EXPLORING THE TRANSITION FROM INITIATION TO DEPENDENCE ON ALCOHOL

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ABSTRACT

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Objective: To explore the transition from first full drink to dependence within the first year of use by: broadening the existing estimate by age, male-female differences, and adding recent year data. I also estimated days of drinking for newly incident drinkers (NID) versus Alcohol Dependent (AD) individuals, and compared the newer alcohol use disorders (AUD) case definition with the older AD case definition. I obtained human subjects committee approval of a protocol I wrote for future research. **Study Design:** The United States National Surveys on Drug Use and Health (US, NSDUH, 2002-2019) drew population samples of all US non-institutionalized civilian residents aged 12 years and older, took standardized measurements, and produced public use datasets. After obtaining estimates, I produced meta-analytic summaries with 95% confidence intervals (CI). Frequency distributions are used for estimates involving days of drinking. **Results:** The meta-analytic summary for the transition from NID to AD was 1.67%. The female excess in the estimate for the transition from NID to AD was unremarkable when the 95% CI is taken into account (female: 1.86% [95%CI:(1.6, 2.2)] & male: 1.47% [95%CI:(1.2, 1.8)]. Individuals with AD spent more days drinking on average than NID. An estimated 9.9% qualified for DSM-5 AUD, while an estimated 3.2% had DSM-IV AD in 2020. **Conclusion:** The aggregated meta-analytic estimate is 1.7% for the transition from NID to AD from 2002-2019. The 2020 estimates show an increased caseload for alcohol treatment services when the DSM-5 AUD criteria is used. In clinical practice, the shift to DSM-5 AUD criteria may prompt earlier outreach and intervention strategies.

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KEY TO ABBREVIATIONS

AA- Alcohol Abuse

AD- Alcohol Dependence

AUD- Alcohol Use Disorder

B.C.E- Before Common Era

C.E.- Common Era

CI- Confidence Intervals

DSM-IV- Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition

DSM-5- Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition

U.S.- United States

NID- Newly Incident Drinkers

NSDUH- National Survey on Drug Use and Health

SAMHSA: Substance Abuse and Mental Health Services Administration

SUD- Substance Use Disorder

CHAPTER 1: INTRODUCTION

Prehistoric evidence clearly shows that drinking alcoholic beverages appeared in the human behavioral repertoire at least 7000 years ago (McGovern et al., 2004). In cuneiform and other texts, there is written evidence to show that social and medical attention was given to the potential adverse effects of alcohol, including intoxication and disease, perhaps as early as 2600 B.C.E., as discovered near the Tigris and Euphrates Rivers of Mesopotamia (Damerow, 2012). Some readers of this thesis report might be surprised to find alcohol regulations mentioned in the Code of Hammurabi, composed 1755-1750 B.C.E., which specified a penalty of 'death by drowning' if the beer vendor failed to fill the customer's beer vessel by the price paid (Mark, 2018).

As described in Chapter 2 of this master's thesis research project, conceptual antecedents of our modern concepts of 'alcoholism,' 'alcohol dependency,' 'alcohol abuse,' and 'alcohol use disorders' had emerged by roughly 1750 C.E. The mass manufacture of distilled spirits such as gin, and unregulated sales of relatively inexpensive spirits had prompted press coverage of previously more hidden displays of public intoxication, illustrated by William Hogarth's 'Gin Lane' (White, 2003).

It is possible that the mass manufacture of distilled spirits, and a shift from prior drinking customs, might have contributed to an acceleration of ideas about alcohol's complications. For example, drinking beer and mead throughout the day in the British Isles seems to have been common practice. Furthermore, drinking alcohol might have had protective benefits during epidemics of water-borne illnesses such as cholera (Snow, 1855, pg. 42). Nevertheless, historical studies by Withington (2011) suggest that increased consumption of

beer and wine in the British Isles promoted the increased appearance of terms such as ‘drunkenness’ and ‘drunkard’ in English publications during the 17th century. As such, the ‘alcoholism-related concepts might have emerged even without the evolution of the distilled spirits industry.

In recent years, the majority of the reviews of concepts such as ‘alcoholism’ and ‘alcohol dependence’ are inspired by the American Psychiatric Association Diagnostic and Statistical Manual, Fifth Edition (DSM-5), which most recently has combined 'alcohol dependence' (AD) and 'alcohol abuse' to form a more integrated construct of 'alcohol use disorder.' Modifications from the Fourth Edition (DSM-IV) to DSM-5 are presented in Chapter 2. It seems that DSM-IV ‘abuse’ now is re-cast as ‘mild’ AUD; a larger proportion of DSM-IV AD cases now qualify as more ‘severe’ forms of AUD.

In my research, I focused on 'Alcohol Dependence' due to the lack of epidemiological evidence on the DSM-5 conceptualization of 'Alcohol Use Disorders.' In my literature review, I found estimates of DSM-IV alcohol dependence that suggested a narrowing of traditionally observed male excess in the occurrence of alcohol dependence during the first 12-24 months after the first drink of an alcoholic beverage (Cheng et al., 2013, 2016). The published estimates for early-onset newly incident drinkers (NID), with drinking onsets observed during the adolescent and transitional adulthood years, suggest that for every 100 NID, about two AD cases have occurred within 6-12 months after drinking onset (i.e., incidence estimate of ~2%). Some estimates suggest that female NID are more likely to rapidly transition into alcohol dependence soon after drinking onset – especially when drinking starts in adolescence (Cheng et al., 2016).

The most recently published evidence from the United States on the transition from NID to AD was last updated with data gathered almost ten years ago. More recent epidemiological evidence from multi-stage area probability sample surveys is available through 2020. Given the availability of these current estimates, I chose to investigate whether the more recent data is compatible with the most recently published estimate of roughly 2% and whether newer estimates do or do not confirm a previously described female-male gap in this transition. In addition, I have addressed several supporting aims to help understand the evolving epidemiology of alcohol dependence and related conditions during these first decades of the 21st century.

My aims also discuss how shifting from the DSM-IV to the DSM-5 diagnostic criteria can challenge epidemiological time trend research. Even before evidence is considered, the nature of the shift, with a reduced threshold count of clinical features and consideration of obsession-like 'craving,' suggests that there might be an increase in the estimated occurrence of alcohol problems when DSM-5 AUD criteria are applied versus the DSM-IV specification.

I have also provided a proposed protocol pertinent to this shift from DSM-IV to DSM-5 and intended to evaluate the nature of criterion-weighting in DSM-IV and DSM-5. Common practice is to give each criterion the same unit weight. The approach is to sum up the number of criteria each person's alcohol consumption qualifies for and set a threshold. The threshold in DSM-IV is set at three criteria. In DSM-5, there was a downward shift to two criteria.

Accordingly, my thesis research project included my development of an IRB-approved protocol in asking expert clinicians their preference for a re-weighting of the criteria so that

each criterion might have its own weight. The intent is to work toward a future alternative to the current DSM-IV and DSM-5 approach of giving each criterion equal weight.

Via the proposed protocol, I wish to examine whether expert clinicians believe some criteria (e.g., tolerance, withdrawal) should be given more weight than other criteria (e.g., drinking more than one intended). As part of my thesis work, I developed this protocol to the point that the institutional review board approved it. Based on this protocol, I also conducted some initial pilot assessments, but I opted to be conservative and provide the protocol as evidence of my work for the thesis. The publication of the expert clinician survey results will be left for a later stage of my research on alcohol problems.

For the first part of my thesis research project, I stated the following aim:

To explore the transition from the first full drink of alcohol (initiation) to alcohol dependence within the first year of use (i.e., 0-365 days after drinking onset). This aim will be accomplished through a meta-analysis approach that can be used to produce multi-year U.S. population summary estimates for the individuals who consume their first full drink of alcohol (new initiates) and then are observed to have become cases of DSM-IV alcohol dependence within the interval from drinking onset until the date of a survey assessment (never more than 365 days). There are prior estimates of about 2% of US newly incident drinkers making this transition within 12 months, but these estimates are based on surveys conducted almost ten years ago. Plus, the published estimates do not encompass all newly incident drinkers; they are restricted to adolescent-onset drinkers and those who started to drink during the first years of transitional adulthood (Cheng et al., 2016). The meta-analysis approach is made possible

because the federal government has conducted epidemiological surveys across the interval from 2002 onward and has produced public use datasets that combine years in two-year pairs. I also consider female-male variations in the occurrence of the transition from first full drink to DSM-IV alcohol dependence within the first year after the first full drink.

A secondary goal of this research has been to understand the potential association that links days of drinking in newly initiated alcohol users with the formation of DSM-IV AD among newly incident drinkers. The analyses for this aim focused on differences observed for all NID versus NID who had become alcohol dependent.

The third aim will examine the changes in DSM-IV and DSM-5 regarding alcohol use, thus exploring a 2020 shift in survey procedures with the addition of new questions and changes in the diagnostic threshold as the national survey shifted focus from DSM-IV to DSM-5 criteria.

Finally, I will describe my proposed protocol designed to secure a clinician-level clinical perspective on the issue of unit-weighting versus alternative weights given to the individual DSM-5 diagnostic criteria. The proposed protocol can be used in future research. As part of my thesis research, I was able to refine the protocol and secure IRB approval for its use in future contacts with samples of clinicians.

A roadmap for the remaining chapters of this thesis research report follows. I already offered a brief initial sketch of the human history with alcoholic beverages and pertinent consequences. I noted that 'alcoholism'-related concepts show an evolution contemporaneous with the emergence of mass manufacture of distilled spirits such as 'gin' roughly 300 years ago but might have been anticipated by increased consumption of beer and wine during the 17th

century. Chapter 2 provides a more rigorous scholarly review of the history and literature on this subject matter. It ends with a section on the clinical significance and potential public health impacts of the evidence I sought to obtain when I set out to complete my thesis research project.

The next chapter includes a description of the United States populations under study, how the samples were drawn, the assessment approach, and details about my analysis approaches. The following section, Chapter 4, is organized aim by aim regarding my results. Chapter 5 provides a concise summary of the main findings of my research project. Additionally, this chapter reflects my estimates and previous literature evidence, notes on my research approach's limitations, and some ideas about directions for future research. A conclusion summary offers some final comments.

CHAPTER 2: BACKGROUND AND SIGNIFICANCE

This is a road map to what I try to cover in Chapter 2. I first describe the history of human alcohol consumption and the earliest publications on the consequences of drinking. Second, I consider prior scholarship and epidemiological evidence on the several specific aims I sought to investigate, focusing on female-male variations. This chapter will discuss the definition of 'Sex as a Biological Variable' (SAGV) used by the National Institutes of Health and distinguish concepts about gender identity and social roles. Since the 1960s, researchers such as Edith Gomberg have drawn attention to the possibility that diagnostic case definitions for alcohol problems may neglect the effects of drinking on women who work at home (e.g., as female heads of households) and did not enter the labor force and work for pay. The third part of this chapter summarizes some epidemiological evidence on female-male differences in terms of prevalence and cumulative occurrence of alcohol dependence syndromes since Griffith Edwards and his colleagues introduced the alcohol dependence syndrome construct in the early 1970s.

Furthermore, I distinguish my research approach, which focuses on the first months after drinking onset, from the cumulative lifetime approach and estimation of the prevalence of recently active drinking. I also summarize the work of Cheng and colleagues and that of others who have examined the rapid transition from the first drink to the onset of alcohol dependence. Fourth, I suggest some of the potential public health implications of this work and some potential clinical significance that may interest clinicians.

Alcohol is among the most consumed drugs worldwide, with approximately 2.4 billion people consuming alcohol yearly. (Degenhardt et al., 2008). Alcohol dependence (AD), defined

as a chronic disease in which a person cannot control their drinking, is a significant public health burden (United States, 2019): Consistent findings have shown that half of all alcohol consumed in the United States is consumed by about ten percent of the alcohol drinkers.

Alcohol dependence causes detrimental physical, mental, and socioeconomic consequences. Health and mental consequences include major depression, mania, neurologic impairment, liver disease, and cancer (Cargiulo, 2007). Alcohol dependence is associated with an increased risk of hypertension and ischemic stroke (Cargiulo, 2007). Furthermore, alcohol dependence increases the risk of injury caused by diminished coordination, impaired attention and judgment, and increased reaction time (Ksir et al., 2008). Eighty-eight thousand deaths are associated with alcohol consumption yearly in the United States (Kranzler & Soyka, 2018). According to the CDC, excessive alcohol use is responsible for 140,000 deaths annually (Center for Disease Control and Prevention, 2022).

Alcohol consumption can be traced back thousands of years (Ksir et al., 2008). Beer and wine were used around 6400 BC, with grape wine dating to 300 BC (Ksir et al., 2008; Damerow, 2012). Possibly the oldest alcoholic beverage, mead, made from honey, appeared in the Paleolithic Age, around 8000 BCE. There is still debate over the discovery of the distillation process, but many historians believe it began in Arabia about 800 BCE, with mass manufacturing delayed until the 17th and 18th century18th-century era (Ksir et al., 2008),

The word 'alcohol' comes from an Arabic word meaning 'finely divided spirit' (Ksir et al., 2008). Mcgovern (2015) reported that some of the earliest confirmed evidence of ancient alcohol consumption is barley beer discovered at Godin Tepe in the central Zagros Mountain of Iran around 3400-3000 BC. Carbonized six-row barley was agriculturally common in the area,

and organic residue from pottery vessels pointed towards the fermentation of barley to make beer. This residue generates a positive test for oxalate ion, a beer stone component. Beer stone is the scale that forms in beer brewing tanks (Mcgovern, 2015).

