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Assessment of the Impact of Attention Deficit Hyperactivity Disorder on Diabetes
Management and Glycemic Control among Adolescents and Young Adults with Type 1 Diabetes

by

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A dissertation submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy in Epidemiology
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ABSTRACT

Individual day-to-day management and effective control of type 1 diabetes (T1D) is ultimately driven by decisions made by the individual. Individuals with attention deficit hyperactivity disorder (ADHD) have a higher tendency to be inattentive, impulsive, and hyperactive. Attention deficits and impulsivity among adolescents and adults with T1D could result in poor diabetes management through infrequent self-monitoring of blood glucose and inadequate insulin dosing – key components of achieving optimal glycemic control.

This study included 7,380 adolescents and young adults, ages 13-25 years, participating in the T1D Exchange clinic registry (median age 17.4 years, duration 7.7 yrs, 50% female, 81% white). Participants were classified into 3 groups for the primary analyses using participant reported diagnosis and medication use: 1) No ADHD; 2) ADHD with current medication; 3) ADHD without current medication. Groups were compared in logistic and linear regression models for: self-monitoring of blood glucose (SMBG) /day, missed insulin dose ≥ 1 time/week, HbA1c, and at least 1 diabetic ketoacidosis (DKA) and severe hypoglycemic (SH) event in the past 3 months.

Overall, 774 (10%) participants reported a diagnosis of ADHD of whom 371 currently took medication. Mean SMBG/day was 4.7, 5.0, and 4.9 in the ADHD w/o meds, ADHD with meds, and no ADHD groups, respectively. ADHD patients w/o meds (36%, $P=0.02$) or with meds (39%, $P=0.003$) were more likely to report missing insulin doses compared with no ADHD pts (30%). Mean HbA1c was higher in ADHD w/o meds (9.0%, $P<0.001$) and ADHD with

meds (8.9%, $P=0.002$) compared with no ADHD pts (8.6%). The odds of having at least one DKA event in the past 3 months was 1.8 and 1.5 times higher in the ADHD w/o meds ($P<0.001$) and ADHD with meds ($P=0.01$) group compared with no ADHD. The ADHD w/o meds group was significantly more likely to have had a SH event (OR 1.7 95% CI 1.2-2.3; $P<0.001$) compared with the no ADHD group but the occurrence of SH in the ADHD with meds group was similar to the no ADHD.

Results of this study supported the working hypothesis that ADHD without treatment with medication has a negative impact on aspects of diabetes management and glycemic control. Participants with ADHD with and without medication were more likely to miss insulin doses, less likely to use an insulin pump, more likely to have high HbA1c levels, and had a higher frequency of DKA and SH. These results have important public health implications for adolescents and young adults with T1D who are already at risk for poor glycemic control. Since ADHD has a meaningful impact on glycemic outcomes it is important for providers of adolescents and young adults with T1D to review history and signs of an ADHD diagnosis along with diagnosis of other psychosocial disorders with their patients and consider recommending psychosocial services.

CHAPTER 1:

INTRODUCION

Individual day-to-day management and effective control of type 1 diabetes (T1D) is ultimately driven by decisions made by the individual. Individuals with attention deficit hyperactivity disorder (ADHD) have a higher tendency to be inattentive, impulsive, and hyperactive. Attention deficits and impulsivity among adolescents and adults with T1D could result in poor diabetes management through infrequent self-monitoring of blood glucose and inadequate insulin dosing – key components of achieving optimal glycemic control. The role of ADHD on glycemic control among adolescents and adults with T1D has not been studied. Lack of such knowledge is an important public health problem because poor glycemic control is causally related to long- term microvascular complications of T1D, such as retinopathy and nephropathy as well as macrovascular complications such as coronary artery disease.

The specific aims for this proposal are as follows:

1. Compare Glycemic Control among Adolescents and Young Adults with T1D across ADHD Status Groups.

Working hypothesis: Adolescents and adults with T1D and untreated ADHD will have worse glycemic control compared with those without ADHD.

2. *Assess the Relationship between ADHD Status and Diabetes Management Including Frequency of Self-Monitoring of Blood Glucose and Insulin Administration in Adolescents and Young Adults with T1D.*

Working hypothesis: Adolescents and adults with T1D and untreated ADHD will check their blood sugar less often and be more likely to miss an insulin dose.

3. *Assess the Association between ADHD Status and the Frequency of Diabetic Ketoacidosis (DKA) and Severe Hypoglycemia among Adolescents and Young Adults with T1D.*

Working hypothesis: Adolescents and adults with T1D and untreated ADHD will have a higher frequency of DKA and severe hypoglycemia compared with those without ADHD.

The expected outcome of these aims will identify whether or not ADHD adversely influences the day-to-day management of T1D among adolescents and young adults 13 -<26 years of age. Such results are expected to have an important health impact because they will lead to the determination of optimal treatment regimens and behavioral interventions for this special population.

CHAPTER 2:

LITERATURE REVIEW

Type 1 Diabetes

Type 1 diabetes (T1D) is an autoimmune disorder, characterized by immune system destruction of the insulin producing beta cells of the pancreas. The exact trigger of the destruction of the beta cells is not known but it is believed that both genetic and environmental factors play a role. The well-known model for the natural history of T1D is a process where individuals who are at a genetic risk for T1D with a set number of beta cells are exposed to some type of environmental trigger that sets off an autoimmune reaction where islet related antibodies develop and t-cells begin destroying beta cells resulting in the near complete loss of endogenous insulin (Atkinson & Chervonsky, 2012; Eisenbarth, 1986). The marked or complete loss of endogenous insulin, in the absence of exogenous insulin administration will lead to death.

Diagnosis of T1D

According to American Diabetes Association (ADA) clinical guidelines, a diagnosis of diabetes should be made if any of the following are present (1) Hemoglobin A1c of $\geq 6.5\%$, (2) fasting plasma glucose ≥ 126 mg/dL (7.0 mmol/L), (3) 2 hour plasma glucose ≥ 200 mg/dL (11.1mmol/L) during an oral glucose tolerance test (OGTT), or (4) random plasma glucose of ≥ 200 mg/dL with common symptoms of hyperglycemic crisis including polyuria, polydipsia, and unexplained weight loss (American Diabetes Association, 2015). Generally people with type 1 diabetes present with acute symptoms and it is not uncommon for diabetic ketoacidoses (DKA),

a life threatening condition, to occur at onset. In approximately 85-90% of T1D cases, evidence of the autoimmune beta cell destruction process is evident through the presence of antibodies including islet cell, GAD, IA-2, IA- 2 β , or insulin autoantibodies (Donaghue, Chiarelli, Trotta, Allgrove, & Dahl-Jorgensen, 2007).

T1D is most often diagnosed in children and adolescents and at one time was referred to as juvenile diabetes. The presentation of T1D most commonly occurs between 5-7 years of age and around puberty (Harjutsalo, Sjoberg, & Tuomilehto, 2008). Recently, more cases of T1D are being diagnosed in adulthood. Diagnosing T1D in adulthood is particularly challenging due to the growing rates of adult obesity which muddles the distinction between type 1 and type 2 diabetes. A different classification of T1D referred to as latent autoimmune diabetes in adulthood or LADA has grown popularity over the past decade (Pozzilli & Di Mario, 2001; Zimmet, Turner, McCarty, Rowley, & Mackay, 1999). Whether or not T1D that presents in adulthood is the same disease that presents in childhood is not clear. Individuals diagnosed as adults tend to have more C-peptide at diagnosis, an assessment of endogenous insulin production, and are able to preserve C-peptide for longer durations (Merger, Leslie, & Boehm, 2013) Adults with LADA can often regulate glucose with oral medications without the need for insulin for some period of time but eventually require exogenous insulin (Merger et al., 2013). It is estimated that 20% of all adults diagnosed with type 2 diabetes actually have LADA (Landin-Olsson, 2002). Most T1D cases show evidence of autoimmunity such as presence of diabetes related antibodies or genes controlling the immune response, however this is not true for all cases. Cases of T1D that have evidence of an immune related pathogenesis are referred to as type 1A or autoimmune diabetes. Around 80% of T1D cases are classified as type 1A and the

remaining cases are referred to as type 1B or idiopathic T1D without a known autoimmune cause (Atkinson, Eisenbarth, & Michels, 2014; Eisenbarth, 2007).

Epidemiology of T1D

The Search for Diabetes in Youth (SEARCH) study was designed to assess incident and prevalent cases of diabetes in youth < 20 years of age in the US. In SEARCH, incidence rates of T1D per 100,000 person years were 14.3 (12.9-15.9) in 0-<5 year olds, 22.1 (20.3-24.1) in 5-<10 year olds, 25.9 (24.0-27.9) in 10<15 year olds, and 13.1 (11.8-14.6) in 15-<20 year olds (Dabelea et al., 2007). The Diabetes Mondiale (DiaMond) project group assessed the incidence of type 1 diabetes in children < 14 years of age from 1990-1994 in 50 different countries. There was a wide variation between countries with incidence of T1D ranging from 0.1/100,000 per year in China and Venezuela to 36.8/100,000 per year in Sardinia and 36.5/100,000 per year in Finland ("Incidence and trends of childhood Type 1 diabetes worldwide 1990-1999," 2006). Similar results were observed in the EURODIAB ACE study group which assessed the incidence of T1D in 44 centers across Europe and Israel among approximately 28 million children. Incidence rates in the EURODIAB study ranged from 3.2 in Macedonia to >40 per 100,000 person years in Finland (Patterson, Dahlquist, Gyurus, Green, & Soltesz, 2009). Incidence of T1D in adults is less common than in children, however approximately 25% of individuals with T1D are diagnosed as adults. Incident cases have been rising over the past decade with increases of 2.4% in Finland, 2.6% in Germany, and 3.3% in Norway with the most substantial incidence rise occurring in children < 5 years of age (Atkinson et al., 2014). The exact reason for the rise in incident cases is not known but has been credited to environmental risk factors (Atkinson et al., 2014).

There are both genetic and environmental risk factors for T1D. In the general population the lifetime risk of developing T1D is about 0.4% (Mehers & Gillespie, 2008). The risk for someone with a first degree relative affected by T1D ranges from 1% to 6% depending on the affected relative, with the highest risk if a sibling or father has T1D (3% to 6%) and lowest if a Mother has T1D (1% to 2%) (Steck et al., 2005). The rate of T1D concordance has been shown to be approximately 23% in monozygotic twins and approximately 4% in dizygotic twins (Hyttinen, Kaprio, Kinnunen, Koskenvuo, & Tuomilehto, 2003). An association with the human leukocyte antigen (HLA) was discovered in the early 1970s (Cudworth & Woodrow, 1975; Singal & Blajchman, 1973). HLA variants account for approximately 50% of the genetic risk for T1D (Lambert et al., 2004). The risk of type 1 diabetes has been shown to be strongest among certain combination of HLA-DR-DQ genotypes particularly the DRB1, DQA1 and DQB1 alleles (Erlich et al., 2008). Other genetic contributors include polymorphisms in encoding proinsulin and PTPN22 that influence T-cell regulation (Bell, Horita, & Karam, 1984; Bottini et al., 2004).

