# THE ASSOCIATION BETWEEN INSULIN AND LIVER DISEASE

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## ABSTRACT

**Introduction:** Over the past three decades, the prevalence of diabetes has steadily increased. Additionally, diabetes has contributed to more diagnosed cases of liver disease (LD) suggesting that liver health is increasingly vulnerable to insulin levels. Several studies have found that endogenous insulin levels were important indicators in the development and progression of LD. However, to our knowledge, no studies have assessed the association of exogenous insulin intake and LD.

**Methods:** Using nationally representative data from the 2013-2014 (n=5769) and 2015-2016 (n=5719) National Health and Nutrition Examination Survey, this study assessed the association between exogenous insulin use and liver disease as well as duration of insulin use. Descriptive statistics were calculated. Sex and race were tested as potential effect modifiers of the relationship between taking insulin and insulin duration and LD and multivariable logistic regression models were run.

**Results:** Overall, participants were about 52% female in 2013-2014 and 2015-2016 with an average age of 47.5. Ever taking insulin was significantly positively associated with having a current liver condition in 2013-2014 (OR: 3.12; 95% CI: 1.06-9.23) and 2015-2016 (OR=4.16; 95% CI: 1.10-15.8). Respondents in cycle 2013-2014 taking insulin for five or more years had significantly greater odds of having a current liver condition (OR 3.26; 95% CI: 1.08-9.84) compared to taking insulin for zero years. Sex and race were effect modifiers for the duration of

insulin intake in cycle 2015-2016, however due to the small sample sizes stratification was not performed.

**Conclusion:** Taking insulin and duration of insulin intake is positively associated with participants having a current liver condition. This finding suggests that further increases in the prevalence of diabetes will impact the prevalence of liver conditions and ultimately increase related healthcare costs and decrease quality of life.

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# CHAPTER 1

# BACKGROUND

## Liver Disease

Liver disease (LD) is any condition that damages the liver (Liver Disease, 2018) whereas chronic liver disease (CLD) is the gradual destruction of the liver greater than six months that leads to cirrhosis and fibrosis of the liver and ultimately liver cancer (Chronic Liver Disease n.d.; Liver Cancer, 2018, Chronic liver disease (CLD) compensated, 2017)

The most commonly diagnosed chronic liver diseases are Non-alcoholic fatty liver disease (NAFLD), hepatitis C, alcoholic liver disease, hepatitis B, cirrhosis and fibrosis (Liver Disease, 2018; Diseases Of The Liver, n.d.& Liver Disease, n.d.), which are the focus of this research and described in subsequent sections. Infrequently diagnosed liver diseases include autoimmune hepatitis, primary biliary cholangitis, primary sclerosing cholangitis, hepatitis A, liver cancer, genetic liver diseases such as Alpha-1-antitrypsin deficiency, hemochromatosis and Wilson's disease and abnormal liver growths such as liver abscess and liver cysts (Liver Disease, 2018; Diseases Of The Liver, n.d.& Liver Disease, n.d.). For example, while Hepatitis A incidence has fluctuated, since 2014 it has remained at 0.4/100,000 people (U.S. 2015 Surveillance Data for Viral Hepatitis, n.d.).

Liver disease has been an increasing public health issue over the past decade and a major source of morbidity and mortality in the U.S. (Marcellin & Kutala, 2018). About 4.5 million Americans are affected by liver disease (FastStats-Chronic Liver Disease or Cirrhosis, n.d.). Further, the United States age-standardized death rate for liver disease in 2007 was 21.9/100,000 and increased to 24.9/100,000 in 2016 (Brunk, 2018).

**Incidence of Liver Disease**

Liver disease diagnoses are rising worldwide (Marcellin & Kutala, 2018). However, it is very difficult to determine the accurate incidence rates for liver disease because it has a long latent period between initial occurrence and diagnosis (Udompap, Kim & Kim, 2015). Approximately, 844 million people worldwide are living with liver disease (Marcellin & Kutala, 2018). In the United States, the percentage of adults diagnosed with liver disease has increased over the past few decades from 11.78% to 14.78% from 1988-2008 (Younossi et al, 2011).

Various diseases constitute liver disease. The most commonly diagnosed liver diseases are Non-alcoholic fatty liver disease (NAFLD), hepatitis B and C, alcoholic liver disease, cirrhosis and fibrosis (Liver Disease, 2018; Diseases Of The Liver, n.d.& Liver Disease, n.d.).

NAFLD is the most common chronic liver disease (Seitawan, 2016). Currently, NAFLD affects 100 million people in the U.S. (Non-Alcoholic Fatty Liver Disease, n.d.). NAFLD prevalence in the U.S. increased from 18% in 1988-

1991 to 31% in 2011-2012 (Ruhl and Everhart, 2014). NAFLD, a condition in which excess fat is stored in the liver, (Definition & Facts of NAFLD & NASH | NIDDK, 2016), is the most commonly studied LD (Younossi et al, 2018). However, there are two types of NAFLD – simple fatty liver or non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH). NAFL is a bland accumulation of fat in the liver without inflammation or fibrosis and it is a benign condition that does not typically progress to cause liver damage or complications and most people have this form (Definition & Facts of NAFLD & NASH | NIDDK, 2016, Alkhouri, Poordad, and Lawitz, 2018). NASH is liver inflammation caused by liver cell damage and a buildup of fat in the liver. It can cause severe complications such as cirrhosis and liver failure. Thus, NASH is the most important type of NAFLD as it increases the chance of liver morbidity and mortality (Definition & Facts of NAFLD & NASH | NIDDK, 2016). Approximately 20% of U.S. Americans have NASH (Definition & Facts of NAFLD & NASH | NIDDK, 2016, Alkhouri, Poordad, and Lawitz, 2018).

Historically, the most common type of liver disease was hepatitis C (Live Disease, 2018); however, it is now the second most prevalent liver disease. Hepatitis C is most prevalent with 148,932/100,000 newly diagnosed cases in 2016 compared to 14,847/100,000 for hepatitis B and 2,007/100,000 for hepatitis A (Commentary U.S. 2016 Surveillance Data for Viral Hepatitis Statistics & Surveillance Division of Viral Hepatitis CDC, n.d.). Approximately 2.4 million people in the U.S. were infected with hepatitis C compared to 850,000 infected with hepatitis B in 2016 (Hepatitis C Questions and Answers for the Public, n.d.)

Overall, nearly 5 million Americans live with hepatitis B or C in the U.S. (Liver Disease Statistics, 2018).

Alcoholic-related liver disease remains one of the most common forms of liver cirrhosis after hepatitis C (Alcohol Related Liver Disease and Alcohol Damage, n.d.). Approximately 67.3% of the U.S. drinks alcohol (Vozzo, Welch, Romero-Marrero, Fairbanks, 2018) and about 35% will develop alcoholic hepatitis and 10%-20% will develop liver cirrhosis (Alcohol Related Liver Disease and Alcohol Damage, n.d.). Further, about 20%-25% of liver cirrhosis cases are from alcohol-related liver disease (Liver Disease Statistics, 2018) and is one of the most severe type of liver disease. Liver cirrhosis is one of the end stages of liver disease and effects 1 in 400 adults in the U.S. (Definition and Facts about Cirrhosis, 2018). However, the number of people living with cirrhosis in the U.S. is said to be much higher because many people go undiagnosed (Definition and Facts about Cirrhosis, 2018).

**Mortality of Liver Disease**

Liver disease and cirrhosis are the 12$^{th}$ leading cause of death in the U.S. (Chronic Liver Disease or Cirrhosis, n.d.) The number of deaths and life years lost due to liver disease has also increased since 2007 (GBD Mortality and Causes of Death Collaborators, 2013, Kim et al., 2018). For example, liver disease is responsible for over 2 million deaths worldwide each year (Marcellin & Kutala, 2018). In addition, the CDC reported that chronic liver disease or cirrhosis mortality in the U.S. was 12.5/100,00 persons in 2016 (FastStatsChronic Liver Disease or Cirrhosis, n.d.). However, a study by Mayo clinic researchers

calculated that liver related deaths in the U.S. were underestimated and annual liver disease deaths are estimated to be an additional >2 fold or 11.7/100,000 to 25.7 /100,000 more deaths per year (Asrani, Larson, Yawn, Therneau & Kim, 2013). The leading cause of liver mortality ranks from NAFLD, viral hepatitis, alcohol-related liver disease and cirrhosis.

