.8 | 37.2,45.1 |
| **2018** | 20.5,28.6 | 29.9,38.7 | 31.3,38.4 | 31.5,40.0 | 39.9,47.0 | 38.1,43.3 |
| **2019** | 26.6,34.7 | 31.6,39.7 | 31.6,40.8 | 34.0,40.3 | 40.2,47.1 | 41.7,48.8 |
| **2020** | 16.8,29.8 | 27.1,40.4 | 33.8,49.5 | 33.2,47.2 | 37.4,53.3 | 35.7,51.2 |
| **Frequentist meta-analysis summary estimate 95% CI** | 30.0,34.3 | 32.3,34.9 | 34.9,37.2 | 37.9,40.5 | 39.3,41.8 | 40.9,42.6 |
| **Bayesian meta-analysis summary estimate 95% CRINT** | 32.2,34.0 | 32.9,34.7 | 35.3,36.7 | 38.6,40.1 | 39.7,41.3 | 40.9,42.5 |
| **(C) Standard errors for estimates in (A)** | | | | | | |
| **2004** | 1.6 | 1.5 | 1.9 | 1.5 | 1.8 | 1.6 |
| **2005** | 2.0 | 1.9 | 1.7 | 1.6 | 1.8 | 1.6 |
| **2006** | 1.3 | 1.7 | 1.7 | 1.7 | 1.8 | 1.6 |
| **2007** | 1.9 | 1.7 | 1.8 | 1.7 | 1.6 | 1.8 |
| **2008** | 2.3 | 1.6 | 1.7 | 1.6 | 1.7 | 1.3 |
| **2009** | 1.8 | 1.7 | 1.2 | 1.6 | 1.8 | 1.8 |
| **2010** | 1.8 | 1.7 | 1.7 | 1.7 | 1.6 | 1.5 |
| **2011** | 1.6 | 1.6 | 1.6 | 1.6 | 1.5 | 1.6 |
| **2012** | 2.1 | 1.7 | 1.5 | 1.7 | 1.8 | 1.4 |
| **2013** | 1.7 | 1.9 | 1.6 | 1.5 | 1.8 | 2.1 |
| **2014** | 1.7 | 1.9 | 1.5 | 1.9 | 1.9 | 2.0 |
| **2015** | 1.9 | 2.0 | 1.7 | 1.9 | 1.9 | 2.0 |
| **2016** | 1.9 | 1.8 | 1.7 | 1.6 | 2.1 | 1.9 |
| **2017** | 1.7 | 2.1 | 2.1 | 1.8 | 1.7 | 2.0 |
| **2018** | 2.1 | 2.3 | 1.8 | 2.2 | 1.8 | 1.4 |
| **2019** | 2.1 | 2.1 | 2.4 | 1.6 | 1.8 | 1.8 |
| **2020** | 3.3 | 3.4 | 4.0 | 3.6 | 4.1 | 4.0 |

## APPENDIX B: IRB DOCUMENTATION

Figure 12. IRB Documentation.



MICHIGAN STATE
UNIVERSITY

**DETERMINED NOT "HUMAN SUBJECTS"**
**Revised Common Rule**

November 3, 2021

To: Villisha Gregoire

Re: **MSU Study ID:** STUDY00006886
**Principal Investigator**: Villisha Gregoire
**Determination Date:** 11/3/2021

Title: Contributions to the Epidemiology of Mood Disturbances and Health Disparities Research.

The activity described in this submission was determined not to involve "human subjects" as defined by the Common Rule as codified in the U.S. Department of Health and Human Services (DHHS) regulations for the protection of human research subjects.

**Definition of Human Subject**
For DHHS, "*Human subject* means a living individual about whom an investigator (whether professional or student) conducting research:

(i) Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or

(ii) Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens." [45 CFR 46.102(e)(1)]

**Determination**
**Based upon the submission, the activity involves use of de-identifiable data. Hence, the activity does not involve human subjects.**

Therefore, the federal regulations for the protection of human subjects would not apply to this activity and Michigan State University (MSU) Institutional Review Board (IRB) approval is not needed to proceed. However, please note that while MSU IRB approval is not required, other federal, state, or local regulations or requirements or ethical or professional standards may still be applicable based on the activity.

