2015

# The Distribution of Type 1 Diabetes Onset in the United States by Demographic Factors

Margaret Beckstrand
*Walden University*

# Walden University

College of Health Sciences

This is to certify that the doctoral dissertation by

Margaret Beckstrand

has been found to be complete and satisfactory in all respects,
and that any and all revisions required by
the review committee have been made.

Review Committee
Dr. Joseph Robare, Committee Chairperson, Public Health Faculty
Dr. Shana Morrell, Committee Member, Public Health Faculty
Dr. Gudeta Fufaa, University Reviewer, Public Health Faculty

Chief Academic Officer
Eric Riedel, Ph.D.

Walden University
2015

Abstract

The Distribution of Type 1 Diabetes Onset in the United States by Demographic Factors

by

Margaret Beckstrand

MPH, University of California at Los Angeles, 1997

BS, California Polytechnic at San Luis Obispo, 1994

Dissertation Submitted in Partial Fulfillment

of the Requirements for the Degree of

Doctor of Philosophy

Public Health

Walden University

May 2015

Abstract

Type 1 diabetes (T1D) is a chronic and lifelong condition, often diagnosed in childhood. Patients with T1D are at elevated risks of associated health complications, comorbidities, and mortality. Occurrence, clinical presentation, and complications related to T1D differ by age of onset, ethnicity, and gender. The last reported population-based estimates regarding the burden of T1D in children using the National Health and Nutrition Examination Survey (NHANES) were published in 2008, and these estimates were not well stratified by age of onset, ethnicity, and gender. The purpose of this study was to examine these demographics within the conceptual framework of the hygiene hypothesis using data from NHANES from 1999 to 2012. A cross-sectional study design was used to determine the average age of onset of T1D with respect to ethnicity and gender and to assess if age of onset is associated with ethnicity and gender. The average age of onset was 10.5 years for males and 11.8 years for females. The average age of onset was 13.0 years for Hispanics, 12.7 years for Non-Hispanic Blacks, and 10.6 years for Non-Hispanic Whites. Regression analysis indicated that there was no significant association between age of onset and gender ($\beta = 1.1$, $p = 0.386$) and between age of onset and ethnicity ($\beta = 2.1$, $p = 0.070$ for Hispanic White; $\beta = 1.9$, $p = 0.101$ for Non-Hispanic Black) having considered the Non-Hispanic White as the reference population. The result of this study may contribute to positive social change by providing better insight on demographic determinants of the risk of T1D, which is crucially important in the planning and implementation of prevention measures in highly susceptible populations.

# The Distribution of Type 1 Diabetes Onset in the United States by Demographic Factors

by

Margaret Beckstrand

MPH, University of California at Los Angeles

BS, California Polytechnic at San Luis Obispo

Dissertation Submitted in Partial Fulfillment

of the Requirements for the Degree of

Doctor of Philosophy

Public Health

Walden University

May 2015

# Dedication

This dissertation is lovingly dedicated to my children, whose contagious smiles, generous hearts, and bright futures provided me with the courage to pursue diabetes research in the face of all its uncertainties. I would also like to dedicate this massive undertaking to my husband, whose support and infinite patience have enabled me to progress so far. Plus, the daily laughter he creates has been crucial for me on this academy journey; it has helped though the tough/multitasking-times and "see the forest through the trees." Finally, I would also like to dedicate this research to my parents. They are the inspiration for this work and it is mainly because of their love and wisdom that I am who I am today. I feel overwhelmingly blessed to have such thoughtful and exceptional parents. I am deeply indebted to these five key players in my life who, along with others, motivate and encourage me each and every day; I love you all so very, very much.

# Acknowledgments

I would like to express my deepest appreciation to my committee chair, Dr. Joseph Robare, whose sincere guidance and involvement was indispensable to me during this process. I would also like to thank my committee members, Dr. Shana Morrell and Dr. Gudeta Fufaa, for their expert insight and hours of review. In particular, I am profoundly thankful for Dr. Morrell's assistance with editing and analyzing the content of this dissertation. Dr. Morrell's perceptive questions, extensive knowledge, considered and thoughtful approach to this important work was truly invaluable.

This dissertation could not have been possible without the CDC's work on our United States National Health and Nutrition Examination Survey (NHANES) program. From the questionnaire designers and interviewers, to the database managers and SAS programmers, the CDC staff's diligent work provided the excellent documentation and important data integral to my dissertation. Also, I appreciate the over seventy thousand people who participated in NHANES across our nation; this dissertation would not have been feasible without them.

Lastly, I would like to thank all of my family and friends for their words of encouragement. Thank you…thank you…thank you…

Table of Contents

List of Tables

List of Figures

# Chapter 1: Introduction to the Study

Type 1 diabetes (T1D) is a pancreatic condition in which insulin cannot be produced due to a T cell autoimmune reaction that progressively destroys insulin secreting pancreatic β cells (Amador-Patarroyo, Rodriguez-Rodriguez, & Montoya-Ortiz, 2012). No new population-based estimates regarding the burden of T1D in children using the National Health and Nutrition Examination Survey (NHANES) have been published since 2008 (Centers for Disease Control and Prevention [CDC], 2008), and these prior estimates were not well stratified. Stratification using updated estimates has the potential for providing new insights which scholars and practitioners can use to promote positive social change. In this chapter, I provide background information regarding the burden of T1D and significance information regarding importance of stratification by age of onset, ethnicity, and gender. I also provide an overview of the study design and the hypotheses that were tested to inform the burden of T1D in the United States and discuss the conceptual framework.

## Background

A variety of researchers have conducted investigations regarding the age of onset of T1D. The CDC (2011) provided diabetes information from the Search for Diabetes in Youth Study (SEARCH) from the years 2002 to 2005. This information indicated that children younger than 10 years old had a higher incidence of T1D than children 10 to 19 years old. However, SEARCH is not nationally representative (SEARCH for Diabetes in Youth, 2014), unlike NHANES (CDC, 2014b). The CDC has provided a variety of fact sheets using NHANES to describe T1D statistics (e.g., CDC, 2004, 2008, 2011).

However, in 2011 the CDC only used NHANES to report on the adult population (age of onset of T1D over 20 years). In order to provide statistics on patients less than 20 years old, in 2011 the CDC used the SEARCH Study rather than NHANES. Only in older fact sheets, from 2004 and 2008, did the CDC use NHANES to report on the prevalence of diabetes for patients less than 20 years old. Two research groups have published a population-based analysis of T1D in children (Demmer, Zuk, Rosenbaum, & Desvarieux, 2013; Lee, Wu, Tarini, Herman, & Yoon, 2011). Lee et al. (2011) provided an analysis using NHANES 1999-2004 respondents aged 12 to 79 years old, while Demmer et al. (2013) provided an analysis using NHANES 1999-2010 respondents aged 12 to 19 years old. Neither of these research groups included children 1 to 11 years old, and therefore this remains a gap in the literature.

In addition to the gap in the literature for nationally representative estimates in young children, the CDC reports were not well stratified by age of onset, gender, and ethnicity, which have important ramifications for health outcomes (Black et al., 2011; Dahlquist, Möllsten, & Källén, 2008; Doggen et al., 2012; Finne, Reunanen, Stenmanm Groop, & Gronhagen-Riska, 2005; Hietala, Forsblom, Summanen, & Groop, 2013; Levy-Shraga et al., 2013; Sander, Larsen, Anderson, & Lund-Anderson, 2013). While many authors have described the important roles age of onset, ethnicity, and gender play with regard to the public health burden in the United States, it is clear that there remains an important gap. The study used stratification and NHANES, an updated population-based data source, in order to provide new data which can be used to promote positive social change.

## Problem Statement

In 2009, Pettitt et al. (2014) estimated the prevalence of T1D as 166,984 among children less than 20 years old in the United States. In addition to daily treatment burden required for T1D treatment, T1D has also been associated with a variety of detrimental effects including diabetic neuropathy (Bjornstad et al., 2013), end-stage renal disease (Luk et al., 2014), hypoglycemia and ketoacidosis (Craig, Jones, Silink, & Ping, 2007), and retinopathy (Kramer & Retnakaran, 2013). Furthermore, multiple authors have reported that the incidence is increasing (Berhan, Waernbaum, Lind, Mollsten, & Dahlquist, 2011; Dahlquist, Nyström, & Patterson, 2011; Derraik, et al., 2012; Evertsen, Alemzadeh, & Wang, 2009; Harjutsalo, Sjöberg, & Tuomilehto, 2008; Hussen, Yang, Cnattingius, & Moradi, 2013; Imperatore et al., 2012; Lipman et al., 2013; Patterson, Dahlquist, Gyürüs, Green, & Soltész, 2009; Patterson et al., 2012; Pettitt et al., 2014).

The public health burden of T1D is high and health outcomes are often severe. In order to reduce this burden, further research regarding the relationship between age of onset of T1D with ethnicity and gender is necessary. Researchers have already reported that the occurrence of T1D differs by age of onset (Berhan et al., 2011; Dahlquist et al., 2011; Harjutsalo, 2008; Hodgson, Beale, Parslow, Feltbower, & Jarup, 2012; Imperatore et al., 2012; Lipman et al., 2013; Patterson, Dahlquist, Soltesz, & Green, 2000; Smith, Drum, & Lipton, 2007; Zung et al., 2012), ethnicity (Derraik et al., 2012, Dabelea, Mayer-Davis, et al., 2014; Pettitt et al., 2014), and gender (Doggen et al., 2012; Evertsen et al., 2013; Lipman et al., 2013; Zung et al., 2012). Furthermore, there has been evidence that complications related to T1D differ by age of onset (Dalhquist et al., 2008; Doggen

et al., 2012; Finne, et al., 2005; Hietala, et al., 2013; Levy-Shraga et al., 2013; Svensson, Nystrom, Schon, & Dahlquist, 2006; Takii et al., 2011), ethnicity (Black et al., 2011), and gender (Costacou & Orchard, 2013; Dalhquist et al., 2008; Sahakyan, Klein, Lee, Myers, & Klein, 2011). There are few publications that reported average age of onset of T1D stratified by demographic factors. Instead, much of the research in the United States has been done using age categories. For example, Lipman et al. (2013) reported no statistically significant differences for incidence rates stratified by age groups and ethnicity, based on children in Philadelphia. In contrast, the CDC (2011) reported that children younger than 10 years old had a higher incidence of T1D onset than children 10 to 19 years old (CDC, 2011). The above data demonstrate that existing reports have been contradictory, not well stratified, and not based on nationally representative samples. Therefore, stratification using an updated, population-based data source such as NHANES has the potential to fill this gap in the literature.

## Purpose of the Study

The purpose of this study was to investigate age of onset of T1D by demographic factors using a population-based study. The results of this study may provide public health researchers with the data to design more targeted prevention trials and obtain further information about risk factors. The quantitative study design includes age of onset as the dependent variable with ethnicity and gender as the independent variables.

## Research Question and Hypotheses

The following research question was investigated using data from the NHANES between 1999 and 2012: What is the average age of onset of T1D with respect to ethnicity and gender? The research hypotheses were as follows:

- $H_0$1: There is no association between age of onset of T1D and gender.
- $H_a$1: There is an association between age of onset of T1D and gender.
- $H_0$2: There is no association between age of onset of T1D and ethnicity.
- $H_a$2: There is an association between age of onset of T1D and ethnicity.
- $H_0$3: There is no association between age of onset of T1D and ethnicity, after adjusting for gender.
- $H_a$3: There is an association between age of onset of T1D and ethnicity, after adjusting for gender.

## Nature of the Study

This was a quantitative study involving statistical analysis of data from the CDC's nationwide NHANES survey. NHANES provides cross-sectional data on a nationally representative sample of the United States population. Cross-sectional studies can be used to determine disease frequency and explore the variables associated with the disease (Lilienfeld & Stolley, 1994). NHANES was used examine three variables: age of onset of T1D, ethnicity, and gender.

## Operational Definition of Terms

*Age of onset of T1D*: Age of patient at the time of T1D diagnosis. In the context of NHANES, survey participants self-reported this information.

*Ethnicity*: Categorized as White, Black, Asian, and Other, and then further classified as Hispanic or non-Hispanic. In the context of NHANES, survey participants self-reported this information via multiple questions. The CDC created the ethnicity variable by combining the race information with the Hispanic information from these multiple questions.

*Gender*: Categorized as male or female. In the context of NHANES, interviewers documented this variable; interviewers only asked participants to self-report gender if it was not obvious to the interviewer.

*Insulin*: According to Wardlaw, Insel, and Seyler (1992), "a hormone produced by the beta cells of the pancreas. Insulin increases the synthesis of glycogen in the liver and the movement of glucose from the bloodstream into muscle and adipose cells, among other processes" (pp. G-10). The hormone is necessary during food digestion in order metabolize the glucose in the food and properly make it available to cells in the blood stream. In the context of NHANES, survey participants self-reported their use of insulin as a treatment for their diabetes. This was used to operationally identify the patients with T1D.

*T1D*: A pancreatic condition in which insulin cannot be produced due to a T cell autoimmune reaction that progressively destroys insulin-secreting pancreatic β cells (Amador-Patarroyo et al., 2012). For this study, patients were operationally classified as having T1D if their survey responses indicated that they were diagnosed with diabetes and taking only insulin without diabetic pills. Demmer et al. (2013) also employed this operational definition in the analysis of NHANES.

## Assumptions

I assumed that the complex sampling methods employed by the CDC in the administration of NHANES would provide weighted data that was nationally representative of the United States population. This assumption was necessary in order to generalize study results.

It was assumed that the responses obtained from the administration of NHANES were reliable and valid. This assumption was necessary in order to assume that participants accurately responded.

## Limitations

Because this study did not include patients who reported that they were diagnosed with diabetes at age 0 (i.e., only between 1 and 19 years) and because NHANES does not collect diabetes data on patients less than 1 year old at the time of questionnaire completion, analysis of the mean age of onset may have been biased upwards. However, researchers have indicated that most diabetic presentations at less than 6 to 9 months old were not due to an autoimmune disorder (T1D), but instead due to a monogenic disorder (Rubio-Cabezas & Ellard, 2013; Rubio-Cabezas, Flanagan, Damhuis, Hattersley, & Ellard, 2012).

The inability to unequivocally screen out all type 2 diabetes (T2D) diagnoses for the analysis was a limitation. This should have been minimized given that the CDC (2011) reported few T2D diagnoses occur prior to 10 years old. Furthermore, Elder et al. (2012) reported only 18% of T2D patients (mean age 15.2 years) use only insulin for treatment, as compared to 82% who use insulin in combination with oral antidiabetes

medications. Therefore, to limit misclassification, T1D patients identified in NHANES were classified as such if treatment was reported as insulin only.

Another potential limitation was related to inclusion of only diagnosed cases in the analysis. This, however, should have been minimized given that Lee et al. (2011) provided an analysis using NHANES 1999-2004 respondents aged 12 to 79 years old. These authors reported only a small prevalence (4/1156) of undiagnosed T1D or T2D diabetes in the obese/overweight adolescent group (aged 12 to 18). Additionally, SEARCH researchers have stated that the number of undiagnosed T1D patients less than 20 years old is small, unlike the potentially large number of undiagnosed T2D adult patients (Pettitt et al., 2014).

## Conceptual Framework

The conceptual framework for this study was based on the hygiene hypothesis as one of the potential etiologies of T1D (Strachan, 1989). T1D is an autoimmune disease. The hygiene hypothesis proposes that the immune system requires a certain amount of exposure to immune-provoking agents during childhood in order to adequately develop (Strachan, 1989). In addition, Pfefferle, Teich, and Renz (2009) reported that the timing of exposure to certain bacteria, as well as route and dose, are critical determinants in the development of future immune responses. Without these exposures the development of the immune system may be delayed or changed, which may lead to development of allergic and autoimmune disorders.

Findings by D'Angeli et al. (2010) and Liese et al. (2012) on children under 19 years of age supported the use of the hygiene hypothesis as a conceptual framework for

this study. D'Angeli et al. and Liese et al. reported lower risk of T1D was associated with lower socioeconomic status (SES), including children living in neighborhoods classified as below poverty, receiving social security, or having Medicaid/Medicare insurance. Because SES may be disproportionate across ethnicities and the timing of nonhygienic exposures may affect immune system functioning, the age of onset of T1D was investigated in this study with ethnicity as an independent variable. In addition to providing information regarding the hygiene hypothesis, this study provided estimates stratified by ethnicity.

## Scope of the Study and Delimitations

The scope of this study was to investigate age of onset of T1D by ethnicity and gender in children. This study was delimited to T1D patients with age of onset between 1 and 19 years old. Furthermore, this study was delimited to investigation of only two of the potential demographic variables, gender and ethnicity. SES and other demographic variables related to the hygiene hypothesis were not included in the analysis because their values at the time of T1D diagnosis were not collected in the cross-sectional NHANES data set.

## Significance of the Study

The exact etiology of T1D remains unclear, with few known risk factors or prevention recommendations to avoid T1D (Ramachandran, Bhanu Keerthi, & Dhana Raju, 2014). Advances in the area of prevention are greatly needed. By the time an individual receives a diagnosis, almost all of the β cells have been destroyed and it is currently not clear if they can be regenerated. There are some indicators for what

constitutes a “high risk” for developing T1D, including presence of autoantibodies and a family history to T1D (Sosenko et al., 2012). Current preventative research has often focused on these high risk children. The National Institutes of Health (2012) reported early results from a trial targeted for high risk children indicating that oral insulin may delay the onset of the disease in this population, but more information is needed to determine who is at risk. Data on the risk factors for T1D should enable more efficient studies which can result in more specific prevention data.

Defining the demographic profile of a nationally representative sample of young T1D patients utilizing more recent data can aid in the planning of trials for high risk children and evaluation of the various etiologic theories, which include the hygiene hypothesis. Population-based estimates regarding the burden of T1D in children using the NHANES have not been reported since 2008 (CDC, 2008) and the estimates provided in 2008 were not well stratified. Stratification using updated estimates can provide new data which can be used to promote positive social change.

## Summary and Transition

T1D is a chronic and lifelong condition, often diagnosed in childhood. The exact etiology is unknown, and there is currently no cure and no effective prevention recommendations. There has been evidence indicating that occurrence of T1D differs by age of onset (Berhan et al., 2011; Dahlquist et al., 2011; Harjutsalo, 2008; Hodgson, et al., 2012; Imperatore et al., 2012; Lipman et al., 2013; Patterson et al., 2000; Smith et al., 2007; Zung et al., 2012), ethnicity (Derraik et al., 2012, Dabelea, Mayer-Davis, et al., 2014; Pettitt et al., 2014), and gender (Doggen et al., 2012; Evertsen et al., 2013; Lipman

et al., 2013; Zung et al., 2012). However, researchers have not published population-based estimates of the burden of T1D in children using NHANES since 2008, and those reports were not well stratified by age of onset, ethnicity, and gender. The purpose of this study was to examine these demographics using data from NHANES from 1999 to 2012. These data can provide the necessary variables to examine age of onset stratified by ethnicity and gender. Furthermore, the examination occurred within the context of the hygiene hypothesis (Strachan, 1989), which is one of the etiologic hypotheses regarding T1D. In the next chapter, I provide a thorough review of the literature with more detail regarding the hygiene hypothesis, as well as other the etiologic hypotheses, potential risk factors, and the epidemiology of the disease stratified by age of onset, ethnicity, and gender.

# Chapter 2: Literature Review

T1D is a pancreatic condition in which insulin cannot be produced due to a T cell autoimmune reaction that progressively destroys insulin secreting pancreatic β cells (Ramachandran et al., 2014). T1D is a major public health burden, affecting 166,984 American children in 2009 (Pettitt et al., 2014). The cause is unknown, though it is likely to be multifactorial. Therefore, there are few known risk factors and currently no effective preventative recommendations. Although lifelong treatment options involving exogenous insulin exist, there is currently no cure. Researchers have reported that the incidence of T1D differs by age of onset (Berhan et al., 2011; Dahlquist et al., 2011; Harjutsalo, 2008; Hodgson et al., 2012; Imperatore et al., 2012; Lipman et al., 2013; Patterson et al., 2000; Smith et al., 2007; Zung et al., 2012), ethnicity (Derraik et al., 2012; Dabelea, Mayer-Davis, et al., 2014; Pettitt et al., 2014), and gender (Doggen et al., 2012; Evertsen et al., 2013; Lipman et al., 2013; Zung et al., 2012). Furthermore, there has been evidence that complications related to T1D differ by age of onset (Dalhquist et al., 2008; Doggen et al., 2012; Finne et al., 2005; Hietala, Forsblom, et al., 2013; Levy-Shraga et al., 2013; Svensson et al., 2006; Takii et al., 2011), ethnicity (Black et al., 2011), and gender (Costacou & Orchard, 2013; Dalhquist et al., 2008; Sahakyan et al., 2011). Investigation of these differences can provide insight into potential risk factors and may be helpful to uncovering a cure and relieving the public health burden.

In this chapter, I provide a summary of current T1D research literature related to three primary variables: age of onset, gender, and ethnicity. Furthermore, T1D pathophysiology and etiological theory literature has been summarized. I searched the

literature using three databases: ProQuest Central, ProQuest Nursing and Allied Health Source, and ScienceDirect. I searched these databases with the following key terms in the title or abstract: *diabetes* in combination with *type I* (either Roman numeral I or Arabic 1) or *autoimmune* and also including at least one of the following terms: *age of onset, years, gender, ethnicity, risk factor,* or *hygiene hypothesis*. I limited retrieved results to peer-reviewed articles published after January 1, 2011. Abstracts and methods sections were reviewed to identify the study population's age and country of origin. I excluded most studies with adult populations from the review. However, I did include some studies regarding complications of T1D in adult populations that provided analysis stratified by gender, ethnicity, or duration even when the author did not specify age of onset. Regarding country of origin, all literature based on study populations in the United States was reviewed and summarized in this chapter, when applicable. Literature based on study populations outside the United States was selectively included when references to an author or article appeared frequently in other sources. Seminal publications and authoritative websites were also included in the literature review. These were identified by reviewing the references in the articles obtained in the primary literature search. In addition to chaining references backwards from the literature identified in the primary search, I chained seminal publications and prominent authors forward to identify publications referencing them.

## Diabetes Mellitus

Diabetes mellitus is a pancreatic condition in which the insulin hormone cannot be produced due to insensitive and/or unproductive insulin secreting pancreatic β cells

(Ramachandran et al., 2014). The International Diabetes Federation (2013) estimated 382 million people have diabetes worldwide, and they expected this to increase to 592 million by the year 2035. In 2010, diabetes was the seventh leading cause of death in the United States (Heron, 2013). It was the fourth and fifth leading cause of death among non-Hispanic Blacks (NHB) and Hispanics, respectively (Heron, 2013). Among White children, diabetes was not reported in the top 10 for ages 0 to 14 years, but it was the eighth leading cause of death in 2010 for 15- to 19-year-old children (Heron, 2013). In 2009, Pettitt et al. (2014) estimated the prevalence of T1D among children less than 20 years old in the United States as 166,984. There are three main types of diabetes: T1D, T2D, and gestational diabetes (International Diabetes Federation, 2013). Demmer et al. (2013) reported 69% of diabetes in children ages 12 to 19 years was T1D, while the remaining 31% was T2D. I provide a description of each type in the following sections.

**Type 1 Diabetes**

T1D, a pancreatic condition in which insulin cannot be produced due to a T cell autoimmune reaction that progressively destroys insulin-secreting pancreatic β cells (Amador-Patarroyo et al., 2012), was previously known as *insulin-dependent diabetes mellitus* (Gavin et al., 2003). Insulin is a hormone that is necessary during food digestion in order to bind with the glucose in the food and properly make it available to cells in the blood stream. After glucose is metabolized, it is used as energy for cell and organ functioning as well as stored. When insulin is not available, glucose is not metabolized but instead builds up and causes hyperglycemia. Researchers have claimed the exact mechanism that initiates the T cell autoimmune reaction to be multifaceted, including

both genetics and environmental triggers (CDC, 2011; Cinek, 2011; Knip, 2012; Liese et al., 2012; Samuelsson & Löfman, 2014; TEDDY Study Group, 2008). In this chapter, I examine the epidemiology of this autoimmune reaction as well as detail hypothesized pathophysiological mechanisms and risk factors.

**Type 2 Diabetes**

Unlike T1D patients, pancreatic β cells in T2D patients are typically not destroyed. Instead, they are damaged or have insufficient insulin sensitivity leading to insufficient production of insulin or insulin resistance in muscles and the liver (Ramachandran et al., 2014). Because of this difference, pharmaceutical treatment of T2D, previously known as *noninsulin dependent diabetes mellitus* (Gavin et al., 2003), can be different from the treatment of T1D. Treatment of T2D involves insulin secretagogues, which promote secretion of insulin and insulin sensitizers, such as sulphonyl ureas, meglitinides, biguanides, and thiazolidinedione (Ramachandran et al., 2014). In addition to differences in pathophysiology and treatment of T2D compared to T1D, other differences exist.

Unlike T1D, most literature indicated that T2D patients are older upon diagnosis than T1D patients. Pettitt et al. (2014) reported the prevalence of T2D in 2009 using multicenter United States data. The results showed no cases of T2D in patients aged 0 to 4 years old and less than 0.1 per 1000 in patients aged 5 to 9. Similarly, other researchers have reported no cases of T2D among children between 0 and 4 years old (Imperatore et al., 2012; Lipman et al., 2013) and less than 0.01 per 1000 in children between 5 and 6 years old. There are data on older children. Lipman et al. (2013) reported the incidence of

T2D per 100,000 was 1.6 (95% CI 0.7-3.1) and 15.4 (95% CI 12.4-19.0) in patients aged 5 to 9 and 10 to 14, respectively. Dalhquist et al. (2008) reported 31 T2D patients out of a total of 6,300 prevalent Swedish patients with age of diabetes onset less than 15 years old. These two publications suggested few cases of T2D are diagnosed in patients under 15 years old. However, using the SEARCH study, Imperatore et al. (2012) reported the highest incidence of T2D was at age 14 in children under 20 year old. Although this evidence may appear contrary to the prior two publications, Imperatore et al.'s analysis was based on only 1,534 cases of T2D in patients under 20 years old within a background population of 30,549,412 person-years. These data did indicate that T2D diagnoses in the young are rare and researchers have reported increasing age as a risk factor for T2D (Ramachandran et al., 2014).