NAFLD has contributed to increased rates of liver mortality in the U.S. (Kim et al., 2018). In the U.S., 5 and 8-year all-cause mortality were significantly higher in patients with NAFLD than those without NAFLD (Le et al., 2017). Additionally, NAFLD patients with advanced liver fibrosis had significantly higher 5 and 8-year all-cause mortality compared to NAFLD patients with low fibrosis (Le et al., 2017, Kim, Kim, Kim and Therneau, 2013). Younossi et al meta-analyses on the global NAFLD prevalence and risk factors from 1989-2015 calculated pooled liver-specific and overall mortality estimates among NAFLD cohorts to be 0.77/1,000 person and 15.4/1,000 person respectively (Younossi et al., 2016).

Approximately 2/100,000 people in the U.S. die from viral hepatitis each year (Faststats Viral Hepatitis, n.d.). Hepatitis C mortality rate in 2016 was 4.5/100,00 compared to 0.45/100,00 for Hepatitis B and 0.02/100,000 for hepatitis A. More people die from hepatitis B and C than viral hepatitis A (Faststats Viral Hepatitis, n.d.). The mortality rate for alcohol-related liver disease in the U.S. is estimated to be 88,000 deaths annually (Alcohol Facts and Statistics, n.d.). While, liver cirrhosis and fibrosis mortality rates are unknown but

are believed to have increased due to liver diseases (Hayes et al., 2015, Vilar-Gomez, et al., 2018)

**Cost & Burden of Liver Disease**

Liver disease is also associated with substantial financial burden in care. The overall cost of chronic liver disease in 2004 excluding viral hepatitis C was $2.5 billion (Everhart, 2008) and the cumulative inflation rate from 2004- 2014 of 1.39% would make it $18.2 billion without accounting for new treatment options (Stepanova et al, 2017). In a recent study researchers found that NAFLD alone costs the U.S. healthcare system $32 billion annually (Intermountain Medical Center, 2018) while the increasing burden of cirrhosis from alcohol-related liver disease, hepatitis B and C costs range from $14 million to $2 billion (Neff, Duncan, Schiff, 2011). Overall, liver disease patients had more healthcare usage and healthcare expenses compared to those without liver disease ($19,390/year versus $5,567/year) (Stepanova et al, 2017 & Intermountain Medical Center, 2018). Arsani et al, compared CLD-related hospitalizations with other chronic diseases; congestive heart failure (CHF) and chronic obstructive pulmonary disease (COPD), and found that from 2004-2013 CLD-related hospitalizations increased 92% (1,295/100,000 to 2,490/100,000) compared to 6.7% CHF (3,843/100,000 to 4,103/100,000) and 48.8% COPD (1,775/100,000 to 2,642/100,000) (Arsani et al, 2018). These numbers are expected to increase with the increasing numbers of people diagnosed with viral hepatitis B and C, NAFLD, alcohol-related liver disease, cirrhosis and liver cancer (Menzin, White,

Nichols, & Deniz, 2011, Neff, Duncan, Schiff, 2011, Intermountain Medical Center, 2018 & Gondek et al., 2008).

The most recent information on liver diseases potential societal impact was from a cross-sectional analysis study from the Medical Expenditure Panel Survey (MEPS). Stepanova et al found that CLD patients were less likely to be employed compared to those without CLD (44.7% versus 69.6%), not working due to illness or disability compared to those without CLD (30.5% versus 6.6%), and had higher days missed due to disability (10.2 days versus 3.4 days) compared to those without CLD. Additionally, CLD patient had more comorbidities, worse self-reported general and mental health status (reporting lower health-related quality of life (HRQL) scores) and reported more health-related limitations in their daily activities compared to those without CLD (Stepanova et al, 2017).

**Risk Factors for Liver Disease**

There are a few risk factors most frequently associated with various liver diseases. The major risk factors include 1. obesity/overweight, 2. diabetes, 3. alcohol abuse, 4. insulin use, and 5. other less frequent risk factors (i.e., needle use, sexual intercourse and genetics).

*Obesity, BMI & Liver Disease:*

Excessive BMI from obesity and visceral obesity are risk factors for NAFLD (Chalasani, 2012). Patients with a BMI range of 25-29.9 (pre-obesity) had an increased risk for obesity related conditions and BMI ranges of 30 or

higher had a higher risk of obesity related conditions (Body Mass Index-BI, 2018). About 13% of the world population is obese (Younossi, 2018). The U.S. was estimated to have the highest number of obese people (109,342,839) compared to China (97,256,700) and India (65,619,826) (World Rankings-Obesity Rate by Country, 2017). In the meta-analysis by Younossi et al, the pooled overall global obesity prevalence estimates for NAFLD was 51.34% (95% CI 41.38-61.20) (Younossi et al., 2016).

Researchers project an increase in the prevalence of NAFLD in next decade due to the increasing obesity epidemic in the United States (Kim et al., 2018). A meta-analysis of 8,515,431 individuals on the global NAFLD prevalence and risk factors from 1989-2015, estimated the global prevalence of NAFLD to be 25.24% which is also expected to increase as the global epidemic of obesity and metabolic conditions (i.e. diabetes) increase (Younossi, 2016). Increasing rates of diabetes have contributed to more diagnosed cases of NAFLD (Younossi, 2018) and liver disease progression and mortality (Hamed et al., 2018, Gangopadhay & Singh, 2017).

*Diabetes, Insulin, and Liver Disease:*

Although, there are studies assessing the association between insulin levels and liver disease, these studies have only looked at endogenous insulin levels and not exogenous insulin administered by diabetic patients. Currently, there are no studies available assessing the extensive association between insulin medication and liver disease. However, a review by Gangopadhay & Singh assessing glycemic management of various antidiabetic medications on

liver dysfunction found a case report studying the efficacy of insulin (detemir) in 2 patients with severe NAFLD and hypertriglyceridemia. Insulin (detemir) was found to be less efficacious in achieving glycemic control in both patients. High dosages of insulin (detemir) were required and weight gain was problematic (Whyte, Quaglia and Hopkins, 2015).

In another review by Tacelli et al on the efficacy and safety of antidiabetic drugs in patients with NAFLD, they found no published data on insulin's effect on NAFLD but found that insulin use increased the risk of hepatocellular carcinoma in several case-control and longitudinal studies for patients with cirrhosis (Nkontchou et al. 2011, Hassan et al., 2010). The review also noted that insulin was not an ideal medication of choice because it increased body weight in patients who took it (Pontiroli, Miele and Morabito, 2011). Alongside that information one can infer that this may increase the risk of developing NAFLD because increased body weight is a risk factor for liver disease though, no data is available to make that conclusion.

Diabetes is estimated to be the most common cause of liver disease in the U.S. (Gangopadhay & Singh, 2017). The pooled overall global diabetes prevalence estimate for NAFLD was 22.51% (95% CI 17.92-27.89) (Younossi et al., 2016). Approximately, 422 million people worldwide were living with diabetes in 2016 (Liu et al). Current U.S. data from the National Diabetes Statistics Report in 2017 estimated that 30.3 million Americans were living with diabetes in 2017 (National Diabetes Statistics Report, 2017, Data & Statistics Diabetes, 2018) and 1.5 million Americans will be diagnosed with diabetes each year (Fast Facts,

2017). In 2017, the total estimated cost of diagnosed diabetes was $327 billion, including $237 billion in direct medical cost and $90 billion in reduced productivity (Economic Costs of Diabetes in the U.S., 2017).

Diabetes is a common cause of liver disease in the U.S. particularly type 2 (Gangopadhyay & Singh, 2017). For example, hepatitis C is associated with a higher prevalence of type 2 diabetes (Hum & Jou, 2018). In a study by Mehta et al using the National Health and Nutrition Survey (NHANES) authors found that between 1988-1994 adults aged 40 and over with hepatitis C were four times more likely to have diabetes at the same time compared to those without hepatitis C infection (Mehta et al, 2000). Diabetic patients are at higher risk for worse outcomes with their hepatitis C infection (Hammerstad et al, 2015). Diabetic patients with alcoholic liver disease or NAFLD from 2004-2011 had an increased risk for developing cirrhosis and hepatocellular carcinoma compared to non-diabetics (Raff et al, 2015).

