TRENDS IN ORAL ANTI-DIABETIC UTILIZATION AND FACTORS AFFECTING EFFECTIVENESS IN CHILDREN AND YOUNG ADULTS

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ABSTRACT

Mona H. Cai: Trends in Oral Anti-Diabetic Utilization and Factors Affecting Effectiveness in Children and Young Adults
(Under the direction of M. Alan Brookhart)

Objectives: Our study quantified the trends in filled oral anti-diabetic (OAD) prescriptions, predictors of treatment initiation, and factors related to discontinuation and re-initiation among US privately insured children and adolescents from 2001-2012

Methods: Trends in treatment incidence were estimated monthly and stratified by baseline demographics. The cumulative risks of non-persistence at 30-days, 180-days, and 360-days were calculated and predictors of discontinuation were determined using Cox proportional hazards regression. Rates of re-initiation were summarized and predictors were evaluated using case-crossover analysis.

Results: Time trends demonstrated an overall 43% increase in initiation from 2002 to 2012, with a gradual decrease observed beginning early 2008. Initiators were more likely to be females, age 15-18, from the southern region, and have visited a family practitioner prior to initiation. Among initiators, persistence was low and the cumulative risk of non-persistence at 180 days was 79.0%.

However, 31.4% of patients with extended periods of without drug supply subsequently re-initiated therapy. Case-crossover analysis demonstrated that follow-up care of different forms were independently highly associated with re-initiation, including HbA1c testing during an outpatient visit (odds ratio (OR), 4.4; 95% CI, 3.6-5.5) and LDL testing during an outpatient visit (OR, 4.4; 95% CI, 3.3, 5.8). Single occurrences of HbA1c testing

(OR, 4.1; 95% CI 3.4-5.0), LDL testing (OR 3.8; 95% CI 3.0-4.7), and being diagnosed with a type 2 diabetes complication (OR 3.0; 95% CI 2.2-4.2) were also strongly associated with treatment re-initiation.

Conclusions: Incidence of filled OAD medications in youth has increased over time, especially in patients treated by family practitioners. Poor persistence to index drug was common in this population, although greater follow-up care by physicians may decrease the length or frequency of treatment gaps.

"When there's a will, there's a way"
Mom and dad, who I have become, what I believe, and my ability to persevere through the most challenging times come from all that you have instilled in me. Thank you for always believing in me and being my anchors in life. To my husband, Jerry, thank you for being my #1 fan and being so supportive as I pursued my PhD. I could not have completed this without you by my side.

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LIST OF ABBREVIATIONS

AAP: American Academy of Pediatrics

ADA: American Diabetes Association

BMI: Body Mass Index

CI: Confidence interval

CPT: Current Procedural Terminology

DKA: Diabetic Ketoacidosis

HbA1c: Hemoglobin A1C

HHNK: Hyperglycemic Hyperosmolar Nonketotic Syndrome

ICD-9: International Classification of Diseases, 9th Revision, Clinical Modification

IGT: Impaired Glucose Tolerance

IFG: Impaired Fasting Glucose

IMCL: Intramyocellular Lipid

IR: Insulin Resistance

NDC: National Drug Codes

NHANES: National Health and Nutrition Examination

OAD: Oral Anti-Diabetic

PDC: Proportion of Days Covered

SES: Socioeconomic Status

T2DM: Type 2 Diabetes

US: United States

CHAPTER 1: REVIEW OF THE LITERATURE

1.1 Pathophysiology for the development of T2DM

The biological mechanism for the development of Type 2 diabetes mellitus (T2DM) in children and adolescents is similar to that of adults, where insulin resistance (IR) and insulin secretory defect play the key roles in the progression of this chronic condition. Insulin is a naturally occurring hormone produced by β-cells in the pancreas whose primary function is to regulate both carbohydrate and fat metabolism. Carbohydrates are broken down into simple sugars known as glucose that provide energy to the cells in our bodies. Increased blood glucose levels resulting from the ingestion of carbohydrates stimulates the release of insulin which signals cells in the liver, skeletal muscles, and fat tissues to absorb the glucose from the blood stream. Excess glucose is stored in liver and fat cells and released at times when the body is short on glucose (1, 2).

Under normal conditions, glucose levels remain fairly constant through the regulation and balance of insulin secretion by β-cells and insulin sensitivity by peripheral tissues. IR occurs when the liver and these peripheral tissues, i.e., muscle, and fat cells, do not respond properly to insulin and cannot readily absorb glucose from the bloodstream, causing abnormally high serum glucose levels. The pancreas responds by producing and secreting more insulin, which imposes excessive stress on the pancreas, and over time, results in gradual failure of β-cell function (3). The combination of IR and β-cell response defects eventually leads to pre-diabetes and T2D inception; however, the actual temporal relationship between these two conditions remains unclear and differs by gender and ethnicity (4, 5).

Early detection and treatment of IR, usually with life style modifications, can often prevent or delay T2DM onset. However, this stage is usually asymptomatic and therefore difficult to detect. Adolescents with T2DM have ~50% lower insulin sensitivity and ~75% lower insulin secretion when compared with non-diabetic adolescents matched on BMI and abdominal adiposity (6). Adult T2DM patients display a similar clinical profile, which is unsettling given the overall shorter duration of T2DM in youth compared with their counterparts.

1.2 The epidemiology of T2DM in youth

According to the National Health and Nutrition Examination (NHANES) Survey of 2009-2010, 16.9% of children and adolescents aged 2-19 were obese with a BMI>=95th percentile, demonstrating a doubling in percentage from two decades ago (7). These percentiles convey a child's BMI relative to the children in the U.S. who have participated in previous surveys conducted from 1963-65 to 1988-94 (Kuczmarski et al). As obesity in this population continues to rise due to high caloric diets and sedentary lifestyles, the metabolic syndrome and subsequent comorbidities, previously observed predominately in adults, are rapidly increasing as well (8). Metabolic syndrome is a group of medical disorders, i.e. triglycerides, HDL and LDL cholesterol, blood pressure, and fasting plasma glucose over a predefined cut-point or previously diagnosed diabetes, that when occurring together has been suggested to increase the risk of cardiovascular disease and diabetes. Obese adolescents (BMI>=95th percentile) are at a significantly higher risk for developing one or more metabolic syndrome factors compared to those who are overweight (BMI between 85th-95th percentile) and those with normal weight (BMI<85th percentile), 32.1% vs. 7.1% and 32.1% vs. <1%, respectively (9).

The prevalence of metabolic syndrome amongst children and young adults has been increasing in parallel to the obesity epidemic, resulting in earlier manifestations of

hypertension, hyperlipidemia, and T2DM. T2DM and prediabetes are clinically defined as having a fasting blood glucose level >=126 mg/dl and between the 100-125 mg/dl, respectively (Table 2) (10). In 1995, approximately 17% of all diagnosed diabetes in patients 18 years and younger had T2DM, compared with 2005, where the percentage jumped to ~30%, with a disproportionate burden on ethnic minorities (11). Data on past U.S. incidence of T2DM is scarce, with the majority of estimates extrapolated from small, single clinic-based studies. Assessments from 1982 approximated the incidence for that year to be 0.7 per 100,000 per year (11). More recent estimates have been assessed from SEARCH for Diabetes in Youth, a multi-center, population-based cohort study that enrolled a total of 2435 newly diagnosed T1DM or T2DM patients younger than 20 years of age. Overall, the study estimated ~3,700 adolescents were diagnosed with T2DM per year and projected that this number will rapidly increase over time. Results from the 2002-2003 period for the 15-19 age group showed a large variation in rates by ethnicity, ranging from 49.4 per 100,000 person-years amongst Native-Americans to 5.6 per 100,000/year amongst non-Hispanic whites, with African-Americans, Hispanics, and Asian/Pacific Islanders' rates somewhere in between (19.4, 17.0, and 22.7 per 100,000 person-years, respectively) (12). Similar patterns were observed in the other age groups as well. Conservative comparisons between the incidence from 1982 contrasted with race-specific values from 2002 show dramatic increases in all ethnicities, with an excessive amount of burden placed on minorities. The heightened awareness in the field of youth T2DM has contributed to increased screening and diagnoses in recent years. Hence, caution should be taken when comparing incidence over time in this population, as the observed rates are a function of both rising disease incidence as well as intensified medical monitoring and screening.

Prevalence rates have been estimated using numerous data sources, but the most generalizable U.S. numbers come from the NHANES surveys. Utilizing both interviews and laboratory tests performed on a random sample of the population, NHANES is able to evaluate point prevalence and the burden of both T2DM and prediabetes on the population. Based on the 2005-2006 NHANES survey, prevalence was low at a projected 0.2% amongst those aged 12-19; however, the prevalence of impaired glucose tolerance (IGT) and impaired fasting glucose (IFG), which are clinical indictors of prediabetes, was significantly higher at an estimated 16.1% (95% CI: 11.3-21.2%) (13). This is more than double the rate from the 1999-2000 survey where the prevalence of prediabetes was 7.0% (95% CI: 4.6-9.4%) (14). It is estimated that approximately 25% of those with prediabetes who neglect proper management and treatment will progress to T2DM within 3 years (15).

1.3 Risk factors of T2DM in youth

Obesity, genetic factors, polycystic ovarian syndrome (PCOS), puberty, and intrauterine exposure to hyperglycemia are common risk factors associated with T2DM in youth (5, 16). Figure 1 illustrates these factors and their relationship to one another.