Studies of environmental risk factors have shown an increase in incident cases among children born in the Spring and cases are most likely to present in the Autumn and Winter months ("The Environmental Determinants of Diabetes in the Young (TEDDY) Study," 2008, Kahn et al., 2009; Moltchanova, Schreier, Lammi, & Karvonen, 2009). T1D has been shown to occur more frequently among Caucasians, those with higher income and education, and males (Dabelea et al., 2007; Ostman et al., 2008). Other risk factors that have been shown to be associated with T1D include vitamin D deficiency in childhood (Blanton et al., 2011; Maclaren & Atkinson, 1992; Mohr, Garland, Gorham, & Garland, 2008; Svoren, Volkening, Wood, & Laffel, 2009), early infant formula feeding (Gerstein, 1994; Knip, Virtanen, & Akerblom, 2010), and viruses in childhood (Bach & Chatenoud, 2012; Boerner & Sarvetnick, 2011; Stene &

Rewers, 2012; Yeung, Rawlinson, & Craig, 2011). The EURODIAB study found a reduction in incidence of diabetes among children who received vitamin D supplementation. A large Finnish cohort study suggested a dose response effect with lower incidence of T1D in children who were receiving the highest amount of vitamin D supplementation. In this study there was an 80% reduction in the incidence of T1D among the group of children receiving vitamin D supplementation. Among those taking supplements, a further reduction in risk of 86% was observed for those taking at least 2000 mg. Early formula feeding or exposure to cow's milk has been shown to be associated with an increase in the risk of T1D (Virtanen et al., 1993). However, the Diabetes Autoimmunity Study in the Young found no association between early cow's milk exposure and beta cell autoimmunity among children with a high genetic risk for diabetes (Norris et al., 1996). Several large cohort studies have found an association between maternal enterovirus infection during pregnancy or at the time of delivery, and T1D onset in childhood. Other studies report an association between enterovirus exposures in childhood preceding diabetes onset. The large EURODIAB cohort study found associations with maternal preeclampsia, old maternal age, respiratory disease in infancy, and blood group incompatibility between infant and mother (Dahlquist, Patterson, & Soltesz, 1999). Two more recent pathogenesis hypotheses implicate hygiene and gut microbiome alterations (Boerner & Sarvetnick, 2011).

The rate of insulin production loss in T1D varies between individuals, with the decline of beta-cell function occurring more rapidly in children than adults (ADA 2013 diagnosis and classification of Diabetes). Following diagnosis, there is often a period referred to as the "honeymoon period" where some residual beta cell function is present resulting in a reduced

need for exogenous insulin. As residual beta cell function declines, the complexity of diabetes management of T1D increases and optimal glycemic control becomes more difficult to achieve.

History of T1D Management

Up until 1923 when insulin was first discovered, T1D was a fatal disease marked by frequent urination with a sweet smell and extreme weight loss due to insulin deficiency (Polonsky, 2012). Frederick Banting and Charles Best were the first to extract insulin from healthy dogs' pancreases and insert it into a dog without a pancreas resulting in the lowering of the dog's glucose levels. Banting, Best, and colleagues purified insulin from bovine pancreases and treated the first human with an insulin injection in 1923 (Bliss, 1993). Once insulin injections became available, the life expectancy of someone with diabetes increased from only a few short weeks or months to decades. Subsequent innovations in insulin therapy have dramatically improved the lives of individuals living with T1D. In the 1950s, NovoNordisk began producing an intermediate acting hypurin isophane insulin known as NPH (American Diabetes Association, 2014). NPH is longer acting than regular insulin. In 1963 insulin became the first human protein to be chemically synthesized and in 1978 was the first human protein to be synthetically manufactured by using bacteria to grow the protein. Synthetic insulin, synthesized using the human insulin gene, was called 'human insulin' to distinguish it from the animal derived insulin (Chance & Frank, 1993). The use of synthetic insulin eliminated allergic reactions at the injection site and became widely available in the 1980s (Polonsky, 2012). In 1976 the first insulin pump was manufactured. The insulin pump delivers insulin continuously through a process known as subcutaneous insulin infusion (SCII). In 1979, the first clinical trial comparing SCII with injection therapy was published in the New England Journal of Medicine

(Tamborlane, Sherwin, Genel, & Felig, 1979). This study showed a significant reduction in mean plasma glucose among patients using SCII. In 1996 the Food and Drug Administration approved a modified human insulin analogue called insulin lispro that was specially developed to be more rapidly active following injection through modification of the amino acid structure of human insulin. Fast-acting analogue insulin has been shown to improve post-meal glucose control (Holleman & Hoekstra, 1997). Long acting analogue insulins also were developed to mimic the body's production of insulin in the fasted state. Long-acting or basal insulin has a delayed onset and slow absorption that lasts up to 24 hours.

In the early 19th century, glucose was identified as the sugar substance in urine of people with diabetes. Prior to the invention of blood glucose meters, self-monitoring of glucose was performed using urine test strips. Measuring glucose in the urine was problematic since glucose present in the urine is retrospective by nature and does not represent current blood glucose status (Clarke & Foster, 2012). In 1965, glucose began to be tested using blood in the doctor's office but not at home. It wasn't until the 1980s that the first home blood glucose meters for self-monitoring of blood glucose became available (Clarke & Foster, 2012). Home blood glucose meters have evolved over the past few decades and are now extremely accurate with the use of electrode biosensor strips that require a very small amount of blood. Meters now have the capability to store glucose results and to be downloaded to a computer, facilitating the review of glucose levels.

In 1999 the FDA approved the first continuous glucose monitor for retrospective use. Continuous glucose monitoring (CGM) involves the ability to monitor glucose levels in real time and view trends in and direction of change with alarms for if the glucose is too low or too high. A CGM utilizes a sensor that is inserted into the skin and a transmitter that communicates with a

receiver that shows glucose values. The sensor measures the amount of glucose in the interstitial fluid and is not as accurate as measuring glucose in the blood with a blood glucose meter. The accuracy and comfort/portability of CGM devices have improved drastically over the past decade but improvements in accuracy particularly at low blood and high blood glucose levels are still needed. Real-time CGM devices must be calibrated using a blood glucose meter. CGM is only FDA approved as an adjunctive device and blood glucose monitoring remains the standard of care.

Currently, insulin is administered either through injections or through SCII via an insulin pump. The current standard of care for injection users, is to perform multiple daily injections (MDI), also referred to as a basal/bolus approach, wherein a long-acting insulin is given once or twice daily (basal insulin) and a rapid acting insulin is given with meals and to correct elevated blood sugars. When insulin is given through an insulin pump, insulin is infused continuously at a basal rate and then boluses of insulin are given with meals or when blood sugar is above target. The 2015 ADA standards of care for self-monitoring of blood glucose state “Patients on multiple-dose insulin (MDI) or insulin pump therapy should do SMBG prior to meals and snacks, occasionally after food, at bedtime, prior to exercise, when they suspect low blood glucose, after treating low blood glucose until they are normoglycemic, and prior to critical tasks such as driving” (American Diabetes Association, 2015).

Glycemic Control

Individuals with T1D must take insulin in order to regulate blood glucose levels. Striving to maintain glucose levels in a normal range, defined as glycemic control, requires constant balance between insulin, diet, and exercise.

Glycemic control is often measured using the percentage of glycosylated hemoglobin (amount of glucose attached to a red blood cell protein) referred to as hemoglobin A1C or HbA1c. The A1c corresponds to the amount of sugar in the blood. Since red blood cells have a turn-over of about 8-12 weeks, the HbA1c can be used to assess the average blood glucose over the past 2-3 months (Nathan, Singer, Hurxthal, & Goodson, 1984). Over the past few decades, the HbA1c has become a critical means to assess diabetes care (Gillery, 2013). The ADA and International Society for Pediatric and Adolescent Diabetes (ISPAD) have established clinical guidelines for managing diabetes which include glycemic targets based on HbA1c. The ADA and ISPAD HbA1c target for children and adolescents is < 7.5% and the ADA target for adults is < 7.0%. (Donaghue et al., 2007) and the ADA HbA1c target for age >19 is < 7.0% (American Diabetes Association, 2015).

There are both acute and chronic complications of T1D resulting from poor glycemic control. DKA is a life threatening acute complication characterized by very high blood glucose and ketones present in the urine or blood. Severe hypoglycemia occurs when the blood sugar drops dangerously low and can result in seizure, loss of consciousness or coma, and even death. Chronic complications of T1D include microvascular complications of retinopathy, neuropathy, and nephropathy as well as macrovascular complications including coronary artery disease and stroke.

The advent of blood glucose monitoring at home using a meter, insulin analogs, and insulin pumps greatly improved the ability to achieve optimal glycemic control. The Diabetes Control and Complications Trial (DCCT), a landmark study in T1D, compared intensive management of T1D, using multiple daily insulin injections or an insulin pump and frequent self-monitoring of blood glucose (SMBG), with a conventional therapy control group using 1 or 2

injections per day. The study showed a marked reduction in HbA1c but at the expense of a higher frequency of severe hypoglycemia (The Diabetes Control and Complications Trial Research Group, 1993). Long term follow up of the DCCT cohort has shown that the intensive therapy group has had a lower risk of retinopathy, nephropathy, and neuropathy as well as cardiovascular disease (The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group, 2005).

Numerous studies have shown a strong correlation between the frequency of SMBG and glycemic control (Deiss, Hartmann, Hoeffe, & Kordonouri, 2004; Haller, Stalvey, & Silverstein, 2004; Miller, Beck et al., 2013; Pickup, Freeman, & Sutton, 2011). Recent data from the T1D Exchange clinic registry of approximately 26,000 individuals with T1D demonstrated a mean HbA1c of 8.6% in participants who reported testing 3-4 times per day compared with 7.6% in participants testing ≥ 10 times per day (Miller, Beck et al., 2013). In addition to SMBG frequency, other diabetes management factors that have been associated with good glycemic control in the T1D Exchange clinic registry include: use of an insulin pump, missing fewer insulin doses, giving an insulin bolus (short-acting insulin given at meal time) prior to a meal vs. during or after a meal, altering insulin to carb ratios according to meals, giving insulin with daytime snacks, using a higher ratio of short-acting insulin or bolus insulin to long-acting or basal insulin, and using a lower total daily insulin dose (Campbell, 2013; Simmons, 2013).

A 2008 study conducted by the Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Group found a significant difference in HbA1c among adults age 25 or older randomized to use CGM compared with a control group (The Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group, 2008). A significant treatment group difference in HbA1c was not observed in the 8-<15 or 15-<25 age groups.

Poor glycemic control has been associated with depression and anxiety disorders (Collins, Corcoran, & Perry, 2009; Hood et al., 2006), although which is the cause and which the effect is unclear. Incidences of DKA and severe hypoglycemia also have been associated with a diagnosis of a psychiatric disorder in children and adolescents with T1D (Rewers et al., 2002). Although depression and anxiety have been shown to be strongly correlated with ADHD, the relationship of ADHD with glycemic control among individuals with T1D has not been well studied.

ADHD

Attention deficit/hyperactivity disorder is the most common neurobehavioral disorder of childhood-onset and is characterized by inattentiveness, impulsive behavior, and hyperactivity (Biederman & Faraone, 2005; Rowland, Lesesne, & Abramowitz, 2002). The Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) classifies ADHD into 3 types: predominately inattentive type (ADHD-I), predominately hyperactive type (ADHD-H), and a combined type (ADHD-C) (A. P. Association, 2000). ADHD primarily affects executive functioning causing impairment in attention, working memory, inhibitory processes, set-shifting, and fluency (Barkley, 1997; Kenemans et al., 2005). However, aspects of impaired social cognition and incentive/reward processes appear to play a role (Castellanos, Sonuga-Barke, Milham, & Tannock, 2006; Uekermann et al., 2010). The theoretical model proposed by Barkley suggests a primary deficit in inhibitory processes that impacts all other aspects of executive functioning and results in impaired social intelligence (Barkley, 2000). Compared with age-matched controls, children with ADHD have been shown to have smaller brain volume of the total cortex, cortical grey matter, frontal cortex, caudate nucleus, cerebellum, and anterior

cingulated cortex (Bledsoe, Semrud-Clikeman, & Pliszka, 2011). ADHD is a heterogeneous disorder and a single deficit in brain functioning cannot be pinpointed.