**Modifications:** If any of the activities described in this submission change, please contact the IRB office as the activity may involve human subject research and require IRB approval. For example, this determination is not applicable to activities that may be regulated by U.S. Food & Drug Administration (FDA), such as those involving drugs, medical devices, human food additives, color additives, electronic products, or any other test articles regulated by the FDA.

**Office of Regulatory Affairs**
**Human Research Protection Program**

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## APPENDIX C: NSDUH ADOLESCENTS DEPRESSION QUESTIONNAIRE SPECS

The National Survey of Drug Use and Health (NSDUH) study definition of a Major Depressive Episode is based mainly on the 4th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-4):

- A period of at least two weeks when a person experienced a depressed mood or loss of interest or pleasure in daily activities, and had a majority of specified symptoms, such as problems with sleep, eating, energy, concentration, or self-worth.
- No exclusions were made for major depressive episode symptoms caused by medical illness, substance use disorders, or medication.

Below are the adolescent depression questions from the 2019 National Survey On Drug Use And Health, Final Cai Specifications For Programming.

Adolescent Depression

**YDS21** [IF CURNTAGE = 12-17] Have you ever in your life had a period of time lasting several days or longer when **most of the day** you felt **sad, empty, or depressed**?

1 Yes
2 No
DK/REF

**YDS22** [IF YDS21 = 2 OR DK/REF] Have you ever had a period of time lasting several days or longer when **most of the day** you felt very **discouraged or hopeless** about how things were going in your life?

1 Yes
2 No
DK/REF

**YDS23** [IF YDS22 = 2 OR DK/REF] Have you ever had a period of time lasting several days or longer when you **lost interest and became bored** with most things you usually enjoy, like work, hobbies, and personal relationships?

1 Yes
2 No
DK/REF

**YD01** [IF YDS21 = 1] During times when you felt **sad**, **empty**, or **depressed** most of the day, did you ever feel **discouraged** about how things were going in your life?

1 Yes
2 No
DK/REF

**YD01a** [IF YD01 = 1] During the times when you felt **sad**, **empty**, or **depressed**, did you ever **lose interest and become really bored** with most things like school, work, hobbies, and other things that are usually fun for you, like listening to music, watching TV, movies, or sports, playing computer games, or going out with friends?

1 Yes
2 No

DK/REF

**YD01b**[YD01 = 2 OR DK/REF] During times when you felt sad, empty, or depressed, did you ever **lose interest and become really bored** with most things like school, work, hobbies, and other things that are usually fun for you, like listening to music, watching TV, movies, or sports, playing computer games, or going out with friends?

1 Yes
2 No
DK/REF

**YD02** [IF YDS22 = 1] During times when you felt discouraged about how things were going in your life, did you ever **lose interest and become really bored** with most things like school, work, hobbies, and other things that are usually fun for you, like listening to music, watching TV, movies, or sports, playing computer games, or going out with friends?

1 Yes
2 No
DK/REF

**YD09** [IF YDS23 = 1] Did you ever have a period of time like this that lasted **most of the day almost every day** for **two weeks or longer**?