Various risk factors have been reported for T2D, including age, obesity, Hispanic and African American ethnicity, hypertension, and family history (Ramachandran et al., 2014). Of these risk factors for T2D, researchers have also reported family history to be a factor for T1D, while hypertension has not been reported as a risk factor for T1D. Although obesity is a well-known risk factor for T2D, researchers have recognized that T2D insulin resistance can also occur in nonoverweight individuals (Ramachandran et al., 2014). Pettitt et al. (2014) reported the prevalence of T2D by ethnicity in 2009 using multicenter United States data. In patients aged 10 to 14, the prevalence of T2D among non-Hispanic Whites (NHW) was approximately 0.1 per 1000 and significantly lower than the estimates for Black, Hispanic, and American Indian/Alaskan Native (all < 0.5 per 1000). In patients aged 15 to 19, Pettitt et al. (2014) reported a similar trend by

ethnicity; prevalence for NHW was approximately 0.3 per 1000 and significantly lower than the estimates for American Indian/Alaskan Native (approximately 1.9), Black (approximately 1.6), and Hispanic (approximately 1.2 per 1000). However, not all authors have agreed on ethnicity differences. Contrary to the finding on ethnicity by Pettitt et al., Demmer et al. (2013) reported no significant differences between ethnicities in the prevalence of T2D (diagnosed and undiagnosed) using a nationally representative sample. These inconsistencies and the research gap regarding the etiologies of T1D and T2D support the need for this research regarding T1D.

**Gestational Diabetes**

Gestational diabetes, similar to T2D, results from insensitive and/or unproductive insulin secreting pancreatic β cells (Ramachandran et al., 2014). However, the diagnosis is specific to females and develops during pregnancy (Ramachandran et al., 2014). Results from studies in the United States indicate that the between 3.7% and 4.9% of pregnant women were diagnosed with this form of diabetes (Hunt & Schuller, 2007). Many researchers have focused their efforts on the treatment of gestational diabetes (Kallas-Koeman et al., 2014; Luoto et al., 2010), especially given that the disease and/or the treatment may be associated with fetal and infant complications (Bell, Glinianaia, Tennant, Bilous, & Rankin, 2012).

**Other Forms of Diabetes**

In addition to the three forms of diabetes described above, unique diabetic disease forms exist and are classified as such because they are not caused by either autoimmune β cell destruction (as with T1D) or insulin insensitivity (such as with T2D).

Researchers have demonstrated that most diabetic presentations in infants under 6 months old were not due to an autoimmune disorder, but instead due to a monogenic disorder (Rubio-Cabezas et al., 2012). The American Diabetes Association (2014) suggests classification of these other forms based on their cause; for example genetic defects and pancreatic diseases such as cystic fibrosis.

## Type 1 Diabetes: Pathophysiology

T1D is caused by the destruction of pancreatic insulin secreting β cells by Th1 T cells that produce IFN-γ (Bradley et al, 1999). However, little is known about the exact mechanism that initiates the Th1 T cells on their destructive path. Two proteins that play an important role in the suppression of the autoimmune destruction caused by the Th1 cells are Interleukin 4 (IL-4) and Interleukin 10 (IL-10) (Liu, Liu, Bleich, Salgame, & Gause, 2010). Skapenko, Kalden, Lipsky, & Schulze-Koops (2005) have shown that IL-4 increases activation of T regulatory cells (Tregs). This mechanism may be important to preventing autoimmune behavior by thwarting autoimmune Th1 cell behavior. For example, researchers have reported that Th2 cell activation decreases Th1 activation (Saunders, Raine, Cooke, & Lawrence, 2007) and Tregs suppress IFN-γ production and the ability for Th1 cells to enter the pancreatic islets (Sarween et al., 2004) and impair Th1 cell function within the islets (Chen, Herman, Matos, Mathis, & Benoist, 2005). Furthermore, IL-10 expression is important because, similar to IL-4, it has also been implicated in suppressing the autoimmune destruction caused by the Th1 cells (as mentioned above). IL-10 is an anti-inflammatory agent and has been shown reduce INF-γ production and block diabetes onset in mice (Goudy et al., 2001). Other proteins that play

a role in the onset and/or progression of T1D include IL-6 (Kumar et al., 2007), IL-12 (Fu, Zhen, Yuskavage, & Liu, 2011), and IL-15 (Bobbala et al., 2012). These proteins also interact with infectious agents and genetics, and are discussed in the risk factor section of this chapter. This plethora of protein mechanisms, along with genetic and other potential pathophysiologic mechanisms, highlights the multifaceted nature of T1D etiology and the potential for preventative research targeting the various pathways.

## Type 1 Diabetes: Epidemiology

Authors have reported the incidence of T1D from various studies worldwide. Incidence rates, derived from data within the United States, range from 17.2 per 100,000 (95% confidence interval [CI] 15.2-19.3) based on a population based Philadelphia cohort from 2000 to 2004 (Lipman et al., 2013) to 27.92 per 100,000 (95% CI 26.28–28.98) based on children under 19 years old in southeastern Wisconsin between 1995 and 2004 (Evertsen et al., 2009). Outside the United States, some incidence rates have been published. T1D is quite rare in China, where less than 1.0 per 100,000 Chinese children were diagnosed between 1990 and 2000 (Zhang et al., 2008) and 3.1 per 100,000 children between 1997 and 2011 (Zhao et al., 2014). Sweden has shown higher rates, where 43.9 per 100,000 Swedish children between 2005 and 2007 were diagnosed (Berhan et al., 2011). The incidence of T1D is increasing in the United States (Evertsen et al., 2009; Imperatore et al., 2012; Lipman et al., 2013; Pettitt et al., 2014), Australia (Catanzariti, et al., 2009), China (Zhang et al., 2008; Zhao et al., 2014), Europe (Patterson et al., 2009; Patterson et al., 2012), Sweden (Berhan et al., 2011; Dahlquist et al., 2011; Hussen et al., 2013), Finland (Harjutsalo et al., 2008), Germany (Galler et al., 2010), and New Zealand

(Derraik et al., 2012). Although many authors reported increases, some authors reported either a constant incidence in England (Hodgson et al., 2012) and Czech Republic (Cinek et al., 2012) or a decreasing incidence in Sweden (Samuelsson & Löfman, 2014). These three inconsistent results only occurred at the end of their study timeframes; at the beginning increases were reported. Together, the majority of analyses indicate that the incidence of T1D is increasing in many countries.

The burden of disease is often measured with prevalence. Pettitt et al. (2014) reported an estimated prevalence of 166,984 T1D patients in the United States in 2009, based on the largest United States-based diabetes surveillance study to date for children under 20 years old. In a smaller, yet robust, multisite study within seven states, Dabelea, Mayer-Davis, et al. (2014) reported the prevalence in 2009 of T1D among children < 20 as 1.93 per 1,000. Further, Demmer et al. (2013) reported an estimated prevalence of 125,422 T1D children aged 12 to 19 years old between 1999 and 2010 using NHANES. This nationally representative estimate from NHANES equated to 0.38% prevalence. Pettitt et al. obtained diagnoses from medical records, whereas Demmer et al. classified patients as T1D via a self-report survey (NHANES) indicating that they were diagnosed with diabetes and taking only insulin without diabetic pills. Prevalence estimates in different populations should not be compared, because survival may differ between different populations (Pettitt et al., 2014). Therefore, prevalence estimates outside the United States are not elaborated on further in this discussion.

## Type 1 Diabetes and Relationship to Age, Gender, and Ethnicity

### Age of Onset

Understanding an average age of onset for T1D would enable increased surveillance and targeted clinical trial recruitment efforts. Few authors have reported the mean T1D age of onset in the United States. Using single site studies in Chicago ($N$ = 844), Florida ($N$ = 145), and Pittsburg ($N$ = 104), several authors reported the average age of onset to be between 8.0 and 9.4 years old (Hughes et al., 2013; Johnson & Meltzer, 2002; Smith et al., 2007). Consistent with these findings, Pettitt et al. (2014) reported data from a multisite study based in the United States (SEARCH) containing 6,668 T1D patients less than 20 years old with an average age of T1D onset of 8.1 years. Furthermore, using a subpopulation of SEARCH targeted for a nutritional survey ($N$ = 1,077), Crume et al. (2014) reported the average age of T1D onset as 9.4 years. To date, SEARCH is the only multisite study reporting average age of onset in the United States in current literature, and therefore supports the need for this investigation using a nationally representative dataset.

There is currently more data on age available from outside the United States. Data from Sweden (Carlsson, Forsander, Ludvigsson, Larsen, & Örtqvist, 2013; Lundgren, Lynch, Larsson & Larsson, 2015; Nilsson et al, 2013), Denmark (Sørensen et al., 2013), Germany (Galler et al., 2010), India (Bhadada et al., 2011), and Brazil (Rodacki et al., 2007) reported the mean age of onset between 5.8 and 12 years. Al Rasheed (2011) reported two peaks of age of onset, 7 and 11 years, for Saudia Arabian children. While the results from studies outside the United States were fairly consistent in the reported

age of onset, there were some variations. Luk et al. (2014) and Hietala, Forsblom, et al. (2013) reported the average age of onset as 19.5 years in Hong Kong and 14.1 years in Finland, respectively. In these studies, T2D patients may have been misclassified as T1D patients, hence the age of onset may have been biased upwards. On the whole, the average T1D onset appears to lie between 6 and 12 years old. This pattern appears consistent regardless of location.

Rather than estimating mean age at onset, some authors have reported age of onset of T1D using categorical age groupings. Among study populations in Chicago (Smith et al., 2007), Philadelphia (Lipman et al., 2013), Australia (Catanzariti et al., 2009), China (Zhang et al., 2008; Zhao et al., 2014), England (Hodgson et al., 2012), Europe (Patterson, et al., 2000), Germany (Galler et al., 2010), Sweden (Berhan et al., 2011; Dahlquist et al., 2011), Turkey (Simsek et al., 2013), and Finland (Harjutsalo et al., 2008), authors reported the lowest incidence occurred in children 0 to 4 years old compared to children 5-9 and 10-14 years old. Using different age categories, the CDC (2011) indicated that children younger than 10 years old had a higher incidence of T1D compared to children 10-19 years old (CDC, 2011). The CDC (2011) did not claim that the rates were statistically significantly different (19.7 and 18.6 per 100,000) and analysis may have shown a similar pattern with the groups of children aged 0 to 4 years and 5 to 9 years if the analysis had been stratified differently. Imperatore et al. (2012) reported that incidence of T1D by age in 2002 resembled a bell curve when using SEARCH study dataset, with the highest incidence at 10 years old, and the lowest in the two tails at 0 and 19 years old. Zung et al. (2012) reported the highest frequency between the ages of 10

and 14 years old, with less occurring in the higher and lower age groups using a population-based study in Israel with patients with age of onset was below 18 years. In further support of diminished incidence in late adolescence, Dahlquist et al. (2011) reported decreased incidence after puberty and Smith et al. (2007) reported higher incidence among children between 10 and 14 years (incidence rate [*IR*] = 13.8, 95% CI 12.2-15.6) compared to those between 15 and 17 years old (*IR* = 10.4, 95% CI 8.8-12.3). On the whole, the majority of evidence appears to support the bell shaped curves for age of onset reported by Imperatore et al. and Zung et al. This evidence supports parametric analysis of age of onset of T1D, rather than nonparametric analysis without the assumption of normality.

**Gender and Interaction with Age**

Although there are many studies showing no significant difference in the occurrence of T1D between genders (Berhan et al., 2011; Dabelea, Mayer-Davis, et al., 2014; Derraik et al., 2012; Demmer et al., 2013; Galler et al., 2010; Hodgson et al., 2012; Smith et al., 2007; Welander, Montgomery, Ludvigsson, & Ludvigsson, 2014; Zhang et al., 2008; Zhao et al., 2014), some authors did report gender differences. These authors have reported that females have a lower incidence of T1D using study populations in Philadelphia (Lipman et al., 2013), Wisconsin (Evertsen et al., 2013), Australia (Catanzariti et al., 2009), Belgium (Doggen et al., 2012), and Israel (Zung et al., 2012). Together, these data suggest either no gender differences or lower incidence for females. This supports the use of gender as a variable in T1D analyses regarding age of onset.

However, when age of onset is explored using categories, females have been reported to have a higher incidence only in particular age of onset categories. Dahlquist et al. (2011) reported the highest incidence for females occurred between 5 and 9 years (37.1 per 100,000 person-years) and for males occurred between 10 and 14 years (42.3 per 100,000 person-years). Evertsen et al. (2009) reported females have a higher risk when under 10 years old, but males have a higher risk of T1D at 10 to 19 years old. Looking at specific ages rather than categories, Hodgson et al. (2012) reported that peak incidence of T1D for males was 13 years old and for females between 11 and 12 years old. Similarly, Catanzariti et al. (2009) reported that peak incidence of T1D for males were between 12 and 13 years old and for females between 10 and 11 years old. Together these findings suggest that females are diagnosed at an earlier age than males. Harjutsalo et al. (2008) demonstrated the peak incidence for females occurred 3 years prior to males (age of onset of T1D at 10 compared to 13 years old). Additionally, the incidence remained similar until children were 11 years old then males had a significantly higher incidence at age 13. Consistent with the earlier onset for females, Blasetti et al. (2011), Lawrence et al. (2014), Leidig-Bruckner et al. (2014), Samuelsson et al. (2013), and Valdes et al. (2012) also found that females had a lower mean age of onset of T1D than males. Table 1 reports the literature on gender and age of onset, indicating females typically appear to have a lower age of onset than males.

Table 1

*Age of Onset of T1D by Gender*

| | Location (age range of sample) | Females | | Males | |
|---|---|---|---|---|---|
| | | *n* | Mean (*SD*) | *n* | Mean (*SD*) |
| Blasetti et al. | Italy (1-14 years) | 88 | 6.3 (3.4) | 101 | 7.9 (3.9) |
| Lawrence et al. | United Status (0-19 years) | 2,710 | 9.46 (4.36) | 3,132 | 10.12 (4.62) |
| Leidig-Bruckner et al. | Germany (1-55 years) | 68 | 25.1 (11.1) | 71 | 26.4 (10.2) |
| Samuelsson et al. | Sweden (0-18 years) | 1588 | 9.4 (4.0) | 2020 | 10.2 (4.5) |
| Valdes et al. | Worldwide (0-37 years) | 1703 | 9.96 (7.15) | 1899 | 10.89 (7.49) |

*Note*. *SD*: standard deviation. From sources: Blasetti et al. (2011); Lawrence et al. (2014); Leidig-Bruckner et al. (2014); Samuelsson et al. (2013); Valdes et al. (2012).

**Ethnicity and Interaction with Age**

Many authors have reported T1D rates that varied by ethnicity both outside and within the United States, but most were not statistically significant (Demmer et al., 2013; Imperatore et al., 2012; Lipman et al., 2013; Smith et al., 2007). However, some authors reported significant differences. Dabelea, Mayer-Davis et al. (2014) and Pettitt et al. (2014) reported that the prevalence of T1D, among children between 0 and 19 years old, was significantly different between most of the ethnicities. Dabelea, Mayer-Davis et al. reported the highest prevalence per 1,000 among the White (2.55, 95% confidence interval [CI] 2.48 to 2.62)) and Black (1.62, 95% CI 1.50-1.75) populations, and the lowest among the American Indian population (0.35, 95% CI 0.26-0.47). Using some slightly different ethnic categories, Pettitt et al. reported the highest prevalence in the

NHW population as 2.55 per 1000 (95% CI 2.48–2.62). The prevalence estimates per 1000 for the remaining ethnicities were reported by Pettitt et al. as follows: Black 1.63 (95% CI 1.51–1.77), Hispanic 1.29 (95% CI 1.21–1.37), Asian/Pacific Islander 0.60 (95% CI 0.51–0.70), and American Indian/Alaskan Native 0.35 (95% CI 0.26–0.47).

Other researchers have reported similar results indicating higher occurrence in NHW populations utilizing portions of the SEARCH data with a case control study design (D'Angeli et al., 2010; Liese et al., 2012). Outside the United States, Derraik et al. (2012) reported different incidence rates between some ethnicities in Europe. Although there have been inconsistencies, possibly due to the use of different ethnicity categories/definitions, it appears that the preponderance of findings have suggested that T1D occurrence is different between ethnicities and therefore supports the inclusion of an ethnicity variable in T1D analyses.

Another way to look at the role of ethnicity is to stratify by age of onset. Using the SEARCH study, Pettitt et al. (2014) reported statistically significant differences in the prevalence of T1D in patients under 20 years old when stratified by age categories. For NHW, the prevalence was significantly higher across all age categories (0 to 4, 5 to 9, 10 to 14, and 15 to 19). In contrast, Lipman et al. (2013) reported no statistically significant differences within individual age categories in incidence between ethnicities. The nonsignificant finding was due to the large widths of the confidence intervals. For example, the incidence per 100,000 for children with onset age 10 to 14 was highest in White children 24.3 (95% confidence interval [CI] 17.6-32.6) and lowest in Black

children (17.4, 95% CI 13.0-22.8). Further investigation of age and ethnicity is warranted.

### Clinical Presentation and Relationship to Age, Gender, and Ethnicity

The clinical presentation at onset of T1D can range from mild to life threatening diabetic ketoacidosis (DKA). Al Rashed et al. (2011) reported the most frequent symptoms in children (ages 0 to 18) prior to diabetes diagnosis were nocturia, polyuria (increased urination), polydipsia (excessive thirst), and weight loss. The International Diabetes Federation (2013) reported other symptoms can include increased hunger (polyphagia), slow healing wounds, recurrent infection, and blurred vision. The reported average duration of symptoms prior to diagnosis in children less than 19 years old ranges between 2 and 2.8 weeks (Al Rashed et al., 2011; Galler et al., 2010). Authors have also reported that symptoms can be absent or unnoticed and therefore patients present with DKA (Rewers et al., 2008). Of all the symptoms, DKA appeared most often in my literature review regarding clinical presentation and has been reported to be associated with age of onset (described below).

DKA is sometimes the first event leading to T1D diagnosis, probably because it is the most dramatically noticeable. Rewers et al. (2008) reported 29.4% of T1D diagnoses in children less than 20 years old had presented with DKA. Other authors reported higher percentages, ranging between 30.1% and 49.9% (Al Rashed et al., 2011; Dabelea, Rewers et al., 2014; Rodacki et al., 2007). However, Larsson et al. (2011) reported only 13.1% of children under 5 years old at T1D onset presented with DKA. These results were derived from the TEDDY study, which involved genetic and antibody screening from infancy

(defined as under 4.5 months) and continued follow-up thru 15 years. A limitation of the study is that TEDDY participants may be less likely to present with DKA than participants of large registry studies in the United States and Germany because TEDDY's unique study design increased parental awareness and provided close surveillance. Parental/patient awareness is a factor in DKA diagnosis. Usher-Smith, Thompson, Ercole, and Walter (2012) reported an inverse association between awareness and DKA incidence utilizing a meta-analysis that included 31 countries.

**Age of Onset**

There are also associations between age and DKA. Usher-Smith, Thompson, Sharp, and Walter (2011) reported an increased risk of DKA in younger children. In the 2011 Usher-Smith et al. study, increased odds were reported in children with age of onset less than 2 years compared to children at least 2 years old (odds ratio [*OR*] = 3.41, 95% CI 2.54- 4.59). Although these data were less strong, Usher-Smith et al. (2012) also reported the association when divided at the 5 year mark (*OR* = 1.59, 95% CI 1.38-1.84). Other researchers have also reported an inverse association with age (Dabelea, Rewers et al., 2014; Rewers et al., 2008; Rodacki et al., 2007). Age appears to be a significant factor even after controlling for other variables, suggesting an independent biological mechanism related to age. The above data strongly suggest that T1D commonly presents with DKA and the frequency of this presentation is related to age of onset thereby supporting the need for investigations regarding T1D age of onset.

**Gender**

The relationship between gender and DKA presentation at T1D diagnosis is not completely clear. Although researchers have reported no associations between presentation with DKA at diagnosis and gender (Rewers et al., 2008; Rodacki et al., 2007; Usher-Smith et al., 2011), Al Rasheed et al. (2011) reported females were significantly more likely to present with DKA. In support, Samuelsson et al. (2013) reported higher mean HbA1c in females at onset compared to males ($p < 0.01$).

With regard to other symptoms at presentation, Al Rasheed et al. (2011) reported females were more likely to present with polyuria, polydipsia, fatigue, nocturia, and abdominal pain. In contrast, males were more likely to present with weight loss. While Samuelsson et al. (2013) reported no difference between genders with presentation of polydipsia, polyuria, and weight loss. Al Rasheed et al. reported no association with gender and polyphagia, dehydration, anorexia, fever, delayed wound healing, vomiting, preceding illness, loss of consciousness, and diarrhea.

The above findings suggest that gender may not be a significant factor in clinical presentation, but study findings have not been unanimous. It is important to continue to study gender as a variable in order to determine whether it does play a role in T1D diagnosis and clinical presentation.

**Ethnicity and Socioeconomic Factors**

Data on the relationship between DKA, ethnicity, and socioeconomic factors are more controversial. Findings from analysis of SEARCH study patients under 20 years old found no associations between T1D diagnosis and ethnicity (Rewers et al., 2008).

However, DKA with diabetes diagnosis was significantly more likely in patients with parents who had less than a high school education and family income less than $35,000, as well as having Medicaid insurance, suggesting that SES and education are confounders. In contrast, Rodacki et al. (2007) reported that a significantly higher percentage of non-White patients presented with DKA compared to white T1D patients (49.2% compared to 25.9%). In a multivariate analysis adjusting for age of onset, the odds ratio for non-White patients presenting with DKA upon diagnosis of T1D was 2.2 (95% CI 1.46–3.06) (Rodacki et al., 2007). A limitation of these findings is that Rodacki et al. did not include socioeconomic variables in the analysis; therefore, it is unclear if the significant ethnicity result was due to ethnicity or socioeconomic indicators. Furthermore, Dabelea, Rewers et al. (2014) reported the odds ratio for non-White patients compared to NHW patients was 1.218 (95% confidence interval 1.033–1.436). Similar to Rewers' findings on SES, researchers have reported increased odds of DKA presentation for children with no health insurance or health insurance other than private compared to those with private insurance, and increased odds for children with family income between $25,000 and $50,000 compared to those with incomes between $50,000 and $75,000 (Dabelea, Rewers et al., 2014). Given that Larsson et al. (2011) and Usher Smith et al. (2012) reported an inverse association between DKA frequency and awareness, it may be possible that lower SES indicators may be associated with decreased awareness of DKA and therefore increased diagnosis of DKA. The above findings do suggest that DKA presentation at T1D diagnosis is associated with SES, and possibly ethnicity.

## Health Outcomes Associated with Type 1 Diabetes

T1D has been associated with a variety of detrimental complications, including diabetic neuropathy (Al Rasheed et al., 2011; Bjornstad et al., 2013; Makura, Nirantharakumar, Girling, Saravanan, & Narendran, 2013), nephropathy (Bjornstad et al., 2013; Hagg et al., 2013; Hietala, Forsblom, et al., 2013; Makura et al., 2013), cardiovascular disease (Subedi et al., 2013), congenital heart defects in offspring (Ailes et al., 2012), end-stage renal disease (Harjutsalo et al., 2011; Luk et al., 2014), heart failure (Lind et al., 2011), hypertension (Costacou & Orchard, 2013), hypoglycemia (Blasetti et al., 2011; Carlsson et al., 2013, Cooper, O'Connell, Davis, & Jones, 2013; Craig et al., 2007; Doggen et al., 2012), ketoacidosis (Craig et al., 2007; Doggen et al., 2012; Rodacki et al., 2007; TEDDY Group, 2008), lower extremity amputation (Sahakyan et al., 2011), persistent microalbuminuria (de Boer et al., 2011), reduced gray matter in brain (Hughes et al., 2013), lower intelligence quotient (IQ) (Lin, Northam, Werther, & Cameron, 2015) retinopathy (Al Rasheed et al., 2011; Kramer & Retnakaran, 2013; Makura et al., 2013), proliferative retinopathy (Harjutsalo et al., 2011; Hietala, Forsblom, et al., 2012), sleep insufficiency (Estrada, Danielson, Drum, & Lipton, 2012), and stroke (Hagg et al., 2013). The distribution of these complications may differ by age of onset, duration of T1D, gender, ethnicity, and other demographic variables. The following section describes the recent significant literature on these outcomes.

### Health Outcomes Associated with Age of Onset

Hypoglycemic events are a significant complication for many T1D patients. Levy-Shraga et al. (2013) reported a lower 10 year rate of severe hypoglycemic events in

Israeli children with age of onset greater than 6 years compared to those who were diagnosed younger than 6 years of age, at 6.9 and 4.4 per 100 patient-years, respectively. Similarly, Doggen et al. (2012) found that the risk for hypoglycemia was lower in the oldest age category (16 to 18 years old) compared to younger patients (0 to 15 years old). The researchers reported no significant difference in the 10 year rate of DKA between the age groups, when DKA events occurring at the time of diagnosis were excluded (Doggen et al., 2012). The above findings suggest the risk of hypoglycemic events, but not DKA, may be lower in children that are diagnosed at older ages.

Several authors have analyzed the risk of end-stage renal disease (ESRD) by age of onset. Finne et al. (2005) and Svensson et al. (2006) reported the risk of ESRD was lowest in those diagnosed at 0 to 4 years of age. This finding is contrary to an assumption that complication risk is higher with younger age of onset. Obviously the assumption is not true and, in fact, progression of some diabetic complications may be accelerated when T1D is diagnosed during puberty, due to hormonal changes, rapid growth, and possibly less glycemic control (Svensson et al., 2006). This seems plausible for ESRD given that insulin-like growth factors (IGFs) and growth hormones (GHs) play roles in progression to kidney disease (Flybvjerg, 2000). Absence of an association between age of onset and ESRD when onset is prior to puberty was reported by Harjutsalo et al. (2011). Among males, the lowest cumulative risk of ESRD occurred within patients with age of onset of T1D less than 5 years old and the highest occurred within patients with age of onset between 10 and 14 years. In contrast, this was not seen for females, where the lowest risk of ESRD occurred within patients with age of onset of T1D > 15 years old

and the highest when age of onset was between 5 and 9 years old. Harjutsalo et al. found no gender differences for children diagnosed less than 10 years old. However, T1D female patients with age of onset greater than 9 years old were reported to have significantly less risk of ESRD than male patients. Males with age of onset between 10 and 14 years old had a 91% significantly higher risk than females ($p < 0.0001$). It is possible that the gender differences seen in the long term risk of ESRD may be due to epigenetic modifications dependent on puberty status.

Several authors have reported an association with eye related health outcome and age of onset of T1D. Hietala, Forsblom, et al. (2013) reported the risk of clinically significant macular edema was lowest among patients with a young T1D age of onset. However, Sander et al. (2013) a significantly lower age of onset of T1D in patients with severe macular oedema compared to those without. Similarly, Hietala, Forsblom et al. reported a significantly lower mean age of onset of T1D among patients with proliferative retinopathy [PR] (9.40 years), compared to T1D patients without PR (18.5 years). Similarly, Harjutsalo et al. (2011) reported that, among females, the risk of PR was highest with younger age of onset (< 5 years). However, the risk among males was highest in the 5 to 9 year age group, but not significantly different than the youngest age group and the author reported a significant difference in the 40 year risk of PR between males and females, 72.0% and 52.6% respectively. Similar to ESRD, potential epigenetic modification support the need for T1D research stratified by age of onset and gender.