Controlling diabetes mellitus has become a public health concern (Liu et al, 2018). When healthy lifestyle changes cannot control blood glucose levels antidiabetic medications are prescribed. In 2017, about 17.2% of adults diagnosed with diabetes took insulin only and 15.1% took both insulin and oral medication (Fast Facts, 2017). Despite antidiabetic medications important role in managing diabetes, several studies have found that glucose-lowering medications maybe associated with risks for cancer and liver disease (Liu et al., 2018, Ruiter et al., 2012, Tuccori et al., 2016, Phillips, 2018, Gangopadhay & Singh, 2017).

Insulin's biological role is to help decrease concentrations of glucose in the blood by stimulating the liver to store it in the form of glycogen. Additionally, circulating insulin is also metabolized primarily by the liver (Physiological Effects of Insulin, n.d.). For both type 1 and type 2 diabetes, insulin therapy is a commonly used type of glucose-lowering medication that is administered as the first and or second line of defense. However, excess circulation of insulin in the blood known as hyperinsulinemia, has been associated with increased prevalence of chronic liver disease in both diabetic and non-diabetic patients (Kawaguchi et al., 2011, Rhee, Lee, Cho, Kim and Sung, 2011, Bril et al., 2014, Donadon, Balbi and Zanette, 2009).

In a most recent study by Bril et al, 190 patients (32 without nonalcoholic fatty liver disease (NAFLD), 36 with simple steatosis (SS), and 122 with biopsy-proven NASH) were enrolled in a study to analyze the association between insulin clearance and hyperinsulinemia with chronic liver disease. The researchers found that NASH and SS patients had similar hepatic sensitivity, but NASH patients had more severe adipose tissue insulin resistance and worse hyperinsulinemia. Both NASH and SS patients had a ~30% reduction ($p<0.01$) in hepatic insulin clearance compared to patients without NAFLD. Biopsy's of the liver were also taken to asses liver stages and they found worse histological inflammation and ballooning (not steatosis or fibrosis) were associated with gradual reduction in whole-body insulin clearance ($p<0.001$) (Bril et al, 2014). Insulin levels are an important indicator in liver disease development and progression.

*Alcohol Abuse and Liver Disease:*

The liver is the main organ that metabolizes alcohol (Bruha, Dvorak, & Petrtyl, 2012). Heavy drinking is associated with severe liver damage and disease (Alcohol's Effects on the Body, n.d.) and is one of the primary causes of chronic liver disease (Liver Disease Statistics, n.d.). In the U.S., approximately, 15.1 million adults age 18 years and older and 623,000 adolescents 12-17 years had alcohol use disorder (AUD). Alcohol-related liver disease in 20009 was the cause of 1 in 3 liver transplants in the U.S. (Alcohol Facts and Statistics, n.d.).

Excessive consumption of alcohol can lead to fatty liver disease, alcoholic hepatitis and alcohol-related liver cirrhosis (Liver Disease Statistics, n.d.). Severity and prognosis of alcohol-related liver disease depends on the amount, pattern, duration of alcohol use, nutritional status, diet, genetics, and liver inflammation (Bruha, Dvorak, & Petrtyl, 2012). Fatty liver is the earliest stage of alcohol-related liver disease and the most common. Following that would be alcohol hepatitis which destroys up to 35% of living liver and then alcohol-related liver cirrhosis, the most serious type of alcohol-related liver disease that results when healthy liver cell tissue is replaced by non-living scar tissue (Liver Disease Statistics, n.d.).

*Other Risk Factors*

Contact with infected persons who have viral hepatitis through sexual intercourse, injection drug, blood transfusion, organ transplant, kidney dialysis, persons with HIV,  worked or lived in prisons, have tattoos or body piercings and

have hemophilia and received clotting factor before 1987 (Hepatitis Viral, n.d.). Additionally, person infected with viral hepatitis can also pass on through birth (Hepatitis Viral, n.d.). In addition, age, congenital, hereditary and autoimmune diseases are risk factors for liver disease (Alpha-1-antitrypsin deficiency - Symptoms, Causes, and Treatment. n.d., Hemochromatosis - Symptoms, Causes, and Treatment. n.d., Wilson's disease - Symptoms, Causes, and Treatment. n.d., Primary Sclerosing Cholangitis - Symptoms, Causes, and Treatment, n.d & (Hepatitis A - Symptoms, Causes, and Treatment. n.d).

**Study Aim and Objective**

This study aims to use nationally representative data to assess the association between insulin use and liver disease. It will also investigate the association between duration of insulin use and other demographic information with liver diseases. This cross-sectional analysis will help add to the body of literature about insulin use and provide possible insight about its association with liver diseases.

# CHAPTER 2

# METHODS

## Study Design

This study is a secondary data analysis of cross-sectional data obtained from the NHANES. NHANES is a complex multistage, probability survey program of the noninstitutionalized children and adults in the United States (Sample Design, 2013). NHANES tracks health and nutritional status overtime using interviews, physical examination and laboratory exams. NHANES is managed by the National Center for Health Statistics (NCHS) which is part of the Center for Disease Control and Prevention (CDC) (National Center for Health Statistics, 2017). NHANES data has been annually collected since 1999 (NHANES Web Tutorial Frequently Asked Questions (FAQs), 2014). Annually, approximately 5,000 people from 15 different counties selected from a sampling frame which included all 50 states and the District of Columbia (National Health and Nutrition Examination Survey: Plan and Operations, 1999–2010, 2013).

## Setting

For this study, NHANES data from 2013-2014 and 2015-2016 were collected in continuous ongoing survey cycle (National Health and Nutrition Examination Survey: Sample Design, 2011–2014, 2014). For each of the 50 states and the District of Columbia, local government and health officials are notified about the survey and selected households receive mailed letters from NCHS introducing the survey (National Center for Health Statistics, 2017).

NHANES data collection included a screener, household interviewer and examination. During home visits, a screener would administer a short interview to determine whether any persons in the home were eligible. Once considered eligible, a trained interviewer would collect person-level demographic, health, nutrition information and information about the household. The examination consists of physical measurements, dental examination and collection of blood and urine for laboratory testing. Interviews were administered using the Computer-Assisted Personal Interview (CAPI) system (National Health and Nutrition Examination Survey: Sample Design, 2011–2014, 2014). The average interview time per person was approximately 6.7 hours (National Health and Nutrition Examination Survey: Interviewer Procedure Manual, 2013).

**Participants**

NHANES included people of all ages and races (National Center for Health Statistics, 2017). Overall, a total of 14,332 and 15,327 individuals were selected in cycle 2013-2014 and 2015-2016 respectively. From the selected participants,10,175 and 9,771 completed interviews for cycles 2013-2014 and 2015-2016 respectively (NHANES 2013-2014 Overview, n.d., & NHANES 2015-2016 Overview, n.d.). For this study, participants were included if they answered questions from three specific NHANES datasets (i.e., medical conditions, diabetes and demographics). Overall, 9,770 and 9,575 participants were respectively included from 2013-2014 and 2015-2016. People were excluded if they were in supervised care or custody of an institutional setting, active-duty military personnel or an active-duty family member living overseas or a U.S.

citizen residing outside the 50 states or the District of Columbia (National Health and Nutrition Examination Survey: Plan and Operations, 1999–2010, 2013.).

The target population from 2011-2014 NHANES was oversampled for Hispanics, non-Hispanic Blacks, non-Hispanic Asians, non-Hispanic whites and other people who fell below 130% of the poverty level guidelines from the Department of Health and Human Services, and non-Hispanic whites and other people who are 80 years and over (NHANES 2013-2014 Overview, n.d.). For cycle 2015-2016 the target population was oversampled for Hispanics, non-Hispanic Blacks, non-Hispanic Asian, non-Hispanic whites and other people who fell below 185% of the poverty level and non-Hispanic whites and other people who are 80 years and over (NHANES 2015-2016 Overview, n.d.). Sample selection for both cycles was done in four stages that include selection of primary sampling units (PSUs), selection of segments within primary sampling units, selection of specific households within segments and individuals selected at random within each household given the previously mentioned age-sex-race strata (NHANES 2013-2014 Overview, n.d., & NHANES 2015-2016 Overview, n.d.).

