

HEROIN USE AND DEPRESSION: AN EPIDEMIOLOGICAL STUDY

By

Alyssa Vanderziel

A THESIS

Submitted to
Michigan State University
in partial fulfillment of requirements
for the degree of

Epidemiology- Master of Science

2018

ABSTRACT

HEROIN USE AND DEPRESSION: AN EPIDEMIOLOGICAL STUDY

By

Alyssa Vanderziel

In this thesis research, my aims are: (1) to investigate the associations linking depression with ever-heroin use (EHU), (2) to estimate depression's association with past-year heroin use (PYHU); and (3) to identify an association-optimizing cut-off score for a positive depression screen based on the Patient Health Questionnaire (PHQ-9).

The population under study consists of United States adult community residents, as sampled for the National Health and Nutrition Examination Survey (NHANES), 2005-2014, according to institutional review board-approved protocols. The analysis sample included 16,326 20-to-59-year-olds and estimated odds ratios (OR) and receiver operating characteristic (ROC) curves, with SAS[®] Version 9.4 software.

As compared with never-users, EHU and PYHU are more likely to screen depression-positive (OR=3.30, 95% CI=2.34, 4.65; OR=4.21, 95% CI=1.89, 9.35, respectively). ROC estimates an association-optimizing cut-off PHQ-9 score of 12 versus the standard cut-off of 10.

Subject to limitations such as the self-report interview, the main estimates lead to rejection of a null hypothesis about the heroin-depression association, and help substantiate a need for more research, such as a prospective/longitudinal approach. The standard depression score cut-off might need adaptation in future studies of heroin-depression associations.

One interpretation of this study suggests that heroin use may influence the emergence of depression in US adults 20-59 years old. Results of this research might stimulate a more nuanced approach to understanding depression in the context of the heroin-using population.

ACKNOWLEDGEMENTS

I owe much gratitude to many individuals who contributed to the successful completion of this Master's thesis. First and foremost, I would like to thank the Chair of my thesis committee, Dr. Jim Anthony, for his guidance, support, patience, and extensive knowledge base. I would like to thank Dr. Qing Lu for his statistical direction and kindness. I am particularly thankful for the support of my mentor, Dr. David Barondess, for his constant encouragement and time commitment toward the completion of my thesis. The countless hours that Dr. Barondess has devoted to my academic success is indescribable. Additionally, I would like to thank both Dr. Dorothy Pathak and Dr. Nicole Talge for their incredibly helpful practicum class. Their relentless efforts provided the building blocks for this thesis. Dr. Omayma Alshaarawy deserves much gratitude for the many hours she spent assisting me with programming syntax. In addition to Dr. Alshaarawy, I would like to extend thanks to all of Dr. Anthony's T32 trainees for their continual encouragement. Furthermore, I could not have reached my goals without the perpetual love and support from my mother, Pam Vanderziel. She has truly been the glue that has held me together through the many obstacles of graduate school. The persistent reinforcement from other family members and close friends has also contributed to the success of my thesis. Finally, I would like to thank the Department of Epidemiology and Biostatistics at Michigan State University for providing a supportive environment within which I could complete this thesis. Thank you to all.

TABLE OF CONTENTS

LIST OF TABLES	vi
LIST OF FIGURES	viii
KEY TO ABBREVIATIONS.....	ix
CHAPTER 1. BACKGROUND	1
1.1. Overview	1
1.2. The Heroin Epidemic	1
1.3. Heroin	2
1.4. Heroin Epidemiology	3
1.5. Depression	5
1.6. Depression Epidemiology	6
1.7. The Association of Heroin Use and Depression	6
1.8. PHQ-9	8
CHAPTER 2. AIMS AND OBJECTIVES	10
2.1. Aims	10
2.2. Objectives	10
CHAPTER 3. METHODS	11
3.1. Study Population and Design	11
3.2. Inclusion Criteria	12
3.3. Determination of Depression and Missing Data	14
3.4. Measures of Heroin and Depression	14
3.5. Covariates	16
3.6. Weights	16
3.7. PHQ-9 Cut-off Score Analyses	16
3.8. Logistic Regression Analyses to Estimate Heroin-Depression Association	17
CHAPTER 4. RESULTS	18
4.1. Study Sample	18
4.2. Optimizing the Heroin-Depression Association.....	24
4.3. PHQ Analyses and Post-Estimation Exploration of Alternative Cut-points	24
4.4. Estimation of the Heroin-Depression Association [Ever Use]	30
4.5. Estimation of the Heroin-Depression Association [Past-Year Heroin Use]	33
CHAPTER 5. DISCUSSION.....	37
5.1. Main Findings	37
5.2. Limitations.....	37
5.3. Strengths	38
5.4. Conclusions and Future Directions	39

APPENDIX.....	41
REFERENCES	62

LIST OF TABLES

Table 1. Cross-tabulation of Ever Heroin Use (EHU ^{+/-})* and age, sex, and race-ethnicity. NHANES data gathering cycles 2005-06, 2007-08, 2009-10, 2011-12, 2013-14.....	19
Table 2. Cross-tabulation of Past Year Heroin Use (PYHU ^{+/-})* and age, sex, and race-ethnicity. NHANES data gathering cycles 2005-06, 2007-08, 2009-10, 2011-12, 2013-14.....	21
Table 3. Cross-tabulation of depression and age, sex, and race-ethnicity. NHANES data gathering cycles 2005-06, 2007-08, 2009-10, 2011-12, 2013-14.....	23
Table 4. Odds Ratios (unweighted) for each cut-off score for the National Health and Nutrition Examination Survey (NHANES) [¶]	26
Table 5A. Ever heroin use and its association with depression among participants in NHANES data gathering cycles 2005-2006 through 2013-2014, cut-off score 9/10 (weighted).....	31
Table 5B. Ever heroin use and its association with depression among participants in NHANES data gathering cycles 2005-2006 through 2013-2014, cut-off score 11/12 (weighted).....	32
Table 6A. Past-year heroin use vs. former and their association with depression using NHANES data gathering cycles 2005-2006 through 2012-2014, cut-off score 9/10 (weighted).....	35
Table 6B. Past-year heroin use vs. former and their association with depression using NHANES data gathering cycles 2005-2006 through 2012-2014, cut-off score 11/12 (weighted).....	36
Table A.1. Cross-tabulation of Ever Heroin Use (EHU ^{+/-})* and age, sex, and race-ethnicity. NHANES data gathering cycles 2005-06.....	42
Table A.2. Cross-tabulation of Ever Heroin Use (EHU ^{+/-})* and age, sex, and race-ethnicity. NHANES data gathering cycles 2007-08.....	43
Table A.3. Cross-tabulation of Ever Heroin Use (EHU ^{+/-})* and age, sex, and race-ethnicity. NHANES data gathering cycles 2009-10.....	44
Table A.4. Cross-tabulation of Ever Heroin Use (EHU ^{+/-})* and age, sex, and race-ethnicity. NHANES data gathering cycles 2011-12.....	45

Table A.5. Cross-tabulation of Ever Heroin Use (EHU ^{+/-})* and age, sex, and race-ethnicity. NHANES data gathering cycles 2013-14.....	46
Table A.6. Cross-tabulation of Past Year Heroin Use (PYHU ^{+/-})* and age, sex, and race-ethnicity. NHANES data gathering cycles 2005-06.....	47
Table A.7. Cross-tabulation of Past Year Heroin Use (PYHU ^{+/-})* and age, sex, and race-ethnicity. NHANES data gathering cycles 2007-08.....	48
Table A.8. Cross-tabulation of Past Year Heroin Use (PYHU ^{+/-})* and age, sex, and race-ethnicity. NHANES data gathering cycles 2009-10.....	49
Table A.9. Cross-tabulation of Past Year Heroin Use (PYHU ^{+/-})* and age, sex, and race-ethnicity. NHANES data gathering cycles 2011-12.....	50
Table A.10. Cross-tabulation of Past Year Heroin Use (PYHU ^{+/-})* and age, sex, and race-ethnicity. NHANES data gathering cycles 2013-14.....	51
Table A.11. Cross-tabulation of depression and age, sex, and race-ethnicity. NHANES data gathering cycles 2005-06.....	52
Table A.12. Cross-tabulation of depression and age, sex, and race-ethnicity. NHANES data gathering cycles 2007-08.....	53
Table A.13. Cross-tabulation of depression and age, sex, and race-ethnicity. NHANES data gathering cycles 2009-10.....	54
Table A.14. Cross-tabulation of depression and age, sex, and race-ethnicity. NHANES data gathering cycles 2011-12.....	55
Table A.15. Cross-tabulation of depression and age, sex, and race-ethnicity. NHANES data gathering cycles 2013-14.....	56
Table A.16. Odds Ratios (weighted) for each cut-off score for the National Health and Nutrition Examination Survey (NHANES) [¶]	57

LIST OF FIGURES

Figure 1. Process for Identifying Ever Heroin Users and Past-Year Heroin Users.....	13
Figure 2. Odds Ratio Calculations with Varying PHQ-9 Cut-Off Scores.....	25
Figure 3. Receiving Operating Characteristic (ROC) Curve 1: The National Health and Nutrition Examination Survey NHANES data gathering cycles 2005-2006, 2009-2010, and 2013-2014 (Unweighted Estimates).....	28
Figure 4. Receiving Operating Characteristic (ROC) Curve 2: The National Health and Nutrition Examination Survey NHANES data gathering cycles 2007-2008 and 2011-2012 (Unweighted Estimates).....	29
Figure A.1. Receiving Operating Characteristic (ROC) Curve 2: The National Health and Nutrition Examination Survey NHANES data gathering cycles 2007-2008 and 2011-2012 (weighted).....	59
Figure A.2. Receiving Operating Characteristic (ROC) Curve 2: The National Health and Nutrition Examination Survey NHANES data gathering cycles 2007-2008 and 2011-2012 (weighted).....	60

KEY TO ABBREVIATIONS

DAWN	Drug Abuse Warning Network
NHANES	National Health and Nutritional Examination Survey
EHU	Ever heroin use
PYHU	Past-year heroin use
CDC	Centers for Disease Control and Prevention
NCIPC	National Center for Injury Prevention and Control
ASAM	American Society of Addiction Medicine
NSDUH	National Survey on Drug Use and Health
ED	Emergency department
DSM-V	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
NIMH	National Institute of Mental Health
MDD	Major Depressive Disorder
PHQ-9	Nine-Item Patient Health Questionnaire
MEC	Mobile Examination Center
OR	Odds Ratio
AUC	Area under the curve
CI	Confidence interval

CHAPTER 1. BACKGROUND

1.1. Overview

This thesis focuses on heroin use and depression. Section 1.2 presents the background oriented toward an epidemiological perspective on the current opioid epidemic, and specifically the heroin epidemic in the United States (US). Section 1.3 outlines heroin pharmacology. I explore heroin epidemiology in section 1.4; prevalence of heroin use and heroin use, by race-ethnicity and sex, are discussed. Section 1.5 defines depression and the behavioral consequences associated with it, while Section 1.6 outlines depression epidemiology. Section 1.7 introduces literature on the association between heroin and depression. Finally, Section 1.8 presents the nine-item Patient Health Questionnaire (PHQ-9) and explores associated cut-points.

1.2. The Heroin Epidemic

Opioid-related deaths have been on the rise in the US, with correlated increases in overdose from all drugs. Over 60% of 52,000 drug overdose deaths resulted from opioid use in 2015 (2). Whereas prescription opioids have become major driving force of the recent opioid epidemic, the Centers for Disease Control and Prevention (CDC) has recently announced that prescription opioids are no longer responsible for the increase in drug overdoses. The CDC's National Center for Injury Prevention and Control (NCIPC) reports that heroin, along with the synthetic opioid fentanyl, have become the major contributors to the elevated rate of drug overdoses (2). Available data in 2015 suggest 20,101 deaths from prescription pain killers and 12,990 deaths from heroin. Moreover, overdose rates from heroin have increased by 26% during 2013-2014 and have tripled since 2010 (3).

In the background of these epidemiological statistics is a growing population of medical and extra-medical opioid prescription pain relievers, where extramedical use refers to those who “use prescription pain relievers to get high or for other unapproved indications outside the boundaries of what a prescribing physician might intend (4).” As it happens, most medical opioid users do not seek out heroin, but those who do make the transition to heroin (about 4%) account for the majority of individuals who are newly incident heroin users (2).

According to the American Society of Addiction Medicine, in recent years, the leading cause of accidental death in the US is drug overdose (5). Death rates due to prescription pain killer overdoses, drug sales, and treatment for substance use disorder increased concurrently between 1999 and 2008. The sale volume of prescription opioids in 2010 was four times that of 1999 (5). The availability of prescription opioids has increased emergency department visits involving opioids from 144,600 in 2004 to 205,900 in 2008 (6). Additionally, 259 million opioid prescriptions were written in 2012. It is no surprise that 94% of respondents in a 2014 survey of individuals in opioid treatment centers admitted that they chose to use heroin, as prescription opioids were quite expensive relative to heroin, and heroin was easier to obtain (5).