Female gender is associated with higher risk of eating disorders (Striegel-Moore & Bulik, 2007) and researchers have investigated its association with age of onset of T1D

in females. Takii et al. (2011) reported an increased risk of eating disorders for female T1D patients with age of onset between 7 and 18 years, compared to those with age of onset between 0 and 6 years. Patients with both had a mean age of onset of T1D of 13.9 years and a mean age of onset of an eating disorder of 18.2 years. Rather than attributing the increased risk of the disorder with T1D onset during puberty to growth hormones, as done with ESRD, the increased risk maybe due to occurrence of two simultaneously stressful situations, rather than early T1D onset followed by later puberty onset (Takii et al., 2011). These data indicate that eating disorder prevention for patients with T1D diagnosis during these years is critical, because recovery from eating disorders is difficult.

Although autoimmune disease is also more prevalent in females (Gleicher & Barad, 2007), an association with age of onset of T1D has been investigated in both genders. Levi-Shraga et al. (2012) reported an increased risk of celiac disease in T1D patients (males and females) with age of onset between 0 and 6 years, compared to those with age of onset greater than 6 years. However, age of onset of T1D was not associated with Grave's or Hashimoto's disease (Levi-Shraga et al., 2012) or asthma (Black et al., 2011). Taler et al. (2012) reported no significant difference in lag time between T1D diagnosis and celiac disease diagnosis between patients with age of onset of T1D less than 6 years compared to T1D patients diagnosed at older ages. In fact, the relationship between celiac disease and T1D is largely genetic (Ostensson et al., 2013), therefore lack of literature demonstrating relationships with age of onset of T1D is not surprising.

Dalhquist et al. (2008) investigated the risk of hospitalization due to T1D complications and reported increased risk of hospitalization with older age of onset (risk ratio 1.37, 95% CI 1.26–1.56) among Swedish children followed for at least 10 years. However, other researchers have reported no association between age of onset and other combined endpoints, including risk of lower limb amputation due to T1D complications (Sahakyan et al., 2011) and mortality (Feltbower et al., 2008). Overall, the literature demonstrates inconsistent results for a relationship between age of onset and various health outcomes, supporting a great need for additional studies on T1D that stratify by age.

**Health Outcomes Associated with Gender**

Some health outcomes have been associated with gender. Researchers have investigated the relationship between gender, hospitalization, and mortality in T1D patients. Although some researchers reported no mortality difference between genders (Feltbower et al., 2008; Lin et al., 2014; Livingstone et al., 2012), some authors reported increased risk of hospitalization due to T1D complications in females compared to males (Dalhquist et al., 2008; Ying et al., 2011). This female bias may occur because females seek care more often than males (Dalhquist et al., 2008). Sahakyan et al. (2011) reported increased risk of lower extremity amputation due to T1D complications in males compared to females (odds ratio 3.90, 95% CI 2.29-6.65). This difference may be due to females having less peripheral arterial disease (Jude, Eleftheriadou, & Tentolouris, 2010) and better foot care practices (Hokkam, 2009). It is not clear from these data that there is

a firm relationship between gender and mortality among T1D patients, but there may be an increased risk of hospitalization among females and amputation among males.

Authors have reported no difference between genders in the occurrence of asthma (Black et al., 2011), hypertension (Costacou & Orchard, 2013), heart failure (Lind et al., 2011), cholesterol levels (Simsek et al., 2013), severe hypoglycemia (Blasetti et al., 2011; Cooper et al., 2013), and stroke (Hagg et al., 2013). Furthermore, Miller, Secrest, Ellis, Becker, and Orchard (2013) reported no difference between genders in the occurrence of stroke, myocardial infarction, ESRD, or blindness. However, there have been contrasting findings to some of the outcomes analyzed by Miller et al. Some authors found incidence of renal replacement therapy for ESRD was lower for T1D females compared to males (Toppe, Möllsten, Schön, Jönsson, & Dahlquist, 2014). Several other authors have looked at eye related outcomes and although some reported no difference between genders in the occurrence of cataract surgery (Grauslund, Green, & Sjølie, 2011), others reported that female T1D patients in Belgium were more likely to undergo retinopathy screening that males (Doggen et al., 2012). Doggen et al.'s findings are in line with the idea that females may seek care sooner. In summary, although treatment and screening of some complications appear to differ by gender, the literature suggests that asthma, blindness, hypoglycemia, myocardial infarction, and stroke do not differ by gender.

**Health Outcomes Associated with Duration of Type 1 Diabetes**

Many researchers have reported the association between the length of time a patient has had T1D and increased risk of complications, including heart failure (Lind et al., 2011), severe hypoglycemia (Blasetti et al., 2011; Gruden et al., 2012), diabetic

neuropathy (Nin et al., 2011; Simsek et al., 2013), retinopathy (Hietala, Forsblom, et al., 2013; Simsek et al., 2013), macular oedema (Sander et al., 2013), microalbuminuria (Simsek et al., 2013), and stroke (Hagg et al., 2013). However, some researchers have reported no association between duration and the occurrence of myocardial infarction, stroke, ESRD, blindness (Miller at al., 2013), asthma (Black et al., 2011), dyslipidemia (Simsek et al., 2013), hospitalization (Bächle et al., 2013), and mortality (Feltbower et al., 2008). These inconsistent results may be due associations with gender and age of onset. For example, Cooper et al. (2013) reported a significant association between the occurrence of severe hypoglycemia and the duration of T1D in T1D patients with age of onset between 12 and 18 years. This association was not apparent in the 0 to 6 and 6 to 12 age groups. Other examples exist from Hagg et al. (2013) and de Boer et al. (2011). Specifically, Hagg et al. reported a significantly higher mean duration for male T1D patients with hypertension compared to those without hypertension (20.0 and 16.7 years of T1D duration, respectively). This association was not significant for females. de Boer et al. (2011) reported that the cumulative incidence of persistent microalbuminuria increased rapidly in T1D patients with duration between 10 and 20 years, then plateaued after 20 years with the disease. Regarding screening and treatment of complications, researchers have reported no association between duration of T1D and cataract surgery (Grauslund et al., 2011), and screening for retinopathy, microalbuminuria, thyroid autoimmunity, and celiac disease (Doggen et al., 2012). In general, the data demonstrate that the risk of many complications increase with duration of T1D.

### Health Outcomes by Ethnicity and other Demographic Variables

Some researchers have investigated the occurrence of complications by ethnicity. Doggen et al. (2012) reported no association between Belgium ethnicity and DKA as well as screening for retinopathy, thyroid autoimmunity, celiac disease, and microalbuminuria. Additionally, Adlercreutz, Wingren, Vincente, Merlo, and Agardh (2015) reported no association between maternal education level and income, and celiac disease in T1D patients. However, others have reported associations. For example, using SEARCH, Black et al. (2011) reported a significant association between ethnicity and the occurrence of asthma for T1D patients, in which NHW T1D patients were less likely to report asthma while Blacks and Hispanics were more likely to report asthma. Furthermore, Lewis, Clark, and Velarde (2014) reported significant associations between ethnicity and insurance status to the occurrence of DKA events after T1D onset, in which both African American children and those with Medicaid/Chips insurance were more likely to experience DKA after T1D onset (OR 17.4 and 9.3, respectively). Together this evidence suggests differences in T1D care and outcomes between ethnicities, and supports including ethnicity as a variable for investigation in this research.

## Societal Burden of Type 1 Diabetes

The International Diabetes Federation (2013) reported that diabetes costs in the United States and the Caribbean were $263 billion in 2013. The American Diabetes Association (2013) reported that diabetes costs in the United States were $245 billion in 2012. This included $175,819 billion in health care related costs. Specific to T1D, Tao, Pietropaolo, Atkinson, Schatz, and Taylor (2010) estimated the yearly cost of T1D in the

United States as $14.4 billion. Additionally, Ying et al. (2011) reported an average expense of $4,730 per year for T1D patients under 20 years old.

Diabetes related health care costs come from various sources. Bächle et al. (2013) reported the top four health care costs for children with T1D are: self-monitoring test trips and lancets (28.5%), insulin pump and infusion sets (25.0%), Diabetes-related hospitalization (22.1%), and insulin (18.4%). These accounted for 75.6% of the total costs. Similarly, Ying et al. (2011) reported 71% of diabetes-related costs in children were from medications and supplies. Ying et al. also reported females and children of unmarried parents incurred higher cost than their counterparts. This evidence supports examination of T1D by gender.

Not only is the cost of T1D high with respect to dollars, but it is also high with respect to quality of life. Lung, Clarke, Hayes, Stevens, and Farmer (2013) created a model to calculate life expectancy of current 15 year old T1D patients, using data from inside and outside the United States. The author reported 49.9 (95 % CI 38.8–61.2) and 44.3 (95 % CI 32.4–56.1) remaining years for females and males, respectively. This is lower than 64.2 years (CDC, 2009), which is the remaining life expectancy for 15 year olds in the United States. In line with reduced life expectancy, Feltbower et al. (2012) reported that the mortality for the T1D patients in Yorkshire was as much as 6.8 times higher than the background population. In addition, Tao et al. (2010) reported T1D patients missed significantly more school/work days than matched controls and T1D patients over 18 years old earned significantly less income than matched controls. The

cost of T1D is a significant public health burden and more research towards prevention would be beneficial.

## Risk Factors for Type 1 Diabetes

Due to the elusive etiology of T1D, researchers have investigated a variety of factors to identify risk factors for T1D. Genetic and environmental factors have both been implicated. Environmental causes range from infectious and climate exposures, to prenatal and early feeding exposures. In this section I provide a summary of current research literature related T1D risk factors, and when appropriate, their relationship to the study's conceptual framework, the hygiene hypothesis, and its three primary variables: age of onset, gender, and ethnicity.

### Family History and Genetics as Risk Factors for Type 1 Diabetes

The most agreed upon risk factors for T1D is family history and genetics. Researchers have consistently reported an increased risk for T1D among children who had a first degree relative with T1D (Lundgren, et al., 2015; Snell-Bergeon et al., 2012; TEDDY Study Group, 2008; Welander et al., 2014). Authors have reported between 12.8% and 76.5% of T1D patients had a family history of the disease (de Beaufort et al., 2013; Galler et al., 2010; Luk et al., 2014; Smith et al., 2007; Welander et al., 2014). Some research supports increased risk among children in which the parent had either T1D or T2D (D'Angeli et al., 2010). However, D'Angeli et al. (2010) reported no increased risk for children whose mothers had gestational diabetes. Findings of family history associations support continued genetic research.

Genetic investigations have uncovered specific sections of chromosomes and single nucleotide polymorphisms (SNPs) that account for increased risk within families. For example, the human leukocyte antigen (HLA) system on chromosome 6p21 contains genes that are strongly associated with the risk of T1D (Kockum et al., 1999; Snell-Bergeon et al., 2012). In fact, Emery et al. (2005) reported an association between particular HLA genes and age of onset, as well as ethnicity. This evidence underscores the importance of genetics, age of onset, and ethnicity in T1D research.

**Infections as Risk Factors for Type 1 Diabetes**

Given that not all individuals with high risk genotypes develop T1D (Portuesi, Pozzilli, Boehm, Buzzetti, & Filippi, 2013), researchers have investigated infections as potential environmental risk factors. In fact, genetically susceptible individuals may require precisely timed environmental triggers in order to develop T1D (Knip et al., 2005). For example, Tirabassi et al. (2010) reported that the susceptibility of mice to develop T1D in response to *Cytomegalovirus* and *Parvovirus* triggers decreased with increasing age. In human studies, researchers have reported a significant association between T1D and the *Ljungan virus* (Nilsson et al., 2013) and enteroviruses (Lin et al., 2015), as well as the *Mycobacterium avium* subsp. *Paratuberculosis* bacteria (Bitti et al, 2012). Furthermore, these research groups reported that the infections were associated some HLA genotypes. This evidence is in line with the pathophysiology of T1D given that viruses can cause inflammatory responses (Lehuen, Diana, Zaccone, & Cooke, 2010; Seewaldt et al., 2000) and promote IFN (Sakar et al., 2012; Schulte et al., 2012).

**Infections as Protective Risk Factors for Type 1 Diabetes**

Researchers have also reported certain infections as protective environmental triggers. Parasitic worm (helminth) infections initiate physiological responses that suppress and activate different mechanisms that inhibit pancreatic β cell destruction (Liu et al., 2010). Authors have reported an increases in IL-4 or IL-10 and a Th2 shift offered protection against the inflammatory responses that triggered autoimmune destruction from *Trichinella spiralis* (Saunders et al., 2007), *Fasciola hepatica (*Lund et al., 2014), *Heligmosomoides polygyrus* (Saunders et al., 2007) and *Litomosoides sigmodontis* (Hübner, Stocker, & Mitre, 2009). Furthermore, the viral and bacterial infections from nonhelminth sources that have been shown to protect against T1D by increasing IL-10, Tregs, and IFN-γ in mice are *Escherichia coli*. (Pang et al., 2013) and *Salmonella typhimurium (*Caramalho et al., 2011). These findings are consistent with the pathophysiological knowledge regarding the suppressive roles of increased IL-4 and IL-10 on Th1 cells and support the hygiene hypothesis.

The above literature highlights the complex nature of the immune system and how genetics and infections may be involved in both the prevention of and the development of T1D. It is beyond the scope of this study to determine the pathophysiological responses to various infectious triggers and how these may impact T1D prevention or occurrence. However, some of the evidence related to infections supports the hygiene hypothesis and therefore supports its use as a conceptual framework in which to investigate T1D incidence.

**Socioeconomic Indicators as Risk Factors for Type 1 Diabetes**

Various authors have investigated the relationship between T1D and neighborhood based socioeconomic indicators. Liese et al. (2012) reported a protective effect from T1D for children aged 10 to 19 between 2003 and 2006 living in neighborhoods classified as below poverty (adjusted OR = 0.88, 95% confidence interval [CI] 0.78, 0.99) and receiving social security (adjusted OR = 0.85, 95% CI 0.77, 0.93). Cooper et al. (2013) reported 81.3% of T1D patients in Western Australia lived in middle (40.3%) or high (41.1%) socioeconomic areas compared to only 18.6% living in low socioeconomic areas, using a population-based study. Liese et al. reported increased risk of T1D regarding variables that could be associated with higher SES, including: children living in neighborhoods with increased education (adjusted OR = 1.09, 95% CI 1.01, 1.19), increased income (adjusted OR = 1.14, 95% CI 1.03, 1.27), increase vehicle ownership (adjusted OR = 1.18, 95% CI 1.02, 1.37) and increased neighborhood socioeconomic advantage score (adjusted OR = 1.32, 95% CI 0.99, 1.77). Together, literature suggests an association between increased incidence of T1D and high SES and supports T1D research related to the hygiene hypothesis.

Various authors have investigated the relationship between T1D and individual socioeconomic indicators. Although Adlercruetz et al. (2015) reported no association between maternal income and risk of T1D, other authors have reported protective effects from factors associated with low SES: household crowding (Snell-Bergeon et al., 2012), immigrant status (Hussen et al., 2013), Medicaid/Medicare insurance (D'Angeli et al., 2010), children of unmarried mothers (D'Angeli et al., 2010), prenatal care starting after

the first trimester (D'Angeli et al., 2010), and inadequate prenatal care (D'Angeli et al., 2010). Furthermore, education level of parents is associated with SES and decreased risk of T1D has been reported for children whose mother's education level less than 12 years (D'Angeli et al., 2010) and for male children whose parents had less than 10 years of education (Hussen et al., 2013). For female children, Hussen et al. (2013) reported a slightly but not statistically significant increase in T1D risk for children whose parents had less than 10 years of education. In contrast, Adlercruetz et al. (2015) reported a statistically significant decrease in T1D risk for children whose mother had less than 12 years of education. Welander et al. (2014) reported no significant association with maternal education. Because these factors could be associated with low SES and possibly differ by gender, the majority of this evidence supports research related to the hygiene hypothesis and gender.

**Accelerated Growth as a Risk Factor for Type 1 Diabetes**

Similar to BMI as a risk factor for T2D, researchers have investigated growth as a risk factor for T1D. The accelerator and overload hypotheses postulate that accelerated growth, weight gain, or stress in childhood can overload β cells causing stress and insensitivity (Dahlquist, 2006; Knip, 2012; Sepa & Ludvigsson, 2006). In fact, the accelerator hypothesis has been used to describe the etiology of both T1D and T2D because, according to the hypothesis, the pathophysiology of each is similar only T1D manifests sooner in genetically susceptible individuals (Wilkin, 2009). Although this is in contrast to the pathophysiological explanations provided by many authorities (American Diabetes Association, 2014), some researchers have reported results in support of these

hypotheses with respect to BMI (Evertsen et al., 2009), infant exposure to sugar containing beverages (Crume, et al. 2014), maternal insulin resistance (Leech et al., 2010), mother's BMI at delivery and prepregnancy weight (D'Angeli et al., 2010) and stress (Zung et al., 2012). In contradiction, some researchers have reported clinical study results that do not support these hypotheses (D'Angeli et al., 2010; Dabelea, Mayer-Davis et al., 2014; Welander et al., 2014). Together the evidence underscores the elusive nature of the etiology of T1D and supports the need for continued demographic research.

**Climate/Season as a Risk Factor for Type 1 Diabetes**

Environmental factors are involved in the etiology of T1D (Knip, 2012; TEDDY Group, 2008). Specifically, some researchers have investigated the role of season on the occurrence of T1D. For example, Adlercruetz et al. (2015), Lipman et al. (2013), and Zung et al. (2012) reported no significant seasonal effects when analyzing incidence data from population-based data in Sweden, Philadelphia, and Israel, respectively. However, Samuelsson et al. (2013) reported the highest number of diagnosed cases in January thru March, and Galler et al., 2010 reported the lowest in June. Furthermore, Samuelsson et al. reported that the seasonal association is stronger for males than females. Hodgson et al. (2012) reported lower number of male T1D cases aged 5 to 14 in May, June, July and August, this was also somewhat apparent for females. Furthermore, Hodgson et al. reported the highest number of cases occurred in males and females aged 10 to 14, separately, in January using population-based hospital data from 1992 thru 2006 in England. The authors reported that seasonal effects were not as strong for T1D patient with age of onset between 0 and 4. Conclusions in the research appear mixed, but

differences in age of onset and gender support the need for additional studies on T1D that stratify by these two variables.

**Other Environmental Exposures as Risk Factors for Type 1 Diabetes**

Environmental factors are involved in the etiology of T1D (Knip, 2012; TEDDY Group, 2008). Researchers have reported increased of T1D in association with environmental concentrations of barium oxide, manganese oxide, titanium dioxide, copper, lead, nickel, zinc, and mercury (Samuelsson & Löfman, 2014), polybrominated diphenyl ethers (Lim, Lee, & Jacobs, 2008), as well as the timing of dietary gluten introduction (Snell-Burgeon et al., 2012). Snell-Burgeon et al. (2012) reported that T1D islet autoimmunity was more likely to develop among children with early (0 to 3 months) and late (7 to 9 months) exposure to gluten-containing grain (hazard ratio [HR] = 3.14 and 1.41, respectively) compared to exposure between 4 and 6 months. Furthermore, Virtanen (2011) reported that babies with diabetes' related SNPs were at increased risk of developing the disease if they had certain kinds of food before 3 months (eggs, wheat/rye/barley/oat cereal, and/or root vegetables). Although Crume et al. (2014) reported no association between the timing of gluten exposure (as well as vegetables, meat, and dairy) to the age of T1D onset, the authors did report a lower mean age of onset among children introduced to sugar containing beverages (excluding juice) between 3 and 6 months compared to exposure after 12 months of age. The research indicates that age at exposure to potential environmental triggers is important, and supports the use of age of onset as a variable in my study.

The literature indicates a variety of risk factors; some appear to have consistent results across studies while others do not. Furthermore, some appear to support current etiological hypotheses while others do not. Although ambiguity exists, a plethora of evidence does support the hygiene hypothesis and risk factor associations with age and gender. Together the evidence supports the use of the hygiene hypothesis as the conceptual framework for my study and the use of age of onset and gender as variables in my study.

## Prevention, Diagnosis, and Treatment

Currently there are no preventative recommendations for T1D (Ramachandran et al., 2014). In fact, Shalitin and Chase (2011) and Hamman et al (2014) identified prevention as a major goal of T1D research however population-based preventative research is difficult because the human pancreas in hard to access for biopsies, and the onset of the disease often occurs in children and the blood supply is limited in children (Boettler & von Herrath, 2011). Instead, the literature contains a growing body of evidence regarding methods to identify high risk children in order to identify preventative factors. High risk children can be identified by the presence of islet autoantibodies and are detected by measuring glutamic acid decarbolase ($GAD_{65}$), mIAA, and IA-2 (Sosenko et al., 2012; Ziegler et al., 2013). Sosenko et al. (2012) explored the use of a diabetes risk score (DPTRS) in predicting T1D diagnosis in patients with autoantibodies and a family history to T1D. These researchers validated the score algorithm which consisted of a proportional hazards model using BMI, age, fasting glucose, and C-peptide levels. Sosenko et al. reported an 88% (95% CI 79%-94%) risk of T1D diagnosis within 2 years

of testing positive for islet cell antibodies and meeting the 9.0 DPTRS threshold. The risk was reduced to 77% (95% CI 63%-99%) when the definition was modified to require only one of three autoantibodies, specifically GAD, mIAA, IA-2A. Furthermore, Sosenko et al. reported that the use of DPTRS enabled detection of T1D an average of > 9 months prior to diagnosis via standard methods. Together, this research shows that early detection methods are in use in a variety of research projects and supports the purpose of my study which was to provide public health researchers with the data to design more targeted prevention trials and obtain further information about risk factors.

According to the American Diabetes Association (ADA, 2014) there are four standard laboratory methods for diagnosis of T1D (Table 2). The American Diabetes Association (ADA) introduced the first three criteria in 2003 to replace and revise criteria previously recommended by the World Health Organization (1985) and the National Diabetes Data Group (1979). One of the major revisions was the threshold decrease from fasting plasma glucose (FPG) > 140 mg/dl to FPG ≥ 126 mg/dl. The ADA (2013) reported that patients identified via FPG or 2-hour PG would have the same degree of hyperglycemia (Gavin et al., 2003). After release of the first three, the ADA revised the methods to include HbA1c in 2010, specifically the fourth criteria in Table 2. Although there remains controversy in using HbA1c for diagnosis in children (Buse et al., 2013; Lee et al., 2011) and HbA1c is less sensitive than using a fasting glucose threshold of ≥ 126 mg/dL, the ADA surmises that more patients may be diagnosed because HbA1c is a more convenient test (ADA, 2014). This timeline supports the need to identify potential

study patients according to their diagnosis year and include only those diagnosed after 2002.

Table 2

*Criteria for the Diagnosis of Diabetes*

| |
|---|
| FPG ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.* |
| OR |
| Two-hour PG ≥200 mg/dL (11.1 mmol/L) during an OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.* |
| OR |
| In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥ 200 mg/dL (11.1 mmol/L). |
| OR |
| A1C ≥ 6.5%. The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.* |

*Note*. From "Standards of Medical Care in Diabetes - 2014," by the American Diabetes Association, 2014, *Diabetes Care, 37*(1), p. S15. Reprinted with permission (see Appendix).
*In the absence of unequivocal hyperglycemia, result should be confirmed by repeat testing.

When diagnosis occurs early, patients can participate in research to find a cure. Researchers have investigated pharmaceutical options to reverse β cell destruction (Christensen et al., 2014; Haller et al., 2015; Ludvigsson et al., 2012), as well as creation and implantation of insulin producing β cells (Kroon et al., 2008; Li et al., 2014; Rezania et al., 2012). Although creation of functioning β cells sounds promising, this is currently a "black box" process because the exact maturation process of the β cells is unknown and may produce both therapeutically beneficial and deleterious outcomes (Schiesser & Wells, 2014). The evidence supports the need to identify patients prior to destruction of all β cells.

Although there is no cure for T1D, patients are treated with exogenous insulin. Prior to 1923 when insulin became widely distributed, inadequate treatment was varied (including restrictive diets and bloodletting) and children quickly died or lived with debilitating symptoms (King & Rubin, 2003; Raju, 2006; Rosenfeld, 2002). Currently, Basal–bolus is considered the gold standard for insulin treatment (Carlsson, 2013). In fact, Doggen et al. (2012) reported basal-bolus as the most frequent treatment regime among a Belgium cohort of adolescent T1D patients with age of onset under 19 years. Research continues in the area of insulin delivery options, including insulin pumps (Cooper et al., 2013; de Bock et al., 2012, Kallas-Koeman et al., 2014; Lawson et al., 2014; Ly et al., 2013), implantable insulin pumps (van Dijk et al., 2014), handheld computerized feedback systems (Kovatchev et al., 2011), closed loop systems for monitoring and delivery of insulin (Dauber et al., 2013; Hovorka et al., 2010), intensive vs. conventional insulin monitoring regimes (Nathan, 2014), patches to increase insulin absorption (Landau), and varying types of insulin (Heller, Bode, Kozlovski, & Svendsen, 2013; Carlsson et al., 2013). Cooper et al. (2013) researched the prevalence of three different types of treatments, specifically continuous subcutaneous insulin infusion, twice-daily injections, and multiple-daily injections, in T1D patient with age of onset between 0 and 18 years. Cooper et al. reported a decreased risk of hyperglycemic events with the use of an insulin pump compared to twice daily injections (IRR 0.58, 95% CI 0.4, 0.9) in T1D patients with age of onset between 12 and 18 years. This protective effect was not seen in the other age groups, 0 to 6 and 6 to 12 years. Together this evidence shows that T1D patients have a variety of treatment options and the incidence of

hyperglycemic events may be associated with age of onset for specific treatment options, therefore age of onset is a valuable variable in the analysis of T1D.

The ultimate goal of T1D treatment is to create a balanced glycemic status that reduces the frequency of hyperglycemia and hypoglycemia (Kovatchev et al., 2011). Treatment is important because researchers have reported that good glycemic control (e.g., HbA1c levels within range of nondiabetic patients) is associated with reduced or delayed incidence of some complications, including cardiovascular disease (Lachin, Orchard, & Nathan, 2014; Lind et al., 2011), cardiovascular autonomic neuropathy (Martin, Alber, &Pop-Busui, 2014), congenital abnormalities in offspring (Bell et al., 2012), diabetic retinopathy (Aiello, 2014; Hietala, Wadén, et al., 2013), lower limb amputation (Sahakyan et al., 2011) and peripheral neuropathy (Martin et al., 2014). Dias et al. (2013) reported significantly different HbA1c levels between ethnicities during a 2 year intensive insulin treatment study of T1D children under 18 years old. Furthermore, Davison et al. (2012) reported differences in adherence to T1D prescribed diet between ethnicities. This supports the need to include ethnicity in T1D analyses.