ADHD Diagnosis

The DSM-IV has specific criteria for diagnosing ADHD. Symptoms must appear before the age of 7 and persist for at least 6 months. Table 1 below describes the criteria for a diagnosis of ADHD from the DSM-IV (A. P. Association, 2000). The diagnosis of ADHD is often made by a primary care physician rather than a psychologist or psychiatrist (Rowland, 2002). A 1999 study by Wasserman et al reported only 38% of primary care physicians use the DSM criteria to diagnose ADHD (Wasserman et al., 1999). There are no laboratory tests available to diagnose ADHD. The best method to accurately diagnose ADHD utilizes parent and teacher rating scales and/or interviews that can be highly subjective (Rowland et al., 2002).

Table 1. DSM-IV Criteria for Diagnosis of ADHD

All criteria below must be met for diagnosis of ADHD based on DSM-IV

1. Either (A) or (B) must be met:

(A) six or more of the following symptoms of inattention have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:

Inattention:

- 1) often fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activities
- 2) often has difficulty sustaining attention in tasks or play activities

Table 1. (Continued)

-
- 3) often does not seem to listen when spoken to directly
 - 4) often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (not due to oppositional behavior or failure to understand instructions)
 - 5) often has difficulty organizing tasks and activities
 - 6) often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as schoolwork or homework)
 - 7) often loses things necessary for tasks and activities (e.g., toys, school assignments, pencils, books, or tools)
 - 8) is often easily distracted by extraneous stimuli
 - 9) is often forgetful in daily activities

(B) six or more of the following symptoms of hyperactivity-impulsivity have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:

Hyperactivity:

- 1) often fidgets with hands or feet or squirms in seat
- 2) often leaves seat in classroom or in other situations in which remaining in seat is expected
- 3) often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, it may be limited to subjective feelings of restlessness)
- 4) often has difficulty playing or engaging in leisure activities quietly
- 5) is often “on the go” or often acts as if “driven by a motor”
- 6) often talks excessively

Impulsivity

- 7) often blurts out answers before questions have been completed
-

Table 1 (Continued)

-
- 8) often has difficulty awaiting turn
 - 9) often interrupts or intrudes on others (e.g., butts into conversations or games)
 2. Some hyperactive-impulsive or inattentive symptoms that caused impairment were present before age 7 years.
 3. Some impairment from the symptoms is present in two or more settings (e.g., at school [or work] and at home).
 4. There must be clear evidence of clinically significant impairment in social, academic, or occupational functioning.
 5. The symptoms do not occur exclusively during the course of Pervasive Developmental Disorder, Schizophrenia, or other Psychotic Disorder and are not better accounted for by another mental disorder (e.g., Mood disorder, Anxiety Disorder, Dissociative Disorder, or a Personality Disorder).

Based on these criteria, three specific subtypes of ADHD are identified:

1. ADHD, Combined Type: if both criteria 1A and 1B are met for the past 6 months
 2. ADHD, Predominately Inattentive Type: if criterion 1A is met but criterion 1B is not met for the past six months
 3. ADHD, Predominately Hyperactive-Impulsive Type: if Criterion 1B is met but Criterion 1A is not met for the past six months
-

ADHD Epidemiology

Approximately 7 to 15% of school-aged children in the US have a diagnosis of ADHD (Lingineni et al., 2012; Minzenberg, 2012; Visser, Danielson, Bitsko, Perou, & Blumberg, 2013). ADHD has been reported to affect 8-12% of children globally (Minzenberg, 2012; Visser et al.,

2013). Symptoms of ADHD frequently persist into adulthood in as many as 65% of cases (Faraone, Biederman, & Mick, 2006). One study reported a 5% prevalence of ADHD among US adults (Kessler et al., 2006).

ADHD is a heritable disorder, with several reports stating up to 60-70% of offspring are affected (Franke, Neale, & Faraone, 2009; Lesch et al., 2008). A study by Goodman and Stevenson reported concordance of hyperactivity symptoms in 51% of monozygotic twins compared with 33% of dizygotic twins (Goodman & Stevenson, 1989). The main two genetic polymorphisms identified to be genetic risk factors for ADHD reside in the dopamine receptor and dopamine transporter genes (Smith, Mick, & Faraone, 2009; Swanson et al., 2001).

Environmental factors shown to be associated with ADHD include lead exposure, maternal use of alcohol and/or tobacco (Brion et al., 2010; Lindblad & Hjern, 2010), and low birth weight and premature delivery (Froehlich et al., 2011; Mick, Biederman, Faraone, Sayer, & Kleinman, 2002), all of which may be associated with one another. Children and adults affected by ADHD are more likely to be male, non-Hispanic white, and have lower income and education levels (Bernardi et al., 2012; Lingineni et al., 2012). ADHD is independently associated with other psychiatric disorders such as depression, anxiety, conduct, and personality disorders (Rowland et al., 2002; Yoshimasu et al., 2012). A study by Bernardi et al assessed the lifetime impact of ADHD using data from the National Epidemiologic Survey on Alcohol and Related Conditions (Bernardi et al., 2012). Bernardi and colleagues found ADHD to be associated with prevalence of another psychiatric disorder, any alcohol use disorder, problems with money and gambling, reckless driving, quitting a job without a plan, sudden changes in personal career plans, and frequent number of lifetime traumas (Bernardi et al., 2012).

ADHD Treatment

Treatment for ADHD includes medication that alters one or both of the major catecholamine neurotransmitters systems in the brain and/or cognitive behavioral therapy (Minzenberg, 2012). In the National Comorbidity Study Adolescent Supplement, approximately 60% of adolescents' age 13 to 18 years with an ADHD diagnosis had sought treatment for ADHD at the time of the survey (Merikangas et al., 2011). A smaller proportion of adults, only 25% with ADHD diagnosis, reported seeking treatment for ADHD in the National Comorbidity Survey Replication (Kessler et al., 2006). Results from the National Survey of Children's Health reported 66% of children ages 2-17 years were currently taking medication for ADHD, the proportion ranged from 33% in Nevada to 79% in Mississippi. The proportion of children on medication was higher among boys than girls across the age span (Visser et al., 2013). A recent systematic review of randomized control trials assessing the effect of ADHD treatment found that at 14 months treatment with stimulant medication alone or combined with psychotherapy was still effective in minimizing ADHD symptoms (Parker, Wales, Chalhoub, & Harpin, 2013).

T1D and ADHD

In order to adequately manage their diabetes, individuals with T1D must make frequent decisions every day regarding their diabetes. For good glycemic control, it is necessary to frequently monitor blood glucose levels and decide based on those glucose numbers, what to eat, how much insulin to take, and when or if to exercise. All of these decisions are rooted in executive functioning and require organization, working memory, self-regulation, and careful planning and problem solving. It is easy to see how someone with T1D and ADHD could struggle with the day to day requirements of managing diabetes, particularly adolescents and

young adults who already are vulnerable to nonadherence. The adolescent period creates multiple challenges to diabetes management, including the psychological struggle for independence from parents with greater reliance on peer relationships and physiological changes causing insulin resistance, leading to increased insulin requirements and fluctuations in glucose levels. Data from the T1D Exchange registry show that adolescents and young adults have the highest HbA1c with a mean HbA1c of 9.0% among those age 13-<18 and 8.4% among those 18-<26 (Miller, 2015).

Poor adherence to diabetes management is one of the primary reasons for referral of youth with T1D to psychological services (Sanchez 2006). One study evaluating the process of psychological consultation with an outpatient diabetes service found that among the 50 children referred for poor glycemic control, 31% met the criteria for an ADHD diagnosis, 23% for a mood disorder diagnosis, and 7% for an anxiety disorder diagnosis (Gelfand et al., 2004).

Whether ADHD is associated with poor diabetes management behaviors, worsening glycemic control, and increased frequency of acute adverse events including DKA and severe hypoglycemia has not been well studied. No studies specifically assessing the association between ADHD and glycemic control were found in a review of the literature. Case studies of 2 adolescents with T1D and ADHD by Sanchez, Chronis, and Hunter demonstrated an improvement in adherence to diabetes management behaviors following evidence based treatment for ADHD (Sanchez, Chronis, Hunter 2006). An abstract assessing the association between ADHD and diabetes management among adolescents with T1D was presented as a poster at the 72nd American Diabetes Association Scientific Sessions. Duke and colleagues examined data from 64 adolescents (28% with ADHD diagnosis) with poorly controlled diabetes who were participating in a larger study.

The 18 study participants with ADHD were more likely to score lower on the Diabetes Self-Management Profile (DSMP) compared with participants without ADHD (Duke, 2012).

A recent 2010 study by McNally and colleagues investigating the relationship between executive functioning (not specifically ADHD), diabetes adherence and glycemic control in 235 children with T1D found that high levels of executive functioning were associated with better adherence, better adherence was associated with improved glycemic control, and the relationship between executive functioning and glycemic control was modified by treatment adherence (McNally, Rohan, Pendley, Delamater, & Drotar, 2010).

The primary objective of this study is to determine whether ADHD influences glycemic control among adolescents and young adults with T1D. Secondary objectives include assessing the impact of ADHD on diabetes management and acute events including DKA and severe hypoglycemia. It is important to assess the impact of ADHD on glycemic control due to the strong causal relationship between HbA1c (a common measure of glycemic control) and the risk of long-term complications of T1D (The Diabetes Control and Complications Trial Research Group, 1993). Acquisition of such knowledge will allow for the development and testing of behavioral interventions and optimal therapeutic regimens for the studied population.

CHAPTER 3: METHODS

This study was conducted utilizing data from the T1D Exchange Clinic Registry, the first initiative of the T1D Exchange Clinic Network. The T1D Exchange Clinic Network is coordinated by the Jaeb Center for Health Research, a nonprofit clinical research coordinating center in Tampa, Florida. There are 72 pediatric and adult clinical centers that make up the Clinic Network. The centers were selected to provide a broad representation of pediatric and adult patients with T1D covering 32 states including some states that typically have not had centers in multicenter studies of diabetes such as North Dakota, South Dakota, Montana and Idaho (Figure 1). Fifty-six centers are institution-based, 15 are community-based, and 1 is a managed care type center. Of the 72 centers, 37 care for pediatric patients, 22 care for adult patients, and 13 are a mix of both pediatric and adult.



Figure 1. T1D Exchange Clinic Network Clinical Centers

T1D Exchange Clinic Registry Enrollment

To be enrolled in the T1D Exchange Clinic Registry, an individual must have had a clinical diagnosis of presumed autoimmune T1D and either islet cell antibodies present or if antibodies were negative or unknown, then insulin must have been started at or shortly after diagnosis and used continually thereafter (except in the case of a pancreas or islet cell transplant).

Written informed consent was obtained from adult participants and parents/guardians of minor participants, who were required to understand either English or Spanish to participate. Minor participants provide written assent, according to IRB requirements. Data were collected for the registry database at enrollment and are currently being collected annually. Sites are compensated for each enrolled participant and participants receive either a gift card or alternately can select a donation for a T1D charity each time they are asked to complete a questionnaire.

Data Collection at Registry Enrollment

For the 25,833 participants enrolled from August 2010 through July 2012 the enrollment data collection consisted of 2 components: (1) completion of a questionnaire by the participant or parent of participant (parent completed questionnaire if participant's age was < 13 and either the participant or the parent choose to complete questionnaire if participant's age was 13-17) and (2) retrieval of information extracted from the medical record. At enrollment the majority (51%) of participants completed the questionnaire electronically in the clinic on project-supplied iPads or laptop computers, 29% in the clinic on paper, and 20% from home, either on paper or electronically (Beck et al., 2012).

The participant questionnaire was comprised of a series of modules that address diabetes history, management, monitoring and complications; general health; lifestyle; family history; socioeconomic factors; and menstrual and pregnancy history. Both English and Spanish versions of the questionnaire were provided. The clinic chart data extraction captures information on the diagnosis of T1D, acute events such as severe hypoglycemia and DKA, medications, medical conditions and diabetes-related complications, and laboratory results.

Data Collection at Annual Visits

The year 1 data collection consisted of both a participant questionnaire and clinic medical record extraction for the first 17,474 participants. Currently, annual updates for enrolled registry participants consist of medical record extraction only.