1 Yes
2 No
DK/REF

DEFINE FEELFILL:
IF (YD01a = 1), THEN FEELFILL = "were sad, discouraged, or really bored" IF (YD01a = 2 OR DK/REF), THEN FEELFILL = "were sad or discouraged" IF (YD01b = 1), THEN FEELFILL = "were sad or really bored"
IF (YD01b = 2 OR DK/REF) THEN FEELFILL = "were sad"
IF (YD02 = 1), THEN FEELFILL = "were discouraged or really bored"
IF (YD02 = 2 OR DK/REF), THEN FEELFILL = "were discouraged about the way things were going in your life"
IF (YD09 = 1), THEN FEELFILL = "were really bored" ELSE, FEELFILL = BLANK
DEFINE FEELNOUN:
IF (YD01a = 1), THEN FEELNOUN = "sadness, discouragement, or boredom"
IF (YD01a = 2 OR DK/REF), THEN FEELNOUN = "sadness or discouragement" IF (YD01b = 1), THEN FEELNOUN = "sadness or boredom"
IF (YD01b = 2 OR DK/REF), THEN FEELNOUN = "sadness"
IF (YD02 = 1), THEN FEELNOUN = "discouragement or boredom" IF (YD02 = 2 OR DK/REF), THEN FEELNOUN = "discouragement" IF (YD09 = 1), THEN FEELNOUN = "boredom"
ELSE FEELNOUN = BLANK
DEFINE NUMPROBS
IF YD01a NE BLANK OR YD01b = 1 OR YD02 = 1, THEN NUMPROBS = these problems

IF YD01b = (2 OR DK/REF) OR YD02 = (2 OR DK/REF) OR YD09 = 1, THEN
NUMPROBS = this problem
ELSE NUMPROBS = BLANK
DEFINE WASWERE:
IF YD01a NE BLANK OR YD01b = 1 OR YD02 = 1, THEN WASWERE =
"were" IF YD01b = (2 OR DK/REF) OR YD02 = (2 OR DK/REF) OR YD09 =
1, THEN
WASWERE = "was"
ELSE WASWERE =
BLANK

**YD12** [IF YD01a NE BLANK OR YD01b NE BLANK OR YD02 NE BLANK] Think about the times when you [FEELFILL]. Did you ever have a period of time like this that lasted **most of the day, almost every day**, for **two weeks or longer**?

1 Yes
2 No
DK/REF

**YD16** [IF YD09 = 1 OR YD12 = 1] Think of times lasting **two weeks or longer** when [NUMPROBS] with your mood [WASWERE] most **severe and frequent**. During those times, how long did your [FEELNOUN] usually last?

1 Less than 1 hour
2 At least 1 hour but less than 3 hours
3 At least 3 hours but less than 5 hours
4 5 hours or more DK/REF

**YD17** [IF YD16 = 2, 3, 4, OR DK/REF] Still thinking of times lasting two weeks or longer when [NUMPROBS] with your mood [WASWERE] most **severe and frequent**, how strong were your **bad feelings** during those times?

1 Mild
2 Moderate
3 Severe
Very severe DK/REF

**YD18** [IF YD16 = 2, 3, 4, OR DK/REF] Again, think of times lasting two weeks or longer when [NUMPROBS] with your mood [WASWERE] most **severe and frequent**.
How often, during those times, did you feel so bad that **nothing could cheer you up**?

1 Often
2 Sometimes
3 Not very often
4 Never DK/REF

**YD19** [IF YD16 = 2, 3, 4, OR DK/REF] Once again, please think of times lasting two weeks or longer when [NUMPROBS] with your mood [WASWERE] most **severe and frequent**.
How often, during those times, did you feel so bad that you **could not carry out your daily activities**?

1 Often
2 Sometimes

3 Not very often
4 Never DK/REF

**YD21** [IF YD16 = (2, 3, 4 OR DK/REF) AND NOT (YD17 = 1 AND YD18 = 4 AND YD19 = 4) AND (YDS21=1 OR YDS22=1 OR YDS23=1) AND YD09 NE (2 OR DK/REF)] People who have problems with their mood often have other problems at the same time. These problems may include things like changes in:

- sleep
- eating
- energy
- the ability to keep their mind on things
- feeling badly about themselves

Did you ever have any of these problems during a period of time when you [FEELFILL] for **two weeks or longer**?

1 Yes
2 No
DK/REF

**YD22** [IF YD21=1] Think again about these other problems we just mentioned. They include things like changes in:

- sleep
- eating
- energy
- the ability to keep their mind on things
- feeling badly about themselves

Can you think of the **worst** time when you [FEELFILL] for **two weeks or longer** and also had these other problems at the same time?