## Literature Review of Methodology

There are several valid study design options for analyzing the epidemiology of T1D. A case-control design was used by several authors in this literature review to describe potential risk factors for T1D (Leech et al., 2010; Miettinen et al., 2012). Both prospective (de Boer et al., 2011; Sahakyan et al., 2011) and retrospective cohort designs (Levy-Shraga et al., 2012) were used to describe the complications of T1D. Lind et al. (2011) employed the use of a hospital based cross-sectional study designed to investigate

the occurrence of heart failure among T1D patients. I also selected a data source with a cross-sectional design, NHANES, but it was not hospital based. NHANES is a population-based data source and therefore not subject to the potential bias reported by Lind et al. (2011) due to incomplete ascertainment of the T1D population. Furthermore, NHANES is not subject to the potential bias due to small sample size noted in multiple studies reviewed for this chapter (Bruehl, 2011; Chisholm et al., 2011; Takii et al., 2011). I determined the cross-sectional design of NHANES was the best fit for answering my research question because it was population based, has a large sample size, and not subject to incomplete ascertainment.

In addition to bias introduced by incomplete ascertainment, distinguishing T1D from T2D in datasets can lead to bias in T1D research (Dias et al., 2012; Toppe, et al., 2012). In T1D research, various classification algorithms have been employed to reduce this bias (Constantino et al., 2013; D'Angeli et al., 2010; Demmer et al., 2013; Lee et al., 2011). Demmer et al. (2013) employed an algorithm that distinguished T1D from T2D patients via examination of their insulin use within an NHANES sample. Because I also used NHANES, I employed the classification algorithm used by Demmer et al. to distinguish T1D from T2D patients. Only patients who reported using insulin were included in the analysis sample for my study. This inclusion criteria should limit potential misclassification bias given Elder et al. (2012) reported only 18% of T2D patients (mean age 15.2 years) use only insulin for treatment, as compared to 82% who use insulin in combination with oral antidiabetes medications. This evidence supports the inclusion criterion that was used in my study.

Non-response bias is a possibility in cross-sectional survey based studies. Bias from non-responders is introduced if the non-responders significantly differ from the responders (Last, 1995). For example, Black et al. (2011) reported an analysis of survey responses utilizing only 62% of the targeted responders. In order to determine the magnitude of bias from the non-responders, Black et al. compared the non-responders to the responders and found that little or no bias had been introduced due to incomplete recruitment. Similarly, the CDC (2013c) performed an analysis to assess the magnitude of non-response bias in the NHANES cycles ending in 2012 and reported reduced bias with the use of sampling weights. Because my analysis plan includes the use of sampling weights, this evidence supports my decision to employ NHANES.

Selection bias occurs if the selected group differs systematically from the unselected groups. This is often acknowledged as a study design limitation, and noted in multiple studies reviewed for this chapter (Carlsson et al., 2013; Chisholm et al., 2011; Davison et al., 2014; Makura et al., 2013; Takii et al., 2011). In contrast, population-based study designs are often less impacted by selection bias. Furthermore, population-based samples can have the benefit of including an ethnically diverse sample (Black et al., 2011; Dabelea, Mayer-Davis et al., 2014). Because NHANES is population based and employs a complex sampling technique to ensure ethnic representation, my decision to use NHANES is supported.

Other elements that may have weakened some of the study results included in this chapter were the inability to adjust for important variables in the analysis because they were not collected (Toppe et al., 2014), missing information at baseline (Bjornstad et al.,

2013), retrospective medical chart review (Levy-Shraga et al., 2012), incomplete follow-up (Dabelea, Rewers et al., 2014), and matched but not randomized case-control design (de Bock et al., 2012). Due to the cross-sectional survey design, these weaknesses are not a threat in NHANES and therefore will not be a threat in my study. Together this evidence demonstrates that study design and data collection are important aspects that can influence interpretation of results. Furthermore, my decision to use NHANES in this study was appropriate and bias was limited.

## Conceptual Framework

The conceptual framework for this study was based on hygiene hypothesis as one of the potential etiologies of T1D. The hygiene hypothesis was first introduced by Strachan in 1989 as an explanation for the rising incidence of allergic hay fever reactions. Strachan (1989) described this as follows:

> [The association between hay fever and position in the household] could be explained if allergic diseases were prevented by infection in early childhood, transmitted by unhygienic contact with older siblings, or acquired prenatally from a mother infected by contact with her children. Later infections or re-infections by younger siblings might confer additional protection against hay fever. Over the past century declining family size, improvements in household amenities and higher standards of personal cleanliness have reduced the opportunity for cross infection in young families. This may have resulted in more widespread clinical

> expression of atopic disease, emerging earlier in wealthier people, as seems to have occurred for hay fever. (Strachan, 1989, p. 1260)

Generally, this hypothesis proposes that the immune system requires a certain amount of exposure to immune-provoking agents during childhood in order to adequately develop; without these exposures (or reduced exposures possibly due to increased hygiene), the development of the immune system may be delayed/changed, which may lead to development of allergic and autoimmune disorders. Furthermore, the timing of exposures is also a critical determinant in the development of future immune responses (Knip, et al., 2005; Pfefferle et al., 2009). This supports including age of onset of T1D as a variable for investigation in this research.

Although the hypothesis was originally introduced as an etiological explanation for hay fever, researchers have investigated it as an etiological explanation for other diseases, such as asthma and T1D. Several authors have reported results in support of the hygiene hypothesis with relationship to many of the factors originally described by Strachan (1989), such as infections (Caramalho et al., 2011; Hübner et al., 2009; Pang et al., 2003; Saunders et al., 2007), older siblings (D'Angeli et al., 2010), family size (Snell-Bergeon et al., 2012), and SES (D'Angeli et al., 2010; Liese et al., 2012). Because SES has often been reported as disproportionate across ethnicities and the timing of nonhygienic exposures may affect immune system functioning, the age of onset of T1D was investigated with respect to ethnicity. In addition to providing information regarding the hygiene hypothesis, this study will provide estimates stratified by ethnicity which will fill the gap in knowledge.

## Summary

T1D, once an entirely fatal disease impacting mostly children, is today a significant public health concern that impacts both children and adults. There are few reliable population level incidence figures available, due to a lack in distinguishing between T1D and T2D diagnoses in survey questionnaires and other records. However, there are approximately 160,000 children under 20 living with T1D in the United States (Pettitt et al., 2014). Due to advances in modern medicine, most of these children will now have the opportunity to reach adulthood and live productive lives. Upon diagnosis and throughout their lives, T1D patients require significant healthcare resources. T1D healthcare costs are thought to reach $6.9 billion annually in the United States (Tao et al., 2010). Although the literature demonstrates there are a variety of treatment options available to patients, the literature also demonstrates that these daily treatment options are a lifelong requirement because the exact etiology of T1D is unclear and therefore no cure exists. One mechanism available to further the etiologic understanding of T1D is investigation of the occurrence by age of onset, ethnicity, and gender using recent, population-based survey findings in the United States. Investigation of these three variables is important because researchers have already reported that the occurrence of T1D differs by age of onset (Berhan et al., 2011; Dahlquist et al., 2011; Harjutsalo, 2008; Hodgson et al., 2012; Imperatore et al., 2012; Lipman et al., 2013; Patterson et al., 2000; Smith et al., 2007; Zung et al., 2012), ethnicity (Derraik et al., 2012, Dabelea, Mayer-Davis et al., 2014; Pettitt et al., 2014), and gender (Doggen et al., 2012; Evertsen et al., 2013; Lipman et al., 2013; Zung et al., 2012). Because population-based estimates for

children less than 20 years old have not been published since 2008, this study will fill an important gap in literature. In the next chapter, I describe a study protocol using a nationally representative sample of children under 20 years old to investigate the relationship between T1D age of onset with ethnicity and gender.

# Chapter 3: Research Method

## Introduction

T1D is currently an incurable disease and a significant public health concern, impacting over 160,000 children less than 20 years old in the United States (Pettitt et al., 2014) and costing $14.4 billion annually in the United States (Tao et al., 2010). The purpose of this study was to examine the relationship between T1D age of onset with ethnicity and gender. This chapter provides a detailed description of the research methods that I used to explore these relationships, including the population-based sample that was used and the statistical tools that were employed.

## Research Design and Rationale

I used a cross-sectional quantitative study design. Creswell (2009) indicated that quantitative designs typically can involve surveys with closed-ended questions. This design involved a statistical analysis of data from the NHANES. All fields used in the analysis were categorical; no open-ended responses needed to be reviewed or coded. The survey data used in this analysis were obtained at a single time point, not a prospective cohort with follow-up time points. NHANES has a cross-sectional study design and can be used to determine disease frequency and explore the variables associated with the disease (Lilienfeld & Stolley, 1994). The cross-sectional nature of the data is consistent with many of the studies reviewed in Chapter 2 and is consistent with the analysis I used to examine the three variables: T1D age of onset, ethnicity, and gender.

# Methodology

## Population

The study population was drawn from a population-based, national survey, which has been used in the past to present data regarding children with T1D. NHANES is used to collect information, every 2 years, on a representative sample of the United States civilian, noninstitutionalized population. The target population for this study was all T1D patients with age of onset under 20 years in the NHANES cycles that occurred between 1999 and 2012. In 2008, the CDC reported the prevalence of diabetes among children under 20 years old using the NHANES cycles ending in 2004 and 2006. Since then, the CDC has employed the use of the SEARCH study to report diabetes statistics among children (CDC, 2011). The use of more recent cycles in my study will provide the most updated information.

## Sampling Strategy

The CDC employed a complex sampling strategy in order to obtain a representative sample of the noninstitutionalized, civilian United States population. The sampling was based on location, income, gender, and ethnicity (CDC, 2013c) and was conducted in four stages:

1. Selection of primary sampling units (PSUs), which are counties or small groups of contiguous counties.
2. Selection of segments within PSUs that constitute a block or group of blocks containing a cluster of households.
3. Selection of specific households within segments.

4. Selection of individuals within a household. (CDC, 2013d)

The CDC employed this sampling strategy for almost all people living within the 50 United States or in the District of Columbia, except those in institutional settings and active-duty military personnel.

Although the age of the target population has not changed since 1999, the CDC has periodically changed the groups that are oversampled within each cycle. For example, prior to 2006 NHANES oversampled only the Mexican American subpopulation of Hispanic (Johnson, Dohrmann, Burt, & Mohadjer, 2014). However, currently they oversample all Hispanics. Changes in oversampled populations do not limit analysis projects involving multiple cycles of data (Johnson et al., 2014).

The data collection process began with a household survey and then potentially moved into individual interviews regarding a subset of the household (Johnson et al., 2014). As a tertiary step, some individuals were also medically screened (e.g., blood draws), but that medical information is outside the scope of my study.

**Data Analysis Plan**

All analyses were performed using SAS 9.3. Initially, the demographics and diabetes datasets, which contain the strata, cluster, and weight value information, were downloaded from the NHANES website and merged using the sequence number (SEQN), as described by the CDC (2014b). Next, I checked to ensure all target variables were named the same across cycles and appended the datasets. Finally, I created analysis datasets by subsetting to include only those patients meeting the study's inclusion criteria. The inclusion criteria for this study were the following:

- Patients with T1D
- Patients diagnosed between the ages of 1 and 19

After analysis datasets were created, I generated descriptive statistics for the study population. The descriptive statistics were as follows:

- Mean age of onset of T1D
- Mean age of onset of T1D by gender
- Mean age of onset of T1D by ethnicity
- Mean age of onset of T1D by gender and ethnicity

Each mean was reported with the 95% confidence interval. As recommended by the CDC (2014), means were derived using SAS PROC SurveyMeans. This SAS procedure is more appropriate than using the traditional PROC Means procedure because it enables estimation with consideration of complex sampling designs by including *strata*, *cluster*, and *weight* statements. The *strata*, *cluster*, and *weight* statements are important for all NHANES analysis due to the complex sampling design employed by the NHANES study design.

In addition to descriptive statistics, I generated statistics to test the following research hypotheses:

- $H_0$1: There is no association between age of onset of T1D and gender.
- $H_a$1: There is an association between age of onset of T1D and gender.
- $H_0$2: There is no association between age of onset of T1D and ethnicity.
- $H_a$2: There is an association between age of onset of T1D and ethnicity.

- $H_0$3: There is no association between age of onset of T1D and ethnicity, after adjusting for gender.
- $H_a$3: There is an association between age of onset of T1D and ethnicity, after adjusting for gender.

These hypotheses were tested using SAS PROC SurveyReg. This SAS procedure is more appropriate than using the traditional PROC Reg or GLM procedures because it enables estimation with consideration of complex sampling designs by including *strata*, *cluster*, and *weight* statements as well as a *model* statement. Furthermore, SAS PROC SurveyReg is recommended by the CDC (2014) for this type of analysis of NHANES.

In the current study, a model was created to test each of the three hypotheses. The form of a simple linear regression model is $y = \alpha + \beta x + e$, where $y$ is the dependent variable and $x$ is the independent variable (Rosner, 1990). The dependent variable for all three models was age of onset. Because age of onset is a continuous variable, linear regression is the appropriate statistical methodology, as opposed to logistic regression where the dependent variable is binomial (Pagano & Gauvreau, 1993). To test the first two hypotheses, gender and ethnicity were employed as the independent variables separately. Independent variables are named as such because they are not dependent on the other variables; instead, they are used to predict the value of the dependent variable in the model (Last, 1995). To test the third hypothesis, I employed a multiple regression technique, which allows for specification of multiple independent variables (Rosner, 1990). Because both gender and ethnicity were specified as independent variables in the model, gender was adjusted for and the third hypothesis was evaluated using the *p*-value

associated with the coefficient of the ethnicity categories. In addition, I used Wald's F-test to evaluate the effect of the specific ethnicity variable in the model (Heering, West, & Berglund, 2010). Because only three hypotheses were evaluated, *p*-value adjustment of multiple comparisons was not employed.

**Operational Definitions**

Four key variables (age of onset, gender, ethnicity, and T1D) were used in identification of the study population and the primary the analysis. Three additional variables were used in descriptive analysis. Each was derived from NHANES survey questions (CDC, 2012a, 2012b); these questions are asked of all participants at least 1 year old (CDC, 2013b) and each question and response is worded in the same manner across all seven NHANES cycles. Tables 3 and 4 provide the frequency distribution of responses to the demographic and diabetes-related questions, respectively, from the NHANES cycle ending in 2012. Operational definitions of the seven variables are described below. Using these definitions inherently screened out unclean data; therefore data cleaning is not incorporated into the analysis plan.

**T1D**. Using NHANES, Demmer et al. (2013) classified patients as T1D via the survey if their responses indicated that they were diagnosed with diabetes and taking only insulin without diabetic pills. The insulin inclusion criterion was deemed necessary because the survey question did not differentiate between T1D and T2D. This same criterion was employed in this study. Specifically, only participants fitting the following criteria was included in this analysis: if DIQ010 = Yes and DIQ050 = Yes and DIQ070 not = to Yes.

**Age of onset**. This variable was defined using the DID040 variable. The CDC codes all responses > 79 years as 80, however this coding will not impact the validity of the planned analysis because the target population consists of only patients with age of onset under 20 years. Specifically, only participants fitting the following criteria was included in this analysis: if ($1 \leq$ DID040 $\leq 19$).

**Gender**. This variable was defined using the RIAGENDR variable.

**Ethnicity**. For the first time in NHANES history, the CDC included the "Non-Hispanic Asian" category in the cycle ending in 2012 (CDC, 2013a). In the past, the CDC reported these participants as "Other Race - Including Multi-Racial". However, given the need to combine data across cycles and the desire to ensure ethnic categories contain an adequate number of observations, the variable REDRETH1 was used which is common to all cycles and automatically codes these "Non-Hispanic Asian"participants as "OtherRace - Including Multi-Racial". In addition to the predefined combination, "Mexican-American" and "Other Hispanic" were combined and reported as "Hispanic". All other categories will remain as reported by the CDC.

**Age of participant at time of survey completion**. This variable was defined using the RIDAGYR variable.

**Duration of diabetes**: This variable was defined as the difference between the participant's age at time of survey completion and the participant's age of onset of T1D (DID040). Therefore, if a 79 year old participant responded that s/he was diagnosed at age 9, the participant's duration of diabetes was calculated as 70 years (79-9).

**Year of diagnosis**. This variable was defined as the difference between the year the participant completed the survey and the duration of diabetes. For example, if a participant with 70 years of diabetes duration completed the survey in 2012, then the participant's year of diagnosis was calculated as 1942 (2012 – 70). Of note, NHANES cycles start in November and end in October of the following year. Because the exact year of the survey completion for each participant is not provided in the datasets and because fewer months were utilized in the first year of the cycle, the second year of each cycle was used as the completion year in the calculation above. For example, participants in the 2001-2002 NHANES cycles were assumed to have completed the survey in 2002.

Table 3

*Unweighted Frequencies of Responses to the Demographic Questions*

| | Variable Name (Dataset) | Response | n |
|---|---|---|---|
| Asked if not obvious: "Is {NAME} male or female?" | RIAGENDR (demo_g) | | |
| | | Male | 4856 |
| | | Female | 4900 |
| | | Missing | 0 |
| Age of participant at the time of screening: CDC derived this value based on the participant's date of birth, if date was missing then the reported age in years was used | RIDAGYR (demo_g) | | |
| | | 0 to 79 years | 9393 |
| | | ≥ 80 | 363 |
| | | Missing | 0 |
| Ethnicity: CDC derived these values based on the following two questions: "{Do you/Does SP} consider {yourself/himself/herself} to be Hispanic or Latino?" "Please look at the categories on this card. What race or races {do you/does SP} consider {yourself/himself/herself} to be? Please select one or more." | RIDRETH3 (demo_g) | | |
| | | Mexican-American | 1355 |
| | | Other Hispanic | 1076 |
| | | Non-Hispanic White | 2973 |
| | | Non-Hispanic Black | 2683 |
| | | Non-Hispanic Asian | 1282 |
| | | Other Non-Hispanic | 387 |
| | | Missing | 0 |

Table 4

*Unweighted Frequencies of Responses to the Diabetes-Related Questions*

| | Variable Name (Dataset) | Response | n |
|---|---|---|---|
| "{Other than during pregnancy, {have you/has SP}/{Have you/Has SP}} **ever** been told by a doctor or other health professional that {you have/{s/he/SP} has} diabetes or sugar diabetes?" | DIQ010 (diq_g) | | |
| | | Yes | 708 |
| | | No | 8524 |
| | | Borderline | 125 |
| | | Refused | 1 |
| | | Don't Know | 5 |
| | | Missing | 1 |
| "How old {was SP/were you} when a doctor or other health professional **first** told {you/him/her} that {you/s/he} had diabetes or sugar diabetes?" | DID040 (diq_g) | | |
| | | 3 to 78 years | 684 |
| | | ≥ 80 | 12 |
| | | Less than 1 year | 5 |
| | | Refused | 0 |
| | | Don't know | 7 |
| | | Missing | 8656 |
| "{Is SP/Are you} **now** taking insulin?" | DIQ050 (diq_g) | | |
| | | Yes | 213 |
| | | No | 9149 |
| | | Refused | 1 |
| | | Don't know | 0 |
| | | Missing | 1 |
| "{Is SP/Are you} **now** taking diabetic pills to lower {{his/her}/your} blood sugar? These are sometimes called oral agents or oral hypoglycemic agents." | DIQ070 (diq_g) | | |
| | | Yes | 546 |
| | | No | 529 |
| | | Refused | 0 |
| | | Don't know | 3 |
| | | Missing | 8286 |

**Sample Size**

Using an appropriate sample size is critical in order to ensure that the statistical tests performed to evaluate the study's null hypotheses have enough power (Pagano & Marcello, 1993). Statistical power (β) is measurement of the ability of a test to reject the null hypothesis if a difference exists (Morrison, 1990). Researchers commonly desire 80% power (Lang & Secic, 2006), hence 80% was used in the power evaluation of this study. The inverse of power is referred to as the probability of a Type II error (1-β); this is the probably of not rejecting the null when it should have been rejected (Morrison, 1990). Another important error, considered when planning sample size and evaluating power, was a Type I error. A type I error (α) occurs when a null hypothesis is rejected when it should not have been rejected (Morrison, 1990). As α becomes smaller it is harder for the researcher to reject the null and find a significant result. Researchers commonly utilize = 0.05 (Lang & Secic, 2006), therefore $\alpha = 0.05$ was used in the power evaluation of this study.

In addition to consideration of α and β when determining sample size, researchers must identify an appropriate effect size because it is the most important determinant of sample size and power (Cohen, 1988). Effect size is a measurement of the amount of variation that is important enough to reject the null hypothesis (Cohen, 1988). Specifically for first hypothesis of this study, effect size is the amount of variation in the mean age of onset of T1D between males and females considered statistically significant; this is calculated as the difference in the mean age of onset of T1D between genders divided by the common standard deviation. For the current study, the desired effect size

was calculated based on the gender-specific means (males 10.12 and females 9.46) reported by Lawrence et al. (2014) and the common standard deviation of 4.6 reported by Smith et al. (2007). Although other authors reported means and standard deviations for age of onset of T1D (Table 1), I chose these two for the calculation because the study populations were most similar to the population of this study. Given the information provided by Lawrence et al. and Smith et al., the desired effect size for this study was calculated as 0.14, which is (10.12 minus 9.46) divided by 4.6. Hence, sample size analysis indicated that in order to investigate the difference in age of onset between genders 1,604 T1D patients (802 females and 802 males) were required to provide 80% power at an $\alpha = 0.05$ significance level to detect an effect size of 0.14. I employed nQuery software using a two sample student's t-test with equal variance to perform the sample size analysis. Because the weighted data from the NHANES between 1999 and 2012 resulted in a sample size of almost 600,000 patients, the study was deemed to have adequate statistical power.

## Threats to Validity

As with other cross-sectional survey studies, possible threats to validity exist. One possible threat comes from non-response bias. The CDC (2013b) reported the unweighted response rate as 72.6% from the NHANES cycle ending in 2012 and response rates in previous cycles (1999-2000) ranged between 78% and 84%. For the lowest rate in 2012, the CDC performed an analysis to assess the impact of non-response bias and reported that the identified bias was prevalent in the unweighted sample but because some of the demographic characteristics associated with non-responders were also associated with the

characteristics used in the complex sampling methods, researchers using the sampling weights in their analyses would reduce the bias (CDC, 2013c). If non-response was associated with higher or lower ages of onset of T1D, then this type of bias may be considered an internal threat to validity. However, because the analysis plans for this study include the use of weights, and there is no reason to believe that non-response poses a threat to validity.

Another threat that I found prevalent in literature was misclassification bias. This bias may occur in investigations regarding T1D and T2D, because diagnosis can be ambiguous. The ADA (2014) defines the difference between T1D and T2D based on etiology, where T1D is classified as such when there is β cell destruction either due to autoimmune or idiopathic causes. On the other hand, Dabelea et al. (2011) identified four types of diabetes: autoimmune and insulin resistant, autoimmune and insulin sensitive, non-autoimmune and insulin resistant, non-autoimmune and insulin sensitive. Dabelea et al. reported that not all patients in the two autoimmune categories were classified as T1D by their health care providers and, in fact, T1D diagnosed patients existed in all four categories. Therefore, these four categories cannot be definitively correlated with physician determination of type of diabetes and underlines the potential ambiguity related to identifying a specific type. In order to limit misclassification bias, which would impose a threat to external validity and the generalizability of the results, Demmer et al. (2013) followed strict classification criteria when analyzing NHANES data. The criteria involved the requirement of insulin-only treatment to distinguish T1D from T2D, and I incorporated this criterion into the operative definition of T1D for this study.

## Ethical Procedures

A variety of ethical issues can arise during the data collection stage of an investigation (Creswell, 2009). Because this study involves an analysis of secondary data, the ethical issues were addressed prior to the beginning of this study. The NHANES cycles that I plan to use in this investigation were collected between 1999 and 2012 and had approval from the NCHS Research Ethics Review Board (ERB) under five protocol numbers (CDC, 2012c) listed in Table 5.

Table 5

*Protocol Numbers for ERB Approval by NHANES Cycle*

| NHANES Survey Cycle | Protocol Number |
|---|---|
| NHANES 2011-2012 | Protocol #2011-17 |
| NHANES 2009-2010 | Continuation of Protocol #2005-06 |
| NHANES 2007-2008 | Continuation of Protocol #2005-06 |
| NHANES 2005-2006 | Protocol #2005-06 |
| NHANES 1999-2004 | Protocol #98-12 |

I obtained IRB approval through Walden University prior to initiation of my study (approval number 12-16-14-0227763). The secondary data used in this study contains no personal information that can be used to identify the survey responder and can be downloaded directly from the NHANES website without permission.

## Summary

This dissertation presents a quantitative study design, utilizing secondary data obtained from the NHANES between 1999 and 2012. The CDC collected this data utilizing a sampling technique that enables researchers to use weights to obtain nationally representative data for the civilian, noninstitutionalized United States population. SAS programming procedures specifically designed to incorporate the complex sample

procedures employed by the CDC was used in the analysis. As described in the analysis plan, I explored the mean age of onset of T1D and its relationship to ethnicity and gender among patients with age of onset less than 20 years old. These results fill a gap in the literature with contemporary and well stratified statistics that can provide new data which can be used to promote positive social change.

# Chapter 4: Results

## Introduction

The purpose of this study was to investigate age of onset of T1D by demographic factors. This study utilized data from seven cycles of the NHANES in order to address the research question: What is the average age of onset of T1D with respect to ethnicity and gender? I tested the following three hypotheses:

- $H_0$1: There is no association between age of onset of T1D and gender.
- $H_a$1: There is an association between age of onset of T1D and gender.
- $H_0$2: There is no association between age of onset of T1D and ethnicity.
- $H_a$2: There is an association between age of onset of T1D and ethnicity.
- $H_0$3: There is no association between age of onset of T1D and ethnicity, after adjusting for gender.
- $H_a$3: There is an association between age of onset of T1D and ethnicity, after adjusting for gender.

The purpose of this chapter is to provide a description of the unweighted data obtained from NHANES and the weighted data utilized as the study's sample for testing the research hypotheses. The results are described using tables and figures. In addition, narrative is provided to highlight the identified statistical significance and some sensitivity analysis is presented. Following the results, a summary section is provided to describe the findings in relationship to the research question.

## Source Data

This study was an analysis of secondary data collected via the seven cycles of NHANES between the years 1999 and 2012. I downloaded the seven cycles individually from the NHANES website and I renamed two primary analysis variables in the five oldest cycles to ensure variable naming consistency prior to joining them into one encompassing dataset. The resulting dataset contained demographic and diabetes information on 71,916 NHANES participants (Figure 1). Only a subset of these participants was included in this study's sample.