Participants included in this study were individuals who were ≥20 years and either non-Hispanic White, non-Hispanic Black, or Mexican American/other Hispanic. These criteria were used because only respondents who were ≥20 years were asked whether they had a current liver condition and sample sizes for other race/ethnicity categories were very small. Approximately 4001 and 3856

respondents were excluded from the study in cycles 2013-2014 and 2015-2016 respectively because they did not meet the age requirement.

## Variables

Individual data regarding participant health history and background came from three NHANES datasets: Medical conditions, Diabetes, and Demographics. The variables included in this study are described below.

### *Main Outcome – Liver Condition*

The main outcome variable was whether a respondent had a current liver condition. Respondents were first asked, “Has a doctor or health professional ever told you that you had a liver condition?” and those who indicated they had, were subsequently asked, “Do you still have a liver condition?” Response categories were: “Yes”, “No”, “Refused” and “Don’t Know”.

### *Main Independent Variables –Insulin Use and Duration of Insulin Use*

To determine whether respondents were taking insulin and the duration they were taking insulin diabetic status needed to be established. Respondents were asked, “Have you ever been told by a doctor or health professional that you have diabetes or sugar diabetes?” and those who indicated they had were subsequently asked “Are you taking insulin now?” with response categories: Yes, No, Refused or Don’t Know”. Respondents who answered “Yes” to currently taking insulin were subsequently asked the following question, “How long have you been taking insulin?” Respondents were able to provide their answer in either “Months or Years”.

*Demographics and Covariates*

Demographics such as age, gender, race, marital status, education, and annual household income were assessed. Participants were asked their age in years. Gender was either male or female. Participants were able to self-identify with multiple races during the interview process from six categories; Mexican American, Other Hispanics, Non-Hispanic Whites, Non-Hispanic Blacks, Non-Hispanic Asians and Other race included Multi-racial. Marital status had six categories which were married, widowed, divorced, separated, never married and living with partner. Education level had five categories, which were less than 9th grade, 9-11th grade (includes 12th grade with no diploma), high school graduate/GED or equivalent, some college or AA degree, and college graduate or above. Annual household income had 14 categories for respondents to choose from, which were ”$ 0 to $ 4,999”, ”$ 5,000 to $ 9,999”, ”$10,000 to $14,999”, ”$15,000 to $19,999”, ”$20,000 to $24,999”, ”$25,000 to $34,999”, ”$35,000 to $44,999”, ”$45,000 to $54,999”, ”$55,000 to $64,999”, ”$65,000 to $74,999”, ”$20,000 and Over”, ”Under $20,000”, ”$75,000 to $99,999” and”$100,000 and over”

**Data sources/measurement and Coding**

All data were self-reported and collected in participant homes by trained interviewers. Data coding and recodes are described below.

*Main Outcome – Liver Condition*

The main outcome question was created in a two-step process. First, the question about ever having a liver condition was used to create a dichotomous variable "*Everlivercond*" where Everlivercond= 0 was "No" never been told about a liver condition and Everlivercond =1 for "Yes" have been told they had a liver condition. Second, the variable for current liver condition was created by Everlivercond as a dichotomous variable where Currentlivercond=0 indicated people did not have a current liver condition and Currentlivercond=1 indicated they did have a current liver condition.

*Main Independent Variables – Insulin Use and Duration of Insulin Use*

The main independent variables were created in a three-step process. First, the question about diabetic status was used to create a dichotomous variable where Diabetic=0 indicated the respondents was not diabetic and *Diabetic=1* indicated they were diabetic. Second, the dichotomous variable for taking insulin was created where those who were not diabetic were coded as Takinginsulin=0 as well as those who were diabetic and said they were not taking insulin. Diabetics who indicated they were taking insulin were coded as Takinginsulin=1. Third, the categorical variable for how long each respondent was taking insulin was created where those who were taking insulin for zero years were coded as Year_Cat=0, those taking insulin for one to four years were coded as Year_Cat=1 and those taking insulin for five or more years were coded as Year_Cat=2. Duration of insulin use was measured this way because measuring duration over longer periods of time (i.e. less than ten years or greater

than ten years) decreased the sample size of the categories and statistical analysis could not properly be performed.

*Demographics and Covariates*

This study only included respondents who identified as either white, Black/African American and Mexican/other Hispanics due to the sample size of various racial categories. The variable race was used to create a categorical variable where Race_R=1 was “Non-Hispanic white” Race_R=2 for “Non-Hispanic Black” and Race_R=3 for “Mexican American/other Hispanics”. Respondents who self-identified as Mexican American were coded as Mexican-American regardless of their other race-ethnicity identities.

The marital status variable was used to create a 4-level categorical variable where maritalstatus_R=1 was “married or living with partner”, maritalstatus_R=2 was “widowed”, Maritalstatus_R=3 was “divorced or separated” and Maritalstatus_R=4 was “never married”. Education level was recoded as a 4-level categorical variable where Education_R=1 combined categories “less than $9^{th}$ grade” and“$9\text{-}11^{th}$ grade including $12^{th}$ grade with no diploma”, Education_R=2 was “high school graduate/GED or equivalent”, Education_R=3 was “some college or AA degree”, and Education_R=4 was “college graduate or above”. In addition, the annual household income variable was recoded as a dichotomous variable where AnnualHHincome=1 was less than $20,000 and AnnualHHincome=2 was “equal to or greater than $20,000. The gender variable was used to create a dichotomous variable where Sex=0 for “male” and Sex=1 for ‘female”.

The age that respondents were first told they had diabetes was created in a two-step process. First, the question about age first told you had a diabetes was used to create a continuous variable “AgeFTD”. Second, the continuous variable for the number of years respondents were diabetic was created by “AgeFTD” where if AgeFTD=0 then Diab_yrs=0 and if AgeFTD>=1 then Diab_yrs= Age – AgeFTD.

Additionally, respondents were asked to provide the age they were first told they had a liver condition regardless of current status. Respondents’ age first told had a liver condition was created in a two-step process. First, the question about age first told you had a liver condition was used to create a continuous variable AgeFTHLC. Second, the continuous variable for the number of years respondents had a liver condition was created by AgeFTHLC where AgeFTHLC=0 then Liver_yrs=0 and if AgeFTHLC>=1 then Liver_yrs= Age – AgeFTHLC.

**Bias**

Using nationally represented data ensures that all people closely match the characteristics of the population being studied so that groups are not over or under-represented. This generally enables repeatability and increases reliability (Aschengrau & Seage, 2020). Efforts to address bias included accounting for the probabilistic sampling in the analyses and recoding variables to maximize the respondents included in the analysis.

## Study Size

The number of unique respondents with data in all three datasets (i.e., Medical conditions, Diabetes, and Demographics) were 9,770 respondents in cycle 2013-2014 and 9,575 in cycle 2015-2016. Given eligibility criteria, the total analytic sample size for 2013-2014 was 5769 (of 9770 respondents) and for 2015-2016 was 5719 (of 9575 respondents).

## Statistical Methods

All statistical analyses were performed using SAS 9.4. (SAS Institute, Cary NC). Testing for frequencies and means were performed using SAS PROCEDURES SurveyFreq and SurveyMeans. Additionally, testing for effect modification, assessing for confounding and conducting multivariable logistic regression was performed using PROCEDURE SurveyLogistic for complex, multistage sampling design. In both cycles, variables sex and race were tested as important effect modifiers for interactions between each potential effect modifier and each exposure variable *Currentlivercond* in the model statement. Significant interactions at $p<0.05$ indicated effect modification. Sample weights were used to control for oversampling, strata was used for stratified sampling and cluster was used for primary units.

Multicollinearity was assessed using SAS PROCEDURES CORR to estimate the correlation between annual household income and ratio of family income to poverty. . In cycle 2013-2014 and 2015-2016 variables annual household income and ratio of family income to poverty were highly correlated at

$R^2$=0.549 and $R^2$=0.547. Thus, because family income to poverty ratio had more missing data in each cycle, annual household income was used in all analyses instead of ratio of family income to poverty.