Different regions of the world have integrated alcohol into every aspect of life, with exceptions, as seen in the Islamic tradition of abstinence from alcohol. Rice and millet beers were prominent in ancient China, and grape wine is central to western religions (Ksir et al., 2008). Even primates have similar consumption patterns, with the Malaysian pen-tailed tree shrew consuming the equivalent of nine glasses of grape wine per night in fermented palm nectar (Mcgovern, 2015).

In ancient Egypt, the pyramid builders received compensation through beer rations (Mcgovern, 2015). With the vast history of drinking alcohol in our civilization, many historians might agree that 'drinking is in our genes' in the sense that, but not all, humans find the behavior of drinking alcoholic beverages to be 'reinforcing' in the Skinnerian sense mind (Ksir et al., 2008).

Although adverse effects from overconsumption of alcohol have been described for thousands of years, there is a tradition of seeing the use of alcoholic beverages as a form of medical treatment for disorders. Mcgovern (2015) noted that before modern medicine, those who drank fermented beverages instead of water were observed to have a longer life expectancy. This outcome was thought to be due to the harmful bacteria in water compared to the fermented beverages (Mcgovern, 2015; Snow, 1855). Moreover, compounds with medicinal properties could be more easily dissolved in an alcoholic medium. Recipes using this method dominate ancient restorative practices (Mcgovern, 2015).

Within the United States (US), drinking alcohol in place of contaminated water advanced during America's revolution (Ksir et al., 2008). It seems that, concurrently, alcohol was the first psychoactive drug to be ‘demonized’ in America. Benjamin Rush, a prominent physician during the American Revolution, was among the first to write a negative view of alcohol. Specifically, "An Inquiry into the Effects of Ardent Spirits on the Mind and Body" aimed at distilled spirits rather than beer and wine (Rush, n.d.). Rush noted a relationship between heavy drinking and health-related outcomes such as jaundice, "madness," and "epilepsy", the latter possibly associated with withdrawal symptoms in the form of seizures (Rush, n.d.). Rush also noted potential social harms of heavy alcohol drinking, including antisocial behaviors and immorality (Rush, n.d.). Rush was also the first physician to link addiction-related ideas to the use of a drug. In a noteworthy description, he describes an overwhelming desire for alcohol (Ksir et al., 2008) as the first time this clinical feature was linked to a disease concept.

Mounting evidence suggests that patterns of alcohol consumption in the U.S. have been changing in recent years. Per capita, alcohol consumption fluctuates but seems to have been increasing per capita since 2002 (Kranzler & Soyka, 2018).

A substantial body of epidemiological work that describes the transitions from alcohol use to dependence in the United States is from studies published by research work groups led by Anthony, Lopez-Quintero, and Cheng. To illustrate, the estimated cumulative probability estimate of transition from first drink to alcohol dependence was roughly 22%-23%, according to a 2011 study conducted by Lopez-Quintero and colleagues and based on the life histories of alcohol experiences (Lopez-Quintero et al. 2011), in an update of prior US estimates published by Wagner & Anthony (2002). The work by Wagner & Anthony (2002) was the first

epidemiological study to discover that some drinkers, roughly 2%-4%, had become dependent upon alcohol within the first 1-2 years after drinking onset. Estimated approximately ten years after drinking onset, their estimate for that transition from first drink to alcohol dependence had increased to just over 10% (i.e., an increment of about 8% of the NID had become dependent between the second and tenth years after drinking onset). Moreover, that cumulative incidence proportion continued to increase across the interval from 10 years post-onset to 20 years post-onset (Wagner & Anthony, 2002).

Stimulated by the focus on the first 1-2 years after drinking onset in work by Wagner & Anthony, the Anthony research work group began to produce estimates of the transition from drinking onset until the formation of AD syndromes in a series of papers for which H.G. Cheng has been the lead author. The estimates from work by Cheng and colleagues (e.g., Cheng et al., 2016) laid the foundation for this thesis research project's estimates, as explained later in this research report.

Most of the other research on the transition from first drink of alcohol to dependence has been focused on experiences of the past year, as experienced among all drinkers, without a focus on newly incident drinkers. For example, estimates published by Grant and colleagues suggest a period-related increase in the twelve-month prevalence of alcohol use, high-risk drinking, and DSM-IV alcohol use disorder between 2001 and 2013 (Grant et al., 2017). According to the 2019 National Survey on Drug Use and Health, an estimated 85%-86% of people ages 18 and older reported drinking alcohol at some point in their lifetime, and 25%-26% of people ages 18 and older reported that they engaged in drinking enough alcohol to

drink an individual's blood alcohol concentration to 0.08% or above in the past month (United States, 2020a).

Furthermore, in 2019 in individuals ages 12 and older, roughly one in 20 (or an estimated 5%-6% percent) of individuals qualified as cases of Alcohol Use Disorder, amounting to a treatment caseload of approximately 14.5 million people in the US (United States, 2020a). In this context, Alcohol Use Disorder is defined by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) as a "medical condition characterized by an impaired ability to stop or control alcohol use despite adverse social, occupational, or health consequences" (NIAAA, 2021). According to NSDUH, an estimated one in 12 (8.0%) of individuals 12 years and older experienced heavy alcohol use in 2019 (United States, 2020a), with ‘heavy alcohol use’ defined as drinking on five or more days in the past 30 days (National Institute of Health, 2014). Cheng et al. found that within ages 12 to 25 years old, a rapid transition from drinking alcohol to dependence occurs in less than 4% of individuals (Cheng et al., 2018). These results suggest that alcohol dependence can develop quite rapidly in a minority of individuals who drink within the first year of use.

In 2017, the risk of AUD peaked in younger adults, with those ages 18-25 having the highest prevalence of AUD (10.7%). (Cheng & Anthony, 2018). In Europe, several European countries showed female excess risk (Slade et al., 2016). In the U.S., around 50% of individuals have taken their first drink by age 16. Wagner et al. found an extended risk period for developing alcohol dependence over 20 years after the first drink (Wagner, 2002). Anthony et al. found that alcohol use was highest among young adults ages 25-34 years (Anthony & Echeagaray-Wagner, 2000).

An important area of prior research is male-female differences in alcohol use and dependence. Parks et al. evaluated gender differences among alcohol-dependent Alaska Natives (Parks et al., 2003). Evidence showed that the time between the age at A.D. diagnosis and the first treatment for A.D. was similar in men and women (Parks et al., 2003). Factors associated with elapsed time between diagnosis and treatment for both men and women included marital status, education level, parenting, and lifetime depression (Parks et al., 2003). Female-male differences in alcohol drinking and dependence have been researched in discussing drinking norms differences between men and women (Cheng et al., 2016; Cheng & Anthony, 2017, 2018). Although older research found a male excess regarding drinking problems, more recent research from Slade et al. suggests a smaller gap between males and females in the estimated prevalence of drinking and related problems (Slade et al., 2016). Cheng et al. expanded on this research by looking at U.S. and European populations, finding that the final estimated female-male difference in risk in the U.S. was 2.1%. Since 2002, adolescent girls have reported higher levels of drinking incidence than boys (Cheng and Anthony, 2017, 2018). Gender differences in alcohol use have narrowed between males and females because drinking declines faster among boys than girls (Keyes et al., 2019). Binge drinking and heavy drinking have increased, mostly due to increases among women (Keyes et al., 2019). Looking at all adults 18 and above, alcohol use and alcohol use disorders have increased in men and women (Keyes et al., 2019).

As mentioned previously, the variable I use to compare male-female estimates is sex as a biological variable (SABV). SABV discussions provide substantial evidence that affects everything from cell physiology to symptoms of manifestation and response to treatment of

disease (Clayton, 2018). In 2015, the National Institute of Health released the “Policy on Consideration of Sex as a Biological Variable (SABV) in NIH-funded Research”. The SABV emphasis has encompassed sex chromosomes and their phenotypic manifestations and hormone differences (Clayton, 2018). Since 2015, the NIH has produced educational materials to expand on this topic, for example, “Sex as a Biological Variable: A Primer,” which was designed to help appropriately integrate SABV in all areas of research and science (Tannenbaum et al., 2019). This policy required researchers to factor sex into all areas of research and reporting of animal and human studies (Clayton, 2018). To further expand on gender identity issues, NSDUH began asking adult respondents a set of questions based on sexual orientation and attraction in 2015 (Schuler et al., 2018). As new NSDUH datasets become available, it should become possible to study transitions from NID to AD and AUD for all of the variations of gender identity captured in these new NSDUH assessments. At present, these nuanced analyses are not possible because adolescents are not asked the gender identity questions, many drinking onsets occur in adolescence, and some of the gender identity categories or latent classes include small numbers of NID.

While my research will expand to all ages assessed by NSDUH, research has shown that alcohol use significantly affects younger individuals' brain development (Lees et al., 2020). Adolescence is a highly vulnerable period of development, where experimentation with risky behaviors starts (Lannoy & Sullivan, 2021; Lees et al., 2020; Spear, 2015). Research supports the damaging effects of adolescent drinking on brain volume and integrity, meaning the normal development from a decrease in gray matter and an increase in the brain's white matter was disturbed (Pfefferbaum et al., 2018). This can affect structural and functional connectivity

(Lannoy & Sullivan, 2021). In a hypothetical example from Jadhav et al., "asynchronous brain system development may result in enhanced reward sensitivity… rendering adolescents susceptible to risk-taking behavior, such as alcohol drinking" (Jadhav & Boutrel, 2019).

Human studies have found that heavy alcohol use is associated with poorer cognitive functioning on a broad range of neuropsychological assessments, including learning, memory, visuospatial functioning, psychomotor speed, attention, executive functioning, and impulsivity (Matošić, 2016). Animal and rodent studies have replicated human findings and demonstrated that adolescent alcohol use might increase reward responsiveness of the dopamine system to alcohol later in life and disrupt adolescent neurogenesis while creating potentially long-lasting neural and behavioral effects into adulthood (Tabakoff & Hoffman, 2000).

The etiology of alcohol use disorder stems from the interactive influences of the environment and genetic factors (Eşel & Dinç, 2017). After many years of argument, the newest research shows that AUD has a vital neurological component and behavioral and environmental factors. (Noronha, 2014). Almost 50% of AUD risk is transmitted from parent to offspring (Noronha, 2014). Models have shown that environmental factors increase a genetic predisposition to AUD (Dube et al., 2002). Recent studies have looked at potential subtypes of AUD. Type 1 patients have a more pronounced dopaminergic transmission deficit, and type 2 patients do not have significantly disturbed dopaminergic transmission but instead have a significant lack of serotonergic transmission (Matošić, 2016). According to Esel et al., the most critical neuroadaptive changes in progression from occasional alcohol intake to dependence include the down-regulation of the dopamine system (Eşel & Dinç, 2017). Recent research has shown the significance of toll-like receptors in alcohol dependence (Czerwińska-Błaszczyk et al.,

2022). This dopaminergic transmission projects to the areas of the brain that regulate motivation and cognitive control (Noronha, 2014). Alcohol consumption affects many neurotransmitter systems, including GABA, cannabinoids, and serotonin (Kranzler et al., 2006).

This master's thesis research explores the transition from alcohol initiation to alcohol dependence within the first year of use. This research aims to reduce the gap in evidence regarding the initiation of alcohol use to dependence on alcohol in the United States. Although Cheng et al. has published NSDUH estimates on alcohol initiation to dependence, such estimates have not been updated since 2013, and alcohol consumption has changed. (Cheng et al., 2018). Additionally, these estimates only include ages 12-25 years old. To increase the evidence base, this research will expand the question of initiation to dependence to ages 12-80 and compare potential male and female differences. The second aim of this research is to understand the possible association between days of drinking in NID and individuals who are alcohol dependent. Furthermore, an additional goal is to examine the changes in DSM-IV and DSM-5 regarding alcohol use, thus exploring the change in the questions that NSDUH uses for the survey each year.

From a clinical perspective, an estimated one in six adults in the United States report ever being asked about their alcohol consumption by a health care professional (Kranzler & Soyka, 2018). This research will support the clinical significance of asking about alcohol consumption patterns to treat and potentially prevent AUD.

CHAPTER 3: MATERIALS AND METHODS

The organization of this chapter follows suggestions offered by my M.S. advisor, Professor Jim Anthony. His recommendations for an epidemiological report intended for publication in a peer-reviewed journal begin with a general research approach or design statement (e.g., whether the design is cross-sectional, prospective, experimental, or other, such as case-crossover). Then, the population under study is defined. An explanation of the sampling approach and sample(s) follows, along with information about participation levels and informed consent processes, as required by institutional review boards (IRB) that help foster the protection of human subjects in research projects. The conceptual model and a measurement plan for assessing each construct are presented. A description of the statistical analysis follows, including any sensitivity analyses and sometimes unanticipated exploratory analyses of post-estimation data.