1.3. Heroin

Heroin is a semi-synthetic opiate derived from morphine, a naturally occurring opiate. Semi-synthetic opiates are composed partially of natural ingredients, while the remaining composition of the drug is synthetically-derived (7). Heroin is often sold as a white or brown powder that is cut (diluted) with sugars, starch, or other substances (6). Highly pure heroin, predominantly produced in South America, generally is white in color and can be insufflated or

smoked, as opposed to injected, which is the preferred route of administration for impure heroin. Another variety of heroin, “black tar,” is sticky in nature and chiefly produced in Mexico (6). Heroin dependence is achieved with repeated exposure, leading to neuroadaptive changes such that neurons function normally only in the presence of the drug. Furthermore, heroin dependence might include a physical disturbance when the drug is withdrawn (9). Short-term effects of opioids include depressed breathing, an increase in the feeling of pleasure, and a decrease in pain sensation. Continuous heroin use results in changes to brain physiology by producing long-term and possibly some irreversible neuronal and hormonal imbalances. In some studies, long-term heroin use has also been associated with deterioration of white matter in the brain, leading to changes in behavior and differences in decision-making abilities (10). Anthony describes the drug dependence syndrome as “the co-occurrence of sustained use of one or more drugs [such as cannabis, cocaine, or heroin] with features such as tolerance or withdrawal, with or without signs and symptoms of secondary harm (e.g., loss of a job, recurrent infection or abscess, drug overdose), as encompassed by the DSM-III concept of ‘psychoactive drug use disorders.’”(11)

1.4. Heroin Epidemiology

According to the National Survey on Drug Use and Health (NSDUH), the number of US community residents dependent on heroin increased from 214,000 in 2002 to 626,000 in 2016 (12). The NSDUH estimates indicate that past-year extramedical use of pain relievers decreased from 1,880,000 in 2012 to 1,539,000 in 2013, while the number of first-time heroin users increased from 156,000 in 2012 to 169,000 in 2013. In time series reports from poison control centers throughout the US “human exposure cases” of hydrocodone, oxycodone, and methadone have remained stable between 2004-2013; heroin use is the only opioid to have increased in

these studies, although trend estimates for synthetics such as fentanyl suggest increases as well (13).

According to The Drug Abuse Warning Network (DAWN), 2004-2011, the numbers of drug-related emergency department (ED) visits due to heroin as well as other opioids were greater for Hispanics, for individuals under age 21, and for those between 21-24 years old (13). A CDC study of mortality (2002-2011) reported that non-Hispanic African American and Hispanic 45-64-year-olds experienced the highest death rates due to heroin overdose (13). In 2011, 18-44-year-old, non-Hispanic Whites experienced a doubling in the rate of heroin overdose. Although overdose mortality rates were not as high for the 18-44-year-olds, non-Hispanic Whites aged 45-64 also experienced a doubling in mortality. A shift in the demographics of heroin users from urban minorities to rural Whites can also be seen (13). Heroin-attributed mortality rates were, have been and continue to be, larger in males than in females (1.9 per 100,000 for males and 0.2 per 100,000 for females in 1999, and 2.1 per 100,000 for males and 0.4 per 100,000 for females in 2012) (13). However, deaths due to heroin overdose tripled in women between 2010 and 2013 (5).

According to results from the NSDUH, 80% of first-time, past-year heroin users, recounted previous extramedical use of prescription opioids (2002-2011) (13). It was also reported that frequent past-year opioid users claimed that heroin was easy to acquire. It has been hypothesized that the shift between prescription pain killers and heroin occurs when “one of the drugs [other opioids] becomes too expensive, too scarce, or too difficult to inject or insufflate, and users shift to other drugs to avoid withdrawal (13).” Thus, the transition from extramedical opioid use to heroin use may be thought of as a shift due to economics, availability, and/or ease of use.

1.5. Depression

According to the *Diagnostic and Statistical Manual of Mental Disorders, 5th edition* (DSM-V), criteria for Major Depressive Disorder (MDD) and depressive episodes must include at least five of the following symptoms which present within the same two-week period and signify a change in functionality: (1) “Depressed mood most of the day, nearly every day, as indicated by either subjective report or observation made by others.” (2) “Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day.” (3) Significant weight loss when not dieting or weight gain or decrease or increase in appetite nearly every day.” (4) Insomnia or hypersomnia nearly every day.” (5) Psychomotor agitation or retardation nearly every day.” (6) Fatigue or loss of energy nearly every day. (7) Feelings of worthlessness or excessive or inappropriate guilt. (8) Diminished ability to think or concentrate, or indecisiveness, nearly every day.” (9) Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.” One of the previous symptoms must be either depressed mood or loss of interest/pleasure; other diagnostic criteria reflect exclusion rules that pertain to known causes (14). Other diagnostic criteria reflect excluded depression syndromes such as those due to reserpine poisoning, a pre-existing schizophrenia, or thyroid disease (15).

Depression is regarded as the leading cause of disability worldwide, and it contributes greatly to the global burden of disease (15) and has economic costs as well. The US alone loses \$193.2 billion in potential earnings each year due to mental illnesses, with depression as a prominent contributor (15). Depression has been established as complex in nature, as it is influenced by both biological and experiential factors that may have occurred in the distant past and/or more recently (16).

1.6. Depression Epidemiology

About 15.7 million adults 18 years or older in the US have experienced at least one major depressive episode in the past year (2014), making depression one of the most common mental disorders in the US (17). According to the National Institute of Mental Health (NIMH), women experience depression more often than men, however, many men often fail to recognize the signs and symptoms of depression and therefore do not as often seek treatment. Increased rates of depression in women are thought to occur due to biological and hormonal factors, as well as male-female societal differences (18).

1.7. The Association of Heroin Use and Depression

Major depression affects heroin users more often compared to the general population, with almost one-half of heroin users meeting criteria for a depression diagnosis (19). Moreover, individuals who use heroin often have elevated rates of childhood abuse, both sexual and physical, and are often socially disadvantaged, which are overlapping predictors of depression (19). The heroin-using population subset presents an increased risk for excessive morbidity when compared to the general population (20). A report of the *Morbidity and Mortality Weekly Report* (MMWR) included NSDUH data analyses by The Food and Drug Administration (FDA) and the CDC regarding trends in heroin use and characteristics associated with dependence. It found that 96% of past-year heroin users have used at least one other drug during the past 12 months, while 61% of users reported using three or more drugs during the past 12 months (21). Additionally, while heroin dependence is associated with a 14 times increased risk of suicide compared with the general population, major depression is associated with a 20-fold increased risk of suicide (22). It has been reported that underlying depression is substantial among heroin users; one

finding suggested “antidepressants were present in 24% of drug overdose suicides among heroin users (22).” This same study also describes the “social profile” of those dependent on heroin, as one including unemployment, low education levels, isolation, incarceration, rates of parental alcoholism, psychopathology, and/or high divorce rates (22).

Most studies evaluating the association between heroin and depression rely upon heroin dependence treatment facilities for data collection. According to Harvard *et al.*, studies of heroin users who receive treatment have increased rates of comorbid depression that are considerably higher compared to general population estimates (23). One study has reported that the prevalence of lifetime major depression among opiate users in treatment was 38-56% (23). Another study, focusing on the mental status of heroin users in treatment, reported that 45.8% of this subgroup had depressed mood (24). Teesson *et al.* examined the rate of current MDD among individuals dependent on heroin enrolled in three unique treatment programs (e.g., methadone/buprenorphine maintenance, detoxification, or drug-free residential living) (25). They used a non-treatment group for comparative purposes to examine potential covariates associated with depression. Studying depression among heroin users is particularly important as this subgroup may require a different approach to depression treatment given their past and/or current experience with dependence. For example, prescribing antidepressants may lead to complications related polydrug use. The work by Teesson *et al.* also articulates the concern for a diagnosis of depression, specifically among heroin users, as being “associated with a number of negative correlates (25).” For individuals attempting treatment for drug dependence, depression further complicates the path to recovery via the association with high rates of relapse. In addition, it has been suggested that depression might motivate heroin users to seek treatment for their

dependence, as higher rates of depression were found in treatment entrants when compared to non-treatment groups (25).

Temporality comes into question with respect to the association between heroin use and depression. That is, do depressive episodes lead to drug use, or do risky behaviors, such as drug use, lead to depression? An illustration of this complexity can be seen in research on drug use and sexual activity, as in a longitudinal study by Hallfors *et al.*, which explores the temporal sequencing of sex and drug use in adolescents (16). In this work, adolescents who abstained from sex and drug use had lower rates of depression, whereas those who participated in risky behaviors were at a higher risk for depression. Other studies have claimed that comorbid disorders result from self-medication by drug use, and a retrospective study from the National Comorbidity Study found that 86% of individuals with comorbid disorders report that their mental health condition preceded their drug use. Hallfors *et al.* also report very little support for the “self-medication” theory, but rather conclude that depression occurs subsequent to risky behavior. Furthermore, they report that depression was more prevalent in females than in males, and “even modest involvement in substance use and sexual experimentation elevates depression risk (16).” In sum, their work indicates that in terms of temporality, drug use and other risky behaviors precede depression.

1.8. PHQ-9

The Patient Health Questionnaire (PHQ-9) is a screening instrument for “criteria-based diagnoses of depressive and other mental disorders commonly encountered in primary care (26).” The PHQ-9 cut-off scores range from 0 to 27, according to NHANES, and a score of ≥ 10 is the most commonly used cut-off and is validated by clinical studies to differentiate the

presence or absence of depression (27). Kroenke *et al.* have also examined the sensitivity and specificity of PHQ-9 scores; the best sensitivity/specificity was observed at a cut-off score of 10 (*i.e.*, sensitivity= 88%, specificity= 88%). The authors reported that PHQ-9 scores of <10 are rarely associated with depression, while scores of ≥ 15 are usually associated with a diagnosis of depression. They go on to explain that scores between 10-14 represent a ‘gray zone,’ a range whereby specificity continues to rise and sensitivity decreases (26). A study by Scott *et al.* concluded that the best cut-off score is 14, as it yielded the highest sensitivity and specificity at 85.7% and 73.9% (although these scores are not as noteworthy as other studies), respectively, with an area under the curve of 0.84 (28). In a meta-analysis, 11 studies had more than one cut-off score (which included 10), four studies had cut-off scores of exactly 10, and three studies had cut-off scores other than 10 (29).

CHAPTER 2. AIMS AND OBJECTIVES

2.1. Aims

The aims of the current study are (1) to investigate the association between ever heroin use (EHU) and depression, (2) to investigate the association between past-year heroin use (PYHU) and depression and (3) to determine an association-optimizing PHQ-9 cut-off score for a positive depression screen in hopes to enhance the strength of the heroin-depression association.

2.2. Objectives

The primary objective of the current study is to explore the association between heroin use and depression. It is important to note that the current study does not define depression as a diagnosis, but rather as having a positive screen for depression. Because the heroin-using subgroup differs from the general population in terms of lifestyle choices and behavior, it is important to identify and treat depression in this group. Additionally, individuals who have used or who currently use heroin may require an approach to the treatment of their depression distinctively different from the general population. For example, due to issues with comorbid dependence, treating depression with prescription drugs may be more difficult in the heroin-using population.

This study adds value to current literature, as the National Health and Nutrition Examination Survey (NHANES) provides the sample of the population, whereas previous studies have focused on data collection from drug treatment clinics/facilities. Additionally, no literature with NHANES data currently exists that specifically examines heroin use and its association with a positive depression screen.

CHAPTER 3. METHODS

3.1. Study Population and Design

NHANES is a continuing cross-sectional nationally representative survey of US community residents age 18 years and older, with each successive sample including ~5,000 persons. The survey combines interviews and physical examinations among the non-institutionalized civilian population. This thesis research focuses on a US study population of 20-50-year-old, as sampled for NHANES. Within the NHANES sample, I found 19,032 20-59-year olds with non-missing values from measurements about heroin use and about depression states. (A flowchart in the Methods chapter shows how the NHANES samples from its 2005-2014 cycles were combined and then sub-divided to form the sample for this thesis research project.) The result is a truly representative sample of the US population. NHANES oversamples individuals age 60 years and older, low-income Whites, and African Americans, Asians, and Hispanics (30).

For the current study, five data gathering cycles of NHANES included 2005-2006, 2007-2008, 2009-2010, 2011-2012, and 2013-2014. Data file subsets of interest (*i.e.*, ‘demographics,’ ‘drug use,’ and ‘mental health- depression screener’) were extracted from the individual data gathering cycles and then merged. Exposure and outcome variables were ‘ever heroin use’ (lifetime history), ‘last time used heroin,’ and ‘depression.’ Once merged, all five data gathering cycles were concatenated, resulting in a sample size of 50,965 individuals (Figure1). Of those individuals, 19,674 were never heroin users (NHUs), 499 were EHUs, and 30,892 were unknown. All statistical analyses were performed using SAS version 9.4. This study has been deemed exempt from institutional review board review, as NHANES is a secondary data and does not contain person identifiers.

3.2. Inclusion Criteria

Merging all five NHANES data gathering cycles and limiting the age criteria to individuals between 20-59 years old, yielded a sample of 19,032 individuals. The age eligibility was chosen to be 20-59 years old because this age range was successfully accounted for in the drug use portion of the questionnaire for all data gathering cycles. Individuals who failed to complete the interview administered at the Mobile Examination Center (MEC), and those who were missing data on the depression variable were excluded from the sample. The final analytic sample include 16,326 participants, 15,219 of whom had a negative depression screen and 1,107 of whom had a positive depression screen. Figure 1 below displays the eligibility flowchart.