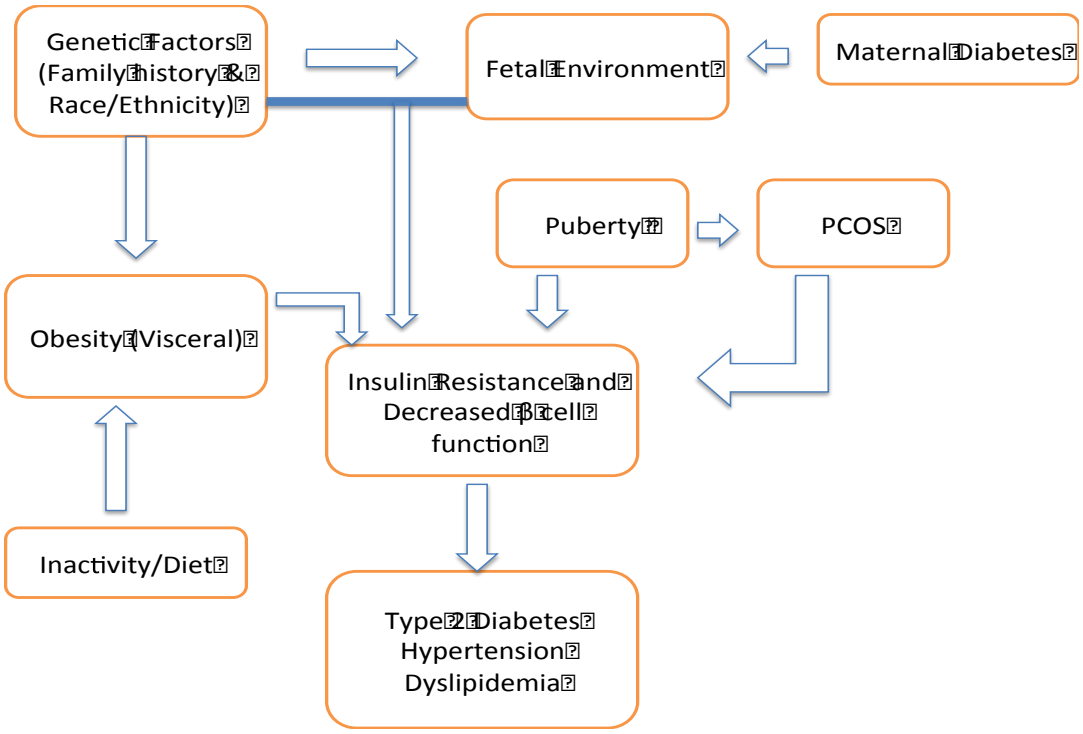

Figure 1. Risk factors involved in insulin resistance and T2DM development

1.3.1 Obesity

The prevalence of IR amongst obese adolescents is 52%, making obesity the strongest risk factor related to T2DM. Obesity accounts for over 55% of the variance in insulin sensitivity and 29.1% of the variance in homeostasis assessment models for IR (17). Abdominal obesity, i.e. visceral adiposity, and intramyocellar lipid deposition (IMCL) are the specific culprits involved in T2DM development amongst obese individuals (3). Studies have shown that the amount of lipid deposition in the visceral adipose tissue is most predictive of the risk for IR compared with fat accumulation in other regions, i.e. subcutaneous, epicardial, pulmonary, periadventitial, perirenal, and bone marrow adipose tissues (16, 18, 19). Adipose tissue is a complex endocrine organ responsible for storing energy and regulating metabolic function in the body (18). Energy in the form of fat is stored in adipocytes while the rest of the adipose tissue is referred to as the stromal vascular fraction. This component includes monocytes, macrophages, vascular cells, pre-adipocytes, T-cells, and mesenchymal stem cells (18). Adipose tissue responds to signals from hormones and the central nervous system, and secretes numerous anti-inflammatory and pro-inflammatory proteins known as adipokines, which are important proteins supporting endocrine function (19). Biological experiments have demonstrated cellular changes and/or overexpression of adipokines in the presence of obesity and high adipose tissue content, especially in the visceral region. Certain proteins, such as NAMPT and IL-6, have shown 2-3 times greater correlation with IR when in the visceral compared with subcutaneous regions (19). Table 1 summarizes the pro-inflammatory proteins that are believed to affect proper insulin function and hence promoting IR.

Table 1. Sources and function of Adipokines involved in insulin resistance (1, 18)

	Primary Source	Function (normal conditions)	Function (obese individuals)
Leptin	Adipocytes	Regulates feeding behavior	Leptin resistance correlated with IR
Resistin	Adipocytes	Activates inflammatory process	Promotes IR and inflammation by activating IL-6 & TNF secretion
RBP4	Adipocytes, liver	Transports vitamin A	Inhibits insulin induced phosphorylation of insulin receptor substrate
TNF-α	Adipocytes, SVF	Inflammation and autoimmune disease	Repress genes involved in glucose storage. Impairs insulin signaling and increases insulin Degradation
IL-6	Adipocytes, liver, Muscle, SVF	Multifaceted roles depending on source	Decreases insulin signaling by reducing expression of insulin receptor signaling components
CCL2	Adipocytes, SVF	Macrophage recruitment to adipose tissue	Promotes glucose intolerance and insulin insensitivity
NAMPT	Adipocytes	Modulator of beta cell differentiation	Effects insulin secretion by β-cells (exact mechanism undetermined)
CXCL5	SVF	Undetermined	Activates JAK-STAT pathway which interferes with insulin signaling in muscles

CCL1, CC-chemokine ligand 2; CXCL5, CXC-chemokine ligand 5; IL, interleukin; JAK, Janus kinase; NAMPT, nicotinamide phosphoribosyltransferase; RBP4, retinol-binding protein 4; STAT, signal transducer and activator of transcription; SVF, Stromal vascular fraction cells; TNF, tumor necrosis factor

The fact that not all obese youth go on to develop IR and T2DM suggests that there are additional components implicated aside from visceral adiposity. Increasingly more evidence is supporting the role of intramyocellular lipid (IMCL) deposition on insulin sensitivity. IMCL are fats stored in muscle cells, also referred to as myocytes, which provide energy during times of muscle exertion. Circulating free fatty acids (FFA) are directed into the muscles when needed and stored as triglycerides in myocytes during rest. Diets high in FFA can overtime raise IMCL volume through fat accumulation. Depending on the duration of high-fat diet and baseline IMCL, IMCL content can increase by 36-90% through the influence of high-fat diets (20). FFA derivatives collected in the IMCL are believed to interrupt insulin signal transduction pathways, which lead to malfunctions in glucose uptake (21). Although there are rare cases where lean individuals with high IMCL content develop T2DM, suggesting IMCL is an independent risk factor for the condition, most data demonstrate a direct association between IMCL and visceral adiposity. Brumbaugh et al. examined the correlation between IMCL and visceral adiposity among prepubertal and pubertal children. Their results were consistent amongst both age groups and showed that for every 10-cm^2 increase in visceral adiposity, IMCL increased by 0.19 units (22).

1.3.2 Genetic factors including family history of T2DM and ethnicity

There is compelling evidence indicating a genetic component in T2DM where family history and ethnicity are both established independent predictors of IR and T2DM. Approximately 45-80% of youth with T2DM have at least one parent with DM and 74-100% have a first- or second- degree relative with T2DM (23). Family history of T2DM is associated with ~25% lower insulin sensitivity when pre-pubertal healthy children with a family history were compared to those without family history. Studies in adult twins found 34-58% and 17% concordance between monozygotic and dizygotic twins, respectively (23,

24). First-degree relatives of T2DM patients have a lifetime risk of 40% for developing T2DM (23). Adult studies that have examined the heritability of traits involved in T2DM onset reported that insulin secretion is more familial than insulin sensitivity (25).

Ethnic minorities have a disproportionate amount of T2DM burden, which signifies a strong predisposition in these populations to develop this chronic condition. A combination of genetic and lifestyle factors have led to a higher prevalence amongst Pima Indians, Native Americans, and African-Americans. Epidemiologic and clinical evidence have established a higher risk of developing T2DM in black and Hispanic children compared to their white counterparts as well as clinical indicators of higher insulin resistance and lower insulin sensitivity (2).

1.3.3 Polycystic ovarian syndrome (PCOS)

PCOS is a common endocrine disorder involving women of the reproductive age with subclinical symptoms including chronic anovulation and hyperandrogenism, and is the leading cause of oligoolvulatory infertility (2). This syndrome affects, depending on diagnostic criteria, anywhere between 5 to 15% of women, with rapid growth rates observed in obese adolescent females (26). The metabolic profile for PCOS suggests an association with insulin resistance and hyperinsulinemia, making PCOS a strong risk factor for T2DM. Adolescents with PCOS have ~50% lower insulin sensitivity and 33% more cases of impaired glucose tolerance compared with obesity matched controls (27). The prevalence of T2DM is 5-10 times higher in women with PCOS compared with women without PCOS (28). It is estimated that the prevalence of overweightness (BMI, 25.0-29.9) and obesity (BMI>=30.0 kg/m^2) amongst PCOS female's aged 18-45 is 24% and 42%, respectively (29). Metformin has been proven highly effective in treating PCOS through regulating menstrual cycle, improving and inducing ovulation, and reducing circulating androgen levels (28).

1.3.4 Puberty

Growth hormones, which are commonly but transiently secreted during puberty, have been linked with hyperinsulinemia and IR. Insulin-like growth factor-I (IGF-I) levels have been illustrated by longitudinal studies to explain ~35% of the variance in insulin sensitivity (30). In normal weight, healthy adolescents, insulin sensitivity was observed to decrease by 50% but was balanced off by a two-fold increase in insulin secretion. This leads to clinical manifestations of hyperinsulinemia; however, overall glucose homeostasis is achieved in most adolescents. Conversely, the natural physiologic occurrence of IR during puberty may precipitate T2DM among those who are more susceptible to the condition.