Instead of emphasizing statistical significance, Professor Anthony taught us to focus on estimating population parameters and 'compatibility intervals' (e.g., frequentist 95% confidence intervals or corresponding Bayesian credible intervals). Based on prior evidence and estimates covered in Chapter 2 of this thesis research project, there is little justification for asking whether the true population parameter is zero (that no one becomes a case of DSM-IV alcohol dependency soon after starting to drink), which might generally be specified as a null hypothesis by anyone conducting a frequentist statistical significance test about that parameter. Previously cited estimates published by Cheng and colleagues are based solely on NSDUH samples of newly incident drinkers who were in adolescence or the early years of transitional adulthood.

The work from Cheng and colleagues suggests a plausible estimate of 2.0% with slightly larger values for female NID relative to male NID. In my research, I asked whether my frequentist 95% confidence intervals (CI) from my expanded sample would be compatible intervals, meaning that they include the 2% value. For the female-male comparisons, I asked whether my frequentist 95% CI for female NID does or does not overlap with the 95% CI for male NID.

3.1 Research Design

The United States (US) National Surveys on Drug Use and Health study design starts with cross-sectional probability sampling followed by recruitment and assessments of participants. In that sense, my thesis research project's study design is that of a cross-sectional survey. However, based on variables created for the NSDUH 'Restricted Data Analysis System' public use datasets and online analysis platform, it has been possible to identify the newly incident drinkers year by year and ask whether they had developed an alcohol dependence syndrome by the assessment date. Hence, the cross-sectional survey data can yield something that approximates a prospective study estimate of the rate at which newly incident drinkers become cases in a relatively short time interval after drinking onset.

3.2 Populations Under Study, Samples, and General Assessment Approach

The NSDUH study population always is specified to consist of individuals residing in the United States who are 12 years of age or older when the sample is drawn, with the exclusion of US residents living in institutions or on military bases. This thesis research project's estimates

primarily are based on the NSDUH surveys conducted each year between 2002 and 2019. The comparison of DSM-IV and DSM-5 adds NSDUH data from 2020 into the project.

After multi-stage probability sampling intended to yield nationally representative samples of the US study population each year, the participants are recruited with consent and assent protocols approved by the NSDUH IRB. There is a specified probability of selection for each designated area under study (e.g., census-defined areas), each sampled dwelling unit within the area, and each designated respondent living in the sampled dwelling unit. For NSDUH fieldwork between 2002 and 2019, assessments primarily were administered by computer-assisted self-interviews (ACASI), which promote reliability, accuracy, and truthfulness of participant reports about potentially sensitive behaviors. For routine demographic details (e.g., US Census variables), an NSDUH field staff member asks the questions and records the answers in what is called a 'computer-assisted personal interview' (CAPI). These details are described in an online monograph entitled "[The] 2019 National Survey on Drug Use and Health: Methodological Summary and Definitions" (United States, 2020b). As part of an NSDUH alcohol module of standardized survey items, each participant was asked about their history of drinking experiences, including questions for NID about drinking onset during the prior 12 months and questions to assess DSM alcohol use disorders. Participants were also asked about the frequency of alcohol use in the past year, equivalent to the number of days of drinking during the interval since the onset of drinking.

A note about 2020 is required because the COVID-19 pandemic disrupted the typical NSDUH fieldwork toward the end of the first quarter of 2020. The survey approach was re-specified to help combat the person-to-person spread of the infection, thus halting recruitment

from the NSDUH field staff. The result was an approach that constrained contact between field staff members and the designated respondents such that participants completed a web-enabled ACASI assessment in place of the previous laptop or tablet assessment approach with the field staff member close at hand. This online assessment model ('web mode') was used in the fourth quarter of 2020. No data was gathered in the second and third quarters of 2020. An online publication provides these details. The publication suggests that the shift to the COVID-adapted approach had little impact on the participation levels, which remained around 60% in each quarter of 2020, not too distant from participation levels in prior years. According to relevant literature on the methods, it appears that NSDUH assessment items are not affected by 'web mode effects' such as shifting sensitivity or specificity. (United States, 2020b).

Unfortunately, the NSDUH dataset for 2020 does not include the survey's standard variable to indicate the quarter of the assessment. For this reason, the available dataset merges the first quarter ACASI data (comparable to all prior quarters) with the fourth quarter web-enabled ACASI assessment. At present, no comparison of Quarter 1 ('standard mode') versus Quarter 4 ('web mode') estimates are possible using the public use datasets now available for 2020.

3.3 Response variables

The primary response variable in this study is the occurrence of alcohol dependence as defined in the American Psychiatric Association (APA) Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). The research questions focus on AD occurrence during the first months after the onset of drinking. NSDUH retained the DSM-IV approach through 2019. In 2020, NSDUH changed its approach to include a methods sub-study to

evaluate newer diagnostic conceptualizations and assessment items based on the APA Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. (United States, 2020b).

Drinking onset is assessed via ACASI standardized items that identify participants who took their first full drink within an interval that is no longer than the 12-month interval before the NSDUH assessment. The exact date of assessment is not disclosed due to concerns of confidentiality.

From 2002-2019, the alcohol dependence (AD) construct was specified in alignment with DSM-IV specifications. AD was characterized by the persistence of use (e.g., more than five separate drinking days since drinking onset) and standardized AD module survey item evidence to indicate that at least three DSM-IV AD diagnostic criteria had been experienced.

This thesis project's 'sex' variable is based on participants' responses, with no allowance for gender identities such as transgender (only male and female) (United States, 2020). When the sex variable was skipped, NSDUH drew upon dwelling unit roster information to create the variable (United States, 2020).

Due to the COVID-19 pandemic, NSDUH assessment methods changed in 2020. According to NSDUH, the primary methodological changes were "(1) virtually no data collection from mid-March 2020 through September 2020, (2) introduction of web data collection in October 2020 with minimal in-person data collection, and (3) questionnaire changes beginning in 2020" (SAMHSA, 2021). These changes need to be examined. The 2020 data should be compared to prior years' estimates with caution. NSDUH also states, "because these changes in data collection coincided with the spread of the COVID-19 pandemic and any related behavioral

or mental health changes, we cannot fully separate the effects of methodological changes from true changes in outcomes" (SAMHSA, 2021).

For these reasons, this study's analysis first yields estimates for each aim, including RDAS data from 2002 to 2019. Next, the analyses include data from 2002 to 2020. The first estimates have no potential clouding from the COVID-19 era methodology changes in 2020. By producing estimates based on the 2020 data in a separate analysis, I can evaluate how different the estimates are between 2020 and previous years. Furthermore, I will be able to assess the impact of the 2020 data in prior years' estimated cumulative incidence proportions.

It was 2020 when the criteria used to categorize AD among NSDUH respondents shifted from DSM-IV to DSM-5 for a sub-sample of the respondents. Regardless of the other pandemic-related methods changes, this reason alone makes AD estimates from 2020 not entirely comparable to DSM-IV estimates from prior years.

3.4 Analysis

The analysis-weighted estimates are based on the occurrence of newly incident drinking, and whether alcohol dependence has developed within the first 1-12 months after newly incident drinking onset. Analysis weights are used to address the variations in sample selection probabilities described in Section 3.2. However, the public use datasets do not include a weight based solely upon the inverse of the probability of selection. After factoring in inverses of selection probabilities, the public use datasets provide a more complex form of analysis weight that factors in variations associated with survey error, such as non-participation levels. Once the probability-based analysis weight is applied to the individual-level data, the post-

stratification adjustment factor (PSAF) is joined with the inverse of the selection probability, and the resulting numbers are grouped into a contingency table with rows and columns based on US Census variables: a binary sex variable (female-male), a categorical 'race-ethnicity' variable [e.g., Hispanic, non-Hispanic based on ethnic self-identification (ESI) questions], and ordinal variables for the age of the individual. Cell by cell, the resulting numbers are compared to the most recently updated US Census population values. When this comparison of numbers indicates variation, the PSAF is created in such a way that the contingency table distributions based on the US Census values match the NSDUH values derived from the PSAF. In the public use datasets, the PSAF is combined with the analysis weight based on the selection probability to yield the analysis weight variable. An additional step to prevent participant reidentification is to draw a large subsample of all NSDUH participants from the public use dataset (typically about 55,000 individuals in the public use dataset, as compared to 60-70,000 participants in the complete unweighted NSDUH dataset). By combining this probability of selection for the public use dataset with the selection probability and PSAF-derived values, the ANALWT variable is derived for analysis weighting; in RDAS analyses, the resulting three-component analysis weight is used to produce analysis-weighted estimates of the US population as a whole. In the NSDUH methodology report for each year of the survey, such as United States (2020b) for the 2020 survey, further details about analysis weights are provided.

A newly incident drinker (NID) variable has been specified by the NSDUH research team, which considered the calendar date of the ACASI assessment and then worked backward to the month and year of the first full drink of an alcoholic beverage. The result is a set of NID with drinking onset within the 12-month interval before the date of the NSDUH survey assessment.

Focusing on these NID, the transition probability from first drink to alcohol dependence among NID was estimated. The primary analysis estimated the transition probability from an analysis-weighted number of alcohol dependence cases (given NID status) in the numerator and an analysis-weighted number of NID (with or without AD) in the denominator always restricted to events occurring within 12 months before the NSDUH survey assessment date.

When the Restricted-use Data Analysis System (RDAS) datasets are used, as in this thesis, the survey years are combined into year pairs to ensure reasonable precision for the estimates. After estimating the NID to AD transition for each year-pair, the set of year-pair-specific estimates were combined using a conventional meta-analysis approach that allows for over-time heterogeneity in the observed estimates.

Glass (1976) defined meta-analysis as "The statistical analysis of a large collection of analysis results from individual studies to integrate the findings" in the social science literature. The meta-analysis performed in this research used year-pair-specific point estimates based on the RDAS online analysis approaches described elsewhere (Vsevolozhskaya & Anthony, 2014).

Haidich (2010) wrote that "meta-analysis is a quantitative, formal, epidemiological study design used to systematically assess previous research studies to derive conclusions about that body of research." The outcomes from a meta-analysis can produce more precise estimates and generally provide a consolidated review of large and complex data (Haidich, 2010). While meta-analysis typically includes multiple studies from a large body of literature, meta-analyses have also been performed previously with NSDUH year-specific or year-pair-specific estimates used

to summarize the extensive datasets spanning many years (Cheng et al., 2016, 2018; Cheng & Anthony, 2018).

As suggested by Vsevolozhskaya & Anthony (2014), after estimation of the year-pair-specific estimates for the NID to AD transition probability (with AD occurring within the < 12-month interval after drinking onset), for the meta-analysis summary estimates, the natural logarithm of the estimated proportion was taken as a constraint (e.g., never to have proportions with negative values, and never to have proportions with estimated values above 1.0)).

This was done using each NSDUH year pair as an independent replication estimate.

Some debate exists regarding whether the meta-analysis approach should be a 'fixed effects' or a 'random effects' one, with a 'random effects' approach considering the possibility of otherwise unobserved sources of variation that would produce differences across replications or over time within a study. The ‘random effects’ approach tends to yield broader frequentist 95% CI. For this reason, given the possibility of across replication variations (e.g., across year and within-year variations), I chose to produce the ‘random effects’ estimates and 95% CI. Borenstein (2010) and Tufanaru et al. (2015) provide additional details and rationale for choosing the ‘random effects’ approach.

The meta-analysis summary estimates support a statistical inference approach that aims to promote the generalizability of inferences based on all available evidence. This approach is consistent with the frequentist school of statistics. In the future, this line of research may benefit from the Bayesian school of statistical inference described below.

To be clear, the meta-analysis approach completed for this study involved an application of the random-effects inverse-variance model with the DerSimonian-Laird estimate of tau^2 (StataCorp, 2021). This approach assumes that the various replications seek to derive a common estimate of a population parameter but allow for a possibility that there might be between-replication variability of note, which would tend to widen confidence intervals as compared with corresponding 'fixed effects' approaches (Higgins et al, 2022). Accordingly, the standard errors of each meta-analysis estimate incorporate a measure of the extent of heterogeneity of estimates across several replications (Higgins et al, 2022). This variation is quantified via a tau-squared ($tau^{2)}$ statistic (Higgins et al, 2022). The tau^2 statistic is derived from the point estimates and standard errors from the several NSDUH year-pair replications included in the meta-analysis (Higgins et al, 2022).

Estimates for the associations linking days of drinking with alcohol dependence were obtained from NSDUH via cross-tabulations of the days of drinking (since drinking onset) variable with the alcohol dependence variable. These estimates were derived for all newly incident drinkers irrespective of alcohol dependence diagnosis and those who had become alcohol dependent. Due to the requirement that NID requires drinking onset within 12 months, these AD variables indicate whether the NID has qualified as an AD case within the same time between drinking onset and NSDUH assessment date.

For the investigation of DSM-5 versus DSM-IV, I turned to the NSDUH Public-use Data Analysis System (PDAS) because the 2020 survey data are available only through PDAS and not through RDAS. The variables to compare DSM-IV to DSM-5 were based on assessments of

alcohol dependence in the past year (DEPNALC and PYUD5ALC, respectively). For this analysis, the PDAS analysis weights were used to derive my thesis research estimates.