Figure 1. Process for Identifying Ever Heroin Users and Past-Year Heroin Users.

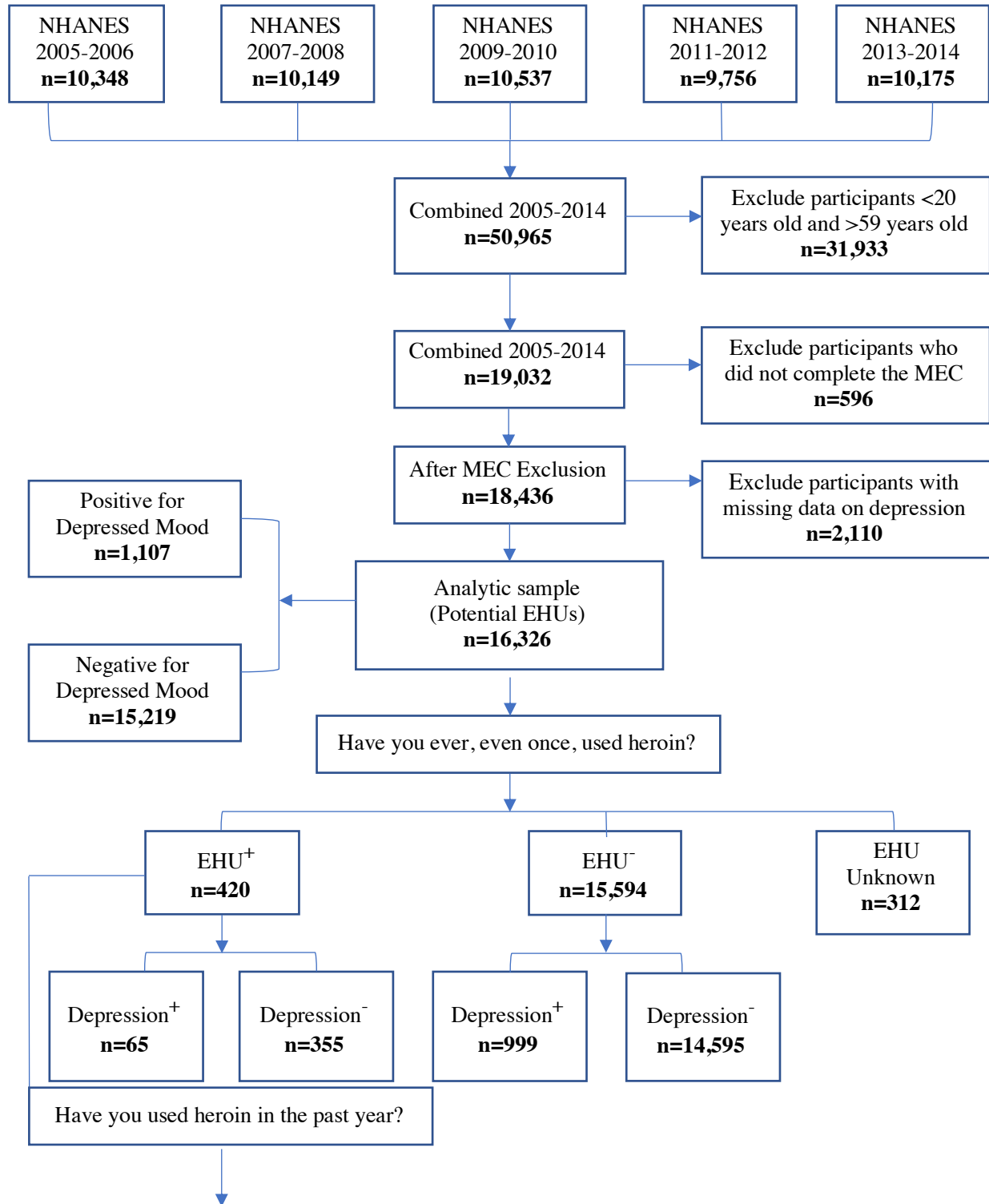
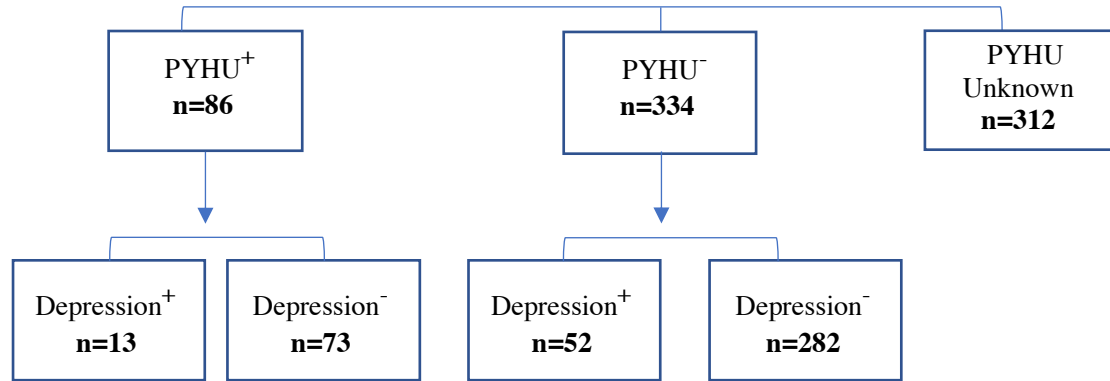


Figure 1 (cont'd).



Mobile Examination Center (MEC); Ever Heroin Users (EHUs); Past-Year Heroin Users (PYHUs).

3.3. Determination of Depression and Missing Data

The heroin prompt involved a gated question. The NHANES survey asked all participants if they had ever used cocaine/crack cocaine/heroin/methamphetamine. Those who answered “no” were assigned to the denominator for purposes of the current analyses. Those who answered “yes” were then asked if they had ever used heroin in their lifetimes (within the five data gathering cycles of the NHANES survey used in this analyses). Missing data were recoded into a new variable, ‘unknown.’ Some individuals may not be comfortable answering questions regarding their drug use, especially a drug as illegal and as potentially fatal as heroin; hence, this type of data may not truly be ‘missing,’ but rather disregarded by survey participants due to personal insecurities and/or fear or judgment or legal repercussions.

3.4. Measures of Heroin and Depression

Depression, the outcome variable of interest in this study, was determined according to a series of nine questions having to do with depressive symptoms, as follows: (1) ‘Have little interest in doing things,’ (2) ‘Feeling down, depressed, or hopeless,’ (3) ‘Trouble sleeping or

sleeping too much,’ (4) ‘Feeling tired or having little energy,’ (5) ‘Poor appetite or overeating,’ (6) ‘Feeling bad about yourself,’ (7) ‘Trouble concentrating on things,’ (8) ‘Moving or speaking slowly or too fast,’ and (9) ‘Thought you would be better off dead.’ Missing data varied by individual question and included individuals refusing to answer, those that reported not knowing the answer, or ‘others’ missing for unknown reasons (21).

For Aim 1, the covariate of main interest, heroin use (EHU), was measured using this survey item: “Have you ever, even once, used heroin?” Analysis codes were 0 for “no,” 1 for “yes,” and 2 for “unknown.” NHANES EHU data are available for 20-59-year-olds (Aim 1). Aim 2 investigated past-year heroin use, with responses coded 0 for “never use,” 1 for “former use,” 2 for “past-year use,” or 3 for “unknown.” For the sake of the heroin-depression estimation model, the heroin covariate is considered as an ‘exposure’ and depression as an outcome. The exposure variable, EHU, was established according to the following question: Have you ever, even once, used heroin?” Responses were categorically coded for analysis as either 0 for “no,” 1 for “yes,” or 2 for “unknown.” The NHANES dataset for the ‘ever used heroin’ variable included males and females between 20 and 59 years old (Aim one). Analysis of Aim 2 investigated past-year heroin use. Responses were coded 0 for “never use,” 1 for “former use,” 2 for “past-year use,” or 3 for “unknown.”

Depression was measured using the PHQ-9, a screening instrument that asks questions about the past-two-weeks of experience of frequency of nine depressed mood experience frequency, coded “not at all,” “several days,” “more than half the days,” or “nearly every day;” to which NHANES assigned scores of 0 to 3, respectively. Scores ranged from 0 (all ‘not at all’) to 27 (all ‘nearly every day’). All measures were administered by trained interviewers using the

Computer-Assisted Personal Interviewing (CAPI) system as part of the Mobile Examination Center (MEC) interview (27).

3.5. Covariates

Other covariates were age, sex, and race-ethnicity ('race'). The measures were standard US Census-like survey items. Standard NHANES race options were Mexican-American, other Hispanic, Non-Hispanic White, Non-Hispanic Black, or other.

3.6. Weights

Analysis and variance estimation variables used here were 'full sample 2-year MEC exam weight,' 'masked variance pseudo-PSU,' and 'masked variance pseudo-stratum.' These variables help account for the NHANES complex survey design, which incorporates oversampling, survey non-response, and post-stratification and to reflect the representativeness of the US Census civilian non-institutionalized population (26). The NHANES complex survey design is one in which observations are sampled with disproportionate sampling probabilities, and involves multi-stage sampling, with local area clusters of observations that affect variance estimates (31). The PSU and stratum variables remove a 'design effect' induced by this complexity.

3.7. PHQ-9 Cut-off Score Analyses

As previously mentioned, literature has recommended using a PHQ-9 score of 10, as this cut-point has "a sensitivity of 88%, a specificity of 88%, and a positive likelihood ratio of 7.1, such that primary care patients with major depression are an estimated seven times more likely to

have a PHQ-9 score of 10 or greater compared to patients without major depression (26).” However, numerous studies that have suggested using cut-off scores other than 10 (25-28), thus motivating this study’s exploration of perhaps a more appropriate cut-off score. Using SAS 9.4, 2X2 contingency tables were produced for all possible cut-points to yield receiver operating characteristics curves as shown in the Results section.

3.8. Logistic Regression Analyses to Estimate a Heroin-Depression Association

Logistic regression analyses were completed to estimate the degree to which heroin use might be associated with depression. Temporal sequencing of this heroin-depression relationship is uncertain. The study model’s response variable was derived from the PHQ score, and heroin was specified as an explanatory covariate.

The regressions yield odds ratio (OR) estimates, with depression regressed on heroin use indicators and other covariates. Covariate-adjusted ORs were then produced after adding one covariate at a time to the model. Then, terms for race and sex were added, respectively. A model fit statistic (Akaike information criterion, or AIC) was used to evaluate model change as covariates were added. (In post-estimation exploratory analyses, these analyses were repeated with different PHQ cut-points; these results are shown in a thesis Appendix.)

Logistic regression analyses were used to explore the association between PYHU-depression (Aim 2). These analyses provide a check on whether it might be recent heroin use, rather than past heroin use that is associated with depression.

Some of the estimations produced in this thesis reflect unweighted sample statistic followed by analysis-weighted statistical estimates. All tables and figures are labeled for indication of unweighted and analysis-weighted estimates of study associations.

CHAPTER 4. RESULTS

4.1. Study Sample

Tables 1, 2, and 3 depict EHU, PYHU, and depression, respectively, in the context of age, sex, and race-ethnicity, based on unweighted data (an Appendix shows these tables for each of the NHANES cycles, whereas Tables 1-3 aggregate all the NHANES cycles in a single pooled analysis).

As can be seen in Table 1, approximately 16,000 individuals (unweighted sample) answered the question, “Have you ever, even once, used heroin?” An analysis-weighted estimate among the US study population is that about 2.6% had used heroin at least once. Except for the oldest age bin, approximately equal percentages of individuals within each ten-year age strata answered yes or no to the EHU question. For the 50-59-year-olds, however, a slightly higher percentage (approximately 30%) answered yes or no to the EHU question. Of those who had ever tried heroin, a greater percentage were males (68.21%) than were female (31.79%), both of which are values weighted to the population.

Of the never heroin users, males and females were roughly equal (~50%), weighted to the population. Of the EHUs, non-Hispanic Whites had the highest weighted percentage (70.97%) while Other Hispanics had the lowest weighted percentage (4.07%), with Mexican-Americans representing the second lowest percentage (5.77%). This same pattern holds for those who had never tried heroin. All reported percentages are weighted estimates.

Table 1. Cross-tabulation of Ever Heroin Use (EHU^{+/−})* and age, sex, and race-ethnicity. NHANES data gathering cycles 2005-06, 2007-08, 2009-10, 2011-12, 2013-14.

	EHU⁺ (n=422)		EHU[−] (n=15,636)		EHU status unknown (n=2,378)	
	n	(%)	n	(%)	n	(%)
Age						
20-29 years	77	(23.01)	4171	(25.51)	535	(22.96)
30-39 years	82	(21.91)	3948	(23.75)	661	(26.72)
40-49 years	112	(25.09)	3947	(26.14)	652	(27.96)
50-59 years	151	(29.99)	3570	(24.60)	530	(22.36)
Sex						
Male	284	(68.21)	7587	(49.55)	996	(43.15)
Female	138	(31.79)	8049	(50.45)	1382	(56.85)
Race-Ethnicity						
Mexican American	40	(5.77)	2763	(9.70)	424	(11.49)
Other Hispanic	26	(4.07)	1430	(5.61)	233	(7.39)
Non-Hispanic White	222	(70.97)	6669	(66.22)	709	(50.93)
Non-Hispanic Black	117	(14.61)	3293	(11.64)	603	(16.54)
Other	17	(4.58)	1481	(6.84)	409	(13.65)

*EHU⁺= Ever Heroin Use (yes)

*EHU[−]=Ever Heroin Use (no)

n=Unweighted frequencies

%=Weighted percentages (due to rounding, the % do not always sum to 100.00%).