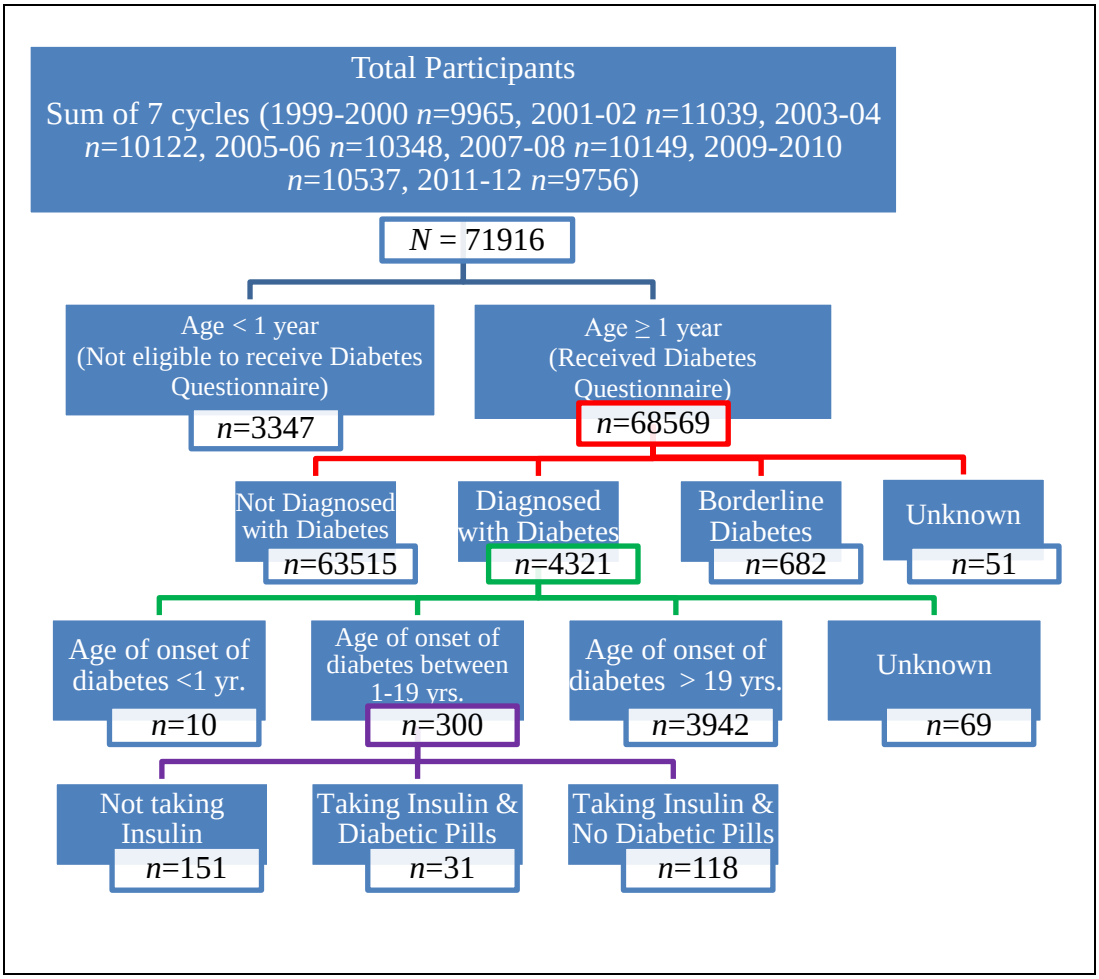


*Figure 1*. Description of source data and identification of final study sample.

Although 68,569 participants were at least 1 year old and therefore eligible to receive the diabetes questionnaire, I only included 118 participants in the sample due to the inclusion criteria. Exclusion of greater than 68,000 participants involved multiple steps, including identification of the 4,321 patients who responded that they had been diagnosed with diabetes. Further reduction in sample size was performed based on the inclusion criteria that required diagnosis between the ages of 1 and 19. This criterion limited the diabetic sample to 300. Finally, the sample was limited further to include only participants with insulin-only treatment ($n$ = 118), rather than no treatment or insulin in combination with oral agents. As planned, this final criterion was utilized to narrow the sample to include only T1D patients, rather than T2D. All primary analyses were performed with a sample size of 118.

## Study Population

Table 6 shows the demographic distribution of the unweighted 118 patients included in the analysis. After accounting for the sophisticated NHANES sampling methods, the weighted analysis resulted in almost 600,000 T1D patients representative of the United States population 1999 thru 2012. The majority of T1D patients were male (56.9%) and NHW (79.5%).

Table 6

*Frequency Distribution of Demographic Characteristics of T1D Patients with Age of Onset 1-19 Years, in the United States, 1999-2012*

| | Unweighted | Weighted | |
|---|---|---|---|
| Characteristic | *n* | *n* | % (*N* = 599,625) |
| Total Sample | 118 | 599,625 | 100.0% |
| Age at Time of Survey Completion | | | |
| 1-19 years | 48 | 159,760 | 26.6% |
| 20-39 years | 33 | 207,406 | 34.6% |
| 40-59 years | 18 | 156,394 | 26.1% |
| ≥ 60 years | 19 | 76,065 | 12.7% |
| Gender | | | |
| Male | 63 | 341,201 | 56.9% |
| Female | 55 | 258,424 | 43.1% |
| Ethnicity | | | |
| Hispanic* | 16 | 38,425 | 6.4% |
| Non-Hispanic Black | 35 | 82,964 | 13.8% |
| Non-Hispanic White | 65 | 476,560 | 79.5% |
| Other | 2 | 1,676 | 0.3% |
| Ethnicity by Gender | | | |
| Male | | | |
| Hispanic | 8 | 12,004 | 2.0% |
| Non-Hispanic Black | 14 | 32,748 | 5.5% |
| Non-Hispanic White | 40 | 295,686 | 49.3% |
| Other | 1 | 764 | 0.1% |
| Female | | | |
| Hispanic | 8 | 26,422 | 4.4% |
| Non-Hispanic Black | 21 | 50,216 | 8.4% |
| Non-Hispanic White | 25 | 180,874 | 30.2% |
| Other | 1 | 912 | 0.2% |

* The weighted frequency for Hispanics (38,425) does not equal the sum of the weighted frequencies of male and female Hispanics (38,426) due to rounding because weights are not whole numbers.

Table 7 shows the distribution of diabetes information in the unweighted and weighted samples. One third of the sample reported age of onset of T1D between 15 and 19 years old, whereas only 13.7% of the patients reported diagnosis between 1 and 4 years old. Next, the relationship between age, ethnicity, and gender is described.

Table 7

*Frequency Distribution of Diabetic Characteristics of T1D Patients with Age of Onset 1-19 Year, in the United States, 1999-2012*

| | Unweighted | Weighted | |
|---|---|---|---|
| Characteristic | *n* | *n* | % (*N* = 599,625) |
| Age of Onset of T1D | | | |
| 1-4 years | 16 | 81,996 | 13.7% |
| 5-9 years | 36 | 179,872 | 30.0% |
| 10-14 years | 29 | 139,657 | 23.3% |
| 15-19 years | 37 | 198,100 | 33.0% |
| Year of Diagnosis | | | |
| 1930-1949 | 6 | 23,567 | 3.9% |
| 1950-1969 | 20 | 129,517 | 21.6% |
| 1970-1989 | 28 | 181,222 | 30.2% |
| 1990-2010 | 63 | 263,539 | 44.0% |
| Unknown | 1 | 1,780 | 0.3% |
| Duration of Diabetes* | | | |
| Less than 10 years | 44 | 154,946 | 25.8% |
| 10-19 | 25 | 124,611 | 20.8% |
| 20-29 | 13 | 96,389 | 16.1% |
| 30-39 | 11 | 84,803 | 14.1% |
| 40-49 | 9 | 63,415 | 10.6% |
| 50-59 | 12 | 55,814 | 9.3% |
| 60-65 | 3 | 17,868 | 3.0% |
| Unknown | 1 | 1,780 | 0.3% |

* The weighted frequency overall (599,625) does not equal the sum of the weighted frequencies in the duration of diabetes category (599,626) due to rounding because weights are not whole numbers.

## Hypothesis Testing

The purpose of this study was to investigate age of onset of T1D by demographic factors via three hypotheses. I tested these hypotheses by using three primary variables: age of onset, ethnicity, and gender. Table 8 reports the mean age of onset for the overall study population (11.1 years), as well as the means for each of the ethnicity/gender-specific hypotheses. I tested each hypotheses using regression analysis, with age of onset as the dependent variable. The results from testing are described in the following sections.

Table 8

*Mean age of Onset of T1D with Age of Onset 1-19 Years*

| Characteristic | *n* | Age of onset of T1D | |
|---|---|---|---|
| | | Mean | 95% confidence limits |
| Total sample | 599,625 | 11.1 | 9.83, 12.28 |
| Gender | | | |
| Male | 341,201 | 10.5 | 8.75, 12.17 |
| Female | 258,424 | 11.8 | 10.10, 13.58 |
| Ethnicity | | | |
| Hispanic | 38,425 | 13.0 | 11.23, 14.86 |
| Non-Hispanic Black | 82,964 | 12.7 | 10.79, 14.70 |
| Non-Hispanic White | 476,560 | 10.6 | 9.17, 12.07 |
| Other | 1,676 | 6.2 | 3.40, 8.96 |
| Ethnicity by gender | | | |
| Male | | | |
| Hispanic | 12,004 | 10.9 | 7.75, 14.03 |
| Non-Hispanic Black | 32,748 | 14.7 | 12.66, 16.82 |
| Non-Hispanic White | 295,686 | 10.0 | 8.05, 11.92 |
| Other | 764 | 4.0 | NR |
| Female | | | |
| Hispanic | 26,422 | 14.0 | 12.08, 15.99 |
| Non-Hispanic Black | 50,216 | 11.4 | 8.21, 14.68 |
| Non-Hispanic White | 180,874 | 11.6 | 9.55, 13.75 |
| Other | 912 | 8.0 | NR |

NR: Confidence limits not reported because unweighted sample size = 1.

**Gender**

Table 8 shows the mean age of onset was 10.5 for males and 11.8 for females. I tested the first hypotheses by employing gender as the independent variable in the regression model to assess its association with age of onset as the dependent variable. Table 9 provides the results of the regression analysis and yielded a *p*-value of 0.2636 for the gender coefficient. At the 0.05 level, the null hypothesis was not rejected. The *p*-value < 0.05 indicated that gender did not have an effect on the age of onset. Although my results showed two different means, I did not find a significant *p*-value, indicating no association between age of onset and gender.

Table 9

*Regression Results: Modeling the Relationship Between Age of Onset and Gender*

| | Coefficient | | | | |
|---|---|---|---|---|---|
| Variable | β | 95% confidence limits | Standard Error | *t*-value | *p*-value |
| Intercept | 10.5 | 8.75, 12.17 | 0.86 | 12.11 | < 0.0001 |
| Gender | | | | | |
| Female | 1.4 | -1.05, 3.81 | 1.23 | 1.12 | 0.2636 |
| Male | -- | -- | -- | -- | -- |

*Note*. Dashes indicate the reference category.

**Ethnicity**

Table 8 shows a range of onset times across ethnicities. Hispanics had the highest mean age of onset (13.0 years), followed by NHB (12.7 years), and NHW (10.6 years). The lowest mean age of onset (6.2 years) was seen in participants reporting other ethnicities, including mixed ethnicities. I tested the ethnicity hypothesis by employing

ethnicity as the independent variable in the regression model. Table 10 provides the results of the regression analysis and yielded significant *p*-values for each ethnicity coefficient. Therefore, I rejected the null hypothesis and accepted the alterative hypothesis, indicating an association between age of onset and ethnicity.

Table 10

*Regression Results: Modeling the Relationship Between Age of Onset and Ethnicity*

| | Coefficient | | | | |
|---|---|---|---|---|---|
| Variable | β | 95% confidence limits | Standard Error | *t*-value | *p*-value |
| Intercept | 6.2 | 3.40, 8.97 | 1.403 | 4.40 | < 0.001 |
| Ethnicity | | | | | < 0.0001[a] |
| Hispanic | 6.9 | 4.41, 9.33 | 1.240 | 5.54 | < 0.0001 |
| Non-Hispanic Black | 6.6 | 3.17,10.00 | 1.715 | 3.86 | 0.0002 |
| Non-Hispanic White | 4.4 | 1.30,7.58 | 1.583 | 2.81 | 0.0060 |
| Other | -- | -- | -- | -- | -- |

*Note*. Dashes indicate the reference category
[a] from test of model effects (Wald's F-test)

**Ethnicity Adjusting for Gender**

In order to test the final hypothesis, multivariate regression was employed with gender and ethnicity as independent variables. Table 11 provides the results of the regression analysis and table 8 shows that the ethnicity variable was significant ($p <$ 0.0001) when the gender variable was included in the model. The regression coefficients were all significant at the 0.05 level. Therefore, the null hypothesis was rejected and the alterative hypothesis was accepted, indicating an association between age of onset and ethnicity after accounting for gender. Overall, results of primary hypotheses revealed significant association between age of onset and ethnicity but not gender.

Table 11

*Regression Results: Modeling the Relationship Between Age of Onset and Ethnicity, Adjusting for Gender*

| | Coefficient | | | | |
|---|---|---|---|---|---|
| Variable | β | 95% confidence limits | Standard Error | *t*-value | *p*-value |
| Intercept | 5.6 | 3.21, 7.99 | 1.2 | 4.64 | < 0.0001 |
| Gender | | | | | |
| Female | 1.1 | -1.33, 3.45 | 1.2 | 0.88 | 0.3809 |
| Male | -- | -- | -- | -- | -- |
| Ethnicity | | | | | < 0.0001[a] |
| Hispanic | 6.7 | 4.70, 8.74 | 1.02 | 6.58 | < 0.0001 |
| Non-Hispanic Black | 6.5 | 3.66, 9.34 | 1.43 | 4.53 | < 0.0001 |
| Non-Hispanic White | 4.6 | 2.11, 7.12 | 1.26 | 3.66 | 0.0004 |
| Other | -- | -- | -- | -- | -- |

*Note*. Dashes indicate the reference category
[a] from test of model effects (Wald's F-test)

## Sensitivity Analysis

Tables 6 and 7 show how single participants in the unweighted sample represent between 674 and 1,780 patients in the weighted sample. Analysis and conclusions based on subpopulations with small sample sizes in the unweighted sample may be biased. To examine this bias, I performed three sensitivity analyses. The first examination pertained to the population of participants who reported Other ethnicities, this included participants who marked multiple ethnicities. The remaining examinations pertained to participants whose year of diagnosis was unable to be determined and participants who indicated being diagnosed prior to their first birthday. Each examination is described in the sections below.

**Ethnicity**

In the primary analysis, examination of mean ages by ethnicity revealed significant association between age of onset and ethnicity, where participants with Other ethnicities, including multiple ethnicities, reported the lowest mean age of onset. Furthermore, this group of participants comprised the smallest sample size in the unweighted data, only 1 female and 1 male. Because my literature review did not uncover any analyses or conclusions related to Other ethnicities, and because the sample size was low, I performed sensitivity analyses by excluding these two participants and comparing the results to the primary regression analysis.

Exclusion of the two unweighted participants who reported Other ethnicities resulted in a weighted sample size of 597,949 (Table 12). Although the weighted sample size decreased by 1,676 participants from my study's sample size, the overall mean age of onset remained 11.1 years and my regression analysis (Table 13) continued to indicate that gender was not significant ($p = 0.3863$). However, unlike the primary analyses, I found ethnicity to not be statistically significant ($p$-values 0.0697 for Hispanics and 0.1140 for NHB). Furthermore, as evidenced by the overlapping 95% confidence intervals in Table 8, these finding indicate that mean age of onset did not differ between Hispanics (13.0 years), NHB (12.7 years), and NHW (10.6 years). These inconsistent results provide evidence to support the sensitivity nature of extracting conclusions from weighted population-based samples when unweighted sample sizes are small and categories, like Other, are not distinct.

Table 12

*Mean age of Onset of T1D with Age of Onset 1-19 Years (Excluding Participants with Other Ethnicities)*

| | | Age of onset of T1D | |
|---|---|---|---|
| Characteristic | N | Mean | 95% confidence limits |
| Total sample | 597,949 | 11.1 | 9.84, 12.30 |
| Gender | | | |
| Male | 340,437 | 10.5 | 8.76, 12.19 |
| Female | 257,512 | 11.9 | 10.10, 13.60 |

Table 13

*Regression Results: Modeling the Relationship Between Age of Onset and Ethnicity, Adjusting for Gender (Excluding Participants with Other Ethnicities)*

| | Coefficient | | | | |
|---|---|---|---|---|---|
| Variable | β | 95% confidence limits | Standard Error | *t*-value | *p*-value |
| Intercept | 10.2 | 8.41, 12.03 | 0.91 | 11.18 | < 0.0001 |
| Gender | | | | | |
| Female | 1.1 | -1.34, 3.45 | 1.21 | 0.87 | 0.3863 |
| Male | -- | -- | -- | -- | -- |
| Ethnicity | | | | | 0.1140[a] |
| Hispanic | 2.1 | -0.17, 4.39 | 1.15 | 1.83 | 0.0697 |
| Non-Hispanic Black | 1.9 | -3.75, 4.15 | 1.14 | 1.65 | 0.1011 |
| Non-Hispanic White | -- | -- | -- | -- | -- |

*Note*. Dashes indicate the reference category
[a] from test of model effects (Wald's F-test)

**Duration of diabetes**

In Table 7 reports I reported one NHW male where I was unable to calculate the duration of diabetes. Although the participant reported being diagnosed at age two, his current age at the time of the NHANES survey was captured in a ceiling category which

included all participants 85 years or older. This ceiling category made it impossible for me to calculate an accurate duration. In addition to the possibility of calculation inaccuracy, the onset age may have been reported inaccurately. For example, assuming the male was 85, duration would be 83. It is known that he completed the NHANES survey in 2002, therefore it could be calculated that he was diagnosed in 1919 (2002 minus 83 years). This was based on the assumption that he was 85; if he was older, the calculated diagnosis year would have been earlier. Although not impossible to be diagnosed in 1919 and still alive in 2002, it is unlikely since the distribution of insulin did not begin until 1923. Due to this potential inaccuracy, and the substantial weight this participant provided to the overall analysis, I performed sensitivity analyses by excluding this participant and comparing the results to previous regression analyses.

Exclusion of the unweighted male participant whose exact diabetes duration could not be calculated resulted in a weighted sample size for males of 338,658 (Table 14) compared to 340,437 (Table 13). Although the weighted sample size decreased with the exclusion of the male who reported his age of onset at 2 years, the mean age of onset in males did not change (10.5 years). This unexpected consistency stemmed from the continued inclusion of more heavily weighted male patients diagnosed at younger ages; six patients with age of onset between 1 and 9 years had weights greater than 10,000 (range 11,771.16-17,247.87) while only four patients with age of onset between 11 and 19 years had weights greater than 10,000 (range12,243.14-15,486.91). Since mean age of onset did not change, I was not surprised to find that the regression results were consistent with previous analyses. Table 15 shows gender continued to not be significant

($p$ = 0.2820). Furthermore, ethnicity (excluding Other ethnicities) continued to not be statistically significant ($p$-values 0.0726 for Hispanic and 0.1048 for NHB). These consistent results provide evidence to support conclusions that gender and ethnicity are not associated with age of onset of T1D.

Table 14

*Mean Age of Onset of T1D with Age of Onset 1-19 years (Excluding Participants with Unknown Duration and Other Ethnicities)*

| | | Age of onset of T1D | |
|---|---|---|---|
| Characteristic | n | Mean | 95% confidence limits |
| Total sample | 596,169 | 11.1 | 9.87, 12.33 |
| Gender | | | |
| Male | 338,658 | 10.5 | 8.80, 12.24 |
| Female | 257,512 | 11.9 | 10.10, 13.60 |
| Ethnicity | | | |
| Hispanic | 38,425 | 13 | 11.23, 14.86 |
| Non-Hispanic Black | 82,964 | 12.7 | 10.79, 14.70 |
| Non-Hispanic White | 474,780 | 10.6 | 9.20, 12.10 |
| Ethnicity by gender | | | |
| Male | | | |
| Hispanic | 12,004 | 10.9 | 7.75, 14.03 |
| Non-Hispanic Black | 32,748 | 14.7 | 12.66, 16.82 |
| Non-Hispanic White | 293,906 | 10 | 8.09, 11.98 |
| Female | | | |
| Hispanic | 26,422 | 14 | 12.08, 15.99 |
| Non-Hispanic Black | 50,216 | 11.4 | 8.21, 14.68 |
| Non-Hispanic White | 180,874 | 11.6 | 9.55, 13.75 |

Table 15

*Regression Results: Modeling the Relationship Between Age of Onset and Ethnicity, Adjusting for Gender (Excluding Participants with Unknown Duration and Other Ethnicities)*

| | Coefficient | | | | |
|---|---|---|---|---|---|
| Variable | β | 95% confidence limits | Standard Error | *t*-value | *p*-value |
| Intercept | 10.3 | 8.45, 12.08 | 0.92 | 11.21 | < 0.0001 |
| Gender | | | | | |
| Female | 1.0 | -1.38, 3.41 | 1.21 | 0.84 | 0.4048 |
| Male | -- | -- | -- | -- | -- |
| Ethnicity | | | | | 0.1191[a] |
| Hispanic | 2.1 | -0.19, 4.37 | 1.15 | 1.81 | 0.0726 |
| Non-Hispanic Black | 1.9 | -0.40, 4.13 | 1.14 | 1.64 | 0.1048 |
| Non-Hispanic White | -- | -- | -- | -- | -- |

*Note*. Dashes indicate the reference category
[a] from test of model effects (Wald's F-test)

**Age at diagnosis**

Exclusion of patients diagnosed prior to their first birthday was discussed as a limitation of the study in chapters one and three. To evaluate the potential bias of this exclusion, a sensitivity analysis was performed. I compared the results from analyses performed that included these participants to the results of the previous regression analyses.

As seen in Figure 1, ten participants reported onset prior to 1 year of age. The distribution of reported treatment among these ten was: 1 participant reported treatment with insulin only, 1 participant reported treatment with diabetic pills only, and 8 participants reported no treatment. Because there is insufficient literature to support the existence for successful treatment of T1D via pills only, or the existence of a cure, I

excluded the nine participants who reported diabetes with no treatment or treatment with pills in the sensitivity analysis. Although clinical trials exist regarding transplantation, beta cell generation, beta cell destruction reversal, and new treatment options, it is unlikely that all 9 of these diabetic patients in the unweighted dataset participated in these trials since that would indicate approximately 9,000 patients in the United States have been successfully cured. However, I did include the one participant who reported treatment with insulin only in the sensitivity analyses. I did this in order to assess the potential bias from exclusion of this participant in the primary analyses.

Table 16 reports an increased weighted sample size in the female category (from 257,512 to 273,194) and NHW category (from 476,560 to 492,242) due to the inclusion of the participant who reported diagnosis prior to her first birthday. As expected, the estimates for mean age of onset decreased as follows:

- overall mean age of onset decreased by 0.3 years (from 11.1 to 10.8 years)
- female mean age of onset decreased by 0.7 years (from 11.9 to 11.2 years)
- NHW mean age of onset decreased by 0.3 years (from 10.6 to 10.3 years)
- female, NHW mean age of onset decreased by 0.9 years (from 11.6 to 10.7 years)

Because the mean age for males was already lower than the females in the primary analysis, the decrease in the mean age for females did not change the analysis conclusions regarding gender. The *p*-value for the gender coefficient in the regression analysis continued to not be statistically significant ($p = 0.6123$).

Table 16

*Mean Age of Onset of T1D with Age of Onset 0-19 Years*

| | | Age of onset of T1D | |
|---|---|---|---|
| Characteristic | n | Mean | 95% confidence limits |
| Total sample | 613,631 | 10.8 | 9.47, 12.10 |
| Gender | | | |
| Male | 340,437 | 10.5 | 8.76, 12.19 |
| Female | 273,194 | 11.2 | 9.11, 13.24 |
| Ethnicity | | | |
| Hispanic | 38,425 | 13.0 | 11.23, 14.86 |
| Non-Hispanic Black | 82,964 | 12.7 | 10.79, 14.70 |
| Non-Hispanic White | 492,242 | 10.3 | 8.72, 11.83 |
| Ethnicity by gender | | | |
| Male | | | |
| Hispanic | 12,004 | 10.9 | 7.75, 14.03 |
| Non-Hispanic Black | 32,748 | 14.7 | 12.66, 16.82 |
| Non-Hispanic White | 295,686 | 10.0 | 8.05, 11.92 |
| Female | | | |
| Hispanic | 26,422 | 14.0 | 12.08, 15.99 |
| Non-Hispanic Black | 50,216 | 11.4 | 8.21, 14.68 |
| Non-Hispanic White | 196,556 | 10.7 | 8.18, 13.26 |

In Table 17, I present the results for the regression analysis. In contrast to Table 13, Table 17 shows that when Other ethnicities were excluded simultaneous with the addition of a NHW participant with onset prior to her first birthday, the coefficient for Hispanic has a significant *p*-value (0.0371). However, examination of the association between mean age of onset and ethnicity via Wald's F-test, after adjusting for gender, did not show a significant *p*-value (0.0602). These inconsistent results provide evidence to support the sensitive nature of extracting conclusions from weighted population-based samples when unweighted sample sizes are small.

Table 17

*Regression results: Modeling the Relationship Between Age of Onset and Ethnicity, Adjusting for Gender*

| Variable | Coefficient β | 95% confidence limits | Standard Error | *t*-value | *p*-value |
|---|---|---|---|---|---|
| Intercept | 10.1 | 8.33, 11.97 | 0.92 | 11.08 | < 0.0001 |
| Gender | | | | | |
| Female | 0.3 | -2.33, 2.98 | 1.34 | 0.24 | 0.8091 |
| Male | -- | -- | -- | -- | -- |
| Ethnicity | | | | | 0.0602[a] |
| Hispanic | 2.7 | 0.16, 5.19 | 1.27 | 2.11 | 0.0371 |
| Non-Hispanic Black | 2.4 | -0.01, 4.80 | 1.21 | 1.98 | 0.0506 |
| Non-Hispanic White | -- | -- | -- | -- | -- |

*Note*. Dashes indicate the reference category
[a] from test of model effects (Wald's F-test)

**Age of Onset by Year of Diagnosis**

Table 18 shows the mean age of onset of T1D stratified by diagnosis year. Compared to the overall mean age of onset in Table 7 (11.1 year, 95% CI 9.83, 12.28), the mean age of onset in recent years (1990-2010) is higher. In fact, Table 18 indicates a rising trend since its lowest point between 1950 and 1969. However, the confidence intervals of mean estimates overlap and therefore differences were not statistically significant.