The web application for the year 1 questionnaire was developed such that the questionnaire completed by each participant was customized to address specific objectives in subsets of participants such as participants using an insulin pump or who report having ADHD. An initial questions module determined which modules a participant would receive based on their answers to key questions (Miller, 2013).

Study Methods

This study includes 7,380 registry participants who were 13 -<26 years of age at the time of completion of the year 1 questionnaire with T1D duration of at least 1 year and not pregnant at the time of the year 1 data collection. Among the 7,380 participants, 774 self-reported a diagnosis of ADHD. Participants who did not report a diagnosis of ADHD but who had a record of a diagnosis or medication in the clinic chart were excluded to avoid misclassification.

Exposure Assessment

The diagnosis of ADHD was obtained through participant report from the 1-year questionnaire with the following question: *Have you ever been told by a doctor (physician, psychiatrist, or psychologist) that you have Attention Deficit Hyperactivity Disorder (ADHD) or Attention Deficit Disorder (ADD)?* Medications and treatment for ADHD were collected through an ADHD module on the year 1 participant questionnaire (Appendix A).

Participants were classified into 3 groups for the primary analyses using participant reported diagnosis and medication use: ADHD w/o meds, ADHD with meds, and No ADHD. Secondary analyses classifying participants into the following groups was conducted: 1) No ADHD; 2) ADHD with medication and psychosocial therapy; 3) ADHD with medication only; 4) ADHD with psychosocial therapy only; 5) ADHD with no treatment. The proportion of participants who have a clinical diagnosis of ADHD and/or medication recorded in the endocrinologist medical chart also was assessed. Sensitivity analysis only including participants with concordant ADHD diagnosis between participant and clinic report was performed.

General Statistical Methods

Pre-planned stratified analyses for age groups of 13-<18 and 18-<26 was conducted since it was expected that these groups may differ in the way diabetes is managed and in access to ADHD medication and treatment. The association between participant demographic and clinical characteristics and ADHD status was assessed using chi-square or t-tests. For all specific aims described below regression diagnostics were performed and the assumption of normality for linear models was assessed through plotting the distribution of residuals. A rank transformation

was used to obtain test of significance if the normality assumption was violated. Participants missing the outcome of interest were excluded from the analysis. For ordinal and continuous co-variables missing values were imputed and an indicator for missing was included in the model to adjust for the imputation. Missing was included as a separate category for categorical co-variables. Analysis was performed using SAS version 9.4. Tests of significance were 2-sided and p values < 0.05 were considered statistically significant.

Methods for Specific Aim #1: Compare Glycemic Control among Adolescents and Young Adults with T1D across ADHD Status Groups.

The study design for specific aim #1 is cross sectional. The most recent available HbA1c level within 6 months prior to the year 1 data collection was compared between ADHD classification groups using a linear mixed model adjusting for random site effects and potential confounders including age group (when not stratified), T1D duration group (based on reviewing distribution of data), gender, race/ethnicity, annual household income (ordinal), insurance status, and clinical diagnosis of depression.

Methods for Specific Aim #2: Assess the Relationship between ADHD Status and Diabetes Management Including Glucose Monitoring and Insulin Administration in Adolescents and Young Adults with T1D.

The study design for specific aim #2 is cross sectional. Participants were classified as insulin pump or injection users from the clinic medical record. A participant was classified as using continuous glucose monitoring (CGM) if both the clinic and participant reported using CGM in the past 30 days. Information on frequency of blood glucose checks per day and missed

insulin doses were obtained from the participant/parent questionnaire with the following questions:

- *About how many times per day are you (is your child) checking your (his/her) blood sugar with a blood glucose meter?*
- *In a typical week, how often do you miss an insulin dose? Never; Less than once a week; 1 to 2 times a week; 3 to 4 times a week; 5 or more times a week; At least once a day.*

Linear mixed models were performed to compare the number of SMBG measurements per day between ADHD classification groups adjusting for random site effects and other potential confounding factors including age group, T1D duration group (based on reviewing distribution of data), gender, race/ethnicity, annual household income (ordinal), and insurance status. Outliers with SMBG > 13 were truncated at 13 for tabulating the mean and in regression models.

Frequency of missing an insulin dose was categorized into a binary variable by collapsing never and less than once a week vs. at least once per week. Differences in binary outcomes between ADHD classification groups were assessed through logistic regression models adjusting for a random site effects and for potential confounders including age group (when not stratified), diabetes duration (based on data distribution), gender, race/ethnicity, annual household income (ordinal), and insurance status.

Methods for Specific Aim #3: Assess the Association between ADHD Status and the Frequency of Diabetic Ketoacidosis (DKA) and Severe Hypoglycemia among Adolescents and Young Adults with T1D.

Frequency of diabetic ketoacidosis (DKA) and severe hypoglycemia in the 3 months prior to the registry 1 year data collection were obtained from the participant questionnaire. The occurrence of participant reported DKA and severe hypoglycemia was obtained in the following way:

In the past 3 months, about how many times have you experienced any of the following events:

- 1. Severe low blood sugar (hypoglycemia) that resulted in passing out, losing consciousness, or seizure:*

0 1 2 3 4 5 6 7 8 9 More than 9

- 2. Diabetic ketoacidosis (high blood sugar plus ketones, also known as DKA) diagnosed by a doctor for which you went to either the hospital, emergency room, or another healthcare facility?*

0 1 2 3 4 5 6 7 8 9 More than 9

Frequency of at least 1 DKA and SH event in the past 3 months was used for analysis instead of the number of events due to concerns with the accuracy of the exact number of participant reported events.

Logistic regression models were performed to compare the frequency of DKA and severe hypoglycemia between ADHD classification groups. Multivariate models were adjusted for

random site effects and other potential confounders including age group (when not stratified), diabetes duration group (based on distribution of data), gender, race/ethnicity, annual household income, and diagnosis of depression.

CHAPTER 4:

RESULTS

Analysis included 7,380 participants age 13 to 25 years with duration of T1D of at least one year who met the eligibility criteria listed above; 183 participants who did not report a diagnosis of ADHD but who had a record of a diagnosis or medication for ADHD entered from the clinic chart were excluded. Participant characteristics overall and by age group are shown in Table 2.

Table 2. Participant Characteristics

	Overall N=7380	Age Group	
		13-<18 years old N=4688	18-<26 years old N=2692
Age - mean±SD	17.4±3.1	15.4±1.4	20.8±2.1
Gender - Female	3663 (50%)	2308 (49%)	1355 (50%)
Race/Ethnicity			
White Non-Hispanic	5948 (81%)	3712 (79%)	2236 (83%)
Black Non-Hispanic	361 (5%)	256 (5%)	105 (4%)
Hispanic or Latino	732 (10%)	494 (11%)	238 (9%)
Other	339 (5%)	226 (5%)	113 (4%)

Table 2 (Continued)

	Overall N=7380	Age Group	
		13-<18 years old N=4688	18-<26 years old N=2692
Annual Household Income			
< \$35,000	109 (15%)	625 (13%)	468 (17%)
\$35,000 - < \$75,000	136 (19%)	890 (19%)	477 (18%)
≥ \$75,000	2683 (36%)	1869 (40%)	814 (30%)
Missing	2237 (30%)	1304 (28%)	933 (35%)
Insurance Status			
Private Insurance	5007 (68%)	3206 (68%)	1801 (67%)
Other Insurance	1499 (20%)	1048 (22%)	451 (17%)
No insurance	76 (1%)	32 (<1%)	44 (2%)
Missing	798 (11%)	402 (9%)	396 (15%)
BMI Category			
Underweight	79 (1%)	44 (<1%)	35 (1%)
Normal weight	4144 (56%)	2852 (61%)	1292 (48%)
Overweight	1838 (25%)	1110 (24%)	728 (27%)
Obese	992 (13%)	636 (14%)	356 (13%)
Missing	327 (4%)	46 (<1%)	281 (10%)
Diabetes Duration (years)- Mean±SD	7.7±4.7	6.4±3.9	9.9±5.1

Table 2. (Continued)

	Overall N=7380	Age Group	
		13-<18 years old N=4688	18-<26 years old N=2692
Diabetes Duration Group			
1-<10 years	4909 (67%)	3574 (76%)	1335 (50%)
10-<20 years	2383 (32%)	1114 (24%)	1269 (47%)
20-<50 years	88 (1%)	0 (0%)	88 (3%)
Insulin Pump Use	4123 (56%)	2640 (56%)	1483 (55%)
CGM Use	361 (5%)	190 (4%)	171 (6%)

A diagnosis of ADHD was self-reported by 774 (10.4%) of the 7,380 participants. A diagnosis of ADHD was more common among participants who were male, were of white non-Hispanic race, had lower SES and had a diagnosis of depression in the medical chart (Table 3).

Table 3. ADHD Diagnosis According to Participant Characteristics

	ADHD Diagnosis		P value
	Overall	# with Diagnosis N (%)	
All	7380	774 (10%)	
Age Group			0.36
13-<18 years old	4688	480 (10%)	
18-<26 years old	2692	294 (11%)	

Table 3 (Continued)

	ADHD Diagnosis		
	Overall	# with Diagnosis N (%)	P value
Gender			<0.001
Female	3663	269 (7%)	
Male	3717	505 (14%)	
Race/Ethnicity			0.003
White Non-Hispanic	5948	654 (11%)	
Black Non-Hispanic	361	28 (8%)	
Hispanic or Latino	732	52 (7%)	
Other Race/Ethnicity	339	40 (12%)	
T1D Duration			0.65
1-2 years	1104	127 (12%)	
3-5 years	1701	175 (10%)	
6-9 years	2104	212 (10%)	
≥ 10 years	2471	260 (11%)	
Annual Household Income			0.005
< \$35,000	1093	148 (14%)	
\$35,000 - < \$75,000	1367	135 (10%)	
≥\$75,000	2683	266 (10%)	
Missing	2237	225 (10%)	

Table 3 (Continued)

	ADHD Diagnosis		
	Overall	# with Diagnosis N (%)	P value
Insurance Category			0.001
Private Insurance	5007	506 (10%)	
Other Insurance	1499	196 (13%)	
No insurance	76	7 (9%)	
Missing	798	65 (8%)	
BMI Category			0.64
Underweight	79	8 (10%)	
Normal weight	4144	432 (10%)	
Overweight	1838	176 (10%)	
Obese	992	114 (11%)	
Missing	327	44 (13%)	
Diagnosis of Depression			<0.001
No	6844	642 (9%)	
Yes	536	132 (25%)	

*Chi-square test was used to obtain p value

The mean±SD age of diagnosis of ADHD was 10.0±4.6 years. A diagnosis of ADHD was made prior to the diagnosis of T1D in 42% of participants, at the same age in 8% of

participants, and after the diagnosis of T1D in 50% of participants. Figure 2 (see page 34) shows the breakdown of ADHD treatment status among the 774 participants with ADHD.