As can be seen from Table 2, based on their responses to the recency question, 86 of the 420 EHUs used heroin in the year prior to the NHANES assessment. Of those who have ever used heroin, there are approximately twice as many 20-29-year-olds, about three times as many 30- to 39-year-olds, about four times as many 40- to 49-year-olds, and approximately seven times as many 50- to 59-year-olds who are former heroin users, but who have not used in the past year (PYHU). With respect to sex, about four times as many males, and about three and half times more females, are former heroin users but have not used heroin in the past year, among participants who answered the EHU question. Approximately twice as many males were past heroin users but had not used in the past year, as compared to females, while roughly twice as many males were recently active heroin users (all unweighted sample estimates). With respect to race-ethnicity, 70.84% non-Hispanic White EHUs were recently active heroin users, while for Mexican-Americans, the estimate was only 4.43% (weighted population estimates).

Table 2. Cross-tabulation of Past Year Heroin Use (PYHU^{+/-})* and age, sex, and race-ethnicity. NHANES data gathering cycles 2005-06, 2007-08, 2009-10, 2011-12, 2013-14.

	PYHU⁺ (n=86)		PYHU- (n=336)		PYHU status unknown (n=2,378)		EHU⁻ (n=15,636)	
	n	(%)	n	(%)	n	(%)	n	(%)
Age								
20-29 years	25	(35.84)	52	(19.81)	535	(22.96)	4171	(25.51)
30-39 years	21	(29.54)	61	(20.00)	661	(26.72)	3948	(23.75)
40-49 years	23	(23.62)	89	(25.46)	652	(27.96)	3947	(26.14)
50-59 years	17	(10.99)	134	(34.73)	530	(22.36)	3570	(24.60)
Sex								
Male	57	(68.15)	227	(68.23)	996	(43.15)	7587	(49.55)
Female	29	(31.85)	109	(31.77)	1382	(56.85)	8049	(50.45)
Race-Ethnicity								
Mexican American	6	(4.43)	34	(6.10)	424	(11.49)	2763	(9.70)
Other Hispanic	7	(5.40)	19	(3.74)	233	(7.39)	1430	(5.61)
Non-Hispanic White	43	(70.84)	179	(71.00)	709	(50.93)	6669	(66.22)
Non-Hispanic Black	28	(17.10)	89	(13.98)	603	(15.54)	3293	(11.64)
Other	2	(2.22)	15	(5.17)	409	(13.65)	1481	(6.84)

*Past-Year Heroin Use= PYHU

Yes (+); No (-)

EHU= Ever Heroin Use

No (-)

n=Unweighted frequencies

%=Weighted percentages (due to rounding, the % do not always sum to 100.00%).

Table 3 cross-tabulations link depression status with age, sex, and race-ethnicity. Of depressed individuals, about 20% were 20-39 years old while about 30% were 40-59 years old. (weighted estimate). Females were more likely to qualify for depression status. To some extent non-Hispanic Black adults were more likely to qualify as depression cases (OR=1.6; 95% CI=1.4, 1.9), with non-Hispanic White as the reference category.

Table 3. Cross-tabulation of depression and age, sex, and race-ethnicity.
NHANES data gathering cycles 2005-06, 2007-08, 2009-10, 2011-12, 2013-14.

	Depression Yes (n=1,107)		Depression No (n=15,219)		Analysis (Weighted Association)	
	n	(%)	n	(%)	OR	95% CI
Age						
20-29 years	213	(19.97)	4074	(25.60)	1.0	--
30-39 years	241	(20.99)	3843	(23.82)	1.2	1.0, 1.4
40-49 years	299	(29.41)	3829	(25.97)	1.2	1.1, 1.4
50-59 years	354	(29.63)	3473	(24.61)	1.1	0.9, 1.2
Sex						
Male	380	(35.31)	7613	(50.89)	1.0	--
Female	727	(64.69)	7606	(49.11)	1.5	1.4, 1.7
Race-Ethnicity						
Mexican American	151	(7.87)	2715	(9.78)	1.2	1.0, 1.4
Other Hispanic	127	(7.77)	1363	(5.51)	1.5	1.3, 1.9
Non-Hispanic White	509	(63.64)	6434	(66.06)	1.0	--
Non-Hispanic Black	259	(15.28)	3214	(11.57)	1.6	1.4, 1.9
Other	61	(5.75)	1493	(7.08)	1.7	1.4, 2.2

n=Unweighted frequencies

%=Weighted percentages (due to rounding, the % do not always sum to 100.00%).

4.2. Optimizing the Heroin-Depression Association

The main analysis of this thesis is based upon the standard PHQ cut-off score of 9/10, but another set of analyses are completed based on an optimized PHQ cut-off score, devised to evoke a statistically robust association by setting the cut-off score to achieve a relatively large odds ratio estimate. This section describes the results of that psychometric work, pursuant to Specific Aim 3.

4.3. PHQ Analyses and Post-Estimation Exploration of Alternative Cut-points

After completing logistic regression analyses based on the standard PHQ cut-off score of 9/10, a series of PHQ analyses helped identify a cut-point that optimized the heroin-depression association. Whereas this project could be completed with a standard PHQ cut-off score for depression, the 9/10 cut-off originally recommended, it seemed important to ask whether that cut-off score optimizes the association between heroin and depression. The example directly below illustrates a series of Receiver Operating Characteristic (ROC) analyses, first with “Ever Heroin Use” as a designation for use and never use status, and with the full range of PHQ cut-off scores used to estimate the OR linking EHU to a higher or lower PHQ score as shown in Figure 2 (OR estimates based on the 11/12 cut-point are presented in Table 4).

Figure 2. Odds Ratio Calculations with Varying PHQ-9 Cut-Off Scores.

		Ever Heroin Use				Ever Heroin Use				Ever Heroin Use	
		Yes	No			Yes	No			Yes	No
PHQ Score	1-27	X ₁₁	X ₁₂	PHQ Score	2-27	X ₁₁	X ₁₂	PHQ Score	27	X ₁₁	X ₁₂
	0	X ₂₁	X ₂₂		0-1	X ₂₁	X ₂₂		0-26	X ₂₁	X ₂₂
OR ₀₁ =(X ₁₁ X ₂₂)/(X ₂₁ X ₁₂)				OR ₁₂ =(X ₁₁ X ₂₂)/(X ₂₁ X ₁₂)				OR _{026/27} =(X ₁₁ X ₂₂)/(X ₂₁ X ₁₂)			

The resulting statistics are plotted on the ROC curves (Figures 2,3) with $X_{11}/(X_{11}+X_{21})$ on the Y-axis (“sensitivity”) and with the complement $X_{22}/(X_{12}+X_{22})$ on the X-axis (“1-specificity”). The PHQ-9 analyses revealed that a cut-off score of 11/12 would optimize the heroin-depression association, as suggested by the size of the OR estimate and its variance. That is, among the points closest to the upper left-hand corner of the ROC curve, cut-point 12 had the largest OR, with the tightest confidence interval (OR=3.40, CI=2.32, 4.97). A cross-validation was performed as follows. One ROC curve was produced using NHANES data gathering cycles 2005-2006, 2009-2010, and 2013-2014 (Figure 3), and the other curve used data gathering cycles 2007-2008 and 2011-2012 (Figure 4). The curves were quite similar, although not identical. The area under the Curve 1 was 0.7968, the upper end of a fair discrimination. The area under the curve (AUC) for Curve 2 had a value of 0.7728, indicating that there is relatively little variation between the subsamples. Figures 2 and 3 depict ROC curves for NHANES data gathering cycles 2005-2006, 2009-2010, and 2013-2014 and for data gathering cycles 2007-2008 and 2011-2012, respectively.

Table 4. Odds Ratios (unweighted) for each cut-off score for the National Health and Nutrition Examination Survey (NHANES).[¶]

Depression Cut-Point 2005-06, 2009-10, & 2013-14				Depression Cut-Point 2007-08 & 2011-12			
Odds Ratio (OR)	Confidence Interval (CI)			Odds Ratio (OR)	Confidence Interval (CI)		
0/1	1.71	1.45	1.98	0/1	2.80	2.38	3.22
1/2	1.92	1.68	2.15	1/2	2.42	2.08	2.76
2/3	2.34	2.12	2.57	2/3	2.52	2.21	2.84
3/4	2.38	2.16	2.60	3/4	2.46	2.15	2.76
4/5	2.50	2.28	2.72	4/5	2.35	2.04	2.66
5/6	2.55	2.32	2.78	5/6	2.32	2.01	2.64
6/7	2.85	2.62	3.09	6/7	2.40	2.07	2.72
7/8	2.82	2.58	3.07	7/8	1.98	1.63	2.34
8/9	2.83	2.57	3.09	8/9	1.75	1.36	2.14
9/10	2.73	2.46	3.01	9/10	1.88	1.47	2.29
10/11	2.62	2.33	2.92	10/11	1.86	1.42	2.30
11/12	2.81	2.50	3.11	11/12	2.06	1.61	2.52
12/13	2.70	2.37	3.04	12/13	2.13	1.65	2.62
13/14	2.84	2.49	3.20	13/14	2.40	1.90	2.90
14/15	2.40	1.98	2.82	14/15	2.39	1.85	2.94
15/16	2.71	2.27	3.15	15/16	2.59	2.01	3.17
16/17	2.68	2.19	3.17	16/17	2.66	2.03	3.29
17/18	2.45	1.88	3.02	17/18	3.39	2.76	4.02
18/19	2.75	2.13	3.37	18/19	3.14	2.41	3.87

Table 4. (cont'd)

19/20	2.86	2.13	3.59	19/20	2.05	1.04	3.06
20/21	3.23	2.45	4.01	20/21	2.51	1.50	3.53
21/22	2.70	1.68	3.72	21/22	3.69	2.66	4.71
22/23	2.61	1.43	3.79	22/23	3.41	2.23	4.59
23/24	2.30	0.86	3.79	23/24	3.17	1.73	4.60

[¶]Unweighted estimates based on combined 2005-06, 2009-10, 2013-14 data gathering cycles analyzed separately from the combined 2007-08 and 2011-12 cycles addressing ROC curve cross-validation.

Figure 3. Receiving Operating Characteristic (ROC) Curve 1: The National Health and Nutrition Examination Survey NHANES data gathering cycles 2005-2006, 2009-2010, and 2013-2014 (Unweighted Estimates).