Table 18

*Mean Age of Onset of T1D with Age of Onset 1-19 years, by Year of Diagnosis*

| | | Age of onset of T1D | |
|---|---|---|---|
| Year of Diagnosis | n | Mean | 95% confidence limits |
| 1930-1949 | 23,567 | 13.5 | 9.71, 17.32 |
| 1950-1969 | 129,517 | 9.7 | 7.39, 12.05 |
| 1970-1989 | 181,222 | 11.2 | 8.57, 13.75 |
| 1990-2010 | 263,539 | 11.5 | 10.08, 12.87 |
| Unknown | 1,780 | 2.0 | NR |

## Summary

I performed an analysis to answer the research question: What is the average age of onset of T1D with respect to gender and ethnicity? The analysis showed that the average age of onset was 10.5 years for males and 11.8 years for females. Regression analysis indicated that there was no significant association between gender and age of onset. Regarding ethnicity, I reported that Hispanics had the highest mean age of onset (13.0 years), followed by NHB (12.7 years), and NHW (10.6 years). I reported lowest mean age of onset (6.2 years) in participants reporting Other ethnicities, including mixed ethnicities. A combination of the primary regression analyses and sensitivity analyses indicated that the mean age of onset among the participants who reported Other ethnicity was lower than the other three categories (Hispanic, NHB, and NHW), however the mean age was not statistically associated with the other three categories (Hispanic, NHB, and NHW). These results are supported in literature. Chapter 5 provides a discussion of these results in relationship to the findings reported in literature, advantages and disadvantages of this study, and recommendations for future research.

# Chapter 5: Discussion, Conclusions, and Recommendations

## Summary and Interpretation of Findings

The purpose of this study was to investigate age of onset of T1D by demographic factors. Overall, this quantitative study found no association between age of onset of T1D and gender or ethnicity. This chapter provides a discussion of these results in relationship to the findings reported in literature, advantages and disadvantages of this study, and recommendations for future research.

### Overall Mean Age of Onset

I found that the overall mean age of onset of T1D in a representative sample of the United States population was 11.1 years. Other authors have reported mean ages in subsets of the United States population between 8.0 and 9.4 years (Hughes et al., 2013; Johnson & Meltzer, 2002; Pettitt et al., 2014; Smith et al., 2007). Studies from Hughes et al. (2013), Johnson and Meltzer (2002), and Smith et al. (2007) consisted of younger patient inclusion criteria and therefore might explain the reason for the younger mean age of onset. However, including the same age group as my study, Pettitt et al. (2014) reported a mean age of onset of 8.1 using 6,668 T1D in the SEARCH study in 2009. The reason for my finding of a higher mean age of onset in the overall population, 11.1 years compared to 8.1 years, is not readily apparent.

There are at least three explanations for the difference in mean age of onset between NHANES and SEARCH. First, NHANES and SEARCH utilize different source data, participant-reported compared to physician-reported, respectively. This source difference may have caused me to include T2D patients in my sample, as well as analyze

inaccurate ages of onsets. Secondly, my sample could not include deceased participants. Although Feltbower et al. (2008) reported no association between age of onset and T1D mortality, if an association does exist then my sample may have been lacking patients with younger onsets and therefore my estimate of mean age of onset was biased upward. Finally, my sample contained patients diagnosed between 1930 and 2010. Pettitt et al. (2014) reported prevalence in 2009, using patients diagnosed between 1990 and 2009. Therefore, the difference between the reported mean ages of onset may possibly be due to the ethnic distribution changes in the United States since 1930. Table 19 shows that Pettitt et al. reported a lower frequency of NHW patients compared to my study. However my analysis concluded no significant association between age of onset and ethnicity, and therefore ethnic distribution differences between the two studies cannot explain the difference in the reported mean ages of onset. These reasons suggest the difference in means can be explained by inaccuracies or by differences in an unknown, underlying characteristic of the two populations that influences age of onset of T1D.

Table 19

*Frequency Distribution of Demographic Characteristics of T1D Patients with Age of Onset 1-19 Years, by Source*

| | NHANES Prevalence 1999-2012 | | SEARCH* Prevalence 2009 | |
|---|---|---|---|---|
| Ethnicity | *n* | % (*N* = 599,625) | *n* | % (*N* = 6,668) |
| Hispanic | 38,425 | 6.4% | 1,040 | 15.6% |
| Non-Hispanic Black | 82,964 | 13.8% | 626 | 9.4% |
| Non-Hispanic White | 476,560 | 79.5% | 4,804 | 72.0% |
| Other | 1,676 | 0.3% | 198 | 3.0% |

* Source: Pettitt et al., 2014.

**Gender**

Among the available literature, many studies showed no significant difference in the occurrence of T1D between genders (Berhan et al., 2011; Dabelea, Mayer-Davis, et al., 2014; Derraik et al., 2012; Demmer et al., 2013; Galler et al., 2010; Hodgson et al., 2012; Smith et al., 2007; Welander, Montgomery, Ludvigsson, & Ludvigsson, 2014; Zhang et al., 2008; Zhao et al., 2014). However, some authors reported gender differences in particular age of onset categories (Dahlquist et al., 2011; Evertsen et al., 2009). For example, Dahlquist et al. (2011) reported the highest incidence for females occurred between 5 and 9 years (37.1 per 100,000 person-years) and for males occurred between 10 and 14 years (42.3 per 100,000 person-years). Consistent with the results showing earlier onset for females, Blasetti et al. (2011), Lawrence et al. (2014), and Valdes et al. (2012) also found that females had a significantly lower mean age of onset of T1D than males. As done in my study, these authors examined specific ages using an analysis comparing means rather than comparing incidence within age categories.

In my review of the literature, I identified five publications that presented mean age of onset separately for females and males. Figure 2 describes these results from literature alongside results from my study. In all five publications, females had lower mean ages of onset than males. Samuelsson et al. (2013), Lawrence et al. (2014), and Valdes et al. (2012) reported that the difference between genders was statistically significant ($p < 0.01$, $p < 0.001$, and $p < 0.005$, respectively). Blasetti et al. (2011) and Leidig-Bruckner et al. (2014) did not perform a statistical test to assess significance; however, with the means, standard deviations, and sample sizes that they reported I

calculated *t* tests that resulted in one significant *p*-value ($p = 0.0032$ and $p = 0.4731$, respectively). Similar to Leidig-Bruckner et al. (2014) and others, I did not find an association between age of onset of T1D and gender in the United States. Furthermore, the results from my study of the United States population showed a lower mean age of onset in males (10.5 years) compared to females (11.8 years), but the result was not statistically significant ($p = 0.2636$). This inconsistency may be due to the potential for less genetic variability in Sweden, the wide age range in the worldwide and German studies, the inclusion of only NHW patients in the United States study, or the smaller age range in the Italian study.

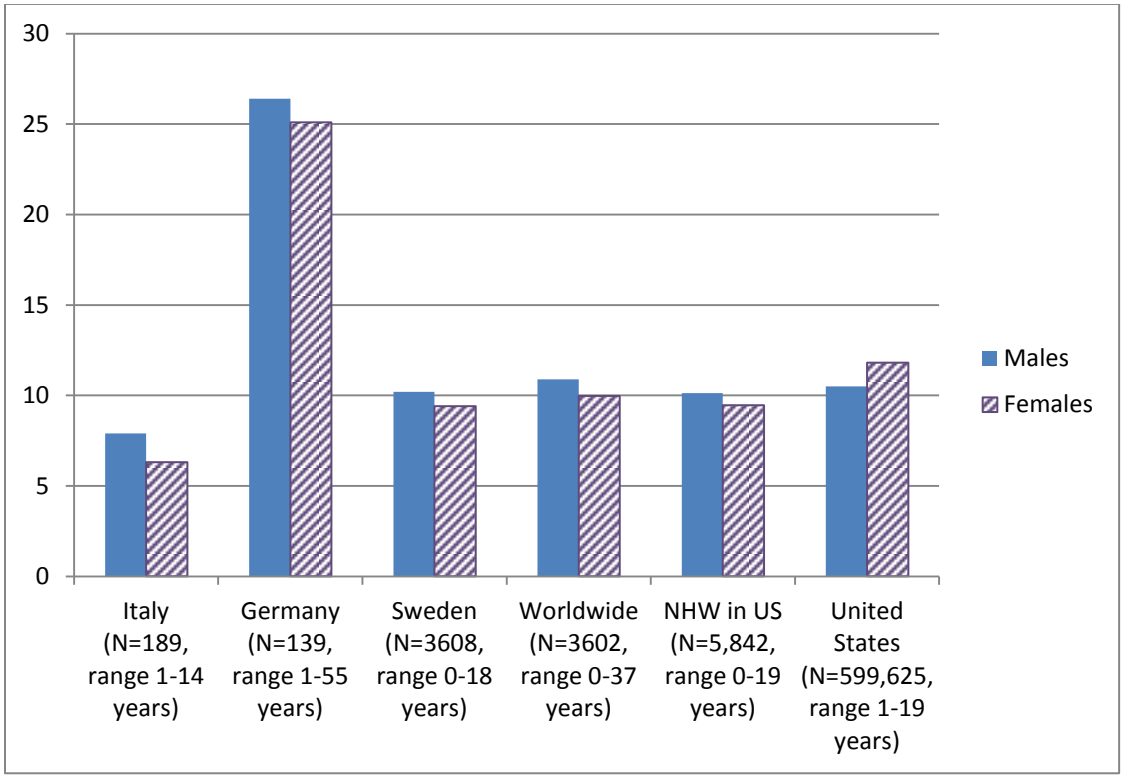


*Figure 2*. Mean age of onset of T1D. From sources: Italy (Blasetti et al., 2011), Germany (Leidig-Bruckner et al., 2014), Sweden (Samuelsson et al., 2013), Worldwide (Valdes et al., 2012), NHW Subset in the United States (Lawrence et al., 2014), and United States (my study).

**Ethnicity**

While some authors repored T1D rates that varied by ethnicity both outside and within the United States, most were not statistically significant (Demmer et al., 2013; Imperatore et al., 2012; Lipman et al., 2013; Smith et al., 2007). However, some authors reported significantly higher rates among White populations compared to Black and American Indian populations (Dabelea, Mayer-Davis et al., 2014; Pettitt et al., 2014). With regards to incidence and prevalence estimates stratified by ethnicity and age categories, similar inconsistent results appeared in the literature. Pettitt et al. (2014) reported statistically significant differences in prevalence between ethnicities within age categories, whereas Lipman et al. (2013) reported no statistically significant differences in incidence between ethnicities within age of onset categories. This supports the need for more investigations of ethnicity and age of onset in T1D research.

In my review of the literature, I did not find any research that compared the mean age of onset between ethnicities. The results of my study showed Hispanics had the highest mean age of onset (13.0 years), followed by NHB (12.7 years), and NHW (10.6 years). The lowest mean age of onset was seen in participants reporting Other ethnicities (6.2 years), including mixed ethnicities. The regression analysis yielded a significant *p*-value $< 0.0001$ for the ethnicity coefficient, indicating an association between age of onset and ethnicity.

However, the results from sensitivity analyses, which excluded the participants who reported Other ethnicity, indicated that the mean age of onset was not associated with the remaining three ethnicities present in my study (Hispanic, NHB, and NHW).

These results were consistent with those reported by Lipman et al. (2013) using similar ethnic categories (Hispanic, Black, and White). Lipman et al. reported no significant differences in the incidence of T1D between ethnicities within age categories (0 to 4, 5 to 9, and 10 to 14). Hence, my results were supported in literature.

### Ethnicity Adjusted for Gender

In order to test the final hypothesis, multivariate regression was employed with gender and ethnicity as independent variables. The primary analysis results indicated that age of onset was significantly associated with ethnicity after adjustment for gender. However, this primary analysis included participants who reported Other ethnicities. When I performed a sensitivity analysis, to examine only Hispanic, NHB, and NHW ethnicities, the significant association was no longer apparent. I expected this result given that I showed my previous univariate analyses to be non-significant. In my literature review, I did not find investigations of age of onset of T1D stratified simultaneously by gender and ethnicity. This supports the importance of my findings, which will add new data to the existing body of research knowledge.

## Advantages and Limitations of the Study

My study consisted of an analysis of secondary data from NHANES, which presented both advantages and limitations. The major advantage to using NHANES was the resulting sample size. As evidenced in Figure 2, to my knowledge to date my study was the largest investigation of mean age of onset of T1D stratified by gender, with a population-based sample size over one hundred times larger than the next largest population-based study in Sweden ($N$ = 599,625 compared to $N$ = 3,608). Furthermore, it

is the first study to stratify mean age of onset by ethnicity. These advantages must be considered alongside the study limitations.

There were inherent limitations in using NHANES. Opposite to the advantage of using weights to obtain a large sample size, is the reliance on using single participants to represent over one thousand T1D patients. As demonstrated in my sensitivity analysis, inclusion or exclusion of one or two participants in the unweighted sample changed the statistical results of the study. NHANES also presents limitations with respect to accuracy. I assumed that the responses obtained from the administration of NHANES were reliable and valid. However, if a few female patients inaccurately reported older onset than actual, the mean age of onset that I derived in this study would have been lower and more in line with prior literature (Blasetti et al., 2011; Leidig-Bruckner et al., 2014; Samuelsson et al., 2013; Valdes et al., 2012).

Additional limitations inherent to NHANES were related to questionnaire design and administration. The diabetes questionnaire did not contain a question that could be used to stratify between T1D and T2D. Therefore, in accordance with Demmer et al (2013), I used insulin only use to identify T1D patient for analysis. Because Elder et al. (2012) reported 18% of T2D patients treat with only insulin, my study may have included T2D patients which, in turn, possibly biased my mean age calculations upwards. Furthermore, if the diabetes questionnaire was administered to all patients, rather than excluding participants under the age of one, my calculation of mean age of onset would not have been biased upwards and possibly would be more consistent with reports in the literature.

## Recommendations

As demonstrated in the discussion of NHANES limitations, changes to the design and administration of the NHANES questionnaire have the potential to provide more robust data to investigate the demographic information of T1D patients. Furthermore, an assessment of the validity of self-reported age of onset of T1D on cross-sectional surveys could inform the validity of age-related T1D research conducted using surveys like NHANES, rather than medical chart abstraction.

Outside of NHANES, I recommend the development of more research related to age of onset. Although I found a higher overall mean age of onset than reported by some (Hughes et al., 2013; Johnson & Meltzer, 2002; Pettitt et al., 2014; Smith et al., 2007), it was lower than reports from others (Hietala, Forsblom, et al., 2013; Luk et al., 2014). Furthermore, I found no association between gender and age of onset and this study unexpectedly showed a higher age of onset in females compared to males. Although not a statistically significant association, the finding is inconsistent with literature (Dahlquist et al., 2011; Evertsen et al., 2009; Hodgson et al., 2012; Catanzariti et al., 2009; Harjutsalo et al., 2008; Blasetti et al., 2011; Valdes et al., 2012). Because etiologic investigations are critical to the prevention of T1D, further age of onset research is warranted.

## Conclusions and Implications for Positive Social Change

Over time, T1D has changed from being an inevitably fatal disease to being a pharmaceutically manageable disease. However, much work remains to determine the etiology and potential means of prevention. I found no association between age of onset of T1D and gender and ethnicity. However, I also found a higher mean age of onset than

previously reported from populations in the United States. This needs to be investigated more thoroughly to provide sufficient foundational data for prevention studies. Further studies are also needed on environmental and infectious risk factors.

T1D is currently an incurable disease and a significant public health concern impacting over 160,000 children less than 20 years old in the United States (Pettitt et al., 2014) and costs $14.4 billion annually in the United States (Tao et al., 2010). To my knowledge, this was the first population-based study in the United States and the largest study worldwide that investigated the mean age of onset of T1D in children between 1 and 19 years old. The results demonstrated that the average age of onset of T1D in the United States was 11.1 years, and age was not associated with gender and ethnicity. Although not statistically significant, the gender and ethnic specific age of onset estimates from this study have the potential to be used to identify high risk children earlier, and therefore have the potential to promote positive social change by reducing the burden of T1D.

# References

Adlercreutz, E. H., Wingren, C. J., Vincente, R. P., Merlo, J., & Agardh, D. (2015). Perinatal risk factors increase the risk of being affected by both type 1 diabetes and coeliac disease. *Acta Paediatrica, 104*(2), 178-184. doi:10.1111/apa.12836

Aiello, L. P. (2014). Diabetic retinopathy and other ocular findings in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study. *Diabetes Care, 37*(1), 17-23. doi:10.2337/dc13-2251

Ailes, E. C., Gilboa, S. M., Riehle-Colarusso, T., Johnson, C. Y., Hobbs, C. A., Correa, A.,…Honein, M. (2014). Prenatal diagnosis of nonsyndromic congenital heart defects: Factors associated with prenatal CHD diagnosis. *Prenatal Diagnosis*, *34*(3), 214–222. doi:10.1002/pd.4282

Al Rashed, A. (2011). Pattern of presentation in type 1 diabetic patients at the diabetes center of a university hospital. *Annals of Saudi Medicine, 31*(3), 243. doi:10.4103/0256-4947.81529

Amador-Patarroyo, M. J., Rodriguez-Rodriguez, A., & Montoya-Ortiz, G. (2012). How does age at onset influence the outcome of autoimmune diseases? *Autoimmune Diseases, 2012,* 1-7. doi:10.1155/2012/251730

American Diabetes Association. (2013). Standards of medical care in diabetes - 2013. *Diabetes Care, 36*(1), S11-S66. doi:10.2337/dc13-S011

American Diabetes Association. (2014). Standards of medical care in diabetes - 2014. *Diabetes Care, 37*(1), S14-S80. doi:10.2337/dc14-S014

Bächle, C., Icks, A., Straßburger, K., Flechtner-Mors, M., Hungele, A., Beyer, P.

,…Rosenbauer, J. (2013). Direct diabetes-related costs in young patients with early-onset, long-lasting type 1 diabetes. *PLoS ONE, 8*(8), e70567. doi:10.1371/journal.pone.0070567

Bell, R., Glinianaia, S. V., Tennant, P. W. G., Bilous, R. W., & Rankin, J. (2012). Peri-conception hyperglycaemia and nephropathy are associated with risk of congenital anomaly in women with pre-existing diabetes: A population-based cohort study. *Diabetologia*, *55*(4), 936–947. doi:10.1007/s00125-012-2455-y

Berhan, Y., Waernbaum, I., Lind, T., Möllsten, A., & Dahlquist, G. (2011). Thirty years of prospective nationwide incidence of childhood type 1 diabetes: The accelerating increase by time tends to level off in Sweden. *Diabetes, 60*(2), 577-81. doi:10.2;i:l7/dbl0-0813/-/DCl

Bhadada, S. K., Kochhar, R., Bhansali, A., Dutta, U., Kumar, P. R., Poornachandra, K. S.,…Singh, K. (2011). Prevalence and clinical profile of celiac disease in type 1 diabetes mellitus in north India: Celiac disease in type 1 diabetes mellitus. *Journal of Gastroenterology and Hepatology*, *26*(2), 378–381. doi:10.1111/j.1440-1746.2010.06508.x

Bitti, M., Masala, S., Capasso, F., Rapini, N., Piccinini, S., Angelini, F.,…Sechi, L. (2012). Mycobacterium avium subsp. paratuberculosis in an Italian cohort of type 1 diabetes pediatric patients. *Clinical & Developmental Immunology*, *2012*. doi:10.1155/2012/785262

Bjornstad, P., Snell-Bergeon, J. K., Rewers, M., Jalal, D., Chonchol, M. B., & Johnson, R. J. (2013). Early diabetic nephropathy: A complication of reduced insulin

sensitivity in type 1 diabetes. *Diabetes Care, 36*(11), 3678-3683. doi:10.2337/dc13-0631

Black, M. H., Anderson, A., Bell, R. A., Dabelea, D., Pihoker, C., Saydah, S.,…Lawrence, J. M. (2011). Prevalence of asthma and its association with glycemic control among youth with diabetes. *Pediatrics, 128*(4), e839–e847. doi:10.1542/peds.2010-3636

Blasetti, A., Di Giulio, C., Tocco, A. M., Verrotti, A., Tumini, S., Chiarelli, F., & Altobelli, E. (2011). Variables associated with severe hypoglycemia in children and adolescents with type 1 diabetes: A population-based study. *Pediatric Diabetes, 12*(1), 4–10. doi:10.1111/j.1399-5448.2010.00655.x

Bluestone, J. A. (2005). Regulatory t-cell therapy: Is it ready for the clinic? *Nature Reviews Immunology, 5*(4), 343–349. doi:10.1038/nri1574

Bobbala, D., Chen, X., Leblanc, C., Mayhue, M., Stankova, J., Tanaka, T.,…Ramanathan, S. (2012). Interleukin-15 plays an essential role in the pathogenesis of autoimmune diabetes in the NOD mouse. *Diabetologia, 55*(11), 3010-3020. doi:10.1007/s00125-012-2675-1

Boettler, T. & von Herrath, M. (2011). Protection against or triggering of type 1 diabetes? Different roles for viral infections. *Expert Reviews Clinical Immunology, 7*(1), 45–53. doi:10.1586/ECI.10.91

Bradley, L. M., Asensio, V. C., Schioetz, L.-K., Harbertson, J., Krahl, T., Patstone, G.,…Sarvetnick, N. (1999). Islet-specific Th1, but not Th2, cells secrete multiple chemokines and promote rapid induction of autoimmune diabetes. *Journal of*

*Immunology*, *162*(5), 2511–2520. Retrieved from http://www.jimmunol.org

Bruehl, H. (2011). Obese adolescents with type 2 diabetes mellitus have hippocampal and frontal lobe volume reductions. *Neuroscience & Medicine, 2*(1), 34–42. doi:10.4236/nm.2011.21005

Buse, J. B., Kaufman, F. R., Linder, B., Hirst, K., El Ghormli, L., & Willi, S. (2013). Diabetes screening with hemoglobin A(1c) versus fasting plasma glucose in a multiethnic middle-school cohort. *Diabetes Care, 36*, 429–435. doi:10.2337/dc12-0295

Caramalho, I., Rodrigues-Duarte, L., Perez, A., Zelenay, S., Penha-Gonçalves, C., & Demengeot, J. (2011). Regulatory t cells contribute to diabetes protection in lipopolysaccharide-treated non-obese diabetic mice: Treg in LPS-mediated diabetes protection. *Scandinavian Journal of Immunology*, *74*(6), 585–595. doi:10.1111/j.1365-3083.2011.02627.x

Carlsson, A., Forsander, G., Ludvigsson, J., Larsen, S., & Örtqvist, E. (2013). A multicenter observational safety study in Swedish children and adolescents using insulin detemir for the treatment of type 1 diabetes. *Pediatric Diabetes*, *14*(5), 358–365. doi:10.1111/pedi.12019

Catanzariti, L., Faulks, K., Moon, L., Waters, A. M., Flack, J., Craig, M.E. (2009). Australia's national trends in the incidence of type 1 diabetes in 0-14-year-olds, 2000–2006. *Diabetic Medicine*, *26*, 596–601. doi:10.1111/j.1464-5491.2009.02737.x

Centers for Disease Control and Prevention. (2004). National diabetes fact sheet: General

information and national estimates on diabetes in the United States, 2003. Retrieved from http://stacks.cdc.gov/view/cdc/7055

Centers for Disease Control and Prevention. (2008). National diabetes fact sheet: General information and national estimates on diabetes in the United States, 2007. Retrieved from http://stacks.cdc.gov/view/cdc/5613

Centers for Disease Control and Prevention. (2009). United States life tables 2009. Retrieved from http://www.cdc.gov/nchs/nvss/mortality/lewk3.htm

Centers for Disease Control and Prevention. (2011). National diabetes fact sheet, 2011. Retrieved from www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf

Centers for Disease Control and Prevention. (2012a). NHANES 2012 diabetes questionnaire. Retrieved from http://www.cdc.gov/nchs/data/nhanes/nhanes_11_12/diq.pdf

Centers for Disease Control and Prevention. (2012b). NHANES 2012 medical conditions questionnaire. Retrieved from http://www.cdc.gov/nchs/data/nhanes/nhanes_11_12/mcq.pdf

Centers for Disease Control and Prevention. (2012c). National Center for Health Statistics research ethics review board (ERB) approval. Retrieved from http://www.cdc.gov/nchs/nhanes/irba98.htm

Centers for Disease Control and Prevention. (2013a). NHANES response rates and population totals. Retrieved from http://www.cdc.gov/nchs/nhanes/response_rates_CPS.htm

Centers for Disease Control and Prevention. (2013b). National health and nutrition

examination survey: 2011 - 2012 data documentation, codebook, and frequencies. Retrieved from http://www.cdc.gov/nchs/nhanes/nhanes2011-2012/DIQ_G.htm#DIQ010

Centers for Disease Control and Prevention. (2013c). National health and nutrition examination survey: Analytic guidelines, 2011 - 2012. Retrieved from http://www.cdc.gov/nchs/data/nhanes/analytic_guidelines_11_12.pdf

Centers for Disease Control and Prevention. (2013d). National health and nutrition examination survey: NHANES 2011 – 2012 overview. Retrieved from http://www.cdc.gov/nchs/nhanes/nhanes2011-2012/overview_g.htm

Centers for Disease Control and Prevention. (2014a). About the national health and nutrition examination survey. Retrieved from http://www.cdc.gov/nchs/nhanes/about_nhanes.htm

Centers for Disease Control and Prevention. (2014b). Continuous NHANES web tutorial. Retrieved from http://www.cdc.gov/NCHS/Tutorials/Nhanes/index_Continuous.htm

Chen, Z., Herman, A.E., Matos, M., Mathis, D., & Benoist, C. (2005). Where CD4+CD25+ T reg cells impinge on autoimmune diabetes. *Journal of Experimental Medicine 202*(10), 1387–1397. doi:10.1084/jem.200514O9

Chisholm, V., Atkinson, L., Donaldson, C., Noyes, K., Payne, A., & Kelnar, C. (2011). Maternal communication style, problem-solving and dietary adherence in young children with type 1 diabetes. *Clinical Child Psychology and Psychiatry, 16*(3), 443–458. doi:10.1177/1359104510373312

Christensen, D. P., Gysemans, C., Lundh, M., Dahllöf, M. S., Noesgaard, D., Schmidt, S.,…Mandrup-Poulsen, T. (2014). Lysine deacetylase inhibition prevents diabetes by chromatin-independent immunoregulation and beta-cell protection. *Proceedings of the National Academy of Sciences of the United States of America, 111*(3), 1055. doi:10.1073/pnas.1320850111

Cinek, O. (2011). Epidemiology of childhood type 1 diabetes mellitus: Lessons from Central and Eastern European data. *Hormone Research in Paediatrics, 76*(s1), 52–56. doi:10.1159/000329168

Cinek, O., Kulich, M., & Sumnik, Z. (2012). The incidence of type 1 diabetes in young Czech children stopped rising: Stagnant incidence of T1D in young Czechs. *Pediatric Diabetes, 13*(7), 559–563. doi:10.1111/j.1399-5448.2012.00858.x

Cohen, J. (1988). *Statistical power analysis for the behavioral sciences* (2nd ed.). New York, NY: Psychology Press.