3.5 DSM-IV and DSM-5

In 2013, the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition was released (DSM-5), with changes in conceptualization and assessment of alcohol dependence and alcohol use disorders, relative to the DSM-IV approaches. To maintain comparability of estimates, the NSDUH research team retained its DSM-IV approach until 2020, when a sub-study was designed to compare DSM-IV and DSM-5 approaches. The NSDUH use of the DSM-5 approach, with some additional questions in the NSDUH alcohol module and with the DSM-5 two-criterion threshold, was delayed until 2020. A chart highlighting the differences between the NSDUH questions between DSM-IV and DSM-5 can be found in the appendix. The changes from DSM-IV to DSM-5 include the addition of the craving criteria for Alcohol Use Disorder (AUD), the removal of legal problems from the evaluation of DSM-5 diagnostic criteria, and the just mentioned change in the threshold for diagnosis (United States, SAMHSA 2021).

As stated in Substance Use and Mental Health Administration reports, an especially significant change from DSM-IV to DSM-5 is the combination of substance abuse and substance dependence into a single SUD diagnosis (United States, SAMHSA 2016). The DSM-5 Substance-Related Disorders Work Group recommended this combination based on findings from over 200,000 study participants. There were several reasons for this change regarding the distinction between abuse and dependence. First, the distinction provided minimal treatment guidance. "Diagnostic orphans" were created, which is the concept that individuals who said 'yes' to two

dependence symptoms and no abuse symptoms were not classified into either disorder category under DSM-IV. There were clinically significant cases requiring intervention, but these cases matched criteria for neither 'abuse' nor 'dependence;' these cases fell between the cracks separating the two forms of alcohol use disorder. Next, the structure of this flowchart did not account for the assumption that abuse often can be a less severe facet of the prodrome for alcohol dependence.

In consequence, DSM-5 merged the abuse and dependence criteria, which requires the presence of two out of the eleven criteria as observed during the 12 months prior to the diagnostic assessment (United States, 2016). A result is that the estimated number of DSM-5-measured AUD cases should always be greater than the estimated number of DSM-IV-measured AD cases. Those 'diagnostic orphans' just mentioned, as well as the DSM-IV 'abuse' cases now should qualify as 'mild' (or perhaps 'moderate') DSM-5 AUD cases. My thesis research findings from the DSM-IV AD and DSM-5 AUD comparison help to substantiate the size of this inequality.

The Michigan State University Institutional Review Board deemed my thesis research project work to qualify as 'non-human subjects research.' I had no contact, direct or indirect, with NSDUH participants, and there is no retention of identifiers for direct or indirect re-identification. The RDAS and PDAS datasets are subject to 'disclosure analysis' protocols. Hence, it is not possible to identify or re-identify NSDUH participants once the public-use datasets are released for scientific and public health analyses as exemplified in this thesis research project.

CHAPTER 4: RESULTS

The chapter is organized around my three aims. I have added a section describing the IRB-approved protocol I developed to gather new evidence about expert-clinician judgments about whether it might be helpful to change from the standard DSM-5 unit-weighting approach to a more sophisticated approach specifying different weights for each of the criteria. In the first section of the chapter, I present my estimates from 2013 forward as well as previously published estimates, constructing a meta-analysis summary of estimates to determine whether there is any female-male variation in the duration of an alcohol dependence syndrome from the time that a female first drinks an alcoholic beverage to the time when a male has fully developed an alcohol dependence syndrome.

In my second aim, I consider whether the occurrence of alcohol dependence syndrome might be related to the frequency of drinking since the first drink. This is an exciting but conceptually challenging problem for reasons Anthony (2010) explained and explored with his research group using the Hill function analysis approach (Vsevolozhskaya & Anthony, 2016, 2017). The problem is conceptually challenging because there is a feedback loop (e.g., a violation of the 'acyclic' assumption made in epidemiology's 21st-century tradition of 'Directed Acyclic Graphing' approaches). That is, many people never drink again after the first drink; they do not perceive the drinking occasion as particularly reinforcing; they do not repeat it. Others find the experience strengthening, increasing their drinking frequency. However, as the frequency of drinking increases, the probability of becoming alcohol dependent increases. Drinking frequency (e.g., the number of drinking days) increases as alcohol dependence severity increases from its prodromal stage to later stages due to a feedback loop.

In this sense, cross-sectional survey designs do not provide the best opportunity to study the link between drinking frequency and alcohol dependence. Nevertheless, I was prompted by some of my thesis guidance committee members to give estimates of the occurrence of alcohol dependence cross-classified by the frequency of drinking observed on the date of the survey assessment (i.e., after AD had developed). In the absence of a prospective or other longitudinal studies of these associations, these results might serve as potentially helpful evidence to guide future studies of a prospective and longitudinal nature.

Next, I compare the DSM-IV and DSM-5 approaches described in my study aims. Finally, I offer my IRB-approved protocol in the appendix for a future study as an additional elaboration of my master's thesis research project. I do not provide any results in that final section of this Results chapter.

4.1 Estimated Transition from NID onset to AD onset

An epidemiology report commonly describes the study sample with unweighted statistics, such as the proportions of females and males in the model, the distribution of age groups, and so on.

NSDUH aggregate unweighted sample examples from 2002 through 2019 are presented in the appendix of this thesis research report. I have not included unweighted samples for each year or year-pair of the NSDUH because these values are readily available in online reports cited in my References section. Reviewing the appendices of the thesis research report, readers will discover that the number of females and males participating in the NSDUH study is generally balanced. Some years, the females slightly outnumber the males, not only because

the female population typically survives longer, but also because community-dwelling females participate more than their male counterparts. The appendix materials also disclose that, in aggregate, across the years from 2002 through 2020, the sample included 1,263,477 participants. Participation levels and specific year data can be found in the appendix. From 2002-2019 there were 36,164 female and 36,312 male newly incident drinkers. In these aggregate statistics, the number of NID who had developed alcohol dependence by the time of the NSDUH survey assessment (within 12 months after drinking onset) was 10,141 for both sexes, with 5,633 female AD cases among the female NID and with 4,508 male AD cases among the male NID.

The analysis-weighted estimates in Table 1 provide my year-pair specific estimates for how many NID transitioned from drinking onset to alcohol dependence syndrome within 12 months after drinking onset. It is cumulative from the time of drinking onset to the date of the survey assessment. The cumulative incidence proportion resembles the attack rate in an epidemiological investigation of foodborne illness. In this case, the analysis-weighted denominator is the estimated number of individuals who consumed alcohol within 12 months of assessment. The analysis-weighted numerator is the estimated number who had drinking onset and then were observed to have experienced alcohol dependence by the assessment date.

As shown in Table 1, the estimated cumulative incidence proportion for the NID to AD transition within the 0-12 month interval separating drinking onset from the date of assessment is 1.7%, which is just below my expected value of two AD cases for every 100 NID, based on the meta-analysis summary estimate and the ‘random effects’ estimation approach. The

corresponding frequentist 95% CI is 1.5% to 1.9%. Hence, the updated meta-analysis summary estimate from this thesis research project is not completely compatible with the anticipated estimate of 2.0% but is not appreciably different from that 2% estimate once the 95% CI of the 2% point estimate is considered.

The accompanying forest plot of Figure 1 is a graphical depiction of the estimates displayed in Table 1. The column label of ‘exp(b)’ conveys that the anti-logarithm of the logarithm-transformed proportion is the estimate shown. The display is for the estimated proportion, not for the logarithm of the estimated proportion. The forest plot also indicates the heterogeneity statistics, which have values consistent across replication variability or heterogeneity in the year-pair estimates. The resulting 95% CI are slightly wider than the corresponding ‘fixed effects’ 95% CI. Using Taylor series linearization mentioned in Chapter 3, the standard errors for the proportions are based on the fact that residents of sampled census block groups within a state tend to resemble one another more than if the sampling approach was simply random without such 'clustering' on local areas.

Figure 2 shows that the meta-analysis summary estimate does not shift appreciably when the most recent 2020 estimate is considered. The pandemic circumstances and the change to a ‘web mode’ of assessment do not seem to have induced any major distortion in the previously observed 2002-2019 estimate for this NID to AD parameter in the US population.

Table 1. Estimated Year-Pair-Specific Estimates for the Cumulative Incidence of alcohol dependence (A.D.) among newly incident drinkers, 2002-2019. (Data from the United States National Surveys on Drug Use & Health, Organized in Year-Pairs)

(A) Estimated A.D. Cumulative Incidence Proportion (%)	
Year-Pairs	**Estimate (%)**
2002-2003	2.3
2004-2005	1.7
2006-2007	2.1
2008-2009	1.9
2010-2011	1.7
2012-2013	1.5
2014-2015	1.3
2016-2017	1.4
2018-2019	1.1
Cumulative Incidence Proportion (%): Meta-Analysis Summary	1.7
(B) 95% confidence intervals for estimates in (A)	
2002-2003	1.9, 2.9
2004-2005	1.4, 2.2
2006-2007	1.7, 2.6
2008-2009	1.5, 2.5
2010-2011	1.4, 2.2
2012-2013	1.1, 1.9
2014-2015	0.9, 1.8
2016-2017	0.9, 2.0
2018-2019	0.7, 1.5
Meta-analysis summary estimate for the estimated %	1.5, 1.9

Figure 1. Forest plot of estimates for the occurrence of alcohol dependence among newly incident drinkers, 2002-2019

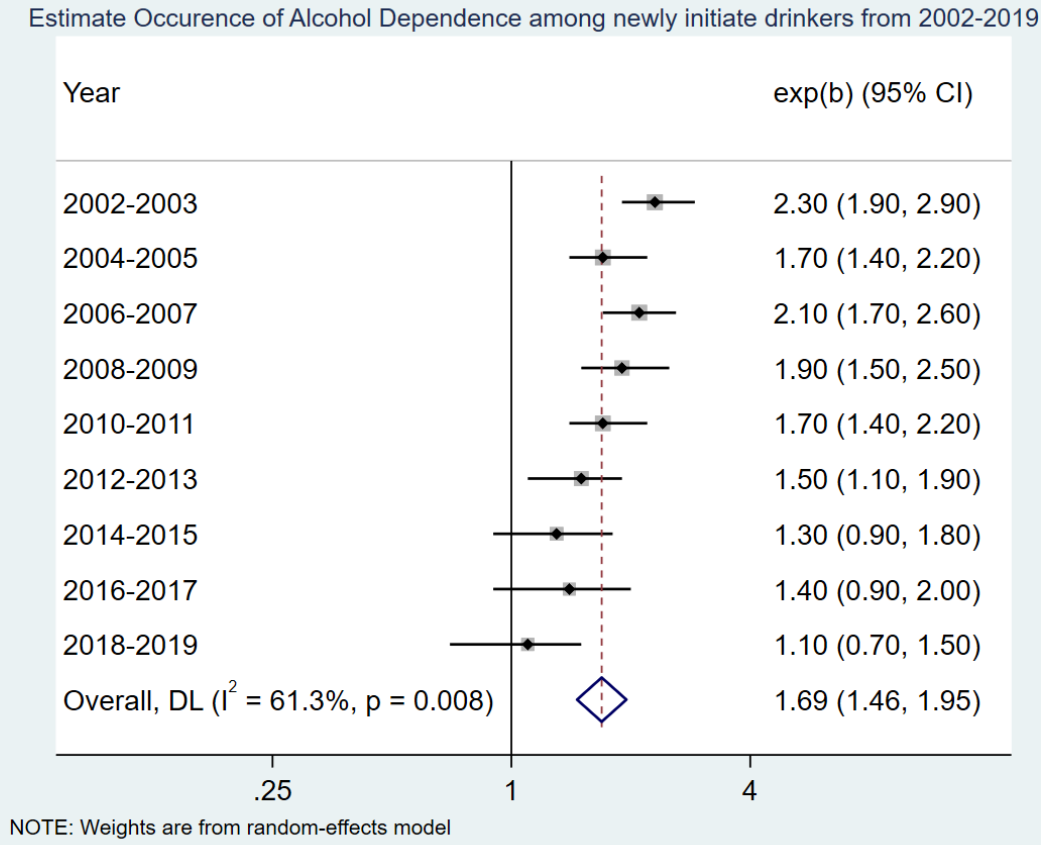
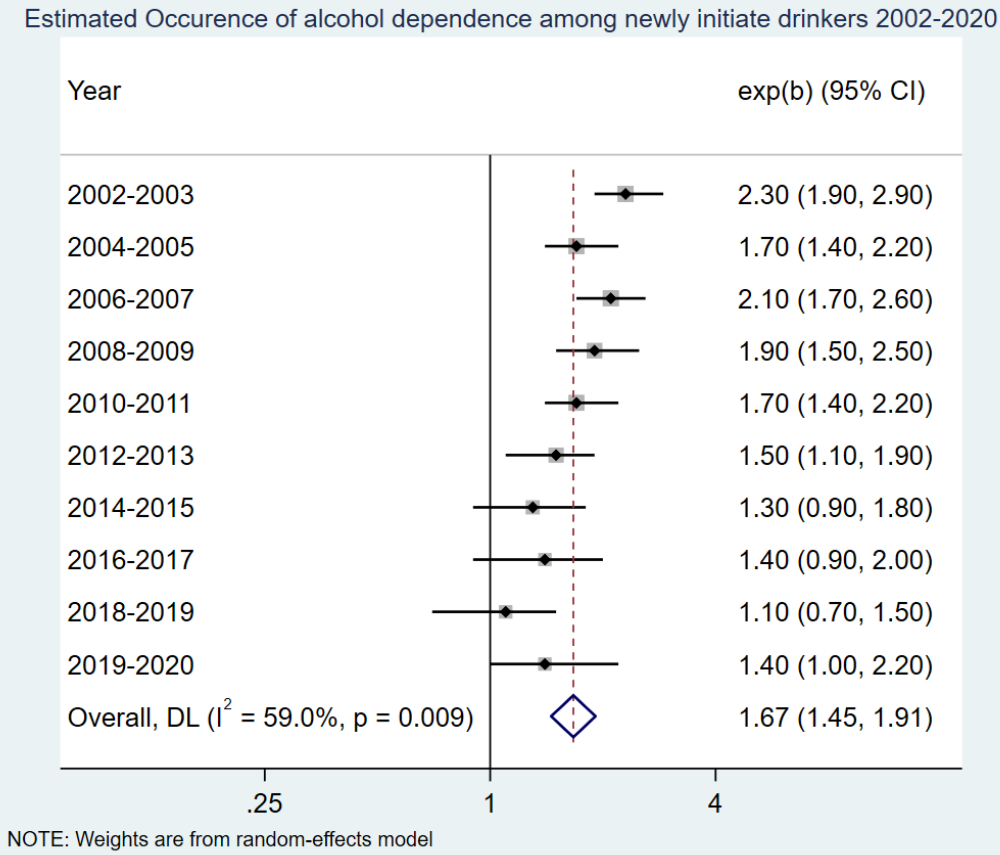