1.3.5 Interuterine exposure to hyperglycemia

Numerous studies have demonstrated a direct association between maternal DM during pregnancy and obesity in offspring throughout childhood and young adulthood. This relationship was further strengthened when comparing a mother's offspring conceived before versus after maternal DM progression, indicatingdifferences in BMI and obesity status in the children (31). A prospective cohort following offspring of diabetic mothers observed that by the age of 12 there was an almost ten-fold higher prevalence of IGT amongst these offspring compared with age- and sex-matched controls (19.3 vs. 2.5%, respectively) (32).

1.3.6 Additional risk factors: exposure to antidepressants and antipsychotics

The therapeutics used in the treatment of depression and psychoses and their association with obesity and T2DM have been heavily studied (33, 34). Part of the complication in examining these therapies is separating out the effect of lifestyle-, disease-, and drug- related influences on obesity, as those are all independent risk factors as well. The association between antidepressants and weight gain has been seen to vary by drug class, with marked increases among tricyclic antidepressant users (~4kg weight gain over 1-6

months of follow-up) (34). Second generation atypical antipsychotics, commonly used in the treatment of schizophrenia and bi-polar disorder, can increase a person's risk for T2DM through body weight gain and biological mechanisms that alter insulin secretion regulation (33). Many patients on atypical antipsychotics are also prescribed Metformin to counterbalance the side effects of such drugs.

1.4 Clinical presentation and chronic complications of T2DM

The clinical presentation at diagnosis of T2DM varies dramatically from being asymptomatic to possessing a life-threatening condition. A study using medical records from Texas Children's Hospital identified youth <=18 years of age newly diagnosed with T2DM. They found that 93% had a BMI>=95th percentile, and 55% and 19.3% had systolic and diastolic blood pressure, respectively, >=90th percentile (35). Also, 94% had acanthosis nigricans, a dermatological clinical marker predicting insulin resistance and T2DM, and is characterized by thickened dark hyperpigmentation of the skin, frequently seen on the posterior and lateral folds of the neck (35). Evidence of polyuria and/or polydipsia is commonly observed but severe cases of diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar nonketotic syndrome (HHNK) have been ascertained as well. DKA occurs in the presence of low insulin concentrations and is most frequently observed in T1DM patients, although increasing rates have been noted in severe cases of T2DM. As beta-cell function progressively weakens, serum insulin levels will gradually decrease as well. Under low insulin conditions, the liver releases high levels of glucose and the kidney reacts by filtering excess glucose through the urine resulting in polyuria. Adipose tissues respond to low glucose levels by releasing FFA that is converted into ketone bodies as an alternative source of fuel for the body. Ketones have a low pH, which turns the blood acidic leading to DKA. At diagnosis, approximately 33% and 5-25% of youth have ketonuria and DKA, respectively

(36). HHNK occurs in the absence of DKA and is characterized by high blood glucose and high serum osmolality. When circulating blood becomes highly concentrated with glucose and salt, water is drawn out of organs through the process of osmosis and can result in detrimental effects such as coma or death (37). Results from a single center study including newly diagnosed T2DM youth reported a HHNK prevalence of 3.7% (38); in another study, the case-fatality rate for HHNK was estimated at 37% among HHNK patients with a mean age of 15 years old (39).

The risk for developing chronic complications related to T2DM increases with BMI, poor adherence to therapeutics, and diabetes duration (2). Since IR has proven itself to play a decisive role in the progression of metabolic syndrome, cardiovascular disease risk factors are notably present in T2DM youth both at diagnoses and throughout disease progression. According to the SEARCH study, approximately 25% of youth aged 10-19 with T2DM have 2 or more cardiovascular risk factors, with higher rates among females (23% vs. 19%) and ethnic minorities (68% American Indians, 37% Asian/Pacific Islanders, 32% African Americans, 35% Hispanics, vs. 16% non-Hispanic whites) (40). The study also found that among T2DM patients, 33% had total cholesterol >200mg/dl, 24% had LDL>130mg/dl, and 44% had HDL<40mg/dl (4). Data on the prevalence and incidence of retinopathy, diabetic nephropathy, and diabetic neuropathy in children and adolescence with T2DM are extremely limited. A cohort of 40 pediatric patients found one patient (2.5%) who had retinopathy and 9 patients (27.3%) who had signs of microalbuminuria (41). Incidence data were ascertained in a cohort of 178 young Pima Indians (less than 20 years at T2DM diagnoses) who were followed longitudinally and found rates of 90 per 1,000 P-Y and 75 per 1,000 P-Y for nephropathy and retinopathy, respectively after 15-20 years of diabetes duration (42). When

these rates were compared with those from the adult-onset diabetes cohort, rates were non-significant for nephropathy and statistically significantly lower for retinopathy, highlighting the seriousness of childhood-onset diabetes. Although T2DM in youth is a relatively new epidemic, as these children progress into early adult-hood, complications and severity of these conditions will present themselves earlier in life compared to what practitioners are familiar with, leading to unforeseeable public health challenges.

1.5 Treatment guidelines and management of T2DM

The first guidelines pertaining to the screening and treatment of T2DM specifically in children and young adults were released in 2000 by the American Diabetes Association (ADA) (39). The ADA and American Academy of Pediatrics (AAP), based on the latest evidence from the scientific community, updated the management guidelines in early 2013. The diagnosis criteria for T2DM have remained unchanged from adults but screening and treatment recommendations have gone through minor revisions.

The ADA recommends screening every two years in high-risk individuals. Screening for low- or moderate- risk patients should be based on clinical judgment (Table 2), where the level of risk is defined based on the number of risk factors the patient has. Based on survey data collected from pediatricians, ~21% of clinicians reported ADA-consistent screening practices and ~60% of responders would consider screening moderately high- and high-risk patients (43). A retrospective chart review conducted in an urban primary care clinic found that more than half of adolescents who should have been screened based on guidelines were in fact, not screened; however, many of those who were screened did not meet the criteria set by the ADA (44). The observed low acceptance rate of treatment guidelines by practitioners could be caused by unfamiliarity of these recommendations or could signify that many

practicing physicians treating these children do not find these guidelines adequate in identifying high-risk individuals.

1.5.1 Prevention measures for T2DM in youth

Methods targeting T2DM prevention have been directed at many stages of disease progression. Primordial prevention occurs prior to the manifestation of risk factors and encompasses measures to prevent obesity usually through diet, exercise, and behavior modifications. Due to the accumulation of a variety of factors in the past 30 years, including high caloric diets and reduced physical activity attributable to the increasing popularity of TV and video games, this mode of prevention has proven to be highly difficult to instill. Countless interventions aiming at various facets of primary prevention have been undertaken in recent years focusing on both schools systems and parental education. Evidence from a meta-analysis of randomized controlled trials (RCTs) targeting lifestyle and drug interventions for treatment of obesity in children <=18 years of age found overall low success rates in achieving optimal weight reduction (45). Results suggested that lifestyle modification by itself is not efficacious in maintaining weight loss but can be effective when combined with obesity medication such as sibutramine and orlistat.

Table 2. Guidelines for Diagnosis and Management of T2DM in Youth (2, 10, 39)

Screening Guidelines	Prediabetes and T2DM definition*	Management Recommendations for Clinicians**
• >=10 years and • BMI>85th percentile and • Two of the following risk factors: (1) Family history of T2DM (2) Minority group (3) Signs of IR or conditions associated with IR (4) Maternal history of diabetes or gestational diabetes • Using fasting plasma glucose test or oral glucose tolerance test	Prediabetes • 5.7<=HbA1c<=6.4% or • Fasting plasma glucose >=100-125mg/dL or • 2-hour plasma glucose>= 126 but <=200mg/dL T2DM: • HbA1c>=6.5% or • Fasting plasma glucose >=126ml/dL, or[1] • 2-hour plasma glucose >=200 mg/dL, or[1] • random plasma glucose >=200mg/dL with symptoms of hyperglycemia	• Initiating insulin therapy if the child/ adolescent is ketotic or show signs of DKA, or if distinction between T1DM and T2DM cannot be made • Introduce lifestyle modification measures and Metformin (first line agent) at diagnoses • Clinicians should follow *Pediatric Weight Management Evidence-Based Nutrition Practice Guidelines* in their dietary counseling • HbA1c concentrations should be monitored every 3 months and intensified if necessary • Encourage patients to engage in moderate-to-vigorous exercise for at least 60 minutes daily • Advise patients to monitor blood glucose with finger-stick tests if: (1) They are at risk for being hypoglycemic, e.g. insulin users, or (2) Are initiating or changing treatment regimen, or (3) Have not met treatment goals, or (4) Have intercurrent illnesses

*Updated in 2004, definition applies to youth and adults

**Updated in 2013, management specific for youth with T2DM

[1]fasting plasma glucose and 2-hour plasma glucose test often done in conjunction as an oral glucose tolerance test

1.5.2 Monitoring children with T2DM

Diligent glucose monitoring is an imperative step in proper diabetes management and control, most frequently performed with glucose meters and blood samples from a fingerstick. Fasting, 2-hour, and random plasma glucose tests as well as Hemoglobin A1C (HbA1c) tests can all be used to assess glucose levels. Fasting plasma glucose test is conducted after at least 8 hours of fasting and is both easy to administer and cost effective, making it the preferred screening test recommended by the ADA. However, it is often difficult to ask a child to fast for 8 hours so HbA1c tests are often used as well both for screening and long-term monitoring. Properties of HbA1c make it the ideal blood test for long-term assessments of glycemic control. HbA1c is formed through the glycosylation of hemoglobin exposed to plasma glucose, and its rate of binding is proportional to the level of circulating blood glucose concentrations. This detail allows HbA1c to serve as a meaningful proxy for average blood glucose levels over prolonged periods, especially over the last 3 months, of time (2).