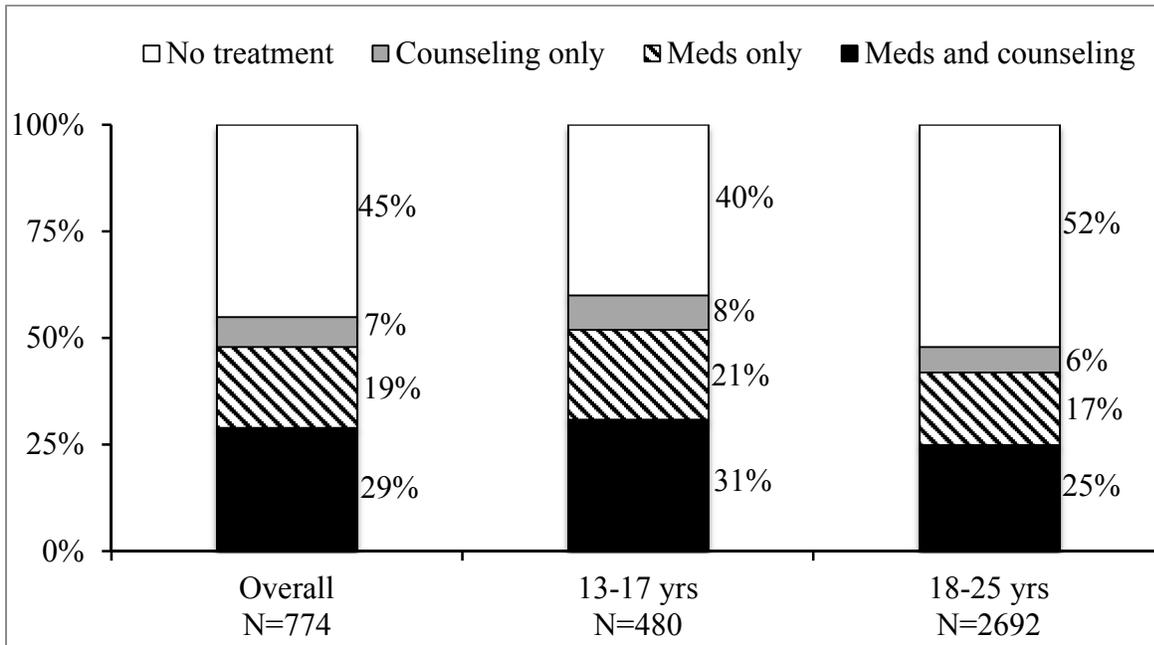


Figure 2. ADHD Treatment Status

A crosstab of self-reported ADHD diagnosis and medication use and clinic reported diagnosis and medication use is shown in Table 4 (see page 35).

Participants who reported no ADHD diagnosis or who responded ‘do not wish to answer’ but had a diagnosis of ADHD in the medical chart or an ADHD medication were excluded (N=183).

Among the 7,380 participants, 403 (5%) had a self-reported diagnosis of ADHD and were not currently taking medication (Group A: ADHD w/o meds), 371(5%) had a diagnosis of ADHD and were currently taking medication (Group B: ADHD with meds), and 6,606 (90%) did not have a diagnosis of ADHD (Group C: No ADHD).

Table 4. Crosstab of ADHD Self-Reported Status and Clinic Reported Status

Self-Reported ADHD Status	Clinic ADHD Status				Total
	ADHD without meds	ADHD with meds	No ADHD	Med for ADHD but no diagnosis in chart	
ADHD not on meds	80	43	255	25	403
	1.06	0.57	3.37	0.33	5.33
	19.85	10.67	63.28	6.20	
	53.69	17.41	3.65	14.37	
ADHD on meds	37	167	61	106	371
	0.49	2.21	0.81	1.40	4.91
	9.97	45.01	16.44	28.57	
	24.83	67.61	0.87	60.92	
No ADHD	29	31	6606	41	6707
	0.38	0.41	87.35	0.54	88.68
	0.43	0.46	98.49	0.61	
	19.46	12.55	94.47	23.56	
Do not wish to answer	3	6	71	2	82
	0.04	0.08	0.94	0.03	1.08
	3.66	7.32	86.59	2.44	
	2.01	2.43	1.02	1.15	
Total	149	247	6993	174	7563
	1.97	3.27	92.46	2.30	100.00

ADHD status groups differed with respect to age, race/ethnicity and SES with the ADHD with meds group having a higher percentage of adolescents, white non-hispanic, and higher SES participants compared with the ADHD w/o meds group (Table 5, see page 36).

Table 5. Participant Characteristics According to ADHD Status Groups

	ADHD Status			P Value
	Group A: ADHD w/o meds N=403 N (%)	Group B: ADHD with meds N=371 N (%)	Group C: No ADHD N=6,606 N (%)	
Age Group – N(%)				0.02
13-<18 years old	232 (58%)	248 (67%)	4208 (64%)	
18-<26 years old	171 (42%)	123 (33%)	2398 (36%)	
Gender				<0.001
Female	138 (34%)	131 (35%)	3394 (51%)	
Male	265 (66%)	240 (65%)	3212 (49%)	
Race/Ethnicity				<0.001
White Non-Hispanic	322 (80%)	332 (89%)	5294 (80%)	
Black Non-Hispanic	19 (5%)	9 (2%)	333 (5%)	
Hispanic or Latino	33 (8%)	19 (5%)	680 (10%)	
Other Race/Ethnicity	29 (7%)	11 (3%)	299 (5%)	
T1D Duration Group				0.88
1-2 years	62 (15%)	65 (18%)	977 (15%)	
3-5 years	93 (23%)	82 (22%)	1526 (23%)	
6-9 years	113 (28%)	99 (27%)	1892 (29%)	
≥ 10 years	135 (33%)	125 (34%)	2211 (33%)	
Annual Household Income				<0.001
< \$35,000	89 (22%)	59 (16%)	945 (14%)	
\$35,000 - < \$75,000	75 (19%)	60 (16%)	1232 (19%)	
≥ \$75,000	114 (28%)	152 (41%)	2417 (37%)	
Missing	125 (31%)	100 (27%)	2012 (30%)	

Table 5 (Continued)

	ADHD Status			P Value
	Group A: ADHD w/o meds N=403 N (%)	Group B: ADHD with meds N=371 N (%)	Group C: No ADHD N=6,606 N (%)	
Insurance Category				<0.001
Private Insurance	246 (61%)	260 (70%)	4501 (68%)	
Other Insurance	119 (30%)	77 (21%)	1303 (20%)	
No insurance	7 (2%)	0 -	69 (1%)	
Missing	31 (8%)	34 (9%)	733 (11%)	
BMI Category				0.89
Underweight	3 (<1%)	5 (1%)	71 (1%)	
Normal	216 (54%)	216 (58%)	3712 (56%)	
Overweight	90 (22%)	86 (23%)	1662 (25%)	
Obese	70 (17%)	44 (12%)	878 (13%)	
Missing	24 (6%)	20 (5%)	283 (4%)	
Depression Diagnosis				<0.001
No	342 (85%)	300 (81%)	6202 (94%)	
Yes	61 (15%)	71 (19%)	404 (6%)	

Specific Aim 1: Glycemic Control

Mean HbA1c was significantly higher in the ADHD w/o meds (mean 9.0%±1.8%, p<0.001) and ADHD with meds (8.9%±1.7%, p=0.002) compared with the No ADHD group (8.6%±1.7) (Figure 3, see page 38).

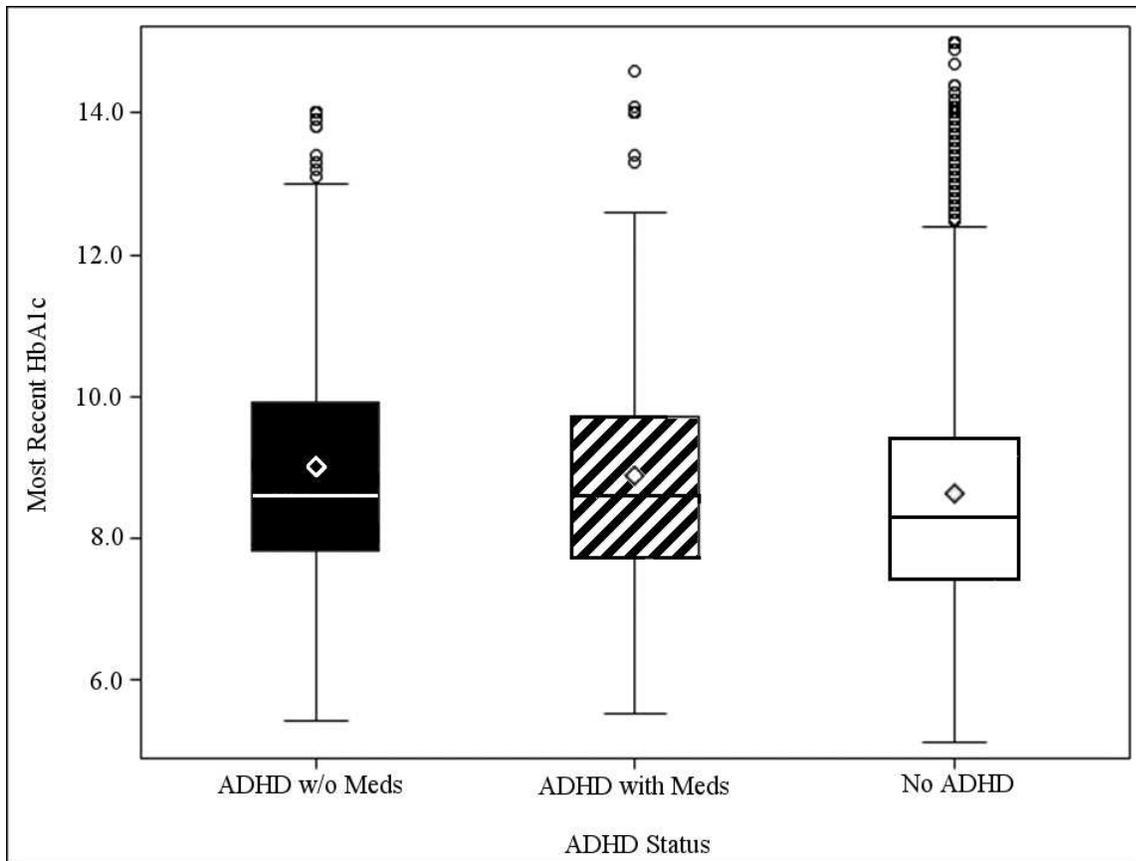


Figure 3. Boxplot of HbA1c by ADHD Status

This relationship remained consistent after adjustment for confounders including age group, gender, race/ethnicity, annual household income, insurance status and clinical diagnosis of depression and within both age group strata (Table 6, see page 39).

Significant differences between the No ADHD and ADHD w/o meds ($P=0.002$) and ADHD with meds ($P=0.001$) remained when adjustment for insulin pump use (potentially on the causal pathway) was added to the adjusted model and when depression was removed as a covariate in the adjusted model ($P<0.001$ for both ADHD groups vs. no ADHD). A similar relationship was observed when analysis was limited to those with clinic confirmed ADHD diagnosis (Table 7, see page 40).

Table 6. Glycemic Control and ADHD Status

	HbA1c*		Unadjusted Estimate (95% CI) for difference	Unadjusted P-value	Adjusted Estimate (95% CI) for difference ^a	Adjusted P-value ^a
	N	Mean±Std				
Overall						
A. ADHD w/o meds	389	9.0%±1.8%	0.4% (0.2%, 0.6%)	<0.001	0.3% (0.1%, 0.5%)	<0.001
B. ADHD with meds	365	8.9%±1.7%	0.3% (0.1%, 0.5%)	<0.001	0.3% (0.1%, 0.5%)	0.002
C. No ADHD	6511	8.6%±1.7%				
Age Group: 13-<18 years						
A. ADHD w/o meds	225	9.1%±1.9%	0.4% (0.2%, 0.6%)	<0.001	0.2% (0.01%, 0.4%)	0.04
B. ADHD with meds	244	9.0%±1.6%	0.3% (0.1%, 0.5%)	0.02	0.2% (0.02%, 0.4%)	0.03
C. No ADHD	4172	8.7%±1.7%				
Age Group: 18-<26 years						
A. ADHD w/o meds	164	8.8%±1.7%	0.4% (0.1%, 0.7%)	0.003	0.4% (0.1%, 0.6%)	0.01
B. ADHD with meds	121	8.7%±1.9%	0.4% (0.1%, 0.7%)	0.03	0.4% (0.1%, 0.7%)	0.01
C. No ADHD	2339	8.4%±1.8%				

*HbA1c is missing for 14 (3%) participants in the ADHD w/o meds group, 6 (2%) participants in the ADHD with meds group and 95 (2%) in the no ADHD group

^aAdjusted for age group (when not stratified), T1D duration, gender, race/ethnicity, annual household income, insurance status and depression diagnosis

Table 7. Glycemic Control and Clinic Confirmed ADHD Status

	N	HbA1c	Adjusted Estimate (95% CI) for difference	P-value
		Mean±Std		
Clinic confirmed ADHD w/o meds	119	9.1%±1.7%	0.4% (0.1%, 0.7%)	0.007
Clinic confirmed ADHD with meds	199	8.9%±1.7%	0.3% (0.1%, 0.5%)	0.02
Clinic confirmed NO ADHD	6513	8.6%±1.7%		

*Adjusted for age group (when not stratified), T1D duration, gender, race/ethnicity, annual household income, insurance status and depression diagnosis

When further classifying ADHD status by whether or not the participant was receiving psychological counseling significantly higher HbA1c levels were observed for all ADHD groups compared with No ADHD except for the group who reported taking medication and receiving psychological therapy (Table 8).