Figure 2. Forest plot of estimates for the occurrence of alcohol dependence among newly incident drinkers, 2002-2020



4.2 Estimated Sex-Specific Transition from NID onset to AD onset, 2002-2019

This section turns to the female-male contrasts as specified in the thesis research project's aims. Figure 3 shows estimates for male NID, with a meta-analysis summary estimate of roughly 1.5% (1.47%) and a frequentist confidence interval of 1.2%, 1.8%. Demonstrated again in this estimate, the heterogeneity test statistic suggests across-replication variability and the resulting 95% CI are broadened relative to the alternative 'fixed effects' approach.

The corresponding estimate for female NID transitioning to AD, shown in Figure 2B, rounds to 1.9%, no more than slightly larger than the male estimate of 1.5%. In addition, there is substantial overlap of the frequentist 95% CI for the male estimate (95% CI = 1.2%, 1.8%) and the female estimate (95% CI = 1.6%, 2.2%, rounded). This result provides little support for the idea that female NID are more likely to transition to AD soon after drinking onset. There is also evidence of heterogeneity across replications so that the 95% CI, as shown, are somewhat wider than the corresponding 'fixed effects' 95% CI.

Figure 3. Forest plot of estimated sex-specific male occurrence of alcohol dependence among newly initiate drinkers 2002-2019

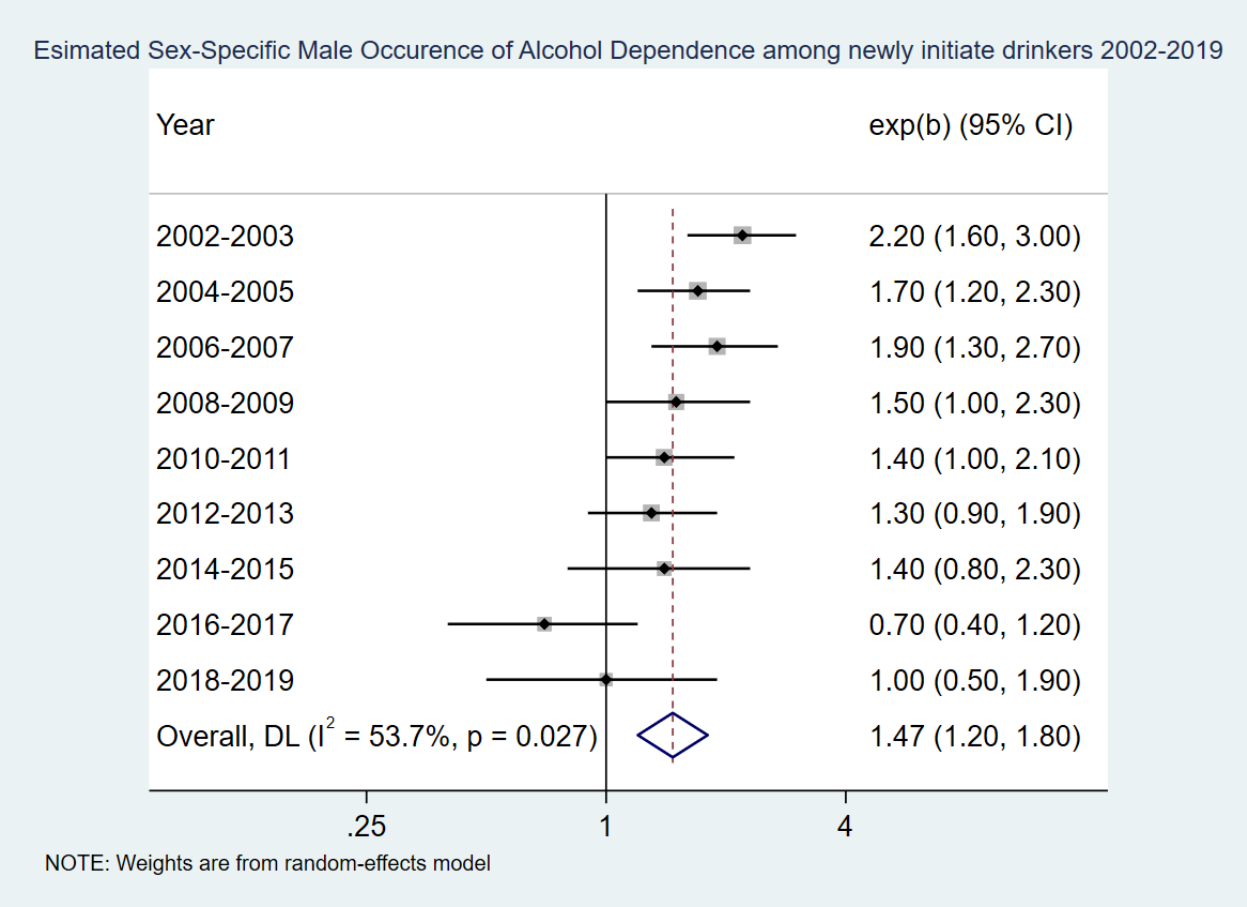
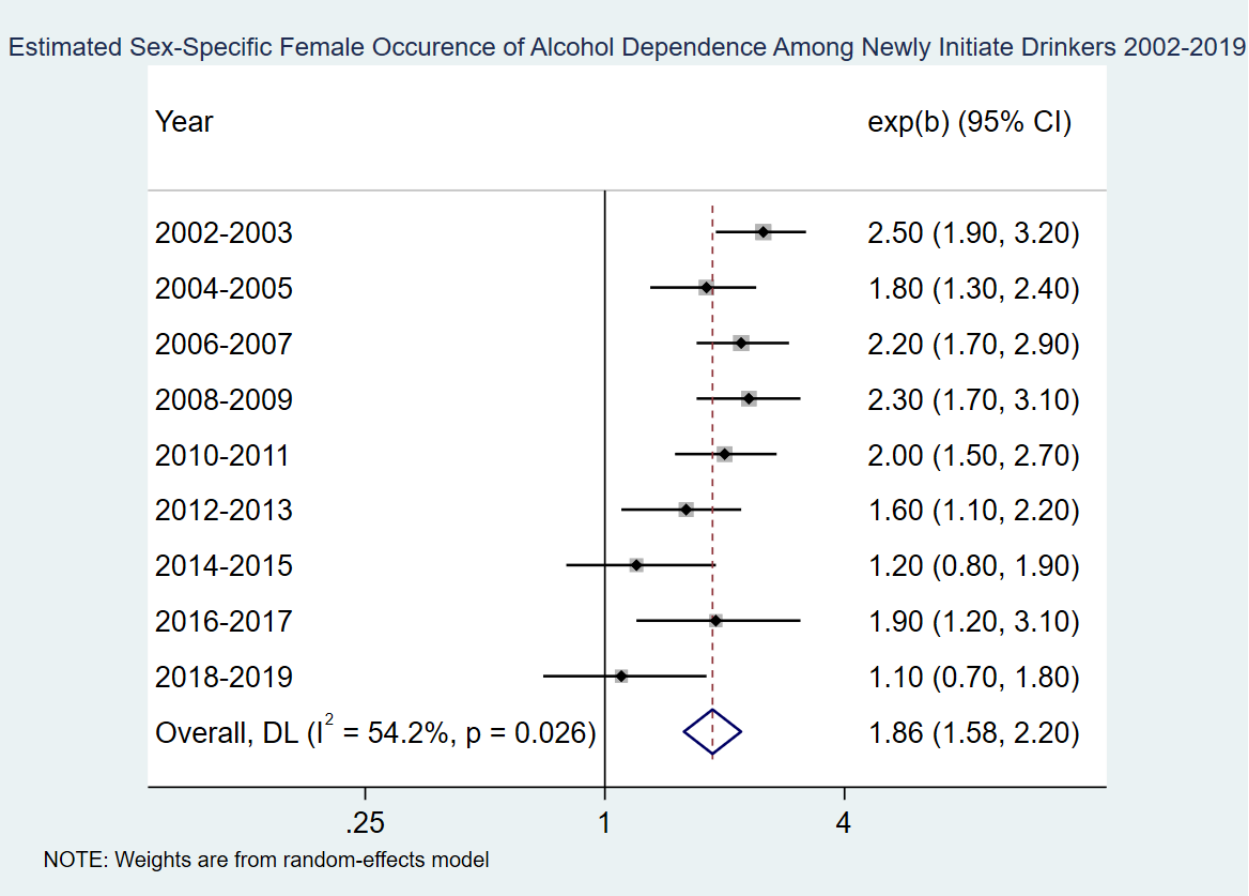


Figure 4. Forest plots of estimated sex-specific female occurrence of alcohol dependence among newly initiate drinkers 2002-2019



4.3 Estimated Sex-Specific Transition from NID onset to AD onset, 2002-2020

The corresponding estimates for male and female NID transitioning to AD, once the NSDUH data from 2020 are taken into account, are shown in Figures 5 and 6. An estimated 1.34% of male NID rapidly transition into AD (95% CI = 1.06, 1.71) versus an estimated 1.90% for female NID (95% CI = 1.63%, 2.21%), again with no appreciable female-male variation observed in this thesis research project's estimates for NID of all ages. Please note that the size of the heterogeneity test statistics (and corresponding p-values) indicates departures from the null hypothesis of little or no variation of estimates across the NSDUH year-pair replications.

Table 2 provides a summary overview that might be helpful to readers of this thesis research report. It summarizes in table format what is conveyed in the forest plots shown in the figures with forest plots.

Figure 5. Forest plot of estimated sex-specific male occurrence of alcohol dependence among newly initiate drinkers 2002-2020

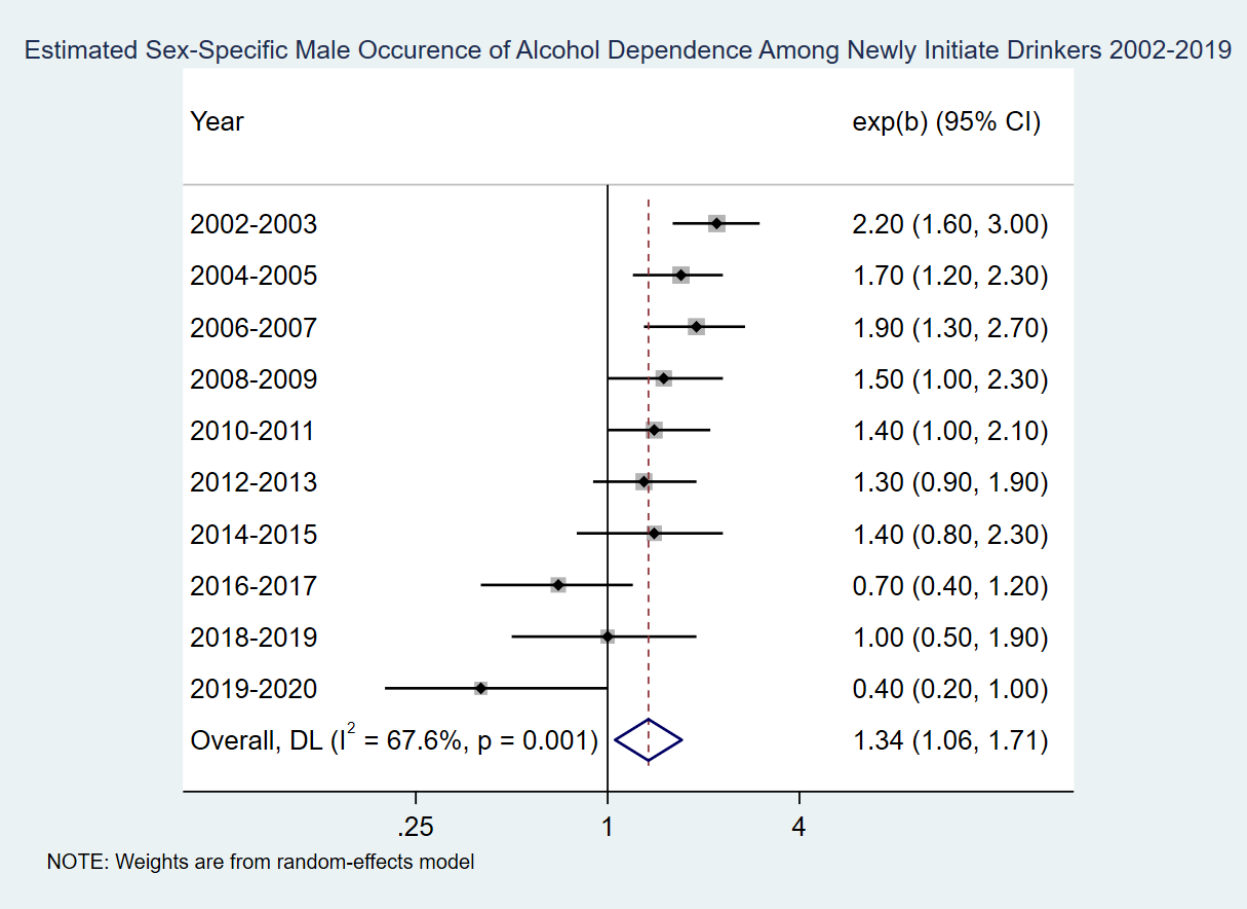


Figure 6. Forest plots of estimated sex-specific female occurrence of alcohol dependence among newly initiate drinkers 2002-2020