1.5.3 Therapeutic options for pediatrics and young adults

Insulin and metformin are currently the only drugs approved by the FDA to control T2DM in children and adolescents. Under rare circumstances where the child is extremely sick at diagnosis with signs of DKA, treatment guidelines recommend initiation of insulin therapy until symptoms subside. Metformin is added to the regimen while insulin dose is gradually reduced and eventually stopped. Most of the willingness to use insulin in the treatment of T2DM in youth stems from the familiarity of pediatricians in using these drugs in this population. Based on large survey data from 130 pediatric endocrinology practices, between 23% to 44% of children and adolescents with T2DM in the United States and Canada are being treated by insulin mono-therapy (46).

Metformin was approved in December 2000 for use in pediatric patients 10 years of age and older with T2DM. The drug is part of the biguanide family, one of five families of oral antidiabetic (OAD) agents on the market today in the United States (Figure 2), and acts by decreasing insulin secretion in hepatic tissues and increasing insulin sensitivity in peripheral tissues (47). Metformin has also demonstrated itself effective in other areas of the metabolic syndrome including lowering of circulating free fatty acid concentrations, decreasing plasma triglycerides and LDL levels, and increasing HDL levels (47). Its mechanism of action includes the activation of adenosine monophosphate (AMP) –activated protein kinase pathway (AMPK), which results in decreased production of glucose and increased fatty acid oxidation in liver and skeletal muscles (28).

One of the first and largest pediatric clinical trials of metformin was conducted on 82 subjects aged 10-16 years for up to 16 weeks of follow-up. At the end of 16 weeks, placebo recipients had increased their mean FPG by 20mg/dl while metformin users had decreased their mean FPG by 44mg/dl, with average HbA1c levels of 8.6% vs. 7.5%, respectively (48). Common adverse effects are gastrointestinal related and include abdominal discomfort, upset stomach, nausea, indigestion, heartburn, and/or diarrhea. Effects are usually mild to moderate and can be reduced with slow titration. Metformin is available in 500-, 850-, and 1000- mg tablets and offers three forms on the market today – metformin immediate release (taken 2x daily), extended release (taken 1x daily), and Riomet (metformin oral solution taken 2x daily) (47). Guidelines recommend pediatricians start monotherapy at 500 mg daily with increases every 1 to 2 weeks, up to the ideal dosage or maximum dosage of 2000 mg daily, with the option of adding on sulfonylurea or insulin after 3-6 months of unsuccessful glucose control. Though guidelines recommend metformin as the OAD of choice, surveys

and studies of large pharmacy databases have revealed that up to 30% of youth treated with an OAD were treated with other OADs, including sulfonylureas, thiazolidinediones, and meglitinide (49-51).

Aside from its use in T2DM treatment, metformin has also been studied adjunctively with insulin in adolescents with T1DM (52, 53). Based on two placebo-controlled RCTs with small sample sizes (n<27) and 3-months of follow-up, metformin combined with insulin yielded improved glycemic control in some patients. The evaluation of long-term benefits and safety of adjunctive therapy in T1DM patients is warranted before endocrinologists begin utilizing this treatment option.

1.6 Clinical and public health relevancy of proposed study

The diagnosis and treatment of T2DM in children and adolescents has advanced in recent years in response to the rapid growth of T2DM in this population; however, the literature has not kept up with this ever-evolving field.

1.6.1 Trends and predictors of treatment initiation

Trends in oral anti-diabetic (OAD) initiation and utilization in youth have changed as a reflection of the growing number of T2DM cases in this population as well as advancements in treatment practices and guidelines. Understanding the patterns in prescription rates and recognizing who is being treated will help form the basis of pharmacoepidemiologic research conducted in this field. Two studies were identified that examined the prevalence in usage of OADs amongst children and adolescents in the United States. Cox et al. and Liberman et al. used prescription claims data from commercially insured individuals aged 5-19 and 6-18, respectively, to assess patterns over a 4-year period (2002-2005 and 2004-2007, respectively). Conclusions drawn from both studies were

consistent and illustrated an approximate doubling in overall prevalence, peaking at 0.6 (54) and 0.5 per 1,000 child (51), respectively, at the end of each corresponding study period.

The proposed research will improve upon the current state of knowledge by (1) increasing the study window to ten years (2001-2011) to provide an accurate and up-to-date depiction by year, (2) assessing incidence of OAD prescriptions, (3) performing time trend analyses, (4) setting more rigorous exclusion criteria to ensure all results are specific to the T2DM population, and (5) examining additional factors that could influence prescribing habits. Incidence estimates will provide useful data on the number of new users of OADs per year. Statistical time trend analyses are missing in the current literature but are valuable in that they demonstrate the extent for which the perceived changes in trends are based on chance alone. Also absent in the literature are assessments for variables that potentially influence prescribing patterns. Phan et al. utilized National Ambulatory Medical Care Survey (NAMCS) data from the years 1996-2005 to describe physician specialty, insurance type, and demographic factors in T2DM adolescent patients visiting outpatient clinics. Their study did not attempt to differentiate between treated and untreated T2DM individuals, making it difficult to evaluate prescribing paradigms. Cox and Liberman et al. reported sub-group specific rates for gender and age whose combined data spanned the years 2002-2007, but failed to examine other meaningful variables. Our study will consider additional factors including comorbidities, common diagnoses codes, concomitant medication use, characteristics of treating physicians, and ordered laboratory tests in the months leading up to treatment initiation. This will provide a more complete representation of who is being treated and aspects affecting treatment modalities.

1.6.2 Persistence, discontinuation, and re-initiation of therapeutics

Medical adherence (i.e. compliance) is defined as the extent for which a patient follows the therapeutic regimen (medication or lifestyle modifications) prescribed by his or her health care provider. Another term related to medication use is persistence, which is defined as the duration of time from drug initiation to discontinuation of therapy, allowing for a permissible gap between refills. Consequences of nonadherence can manifest in a multitude of ways and affect the health of an individual and communities (55). Adherence to OADs has been extensively investigated in adults. A recent meta-analysis of such studies determined that 58% of adult patients taking an OAD had a 12-month medication possession ratio (MPR) > 80% (56). Pediatric literature on compliance is scarce and usually based on small samples of patients (n<100) but results consistently indicate low adherence in this group. Prospective studies and clinical trials persistently suffer from high attrition rates (~20-60%) and poor glycemic control amongst those who remained in the study (57, 58), indicating how difficult it is to implement medication in this population. The lack of appreciation for the long-term implications of ineffective management of T2DM, socioeconomic factors, and treatment complications have been linked to non-adherence amongst all age groups (56). Other factors unique to adolescents such as hormonal changes complicating glycemic management and mental and emotional challenges faced by pediatrics transitioning into early adulthood have also been shown to influence compliance in this population (59).

Self-reported adherence data from small, single-center studies have demonstrated adherence to be the strongest predictor of glycemic control and HbA1c levels in youth independent of clinical characteristics such as age, BMI, and baseline HbA1c levels (60, 61). Therefore, adherence and factors affecting adherence need to be understood in order to

adequately manage glycemic levels and delay and/or avoid diabetes complications in this population. Only one study was identified which examined adherence and persistence to OADs in pediatrics. The study population was drawn from Texas Medicaid data and mean Medication Possession Ratio (MPR) was used as a proxy for adherence (62). They concluded after one-year follow-up that adherence and persistence was suboptimal (MPR mean, SD: 45%, 27%) and differed by gender, race, and age, and acknowledged lack of generalizability to be a major limitation given the fact that Texas Medicaid is comprised predominately of minority races and those of low socioeconomic status (SES). Similarly, in the treated adult T2DM population, low persistence is notably common with rates fluctuating between 36 and 79% (63, 64). However, studies in adult populations have demonstrated high reinitiation rates of OADs, which emphasizes the dynamic use of OADs in populations (64, 65). To our knowledge, the rates of reinitiation and factors predicting such occurrences have yet to be explored.

The proposed research will focus on enhancing the understanding of persistence and factors prompting patients to reinitiate therapy in a population of pediatric T2DM patients. It will examine a more diverse population than the Texas Medicaid study and include an extensive list of potential predictors of persistence - demographic characteristics, healthcare utilization variables, and concomitant medications. These medications include a combination of drugs targeting metabolic syndrome (antihypertensives, statins, fibric acid derivations) and drugs that are linked with obesity and T2DM onset (antipsychotics, antidepressants) (66, 67).

Furthermore, we will examine the rate of discontinuation and modifiable factors associated with patients re-initiating therapy. Results from this comprehensive investigation

on discontinuation and re-initiation will potentially serve as a reference for treatment decisions and practices by physicians as well as fill a significant void in pediatric quality improvement treatment literature.

CHAPTER 2: STATEMENT OF SPECIFIC AIMS

*2.1 Aim 1***:** *To describe time trends and identify predictors of treatment initiation for youth treated for T2DM.* We will examine overall incidence of treatment of T2DM and incidence stratified by drug class, physician specialty, age group, geographic region, and gender.

Hypothesis*:* We anticipate increasing use of oral antidiabetics over time and increasing use among primary care pediatricians.