Table 8. Glycemic Control and ADHD Combined Treatment Status

	N	HbA1c	Adjusted Estimate (95% CI) for difference*	P-value*
		Mean±Std		
On meds and seeing psych	215	8.8%±1.7%	0.2% (-0.0%, 0.4%)	0.10
On meds and NOT seeing psych	150	8.9%±1.7%	0.4% (0.2%, 0.7%)	0.002
Not on meds but seeing psych	56	9.6%±1.9%	0.6% (0.2%, 1.0%)	0.005
Not on meds or seeing psych	334	8.9%±1.8%	0.2% (0.1%, 0.4%)	0.01
No ADHD	6513	8.6%±1.7%		

*Adjusted for age group (when not stratified), T1D duration, gender, race/ethnicity, annual household income, insurance status and depression diagnosis

Participants with ADHD with or without meds were significantly less likely to meet the ADA clinical target for HbA1c of < 7.5% for participants 13- 17 years and < 7.0% for participants 18- 25 years (Figure 4)

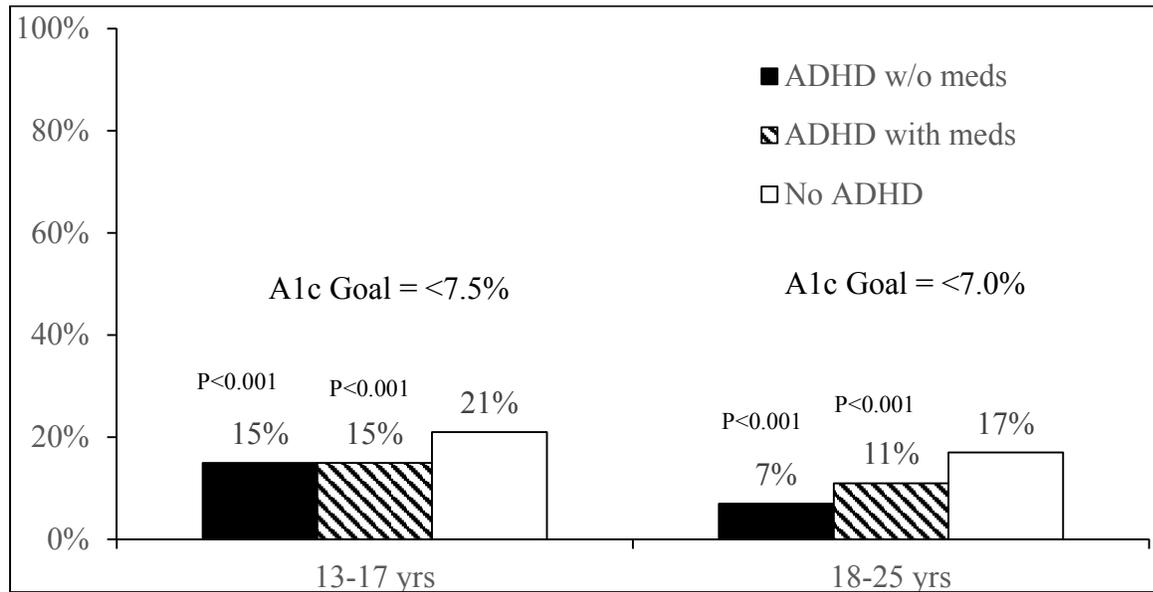


Figure 4. Proportion of Participants Meeting ADA Targets According to ADHD Status

Specific Aim 2: Assess the Relationship between ADHD Status and Diabetes Management Including Glucose Monitoring and Insulin Administration in Adolescents and Young Adults with T1D.

SMBG

Mean SMBG per day was 4.7, 5.1, and 4.9 in the ADHD w/o meds, ADHD with meds, and No ADHD groups, respectively (Figure 5, page 42).

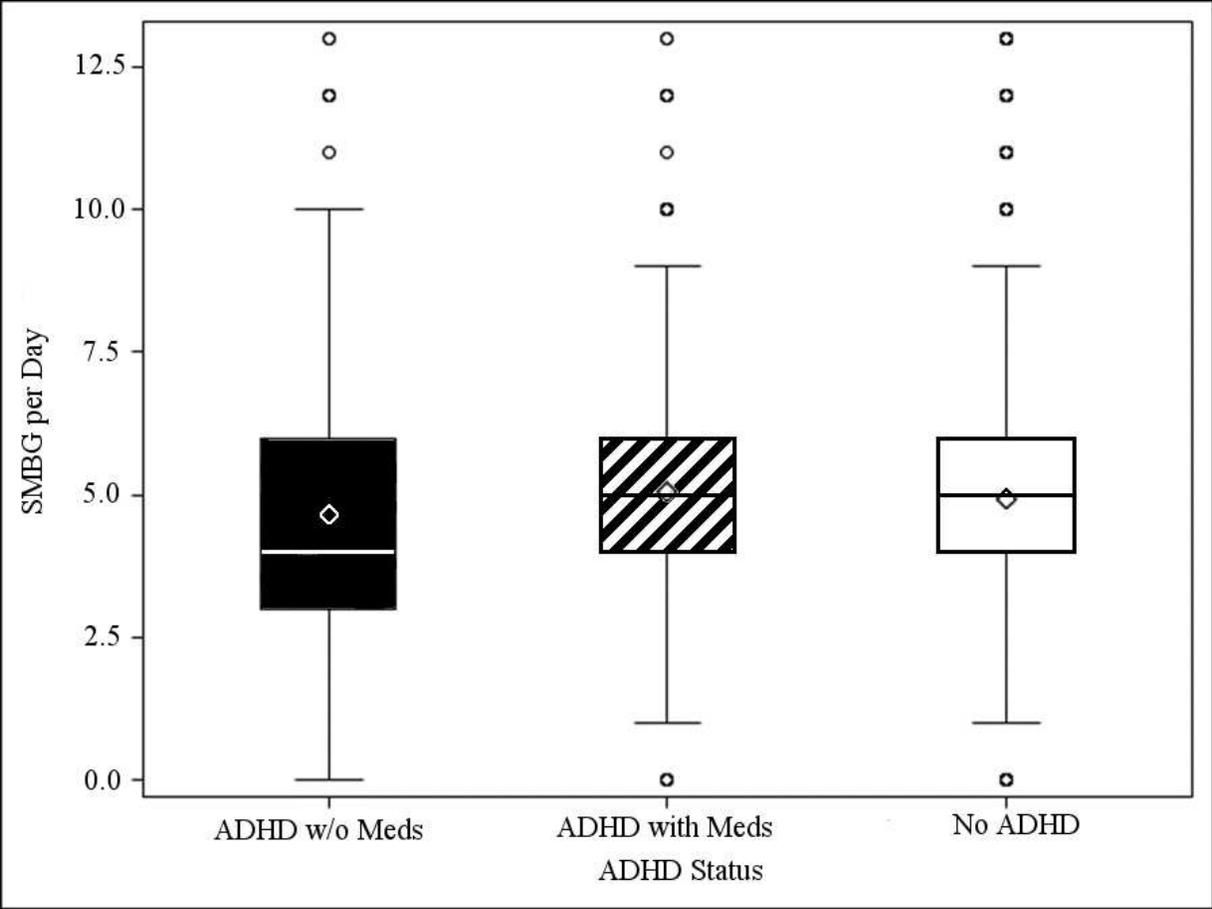


Figure 5. SMBG by ADHD Status

No significant differences between ADHD status groups were observed in an adjusted model overall or stratified by age group (Table 9, see page 43).

Overall, 33% of participants in the ADHD w/o meds reported performing SMBG less than the recommended 4 times per day compared with 26% of participants in the no ADHD group (Figure 6, see page 44).

Table 9. SMBG per Day and ADHD Status

	SMBG		Unadjusted Estimate (95% CI) for difference	Unadjusted P-value	Adjusted Estimate (95% CI) for difference ^a	Adjusted P-value ^a
	N	Mean				
Overall						
A. ADHD w/o meds	394	4.7±2.3	-0.2 (-0.5, 0.0)	0.05	-0.0 (-0.2, 0.2)	0.87
B. ADHD with meds	362	5.0±2.4	0.1 (-0.1, 0.3)	0.38	0.1 (-0.1, 0.3)	0.43
C. NO ADHD	6498	4.9±2.2				
Age Group: 13- <18 years						
A. ADHD w/o meds	228	5.1±2.4	-0.1 (-0.4, 0.2)	0.53	0.1 (-0.2, 0.3)	0.70
B. ADHD with meds	247	5.4±2.2	0.2 (-0.1, 0.5)	0.15	0.2 (-0.0, 0.5)	0.07
C. NO ADHD	4152	5.2±2.1				
Age Group: 18- <26 years						
A. ADHD w/o meds	166	4.1±2.1	-0.3 (-0.7, 0.1)	0.09	-0.1 (-0.5, 0.2)	0.43
B. ADHD with meds	115	4.2±2.4	-0.2 (-0.6, 0.2)	0.36	-0.3 (-0.7, 0.1)	0.18
C. NO ADHD	2346	4.4±2.3				

*SMBG is missing for 9 (2%) participants in the ADHD w/o meds group, 9 (2%) participants in the ADHD with meds group and 108 (2%) in the no ADHD group

^aAdjusted for age group (when not stratified), site, T1D duration, gender, race/ethnicity, annual household income, insurance status, and depression diagnosis

Continuous Glucose Monitoring

A continuous glucose monitor was being use by 5%, 7% and 5% of participants in the ADHD w/o meds, ADHD with meds, and No ADHD groups, respectively. Significant

differences between groups was not observed for the overall cohort but there was a trend towards higher CGM use in the ADHD with meds group among young adults (Table 10, see page 45).