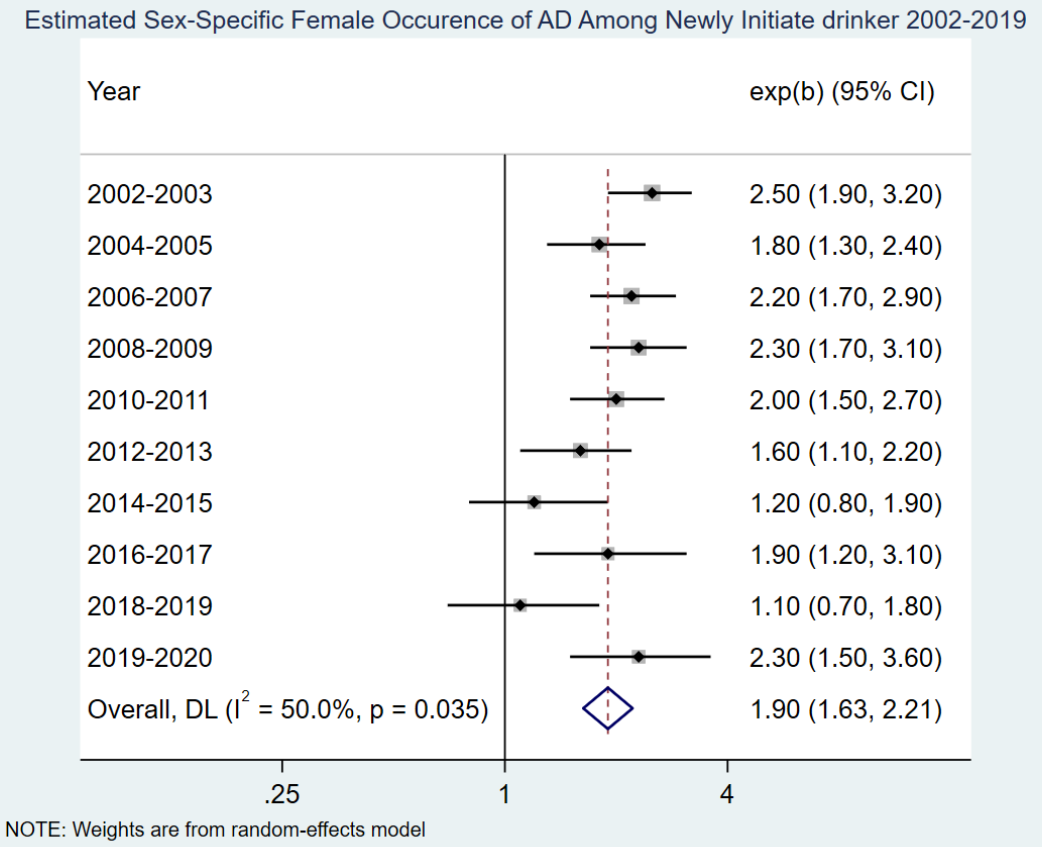


Table 2. Estimated Year-Pair-Specific and Sex-specific Estimates for the Cumulative Incidence of alcohol dependence among newly incident drinkers, 2002-2019. (Data from the United States National Surveys on Drug Use & Health, Organized in Year-Pairs and Sex-pairs)

(A) Estimated A.D. Cumulative Incidence Proportion by sex (%)		
	Estimate (%) male	**Estimate (%) female**
2002-2003	2.2	2.5
2004-2005	1.7	1.8
2006-2007	1.9	2.2
2008-2009	1.5	2.3
2010-2011	1.4	2.0
2012-2013	1.3	1.6
2014-2015	1.4	1.2
2016-2017	0.7	1.9
2018-2019	1.0	1.1
Cumulative Incidence Proportion (%): Meta-Analysis Summary	1.5	1.9
(B) 95% confidence intervals for estimates in (A)		
2002-2003	1.6, 3.0	1.9, 3.2
2004-2005	1.2, 2.3	1.3, 2.4
2006-2007	1.3, 2.7	1.7, 2.9
2008-2009	1.0, 2.3	1.7, 3.1
2010-2011	1.0, 2.1	1.5, 2.7
2012-2013	0.9, 1.9	1.1, 2.2
2014-2015	0.8, 2.3	0.8, 1.9
2016-2017	0.4, 1.2	1.2, 3.1
2018-2019	0.5, 1.9	0.7, 1.8
Meta-analysis summary estimate for the estimated %	1.2, 1.8	1.6, 2.2

4.4 Estimated Links between NID-AD and Number of Drinking Days Since Drinking Onset

As explained in prior sections of this thesis research report, it makes sense that NID who have transitioned into AD might have a rightward shift in the distribution of the number of drinking days. A simple explanation is that many newly incident drinkers consume alcohol for no more than a few days; these NID are less likely to become alcohol dependent. A more complex explanation is that when a NID starts to develop alcohol dependence, the dependence process generally can drive up the number of drinking days. Potentially, there is a feedback loop such that an alcohol-dependent individual who drinks will drink on more days than a NID who has not become an AD case. The complex issues of this feedback loop have been explained, in detail, by Vsevolozhskaya & Anthony in papers published in 2016 and 2017.

Despite this, my thesis guidance committee suggested that I examine the distribution of drinking days since onset for the NID as a group and for the NID who developed AD as a subset of that group and report whether there were differences. I have not attempted to make statistical inferences about these different distributions because these are not independent subgroups. That is, the NID who become AD cases is a set entirely nested within the group of NID overall. Instead, I offer a simple description of the two distributions.

Before presenting those distributions, I should draw attention to the fact that the NSDUH approach to AD assessment is ‘gated’ by the question of the number of drinking days. Many epidemiological surveys of tobacco, alcohol, and other drug use 'gate' the assessment of dependence constructs, so that AD module items are not asked unless the NID reports a certain number of drinking days since drinking commenced. Unless the NID indicates that drinking has occurred for at least five days since drinking onset, the AD assessment module items are not

requested in the NSDUH protocol. According to this protocol, there will always be an observed rightward shift in drinking days for NID drinkers who developed AD compared to NID drinkers who did not develop AD.

Be that as it may, Table 3(A) shows the analysis-weighted distribution of drinking days for all NID, irrespective of their AD status when assessed. As established, roughly three-fourths of the NID had experienced fewer than 12 drinking days since drinking onset (71%) and fewer than 4% had experienced 100 or more drinking days. The distribution for individuals who are AD cases at the time of assessment shows the anticipated rightward shift of the distribution. Fewer than 2% of these cases fall into the 1-11 days of drinking category; more than 70% had 100 or more drinking days during that interval since drinking onset. Figures 3-4 provide graphical displays of these analysis-weighted distributions.

Table 3. Days of Drinking for Newly Initiate Alcohol Drinkers and Alcohol Dependent Individuals 2002-2019

(A) **Estimated Days of Alcohol Use in New Initiates**					
	1-11 days	**12-49 days**	**50-99 days**	**100-299 days**	**300-365 days**
2002-2003	72.2	20.5	4.6	2.6	6.4
2004-2005	71.2	21.3	4.5	2.9	0.1
2006-2007	70	22.3	4.9	2.8	0
2008-2009	71.5	21.3	4.7	2.5	0.1
2010-2011	0	0	0	0	0
2012-2013	72.8	20.1	4.5	2.5	0.1
2014-2015	71.4	20.3	5.3	2.9	0.1
2016-2017	73.4	19.4	4.8	2.4	0
2018-2019	0	0	0	0	0
Mean	71.8	20.7	4.8	2.7	1.0

(B) Estimated Days of Alcohol Use in Individuals who are Alcohol Dependent					
	1-11 days	**12-49 days**	**50-99 days**	**100-299 days**	**300-365 days**
2002-2003	1	10.4	14.7	54.2	19.3
2004-2005	1.4	10.1	11.5	59.5	17.5
2006-2007	1.3	10.3	13.4	57.1	17.9
2008-2009	1.5	9.9	13	57.2	18.4
2010-2011	1.6	10.2	12.3	59.1	16.9
2012-2013	0.9	10	11.7	58.6	18.8
2014-2015	1.1	9.3	11.3	58.4	19.9
2016-2017	1.1	10.7	11.5	55.1	21.6
2018-2019	1.5	10.3	11.9	56.3	20.1
Mean	1.3	10.1	12.4	57.3	18.9

Figure 7. Estimated distribution of days spent drinking alcohol among individuals who are new initiate drinkers 2002-2017

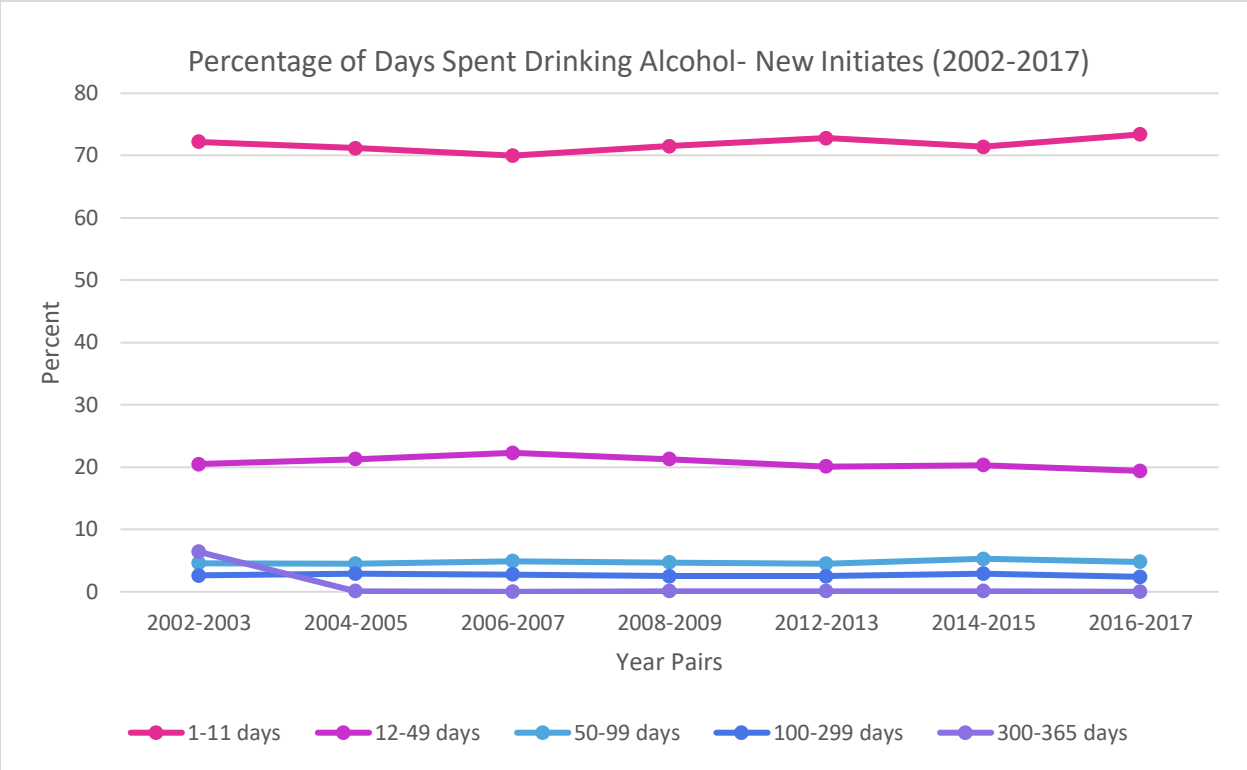
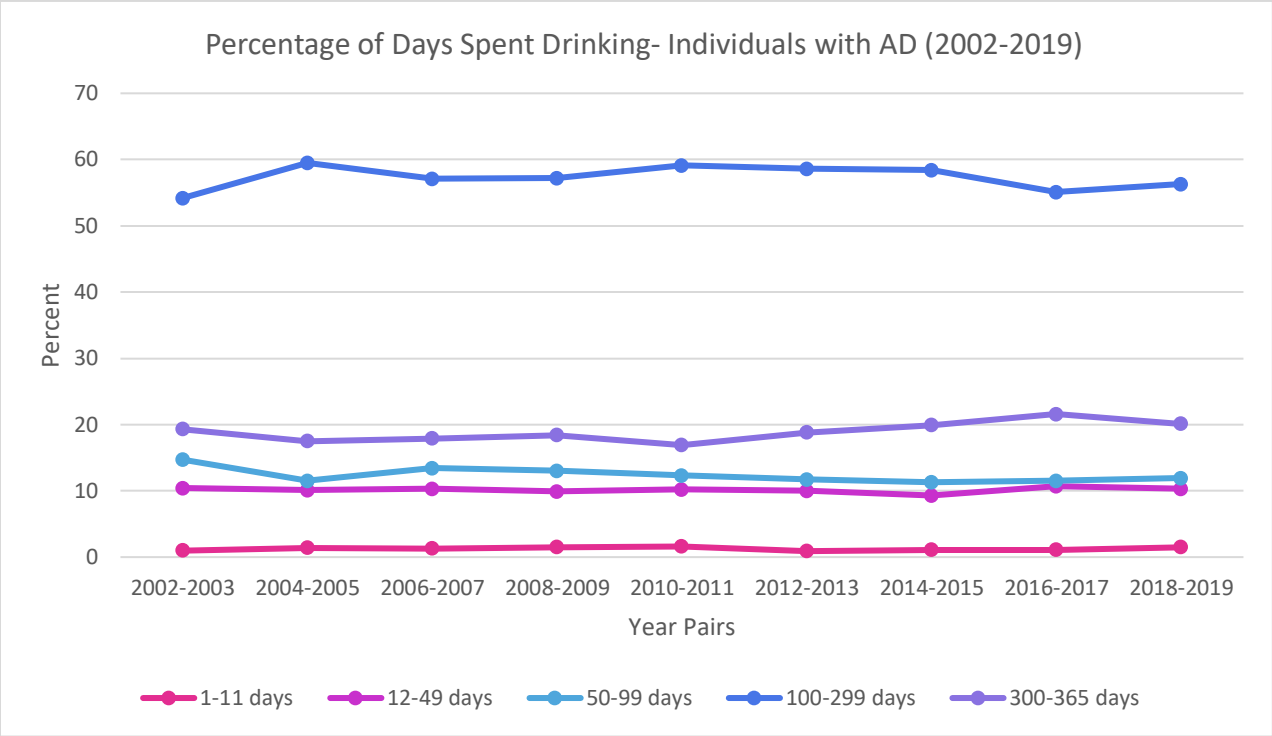