Rationale*:* Previous studies have assessed period prevalence but none have studied the rates of new users, or characteristics of these new users. It is important for clinicians and researchers to understand the characteristics of patients who are starting treatment and how that has changed over time in order to better treat this patient population.

*2.2 Aim 2***:** *To describe rates of oral antidiabetic medication persistence using prescription refill data, overall and compared within clinically relevant subgroups. Furthermore, to assess rates of re-initiation among patients with extended periods of non-adherence and to determine factors predicting re-initiation.*

Hypothesis*:* Overall persistence will be low with levels depending on patient characteristics and drug class. Rates of re-initiation will be moderate with increased follow-up being a strong predictor of restarting therapy.

Rationale*:* Identifying the factors predicting treatment initiation can potentially help to decrease the frequency or gaps in treatment for these patients. This information is critical in the overall management strategy of T2DM in the pediatric population.

CHAPTER 3: METHODS

3.1 Study 1 methods: trends and determinants of oral anti-diabetic initiation in youth with suspected type 2 diabetes

3.1.1 Data source

Using the Marketscan™ Research Database, we studied a population of youth enrolled in an employer-provided private insurance plan between the years 2001 to 2012. Marketscan is comprised of a large and diverse sample of the U.S. commercially insured population and contains comprehensive individual-level records on patient demographics, enrollment information, inpatient, outpatient, and prescription drug claims (68). In 2012, the database included approximately 5.5 million youth aged 6-17, equivalent to 10% of the overall population and 20% of the commercially insured population in the US for that age group (69, 70).

3.1.2 Patient population

Patients aged 8-18 years newly initiated on a therapy from any class of OADs (metformin, sulfonylureas, thiazolidinediones, alpha-glucosidase, meglitinide analogs, glucagon-like peptide-1 agonist, and dipeptidyl peptidase-4 inhibitors) during the index period of January 2002-Decemeber 2012 were identified. Patients on insulin only without evidence of OADs were excluded. "New users" were defined based on the following criterion: (1) patients had ≥12-months of continuous enrollment prior to their oral drug fill date and (2) patients without an OAD medication in the 12-months prior to their drug fill date, hereon referred to as their "index drug" date. Youth likely to have any of the following diagnoses, as indicated by ICD-9 codes associated with inpatient or outpatient claims, were

excluded from the study population: type 1 diabetes (ICD-9: 250.x1, 250.x3), gestational diabetes (ICD-9: 648.8), and females with polycystic ovarian syndrome (PCOS) (ICD-9: 256.4. Furthermore, females with diagnosis codes for symptoms of PCOS including hirsutism (ICD-9: 704.1) and ovarian cysts (ICD-9 620.0 and 620.2) were also excluded.

3.1.3 Predictors of treatment initiation

Potential predictors of treatment initiation were determined at baseline and included age (age groups: 8-10, 11-14, and 15-18), gender, the U.S geographic region (Northeast, North Central, South, and West) that the patient resided in, and physician specialty (family practice, pediatrician, both, and other). The defined age categories considered that young children are off-label users, and early teen versus late-teen initiation rates may vary as T2DM disproportionately affects late-teens, e.g. 15-19 year olds (71). Physician specialty was categorized based on those who had at least one visit to a pediatrician, family practitioner (FP), both a pediatrician and FP, and specialties other than pediatrician and FP in the three-months prior to their index date. Analyses utilizing a six-month physician visit window were also performed to evaluate the impact of the pre-defined window on study results. All other predictors were pre-categorized in the Marketscan database.

3.1.4 Statistical analysis

Treatment incidence among children and adolescents initiating OAD therapy was estimated monthly from January 1, 2002 through December 31, 2012. Rates for each month of the study period were calculated by dividing the number of eligible patients with an index date falling in that month by the total number of youth who would have been in the numerator had they filled their index prescription in that month, i.e. age-eligible persons continuously enrolled in the 12-months prior who did not satisfy any exclusion criteria. Initiators were omitted from the denominator in the subsequent months after their index date.

Descriptive analyses included mean monthly frequencies for baseline characteristics, reported separately for the general denominator and the new user populations, and mean monthly incidences. Mean monthly incidences and 95% CIs were calculated per 100,000 youth per month and were reported for the entire population as well as by explanatory variables. In order to evaluate the strength of *a priori* identified predictors, mean monthly relative risks (RR) and 95% CIs were calculated and assessed over calendar time. Trends in prescription rates, smoothed using local polynomial regression (72), were graphed along with 95% confidence intervals (CIs) monthly for the overall population as well as for each predictor subgroup. The graph by physician specialty included plots for the subgroups of patients who only visited either a pediatrician or FP in the 3-months prior to their index date. All analyses reported monthly means for the calendar periods of 2002-2012, 2002-2003, 2004-2005, 2006-2007, 2008-2009, and 2010-2012.

3.2 Study 2 methods: persistence and re-initiation following discontinuation of oral anti-diabetic agents in children and adolescents

3.2.1 Data source

We identified a population of patients who were enrolled in Truven Marketscan Research Database between the years 2001-2012. Marketscan is an administrative claims database that includes beneficiaries enrolled in employer-sponsored health care plans and contains individual-level records on patient demographics, enrollment information, as well as inpatient, outpatient, and prescription drug claims (68). In 2012, the database included approximately 5.5 million youth aged 6-17, equivalent to 10% of the overall population and 20% of the commercially insured population in the U.S. for that age group (69, 70).

3.2.2 Study population

Patients included in the present study were aged 8-18 years who were newly initiated on a therapy from any class of OADs (metformin, sulfonylureas, thiazolidinediones, alpha-glucosidase inhibitors, meglitinide analogs, and dipeptidyl peptidase-4 inhibitors) during the period of January 2002-Decemeber 2012. New users were identified based on the following criterion: (1) patients had ≥12-months of continuous enrollment prior to their OAD drug fill date, hereon referred to as their "index drug" date and (2) patients without an OAD medication in the 12-months prior to their index drug date. Youth with any of the following diagnoses at baseline, as indicated by *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9)* codes associated with inpatient or outpatient claims, were excluded from the study population: type 1 diabetes (ICD-9: 250.x1, 250.x3), gestational diabetes (ICD-9: 648.8), and females with polycystic ovarian syndrome (PCOS) (ICD-9: 256.4. Furthermore, females with diagnosis codes for symptoms of PCOS including hirsutism (ICD-9: 704.1) and ovarian cysts (ICD-9 620.0 and 620.2) were also excluded.

3.2.3 Outcome assessment

From the database, we created a drug coverage file for all identified new users by linking their filled OAD prescriptions from their index date to their last fill date or the end of their enrollment period or December 2012 (administrative end to follow-up), whichever came first. Using the dispensing dates and days' supply corresponding with each prescription, we attempted to identify periods of continuous use and discontinuation.

Persistence was defined as the length of time between the dates of treatment initiation to when the last filled prescription would have been depleted, after accounting for a 90-day permissible gap. Patients who switched from their index drug class to another drug class within a 90-day permissible gap were considered persistent. Patients who had a period of 90

days or more without any filled OAD prescriptions after stopping therapy were considered discontinuators. In other words, patients were considered persistent until they had a discontinuation event. Reinitiation was defined as filling at least one prescription for any OAD following a period of discontinuation.

3.2.4 Predictors of persistence and reinitiation

Potential predictors of persistence were determined at study baseline and included age (age groups: 8-12, 13-15, and 16-18), gender, copayment costs of the index OAD agent ($0, $1-5, $6-10, $11-15, and >$15), and the specialty of the treating physician (family practice and pediatrician). The pre-defined age categories considered that younger children and adolescent persistence may be influenced by very different factors as younger children are generally affected by parental motivation (73) while adolescents' persistence is influenced more by their experienced mental and emotional challenges (59). Copay categories were established *a priori* but were confirmed after assessing the quintiles of the copay variable from the data. Physician specialty was assessed among those who had at least one visit to a pediatrician, a family practitioner (FP), both specialties, or other specialties in the three-months prior to their index date.

We focused on modifiable factors to assess as potential predictors of reinitiation after a period of discontinuation. This included the following procedures specified by *Current Procedural Terminology (CPT)* codes: outpatient medical encounters (CPT: 99201-99205, 99211-99215), LDL tests (CPT: 80061, 83700, 83701, 83704 83721), and HbA1c and related glucose monitoring tests (CPT: 83036, 83037, 82962, 82948, 82950, 82947). In addition, the following T2DM complications regarded as clinical manifestations of disease progression were also considered: hypertension (ICD-9: 401.9), hyperlipidemia (ICD-9: 272.4), acanthosis nigricans (ICD-9: 701.2), polyuria/nocturia (ICD-9: 788.42, 788.43), polydipsia

(ICD-9: 783.5), and hyperosmolar hyperglycemic state (ICD-9: 250.2). Dual occurrences of T2DM complications and medical encounters, LDL testing and medical encounters, and HbA1c testing and medical encounters were considered as well.

3.2.5 Statistical analysis

Descriptive and univariate analyses of baseline characteristics for incident OAD users were summarized. Three binary variables were created to flag the frequency of patients who were non-persistent at (1) 30-days, (2) 180-days, and (3) 360-days, allowing for a 90-day gap, and were assessed based on cumulative risks for the overall cohort and by the aforementioned predictors of persistence. Additional sensitivity analyses were conducted using different permissible gaps including a 30-day and 60-day gap. Cox proportional hazards regression models were used to approximate unadjusted hazard ratios (HR) of discontinuation by day 360 for potential predictors.