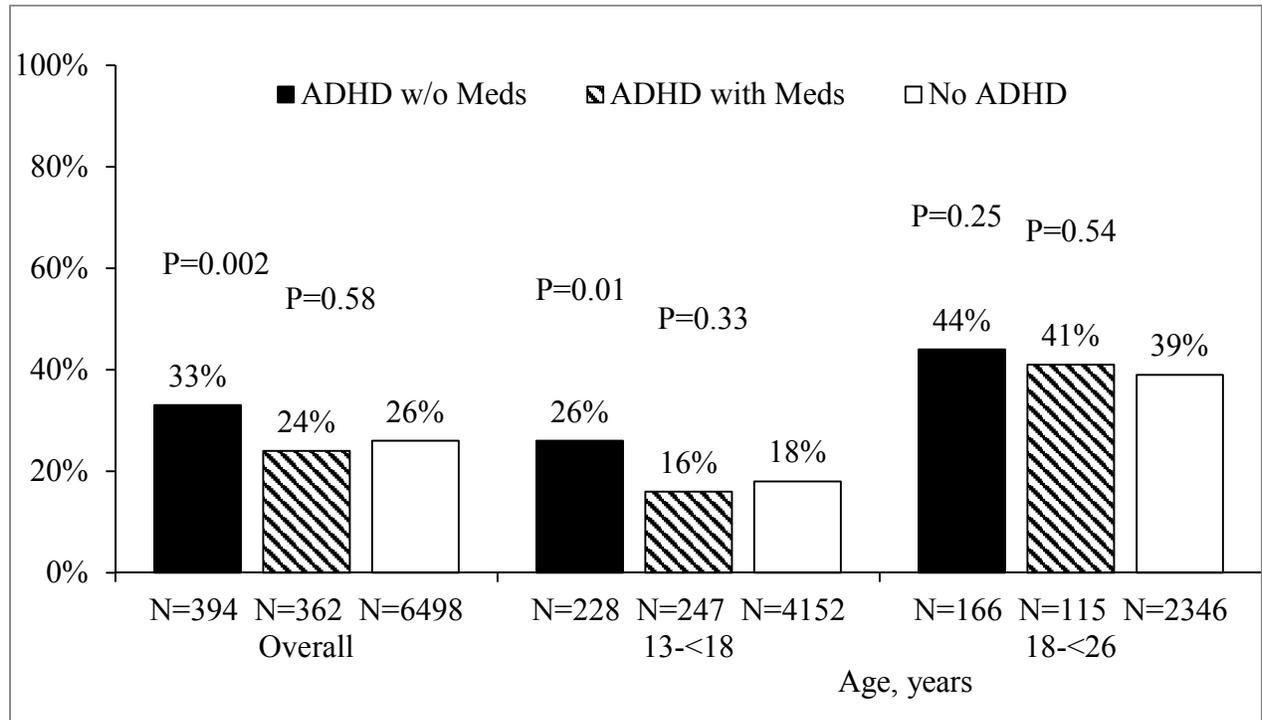


Figure 6. SMBG <4 times per day and ADHD Status

Insulin Delivery Method

An insulin pump was being used for insulin delivery by 47%, 58% and 56% of participants in the ADHD w/o meds, ADHD with meds, and No ADHD groups, respectively. Overall the ADHD w/o meds participants were significantly less likely to be using an insulin pump compared with participants who did not have ADHD (P=0.02) (Table 11, see page 46).

Table 10. Continuous Glucose Monitoring Use by ADHD Status

	CGM Use		Unadjusted Odds Ratio (95% CI)	Unadjusted P-value	Adjusted Odds Ratio (95% CI)	Adjusted P-value*
	N	#(%)				
Overall						
A. ADHD w/o meds	403	21 (5%)	1.08 (0.69, 1.71)	0.73	1.16 (0.73, 1.84)	0.54
B. ADHD with meds	371	26 (7%)	1.48 (0.97, 2.26)	0.07	1.46 (0.95, 2.24)	0.08
C. NO ADHD	6606	314 (5%)				
Age Group: 13- <18 years						
A. ADHD w/o meds	232	10 (4%)	1.06 (0.55, 2.04)	0.87	1.20 (0.62, 2.33)	0.59
B. ADHD with meds	248	12 (5%)	1.21 (0.66, 2.22)	0.54	1.21 (0.65, 2.24)	0.55
C. NO ADHD	4208	168 (4%)				
Age Group: 18- <26 years						
A. ADHD w/o meds	171	11 (6%)	1.07 (0.56, 2.02)	0.84	1.14 (0.59, 2.18)	0.70
B. ADHD with meds	123	14 (11%)	1.86 (1.03, 3.37)	0.04	1.72 (0.94, 3.15)	0.08
C. NO ADHD	2398	146 (6%)				

*Adjusted for age group (when not stratified), site, T1D duration, gender, race/ethnicity, annual household income, and insurance status

Missed Insulin Doses

Missing an insulin dose at least 1 time per week was reported by 36%, 39% and 30% of participants in the ADHD w/o meds, ADHD with meds, and No ADHD groups, respectively. Overall, participants with ADHD with or w/o meds were significantly more likely to report missing an insulin dose (Table 12, see page 47).

Table 11. Insulin Pump Use by ADHD Status

	Pump Use		Unadjusted Odds Ratio (95% CI)	Unadjusted P-value	Adjusted Odds Ratio (95% CI)	Adjusted P-value*
	N	#(%)				
Overall						
A. ADHD w/o meds	403	191 (47%)	0.65 (0.54, 0.82)	<0.001	0.77 (0.61, 0.95)	0.02
B. ADHD with meds	371	216 (58%)	1.07 (0.86, 1.34)	0.52	1.07 (0.85, 1.35)	0.57
C. NO ADHD	6606	3716 (56%)				
Age Group: 13- <18 years						
A. ADHD w/o meds	232	111 (48%)	0.65 (0.49, 0.86)	0.003	0.74 (0.55, 1.0)	0.05
B. ADHD with meds	248	142 (57%)	1.03 (0.78, 1.35)	0.85	1.03 (0.77, 1.37)	0.85
C. NO ADHD	4208	2387 (57%)				
Age Group: 18- <26 years						
A. ADHD w/o meds	171	80 (47%)	0.71 (0.51, 0.97)	0.03	0.79 (0.57, 1.1)	0.16
B. ADHD with meds	123	74 (60%)	1.19 (0.81, 1.73)	0.38	1.12 (0.76, 1.65)	0.58
C. NO ADHD	2398	1329 (55%)				

*Adjusted for age group (when not stratified), site, T1D duration, gender, race/ethnicity, annual household income, insurance status

Specific Aim 3: Assess the Association between ADHD Status and the Frequency of Diabetic Ketoacidosis (DKA) and Severe Hypoglycemia among Adolescents and Young Adults with T1D.

Diabetic Ketoacidosis

The occurrence of ≥ 1 DKA event in the past 3 months by ADHD Status is shown in Table 11. The odds of having at least one DKA event in the past 3 months was 1.8 and 1.5 times

higher in the ADHD w/o meds (P<0.001) and ADHD with meds (P=0.01) group compared with no ADHD (Table 13, see page 28).

Table 12. Missing Insulin Doses by ADHD Status

	Frequency of Missing Insulin Doses at least 1 time per week		Unadjusted Odds Ratio (95% CI)	Unadjusted P-value	Adjusted Odds Ratio (95% CI)	Adjusted P-value
	N	#(%)				
Overall						
A. ADHD w/o meds	403	146 (36%)	1.32 (1.07, 1.64)	0.01	1.31 (1.05, 1.63)	0.02
B. ADHD with meds	371	143 (39%)	1.49 (1.20, 1.86)	<0.001	1.41 (1.13, 1.77)	0.003
C. NO ADHD	6606	1975 (30%)				
Age Group: 13-<18 years						
A. ADHD w/o meds	232	81 (35%)	1.32 (1.00, 1.78)	0.05	1.32 (0.99, 1.76)	0.06
B. ADHD with meds	248	92 (37%)	1.52 (1.16, 2.00)	0.003	1.42 (1.07, 1.87)	0.01
C. NO ADHD	4208	1195 (28%)				
Age Group: 18-<26 years						
A. ADHD w/o meds	171	65 (38%)	1.27 (0.92, 1.76)	0.14	1.28 (0.92, 1.79)	0.14
B. ADHD with meds	123	51 (42%)	1.49 (1.03, 2.16)	0.04	1.38 (0.95, 2.03)	0.09
C. No ADHD	2398	780 (33%)				

*Adjusted for age, site, T1D duration, gender, race/ethnicity, annual household income, insurance status, and depression diagnosis

Table 13. DKA According to ADHD Status

	≥ 1 DKA Event in Past 3 Months		Unadjusted Odds Ratio (95% CI)	Unadjusted P-value	Adjusted Odds Ratio (95% CI)	Adjusted P-value*
	N	#(%)				
Overall						
A. ADHD w/o meds	403	62 (15%)	1.96 (1.47, 2.60)	<0.001	1.79 (1.33, 2.41)	<0.001
B. ADHD with meds	371	46 (12%)	1.53 (1.11, 2.11)	0.01	1.52 (1.09, 2.13)	0.01
C. NO ADHD	6606	563 (9%)				
Age Group: 13- <18 years						
A. ADHD w/o meds	232	37 (16%)	1.85 (1.28, 2.67)	0.001	1.58 (1.07, 2.31)	0.02
B. ADHD with meds	248	33 (13%)	1.51 (1.03, 2.22)	0.03	1.44 (0.97, 2.15)	0.07
C. No ADHD	4208	387 (9%)				
Age Group: 18- <26 years						
A. ADHD w/o meds	171	25 (15%)	2.19 (1.39, 3.44)	<0.001	2.30 (1.43, 3.71)	<0.001
B. ADHD with meds	123	13 (11%)	1.51 (0.83, 2.76)	0.17	1.70 (0.92, 3.16)	0.09
C. No ADHD	2398	176 (7%)				

*Adjusted for age group (when not stratified), site, T1D duration, gender, race/ethnicity, annual household income, insurance status and depression diagnosis

Severe Hypoglycemia

The occurrence of ≥ 1 SH event in the past 3 months by ADHD Status is shown in Table 14 (see page 49). The ADHD w/o meds group was significantly more likely to have had a SH event (OR 1.7 95% CI 1.2-2.3; P<0.001) compared with the no ADHD group but the occurrence of SH in the ADHD with meds group was similar to the no ADHD.

Table 14. Occurrence of ≥ 1 SH event in the past 3 months by ADHD Status

	≥ 1 DKA Event in Past 3 Months		Unadjusted Odds Ratio (95% CI)	Unadjusted P-value	Adjusted Odds Ratio (95% CI)	Adjusted P-value*
	N	#(%)				
Overall						
A. ADHD w/o meds	403	53 (13%)	1.86 (1.37, 2.52)	<0.001	1.70 (1.24, 2.34)	<0.001
B. ADHD with meds	371	33 (9%)	1.23 (0.85, 1.79)	0.27	1.25 (0.86, 1.84)	0.24
C. NO ADHD	6606	492 (7%)				
Age Group: 13-<18 years						
A. ADHD w/o meds	232	31 (13%)	1.94 (1.30, 2.89)	0.001	1.73 (1.14, 2.62)	0.008
B. ADHD with meds	248	23 (9%)	1.35 (0.86, 2.11)	0.19	1.31 (0.82, 2.09)	0.25
C. NO ADHD	4208	302 (7%)				
Age Group: 18-<26 years						
A. ADHD w/o meds	171	22 (13%)	1.71 (1.06, 2.75)	0.03	1.72 (1.04, 1.05)	0.03
B. ADHD with meds	123	10 (8%)	1.03 (0.53, 2.00)	0.93	1.17 (0.59, 2.32)	0.64
C. NO ADHD	2398	190 (8%)				

*Adjusted for age, site, T1D duration, gender, race/ethnicity, annual household income, insurance status and depression diagnosis

CHAPTER 5:

DISCUSSION

In this large cohort of adolescents and young adults with T1D, participants with a diagnosis of ADHD with or without current medication had significantly worse glycemic control compared with their no ADHD diagnosis counterparts even after adjustment for confounders such as socioeconomic status, gender, and the presence of co-morbid depression. A similar association was observed within adolescent (13-17) and young adult (18-25) age groups and when analysis was limited to those with a concurrent participant and clinic reported diagnosis. The average HbA1c among participants with a diagnosis of ADHD who were and were not currently taking an ADHD medication was 9.0% and 8.9% which is higher than the average HbA1c of 8.8% observed in the conventional therapy group of the DCCT over 30 years ago (The Diabetes Control and Complications Trial Research Group, 1993).

The highest HbA1c was observed among ADHD teenagers who self-reported not currently taking medication with an average HbA1c level of 9.1%. Only 15% of adolescents with ADHD both not currently and 15% of those currently taking medication had an HbA1c below the ADA clinical target of < 7.5% for youth less than 18 years of age. This was a significantly lower percentage than that of participants without ADHD.

The majority of young adults age 18 to 25 also failed to achieve HbA1c levels below the ADA target with only 7% and 11% of participants with ADHD not currently taking and currently taking medication, respectively, having a most recent HbA1c that was below 7.0%. The

proportion meeting the ADA target was slightly higher among young adults without a diagnosis of ADHD (17%) but still less than a quarter.