To assess for confounding the 10% change-in-estimate rule (Aschengrau & Seage, 2020) was used. The two final multivariable regression models for cycle 2013-2014 were 1) the number of years taking insulin with having a current liver condition while controlling for confounders of race, marital status and age and 2) taking insulin with having a current liver condition while controlling for confounders of race, marital status and age. For cycle 2015-2016, the two final multivariable regression models were 1) the number of years taking insulin with having a current liver condition while controlling for confounders of race and age and 2) taking insulin with having a current liver condition while controlling for confounders of race, annual household income and age.

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# CHAPTER 3

# RESULTS

## Respondent Characteristics

Overall, participants were about 52% female in 2013-2014 and 2015-2016 (see Tables 1 & 2). The mean age was 47.5 in which 71.6% and 70.6% were non-Hispanic Whites in 2013-2014 and 2015-2016 respectively. In total, 62.8% of the sample had some college or graduate level degree in 2013-2014 whereas in 2015-2016 65.4% had some college or graduate level degree. About 62% and 64% of the sample population was married in 2013-2014 and 2015-2016 respectively. In addition, greater than 85% of the sample had an annual household income greater than or equal to $20,000.

The percentage of female and male respondents in cycle 2013-2014 with a current liver condition was 1.10% and 0.922% respectively. In 2015-2016, the percentage of female and male respondents with a current liver condition were 1.09% and 1.07% respectively. Respondents' mean age with a current liver condition was 54.1 (2013-2014) and 53.1 (2015-2016) whereas the mean age for respondents without a current liver condition was 47.3 (2-13-2014) and 47.8 (2015-2016) (see Tables 1 & 2).

Respondents in 2013-2014 with a current liver condition compared to those without a liver condition were 1.49% and 70.1% non-Hispanic White, 0.131% and 12.3% non-Hispanic Black and 0.343% and 15.6% Mexican American/Other Hispanic. For respondents in 2015-2016 with a current liver

condition compared to those without a liver condition were 1.58% and 69% non-Hispanic White, 0.114%and 12.5% non-Hispanic Black and 0.354% and 16.5% Mexican American/Other Hispanic (Tables 1 and 2).

In total, 1.21% of the sample with a current liver condition had some college or graduate level degree compared to 61.6% of respondents without a current liver condition in 2013-2014. In 2015-2016, a total of 1.35% of the sample with a current liver condition had some college or graduate level degree compared to 63.5% of respondents without a current liver condition. Approximately, 1% and 61.2% of sample participants with a current liver condition and without a current liver condition respectively, were married in 2013-2014 whereas in 2015-2016 1.34% and 62.6% of participants with a current liver condition and without a current liver condition respectively, were married.

About 1.6% and 84% of participants with and without a current liver condition respectively had an annual income of greater than or equal to $20,000 in 2013-2014 whereas about 0.5% and 14% had an annual income of less than $20,000. Additionally, 1.5% and 86% of participants in 2015-2016 with and without a liver condition respectively, had an annual income of greater than or equal to $20,000 whereas about 0.6% and 12% had an annual income of less than $20,000.

In cycle 2013-2014, approximately 1.5% of participants with a current liver condition and 89% without a liver condition were not diabetic whereas 0.6% and 9% with and without a liver condition respectively were diabetic. Approximately,

1.5% and 88% of participants in cycle 2015-2016 with and without a liver condition respectively were not diabetic whereas 0.7% and 10% were diabetic.

About 1.8% and 95% of sample participants with and without a current liver condition respectively were not taking insulin in 2013-2014 whereas 0.18% and 2% were taking insulin. In 2015-2016, 1.9% and 95% of sample participants with and without a current liver condition respectively were not taking insulin whereas 0.25% and 3% were taking insulin.

## Main Logistic Regression Modeling Results

*Taking Insulin with a Current Liver Condition*

Cycle 2013-2014

The multivariable logistic regression modeling results for cycle 2013-2014 are in Table 3. After adjustment for race, marital status and age (regression: current liver condition = taking insulin + marital status + race + age), respondents taking insulin had 3.12 (95% CI 1.06-9.23) times the odds of having a current liver condition compared to respondents who were not taking insulin. Also, with each one-unit increase in age the odds of having a current liver condition increased by 1.02 (95% CI 1.01-1.03). Further, divorced/separated respondents had 2.43 (95% CI 1.21-4.86) times the odds of having a current liver condition compared to respondents who were married. Black respondents had lower odds (OR=0.464; 95% CI 0.226-0.954) of having a liver condition compared to whites. (Table 3).

Cycle 2015-2016

The multivariable logistic regression modeling results for cycle 2015-2016, are in Table 3. After adjusting for race, annual household income and age (regression: current liver condition = taking insulin + annual household income + race +age) respondents taking insulin had 4.16 (95% CI 1.20-15.8*)* times the odds of having a current liver condition compared to respondents who were not taking insulin. Additionally, the annual household income of less than $20,000 was 2.49 (95% CI 1.38-4.51) times the odds of having a current liver condition compared to respondents not taking insulin who made greater than $20,000 Black respondents again had lower odds (OR=0.245; 95% CI 0.098-0.614) of having a liver condition compared to whites. Age was not statistically associated with liver condition (Table 3).

*Duration of Insulin Intake and Current Liver Condition*

Cycle 2013-2014

The multivariable logistic regression modeling results for cycle 2013-2014 are in Table 4. (regression: current liver condition = duration of insulin intake + marital status + age) After adjustment for marital status and age respondents taking insulin for five or more years had 3.26 (95% CI 1.08-9.84) times the odds of having a current liver condition compared to respondents who were taking insulin for zero years. However, taking insulin for one to four years was not statistically associated with liver conditions. Additionally, with each one unit increase in age the odds of having a current liver condition increased 1.02 (95%

CI 1.01-1.03) while holding marital status and insulin duration constant. Furthermore, divorced/separated respondents had 2.46 (95% CI 1.28-4.72) times the odds of having a current liver condition compared to respondents who were married (Table 4).

Cycle 2015-2016

The multivariable logistic regression modeling results for cycle 2015-2016 are in Table 4. (regression: current liver condition = duration of insulin intake + race + annual household income + age) After adjusting for race, annual household income and age respondents taking insulin for one to four years and five or more years were not statistically associated with liver condition.

However, respondents with an annual household income less than $20,000 had 2.50 (95% CI 1.378-4.515) times the odds of having a current liver condition compared to respondents with zero years taking insulin who made greater than $20,000 per year Black respondents had 0.245 (95% CI 0.097-0.617) times the odds of not having a liver condition compared to whites. Age was not statistically associated with liver condition. Sex and race were effect modifiers at $p<0.02$ and $p<0.001$ respectively. However due to the small sample sizes they were not stratified (Table 4).

***Table 1. 2013-2014 Socio-Demographic characteristics of study participants N=5769***

| ***Respondent Characteristics*** | ***Overall N=XXXX N=5769*** | | | ***Current Liver Condition N=XXX N=132*** | | | ***Without Liver Condition N=XXXX N=5608*** | | |
|---|---|---|---|---|---|---|---|---|---|
| | *N=* | *Weighted %* | *SE* | *N=* | *Weighted %* | *SE* | *N=* | *Weighted %* | *SE* |
| ***Sex*** | | | | | | | | | |
| Male | 2758 | 48.1 | 0.587 | 58 | 0.922 | 0.176 | 2684 | 47.1 | 0.554 |
| Female | 3011 | 51.9 | 0.587 | 74 | 1.10 | 0.146 | 2924 | 50.9 | 0.539 |
| | | | | | | | | | |
| ***Mean Age (years, range)*** | 5769 | 47.5 (20-80) | 0.378 | 132 | 54.1 (25-80) | 1.32 | 5608 | 47.3 (20-80) | 0.394 |
| | | | | | | | | | |
| ***Race*** | | | | | | | | | |
| Non-Hispanic White | 2472 | 71.6 | 3.36 | 56 | 1.49 | 0.226 | 2407 | 70.1 | 3.35 |
| Non-Hispanic Black | 1177 | 12.5 | 1.78 | 18 | 0.131 | 0.048 | 1152 | 12.3 | 1.75 |
| Mexican American/ Other Hispanic | 1275 | 16.0 | 2.59 | 35 | 0.343 | 0.095 | 1231 | 15.6 | 2.51 |
| | | | | | | | | | |
| ***Education*** | | | | | | | | | |
| Less than 9th grade/9-11th grade (Includes 12th grade with no diploma) | 1246 | 15.3 | 1.58 | 35 | 0.322 | 0.063 | 1203 | 15.0 | 1.56 |
| High school graduate/GED or equivalent | 1303 | 21.9 | 1.16 | 27 | 0.492 | 0.123 | 1271 | 21.4 | 1.19 |
| Some college or AA degree | 1770 | 32.6 | 1.06 | 45 | 0.707 | 0.145 | 1716 | 31.9 | 1.08 |
| College graduate or above | 1443 | 30.2 | 1.95 | 25 | 0.500 | 0.121 | 1411 | 29.7 | 1.95 |
| | | | | | | | | | |
| ***Marital Status*** | | | | | | | | | |
| Married/Living with partner | 3382 | 62.1 | 1.26 | 65 | 0.964 | 0.130 | 3300 | 61.2 | 1.34 |
| Widowed | 436 | 5.89 | 0.428 | 20 | 0.256 | 0.053 | 413 | 5.64 | 0.450 |