1 Yes
2 No
DK/REF

**YD22a** [IF YD22 = 1] How old were you when that worst period of time started?

AGE: _____

DK/REF **YD22c** [IF YD22 = 2 OR DK/REF] Then think of the **most recent** time you [FEELFILL] for **two weeks or longer** and you had these other problems at the same time. How old were you when that time started?

[RANGE: 1-17]

DEFINE TIMEFILL:
IF YD22a NE BLANK, THEN TIMEFILL = 'worst'
IF YD22c NE BLANK, THEN TIMEFILL = 'most recent'

**YD24a** [IF YD22a NE BLANK] In answering the next questions, think about the period of time when your [FEELNOUN] and other problems were the **worst**.
[IF YD22c NE BLANK] In answering the next questions, think about the **most recent** period of time when you [FEELFILL] and had other problems at the same time.
During that time, did you feel sad, empty, or depressed for **most of the day nearly every day**?

1 Yes

2 No
DK/REF

**YD24c** [IF YD22a NE BLANK OR YD22c NE BLANK] During that [**TIMEFILL**] period of time, did you feel discouraged about how things were going in your life most of the day nearly every day?

1 Yes
2 No
DK/REF

**YD24e** [IF YD22a NE BLANK OR YD22c NE BLANK] During that [**TIMEFILL**] period of time, did you become bored with almost everything like school, work, hobbies, and things you like to do for fun?

1 Yes
2 No
DK/REF

**YD24f** [IF YD22a NE BLANK OR YD22c NE BLANK] During that [**TIMEFILL**] period of time, did you feel like nothing was fun even when good things were happening?

1 Yes
2 No
DK/REF

**YD26a** [IF ANY YD24a - YD24f = 1] The next questions are about changes in appetite and weight.
[IF YD22a NE BLANK] In answering these questions, think about the period of time when your [FEELNOUN] and other problems were the **worst**.
[IF YD22c NE BLANK] In answering these questions, think about the **most recent** period of time when you [FEELFILL] and had other problems at the same time.
Did you eat much less than usual almost every day during that time?

1 Yes
2 No
DK/REF

**YD26b** [IF YD26a = 2 OR DK/REF] Did you eat much **more** than usual almost every day?

1 Yes
2 No
DK/REF

**YD26c** [IF YD26a = 2 OR DK/REF]Did you gain weight without trying to during that [**TIMEFILL**] period of time?

1 Yes
2 No
DK/REF

**YD26c1** [IF YD26c = 1] Did you gain weight without trying to because you were growing?

1 Yes
2 No
DK/REF

**YD26c2** [IF YD26c1 = (2 OR DK/REF) AND QD01 = 9] Did you gain weight

without trying to because you were pregnant?
1 Yes
2 No
DK/REF

**YD26d** [IF (YD26c1=(2 OR DK/REF) AND YD26c2=BLANK, 2 OR DK/REF] How many pounds did you gain?
Please enter your answer as a whole number.
# OF POUNDS:_____ DK/REF
[RANGE: 0-200]

**YD26e** [IF YD26a = 1 OR YD26c = (2 OR DK/REF)] Did you **lose** weight without trying to?
1 Yes
2 No
DK/REF

**YD26e1** [IF YD26e = 1] Did you lose weight without trying to because you were sick or on a diet?
1 Yes
2 No
DK/REF

**YD26f** [IF YD26e1=2 OR DK/REF] How many pounds did you lose?
Please enter your answer as a whole number.
# OF POUNDS:_____ DK/REF

**YD26g** [IF YD26a NE BLANK]
[RANGE: 0-200]
[IF YD22a NE BLANK] Again, please think about the period of time when your [FEELNOUN] and other problems were the **worst**.
[IF YD22c NE BLANK] Again, please think about the **most recent** period of time when you [FEELFILL]and had other problems at the same time.
Did you have a lot more trouble than usual falling asleep or staying asleep most nights or waking too early most mornings during that [**TIMEFILL**] time?
1 Yes
2 No
DK/REF

**YD26h** [IF YD26g=2 OR DK/REF]During that [**TIMEFILL**] period of time, did you sleep a lot more than usual?
1 Yes
2 No
DK/REF