Figure 8. Estimated distribution of days spent drinking alcohol among individuals who are alcohol dependent 2002-2019



4.5 Comparison of Diagnostic Criteria and resulting estimates for DSM-IV and DSM-V

The estimated incidence of alcohol-dependent individuals using DSM-IV criteria in 2020 is different from the estimated incidence of AUD individuals using DSM-5 criteria in 2020 (3.2 95% CI (2.9, 3.5) and 9.9, 95%CI (9.4, 10.6) respectively) (Table 4). As stated in the methods section, I cannot directly compare these estimates as the criteria have changed. I was not able to produce estimates of the cumulative incidence proportions for DSM-IV versus DSM-5 approaches as I had planned, due to the pandemic disruption of the planned NSDUH survey approach.

Table 4. Comparison of Diagnostic Criteria for DSM-IV and DSM-V. (Data from the United States National Survey on Drug Use & Health, 2020

(A) Estimated Cumulative Incidence Proportion of Alcohol Related Diagnosis by DSM-IV and DSM-5 (%)		
	Estimate (%) DSM-IV- AD	**Estimate (%) DSM-5- AUD**
2020	3.2	9.9
(B) 95% confidence intervals for estimates in (A)		
2020	(2.9, 3.5)	(9.4, 10.6)

4.6 Estimated Transition from NID onset to AD onset including 2020 data

Tables 5 and 6 provide a summary overview that might be helpful to readers of this thesis research report. It summarizes in table format what is conveyed in the forest plots shown in the figures with forest plots with the addition from 2002-2020.

Table 5. Estimated Year-Pair-Specific Estimates for the Cumulative Incidence of alcohol dependence (A.D.) among newly incident drinkers, 2002-2020. (Data from the United States National Surveys on Drug Use & Health, Organized in Year-Pairs)

(A) Estimated A.D. Cumulative Incidence Proportion (%)	
Year-Pairs	**Estimate (%)**
2002-2003	2.3
2004-2005	1.7
2006-2007	2.1
2008-2009	1.9
2010-2011	1.7
2012-2013	1.5
2014-2015	1.3
2016-2017	1.4
2018-2019	1.1
2019-2020	1.4
Cumulative Incidence Proportion (%): Meta-Analysis Summary	1.7
(B) 95% confidence intervals for estimates in (A)	
2002-2003	1.9, 2.9
2004-2005	1.4, 2.2
2006-2007	1.7, 2.6
2008-2009	1.5, 2.5
2010-2011	1.4, 2.2
2012-2013	1.1, 1.9
2014-2015	0.9, 1.8
2016-2017	0.9, 2.0
2018-2019	0.7, 1.5
2019-2020	1.0, 2.2
Meta-analysis summary estimate for the estimated %	1.5, 1.9

Table 6. Estimated Year-Pair-Specific and Sex-specific Estimates for the Cumulative Incidence of alcohol dependence among newly incident drinkers, 2002-2020. (Data from the United States National Surveys on Drug Use & Health, Organized in Year-Pairs and Sex-pairs

(A) Estimated A.D. Cumulative Incidence Proportion by sex (%)		
	Estimate (%) male	**Estimate (%) female**
2002-2003	2.2	2.5
2004-2005	1.7	1.8
2006-2007	1.9	2.2
2008-2009	1.5	2.3
2010-2011	1.4	2.0
2012-2013	1.3	1.6
2014-2015	1.4	1.2
2016-2017	0.7	1.9
2018-2019	1.0	1.1
2019-2020	0.4	2.3
Cumulative Incidence Proportion (%): Meta-Analysis Summary	1.3	1.9
(B) 95% confidence intervals for estimates in (A)		
2002-2003	1.6, 3.0	1.9, 3.2
2004-2005	1.2, 2.3	1.3, 2.4
2006-2007	1.3, 2.7	1.7, 2.9
2008-2009	1.0, 2.3	1.7, 3.1
2010-2011	1.0, 2.1	1.5, 2.7
2012-2013	0.9, 1.9	1.1, 2.2
2014-2015	0.8, 2.3	0.8, 1.9
2016-2017	0.4, 1.2	1.2, 3.1
2018-2019	0.5, 1.9	0.7, 1.8
2019-2020	0.2, 1.0	1.5, 3.6
Meta-analysis summary estimate for the estimated %	1.1, 1.7	1.6, 2.2

CHAPTER 5: DISCUSSION AND DIRECTIONS FOR FUTURE RESEARCH

My thesis research project is summarized in a brief roadmap for this chapter. As I examine each finding, I sketch its convergence (or non-convergence) with what others have theorized or discovered. Additionally, I provide notes about methods, concepts, and other relevant issues that readers may want to consider as they reflect on these findings. I also outline my study's main limitations, focusing on generic topics such as the cross-sectional design and whether people accurately report their drinking experiences within the first 12 months after drinking began. Non-participation levels also deserve consideration in this section on limitations.

Notwithstanding the limitations, there are some strengths, which I will mention. In closing, I will offer some suggestions on possible future directions for research, perhaps in the context of a doctoral dissertation. My final paragraph offers my main conclusions.

5.1 Main Findings

First, in the US study population, as estimated from 2002 through 2019 (and 2020), the estimated cumulative incidence proportion for the rapid transition from the first full drink of alcohol to the occurrence of alcohol dependence within the 0-12 months after drinking onset was just under two percent. The estimated cumulative incidence proportion did not change appreciably when I added the 2020 estimate to the 2002-2019 meta-analysis findings.

Second, as gauged by point estimates and without regard for the precision of the estimates, female newly incident drinkers in the US study population seem to be at a higher risk than male NID for transitioning from the first full drink to dependence within the first year of

use, as observed from 2002 to 2019. Minor fluctuations occurred when 2020 data were taken into account. Nonetheless, frequentist 95% CI overlap indicates no substantial female-male variation.

Third, I presented the estimated analysis-weighted distributions for days of drinking since drinking onset for all NID and for NID who had transitioned to AD. These distributions appear quite different, with a rightward shift when AD has developed (i.e., more days of drinking among AD cases). It is logical that individuals who are alcohol dependent spend more days drinking on average than individuals who are new initiates of alcohol but not AD cases.

Fourth, the number of individuals with alcohol disorders captured with DSM-5 criteria is much higher than those captured with DSM-IV criteria. These preliminary findings deserve greater attention. If confirmed after 2020, the pandemic year dataset, this observed variation must be considered in future epidemiological comparisons of DSM-IV and DSM-5 based studies.

In this study, the incidence rates ('cumulative incidence proportions during the interval of observation) were estimated, with appropriate analysis weights, based on multi-stage area probability sampling designed to yield nationally representative samples of community-dwelling US residents aged 12 and older. Concerning the central aim of exploring the transition from drinking initiation to the dependence on alcohol within the first year of use, these results suggest that alcohol dependence can develop rapidly after the first full drink. This study's estimates suggest that AD affects an estimated 1.5% and possibly as many as 2% of newly incident drinkers 12 and older in the United States within 0-12 months after drinking onset. These findings are consistent with previously published work using the same or similar methods. This study differs from previous work by considering all ages, while previous studies

focused on adolescents and transitional adult experiences. Previous work showed a 2% to 4% estimate in 12-17-year-old individuals (Cheng et al., 2013, 2016). This study is consistent with those findings while sampling a larger population with a broader age range.

In terms of the main finding regarding the transition from the first drink until an alcohol use disorder forms, there is convergence with recent publications (e.g., Cheng et al., 2013, 2016), but some departure from a long history of evidence that males are more likely to develop alcohol use disorders. From a clinical perspective, evidence has shown that this male excess might be due to shifts in social judgments about women drinking (Iwamoto et al., 2020), but the NSDUH constrains social judgments that are seen when it is clinicians who diagnose AD; here, the NSDUH relies upon standardized ACASI assessments without reliance on clinicians and their social decisions. Additionally, this diminishment of a male excess could be due to increased reporting of alcohol use among women because of increased permissiveness in recent decades (i.e., women are more likely to report drinking and drinking consequences). Overall, as a society, the perceived risk of alcohol has decreased, and increased alcohol use has been reported (the United States, 2018).

My thesis project approach is aligned with the same process that Cheng and colleagues used when a female excess was reported. One exception is their restriction of study population coverage to adolescent- and transitional adult-onset drinkers. The approach used in this study differs from those used in most prior studies, which produced estimates of recent alcohol use disorders or lifetime prevalence of these disorders (cumulative incidence proportions). The male excess might be present with time since the first drink. Future research could explore this possibility.

Regarding the central finding on female-male variations of alcohol dependence among NID, the overall results for male and female estimates are consistent with previous literature. These estimates differ from old literature, which generally found a male excess, but are more consistent with recent literature, finding female excess compared to males in the transition from first full drink to alcohol dependence among NID.

Regarding the findings on the frequency distribution of days of drinking for NID compared to NID who have become alcohol dependent, the results are consistent with other alcohol consumption statistics in the United States. Based on the estimates, individuals who are alcohol dependent on average drank more days within the past year than NID. If we were to compare the cumulative incidence of NID who became dependent (1.7%, 95% CI =1.5%, 1.9%) and the days they spent drinking in the past year, around 4% of those individuals spent the same amount of time drinking as individuals who have developed AD.

5.2 Strengths and Limitations

Large nationally representative samples of a predefined US study population of community-dwelling residents across the whole lifespan who are likely to be affected by drinking onsets and subsequent consequences such as alcohol dependence are major strengths of this study. The standardized NSDUH sampling, recruitment, consent, and assessment protocols also represent major strengths. The sampling frames include residents of homeless shelters, college dormitories, and other non-institutional dwelling units and household residences. By using ACASI assessment approaches, measurement problems such as unwillingness to discuss sensitive topics in the DSM criteria for alcohol dependence can be

avoided. It is also a strength that the recall intervals are restricted to 12 months to limit memory problems associated with describing a lifetime history of drinking. Additionally, I have established my thesis research on multiple years and year-pairs of the NSDUH.

In contrast to many published studies based on national surveys, I have not ignored the multi-stage area probability sampling approach and the non-independence of participant observations arising from sampling within local units like census tracts, block groups, and dwellings (e.g., college dormitories). Additionally, I used Taylor series linearization to estimate variances, standard errors, and frequentist confidence intervals, in contrast to some articles that omit participant observation non-independence and present estimates based on unweighted sample characteristics without estimating the precision of the reported results.