Patients who discontinued for 90 days or more and subsequently reinitiated therapy were identified. We performed a case-crossover analysis on identified reinitiators by comparing the frequencies of events in the 30-days immediately preceding OAD reinitiation (hazard period) with the 30-days immediately preceding the hazard period (control period). In a case-crossover analysis, a patient's own past history serves as their "control" allowing for within subject comparisons, which provides effective control of confounding by measured and unmeasured patient characteristics that are constant over time (74). Unadjusted conditional logistic regression models stratified on each patient was used to estimate odds ratios (ORs) for reinitiation by relevant potential predictors. A sensitivity analysis was conducted and involved the same approach but shortened the hazard and control periods to 15 days each.

CHAPTER 4: RESULTS

4.1 Study 1 results: trends and determinants of oral anti-diabetic initiation in youth with suspected type 2 diabetes

The average monthly population size increased 6-fold over the course of the study period (Table 1) as the Marketscan Research Database increased in size over that time from 700,000 to over 4 million individuals, with a median population size of 2.2 million. Frequency distributions in age, sex, and geographic region remained consistent in the population sample throughout the study period, while minor variations in physician specialty encounters were recorded, signifying a small increase in primary care utilization by this population (Table 1).

A total of 13,824 new users of any OAD prescriptions were identified between 2002 and 2012 (Table 2). Baseline characteristics of OAD initiators fluctuated slightly over the years as the percentage of females, 8-10 year olds, and patients from southern region increased by 4.7%, 13.7%, and 13.8%, respectively, from 2002-2003 to 2010-2012. Notable decreases were seen in the 15-18 year olds (6.1%) and patients from the Northeastern (15.1%) and Western (19.6%) regions. Metformin was the most commonly initiated OAD drug class overall (88.6%) and showed a 21.2% increase in usage from 2002-2003 to 2010-2012. Usage of all other drug classes went down from 21.1% to 4.4% by the end of the study period. The proportion of new users who visited a pediatrician or FP in the 3-months prior to index date from 2002-2003 to 2010-2012 increased from 19.2 to 25.4% or 20.5 to 24.1%, respectively.

The overall monthly incidence in the population was 4.6 (95% CI=3.6, 5.5) per 100,000 youths (Table 3). Patients who initiated treatment were more likely to be females (RR=2.57; 95% CI=1.59, 4.39), age 15 to 18 (8-10 years, RR=4.74; 95% CI=2.04, 13.60; 11-14 years, RR =1.69; 95% CI=1.03, 2.90), and residents of the southern region (Northeast, RR=1.91; 95% CI=0.77, 6.02); North Central, RR=1.22; 95% CI=0.70, 2.31; West, RR=1.72; 95% CI=0.88, 3.85). They were also twice as likely to have visited a family practitioner, compared to a general pediatrician, in the 3-months prior to OAD initiation (RR=2.00; 95% CI=1.02, 5.02).

4.1.1 Trends in incidence of use

The temporal trends in overall and subgroup specific monthly incidence rates are presented in Table 3 and visually depicted in figures 1-4. Fig. 1 illustrates an increase in overall incidence between years 2002 (3.0 per 100,000 youth) to early 2008 (5.3 per 100,000), before gradually declining during the remainder of the study period (4.3 per 100,000 in 2012), suggesting a corresponding 43% increase in new users over the course of 11 years. This pattern was also reflected consistently in all age group specific trends (Fig. 2) and to a lesser extent, the regional trends. Gender-specific initiation rates over time illustrated differences in temporal trends between male and female patients (Fig. 3). Female incidence increased by 45% between 2002 to early 2008 before experiencing a 12% decrease for the remainder of the study period. Overall, the female population underwent a 62% increase in usage over 11-years. The male population experienced their peak in incidence 2-years earlier than females in 2006 where rates increased by 67% from 2002. Their overall increase during the study period was 28%, demonstrating a lesser increase compared to their female counterparts. At all timepoints, individuals with visits to a FP physician were approximately twice as likely to initiate OAD as compared to individuals with visits to a

general pediatrician (Fig. 4). Individual trends show an 89% increase in FP prescriptions from 2002 to mid-2009 and then dropping by 11% during the remainder of the study. Pediatrician trends suggest a 95% increase in prescriptions from 2002 to early 2007, before experiencing a 14% drop over the course of the remaining 5-years of the study period. Overall, FPs and pediatricians experienced similar percent increases in prescriptions over the duration of the study, 67% and 68%, respectively.

4.1.2 Tables and figures

Table 3. Beneficiary Baseline Characteristics by Study Period

Characteristic	Study Period				
	2002-2003	2004-2005	2006-2007	2008-2009	2010-2012
Mean population size per month N (SD)	783 890 (225 623)	1 704 762 (286 599)	1 975 504 (200 922)	2 661 589 (530 239)	3 393 037 (464 836)
Age (%)					
8-10	23.5	24.1	24.2	24.8	24.9
11-14	36.5	36.3	35.8	35.7	36.1
15-18	40.0	39.6	40.0	39.5	38.9
Gender (%)					
Female	48.7	48.7	48.8	48.8	48.8
Region (%)					
NE	13.2	9.3	11.1	10.1	13.9
NC	28.6	24.0	27.3	26.9	26.4
South	38.3	37.9	41.9	43.6	39.8
West	20.0	28.7	19.7	19.4	19.9
Physician Specialty[a] (%)					
Family practice	8.4	9.5	10.2	10.2	8.7
Pediatrician	13.3	14.5	16.8	18.1	18.6
Both	0.5	0.6	0.7	0.8	0.8
Other	77.9	75.4	72.3	70.9	71.9

SD, Standard deviation; NE, Northeast; NC, North Central

[a] Mean monthly percentage of population with medical encounters in the 3-months prior

Table 4. Baseline Characteristics of New Users of Oral Anti-Diabetic Agents by Study Period

Characteristic	Study Period				
	2002-2003 (n=616)	2004-2005 (n=1784)	2006-2007 (n=2429)	2008-2009 (n=3246)	2010-2012 (n=5749)
Age (%)					
8-10	7.3	8.5	10.2	8.9	8.3
11-14	30.7	32.2	32.8	33.6	33.5
15-18	62.0	59.4	57.0	57.6	58.2
Gender (%)					
Female	68.5	67.5	70.0	70.6	71.7
Region (%)					
NE	13.9	7.3	7.3	6.4	11.8
NC	26.4	25.4	27.7	29.3	26.9
South	39.8	45.2	51.7	49.8	45.3
West	19.9	22.0	13.3	14.4	16.0
Index Drug Type (%)					
Metformin	78.9	84.9	89.4	94.5	95.6
Sulfonylurea	6.0	5.8	3.5	1.9	1.5
TZD	8.9	4.5	3.5	1.2	0.6
Other Classes[a]	1.8	1.6	2.3	1.2	1.8
Metformin + Sulfonylurea	3.6	1.4	0.7	0.6	0.3
Metformin+ TZD	0.8	1.8	0.5	0.5	0.2
Physician Specialty[b]					
Family Practice	20.5	24.2	25.4	26.1	24.1
Pediatrician	19.2	21.8	24.7	24.3	25.4
Both	4.3	3.6	2.5	3.2	2.8
Other	54.7	51.3	47.6	46.7	47.8

NE, Northeast; NC, North Central; TZD, Thiazolidinediones

[a] Includes alpha-glucosidase, meglitinide analogs, glucagon-like peptide-1 agonist, and dipeptidyl peptidase-4 inhibitors

[b] Based on medical encounters in the 3-months prior to index drug date

Table 5. Monthly Mean Incidence (95% CI) Per 100 000 Commercially Insured Children: Overall and by Predictor Subgroups

Characteristic	Study Period					
	2002-2012	2002-2003	2004-2005	2006-2007	2008-2009	2010-2012
Overall	4.6 (3.6, 5.5)	3.3 (2.0, 4.6)	4.4 (3.4, 5.4)	5.1 (4.1, 6.1)	5.1 (4.2, 6.0)	4.8 (4.0, 5.5)
Age						
8-10	1.4 (0.4, 2.3)	1.1 (-0.4, 2.5)	1.3 (0.3, 2.2)	1.8 (0.7, 2.8)	1.4 (0.6, 2.1)	1.3 (0.6, 2.0)
11-14	3.4 (2.1, 4.6)	2.5 (0.7, 4.3)	3.2 (1.9, 4.5)	3.8 (2.5, 5.0)	3.6 (2.5, 4.6)	3.6 (2.6, 4.5)
15-18	5.5 (3.9, 7.0)	4.5 (2.3, 6.8)	5.5 (3.8, 7.1)	5.9 (4.4, 7.4)	5.6 (4.3, 6.9)	5.7 (4.5, 6.9)
Gender						
Female	6.5 (4.9, 8.2)	4.7 (2.4, 6.9)	6.1 (4.4, 7.8)	7.4 (5.6, 9.1)	7.4 (5.9, 8.9)	7.0 (5.7, 8.3)
Male	2.7 (1.6, 3.7)	2.0 (0.6, 3.5)	2.7 (1.6, 3.8)	3.0 (1.9, 4.1)	2.9 (2.0, 3.8)	2.7 (1.9, 3.4)
Region						
NE	3.4 (1.0, 5.8)	2.6 (-0.05, 5.8)	3.5 (0.5, 6.4)	3.4 (1.0, 5.8)	3.3 (1.1, 5.4)	4.0 (2.2, 5.8)
NC	4.7 (2.8, 6.6)	3.3 (0.9, 5.7)	4.6 (2.5, 6.7)	5.4 (3.3, 7.2)	5.6 (3.8, 7.4)	4.9 (3.4, 6.3)
South	5.5 (3.8, 7.1)	4.1 (1.8, 6.5)	5.3 (3.5, 7.1)	6.4 (4.7, 8.2)	5.9 (4.5, 7.3)	5.5 (4.2, 6.8)
West	3.6 (1.7, 5.5)	3.1 (0.1, 6.2)	3.3 (1.7, 5.0)	3.5 (1.6, 5.3)	3.8 (2.1, 5.5)	3.9 (2.4, 5.4)
Physician Specialty[a, b]						
Family Practice	11.9 (6.8, 17.0)	8.2 (1.2, 15.1)	11.4 (6.1, 16.6)	12.8 ‘ (7.8, 17.7)	13.3 (8.9, 17.7)	13.2 (9.1, 17.4)
Pediatrician	6.5 (3.6, 9.3)	4.7 (0.5, 8.9)	6.6 (3.3, 9.8)	7.6 (4.6, 10.5)	6.8 (4.5, 9.2)	6.5 (4.5, 8.5)
Both	2.0 (-0.3, 4.2)	3.0 (-2.1, 8.1)	2.4 (-0.4, 5.3)	1.8 (-0.4, 4.0)	2.0 (0.1, 3.8)	1.6 (0.2, 3.0)