**YD26j** [IF YD26a NE BLANK] On most days during that [**TIMEFILL**] period of time, did you feel that you didn't have much energy?
1 Yes
2 No
DK/REF

**YD26l** [IF YD26a NE BLANK] Did you feel as though you were talking or moving more slowly than usual on most days during that [**TIMEFILL**] period of time?
1 Yes

2 No
DK/REF

**YD26m**[IF YD26l = 1] Did anyone else notice that you were talking or moving more slowly than usual?
1 Yes
2 No
DK/REF

**YD26n**[IF YD26l = 2 OR DK/REF] Were you so restless or jittery that you walked up or down or couldn't sit still?
1 Yes
2 No
DK/REF

**YD26o** [IF YD26n = 1] Did anyone else notice that you couldn't sit still?
1 Yes
2 No
DK/REF

**YD26p**[IF YD26a NE BLANK] The next questions are about changes in your ability to concentrate, and your feelings about yourself.
[IF YD22a NE BLANK] Again, in answering these questions, think about the period of time when your [FEELNOUN] and other problems were the **worst**.
[IF YD22c NE BLANK] Again, in answering these questions, think about the **most recent** period of time when you [FEELFILL] and had other problems at the same time.
On most days during that [**TIMEFILL**] time, did your thinking seem slower than usual or seem mixed up?
1 Yes
2 No
DK/REF

**YD26r** [IF YD26a NE BLANK] On most days, did you have a lot more trouble than usual keeping your mind on things?
1 Yes
2 No
DK/REF

**YD26s** [IF YD26a NE BLANK] Were you unable to make up your mind about things you ordinarily have no trouble deciding about?
1 Yes
2 No
DK/REF

**YD26u** [IF YD26a NE BLANK] Did you feel that you were not as good as other people nearly every day?

1 Yes
2 No
DK/REF

**YD26v**[IF YD26u = 1] Did you feel totally worthless nearly every day?

1 Yes
2 No
DK/REF

**YD26aa**[IF YD26a NE BLANK] The next questions are about thoughts of death or suicide.
[IF YD22a NE BLANK] Again, in answering these questions, think about the period of time when your [FEELNOUN] and other problems were the **worst**.
[IF YD22c NE BLANK] Again, in answering these questions, think about the **most recent** period of time when you [FEELFILL] and had other problems at the same time.
Did you often think a lot about death, either your own, someone else's, or death in general?

1 Yes
2 No
DK/REF

**YD26bb** [IF YD26a NE BLANK] During that time, did you ever think that it would be better if you were dead?

1 Yes
2 No
DK/REF

**YD26cc**[IF YD26a NE BLANK] Did you think about killing yourself?

1 Yes
2 No
DK/REF

**YD26dd**[IF YD26cc = 1] Did you make a plan to kill yourself?

1 Yes
2 No
DK/REF

**YD26ee**[IF YD26cc = 1] Did you make a suicide attempt or try to kill yourself?

1 Yes
2 No
DK/REF

DEFINE D_MDEA1Y:
IF YD24A = 1 OR YD24C = 1, THEN D_MDEA1Y= 1
ELSE IF YD24A = 2 AND YD24C = 2, THEN D_MDEA1Y= 2
ELSE IF YD24A = DK OR YD24C = DK, THEN D_MDEA1Y=
DK
ELSE IF YD24A = REF OR YD24C = REF, THEN D_MDEA1Y=
REF ELSE D_MDEA1Y= BLANK
DEFINE D_MDEA2Y:
IF YD09 = 1 OR YD24E = 1 OR YD24F = 1 THEN D_MDEA2Y = 1
ELSE IF (YDS21 = 1 OR YDS22 = 1 OR YD09 = 2) AND YD24E = 2 AND YD24F =
2 THEN D_MDEA2Y = 2 ELSE IF YD09 = DK OR YD24E = DK OR YD24F = DK
THEN D_MDEA2Y = DK ELSE IF YD09 = REF OR YD24E = REF OR YD24F =
REF THEN D_MDEA2Y = REF