As an alternative to the more typical approach of 'pooling' the data across multiple survey datasets, I have produced estimates for each year pair from 2002-2003 onward. I then used conventional meta-analysis approaches to derive summary estimates.

As for the limitations of this thesis research project, there are several that deserve special attention. First, NSDUH participation levels have dropped from earlier values of close to 80% and are now down to 60%-65%. It is unknown whether new incident drinkers or new incident drinkers who develop AD exhibit differential non-participation. Future research should examine this issue more thoroughly.

This drop in participation levels might help explain why the overall estimate for the transition from initiation to dependence on alcohol within the first full year of use has generally declined over the interval of years under study. It is possible that during these declines, NSDUH started to miss individuals with an alcohol disorder. In one study, Cottler et al. found that

individuals meeting the criteria for an alcohol disorder required almost 20% more contact attempts than those with this disorder (Cottler et al., 1987). This discrepancy stemmed from less availability for initial contact and refusing at a higher rate once contacted (Cottler et al., 1987). Suppose overall participation levels are already dropping, and it is harder to recruit AD cases anyway. In that case, this could be part of the overall decline in the transition from NID to AD. Researchers with access to the NSDUH survey operational variables would have the necessary data to determine whether more AD case individuals were lost when participation levels dropped.

Another potential reason for the decline in the overall transition from NID to AD could be the change in adolescent alcohol use prevalence. Studies like Monitoring the Future (MTF) have shown an increase in perceived risk among adolescents in regard to alcohol use and a decrease in overall drinking prevalence (Johnston et al., 2022). Since adolescent-onset drinking is associated with an estimated 50% increase in the cumulative incidence of an alcohol disorder diagnosis, and if fewer adolescents are drinking alcohol during those apparently higher-risk years, then the decline in adolescent-onset drinkers is a possible reason for the overall transition estimate shifting downwards (Johnston et al., 2022). For example, there was a 7.4% decrease in lifetime drinking of 12^{th} graders from 2020 to 2021 (Johnston et al., 2022).

Based on the relative consistency of the estimates across year pairs, the relatively minor changes in the survey method during those years had little appreciable impact (although year-to-year variations confirmed my 'random effects' approach). A somewhat smaller estimate in 2020 might be the result of the COVID pandemic-related methods change to a web mode (or maybe an artifact of having some 2020 participants answer DSM-IV items while others

answered DSM-5 items). There was no significant change in the meta-analysis summary estimate between 2002 and 2019 as a result of the 2020 estimates.

Another limitation is that there was no estimate available for some year-pairs in days of drinking for new initiates of alcohol (2010-2011 and 2018-2019). In an attempt to combat this limitation, the original analysis included these '0' estimates (Table 3), and the distribution graphs were limited to only year-pairs that had been estimated. The frequency of days of drinking was consistent among all other year-pairs. These findings differ from previous research as they are distinct between NID and individuals who are alcohol dependent. This is a crucial distinction when looking at the frequency distribution of alcohol consumption. Previous research focused on overall alcohol consumption per year or month and based the conclusion of alcohol dependence on these distributions rather than using status in either category as the exposure.

Another strength of this project is the meta-analysis approach, which is an enhancement via multiple independent replications to promote generalizability. The meta-analysis approach also fosters and helps to strengthen an inference of reproducibility of the study findings.

Two major sources of potential bias in this survey design type are recall errors and measurement reactivity. Long-term recall can introduce bias by extending the time between assessment and exposure. If the participant is asked to recall behaviors from a longer period of a previous time, the answers might not be accurate. Here, the recall interval is constrained to be no more than 12 months from drinking onset to AD assessment.

Measurement reactivity occurs when the same individual is assessed on more than one occasion. This source of bias is constrained in cross-sectional projects because participants are not asked the same questions repeatedly as in longitudinal research. There is no reactivity.

In addition, the research approach of focusing on newly initiated alcohol drinkers and focusing the outcome on alcohol dependence since that recent drinking onset (rather than an 'ever dependence' variable) constrains potential bias in the measurement domain. Moreover, to account for the change in methods in 2020, analysis was done with and without the 2020 data to ensure that measurement bias due to 2020 changes was constrained.

With any type of self-report data, the possibility of measurement issues needs to be taken into account. Relying on self-report can create bias, especially with topics like drug use, where individuals might fail to disclose true experiences. When relying on self-report, there is no consideration of what other members of the household, friends, employers, and/or physicians might say about the alcohol-related problems experienced by newly incident drinkers.

Another theme that coincides with issues of self-report data is the concept of denial as a characteristic among people with drinking problems. Schuckit et al. paraphrases denial in the context of AUD as “a group of processes where substance-related problems that are obvious to other are not recognized or appropriately acted upon by the individual with the problems (Schuckit et al., 2020). When using self-report data, it is pertinent to keep the idea that denial can range from an admission of use but denial of frequency to associated problems that occurred because of use (Schuckit et al., 2020). Schuckit goes on to state that the impact of specific criteria in DSM-IV should be evaluated, and at the same time, the relationship of denial

to drinking quantities, the number of alcohol problems, and whether an individual was AA or AD in DSM-IV should be considered (Schuckit et al., 2020).

From a clinical perspective, it should be noted that these results show a potential rapid transition from first full drink to alcohol dependence within the first year of use. This finding has been consistent across multiple studies for years (Cheng et al., 2016, 2018; Wagner, 2002). Clinicians should be aware of this potential transition and reinforce the importance of the period between the first full drink and alcohol dependence. Regular screening for alcohol problems could be implemented to catch this rapid transition.

Recent evidence shows that screening tools for use in primary care settings can effectively identify individuals with unhealthy alcohol patterns (O'Connor et al., 2018). This screening could be implemented in various healthcare settings: emergency rooms, primary care offices, and urgent care facilities.

The U.S. Preventive Services Task Force (USPSTF) is an example of screening methods. USPSTF recommends screening for unhealthy alcohol use in primary care settings for adults 18 years and older (U.S. Preventive Services Task Force, 2018). For those engaging in risky drinking, brief behavioral counseling is recommended to curb unhealthy alcohol use (U.S. Preventive Services Task Force, 2018). Recent literature shows that alcohol dependence within the first ten years of the first drink is even higher at approximately 14-23% (Lopez-Quintero et al., 2011). Clinical intervention at the early stages of drinking could decrease the transition to alcohol dependence. Given that many drinking onsets occur before age 18, the USPSTF recommendation about screening ages might be reconsidered and shifted downward to include adolescent drinkers before the age threshold now set at 18.

This study also explored the potential differences between DSM-IV and DSM-5 AD questions. Combining substance abuse disorder and substance dependence order into a single SUD diagnosis significantly changed in DSM-5. In DSM-IV, an 'abuse' diagnosis required the experience of one or more criteria-qualifying clinical features and no history of dependence for that specific category of drugs. DSM-IV dependence required three or more criteria to be met within an interval of 12 months prior to assessment. Additionally, DSM-IV had a hierarchy that specified if people who met the criteria for abuse and dependence should be diagnosed as having dependence only. The previously mentioned approach was guided by the idea that the hierarchically superior 'dependence' phenomenon might explain any observed 'abuse' phenomenon. I also would like to note the consistency of the estimates that compared 2002-2019 and 2002-2020 estimates. Even with methodological changes due to the pandemic, the estimates do not change appreciably.

A confounding feature is shifting from the 'web mode' to the prior 'personal self-interview mode' in 2020. Regardless, these circumstances did not significantly affect the thesis research project's estimates.

Focusing specifically on alcohol, the evidence is mixed for how DSM-5 changes affect prevalence estimates. Peer and colleagues (2013) found that subjects with alcohol use disorder on DSM-IV or DSM-5 but not both were more likely to have gone from no diagnosis under DSM-IV criteria to being diagnosed with DSM-5 criteria. A population-based study of 5,443 current drinkers in the Netherlands showed a decrease in past-year alcohol use disorder when using DSM-IV compared to DSM-5 (5.4% and 4.4%, respectively; Tuithof et al., 2014). While the evidence differs, this could partially be due to the different study populations. For example,

looking at how these studies calculate estimates, the denominator varies from all participants to participants who used alcohol in the past year and are current drinkers (United States, 2016). Therefore this study chose the same variable in one year to compare the potential differences between DSM-IV and DSM-5 criteria, specifically in the National Survey on Drug Use and Health. Other surveys and study populations cannot be compared as the design can severely vary.

The 2020 DSM-IV and DSM-5 estimates of AD and AUD show a drastic difference. The changes made to the NSDUH questions explained in detail above significantly increased the estimated incidence of alcohol disorders. While these changes were assumed to improve estimates of total individuals captured with substance use orders, this analysis supports that hypothesis.

5.3 Future Directions and Summary Conclusion

I already have mentioned some directions for future research, such as using a Hill function approach to estimate associations between the number of days of drinking since the onset of drinking and the occurrence of alcohol dependence. Another direction for future research stems from the convergence of female and male estimates. This research focused on female-male sex as a binary biological variable. In recent years, non-binary gender identity assessment questions have been added to the NSDUH survey design and assessment protocol. While the convergence of these female-male estimates most likely does not stem from genetic or biological changes in recent years, there has been a shift in gender roles in society. This area of research is expanding.

For example, the ‘Women in the Workplace' study, exploring the state of women in corporate America, is the largest comprehensive study of its kind, with an annual report published every year since 2015. The rationale for this study includes the observation that women have increasingly moved into once male-dominated roles in the workplace. In addition, the rate of stay-at-home dads in the U.S. has increased from 10% to 17% over the past two decades (Pew Research Center, 2021). These shifts could account for the shrinking differences between male and female alcohol dependence cumulative incidence proportions within the first year after drinking onset. With more women and men breaking past traditional societal gender norms, drinking-related outcomes accompanying those roles can also shift (Pew Research Center, 2021).

Another direction for future research addressing the potential gaps due to the binary female-male variable would be analyzed using the more nuanced non-binary sexual attractiveness and gender identity variables recently introduced within the NSDUH assessment protocol. This approach will expand the scope of research beyond ‘sex as a biological variable’ and might help account for misclassification errors in binary female-male variable survey approaches. As the world continues to dissolve sex-specific gender roles, this direction for future research becomes critical to determining potential 'exposure' risks with diverging gender identities.

Finally, as mentioned above, another possibility for future research is to use the Hill function to study the female-male differences presented in this research, including consideration of days of drinking since drinking onset. Vsevolozhskaya and Anthony explored the transition from first drug use to dependence onset using the Hill Function (Vsevolozhskaya

& Anthony, 2016, 2017). The idea was to move in a new direction, "harnessing a functional analysis approach that can be extended from cross-sectional snapshots to dynamic longitudinal data" (Vsevolozhskaya & Anthony, 2016).

As I reflect upon the subject matter and new estimates I have produced for this master's thesis research project, my main conclusions can be summarized within the boundaries of these concluding statements: (1) the estimated transition from initiation to dependence on alcohol within the first year of use has remained steady over the past two decades, (2) the estimates produced show no female-male variation in the transition from initiation to dependence on alcohol within the first year of use, and (3) the criteria changes from DSM-IV to DSM-V capture a larger amount of individuals who have alcohol use disorders. As indicated in Chapter 5, much remains to be learned about the epidemiology of alcohol use, the occurrence of alcohol dependence, and related conditions during the first months and years after drinking onsets. This project represents a step in that direction.

APPENDIX

Table A1. U.S. NSDUH, Overall Samples Sizes and Participation Levels, 2002-2020

Survey Year	Sample Surveyed	WSRP (1)	WIRP (2)	Overall Response Level
2002	68,126	91%	79%	72%
2003	67,784	91%	77%	70%
2004	67,760	91%	77%	70%
2005	68,308	91%	76%	69%
2006	67,802	91%	74%	67%
2007	67,870	89%	74%	66%
2008	68,736	89%	74%	66%
2009	68,700	89%	76%	67%
2010	68,487	89%	75%	66%
2011	70,109	87%	74%	65%
2012	68,309	86%	73%	63%
2013	67,838	84%	72%	60%
2014	67,901	82%	71%	58%
2015	68,073	80%	69%	55%
2016	67,942	78%	68%	53%
2017	68,032	75%	67%	50%
2018	67,791	73%	67%	49%
2019	67,625	71%	65%	46%
2020	36,284	68%	63%	43%

1 Weighted Screening Response Proportion
2 **Weighted Interview Response Proportion**

Table A2. Unweighted Sample Size Estimates, NSDUH, 2002-2020

(A) NID Cases Unweighted Sample Size Estimate, 2002-2020		
Year	**Male**	**Female**
2002-2003	3936	4419
2004-2005	4178	3728
2006-2007	3535	4419
2008-2009	4419	3535
2010-2011	3728	3535
2012-2013	3342	3535
2014-2015	3342	3535
2016-2017	3342	3535
2018-2019	3535	3535
2019-2020	2955	2387
Total	**36313**	**36164**
(B) NID to AD Cases Unweighted Sample Size Estimate, 2002-2020		
Year	**Male**	**Female**
2002-2003	615	739
2004-2005	576	631
2006-2007	548	694
2008-2009	462	642
2010-2011	531	632
2012-2013	513	583
2014-2015	394	456
2016-2017	348	405
2018-2019	300	418
2019-2020	221	432
Total	**4508**	**5633**

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