| *Table 1. 2013-2014 Socio-Demographic characteristics of study participants N=5769* | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Divorced/ Separated | 836 | 13.1 | 0.374 | 30 | 0.509 | 0.132 | 801 | 12.5 | 0.318 |
| Never Married | 1112 | 19.0 | 1.14 | 17 | 0.291 | 0.098 | 1091 | 18.7 | 1.13 |
| | | | | | | | | | |
| ***Annual household income*** | | | | | | | | | |
| < $20,000 | 1147 | 14.9 | 1.81 | 36 | 0.446 | 0.122 | 1100 | 14.4 | 1.75 |
| ≥ $20,000 | 4346 | 85.2 | 1.81 | 93 | 1.60 | 0.272 | 4237 | 83.6 | 1.72 |
| | | | | | | | | | |
| ***Diabetic*** | | | | | | | | | |
| No | 5044 | 90.0 | 0.450 | 92 | 1.46 | 0.233 | 4928 | 88.6 | 0.475 |
| Yes | 722 | 9.98 | 0.450 | 40 | 0.555 | 0.070 | 677 | 9.42 | 0.493 |
| | | | | | | | | | |
| ***Mean years person had diabetes*** | 5761 | 1.1(0-79) | 0.075 | 131 | 2.30-26) | 0.579 | 5602 | 1.11(0-79) | 0.073 |
| | | | | | | | | | |
| ***Taking insulin*** | | | | | | | | | |
| No | 5555 | 97.2 | 0.270 | 118 | 1.84 | 0.240 | 5410 | 95.3 | 0.309 |
| Yes | 211 | 2.84 | 0.270 | 14 | 0.184 | 0.076 | 196 | 2.66 | 0.253 |
| | | | | | | | | | |
| ***Years taking insulin*** | | | | | | | | | |
| 0 years | 5558 | 97.2 | 0.270 | 118 | 1.84 | 0.240 | 5412 | 95.3 | 0.309 |
| 1-4 years | 85 | 1.08 | 0.140 | 4 | 0.052 | 0.027 | 81 | 1.03 | 0.133 |
| ≥ 5 | 125 | 1.75 | 0.224 | 10 | 0.132 | 0.057 | 114 | 1.63 | 0.212 |
| | | | | | | | | | |
| ***Mean years person had a liver condition*** | 5765 | 0.5 (0-60) | 0.062 | 129 | 11.5 (0-60) | 1.17 | 5607 | *0.193 (0-58)* | 0.051 |

| *Table 2. 2015-2016 Socio-Demographic characteristics of study participants N=5719* | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| ***Respondent Characteristics*** | ***Overall N=5719*** | | | ***Current Liver Condition N=133*** | | | ***Without Liver Condition N=5548*** | | |
| | *N=* | *Weighted %* | *SE* | *N=* | *Weighted %* | *SE* | *N=* | *Weighted %* | *SE* |
| ***Sex*** | | | | | | | | | |
| Male | 2747 | 48.1 | 0.573 | 71 | 1.07 | 0.160 | 2657 | 47.0 | 0.587 |
| Female | 2972 | 51.9 | 0.573 | 62 | 1.09 | 0.189 | 2891 | 50.8 | 0.534 |
| | | | | | | | | | |
| ***Mean Age (years, range)*** | 5719 | 47.9 (20-80) | 0.562 | 133 | 53.1 (25-80) | 1.04 | 5548 | 47.8 (20-80) | 0.587 |
| | | | | | | | | | |
| ***Race*** | | | | | | | | | |
| Non-Hispanic White | 1863 | 70.6 | 4.23 | 46 | 1.58 | 0.226 | 1808 | 69.0 | 4.21 |
| Non-Hispanic Black | 1198 | 12.5 | 2.44 | 14 | 0.114 | 0.035 | 1181 | 12.5 | 2.43 |
| Mexican American/ Other Hispanic | 1763 | 16.9 | 2.85 | 46 | 0.354 | 0.061 | 1697 | 16.5 | 2.81 |
| | | | | | | | | | |
| ***Education*** | | | | | | | | | |
| Less than 9th grade/9-11th grade (Includes 12th grade with no diploma) | 1364 | 14.5 | 1.66 | 37 | 0.431 | 0.108 | 1315 | 13.9 | 1.58 |
| High school graduate/GED or equivalent | 1236 | 20.8 | 1.09 | 24 | 0.377 | 0.098 | 1203 | 20.4 | 1.04 |
| Some college or AA degree | 1692 | 32.6 | 1.42 | 45 | 0.890 | 0.147 | 1634 | 31.7 | 1.45 |
| College graduate or above | 1422 | 32.2 | 2.95 | 27 | 0.460 | 0.133 | 1392 | 31.8 | 2.90 |
| | | | | | | | | | |
| ***Marital Status*** | | | | | | | | | |
| Married/ Living with partner | 3441 | 63.9 | 1.54 | 78 | 1.34 | 0.184 | 3340 | 62.6 | 1.52 |
| Widowed | 421 | 5.94 | 0.468 | 12 | 0.110 | 0.045 | 404 | 5.78 | 0.448 |
| Divorced/ Separated | 806 | 12.3 | 0.920 | 26 | 0.360 | 0.095 | 775 | 11.9 | 0.868 |
| Never Married | 1048 | 17.9 | 1.19 | 17 | 0.342 | 0.057 | 1027 | 17.6 | 1.22 |
| | | | | | | | | | |
| ***Annual household income*** | | | | | | | | | |
| < $20,000 | 1113 | 12.9 | 1.22 | 47 | 0.549 | 0.107 | 1055 | 12.3 | 1.15 |
| ≥ $20,000 | 4179 | 87.1 | 1.22 | 72 | 1.50 | 0.200 | 4089 | 85.6 | 1.17 |
| | | | | | | | | | |
| ***Diabetic*** | | | | | | | | | |

| ***Table 2. 2015-2016 Socio-Demographic characteristics of study participants N=5719*** | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| No | 4872 | 89.0 | 0.733 | 86 | 1.46 | 0.162 | 4763 | 87.6 | 0.733 |
| Yes | 844 | 10.1 | 0.733 | 46 | 0.691 | 0.091 | 783 | 10.2 | 0.743 |
| | | | | | | | | | |
| ***Mean years person had diabetes*** | 5707 | 1.23 (0-75, 75) | 0.089 | 133 | 3.20 (0-31, 31) | 0.807 | 5537 | 1.18 (0-75, 75) | 0.092 |
| | | | | | | | | | |
| ***Taking insulin*** | | | | | | | | | |
| No | 5466 | 97.0 | 0.288 | 119 | 1.91 | 0.155 | 5313 | 95.1 | 0.328 |
| Yes | 251 | 3.03 | 0.288 | 14 | 0.246 | 0.101 | 233 | 2.79 | 0.311 |
| | | | | | | | | | |
| ***Years taking insulin*** | | | | | | | | | |
| 0 years | 5468 | 97.0 | 0.287 | 119 | 1.91 | 0.155 | 5315 | 95.1 | 0.327 |
| 1-4 years | 112 | 1.39 | 0.203 | 7 | 0.106 | 0.072 | 102 | 1.28 | 0.182 |
| ≥ 5 | 136 | 1.62 | 0.145 | 7 | 0.140 | 0.070 | 128 | 1.48 | 0.170 |
| | | | | | | | | | |
| ***Mean years person had a liver condition*** | 5715 | 0.559 (0-67) | 0.063 | 130 | 8.62 (0-62) | 1.25 | 5547 | 0.360 (0-65) | 0.067 |