ELSE D_MDEA2Y=BLANK
DEFINE D_MDEA3Y:
IF YD26A = 1 OR YD26B = 1 OR YD26D ≥10 OR YD26F ≥10, THEN
D_MDEA3Y= 1
ELSE IF YD26A = 2 AND YD26B = 2 AND ((YD26D < 10 OR YD26F < 10) OR
(YD26C = (2 OR BLANK) AND YD26E = (2 OR BLANK)) OR (YD26C = 1 AND
(YD26C1
= 1 OR YD26C2 = 1)) OR (YD26E = 1 AND YD26E1 = 1)), THEN D_MDEA3Y= 2
ELSE IF YD26A = DK OR YD26B = DK OR YD26C = DK OR YD26D = DK
OR YD26E = DK OR YD26F = DK, THEN D_MDEA3Y= DK
ELSE IF YD26A = REF OR YD26B = REF OR YD26C = REF OR YD26D = REF OR
YD26E = REF OR YD26F = REF, THEN D_MDEA3Y= REF
ELSE D_MDEA3Y= BLANK
DEFINE D_MDEA4Y:
IF YD26G = 1 OR YD26H = 1, THEN D_MDEA4Y= 1
ELSE IF YD26G = 2 AND YD26H = 2, THEN D_MDEA4Y= 2
ELSE IF YD26G = DK OR YD26H = DK, THEN D_MDEA4Y=
DK
ELSE IF YD26G = REF OR YD26H = REF, THEN D_MDEA4Y=
REF ELSE D_MDEA4Y= BLANK
DEFINE D_MDEA5Y:
IF YD26M = 1 OR YD26O = 1, THEN D_MDEA5Y= 1
ELSE IF (YD26L = (2 OR DK/REF) AND (YD26N = (2 OR DK/REF) OR YD26O
= 2)) OR YD26M = 2, THEN D_MDEA5Y= 2
ELSE IF YD26L = DK OR YD26M = DK OR YD26N = DK OR YD26O = DK, THEN
D_MDEA5Y= DK
ELSE IF YD26L = REF OR YD26M = REF OR YD26N = REF OR YD26O =
REF, THEN D_MDEA5Y= REF
ELSE D_MDEA5Y= BLANK
DEFINE D_MDEA6Y:
D_MDEA6Y= YD26J
DEFINE D_MDEA7Y:
IF YD26V = 1, THEN D_MDEA7Y= 1
ELSE IF YD26U = (2 OR DK/REF) OR YD26V = 2, THEN D_MDEA7Y=
2 ELSE D_MDEA7Y=YD26V
ELSE D_MDEA7Y= BLANK
DEFINE D_MDEA8Y:
IF YD26P = 1 OR YD26R = 1 OR YD26S = 1, THEN D_MDEA8Y= 1
ELSE IF YD26P = 2 AND YD26R = 2 AND YD26S = 2, THEN D_MDEA8Y= 2
ELSE IF YD26P = DK OR YD26R = DK OR YD26S = DK, THEN D_MDEA8Y=
DK ELSE IF YD26P = REF OR YD26R = REF OR YD26S = REF, THEN
D_MDEA8Y= REF
ELSE D_MDEA8Y= BLANK
DEFINE D_MDEA9Y:
IF YD26AA = 1 OR D26BB = 1 OR YD26CC = 1 OR YD26DD = 1 OR YD26EE = 1,
THEN D_MDEA9Y= 1