CI, Confidence Interval; NE, Northeastern; NC, North Central

[a] Based on medical encounters in the 3-months prior to index drug date

[b] Patients who visited “other” specialties were omitted from table

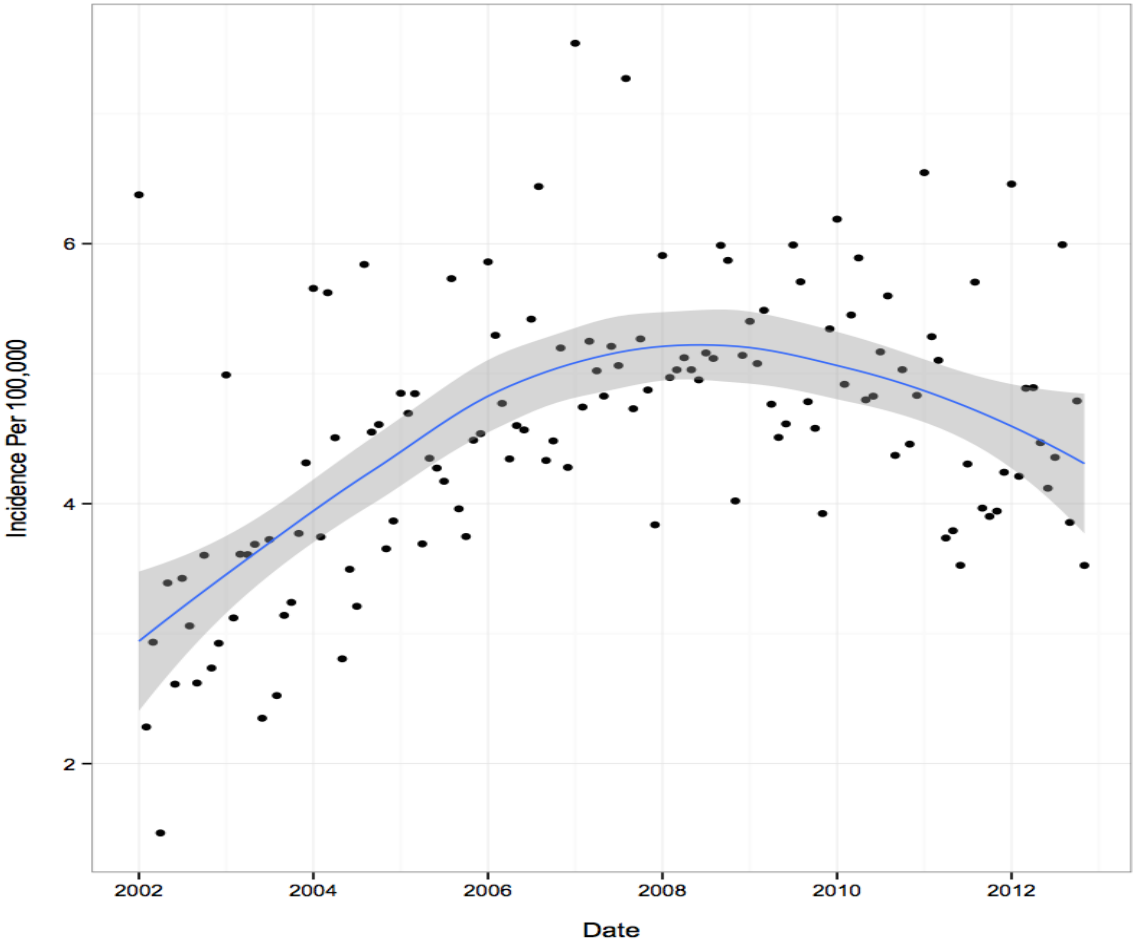

Figure 2. Overall Population Trends: Incidence Trends per 100 000 Youth

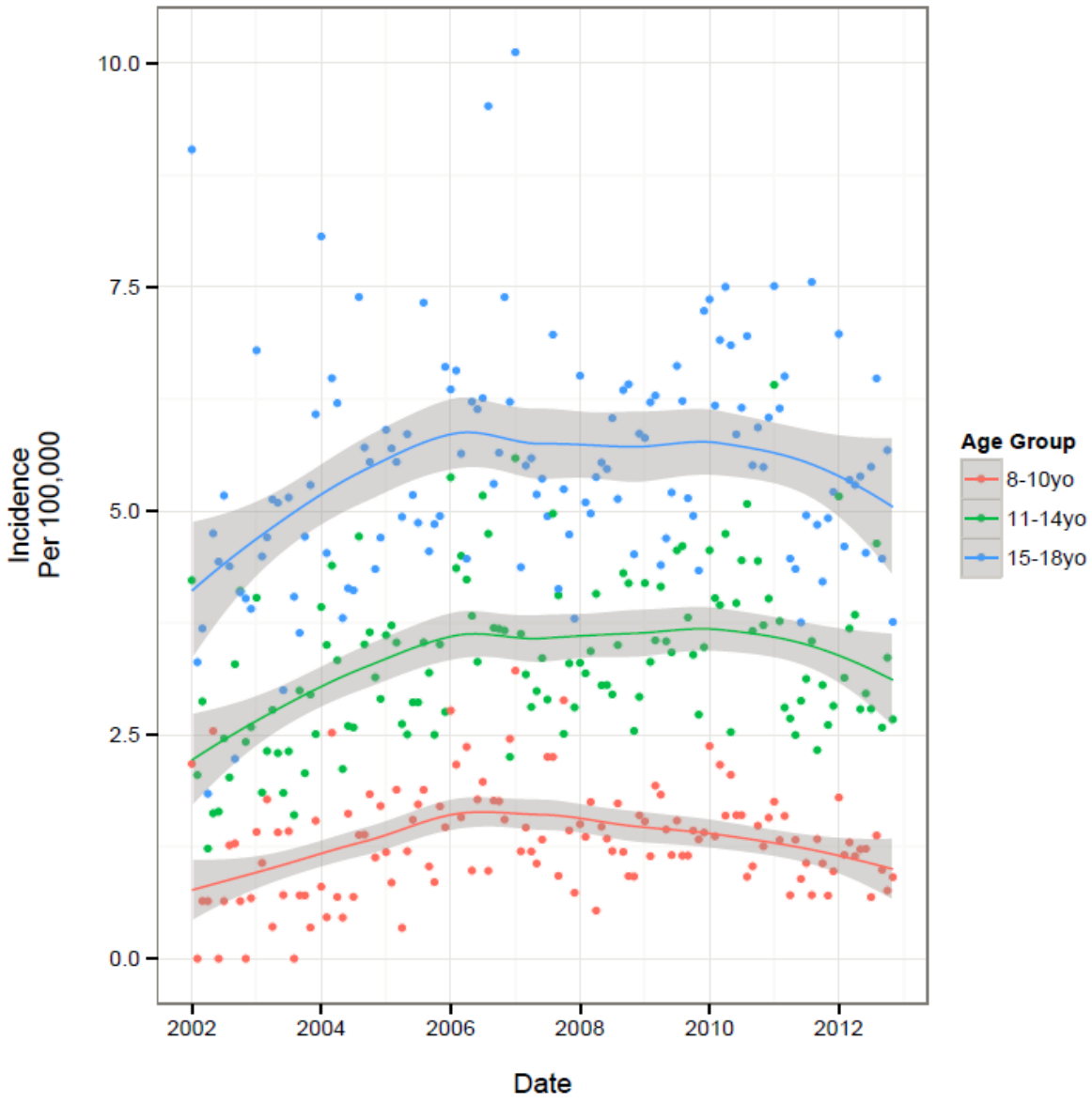

Figure 3. Population Trends by Predictor of Initiation- Age Group Specific Trends: Incidence per 100 000 Youth