*Table 3. Multivariable Association Between Taking Insulin and Current Liver Condition (2013-2014 (N=5769) & 2015-2016 (N=5719))*

| Cycle 2013-2014 (N=5769) | OR (95% CI) | P value |
|---|---|---|
| **Taking insulin** | | |
| No | 1.0 | Referent |
| Yes | 3.12 (1.06-9.23) | 0.041 |
| **Race** | | |
| White | 1.0 | Referent |
| Blacks | 0.464 (0.226-0.954) | 0.018 |
| Mexican American/Other Hispanics | 1.24 (0.825-1.86) | 0.017 |
| **Marital Status** | | |
| Married/living with a partner | 1.0 | Referent |
| Widowed | 1.96 (0.991-3.87) | 0.576 |
| Divorced/Separated | 2.43 (1.21-4.86) | 0.146 |
| Never been Married | 1.64 (0.760-3.54) | 0.950 |
| **Age** | 1.02 (1.01-1.03) | 0.0003 |
| | | |
| **Cycle 2015-2016 (N=5719)** | **OR (95% CI)** | **P value** |
| **Taking insulin** | | |
| No | 1.0 | Referent |
| Yes | 4.16 (1.20-15.8) | 0.038 |
| **Race** | | |
| White | Referent | Referent |
| Blacks | 0.245 (0.098-0.614) | 0.006 |
| Mexican American/Other Hispanics | 0.797 (0.449-1.42) | 0.108 |
| **Annual household income** | | |
| ≥$20,000 | 1.0 | Referent |
| <$20,000 | 2.49 (1.38-4.51) | 0.005 |
| **Age** | 1.01 (0.996-1.02) | 0.168 |

[1] Respondents not taking insulin were used as a reference.

[2] Adjusting for confounders Race (Whites were reference group), Marital status (Married/living with a partner was the reference group), and Age for cycle 2013-2014.

[3] Adjusting for confounders Race (Whites were reference group), Annual household income (>$20,000 was reference) and Age for cycle 2015-2016.

[4] Sampling weight were applied to produce population level estimates

OR = Odds Ratio. 95% CI = Confidence interval. ** P<0.01; *** P<0.001

*Table 4. Multivariable Association Between the Duration of Insulin Intake and Current Liver Condition (2013-2014 (N=5769) & 2015-2016 (N=5719))*

| Cycle 2013-2014 (N=5769) | OR (95% CI) | P value |
|---|---|---|
| **Duration of insulin use** | | |
| 0 year | 1.0 | Referent |
| 1-4 years | 2.08 (0.609-7.08) | 0.754 |
| ≥ 5 years | 3.26 (1.08-9.84) | 0.046 |
| **Marital Status** | | |
| Married/living with a partner | 1.0 | Referent |
| Widowed | 1.88 (0.977-3.60) | 0.536 |
| Divorced/Separated | 2.46 (1.28-4.72) | 0.076 |
| Never been Married | 1.35 (0.631-2.88) | 0.593 |
| **Age** | 1.02 (1.01-1.03) | 0.006 |
| | | |
| **Cycle 2015-2016 (N=5719)** | **OR (95% CI)** | **P value** |
| **Duration of insulin use** | | |
| 0 year | 1.0 | Referent |
| 1-4 years | 4.34 (0.560-33.7) | 0.435 |
| ≥ 5 years | 4.03 (0.942-17.2) | 0.401 |
| **Race** | | |
| White | 1.0 | Referent |
| Blacks | 0.245 (0.097-0.617) | 0.006 |
| Mexican American/Other Hispanics | 0.798 (0.449-1.419) | 0.107 |
| **Annual household income** | | |
| ≥ $20,000 | 1.0 | Referent |
| < $20,000 | 2.50 (1.38-4.52) | 0.005 |
| **Age** | 1.01 (0.996-1.02) | 0.171 |

[1] Taking insulin for 0 years was used as reference.

[2] Adjusting for confounders Marital status (Married/living with a partner was the reference group), and Age for cycle 2013-2014.

[3] Adjusting for confounders Race (Whites were reference group), Annual household income (>$20,000 was reference) and Age for cycle 2015-2016.

[4] Sampling weights were applied to produce population level estimates

OR = Odds Ratio. 95% CI = Confidence interval. ** P<0.01; *** P<0.001

# CHAPTER 4

# DISCUSSION

The objective of this study was to analyze the association between insulin use and current liver conditions. Multiple multivariable logistic regression analyses showed that taking insulin in both cycles were associated with having a current liver condition. Literature on this association has not been analyzed but this study has shown that an association exists. It was also found that taking insulin for five or more years in cycle 2013-2014 was significantly associated with current liver conditions however, additional studies are needed that look at changes in insulin duration over shorter times periods. The use of nationally representative data was the first of its kind.

The association between insulin and having a current liver condition is important to understand because diabetes continues to be an unrelenting public health issue and if taking insulin to control it increases the risk of having a current liver condition then other methods of treatment will need to be used. It is important that public health officials continue to research new medications or treatments that help control diabetes besides insulin.

Liver disease has substantial cost of burden compared to heart disease and obstructive pulmonary disease (Arsani et al, 2018). The addition of a liver condition with diabetes will increase the patients' financial burden as well as the

cost and burden of care on the healthcare system. This may increase the mortality of diabetic patients who die from a liver disease.

## Limitations

*Weaknesses in Design:*

Data were self-reported and not verified through medical records, which could lead to biases such as recall, prevarication or family history bias. This could lead to misclassification of the outcome and lead to biased parameter estimates. Also, while NASH is the type of NAFLD that causes severe liver damage such as fibrosis and cirrhosis and ultimately death and NAFL is a benign liver condition, the NHANES data did not differentiate between NASH and NAFL. Thus, both conditions were included in the analyses, which would likely attenuate findings to the null.

Stratification for effect modifiers sex and race were not performed in the logistic regression analysis between duration of insulin intake and liver condition in cycle 2015-2016 due to small sample sizes of the strata. The interaction term was not included in the analyses and race was included as a covariate, which could obscure different findings for the association by race or sex. Additionally, ratio of family income to poverty was not used in the analysis because it had a smaller sample size then annual household income. However, annual household income is frequently used as a proxy or indicator for socioeconomic status.

Finally, other questionnaire data such as alcohol use, weight and BMI were not adjusted for in this study, which could be considered a limitation that

would impact findings. However, adjusting for respondents' alcohol use and/or weight/BMI was considered inappropriate since weight/BMI is on the causal pathway as a risk factor for diabetes and alcohol is on the causal pathway for liver disease.

**Interpretation**

The current study found that taking insulin and duration of five or more years increased the odds of having a current liver condition. These findings were similar to previous study findings, which reported increasing prevalence of chronic liver disease with excess insulin in the blood among diabetic patients (Kawaguchi et al., 2011, Rhee, Lee, Cho, Kim and Sung, 2011, Bril et al., 2014, Donadon, Balbi and Zanette, 2009).

Duration of insulin intake was only significantly positively associated with liver condition in cycle 2013-2014, and not 2015-2016. This finding was not expected given the nationally representative data and no known systemic shifts in the prevalence of the risk factors or disease from 2013-2014 to 2015-2016. However, these are two different cross-sectional samples with unique participants. which could be due to error or likely that there is a difference in the sample populations. although, all necessary statistical precautions were taken to avoid any such errors or differences. However, to assess this difference a post-hoc test could be done to estimate the difference between the two regression models by setting the two coefficients as equal and testing.