The difference in glycemic control observed between ADHD status groups is likely reflective of differences in adherence to diabetes management standards. Although no significant differences were observed for the average frequency of performing SMBG per day, participants with ADHD without meds were more likely to perform SMBG fewer than the recommended 4 times per day compared with no ADHD participants. Participants with ADHD with or without current medication were more likely to report missing an insulin dose at least once per week with 36% of those with ADHD not on meds and 39% with ADHD currently on meds vs. 30% among those without a diagnosis. The relationship between missing insulin doses and ADHD diagnosis remained even after adjustment for SES, age, gender, insulin delivery method, and the presence of comorbid depression.

Use of an insulin pump for insulin delivery was less common among participants with ADHD without medication. Only 47% of ADHD participants not currently taking medication were using an insulin pump, whereas a pump was being used by 56% of those without an ADHD diagnosis. The difference in insulin delivery method between the ADHD w/o meds and no ADHD groups remained even after adjustment for SES, age, gender, diabetes duration, and diagnosis of comorbid depression. The proportion of participants using an insulin pump in the ADHD with meds group (57%) was similar to those without an ADHD diagnosis. Using an insulin pump has been shown to be associated with lower blood glucose levels (Scrimgeour, 2007; Pickup 2008; Misso, 2010; Blackman, 2013) and may be particularly beneficial to those with ADHD because of the automatic dosing of basal insulin and easier dosing of bolus/meal time insulin.

Although there were not statistically significant differences in CGM use between ADHD status groups it is somewhat surprising that the use of CGM was highest among young adults with ADHD who were currently taking medication. This could be due to CGM being prescribed more often in those taking stimulant medication in order to more closely monitor the possible effects of the medication on blood glucose fluctuations however, if this were the case, it seems a higher frequency of CGM use would be observed among adolescents with ADHD who were currently taking medication. Use of CGM may be particularly beneficial to type 1 patients with ADHD because of the built in alarm features and the ability to have a parent or significant other review continuous blood glucose levels either retrospectively or in real time.

ADHD status was associated with a higher frequency of at least one DKA and severe hypoglycemic event involving seizure or loss of consciousness in the past 3 months. Participants with a diagnosis of ADHD, not currently and currently taking medication, had 1.79 and 1.52 times the odds of reporting at least one DKA event after adjustment for SES, age, gender, race/ethnicity and diabetes duration. DKA occurred in 16% of adolescent participants age 13 to 17 with a diagnosis of ADHD who were not currently taking medication compared with 9% among those without ADHD. Severe hypoglycemia was also more common among ADHD participants not currently taking treatment despite the overall higher HbA1c levels. Unlike the early DCCT data showing higher frequency of severe hypoglycemia with lower HbA1c, recent data from the T1D Exchange and DPV registries show no relationship between severe hypoglycemia and low HbA1c levels likely in part due to advancements in insulin analogs. The higher frequency of severe hypoglycemia observed in ADHD participants not taking medication could be a reflection of greater swings in glucose levels arising from improper insulin dosing

A review of the literature, found only a few small studies that assessed the relationship between ADHD and diabetes management, and no studies assessing the effect of ADHD on glycemic control. Duke and colleagues (2012) found a significant relationship between ADHD and lower scores on a diabetes management index which supports the higher frequency of missed insulin doses among ADHD participants observed in our study.

Previous studies have reported the negative effects of other psychological disorders including depression and anxiety on T1D management and glycemic control. Depression and anxiety are common co-morbid conditions of ADHD. Depression is particularly problematic among teens and young adults with T1D. A diagnosis of depression was recorded in the medical chart for 25% of participants with ADHD and 9% without ADHD in this study population. Adolescents and young adults with ADHD and depression may be more likely to be receiving psychosocial therapy and medication for ADHD than those with ADHD alone which could result in the ADHD with medication group having higher HbA1c levels due to the negative effect of depression. In this study a significant relationship between ADHD and glycemic control was observed even after adjusting for depression.

Strengths

A strength of this study is the large sample size and ability to utilize the T1D Exchange Clinic Network and registry to target a specific objective and collect participant-reported data on ADHD diagnoses and treatment as well as the relatively low percent of missing data. This study was able to address a research question that would be nearly impossible for a single center to evaluate due to the relatively low prevalence of ADHD and T1D. The large sample size allowed for subgroup analysis for adolescent and young adult age groups and ADHD medication status.

Another strength of this analysis is the availability of participant-reported data for diabetes management and DKA and SH events that are believed to be underreported in the medical record (Cengiz, 2013).

Limitations

Although the T1D Exchange clinic registry data are collected from a large number of individuals with T1D across the U.S., it is not population-based. Participation in the registry was predicated on being followed by an endocrinologist and informed consent for each participant was required. This is likely less of an issue with respect to representativeness of the adolescent group in this study population since pediatric patients with T1D generally are cared for by an endocrinologist. However, it is not known where most young adults with T1D receive care and it may be that many are seen by a primary care physician as opposed to an endocrinologist. Where college students receive diabetes care may be particularly problematic as some may return home and see their pediatric endocrinologist while others may terminate their pediatric endocrinology follow up without transition to an adult diabetes provider, thus failing to receive appropriate monitoring by a diabetes specialist. Thus, the young adults in this cohort may or may not be fully representative of young adults with T1D. This affects certain aspects of the data, particularly when assessing prevalence of ADHD but is less likely to affect the primary objective of assessing the association between ADHD and diabetes management and clinical outcomes.

Even though a diagnosis of presumed autoimmune T1D was required for registry participation, it is possible that a small number of registry participants could have been misdiagnosed as having T1D. However, a small number of misclassified T1D participants is not

likely to have a meaningful effect on results due to the large sample size and it is not expected that the misclassification would be differential across ADHD status groups.

It is also possible that there are undiagnosed ADHD cases in the group without ADHD or that the participant report of an ADHD diagnosis was inaccurate. Performing sensitivity analysis limiting to those with participant-reported and clinic-confirmed ADHD helps to reduce the misclassification from erroneous reporting by participants but does not fix the limitation that some cases of ADHD could be missed altogether. Misclassification of ADHD diagnosis would bias results towards the null since there may be participants in the no ADHD group that have ADHD. However, since ADHD has a relatively low prevalence the possible misclassification in the no ADHD group is unlikely to be a major source of bias. Whether or not someone is diagnosed with ADHD may be influenced by their level of glycemic control since they may be more likely to be referred to a psychologist or social worker for poor diabetes management. This phenomenon could have biased results away from the null, although it is only possible for this to have impacted results in the 49% who were diagnosed with ADHD after the diagnosis of T1D.

Another limitation might be cases in the ADHD group that have resolved for the young adults. The questionnaire asked whether a participant had ever been told by a physician or psychologist that they have ADHD and does not specify whether symptoms are still present. It is not uncommon for childhood ADHD to fully or partially resolve in adulthood. Some of the young adults in the ADHD diagnosis group might therefore behave more like those without an ADHD diagnosis resulting in a bias towards the null hypothesis of no difference.

It may be possible that self-reported outcomes (e.g., management) may be less reliable among ADHD patients, possibly biasing results towards the null hypothesis. The lack of

relationship observed between ADHD status and SMBG per day may be due to over-reporting of frequency of SMBG by those with ADHD.

This study focuses on adolescents and young adults between the ages of 13 and 25 years and therefore results cannot be generalized to younger or older age groups. For younger children with T1D, diabetes management is largely driven by parents instead of the individual, making it difficult to discern the effects of ADHD on T1D management and glycemic control. Very few adults above the age of 25 reported a diagnosis of ADHD, therefore this population was excluded do to small exposure sample size.

Finally, this study was a cross-sectional study and cannot conclude a causal association between ADHD and glycemic outcomes.

Summary

Results of this study supported the working hypothesis that ADHD without treatment with medication has a negative impact on aspects of diabetes management and glycemic control. Participants with ADHD with and without medication were more likely to miss insulin doses, less likely to use an insulin pump, more likely to have high HbA1c levels, and had a higher frequency of DKA and SH. These results have important public health implications for adolescents and young adults with T1D who are already at risk for poor glycemic control. There was some beneficial effect of treatment with medication and psychosocial counseling with slightly lower HbA1c levels among those who reported currently taking medication and receiving psychosocial counseling in the past 6 months. Only a subset of participants who reported a diagnosis of ADHD had a diagnosis recorded in the clinic chart. Since ADHD has a meaningful impact on glycemic outcomes it is important for providers of adolescents and young

adults with T1D to review history and signs of an ADHD diagnosis along with diagnosis of other psychosocial disorders with their patients and consider recommending psychosocial services.

Given these results, further studies to assess interventions to improve glycemic control in patients with T1D and ADHD are warranted.

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APPENDIX A :

ADHD and ADD Data Collection Module

1. How old were you when you were diagnosed by a doctor with ADHD or ADD?

_____ years old

2. Have you ever taken medication for ADHD or ADD?

Yes No

If YES, please answer question 3. If NO, skip to question 4.

3. Are you currently taking medication for ADHD or ADD?

Yes No

4. Are you currently seeing (at least once every 3 months) a psychiatrist, psychologist, or counselor for your ADHD or ADD?

Yes No

APPENDIX B:

Institutional Review Board Letter



RESEARCH INTEGRITY AND COMPLIANCE
Institutional Review Boards, FWA No. 00001669
12901 Bruce B. Downs Blvd., MDC035 • Tampa, FL 33612-4799
(813) 974-5638 • FAX (813) 974-7091

2/5/2015

Kellee Miller
Epidemiology and Biostatistics
15310 amberly drive
Tampa, FL 33647

RE: **NOT Human Research Activities Determination**

IRB#: Pro00017918

Title: Assessment of the impact of Attention Deficit Hyperactivity Disorder (ADHD) on Diabetes Management and Glycemic Control among Adolescents and Young Adults with Type 1 Diabetes (T1D)

Dear Ms. Miller:

The Institutional Review Board (IRB) has reviewed the information you provided regarding the above referenced project and has determined the activities do not meet the definition of human subjects research. Therefore, IRB approval is not required. If, in the future, you change this activity such that it becomes human subjects research, IRB approval will be required. If you wish to obtain a determination about whether the activity, with the proposed changes, will be human subjects research, please contact the IRB for further guidance.

All research activities, regardless of the level of IRB oversight, must be conducted in a manner that is consistent with the ethical principles of your profession and the ethical guidelines for the protection of human subjects. As principal investigator, it is your responsibility to ensure subjects' rights and welfare are protected during the execution of this project

Also, please note that there may be requirements under the HIPAA Privacy Rule that apply to the information/data you will use in your activities. For further information about any existing HIPAA requirements for this project, please contact a HIPAA Program administrator at 813-974-5638.

We appreciate your dedication to the ethical conduct of human subject research at the University of South Florida and your continued commitment to human research protections. If you have any questions regarding this matter, please call 813-974-5638.

Sincerely,

A handwritten signature in blue ink that reads "Vjorgensen MD". The signature is written in a cursive style with a large initial "V".

E. Verena Jorgensen, M.D., Chairperson
USF Institutional Review Board

ABOUT THE AUTHOR

Kellee Michele Miller was born in Saint Petersburg, Florida. Ms. Miller received a Masters in Public Health from Florida State University in 2007 with a concentration in epidemiology and biostatistics. Over the past 3 years Ms. Miller has served as the Assistant Director of the T1D Exchange Clinic Network under the supervision of Roy Beck, MD, PhD Executive Director of the Jaeb Center for Health Research and Director of the T1D Exchange Clinic Network. Ms. Miller is the Principal Investigator and Coordinating Center Director for several ongoing T1D Exchange studies. She has worked at the Jaeb Center for Health Research for 8 years. Ms. Miller is in the process of completing her Ph.D. in epidemiology at the University of South Florida, College of Public Health and plans to graduate in August 2015