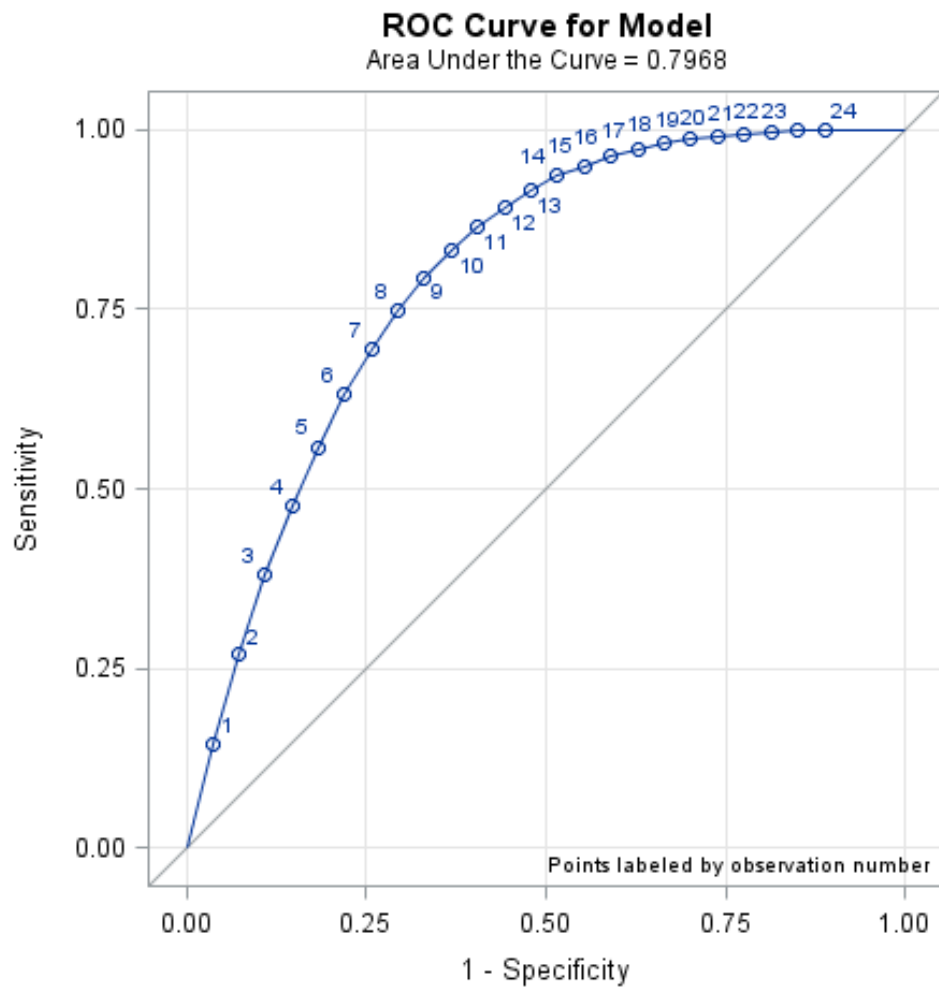
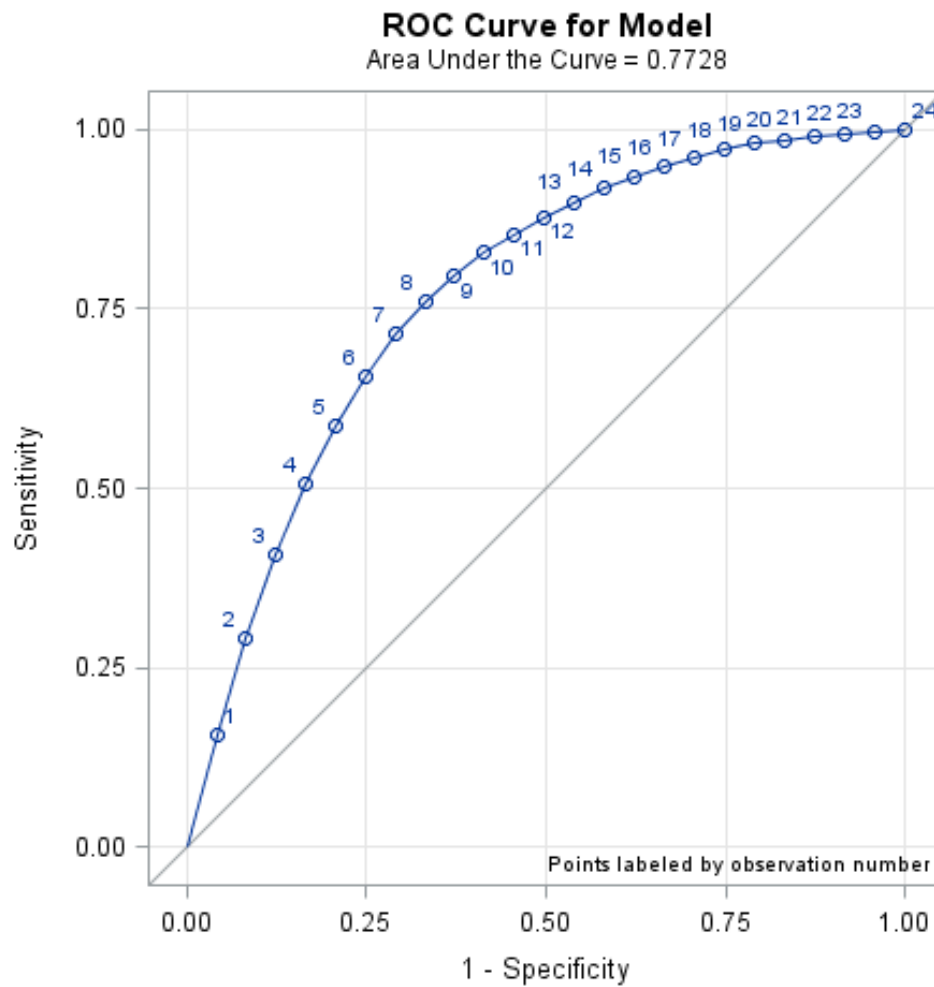


Figure 4. Receiving Operating Characteristic (ROC) Curve 2: The National Health and Nutrition Examination Survey NHANES data gathering cycles 2007-2008 and 2011-2012 (Unweighted Estimates).



For the ROC estimates shown here, the first data line column included all depression/non-depression cut-points 0-27. The second and third data lines contained data on ever heroin use and those individuals with a positive depression screen, respectively. The fourth data line included the total number of individuals surveyed within NHANES data gathering cycles 2005-2006, 2009-2010, and 2013-2014. In order to observe the potential variation among NHANES data gathering cycles, the same analysis was carried out for years 2007-2008 and 20011-2012.

4.4. Estimation of the Heroin-Depression Association [Ever Use]

Pursuant to Specific Aim 1, Table 5A is based on a standard PHQ cut-off score of 9/10. Model 1 included covariate terms for heroin use status and produced an odds ratio (OR) estimate is 2.7 (95% CI=2.1, 3.6; AIC=83,010,193). Model 2 adds an age covariate term and yields an OR=2.7 (95% CI=2.1, 3.6; AIC=82,801,826). Model 3 adds a term for sex and yields an OR=3.2 (95% CI=2.4, 4.2; AIC=81,520,444). Model 4 adds terms for race-ethnicity and yields an OR=3.1 (95% CI=2.3, 4.2; AIC=81,227,080). Table 5B is based on an optimized PHQ cut-off score of 11/12, derived as described in section 3.7, with estimates reported in section 4.5. When the PHQ cut-off score of 11/12 is used, Model 1 yields an OR=2.9 (95% CI=2.1, 4.1; AIC=64,587,922). Results for Model 2, with age added, disclosed a slightly smaller OR of 2.9 (95% CI=2.1, 4.0; AIC=64,370,467). Model 3 added sex and resulted in an OR=3.3 (95% CI=2.4, 4.7; AIC=63,505,366). Lastly, after adding race-ethnicity in Model 4, the resulting OR=3.3 (95% CI=2.3, 4.7; AIC=63,314,225). It seems that in any given logistic regression model, ‘ever users’ of heroin have roughly three times the odds of depression.

Table 5A. Ever heroin use and its association with depression among participants in NHANES data gathering cycles 2005-2006 through 2013-2014, cut-off score 9/10 (weighted).

	Depression (MAX n=16,326)					
	Positive Depression Screen n[†]	Negative Depression Screen¹ n[†]	Model 1 OR (95% CI)	Model 2 aOR (95% CI)	Model 3 aOR (95% CI)	Model 4 aOR (95% CI)
Heroin Use, Ever						
Yes	87	333	2.7 (2.1, 3.6)	2.7 (2.1, 3.6)	3.2 (2.4, 4.2)	3.1 (2.3, 4.2)
No ¹	1,440	14,154	---	---	---	---
Unknown*	55	257	2.4 (1.6, 3.5)	2.2 (1.5, 3.3)	2.2 (1.5, 3.3)	2.2 (1.5, 3.2)
AIC			83,010,1093	82,801,826	81,520,444	81,227,080

Logistic regression models of EHU and depression.

[†]Unweighted frequencies, n

¹Referent category

*Missing data on heroin use

Model 1: unadjusted

Model 2: Model 1 + age

Model 3: Model 2 + sex

Model 4: Model 3 + race-ethnicity

Table 5B. Ever heroin use and its association with depression among participants in NHANES data gathering cycles 2005-2006 through 2013-2014, cut-off score 11/12 (weighted).

	Depression (MAX n=16,326)					
	Positive Depression Screen	Negative Depression Screen[†]	Model 1	Model 2	Model 3	Model 4
	n[†]	n[†]	OR (95% CI)	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)
Heroin Use, Ever						
Yes	65	355	2.9 (2.1, 4.1)	2.9 (2.1, 4.0)	3.3 (2.4, 4.7)	3.3 (2.3, 4.7)
No ¹	999	14,595	---	---	---	---
Unknown [*]	43	269	2.9 (1.9, 4.4)	2.7 (1.8, 4.1)	2.7 (1.8, 4.2)	2.7 (1.8, 4.1)
AIC			64,587,922	64,370,467	63,505,366	63,314,225

Logistic regression models of EHU and depression.

[†]Unweighted frequencies, n

¹ Referent category

^{*}Missing data on heroin use

Model 1: unadjusted

Model 2: Model 1 + age

Model 3: Model 2 + sex

Model 4: Model 3 + race-ethnicity

The use of a 9/10 cut-point and the use of an optimized 11/12 cut-point produced odds ratio estimates that did not differ appreciably. For example, whereas the size of the Model 1 association was 2.93 (95% CI=2.11, 4.06) with the 11/12 cut-off score, it was 2.75 (95% CI=2.09, 3.61) with the 9/10 cut-off score. Appendix materials present OR estimates from the other models.

Two issues deserve mention at this point. First, the overall results did not differ appreciably when the PHQ cut-off score of 11/12 was used (relative to with a score of 9/10). Second, the odds of depression appear to be elevated for participants who declined to report on their heroin status or had missing or unknown values for other reasons. These issues are further addressed in Chapter 5, “Discussion.”

4.5. Estimation of the Heroin-Depression Association [Past-Year Heroin Use]

Pursuant to Specific Aim 2, Table 6A presents estimates of the association that links past-year heroin use (PYHU) with depression based on logistic regression analyses with a PHQ cut-off score of 9/10. Per Table 6A, the PYHU-depression association is indicated by an OR=3.6 (95% CI=1.7, 7.3; AIC=82,999,617) in the model without sociodemographic covariates. Based on Model 2, the OR is 3.8 (95% CI=1.8,7.7). From Model 3, the OR is 4.4 (95% CI=2.1, 9.1). Finally, from Model 4, the OR is 4.3 (95% CI=2.0, 9.0). Table 6B is based on PHQ cut-off score 11/12. In Table 6B, Model 1 estimation for PYHU resulted in an OR=3.5 (95% CI=1.6, 7.8; AIC=64,583,719). Model 2 increased to an OR=3.8 (95% CI=1.7, 8.2; AIC=82,785,431), followed by Model 3 with an OR=4.3 (95% CI=2.0, 9.5; AIC=63,497,245). Finally, Model 4 resulted in an OR=4.2 (95% CI=1.9, 9.4; AIC=63,307,273). Tables 6A and 6B also show associations for depression odds, as it varies across the contrast of (a) former heroin users (no

use in the past year) versus (b) never users. Based on this contrast, there is an association linking former heroin use with depression status (Table 6A and Table 6B). That is, among those who quit heroin use, there is excess odds of depression.

Table 6A. Past-year heroin use vs. former and their association with depression using NHANES data gathering cycles 2005-2006 through 2012-2014, cut-off score 9/10 (weighted).

	Depression Screen (MAX n=16,326)					
	Positive Depression Screen n [†]	Negative Depression Screen [†] n [†]	Model 1 OR (95% CI)	Model 2 aOR (95% CI)	Model 3 aOR (95% CI)	Model 4 aOR (95% CI)
Heroin Use						
PYHU	20	66	3.6 (1.7, 7.3)	3.8 (1.8, 7.7)	4.4 (2.1, 9.1)	4.3 (2.0, 9.0)
Former use	67	267	2.6 (1.8, 3.6)	2.5 (1.8, 3.4)	2.9 (2.1, 4.1)	2.9 (2.1, 4.1)
No ¹	1,440	14,154	---	---	---	---
Unknown*	55	257	2.3 (1.6, 3.5)	2.2 (1.5, 3.3)	2.2 (1.5, 3.3)	2.2 (1.5, 3.2)
AIC			82,999,617	82,785,431	81,504,473	81,212,611

Logistic regression models of past-year heroin use and depression.

Past-Year Heroin Use= PYHU

Former use= EHU who have not used in the past year

[†]Unweighted frequencies, n

¹ Referent category

*Missing data on heroin use

Model 1: unadjusted

Model 2: Model 1 + age

Model 3: Model 2 + sex

Model 4: Model 3 + race-ethnicity

Table 6B. Past-year heroin use vs. former and their association with depression using NHANES data gathering cycles 2005-2006 through 2012-2014, cut-off score 11/12 (weighted).

	Depression Screen (MAX n=16,326)					
	Positive Depression Screen n [†]	Negative Depression Screen ¹ n [†]	Model 1 OR (95% CI)	Model 2 aOR (95% CI)	Model 3 aOR (95% CI)	Model 4 aOR (95% CI)
Heroin Use						
PYHU	13	73	3.5 (1.6, 7.8)	3.8 (1.7, 8.2)	4.3 (2.0, 9.5)	4.2 (1.9, 9.4)
Former use	52	282	2.8 (1.9, 4.1)	2.7 (1.8, 4.0)	3.1 (2.1, 4.6)	3.1 (2.1, 4.6)
No ¹	999	14,595	---	---	---	---
Unknown*	43	269	2.9 (1.9, 4.4)	2.7 (1.8, 4.1)	2.7 (1.8, 4.2)	2.7 (1.8, 4.1)
AIC			64,583,719	64,362,037	63,497,245	63,307,273

Logistic regression models of past-year heroin use and depression.

Past-Year Heroin Use= PYHU

Former use= EHU who have not used in the past year

[†]Unweighted frequencies, n

¹ Referent category

*Missing data on heroin use

Model 1: unadjusted

Model 2: Model 1 + age

Model 3: Model 2 + sex

Model 4: Model 3 + race-ethnicity

CHAPTER 5. DISCUSSION

5.1. Main Findings

This thesis has several primary findings. First, there is a statistically robust association linking lifetime history of heroin use (ever use) with recently active depression when the standard PHQ depression cut-point is used, before and after covariate adjustment for age, sex, and race-ethnicity. Second, if the goal were to optimize the strength of association of the EHU-depression association, an optimized PHQ cut-point is at 11/12 (i.e., 12+ indicating depression); Third, there also is an association linking recently active (past year) heroin use and depression. Before detailed discussion, some limitations should be mentioned.