Studies assessing the increasing prevalence of diabetes have found more diagnosed cases of liver conditions among diabetic patients (Gangopadhay & Singh, 2017, Younossi, 2018). However, currently, no available data exist assessing the association of current exogenous insulin intake and duration of insulin use with liver disease for comparison to the current study. A review by Tacelli et al reported insulin use increased the risk of hepatocellular carcinoma, a result of liver disease (Tacelli et al, 2018). In another review by Gangopadhay & Singh (2017), insulin use for two patients with severe NAFLD could not maintain proper glycemic control. It could be inferred that insulin use concurrent with a current liver condition will progressively worsen the liver condition along with overall health. This could be because the liver is already compromised and unable to help regulate glucose; however, the biological mechanisms/pathway would need to be studied.

Respondents in this study currently taking insulin and taking it for five or more years were also at significantly greater odds for having a current liver condition even after adjustment for age. Most respondents with current liver conditions were above the age of 50 years. Studies have shown that increased age is associated with the severity and prognosis of various liver conditions such as NAFLD (Kim, Kisseleva & Brenner, 2015). Biologically, the liver goes through various changes as a person ages such as a decrease in liver volume, blood flow and cytochrome P450 which is involved in drug metabolism (Kim, Kisseleva & Brenner, 2015) and therefore, it can be inferred that taking insulin greater than 50 years of age will increase and exacerbate respondents' risk for liver disease.

The independent effects of annual household income and marital status significantly increased the odds for having a current liver condition in this study as well. Respondents who fell between 100% and 400% of the Federal Poverty Level (FPL) were also known to have an increased risk for obesity and diabetes (Chien, Li & Staudt, 2017). A study assessing marital status and health in the U.S. using NHANES found that married couples were much healthier than adults in any marital category (Schoenborn, 2004). In 2008, single parent homes were six times more likely to be in poverty compared to married couples (Marriage America's greatest Weapon Against Child Poverty, n.d.). Meaning that marital status has a significant effect on the health and financial level for people.

These concomitant socioeconomic disparities have been associated with increased risk for diabetes in which the consequence is the additional risk for comorbidities such as chronic liver conditions (Cornelis et al, 2014, Saydah, Imperatore, & Beckles, 2013). Addressing these disparities could decrease the prevalence of diabetes and chronic liver conditions associated with insulin levels. However, without taking these socioeconomic factors into account liver conditions related to diabetes will continue to rise.

This study also found that Blacks had lower odds of having a current liver condition compared to whites. This does not follow recent studies that have found Blacks are more likely to have liver disease compared to whites (Levy, Catana, Durbin-Johnson, Halsted, & Medici, 2015 & Flores, et al., 2008). This could be because Blacks in this study were younger than those in other studies and liver disease develops with increasing age. However, because we adjusted

for age, this is not likely. A more plausible explanation is that there could be differential misclassification of exposure or the outcomes since the answers to the survey questions were self-reported. For example, Blacks may have reported not having a liver condition when they actually have a liver condition.

In the current study, exogenous insulin intake and duration are positively associated with having current liver conditions. Thus, the population at greatest risk for developing liver disease are diabetic patients. Tackling diabetes has been challenging as the number of people diagnosed with diabetes continue to rise in the U.S. despite the overwhelming evidence that it is a public health issue. The increased incidence of diabetes will increase the number of people taking insulin which will impact the healthcare system cost as well as societal costs and quality of life. Mortality due to diabetic associated liver disease will also increase.

Importantly, being overweight or obese substantially increases the risk for non-communicable diseases such as diabetes (Obesity and Overweight, n.d.). People with a BMI ≥30 (obese) were more likely to be diagnosed with diabetes than those <30 BMI (Ganz, Wintfeld, Li, Alas, Langer, & Hammer, 2014). Controlling for diabetes and having a normal BMI between 18.5-24.9 would reduce the risk of diabetes (Caballero, 2019) and subsequent reduce exogenous insulin use.

Reducing obesity is a high priority for the World Health Organization (WHO), which included a target goal to “Halt the rise in obesity” and match obesity rates of 2010 by 2025 (Obesity and Overweight, n.d.). Additionally, the WHO’s “Global Action Plan for the Prevention and Control of Noncommunicable

Diseases 2013-2020" was implemented to reach its target goals for 9 NCD's including diabetes by 2025 and to decrease premature mortality due to NCDs by 25% (Obesity and Overweight, n.d.).

The population subgroups at risk for developing liver disease; obese people, diabetics, diabetics taking insulin and people abusing alcohol develop these risks from poor lifestyle management. Researchers from Harvard School of Public Health conducted a study using data from the Nurses' Health Study to analyze the impact of health habits on life expectancy. Defining a healthy lifestyle using five low-risk, healthy lifestyle factors that have a large impact on death (i.e., healthy diet, healthy physical activity level, healthy weight (defined by normal BMI level), not smoking (defined as never smoked) and moderate alcohol intake), having healthy lifestyle factors significantly decreased the risk of mortality (Li, et al., 2018). Those without a healthy lifestyle were more likely to die prematurely from chronic diseases and cancer (Li, et al., 2018). Therefore, efforts in preventing poor lifestyle choices/behavior and improving lifestyle habits are important to decreasing the risks for becoming obese, an alcoholic, diabetic and taking insulin due to diabetic status.

Healthy eating and exercise help some people control their diabetes (Medication, n.d.) About 17.1% of Americans with diabetes do not take insulin or oral medication and 50.6% only take oral medication (Fast Facts, 2017). A study in the New England Journal of Medicine found that lifestyle changes (weight-loss, physical activity and diet) decreased the incidence of diabetes by 58% compared to 31% taking metformin. Also, the incidence of diabetes cases was 4.8/100

person years in the lifestyle changes group compared to 11.0/100 person years for placebo and 7.8/100 person years for metformin over a 2.8-year follow-up (Reduction in the Incidence of Type 2 Diabetes with Lifestyle Intervention or Metformin, 2002). Insulin use is not always permanent, if diabetics can get their glucose levels under control with diet and exercise (Why Insulin Use Isn't Always Permanent for Type 2 Diabetes, n.d.) Greater emphasis on controlling blood sugar levels through physical activity and diet will help reduce the number of people diagnosed with diabetes who will take insulin and perhaps those who may concurrently become diagnosed with a liver condition.

Additionally, those who are unable to control their diabetes with physical activity and diet should consider other options such as surgery or weight management medication. About 85.2% of Americans with type 2 diabetes are overweight or obese (Fast Facts, 2017). Losing weight is an important goal for diabetics which is why bariatric surgery became a weight-loss option. Bariatric surgery has reduced diabetes-related morbidity and mortality and helped control diabetes for longer (Keidar, 2011). Approximately, 90% of bariatric patients had lower blood sugar levels, reduced dosage or type of medication and reduced diabetic-related health problems while about 78% of patients had reduced blood sugar levels to normal and did not require the use of medication (Surgery for Diabetes Patient Learning Center ASMBS, n.d.). Bypass procedures such as Roux-en-Y gastric bypass (RYGBP) and biliopancreatic diversion (BPD) are more effective treatments for diabetes and Laparoscopic Adjustable Gastric Banding (LAGB) and Sleeve Gastrectomy (SG) are the most effective

procedures in returning insulin to normal levels (Koliaki, C., Liatis, S., Roux, C. W., & Kokkinos, A. 2017 & Keidar, 2011). Bypass surgeries have even helped diabetes go into long-lasting remission (Surgery for Diabetes Patient Learning Center ASMBS, n.d.).

Further, prescription weight-loss medications are also useful in treating chronic overweight/obese individuals who cannot lose weight with lifestyle changes alone. Weight-loss medications are usually prescribed by healthcare professional to patients with a BMI ≥30 and >27 for those experiencing severe health problems (Prescription Medications to Treat Overweight and Obesity, 2016). Long-term use of prescription weight-loss medication orlistat, lorcaserin and phentermine plus topiramate-extended release with lifestyles changes has shown to produce additional weight-loss compared to a placebo (Yanovski & Yanovski). If weight-loss medications are used with diet and exercise it will decrease the number of diabetics that may use insulin therapy to help control blood sugar thereby, preventing new cases of diabetics with concomitant liver conditions.

**Generalizability**

This study used nationally representative NHANES data and sampling weights were appropriately applied given the probabilistic sampling. Oversampling of participants who were Hispanics, non-Hispanic Blacks, non-Hispanic Asians, non-Hispanic whites, below 130% and 185% of the poverty level was done to make sure that the data was representative of the U.S. population.

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