ELSE IF YD26AA = 2 AND YD26BB = 2 AND YD26CC = 2, THEN
D_MDEA9Y= 2 ELSE IF YD26AA = DK OR YD26BB = DK OR YD26CC = DK
OR YD26DD = DK OR YD26EE = DK, THEN D_MDEA9Y= DK
ELSE IF YD26AA = REF OR YD26BB = REF OR YD26CC = REF OR YD26DD
= REF OR YD26EE = REF, THEN D_MDEA9Y= REF
ELSE D_MDEA9Y= BLANK
DEFINE DSMMDEAY:
IF SUM (D_MDEA1Y = 1, D_MDEA2Y = 1, D_MDEA3Y = 1, D_MDEA4Y = 1,
D_MDEA5Y = 1, D_MDEA6Y = 1, D_MDEA7Y = 1, D_MDEA8Y = 1, D_MDEA9Y
= 1) ≥ 5, THEN DSMMDEAY = 1
ELSE IF SUM (D_MDEA1Y = (1 OR DK/REF), D_MDEA2Y = (1 OR
DK/REF), D_MDEA3Y = (1 OR DK/REF), D_MDEA4Y = (1 OR DK/REF),
D_MDEA5Y = (1 OR DK/REF), D_MDEA6Y = (1 OR DK/REF), D_MDEA7Y
= (1 OR DK/REF), D_MDEA8Y = (1 OR DK/REF), D_MDEA9Y = (1 OR
DK/REF)) < 5 AND N(OF D_MDEA1Y-D_MDEA9Y) > 0, THEN
DSMMDEAY = 2
ELSE IF D_MDEA1Y = DK OR D_MDEA2Y = DK OR D_MDEA3Y = DK OR
D_MDEA4Y = DK OR D_MDEA5 = DK OR D_MDEA6Y = DK OR
D_MDEA7Y = DK OR D_MDEA8Y = DK OR D_MDEA9Y = DK, THEN
DSMMDEAY = DK
ELSE IF D_MDEA1Y = REF OR D_MDEA2Y = REF OR D_MDEA3Y = REF OR
D_MDEA4Y = REF OR D_MDEA5Y = REF OR D_MDEA6Y = REF OR
D_MDEA7Y
= REF OR D_MDEA8Y = REF OR D_MDEA9Y = REF, THEN DSMMDEAY = REF

**YD28** [IF D_MDEA9Y = 1 OR DSMMDEAY = 1] You mentioned having some of the problems I just asked you about.
During that [**TIMEFILL**] period of time, how much did your [FEELNOUN] interfere or cause problems with your school work, your job, or your relationships with family and friends?

1 Not at all
2 A little
3 Some
4 A lot
5 Extremely
DK/REF

**YD28a** [IF YD28 = 2, 3, 4, 5 OR DK/REF] During that [**TIMEFILL**] period of time, how often were you unable to carry out your daily activities or to take care of yourself because of these problems with your mood?

1 Often
2 Sometimes
3 Not very often
4 Never
DK/REF

**YD37** [IF YD28 NE BLANK] Think of the **very first period of time** in your life lasting **two weeks or longer** when you [FEELFILL] and also had some of the other problems we just asked about.

Can you remember your exact age?

1 Yes
2 No
DK/REF

**YD37a** [IF YD37 = 1] How old were you?

AGE:_____ DK/REF

**YD37b** [IF YD37 = 2 OR DK] **About** how old were you when you first had a period of time like this?

AGE:_____ DK/REF
[RANGE: 1-17]

**YD38** [IF YD28 NE BLANK] **In the past 12 months**, did you have a period of time when you felt [FEELNOUN] for **two weeks or longer** while also having some of the other problems we asked about?

1 Yes
2 No
DK/REF

PROGRAMMER: SHOW 12 MONTH CALENDAR

**YD52** [IF YD28 NE BLANK] In your entire life, how many times did you feel [FEELNOUN] for **two weeks or longer** while also having some of the other problems we asked about?
If you are not sure of your answer, just make your best guess.
# OF EPISODES_____
[RANGE: 1-1000] DK/REF

**YD66a** [IF YD38 = 1] Think about the time in the past 12 months when [NUMPROBS] with your mood [WASWERE] the **worst**.
Using the 0 to 10 scale shown below, where 0 means **no** problems and 10 means very **severe** problems, select the number that describes how much your [FEELNOUN] caused problems with your **ability to do** each of the following activities during that time. You can use any number between 0 and 10 to answer.
How much did your [FEELNOUN] cause problems with your chores at home?
NUMBER: _____[RANGE: 0-10] DK/REF

**YD66b** [IF YD38 = 1] During that time in the past 12 months when your [FEELNOUN] was worst, how much did this cause problems with your **ability to do well at school or work**?