5.2. Limitations

Epidemiological study designs of this type are subject to a variety of study limitations, which can range from issues with the sample to assessments, data quality control checks, post-estimation processes, interpretation, statistical inference, and the presentation of the evidence. Here, in this thesis research project, the most serious limitation is most likely in the realm of measurement, specifically in relation to potential bias in falsely negative depression results and/or falsely negative heroin use survey responses. That is, the primary analyses for this thesis are based on the NHANES ‘standard depression screen’ cut-point of 9/10. This cut-point might be best if the goal is to optimize the heroin-depression association. An optimized cut-point of 11/12 is suggested for future research on this association.

In addition to measurement limitations, the study faces potential problems with the sampling approach, as not all individuals consented to participate in the study. Considering that NHANES is a government-sponsored survey, non-participation may be even greater if heroin users fear getting into trouble with the law for using heroin; this would result in ‘left-censoring’

of heroin users who are sampled but chose not to participate in the study. Another possible limitation involves left-truncation, which can become an issue of importance. For example, consider heroin users in the hospital or in correctional institutions (deliberately excluded from the study population), and heroin users who do not have a permanent residence. This example illustrates left-truncation of a heroin user.

Finally, ‘omitted variables’ and ‘model mis-specification’ are limitations that deserve notice. We undertake epidemiological studies in the absence of full knowledge equivalent to what physicists and chemists might rely upon in the form of ‘lawful relationships’ of the type identified by Boyle and Newton in those branches of science. Here, omitted variables and model mis-specification in family history of depression, and either individual-level or community-level influences such as neighborhood disadvantage, as examples of variables that were not measured.

5.3. Strengths

If we can set aside limitations such as these, a major strength of this study is its external validity. This type of epidemiological research has superior generalizability when compared to more tightly controlled experiments and to clinical investigations of patients. Another strength is that epidemiological studies create ways to quantify the size of errors that may result from sampling approaches.

Another strength of this study involved its ability to present a nuanced view of the heroin-depression association in relation to recency of heroin use. In consequence, it was found that the heroin-depression link might be stronger for past-year heroin users.

The exploration of the NHANES depression screen cut-off score using ROC analyses was a key strength of this study. The procedures involved use of ROC curves, odds ratio estimates,

confidence intervals, and model fit statistics, as well as a cross-validation approach with half-samples.

Further strengths include the nationally representative design of the NHANES sample as well as the use of analysis weights, which balance selection probabilities and US census distributions (i.e., via post-stratification); nearly all prior studies had based their samples on individuals in drug treatment facilities. In previous clinical investigations with patients, internal validity may have been greater than is the case, but external validity is better in NHANES research.

A final strength deserving mention is the treatment of missing values for heroin use. As opposed to dropping individuals with missing data on heroin use, a separate group was created to account for these potential heroin users. Heroin users may not choose to admit to their use due to fear of incarceration and/or for social reasons. This created group does not assume that no heroin use.

5.4 Conclusions and Future Directions

The main conclusion of this thesis is that depression as indicated by an elevated PHQ score is associated with both a lifetime history of using heroin and also with recently active (past-year) heroin use. Three potential interpretations might be concluded: (1) heroin use may trigger the presence of depression or may aggravate depression when it occurs (severity); (2) depression might prompt either initial or persistent heroin use (heroin could be used to self-medicate mood disturbances, such as depression); (3) there is the possibility of some shared vulnerability not studied in this work that accounts for the association (i.e., omission of variables and/or mis-specification of our conceptual models). As for the future direction of heroin-

depression research, investigators using the PHQ-9 depression screen may consider using a cut-point of 11/12 opposed to the ‘standard’ NHANES cut-point of 9/10, as methodological findings suggest optimization of odds ratios and confidence intervals using the optimized 11/12 cut-off score. It is of course possible that this cut-point may not serve well in all future research, as using a drug or exposure other than heroin may require a different cut-point. This study’s use of cross-validation samples and use of ROC model fit for the selection of an association-optimizing cut-point may help future studies in working with the NHANES depression screen or other screening tools. It may be noteworthy that the NHANES data has generally been under-utilized in National Institute on Drug Abuse research. The NHANES might provide useful information that complements what can be learned from other field survey projects now underway such as the National Surveys on Drug Use and Health (NSDUH). Because heroin survey prompts were not added to NHANES data assessments until 2005, much of the existing literature on heroin has used these other data sources, such as NSDUH.

It is hoped that this research project has contributed useful new evidence on the heroin-depression association. Exploring recent heroin use may tease out individuals who are depressed for reasons other than heroin use. Residual areas of uncertainty include the possibility that heroin-using individuals, or those with a past history of heroin use, might require a different tailoring of treatment options for depression. Research that clears up the temporal sequencing of heroin use onset and the onset of depression represents a continual important focal point in future research.

APPENDIX

Table A.1. Cross-tabulation of Ever Heroin Use (EHU^{+/-})* and age, sex, and race-ethnicity. NHANES data gathering cycles 2005-06.

	EHU⁺ (n=79)		EHU⁻ (n=2,835)		EHU status unknown (n=371)	
	n	(%)	n	(%)	n	(%)
Age						
20-29 years	23	(33.28)	876	(24.11)	122	(27.67)
30-39 years	12	(13.19)	708	(24.91)	98	(25.35)
40-49 years	16	(22.38)	711	(27.87)	88	(26.75)
50-59 years	28	(31.16)	540	(23.11)	63	(20.23)
Sex						
Male	51	(63.30)	1303	(49.12)	168	(47.72)
Female	28	(36.70)	1532	(50.88)	203	(52.28)
Race-Ethnicity						
Mexican American	11	(6.69)	622	(8.76)	105	(14.43)
Other Hispanic	3	(4.25)	100	(3.50)	25	(8.30)
Non-Hispanic White	39	(69.24)	1350	(70.95)	95	(45.59)
Non-Hispanic Black	24	(16.99)	637	(11.31)	118	(20.66)
Other	2	(2.83)	126	(5.49)	28	(11.03)

*EHU⁺=Ever Heroin Use (yes)

*EHU⁻=Ever Heroin Use (no)

n=Unweighted frequencies

%=Weighted percentages

Table A.2. Cross-tabulation of Ever Heroin Use (EHU^{+/−})* and age, sex, and race-ethnicity. NHANES data gathering cycles 2007-08.

	EHU⁺ (n=75)		EHU[−] (n=3,176)		EHU status unknown (n=411)	
	n	(%)	n	(%)	n	(%)
Age						
20-29 years	13	(26.37)	769	(25.39)	85	(21.78)
30-39 years	16	(21.41)	851	(24.28)	110	(23.79)
40-49 years	20	(27.83)	799	(26.66)	108	(28.26)
50-59 years	26	(24.39)	757	(23.67)	108	(26.18)
Sex						
Male	54	(72.99)	1548	(49.03)	193	(47.74)
Female	21	(27.01)	1628	(50.97)	218	(52.26)
Race-Ethnicity						
Mexican American	5	(2.49)	658	(10.02)	75	(8.73)
Other Hispanic	6	(2.96)	377	(5.44)	51	(5.71)
Non-Hispanic White	45	(75.99)	1358	(67.05)	143	(57.68)
Non-Hispanic Black	16	(11.65)	658	(11.97)	96	(13.21)
Other	3	(6.91)	125	(5.52)	46	(14.68)

*EHU⁺=Ever Heroin Use (yes)

*EHU[−]=Ever Heroin Use (no)

n=Unweighted frequencies

%=Weighted percentages

Table A.3. Cross-tabulation of Ever Heroin Use (EHU^{+/−})* and age, sex, and race-ethnicity. NHANES data gathering cycles 2009-10.

	EHU⁺ (n=123)		EHU[−] (n=3,345)		EHU status unknown (n=586)	
	n	(%)	n	(%)	n	(%)
Age						
20-29 years	20	(21.60)	869	(25.43)	133	(25.50)
30-39 years	21	(17.40)	810	(23.30)	180	(28.47)
40-49 years	39	(27.80)	897	(26.47)	151	(25.72)
50-59 years	43	(33.20)	769	(24.80)	122	(20.31)
Sex						
Male	85	(67.64)	1635	(50.25)	228	(40.69)
Female	38	(32.36)	1710	(49.75)	358	(59.31)
Race-Ethnicity						
Mexican American	9	(5.57)	679	(9.93)	118	(10.38)
Other Hispanic	7	(3.50)	377	(5.91)	57	(5.39)
Non-Hispanic White	57	(65.61)	1527	(65.86)	220	(54.28)
Non-Hispanic Black	46	(21.28)	571	(11.26)	132	(15.97)
Other	4	(4.03)	191	(7.04)	59	(14.00)

*EHU=Ever Heroin Use (yes)

*EHU=Ever Heroin Use (no)

n=Unweighted frequencies

%=Weighted percentages

Table A.4. Cross-tabulation of Ever Heroin Use (EHU^{+/-})* and age, sex, and race-ethnicity.
NHANES data gathering cycles 2011-12.

	EHU⁺ (n=65)		EHU⁻ (n=2,986)		EHU status unknown (n=581)	
	n	(%)	n	(%)	n	(%)
Age						
20-29 years	5	(6.37)	835	(26.57)	114	(19.09)
30-39 years	17	(32.92)	736	(22.48)	171	(30.09)
40-49 years	18	(30.65)	705	(25.08)	152	(26.25)
50-59 years	25	(30.07)	710	(25.86)	144	(24.56)
Sex						
Male	41	(68.87)	1509	(49.92)	231	(39.88)
Female	24	(31.13)	1477	(50.08)	350	(60.12)
Race-Ethnicity						
Mexican American	6	(7.19)	323	(8.87)	75	(13.28)
Other Hispanic	2	(2.07)	278	(6.88)	64	(10.40)
Non-Hispanic White	34	(75.98)	1077	(64.63)	130	(47.54)
Non-Hispanic Black	20	(12.87)	775	(11.91)	148	(15.59)
Other	3	(1.89)	533	(7.71)	164	(13.19)

*EHU⁺=Ever Heroin Use (yes)

*EHU⁻=Ever Heroin Use (no)

n=Unweighted frequencies

%=Weighted percentages

Table A.5. Cross-tabulation of Ever Heroin Use (EHU^{+/−})* and age, sex, and race-ethnicity. NHANES data gathering cycles 2013-14.

	EHU⁺ (n=80)		EHU[−] (n=3,294)		EHU status unknown (n=429)	
	n	(%)	n	(%)	n	(%)
Age						
20-29 years	16	(26.38)	822	(26.05)	81	(21.20)
30-39 years	16	(36.93)	843	(23.78)	102	(24.31)
40-49 years	19	(16.25)	835	(24.66)	153	(34.55)
50-59 years	29	(30.45)	794	(25.51)	93	(19.94)
Sex						
Male	53	(68.27)	1592	(49.45)	176	(41.26)
Female	27	(31.73)	1702	(50.55)	253	(58.74)
Race-Ethnicity						
Mexican American	9	(7.21)	481	(10.86)	51	(10.98)
Other Hispanic	8	(7.67)	298	(6.30)	36	(7.23)
Non-Hispanic White	47	(69.80)	1357	(62.72)	121	(48.05)
Non-Hispanic Black	11	(8.19)	652	(11.73)	109	(18.52)
Other	5	(7.13)	506	(8.39)	112	(15.22)

*EHU⁺=Ever Heroin Use (yes)

*EHU[−]=Ever Heroin Use (no)

n=Unweighted frequencies

%=Weighted percentages

Table A.6. Cross-tabulation of Past Year Heroin Use (PYHU^{+/-})* and age, sex, and race-ethnicity. NHANES data gathering cycles 2005-06.

	PYHU⁺ (n=18)		PYHU⁻ (n=61)		PYHU status unknown (n=371)		EHU⁻ (n=2,835)	
	n	(%)	n	(%)	n	(%)	n	(%)
Age								
20-29 years	8	(43.09)	15	(31.05)	122	(27.27)	876	(24.11)
30-39 years	6	(41.00)	6	(6.89)	98	(25.35)	708	(24.91)
40-49 years	3	(10.80)	13	(25.00)	88	(26.75)	711	(27.87)
50-59 years	1	(5.11)	27	(37.05)	63	(20.23)	540	(23.11)
Sex								
Male	9	(47.18)	42	(66.95)	168	(47.72)	1303	(49.12)
Female	9	(52.82)	19	(33.05)	203	(52.28)	1532	(50.88)
Race-Ethnicity								
Mexican American	4	(13.03)	7	(5.25)	105	(14.43)	622	(8.76)
Other Hispanic	2	(15.26)	1	(1.76)	25	(8.30)	100	(3.50)
Non-Hispanic White	7	(47.01)	32	(74.27)	95	(45.59)	1350	(70.95)
Non-Hispanic Black	4	(14.59)	20	(17.54)	118	(20.66)	637	(11.31)
Other	1	(10.11)	1	(1.19)	28	(11.03)	126	(5.49)

*Past-Year Heroin Use= PYHU

Yes (+); No (-)

EHU= Ever Heroin Use

No (-)

n=Unweighted frequencies

%=Weighted percentages

Table A.7. Cross-tabulation of Past Year Heroin Use (PYHU^{+/−})* and age, sex, and race-ethnicity. NHANES data gathering cycles 2007-08.