Constantino, M. I., Molyneaux, L., Limacher-Gisler, F., Al-Saeed, A., Luo, C., Wu, T.,…Wong, J. (2013). Long-term complications and mortality in young-onset diabetes: Type 2 diabetes is more hazardous and lethal than type 1 diabetes. *Diabetes Care, 36*(12), 3863–3869. doi:10.2337/dc12-2455

Cooper, M. N., O'Connell, S. M., Davis, E. A., & Jones, T. W. (2013). A population-based study of risk factors for severe hypoglycaemia in a contemporary cohort of childhood-onset type 1 diabetes. *Diabetologia, 56*(10), 2164–2170. doi:10.1007/s00125-013-2982-1

Costacou, T., & Orchard, T. J. (2013). Differential effect of glycemia on the incidence of

hypertension by sex: The epidemiology of diabetes complications study. *Diabetes Care, 36*(1), 77-83. doi:10.2337/dcl2-0708

Craig, M. E., Jones, T. W., Silink, M., & Ping, Y. J. (2007). Diabetes care, glycemic control, and complications in children with type 1 diabetes from Asia and the Western Pacific region. *Journal of Diabetes and its Complications, 21*(5), 280-287. doi:10.1016/j.jdiacomp.2006.04.005

Creswell, J. (2009). *Research design: Qualitative, quantitative, and mixed methods approaches* (3rd ed.). Thousand Oaks, CA: Sage Publications.

Crume, T. L., Crandell, J., Norris, J. M., Dabelea, D., Fangman, M. T., Pettitt, D. J.,...Mayer-Davis, E. (2014). Timing of complementary food introduction and age at diagnosis of type 1 diabetes: The SEARCH nutrition ancillary study (SNAS). *European Journal of Clinical Nutrition, 68*(11), 1258-1260. doi:10.1038/ejcn.2014.159

Dabelea, D., Mayer-Davis, E. J., Saydah, S., Imperatore, G., Linder, B., Divers, J.,…Hamman, R. F. (2014). Prevalence of type 1 and type 2 diabetes among children and adolescents from 2001 to 2009. *Journal of the American Medical Association, 311*(17), 1778-1786. doi:10.1001/jama.2014.3201

Dabelea, D., Pihoker, C., Talton, J. W., D'Agostino, R. B., Fujimoto, W., Klingensmith, G. J.,…Dolan, L. (2011). Etiological approach to characterization of diabetes type: The SEARCH for Diabetes in Youth Study. *Diabetes Care, 34*(7), 1628–1633. doi:10.2337/dc10-2324

Dabelea, D., Rewers, A., Stafford, J. M., Standiford, D. A., Lawrence, J. M., Saydah,

S.,…Pihoker, C.. (2014). Trends in the prevalence of ketoacidosis at diabetes diagnosis: The SEARCH for Diabetes in Youth Study. *Pediatrics, 133*(4), e938–e945. doi:10.1542/peds.2013-2795

Dahlquist, G. (2006). Can we slow the rising incidence of childhood-onset autoimmune diabetes? The overload hypothesis. *Diabetologia, 49*, 20–24. doi:10.1007/s00125-005-0076-4

Dahlquist, G., Möllsten, A., & Källén, B. (2008). Hospitalization for vascular complications in childhood onset type 1 diabetes - effects of gender and age at onset. *Acta Paediatrica, 97*(4), 483-488. doi:10.1111/j.1651-2227.2008.00680.x

Dahlquist, G., Nyström, L., & Patterson, C. (2011). Incidence of type 1 diabetes in Sweden among individuals aged 0-34 years, 1983-2007: an analysis of time trends. *Diabetes Care, 34*(8), 1754-1759. doi:10.2337/dc11-0056

D'Angeli, M. A., Merzon, E., Valbuena, L. F., Tirschwell, D., Paris, C. A., & Mueller, B. A. (2010). Environmental factors associated with childhood-onset type 1 diabetes mellitus: An exploration of the hygiene and overload hypotheses. *Archives of Pediatrics & Adolescent Medicine, 164*(8), 732-738. doi:10.1001/archpediatrics.2010.115

Dauber, A., Corcia, L., Safer, J., Agus, M. S., Einis, S., & Steil, G. M. (2013). Closed-loop insulin therapy improves glycemic control in children aged < 7 years: A randomized controlled trial. *Diabetes Care, 36*(2), 222–227. doi:10.2337/dc12-1079

Davison, K. A., Negrato, C. A., Cobas, R., Matheus, A., Tannus, L., Palma, C.

S.,…Gomes, M. (2014). Relationship between adherence to diet, glycemic control and cardiovascular risk factors in patients with type 1 diabetes: A nationwide survey in Brazil. *Nutrition Journal*, *13*(1), 1-11. doi:10.1186/1475-2891-13-19

de Beaufort, C. E., Lange, K., Swift, P. G., Aman, J., Cameron, F., Castano, L.,…Mortensen, H. (2013). Metabolic outcomes in young children with type 1 diabetes differ between treatment centers: The Hvidoere Study in Young Children 2009: Center differences persist in young children. *Pediatric Diabetes*, *14*(6), 422–428. doi:10.1111/j.1399-5448.2012.00922.x

de Bock, M., Gunn, A. J., Holt, J.-A., Derraik, J. G. B., Reed, P., Cutfield, W.,…Jefferies, C. (2012). Impact of insulin pumps on glycaemic control in a pump-naïve paediatric regional population. *Journal of Paediatrics and Child Health*, *48*(3), 247–252. doi:10.1111/j.1440-1754.2011.02245.x

de Boer, I. H., Ruer, T., Cleary, P., Lachin, J., Molitch, M., Steffes, M.,…Brunzell, J. (2011). Long-term renal outcomes of patients with type 1 diabetes mellitus and microalbuminuria: An analysis of the DCCT/EDIC cohort. *Archives of Internal Medicine, 171*(5), 412-420. doi:10.1001/archinternmed.2011.16

Demmer, R. T., Zuk, A. M., Rosenbaum, M., & Desvarieux, M. (2013). Prevalence of diagnosed and undiagnosed type 2 diabetes mellitus among US adolescents: Results from the continuous NHANES, 1999-2010. *American Journal of Epidemiology, 178*(7), 1106-1113. doi:10.1093/aje/kwt088

Derraik, J. G. B., Reed, P. W., Jefferies, C., Cutfield, S. W., Hofman, P. L., & Cutfield, W. S. (2012). Increasing incidence and age at diagnosis among children with type

1 diabetes mellitus over a 20-year period in Auckland (New Zealand). *PLoS One, 7*(2), 1-4. doi:10.1371/journal.pone.0032640

Dias, R. P., Brown, F., Wyatt, C., Cheema, S., Allgrove, J., & Amin, R. (2013). The effect of insulin intensification in children and young persons with type 1 diabetes differs in relation to ethnic group; A prospective observational study. *Diabetic Medicine*, *30*(4), 495–501. doi:10.1111/dme.12022

Doggen, K., Debacker, N., Beckers, D., Casteels, K., Coeckelberghs, M., Dooms, L.,…Casteren, V. (2012). Care delivery and outcomes among Belgian children and adolescents with type 1 diabetes. *European Journal of Pediatrics*, *171*(11), 1679–1685. doi:10.1007/s00431-012-1809-2

Elder, D. A., Herbers, P. M., Weis, T., Standiford, D., Woo, J. G., & D'Alessio, D. A. (2012). β-cell dysfunction in adolescents and adults with newly diagnosed type 2 diabetes mellitus. *Journal of Pediatrics, 160*(6), 904–910. doi:10.1016/j.jpeds.2011.12.002

Emery, L. M., Babu, S., Bugawan, T. L., Norris, J. M., Erlich, H. A., Eisenbarth, G. S., & Rewers, M. (2005). Newborn HLA-DR, DQ genotype screening: age-and ethnicity-specific type 1 diabetes risk estimates. *Pediatric Diabetes*, *6*(3), 136–144. doi:10.1111/j.1399-543X.2005.00117.x

Estrada, C. L., Danielson, K. K., Drum, M. L., & Lipton, R. B. (2012). Insufficient sleep in young patients with diabetes and their families. *Biological Research For Nursing*, *14*(1), 48–54. doi:10.1177/1099800410395569

Evertsen, J., Alemzadeh, R., & Wang, X. (2009). Increasing incidence of pediatric type 1

diabetes mellitus in southeastern Wisconsin: Relationship with body weight at diagnosis. *PLoS One, 4*(9), 1-5. doi:10.1371/journal.pone.0006873

Feltbower, R. G., Bodansky, H. J., Patterson, C. C., Parslow, R. C., Stephenson, C. R., Reynolds, C., & McKinney, P. A. (2008). Acute complications and drug misuse are important causes of death for children and young adults with type 1 diabetes: Results from the Yorkshire Register of Diabetes in Children and Young Adults. *Diabetes Care, 31*(5), 922-926. doi:10.2337/dc07-2029

Finne, P., Reunanen, A., Stenman, S., Groop, P. H., & Grönhagen-Riska, C. (2005). Incidence of end-stage renal disease in patients with type 1 diabetes. *Journal of the American Medical Association, 294*(14), 1782-1787. doi:10.1001/jama.294.14.1782

Flyvbjerg, A. (2000). Putative pathophysiological role of growth factors and cytokines in experimental diabetic kidney disease. *Diabetologia, 43*(10), 1205–1223. doi:10.1007/s001250051515

Fu, Z., Zhen, W., Yuskavage, J., & Liu, D. (2011). Epigallocatechin gallate delays the onset of type 1 diabetes in spontaneous non-obese diabetic mice. *British Journal of Nutrition, 105*(8), 1218–1225. doi:10.1017/S0007114510004824

Galler, A., Stange, T., Müller, G., Näke, A., Vogel, C., Kapellen, T.,…Rothe, U. (2010). Incidence of childhood diabetes in children aged less than 15 years and its clinical and metabolic characteristics at the time of diagnosis: Data from the Childhood Diabetes Registry of Saxony, Germany. *Hormone Research in Paediatrics, 74*(4), 285–291. doi:10.1159/000303141

Gavin, J. R., Alberti, K. G., Davidson, M. B., DeFronzo, R. A., Drash, A., Gabbe, S. G.,…Stern, M. P. (2003). Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care, 26*(1), S5-S20. doi:10.2337/diacare.25.2007.S5

Gleicher, N., & Barad, D. H. (2007). Gender as risk factor for autoimmune diseases. *Journal of autoimmunity, 28*(1), 1-6. doi:10.1016/j.jaut.2006.12.004

Goudy, K., Song, S., Wasserfall, C., Zhang, Y. C., Kapturczak, M., Muir, A.,…Atkinson, M.. (2001). Adeno-associated virus vector-mediated IL-10 gene delivery prevents type 1 diabetes in NOD mice. *Proceedings of the National Academy of Sciences, 98*(24), 13913–13918. doi:10.1073_pnas.251532298

Grauslund, J., Green, A., & Sjølie, A. K. (2011). Cataract surgery in a population-based cohort of patients with type 1 diabetes: Long-term incidence and risk factors. *Acta Ophthalmologica, 89*(1), 25–29. doi:10.1111/j.1755-3768.2009.01619.x

Gruden, G., Giunti, S., Barutta, F., Chaturvedi, N., Witte, D. R., Tricarico, M.,…Bruno, G. (2012). QTc interval prolongation is independently associated with severe hypoglycemic attacks in type 1 diabetes From the Eurodiab IDDM Complications Study. *Diabetes Care, 35*(1), 125–127. doi:10.2337/dc11-1739

Hägg, S., Thorn, L. M., Putaala, J., Liebkind, R., Harjutsalo, V., Forsblom, C. M.,…Tatlisumak, T. (2013). Incidence of stroke according to presence of diabetic nephropathy and severe diabetic retinopathy in patients with type 1 diabetes. *Diabetes Care, 36*(12), 4140-4146. doi:10.2337/dc13-0669

Haller, M. J., Gitelman, S. E., Gottlieb, P. A., Michels, A. W., Rosenthal, S. M., Shuster,

J. J.,... Schatz, D. A. (2015). Anti-thymocyte globulin/G-CSF treatment preserves beta cell function in patients with established type 1 diabetes. *Journal of Clinical Investigation, 125*(1), 448-455. doi:10.1172/JCI78492

Hamman, R. F., Bell, R. A., Dabelea, D., D'Agostino, R. B., Jr, Dolan, L., Imperatore, G.,... Saydah, S. (2014). The SEARCH for diabetes in youth study: Rationale, findings, and future directions. *Diabetes Care, 37*(12), 3336-3344. doi:10.2337/dc14-0574

Harjutsalo, V., Sjöberg, L., & Tuomilehto, J. (2008). Time trends in the incidence of type 1 diabetes in Finnish children: A cohort study. *Lancet, 371,* 1777-82. doi:10.1016/S0140-6736(08)60765-5

Heering, S. G., West, B. T., & Berglund P. A. (2010). *Applied survey data analysis*. Boca Raton, FL: CRC Press.

Heller, S., Bode, B., Kozlovski, P., & Svendsen, A. L. (2013). Meta-analysis of insulin aspart versus regular human insulin used in a basal-bolus regimen for the treatment of diabetes mellitus. *Journal of Diabetes, 5*(4), 482-491. doi:10.1111/1753-0407.12060

Heron, M. (2013). Deaths: Leading causes for 2010. *National vital statistics reports, 62*(6), 1-96. Retrieved from www.cdc.gov/nchs/data/nvsr/nvsr62/nvsr62_06.pdf

Hietala, K., Forsblom, C., Summanen, P., & Groop, P. (2013). Higher age at onset of type 1 diabetes increases risk of macular oedema. *Acta Ophthalmologica, 91*(8), 709-715. doi:10.1111/j.1755-3768.2012.02522.x

Hietala, K., Wadén, J., Forsblom, C., Harjutsalo, V., Kytö, J., Summanen, P., & Groop,

P.H. (2013). HbA1c variability is associated with an increased risk of retinopathy requiring laser treatment in type 1 diabetes. *Diabetologia*, *56*(4), 737–745. doi:10.1007/s00125-012-2816-6

Hodgson, S., Beale, L., Parslow, R. C., Feltbower, R. G., & Jarup, L. (2012). Creating a national register of childhood type 1 diabetes using routinely collected hospital data. *Pediatric Diabetes*, *13*(3), 235–243. doi:10.1111/j.1399-5448.2011.00815.x

Hokkam, E. N. (2009). Assessment of risk factors in diabetic foot ulceration and their impact on the outcome of the disease. *Primary Care in Diabetes, 3,* 219-224. doi:10.1016/j.pcd.2009.08.009

Hovorka, R., Allen, J. M., Elleri, D., Chassin, L. J., Harris, J., Xing, D.,…Dunger, D. B. (2010). Manual closed-loop insulin delivery in children and adolescents with type 1 diabetes: A phase 2 randomised crossover trial. *Lancet, 375,* 743–51. doi:10.1016/S0140-6736(09)61998-X

Howard, S. G. (2011). Comment on: Berhan. Thirty years of prospective nationwide incidence of childhood type 1 diabetes: The accelerating increase by time tends to level off in Sweden. *Diabetes*, *60*(9), e25. doi:10.2337/db11-0899

Hübner, M. P., Stocker, J. T. & Mitre, E. (2009). Inhibition of type 1 diabetes in filaria-infected non-obese diabetic mice is associated with a T helper type 2 shift and induction of FoxP3+ regulatory T cells. *Immunology*, *127*(4), 512–522. doi:10.1111/j.1365-2567.2008.02958.x

Hughes, T. M., Ryan, C. M., Aizenstein, H. J., Nunley, K., Gianaros, P. J., Miller, R.,…Rosano, C. (2013). Frontal gray matter atrophy in middle aged adults with

type 1 diabetes is independent of cardiovascular risk factors and diabetes complications. *Journal of Diabetes and Its Complications, 27*(6), 558–564. doi:10.1016/j.jdiacomp.2013.07.001

Hunt, K. J., & Schuller, K. L. (2007). The increasing prevalence of diabetes in pregnancy. *Obstetrics and Gynecology Clinics of North America, 34*,173-199. doi:10.1016/j.ogc.2007.03.00

Hussen, H. I., Yang, D., Cnattingius, S., & Moradi, T. (2013). Type I diabetes among children and young adults: The role of country of birth, socioeconomic position and sex: Immigration, type 1 diabetes in Sweden. *Pediatric Diabetes, 14*(2), 138–148. doi:10.1111/j.1399-5448.2012.00904.x

Imperatore, G., Boyle, J. P., Thompson, T .J., Case, D., Dabelea, D., Hamman, R. F., …& Standiford, D. (2012). Projections of type 1 and type 2 diabetes burden in the U.S. population aged <20 years through 2050: Dynamic modeling of incidence, mortality, and population growth. *Diabetes Care, 35*(12), 2515–20. doi:10.2337/dc12-0669

International Diabetes Federation. (2013). IDF diabetes atlas (6th ed.). Retrieved from http://www.diabetesatlas.org

Johnson, C. L., Dohrmann, S. M., Burt, V. L., & Mohadjer, L. K. (2014). National Health and Nutrition Examination Survey: Sample design, 2011–2014. National Center for Health Statistics. *Vital Health Statistics, 2*(162). Retrieved from stacks.cdc.gov/view/cdc/22155

Johnson, S. B. & Meltzer, L. J. (2002). Disentangling the effects of current age, onset

age, and disease duration: Parent and child attitudes toward diabetes as an exemplar. *Journal of Pediatric Psychology, 27*(1), 77-86. doi:10.1093/jpepsy/27.1.77

Jude, E. B., Eleftheriadou, I. & Tentolouris, N. (2010). Peripheral arterial disease in diabetes: A review. *Diabetic Medicine, 27,* 4-14. doi:10.1111/j.1464-5491.2009.02866.x

Kallas-Koeman, M., Kong, J. M., Klinke, J. A., Butalia, S., Lodha, A. K., Lim, K. I.,…Donovan, L. E. (2014). Insulin pump use in pregnancy is associated with lower $HbA_{1c}$ without increasing the rate of severe hypoglycaemia or diabetic ketoacidosis in women with type 1 diabetes. *Diabetologia, 57*(4), 681-689. doi:10.1007/s00125-014-3163-6

King, K., & Rubin, G. (2003). A history of diabetes: From antiquity to discovering insulin. *British Journal of Nursing, 12*(18), 1091-1095. doi:10.12968/bjon.2003.12.18.11775

Knip, M. (2012). Descriptive epidemiology of type 1 diabetes—is it still in? *Diabetologia, 55*(5), 1227–1230. doi:10.1007/s00125-012-2522-4

Knip, M., Veijola, R., Virtanen, S. M., Hyöty, H., Vaarala, O., & Akerblom, H. K. (2005). Environmental triggers and determinants of type 1 diabetes. *Diabetes, 54*(suppl 2), S125–S136. doi:10.2337/diabetes.54.suppl_2.S125

Kockum, I., Sanjeevi, C. B., Eastman, S., Landin-Olsson, M., Dahlquist, G., & Lernmark, A. (1999). Complex interaction between HLA DR and DQ in conferring risk for childhood type 1 diabetes. *European Journal of Immunogenetics, 26*(5), 361–372.

doi:10.1086/318799

Kovatchev, B. P., Mendosa, P., Anderson, S., Hawley, J. S., Ritterband, L. M., & Gonder-Frederick, L. (2011). Effect of automated bio-behavioral feedback on the control of type 1 diabetes. *Diabetes care, 34*(2), 302-307. doi:10.2337/dc10-1366

Kramer, C. K., & Retnakaran, R. (2013). Concordance of retinopathy and nephropathy over time in type 1 diabetes: An analysis of data from the Diabetes Control and Complications Trial. *Diabetic Medicine*, *30*(11), 1333–1341. doi:10.1111/dme.12296

Kroon, E., Martinson, L. A., Kadoya, K., Bang, A. G., Kelly, O. G., Eliazer, S.,…Baetge, E. E. (2008). Pancreatic endoderm derived from human embryonic stem cells generates glucose-responsive insulin-secreting cells in vivo. *Nature Biotechnology*, *26*(4), 443-452. doi:10.1038/nbt1393

Kumar, R., Goswami, R., Agarwal, S., Israni, N., Singh, S. K., & Rani, R. (2007). Association and interaction of the TNF-alpha gene with other pro- and anti-inflammatory cytokine genes and HLA genes in patients with type 1 diabetes from North India. *Tissue Antigens*, *69*(6), 557–567. doi:10.1111/j.1399-0039.2007.00817.x

Lachin, J. M., Orchard, T. J., & Nathan, D. M. (2014). Update on cardiovascular outcomes at 30 years of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study. *Diabetes Care*, *37*(1), 39-43. doi:10.2337/dc13-2116

Landau, Z., Klonoff, D., Nayberg, I., Feldman, D., Levit, S. B., Lender, D.,...Wainstein,

J. (2014). Improved pharmacokinetic and pharmacodynamic profiles of insulin analogues using InsuPatch, a local heating device. *Diabetes Metabolism Research and Reviews*, *30*(8), 686-92. doi:10.1002/dmrr.2536

Lang, T. A., & Secic, M. (2006). *How to report statistics in medicine*. Philadelphia, PA: American College of Physicians.

Larsson, H. E., Vehik, K., Bell, R., Dabelea, D., Dolan, L., Pihoker, C.,…Haller, M. J. (2011). Reduced prevalence of diabetic ketoacidosis at diagnosis of type 1 diabetes in young children participating in longitudinal follow-up. *Diabetes care*, *34*(11), 2347-2352. doi:10.2337/dc11-1026

Last, J. M. (1995). *A dictionary of epidemiology*. New York, NY. Oxford University Press.

Lawrence, J. M., Imperatore, G., Dabelea, D., Mayer-Davis, E., Linder, B., Saydah, S.,...D'Agostino, R. B., Jr. (2014). Trends in incidence of type 1 diabetes among Non-Hispanic White youth in the U.S., 2002-2009. *Diabetes*, *63*(11), 3938. doi:10.2337/db13-1891

Lawson, M. L., Bradley, B., McAssey, K., Clarson, C., Kirsch, S. E., Mahmud, F. H.,...Barrowman, N. (2014). The JDRF CCTN CGM TIME trial: Timing of initiation of continuous glucose monitoring in established pediatric type 1 diabetes: Study protocol, recruitment and baseline characteristics. *BMC Pediatrics*, *14*(183), 1-9. doi:10.1186/1471-2431-14-183

Lee, J., Wu, E., Tarini, B., Herman, W., & Yoon, E. (2011). Diagnosis of diabetes using hemoglobin A1c: Should recommendations in adults be extrapolated to

adolescents? *Journal of Pediatrics, 158*(6), 947–952. doi:10.1016/j.jpeds.2010.11.026

Leech, N. J., O'Sullivan, J., Avery, P., Howey, C., Burling, K., Iyer, S.,…Cheetham, T. (2010). Increased maternal homeostasis model assessment of insulin resistance (HOMA-IR) associated with older age at diagnosis of type 1 diabetes in offspring: Phenotype and diagnosis of type 1 diabetes. *Diabetic Medicine, 27*(12), 1450–1453. doi:10.1111/j.1464-5491.2010.03130.x

Lehuen, A., Diana, J., Zaccone, P., & Cooke, A. (2010). Immune cell crosstalk in type 1 diabetes. *Nature Reviews. Immunology, 10*(7), 501-513. doi:10.1038/nri2787

Leidig-Bruckner, G., Grobholz, S., Bruckner, T., Scheidt-Nave, C., Nawroth, P., & Schneider, J. G. (2014). Prevalence and determinants of osteoporosis in patients with type 1 and type 2 diabetes mellitus. *BMC Endocrine Disorders, 14*(33), 1-13. doi:10.1186/1472-6823-14-33

Levy-Shraga, Y., Lerner-Geva, L., Boyko V., Graph-Barel, G., Mazor-Aronovitch, K., Modan-Moses, D., & Pinhas-Hamiel, O. (2012). Type 1 diabetes in pre-school children: Long-term metabolic control, associated autoimmunity and complications. *Diabetic Medicine, 29*, 1291–1296. doi:10.1111/j.1464-5491.2012.03682.x

Lewis, K. R., Clark, C., & Velarde, M. C. (2014). Socioeconomic factors associated with pediatric diabetic ketoacidosis admissions in southern West Virginia. *Clinical Endocrinology, 81*(2), 218-221. doi:10.1111/cen.12350

Li, K., Zhu, S., Russ, K., Xu, S., Xu, T., Ma, T.,…Ding, S. (2014). Small molecules

facilitate the reprogramming of mouse fibroblasts into pancreatic lineages. *Cell Stem Cell, 14*(2), 228-236. doi:10.1016/j.stem.2014.01.006

Liese, A. D., Puett, R. C., Lamichhane, A. P., Nichols, M. D., Dabelea, D., Lawson, A. B.,…Mayer-Davis, E. (2012). Neighborhood level risk factors for type 1 diabetes in youth: The SEARCH case-control study. *International Journal of Health Geographics, 11*, 1-9. doi:10.1186/1476-072X-11-1

Lilienfeld, D., & Stolley, P. (1994). *Foundations of epidemiology*. New York, NY: Oxford University Press, Inc.

Lim, J. S., Lee, D. H., & Jacobs, D. R. (2008). Association of brominated flame retardants with diabetes and metabolic syndrome in the U.S. population, 2003–2004. *Diabetes Care, 31,* 1802–1807. doi:10.2337/dc08-0850.

Lin, A., Northam, E. A., Werther, G. A., & Cameron, F. J. (2015). Risk factors for decline in IQ in youth with type 1 diabetes over the 12 years from Diagnosis/Illness onset. *Diabetes Care, 38*(2), 236-242. doi:10.2337/dc14-1385

Lin, H., Wang, C., Tsai, F., Hwang, K., Chen, W., Lin, C., & Li, T. (2015). Enterovirus infection is associated with an increased risk of childhood type 1 diabetes in Taiwan: A nationwide population-based cohort study. *Diabetologia, 58*(1), 79-86. doi:10.1007/s00125-014-3400-z

Lin, W. H., Wang, M. C., Wang, W. M., Yang, D. C., Lam, C. F., Roan, J. N., & Li, C. Y. (2014). Incidence of and mortality from type I diabetes in Taiwan from 1999 through 2010: A nationwide cohort study. *PLoS ONE, 9*(1), 1-7. doi:10.1371/journal.pone.0086172

Lind, M., Bounias, I., Olsson, M., Gudbjörnsdottir, S., Svensson, A. M., & Rosengren, A. (2011). Glycaemic control and incidence of heart failure in 20985 patients with type 1 diabetes: An observational study. *Lancet, 378*, 140-146. doi:10.1016/S0140-6736(11)60471-6.