You can use any number between 0 and 10 to answer

**YD66c** [IF YD38 = 1] How much did your [FEELNOUN] cause problems with your **ability to get along with your family** during that time? You can use any number between 0 and 10 to answer.

NUMBER: _____[RANGE: 0-10] DK/REF

**YD66d** [IF YD38 = 1] How much did your [FEELNOUN] cause problems with your **ability to have a social life** during that time?
You can use any number between 0 and 10 to answer.
NUMBER: _____[RANGE: 0-10] DK/REF

**YD68** [IF ANY RESPONSES TO YD66a – YD66d = 1-10] About how many days out of 365 in the past 12 months were you **totally unable** to go to school or work or carry out your normal activities because of your [FEELNOUN]?

You can use any number between 0 and 365 to answer. # OF DAYS:_____ [RANGE: 0-365]
DK/REF
PROGRAMMER: SHOW 12 MONTH CALENDAR

**YD86** [IF YD38 NE BLANK] Here is a list of professionals some people talk to about the problems we have been asking about:
General practitioner or family doctor
Other medical doctor like a cardiologist, gynecologist, urologist Psychologist
Psychiatrist or psychotherapist Social Worker
Counselor
Other mental health professional, like a mental health nurse A nurse, occupational therapist, or other health professional A religious or spiritual advisor like a minister, priest, or rabbi
Another healer, like an herbalist, chiropractor, acupuncturist, or massage therapist
At any time **in the past 12 months**, did you see or talk to a medical doctor or other professional about your [FEELNOUN]?

1 Yes
2 No
DK/REF
PROGRAMMER: SHOW 12 MONTH CALENDAR

**YD86a**[IF YD86 = 1] **During the past 12 months**, which professionals did you see or talk to about [NUMPROBS] with your mood?
To select more than one professional from the list, press the space bar between each number you type. When you have finished, press the [ENTER] key to go to the next question.

1 General practitioner or family doctor
2 Other medical doctor like a cardiologist, gynecologist, urologist
3 Psychologist
4 Psychiatrist or psychotherapist
5 Social Worker
6 Counselor
7 Other mental health professional, like a mental health nurse
8 A nurse, occupational therapist, or other health professional
9 A religious or spiritual advisor like a minister, priest, or rabbi
10 An herbalist, chiropractor, acupuncturist, or massage therapist
11 Another type of helping professional DK/REF

PROGRAMMER: SHOW 12 MONTH CALENDAR

**YD86aSP** [IF ANY RESPONSE IN YD86a =11] Please type in the type of other professional you saw or talked to during the past 12 months about your [FEELNOUN]. When you have finished typing your answer, press the [ENTER] key to go to the next question.

_____ [RANGE: 50 CHARACTERS] DK/REF

PROGRAMMER: DO NOT ALLOW BLANKS IN YD86aSP.

**YD86b** [IF YD86= 1] Are you **currently** receiving treatment or counseling for [NUMPROBS] with your mood?

1 Yes
2 No
DK/REF

**YD86c** [IF YD38 NE BLANK] **During the past 12 months**, did you take prescription medication that was prescribed for[NUMPROBS]?

1 Yes
2 No
DK/REF

PROGRAMMER: SHOW 12 MONTH CALENDAR

**YD86d** [IF YD86c = 1] Are you **currently** taking prescription medication that was prescribed for [NUMPROBS]?

1 Yes
2 No
DK/REF

**YD86e** [IF YD86c = 1] **During the past 12 months**, how much has this prescription medication helped you?

1 Not at all
2 A little
3 Some
4 A lot
5 Extremely DK/REF

PROGRAMMER: SHOW 12 MONTH CALENDAR

**YD86f** [IF YD86 = 1] **During the past 12 months**, how much has treatment or counseling helped you?

1 Not at all
2 A little
3 Some
4 A lot
5 Extremely
6 DK/REF