	PYHU⁺ (n=12)		PYHU- (n=63)		PYHU status unknown (n=411)		EHU⁻ (n=3,176)	
	n	(%)	n	(%)	n	(%)	n	(%)
Age								
20-29 years	5	(57.49)	8	(19.27)	85	(21.78)	769	(25.39)
30-39 years	3	(9.07)	13	(24.22)	110	(23.79)	851	(24.28)
40-49 years	1	(14.70)	19	(30.82)	108	(28.26)	799	(26.66)
50-59 years	3	(18.74)	23	(25.68)	108	(26.18)	757	(23.67)
Sex								
Male	8	(57.79)	46	(76.46)	193	(47.74)	1548	(49.03)
Female	4	(42.21)	17	(23.54)	218	(52.26)	1628	(50.97)
Race-Ethnicity								
Mexican American	0	--	5	(3.06)	75	(8.73)	658	(10.02)
Other Hispanic	0	--	6	(3.63)	51	(5.71)	377	(5.44)
Non-Hispanic White	11	(96.69)	34	(71.26)	143	(57.68)	1358	(67.05)
Non-Hispanic Black	1	(3.31)	15	(13.56)	96	(13.21)	658	(11.97)
Other	0	--	3	(8.49)	46	(14.68)	125	(5.52)

*Past-Year Heroin Use= PYHU

Yes (+); No (-)

EHU= Ever Heroin Use

No (-)

n=Unweighted frequencies

%=Weighted percentages

Table A.8. Cross-tabulation of Past Year Heroin Use (PYHU^{+/-})* and age, sex, and race-ethnicity. NHANES data gathering cycles 2009-10.

	PYHU⁺ (n=20)		PYHU- (n=103)		PYHU status unknown (n=586)		EHU⁻ (n=3,345)	
	n	(%)	n	(%)	n	(%)	n	(%)
Age								
20-29 years	4	(42.75)	16	(18.34)	133	(25.50)	869	(25.43)
30-39 years	3	(13.29)	18	(18.03)	180	(28.47)	810	(23.30)
40-49 years	9	(32.71)	30	(27.04)	151	(25.72)	897	(26.47)
50-59 years	4	(11.25)	39	(36.58)	122	(20.31)	769	(24.80)
Sex								
Male	14	(76.21)	71	(66.32)	228	(40.69)	1635	(50.25)
Female	6	(23.79)	32	(33.68)	358	(59.31)	1710	(49.75)
Race-Ethnicity								
Mexican American	1	(4.78)	8	(5.79)	118	(10.38)	679	(9.93)
Other Hispanic	3	(10.58)	4	(2.41)	57	(5.39)	377	(5.91)
Non-Hispanic White	4	(40.88)	53	(69.42)	220	(54.38)	1527	(65.86)
Non-Hispanic Black	12	(43.77)	34	(17.82)	132	(15.97)	571	(11.26)
Other	0	--	4	(4.65)	59	(14.00)	191	(7.04)

*Past-Year Heroin Use= PYHU

Yes (+); No (-)

EHU= Ever Heroin Use

No (-)

n=Unweighted frequencies

%=Weighted percentages

Table A.9. Cross-tabulation of Past Year Heroin Use (PYHU^{+/−})* and age, sex, and race-ethnicity. NHANES data gathering cycles 2011-12.

	PYHU⁺ (n=15)		PYHU⁻ (n=50)		PYHU status unknown (n=581)		EHU⁻ (n=2,986)	
	n	(%)	n	(%)	n	(%)	n	(%)
Age								
20-29 years	2	(3.48)	3	(5.02)	114	(19.09)	835	(26.57)
30-39 years	3	(37.54)	14	(31.18)	171	(30.09)	736	(22.48)
40-49 years	6	(44.39)	12	(25.48)	152	(26.25)	705	(25.08)
50-59 years	4	(8.11)	21	(38.32)	144	(24.56)	710	(25.86)
Sex								
Male	13	(95.91)	28	(58.70)	231	(39.88)	1509	(49.92)
Female	2	(4.09)	22	(41.30)	350	(60.12)	1477	(50.08)
Race-Ethnicity								
Mexican American	1	(5.63)	5	(3.71)	75	(13.28)	323	(8.87)
Other Hispanic	0	(--)	2	(2.85)	64	(10.40)	278	(6.88)
Non-Hispanic White	7	(79.61)	27	(74.61)	130	(47.54)	1077	(64.63)
Non-Hispanic Black	6	(12.91)	14	(12.85)	148	(15.59)	775	(11.91)
Other	1	(1.86)	2	(1.90)	164	(13.19)	533	(7.71)

*Past-Year Heroin Use= PYHU

Yes (+); No (-)

EHU= Ever Heroin Use

No (-)

n=Unweighted frequencies

%=Weighted percentages

Table A.10. Cross-tabulation of Past Year Heroin Use (PYHU^{+/-})* and age, sex, and race-ethnicity. NHANES data gathering cycles 2013-14.

	PYHU⁺ (n=21)		PYHU⁻ (n=59)		PYHU status unknown (n=429)		EHU⁻ (n=3,294)	
	n	(%)	n	(%)	n	(%)	n	(%)
Age								
20-29 years	6	(34.91)	10	(23.56)	81	(21.20)	822	(26.05)
30-39 years	6	(40.33)	10	(22.51)	102	(24.31)	843	(23.78)
40-49 years	4	(12.68)	15	(17.43)	153	(34.55)	835	(24.66)
50-59 years	5	(12.08)	24	(36.51)	93	(19.94)	794	(25.51)
Sex								
Male	13	(58.03)	40	(71.65)	176	(41.26)	1592	(49.45)
Female	8	(41.97)	19	(28.35)	253	(58.74)	1702	(50.55)
Race-Ethnicity								
Mexican American	0	(--)	9	(9.59)	51	(10.98)	481	(10.86)
Other Hispanic	2	(4.13)	6	(8.83)	36	(7.23)	298	(6.30)
Non-Hispanic White	14	(80.30)	33	(66.27)	121	(48.05)	1357	(62.72)
Non-Hispanic Black	5	(15.37)	6	(5.82)	109	(18.52)	652	(11.73)
Other	0	(--)	5	(9.48)	112	(15.22)	506	(8.39)

*Past-Year Heroin Use= PYHU

Yes (+); No (-)

EHU= Ever Heroin Use

No (-)

n=Unweighted frequencies

%=Weighted percentages

Table A.11. Cross-tabulation of depression and age, sex, and race-ethnicity.
NHANES data gathering cycles 2005-06.

	Depression Yes (n=146)		Depression No (n=2,827)	
	n	(%)	n	(%)
Age				
20-29 years	33	(16.42)	880	(24.61)
30-39 years	24	(18.63)	712	(24.92)
40-49 years	40	(33.35)	700	(27.53)
50-59 years	49	(31.59)	535	(22.94)
Sex				
Male	52	(36.00)	1332	(50.09)
Female	94	(64.00)	1495	(49.91)
Race-Ethnicity				
Mexican American	28	(8.21)	629	(8.95)
Other Hispanic	8	(5.69)	104	(3.68)
Non-Hispanic White	67	(67.25)	1324	(70.19)
Non-Hispanic Black	37	(14.09)	640	(11.47)
Other	6	(4.77)	130	(5.70)

n=Unweighted frequencies

%=Weighted percentages

Table A.12. Cross-tabulation of depression and age, sex, and race-ethnicity.
NHANES data gathering cycles 2007-08.

	Depression Yes (n=265)		Depression No (n=3,053)	
	n	(%)	n	(%)
Age				
20-29 years	40	(16.17)	750	(25.71)
30-39 years	71	(25.93)	805	(23.89)
40-49 years	71	(30.84)	767	(26.55)
50-59 years	83	(27.06)	731	(23.85)
Sex				
Male	86	(31.93)	1549	(50.70)
Female	179	(68.07)	1504	(49.30)
Race-Ethnicity				
Mexican American	35	(7.10)	643	(10.04)
Other Hispanic	35	(7.10)	357	(5.28)
Non-Hispanic White	122	(63.85)	1300	(67.04)
Non-Hispanic Black	64	(17.33)	626	(11.67)
Other	9	(4.61)	127	(5.97)

n=Unweighted frequencies

%=Weighted percentages

Table A.13. Cross-tabulation of depression and age, sex, and race-ethnicity.
NHANES data gathering cycles 2009-10.

	Depression Yes (n=271)		Depression No (n=3,528)	
	n	(%)	n	(%)
Age				
20-29 years	61	(22.85)	837	(25.24)
30-39 years	51	(18.01)	793	(23.34)
40-49 years	75	(28.16)	873	(26.38)
50-59 years	84	(30.98)	755	(25.04)
Sex				
Male	96	(38.09)	1645	(51.48)
Female	175	(61.91)	1613	(48.52)
Race-Ethnicity				
Mexican American	48	(10.37)	655	(9.81)
Other Hispanic	32	(7.34)	359	(5.77)
Non-Hispanic White	118	(58.98)	1482	(65.80)
Non-Hispanic Black	64	(19.78)	568	(11.18)
Other	9	(3.53)	194	(7.44)

n=Unweighted frequencies

%=Weighted percentages

Table A.14. Cross-tabulation of depression and age, sex, and race-ethnicity.
NHANES data gathering cycles 2011-12.

	Depression Yes (n=206)		Depression No (n=2,888)	
	n	(%)	n	(%)
Age				
20-29 years	40	(20.86)	804	(26.29)
30-39 years	47	(19.53)	716	(22.95)
40-49 years	55	(29.97)	677	(24.91)
50-59 years	64	(29.65)	691	(25.85)
Sex				
Male	82	(40.69)	1492	(51.20)
Female	124	(59.31)	1396	(48.80)
Race-Ethnicity				
Mexican American	15	(6.26)	321	(9.12)
Other Hispanic	29	(11.46)	256	(6.50)
Non-Hispanic White	94	(62.97)	1024	(64.71)
Non-Hispanic Black	53	(13.35)	748	(11.81)
Other	15	(5.96)	539	(7.86)

n=Unweighted frequencies

%=Weighted percentages

Table A.15. Cross-tabulation of depression and age, sex, and race-ethnicity.
NHANES data gathering cycles 2013-14.

	Depression Yes (n=219)		Depression No (n=3,193)	
	n	(%)	n	(%)
Age				
20-29 years	39	(22.67)	803	(26.17)
30-39 years	48	(21.91)	817	(23.92)
40-49 years	58	(25.88)	812	(24.51)
50-59 years	74	(29.53)	761	(25.39)
Sex				
Male	64	(30.42)	1595	(51.01)
Female	155	(69.58)	1598	(48.99)
Race-Ethnicity				
Mexican American	25	(7.58)	467	(10.94)
Other Hispanic	23	(6.73)	287	(6.35)
Non-Hispanic White	108	(64.57)	1304	(62.55)
Non-Hispanic Black	41	(11.68)	632	(11.72)
Other	22	(9.45)	503	(8.44)

n=Unweighted frequencies

%=Weighted percentages

Table A.16. Odds Ratios (weighted) for each cut-off score for the National Health and Nutrition Examination Survey (NHANES).[¶]

Depression Cut-Point 2005-06, 2009-10, & 2013-14	Odds Ratio (OR)	Confidence Interval (CI)		Depression Cut-Point 2007-08 & 2011-12	Odds Ratio (OR)	Confidence Interval (CI)	
0/1	1.79	1.26	2.56	0/1	2.93	1.52	5.67
1/2	2.06	1.50	2.83	1/2	2.46	1.47	4.12
2/3	2.74	2.02	3.70	2/3	2.77	1.72	4.45
3/4	2.79	2.07	3.77	3/4	2.65	1.79	3.93
4/5	2.80	2.10	3.72	4/5	2.66	1.76	4.02
5/6	2.86	2.14	3.82	5/6	2.74	1.79	4.21
6/7	3.30	2.50	4.36	6/7	2.73	1.73	4.30
7/8	3.42	2.56	4.56	7/8	2.23	1.21	4.10
8/9	3.29	2.44	4.43	8/9	1.67	1.06	2.65
9/10	3.22	2.31	4.50	9/10	1.83	1.17	2.86
10/11	3.24	2.28	4.61	10/11	1.82	1.07	3.11
11/12	3.39	2.32	4.97	11/12	1.97	1.10	3.55
12/13	3.48	2.30	5.28	12/13	2.22	1.19	4.14
13/14	3.54	2.27	5.53	13/14	2.59	1.42	4.74
14/15	2.60	1.57	4.31	14/15	2.12	1.16	3.89
15/16	3.08	1.80	5.26	15/16	2.61	1.41	4.84
16/17	2.86	1.51	5.44	16/17	2.74	1.48	5.04
17/18	2.90	1.31	6.41	17/18	3.45	1.87	6.37
18/19	3.40	1.45	7.98	18/19	2.49	1.41	4.42

Table A.16. (cont'd)

19/20	4.18	1.50	11.65	19/20	1.58	0.76	3.27
20/21	4.97	1.73	14.31	20/21	1.99	0.97	4.09
21/22	2.39	0.76	7.50	21/22	3.11	1.46	6.63
22/23	2.26	0.60	8.59	22/23	2.38	0.74	7.67
23/24	2.08	0.39	11.01	23/24	2.31	0.58	9.20

[¶]Combined 2005-06, 2009-10, 2013-14 data gathering cycles analyzed separately from the combined 2007-08 and 2011-12 cycles addressing ROC curve cross-validation.