Lipman, T., Katz, L., Ratcliffe, S. J., Murphy, K., Aguilar, A., Rezvani, I.,…Suarez, E. (2013). Increasing incidence of type 1 diabetes in youth twenty years of the Philadelphia pediatric diabetes registry. *Diabetes Care, 36*(6), 1597-603. doi:10.2337/dc12-0767

Liu, Z., Liu, Q., Bleich, D., Salgame, P., & Gause, W. C. (2010). Regulation of type 1 diabetes, tuberculosis, and asthma by parasites. *Journal of Molecular Medicine*, *88*(1), 27-38. doi:10.1007/s00109-009-0546-0

Livingstone, S. J., Looker, H. C., Hothersall, E. J., Wild, S. H., Lindsay, R. S., Chalmers, J.,…Colhoun, H. M. (2012). Risk of cardiovascular disease and total mortality in adults with type 1 diabetes: Scottish registry linkage study. *PLoS Medicine*, *9*(10), e1001321. doi:10.1371/journal.pmed.1001321

Ludvigsson, J., Krisky, D., Casas, R., Battelino, T., Castaño, L., Greening, J.,…Palmer, J. (2012). GAD65 antigen therapy in recently diagnosed type 1 diabetes mellitus. *New England Journal of Medicine*, *366*(5), 433–442. doi:10.1056/NEJMoa1107096

Luk, A. O., Lau, E. S., So, W. Y., Ma, R. C., Kong, A. P., Ozaki, R.,…Chan, J. C. (2014). Prospective study on the incidences of cardiovascular-renal complications in Chinese patients with young-onset type 1 and type 2 diabetes. *Diabetes Care*,

*37*(1), 149-57. doi:10.2337/dc13-1336

Lund, M. E., Hutchinson, A. T., Robinson, M. W., Simpson, A. M., Dalton, J. P., & Donnelly, S. (2014). Secreted proteins from the helminth fasciola hepatica inhibit the initiation of autoreactive T cell responses and prevent diabetes in the NOD mouse. *PLoS One, 9*(1), 1-10. doi:10.1371/journal.pone.0086289

Lundgren, M., Lynch, K., Larsson, C., & Larsson, H. (2015). Cord blood insulinoma-associated protein 2 autoantibodies are associated with increased risk of type 1 diabetes in the population-based diabetes prediction in Skåne study. *Diabetologia, 58*(1), 75-78. doi:10.1007/s00125-014-3394-6

Lung, T. W. C., Clarke, P. M., Hayes, A. J., Stevens, R. J., & Farmer, A. (2013). Simulating lifetime outcomes associated with complications for people with type 1 diabetes. *PharmacoEconomics, 31*(6), 509–518. doi:10.1007/s40273-013-0047-4

Luoto, R. M., Kinnunen, T. I., Aittasalo, M., Ojala, K., Mansikkamäki, K., Toropainen, E.,…Vasankari, T. (2010). Prevention of gestational diabetes: Design of a cluster-randomized controlled trial and one-year follow-up. *BMC Pregnancy and Childbirth, 10*(1), 39. doi:10.1186/1471-2393-10-39

Ly, T. T., Nicholas, J. A., Retterath, A., Lim, E. M., Davis, E. A., & Jones, T. W. (2013). Effect of sensor-augmented insulin pump therapy and automated insulin suspension vs standard insulin pump therapy on hypoglycemia in patients with type 1 diabetes: A randomized clinical trial. *Journal of the American Medical Association, 310*(12), 1240-7. doi:10.1001/jama.2013.277818

Makura, C. B., Nirantharakumar, K., Girling, A. J., Saravanan, P., & Narendran, P. (2013). Effects of physical activity on the development and progression of microvascular complications in type 1 diabetes: Retrospective analysis of the DCCT study. *BMC Endocrine Disorders*, *13*(1), 37. doi:10.1186/1472-6823-13-37

Martin, C. L., Albers, J. W., & Pop-Busui, R. (2014). Neuropathy and related findings in the diabetes control and complications Trial/Epidemiology of diabetes interventions and complications study. *Diabetes Care, 37*(1), 31. doi:10.2337/dc13-2114

Miettinen, M. E., Reinert, L., Kinnunen, L., Harjutsalo, V., Koskela, P., Surcel, H. M.,…Tuomilehto, J. (2012). Serum 25-hydroxyvitamin D level during early pregnancy and type 1 diabetes risk in the offspring. *Diabetologia*, *55*(5), 1291–1294. doi:10.1007/s00125-012-2458-8

Miller, R. G., Secrest, A. M., Ellis, D., Becker, D. J., & Orchard, T. J. (2013). Changing impact of modifiable risk factors on the incidence of major outcomes of type 1 diabetes: The Pittsburgh Epidemiology of Diabetes Complications Study. *Diabetes care*, *36*(12), 3999-4006. doi:10.2337/dc13-1142

Morrison, D. F. (1990). *Multivariate statistical methods*. New York, NY: McGraw-Hill Publishing Company.

Nathan, D. M. (2014). The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study at 30 years: Overview. *Diabetes Care*, *37*(1), 9–16. doi:10.2337/dc13-2112

National Diabetes Data Group. (1979). Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. *Diabetes, 28,* 1039-1057. doi:10.2337/diab.28.12.1039

National Institutes of Health. (2012). Oral insulin study (TrialNet). Retrieved from http://www.t1diabetes.nih.gov/t1d_ctcr/study.asp?StudyID=134

Nilsson, A.-L., Vaziri-Sani, F., Andersson, C., Larsson, K., Carlsson, A., Cedervall, E.,…Lernmark, Å. (2013). Relationship between ljungan virus antibodies, HLA-DQ8, and insulin autoantibodies in newly diagnosed type 1 diabetes children. *Viral Immunology*, *26*(3), 207–215. doi:10.1089/vim.2013.0008

Nin, J. W., Jorsal, A., Ferreira, I., Schalkwijk, C. G., Prins, M. H., Parving, H. H.,…Stehouwer, C. D. (2011). Higher plasma levels of advanced glycation end products are associated with incident cardiovascular disease and all-cause mortality in type 1 diabetes: A 12-year follow-up study. *Diabetes Care, 34*(2), 442-447. doi:10.2337/dc10-1087

Östensson, M., Montén, C., Bacelis, J., Gudjonsdottir, A. H., Adamovic, S., Ek, J.,…Torinsson-Naluai, Å. (2013). A possible mechanism behind autoimmune disorders discovered by genome-wide linkage and association analysis in celiac disease. *PLoS ONE*, *8*(8), e70174. doi:10.1371/journal.pone.0070174

Pagano, M., & Gauvreau, K. (1993). *Principles of biostatistics*. Belmont, CA: Duxbury Press.

Pang, W., Wang, H., Shi, L., Sun, Y., Wang, X., Wang, M.,…Shi, G. (2013). Immunomodulatory effects of escherichia coli ATCC 25922 on allergic airway

inflammation in a mouse model. *PLoS ONE, 8*(3), 1-10. doi:10.1371/journal.pone.0059174

Patterson, C. C., Dahlquist, G., Gyürüs, E., Green, A., & Soltész, G. (2009). Incidence trends for childhood type 1 diabetes in Europe during 1989-2003 and predicted new cases 2005-20: A multicentre prospective registration study. *Lancet, 373*(9680), 2027-33. doi:10.1016/S0140-6736(09)60568-7

Patterson, C.C., Dahlquist, G., Soltesz, G., & Green, A. (2000). Variation and trends in incidence of childhood diabetes in Europe. *Lancet, 355*(9207), 873–876. doi:10.1016/S0140-6736(99)07125-1

Patterson, C. C., Gyürüs, E., Rosenbauer, J., Cinek, O., Neu, A., Schober, E.,…Soltész, G. (2012). Trends in childhood type 1 diabetes incidence in Europe during 1989–2008: Evidence of non-uniformity over time in rates of increase. *Diabetologia, 55*(8), 2142–2147. doi:10.1007/s00125-012-2571-8

Pettitt, D. J., Talton, J., Dabelea, D., Divers, J., Imperatore, G., Lawrence, J. M.,…Hamman, R. F. (2014). Prevalence of diabetes mellitus in U.S. youth in 2009: The SEARCH for diabetes in youth study. *Diabetes Care, 37*(1), 402-408. doi:10.2337/dc13-1838

Pfefferle, P. I., Teich, R., & Renz, H. (2009). The immunological basis of the hygiene hypothesis. In R. Pawankar, S. Holgate, & L. Rosenwasser (Eds.), *Allergy frontiers: Epigenetics, allergens and risk factors* (pp. 325-348). Dussledorf, Germany: Springer.

Portuesi, R., Pozzilli, P., Boehm, B., Buzzetti, R., & Filippi, S. (2013). Assessment of

type 1 diabetes risk conferred by HLA-DRB1, INS-VNTR and PTPN22 genes using the bayesian network approach. *PLoS ONE, 8*(11), e79506. doi:10.1371/journal.pone.0079506

Raju, T. (2006). A mysterious something: The discovery of insulin and the 1923 Nobel Prize for Frederick G. Banting (1891–1941) and John J. R. Macleod (1876–1935). *Acta Paediatrica*, *95*(10), 1155–1156. doi:10.1080/08035250600930328

Ramachandran, S., Bhanu Keerthi, A. V., & Dhana Raju, M. D. (2014). Diabetes mellitus: An overview. *Pharma Innovation*, *2*(11), 27-37. Retrieved from http://www.thepharmajournal.com

Rewers, A., Klingensmith, G., Davis, C., Petitti, D. B., Pihoker, C., Rodriguez, B.,…Dabelea, D. (2008). Presence of diabetic ketoacidosis at diagnosis of diabetes mellitus in youth: The Search for Diabetes in Youth Study. *Pediatrics, 121*(5), e1258–e1266. doi:10.1542/peds.2007-1105

Rezania, A., Bruin, J. E., Riedel, M. J., Mojibian, M., Asadi, A., Xu, J.,…Kieffer, T. J. (2012). Maturation of human embryonic stem cell-derived pancreatic progenitors into functional islets capable of treating pre-existing diabetes in mice. *Diabetes, 61*, 2016–2029. doi:10.2337/db11-1711

Rodacki, M., Pereira, J. R., Nabuco de Oliveira, A. M., Barone, B., Mac Dowell, R., Perricelli, P.,…Oliveira, J. E. (2007). Ethnicity and young age influence the frequency of diabetic ketoacidosis at the onset of type 1 diabetes. *Diabetes Research and Clinical Practice, 78*(2), 259-262. doi:10.1016/j.diabres.2007.04.002

Rosenfeld, L. (2002). Insulin: Discovery and controversy. *Clinical Chemistry*, *48*(12), 2270–2288.

Rosner, B. (1990). *Fundamentals of biostatistics*. Boston, MA: PWS-Kent Publishing Company.

Rubio-Cabezas, O. & Ellard, S. (2013). Diabetes mellitus in neonates and infants: Genetic heterogeneity, clinical approach to diagnosis, and therapeutic options. *Hormone Research in Paediatrics*, *80*(3), 137-46. doi:10.1159/000354219

Rubio-Cabezas, O., Flanagan, S. E., Damhuis, A., Hattersley, A. T., & Ellard, S. (2012). K(ATP) channel mutations in infants with permanent diabetes diagnosed after 6 months of life. *Pediatric Diabetes, 13*, 322–325. doi:10.1111/j.1399-5448.2011.00824.x

Sahakyan, K., Klein, B. E., Lee, K. E., Myers, C. E., & Klein, R. (2011). The 25-year cumulative incidence of lower extremity amputations in people with type 1 diabetes. *Diabetes care*, *34*(3), 649-651. doi:10.2337/dc10-1712

Samuelsson, U., Lindblad, B., Carlsson, A., Forsander, G., Ivarsson, S., Kockum, I.,…Ludvigsson, J. (2013). Residual beta cell function at diagnosis of type 1 diabetes in children and adolescents varies with gender and season: Residual Beta Cell Function at Diagnosis. *Diabetes/Metabolism Research and Reviews*, *29*(1), 85–89. doi:10.1002/dmrr.2365

Samuelsson, U., & Löfman, O. (2014). Geochemical correlates to type 1 diabetes incidence in Southeast Sweden: an environmental impact? *Journal of Environmental Health*, *76*(6), 146-154.

Sander, B., Larsen, M., Andersen, E. W., & Lund-Andersen, H. (2013). Impact of changes in metabolic control on progression to photocoagulation for clinically significant macular oedema: A 20 year study of type 1 diabetes. *Diabetologia*, *56*(11), 2359–2366. doi:10.1007/s00125-013-3027-5

Sarkar, S. A., Lee, C. E., Victorino, F., Nguyen, T. T., Walters, J. A., Burrack, A.,…Homann, D. (2012). Expression and regulation of chemokines in murine and human type 1 diabetes. *Diabetes*, *61*(2), 436–446. doi:10.2337/db11-0853

Sarween, N., Chodos, A., Raykundalia, C., Khan, M., Abbas, A. K., & Walker, L. S. (2004). CD4+CD25+ cells controlling a pathogenic CD4 response inhibit cytokine differentiation, CXCR-3 expression, and tissue invasion. *Journal of Immunology*, *173*(5), 2942–2951. doi:10.4049/jimmunol.173.5.2942

Saunders, K. A., Raine, T., Cooke, A., & Lawrence, C. E. (2007). Inhibition of autoimmune type 1 diabetes by gastrointestinal helminth infection. *Infection and Immunity*, *75*(1), 397–407. doi:10.1128/IAI.00664-06

Schiesser, J. V., & Wells, J. M. (2014). Generation of β cells from human pluripotent stem cells: Are we there yet?: β cells from stem cells: how close? *Annals of the New York Academy of Sciences*, *1311*(1), 124–137. doi:10.1111/nyas.12369

Schulte, B. M., Lanke, K. H. W., Piganelli, J. D., Kers-Rebel, E. D., Bottino, R., Trucco, M., …& van Kuppeveld, F. J. M. (2012). Cytokine and chemokine production by human pancreatic islets upon enterovirus infection. *Diabetes*, *61*(8), 2030–2036. doi:10.2337/db11-1547

SEARCH for Diabetes in Youth. (2014). About search. Retrieved from

https://searchfordiabetes.org/public/dspAbout.cfm

Seewaldt, S., Thomas, H. E., Ejrnaes, M., Christen, U., Wolfe, T., Rodrigo, E.,…von Herrath, M. G. (2000). Virus-induced autoimmune diabetes: Most beta-cells die through inflammatory cytokines and not perforin from autoreactive (anti-viral) cytotoxic T-lymphocytes. *Diabetes*, *49*(11), 1801–1809. doi:10.2337/diabetes.49.11.1801

Sepa, A., & Ludvigsson, J. (2006). Psychological stress and the risk of diabetes-related autoimmunity: A review article. *Neuroimmunomodulation, 13*, 301–308. doi:10.1159/000104858

Shalitin, S., & Chase, H. P. (2011). Diabetes technology and treatments in the paediatric age group. *International Journal of Clinical Practice*, *65*(s170), 76–82. doi:10.1111/j.1742-1241.2010.02582.x

Şimsek, D., Aycan, Z., Ozen, S., Cetinkaya, S., Kara, C., Abalı, S.,…Ocal, G. (2013). Diabetes care, glycemic control, complications, and concomitant autoimmune diseases in children with type 1 diabetes in Turkey: A multicenter study. *Journal of Clinical Research in Pediatric Endocrinology*, *5*(1), 20-26. doi:10.4274/Jcrpe.893

Skapenko, A., Kalden, J.R., Lipsky, P.E., Schulze-Koops, H. (2005). The IL-4 receptor alpha-chain-binding cytokines, IL-4 and IL-13, induce forkhead box P3-expressing CD25+CD4+ regulatory T cells from CD25-CD4+ precursors. *Journal of Immunology*. *175*(9), 6107–6116. doi:10.4049/jimmunol.175.9.6107

Smith, T. L., Drum, M. L., & Lipton, R. B. (2007). Incidence of childhood type 1 and

non-type 1 diabetes mellitus in a diverse population: The Chicago Childhood Diabetes Registry, 1994 to 2003. *Journal of Pediatric Endocrinology and Metabolism*, *20*(10), 1093-1107. doi:10.1515/JPEM.2007.20.10.1093

Snell-Bergeon, J. K., Smith, J., Dong, F., Barón, A. E., Barriga, K., Norris, J. M., & Rewers, M. (2012). Early childhood infections and the risk of islet autoimmunity: The Diabetes Autoimmunity Study in the Young (DAISY). *Diabetes care*, *35*(12), 2553-2558. doi:10.2337/dc12-0423

Sørensen, J. S., Johannesen, J., Pociot, F., Kristensen, K., Thomsen, J., Hertel, N. T.,…Birkebaek, N.H., & Danish Society for Diabetes in Childhood and Adolescence (2013). Residual β-cell function 3-6 years after onset of type 1 diabetes reduces risk of severe hypoglycemia in children and adolescents. *Diabetes Care*, *36*(11), 3454-3459. doi:10.2337/dc13-0418

Sosenko, J. M., Skyler, J. S., Mahon, J. Krischer, J. P., Beam, C. A., Boulware, D. C.,…Palmer, J. (2012). The application of the diabetes prevention trial-type 1 risk score for identifying a pre-clinical state of type 1 diabetes. *Diabetes Care*, *35*(7), 1552-1555. doi:10.2337/dc07-1459

Strachan, D. (1989). Hay fever, hygiene and household size. *British Medical Journal, 299*, 1259-1260. doi:10.1136/bmj.299.6710.1259

Striegel-Moore, R. H., & Bulik, C. M. (2007). Risk factors for eating disorders. *American Psychologist*, *62*(3), 181. doi:10.1037/0003-066X.62.3.181

Subedi, B. H., Tota-Maharaj, R., Silverman, M. G., Minder, M., Martin, S., Ashen, D.,…Blaha, M. J. (2013). The role of statins in diabetes treatment. *Diabetes*

*Spectrum, 26*(3), 156-164. doi:10.2337/diaspect.26.3.156

Svensson, M., Nystrom, L., Schon, S., & Dahlquist, G. *(2006).* Age at onset of childhood-onset type 1 diabetes and the development of end-stage renal disease: A nationwide population-based study. *Diabetes Care, 29*(3), 538–542. doi:10.2337/diacare.29.03.06.dc05-1531

Takii, M., Uchigata, Y., Kishimoto, J., Morita, C., Hata, T., Nozaki, T.,…Kubo, C. (2011). The relationship between the age of onset of type 1 diabetes and the subsequent development of a severe eating disorder by female patients. *Pediatric Diabetes, 12*(4.2), 396–401. doi:10.1111/j.1399-5448.2010.00708.x

Taler, I., Phillip, M., Lebenthal, Y., de Vries, L., Shamir, R., & Shalitin, S. (2012). Growth and metabolic control in patients with type 1 diabetes and celiac disease: A longitudinal observational case-control study: Celiac disease and type 1 diabetes. *Pediatric Diabetes, 13*(8), 597–606. doi:10.1111/j.1399-5448.2012.00878.x

Tang, Q., & Bluestone, J. A. (2006). Regulatory T-cell physiology and application to treat autoimmunity. *Immunological Reviews, 212*, 217–237. doi:10.1111/j.0105-2896.2006.00421.x

Tao, B., Pietropaolo, M., Atkinson, M., Schatz, D., & Taylor, D. (2010). Estimating the cost of type 1 diabetes in the U.S.: A propensity score matching method. *PLoS ONE*, *5*(7), e11501. doi:10.1371/journal.pone.0011501

TEDDY Study Group. (2008). The environmental determinants of diabetes in the young (TEDDY) study. *Annals of the New York Academy of Sciences, 1150*, 1–13.

doi:10.1196/annals.1447.062

Tirabassi, R. S., Guberski, D. L., Blankenhorn, E. P., Leif, J. H., Woda, B. A., Liu, Z.,…Mordes, J. P. (2010). Infection with viruses from several families triggers autoimmune diabetes in LEW*1WR1 rats: Prevention of diabetes by maternal immunization. *Diabetes*, *59*(1), 110–118. doi:10.2337/db09-0255

Toppe, C., Möllsten, A., Schön, S., Jönsson, A., & Dahlquist, G. (2014). Renal replacement therapy due to type 1 diabetes; Time trends during 1995-2010 - A Swedish population based register study. *Journal of Diabetes and its Complications*, *28*(2), 152 - 155. doi:10.1016/j.jdiacomp.2013.10.007

Usher-Smith, J. A., Thompson, M. J., Sharp, S. J., & Walter, F. M. (2011). Factors associated with the presence of diabetic ketoacidosis at diagnosis of diabetes in children and young adults: A systematic review. *British Medical Journal*, *343*, 1-16. doi:10.1136/bmj.d4092

Usher-Smith, J. A., Thompson, M., Ercole, A., & Walter, F. M. (2012). Variation between countries in the frequency of diabetic ketoacidosis at first presentation of type 1 diabetes in children: A systematic review. *Diabetologia*, *55*(11), 2878–2894. doi:10.1007/s00125-012-2690-2

Valdes, A., Erlich, H., Carlson, J., Varney, M., Moonsamy, P., & Noble, J. (2012). Use of class I and class II HLA loci for predicting age at onset of type 1 diabetes in multiple populations. *Diabetologia*, *55*(9), 2394-2401. doi:10.1007/s00125-012-2608-z

van Dijk, P. R., Logtenberg, S. J. J., Groenier, K. H., Gans, R. O. B., Kleefstra, N., &

Bilo, H. J. G. (2014). Continuous intraperitoneal insulin infusion in type 1 diabetes: A 6-year post-trial follow-up. *BMC Endocrine Disorders, 14*(30), 1-7. doi:10.1186/1472-6823-14-30

Virtanen, S. M., Takkinen, H. M., Nevalainen, J. J., Kronberg-Kippilä, C. C., Salmenhaara, M. M., Uusitalo, L. L.,…Knip, M. M. (2011). Early introduction of root vegetables in infancy associated with advanced ß-cell autoimmunity in young children with human leukocyte antigen-conferred susceptibility to type 1 diabetes. *Diabetic Medicine, 28*(8), 965-971. doi:10.1111/j.1464-5491.2011.03294.x

Wardlaw, G. M., Insel, P. M., & Seyler, M. F. (1992). *Contemporary nutrition*. St. Louis, MO: Mosby-Year Book, Inc.

Welander, A., Montgomery, S. M., Ludvigsson, J., & Ludvigsson, J. F. (2014). Infectious disease at gluten introduction and risk of childhood diabetes mellitus. *Journal of Pediatrics, 165*(2), 326–331.e1. doi:10.1016/j.jpeds.2014.04.003

Wilkin, T. J. (2009). The accelerator hypothesis: a review of the evidence for insulin resistance as the basis for type I as well as type II diabetes. *International Journal of Obesity, 33*(7), 716–726. doi:10.1038/ijo.2009.97

World Health Organization. (1985). Diabetes mellitus: Report of a WHO study group. Technical report series, 727. Retrieved from http://www.who.int/diabetes/publications/archivepublications/en/

Ying, A.K., Lairson, D.R., Giardino, A.P., Bondy, M.L., Zaheer, I., Haymond, M.W., & Heptulla, R.A. (2011). Predictors of direct costs of diabetes care in pediatric patients with type 1 diabetes. *Pediatric Diabetes, 12*, 177–182.

doi:10.1111/j.1399-5448.2010.00680.x

Zhang, H., Xia, W., Yu, Q., Wang, B., Chen, S., Wang, Z., & Love, E. (2008). Increasing incidence of type 1 diabetes in children aged 0–14 years in Harbin, China (1990–2000*). Primary Care Diabetes, 2*, 121–6. doi:10.1016/j.pcd.2008.06.001

Zhao, Z., Sun, C., Wang, C., Li, P., Wang, W., Ye, J.,...Luo, F. (2014). Rapidly rising incidence of childhood type 1 diabetes in Chinese population: Epidemiology in Shanghai during 1997-2011. *Acta Diabetologica*, *51*(6), 947-953. doi:10.1007/s00592-014-0590-2

Ziegler, A. G., Rewers, M., Simell, O., Simell, T., Lempainen, J., Steck, A.,…Eisenbarth, G. (2013). Seroconversion to multiple islet autoantibodies and risk of progression to diabetes in children. *Journal of the American Medical Association, 309*, 2473–2479. doi:10.1001/jama.2013.6285

Zung, A., Blumenfeld, O., Shehadeh, N., Gottfried, O. D., Rakover, Y. T., Hershkovitz, E.,…Shalitin, S. (2012). Increase in the incidence of type 1 diabetes in Israeli children following the second Lebanon war. *Pediatric Diabetes, 13*(4), 326–333. doi:10.1111/j.1399-5448.2011.00838.x

# Appendix: Copyright Permission from ADA (2014)

American Diabetes Association.
Cure • Care • Commitment

September 16, 2014

Margaret Beckstrand, MPH
Walden University

Associate
Rights and Permissions
Publications
703-549-1500 ext. 1635 - Tel
703-683-2890 - Fax
permissions@diabetes.org

**Permission Request Number:** ***CT091214-WU***

Dear Ms. Beckstrand:

We are pleased to grant permission to you to reprint the following:

✓ **Table 2**

From: **Diabetes Care®, Vol. 37, 2014; S14-S80**
For use in: **Dissertation**

This permission granted is for a one-time use only and the American Diabetes Association takes no responsibility for the accuracy of the translation from English.

This permission is subject to the following conditions:

1. Payment on or before initial publication of the following fee: ***0.***
2. Each copy containing our material that you reproduce or distribute must bear the following copyright notice:
   **"Copyright 2014 American Diabetes Association**
   **From Diabetes Care®, Vol. 37, 2014; S14-S80**
   **Reprinted by permission of the American Diabetes Association."**
3. Permission is granted for use in the following format – **Print & Electronic.**
4. The article will be reprinted and translated exactly as it was originally published.
5. Permission is **non-exclusive** and the American Diabetes Association reserves the right to grant the same permission to others.

If these terms are acceptable, please sign and date the enclosed copy of this agreement and fax it to my attention. This permission agreement is valid for a period of **twelve (12)** months, and the permission granted becomes effective upon our receipt of the signed agreement.

Sincerely,

Christine Myles

**AGREED:** Margaret Beckstrand
**DATE:** December 1, 2014
_____ *We elect not to use this material.*

Unless specifically noted here, the permission granted does not include the use of the American Diabetes Association logo or the cover logo of the journal(s). Permission to reproduce material does not permit the above-named entity or the company sponsoring the resulting product to act as an agent of the American Diabetes Association or the journal(s).