Figure A.1. Receiving Operating Characteristic (ROC) Curve 2: The National Health and Nutrition Examination Survey NHANES data gathering cycles 2007-2008 and 2011-2012 (weighted).

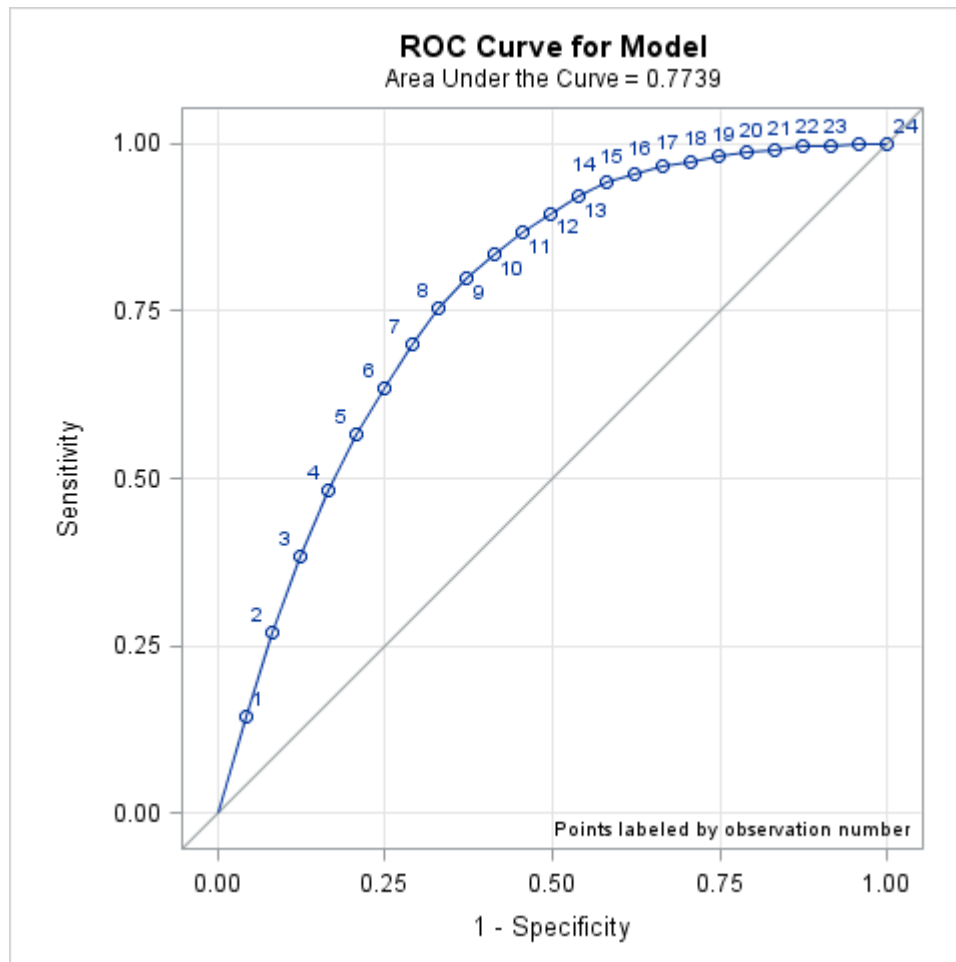
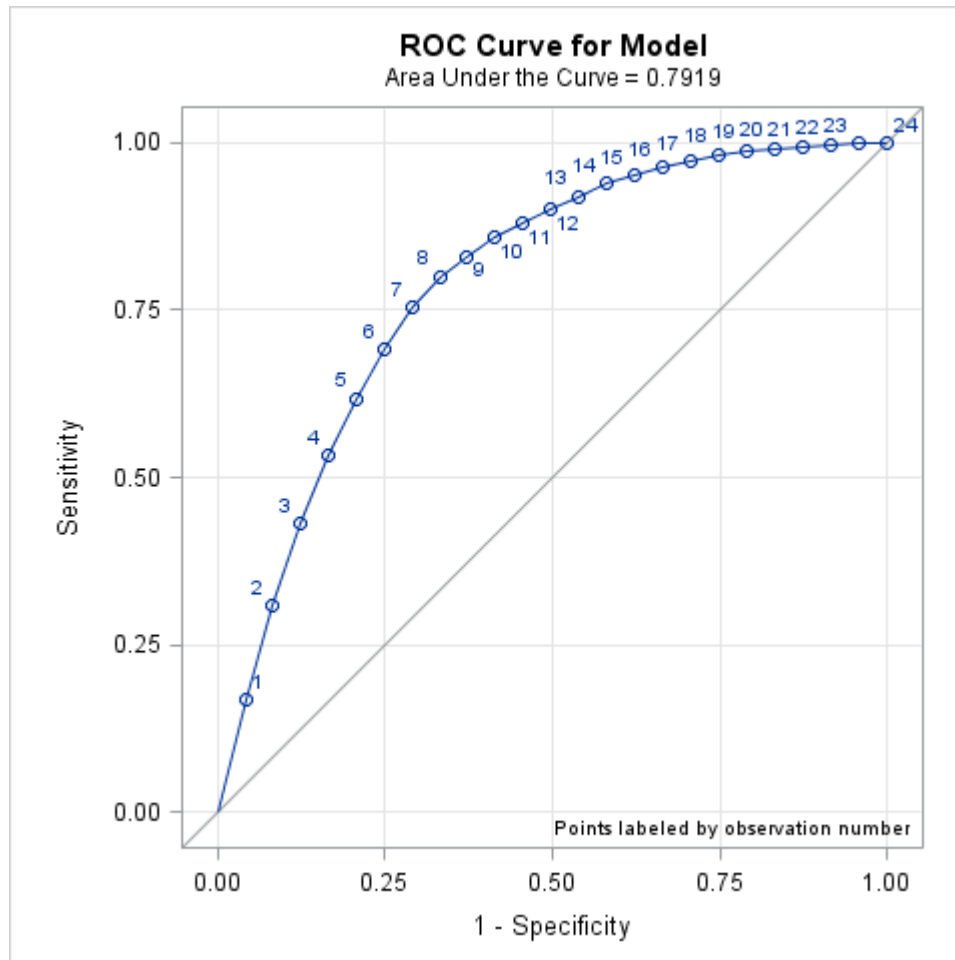


Figure A.2. Receiving Operating Characteristic (ROC) Curve 2: The National Health and Nutrition Examination Survey NHANES data gathering cycles 2007-2008 and 2011-2012 (weighted)



**MICHIGAN STATE
UNIVERSITY**

**Determined Not
"Human Subjects"**

4/10/17

James Anthony
Email: janthony@msu.edu

Re: Determination of Human Subject Research
IRB # 17-540 : "Exploring a possible causal linkage from heroin use to depressed mood"

Dear Dr. Anthony:

It has been determined that the activity described in your application to the IRB submitted 4/10/17 does not meet the definition of "human subjects" as defined by the U.S. Department of Health and Human Services (DHHS) regulations for the protection of human research subjects.

Human Subject

For DHHS, "human subject" means "a living individual about whom an investigator (whether professional or student) conducting research obtains: (1) Data through intervention or interaction with the individual, or (2) Identifiable private information." [45 CFR 46.102(f)].

After reviewing the information you have provided, it has been determined that:

- ☐ Living individuals are not involved
- ☐ The activity is not "about" the living individual
- ☒ Will not obtain data through interaction or intervention or private identifiable information

You will be collecting secondary, publically available survey data from the National Health and Nutritional Examination Survey website. You will not be obtaining data through any interventions or interactions with human subjects.

Hence, your activity does not involve human subjects.

Therefore, the federal regulations for the protection of human subjects would not apply to your project and you do not need MSU IRB approval to proceed. However, please note that while MSU IRB approval is not required, other federal, state, or local regulations or requirements or ethical or professional standards may still be applicable based on your activity.

If any of these circumstances change, please contact the IRB as your activity may involve human subject research and require IRB approval.

If you have any further questions, please contact the MSU IRB office at 517-355-2180.

Sincerely,



Bailey McMillan
IRB Administrator

cc: Alyssa Vanderziel, Qing Lu, David Barondess



Office of Regulatory
Affairs
Human Research
Protection Programs

Biomedical & Health
Institutional Review
Board (BIRB)

Community Research
Institutional Review
Board (CRIRB)

Social Science
Behavioral/Education
Institutional Review
Board (SIRB)

Olds Hall
408 West Circle Drive
Room 207
East Lansing, MI 48824
(517) 355-2180
Fax: (517) 432-4503
Email: irb@msu.edu

REFERENCES

REFERENCES

1. Substance Abuse and Mental Health Services Administration. Results from the 2012 National Survey on Drug Use and Health: Summary of National Findings. 2013;1–63.
2. Houry D. Fentanyl: The Next Wave of the Opioid Crisis. 2017.
3. Rudd RA, Aleshire J, Zibbell JE, Gladden RM. Increases in Drug and Opioid-Overdose Deaths- United States, 2000-2014. CDC. 2016.
4. Meier E a, Troost JP, Anthony JC. Extramedical use of prescription pain relievers by youth aged 12 to 21 years in the United States: national estimates by age and by year. Arch Pediatr Adolesc Med. 2012;166(9):803–7.
5. American Society of Addictive Medicine. Opioid addiction: 2016 facts & figures. 2016;(2014):10–2.
6. Drug Abuse Warning Network. National estimates of drug-related emergency department visits. Substance Abuse and Mental Health Services Administration. 2007.
7. OPIUM. What are Semi-Synthetic Opiates? 2017.
8. Lasagna L, von Felsinger JM, Beecher HK. Drug-Induced Mood Changes in Man. JAMA. 1955;157(12):1006–20.
9. National Institute on Drug Abuse. The Neurobiology of Drug Addiction. 2007.
10. National Institute on Drug Abuse. Heroin. NIH. 2014.
11. Anthony JC, Helzer JE. Epidemiology of Drug Dependence. Textb Psychiatr Epidemiol. 2002;479–561.
12. What is the scope of heroin use in the United States?. National Institute on Drug Abuse. 2018.
13. Maxwell JC. The Pain Reliever and Heroin Epidemic in the United States: Shifting Winds in the Perfect Storm. J Addict Dis. 2015;34(2–3):127–40.
14. Reynolds CR, Kamphaus RW. DSM-5 Diagnostic Criteria. 2013.
15. National Alliance on Mental Illness. Mental Health by the Numbers. 2017.
16. Hallfors DD, Waller MW, Bauer D, Ford CA, Halpern CT. Which comes first in adolescence - Sex and drugs or depression? Am J Prev Med. 2005;29(3):163–70.

17. Anxitey and Depression Association of America. Understand the Facts: Depression. 2016.
18. National Institute of Mental Health. Depression Basics. 2016.
19. Darke S, Mills K, Teesson M, Ross J, Williamson A, Havard A. Patterns of major depression and drug-related problems amongst heroin users across 36 months. *Psychiatry Res.* Elsevier Ireland Ltd; 2009;166(1):7–14.
20. Cornford CS, Umeh K, Manshani N. Heroin users’ experiences of depression : a qualitative study. *Fam Pract.* 2012;29:586–92.
21. Jones CM, Logan J, Gladden RM, Bohm MK. Vital Signs: Demographic and Substance Use Trends Among Heroin Users- United States, 2002 – 2013. *Morb Mortal Wkly Rep.* 2015;64(26):719–25.
22. Darke S, Ross J. Suicide among heroin users: Rates, risk factors and methods. *Addiction.* 2002;97(11):1383–94.
23. Havard A, Teesson M, Darke S, Ross J. Depression among heroin users: 12-Month outcomes from the Australian Treatment Outcome Study (ATOS). *J Subst Abuse Treat.* 2006;30(4):355–62.
24. Maremmani I, Pacini M, Pani PP, Perugi G, Deltito J, Akiskal H. The mental status of 1090 heroin addicts at entry into treatment: should depression be considered a “dual diagnosis”? *Ann Gen Psychiatry.* 2007;6(1):31.
25. Teesson M, Havard A, Fairbairn S, Ross J, Lynskey M, Darke S. Depression among entrants to treatment for heroin dependence in the Australian Treatment Outcome Study (ATOS): Prevalence, correlates and treatment seeking. *Drug Alcohol Depend.* 2005;78(3):309–15.
26. Kroenke K, Spitzer RL, Williams JBW. The PHQ-9. :606–13.
27. CDC. Data Documentation, Codebook, and Frequencies. https://wwwn.cdc.gov/Nchs/Nhanes/2009-2010/DPQ_F.htm.
28. Scott JD, Wang CC, Coppel E, Lau A, Veitengruber J, Roy-Byrne P. Diagnosis of depression in former injection drug users with chronic hepatitis C. *J Clin Gastroenterol.* 2011;45(5):462–7.
29. Manea L. Optimal cut-off score for diagnosing depression with the Patient Health Questionnaire (PHQ-9): a meta-analysis. *CMAJ.* 2012;184(3):191–5.
30. CDC. About the National Health and Nutrition Examination Survey. 2015.
31. Cornell University. What is a complex survey? 1996.