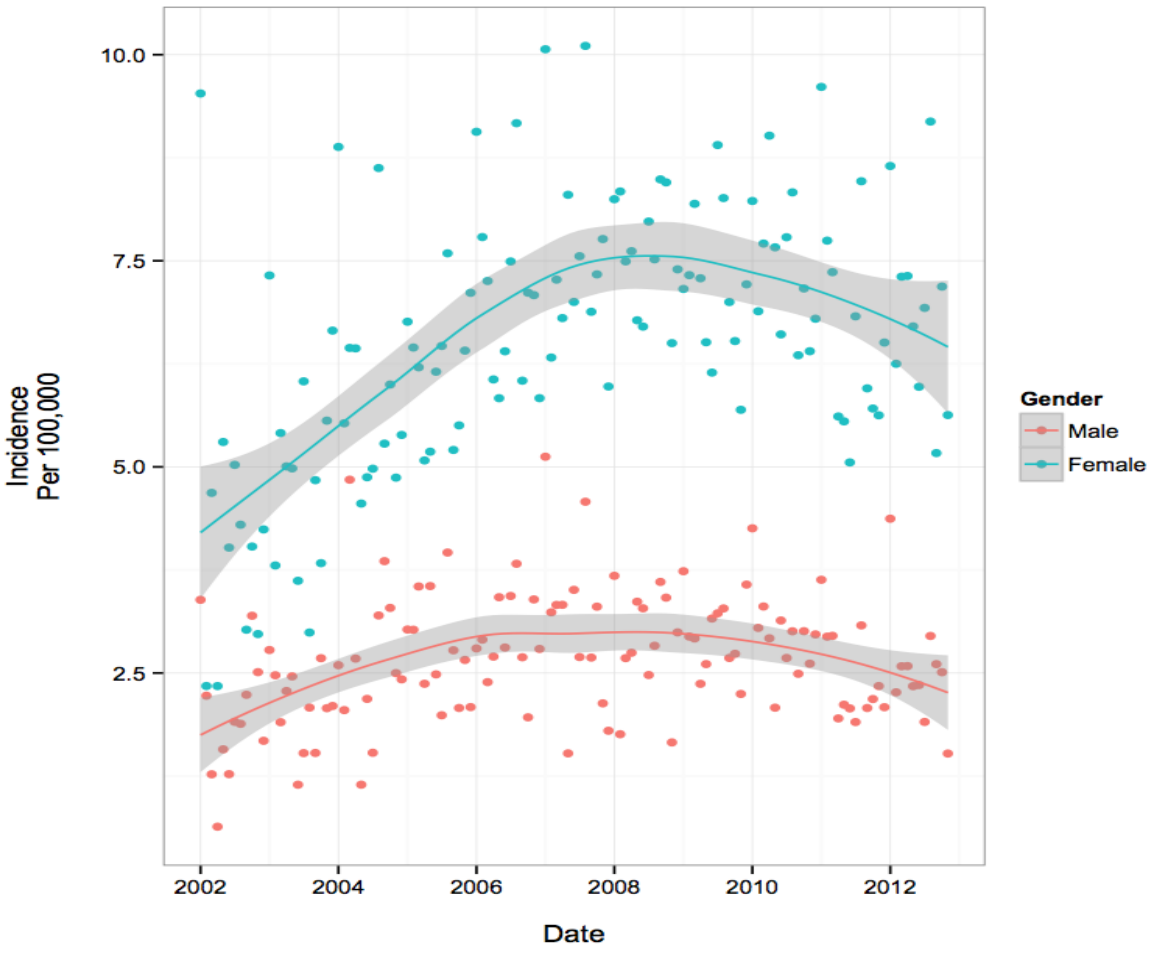

Figure 4. Population Trends by Predictor of Initiation- Gender Specific Trends: Incidence per 100 000 Youth

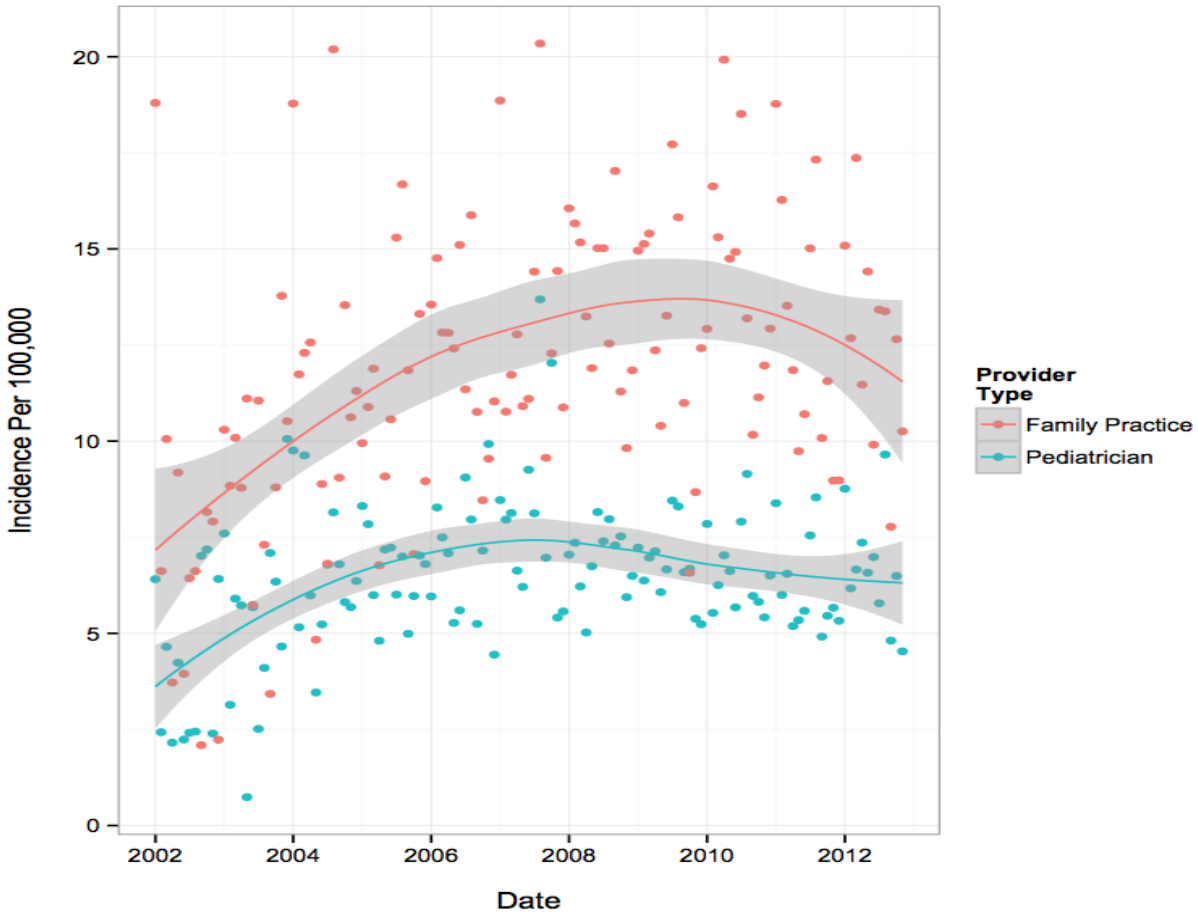

Figure 5. Population Trends by Predictor of Initiation- Physician Specialty Trends: Incidence per 100 000 Youth

4.2 Study 2 results: persistence and re-initiation following discontinuation of oral anti-diabetic agents in children and adolescents

A total of 15,270 new users of OADs between the ages of 8 to 18 were identified between 2002 and 2012. Most of the identified users initiated treatment during the years of 2010 to 2012 (43.7%), were females (72.9%), aged 16-18 (47.1%), and from the southern region (47.5%) (Table 1). In terms of the index drug, off-label use was low as most patients were initiated on metformin (92.4%) and 86.4% of the corresponding copay for the index drug was $10 or less.

The overall mean (standard deviation (STD)) and median (interquartile range (IQR)) days to non-persistence in this population were 190.2 days (256.0 days) and 96 days (199 days), respectively. Cumulative risks of non-persistence demonstrate a rapid drop in persistence, falling to 65.1% (95% CI: 64.3, 65.9%) by 180 days and 83.3% (95% CI: 82.7, 84.0%) by 360 days (table 2). Sensitivity analyses allowing for 30-day and 60-day permissible gaps showed slightly higher risk of non-persistence, although conclusions were comparable between the all analyses. Patients in the oldest age category, 16-18 years, had a higher hazard of discontinuing therapy compared to patients 13-15 and 8-12 (HR=0.88, 95% CI: 0.85, 0.91; HR=0.89, 95% CI: 0.85, 0.93, respectively). Youth treated by pediatricians had a slightly lower hazard of being non-persistent compared with those treated by family practitioners, HR=0.87 (95% CI: 0.82, 0.91). Patients who had an index drug copay over $15 were more persistent compared to patients who did not have a copay on their index drug (HR=0.89, 95% CI: 0.83, 0.95). All other sub-group analyses did not demonstrate any meaningful differences in hazard ratios (Table 2).

Among the identified new OAD users, 10,832 had a period of 90 days or more without drug coverage and 3,404 (31.4%) of these patients subsequently restarted therapy. A

total of 1,897 (55.7%) and 2,844 (83.5%) of reinitiators restarted within six months and one year, respectively, of discontinuation date. The median number of days (IQR) to reinitiation from discontinuation was 164 days (163 days) with a range of 90 to 2,256 days. Among those who reinitiated therapy, switching rates were low as roughly 95% of patients returned to using the same OAD class as their last drug prior to discontinuation. Metformin users who switched tended to move to sulfonylureas (24%) and thiazolidinedione (26%). Non-metformin users who switched tended to move to metformin (100% sulfonylurea switchers reinitiated on metformin).

All events examined were more frequent in the hazard period compared to the control period. More than half of the patients (50.4%) who restarted OAD therapy had at least one outpatient encounter in the hazard period, compared to 27.2% in the control period. Similarly, 16.3% and 4.6% had an HbA1c and related test in the hazard and control periods, respectively (Appendix Table 1). All events studied were strongly associated with restarting OAD therapy (Table 3). The combination of having an A1c and related test with an outpatient medical encounter was the strongest predictor of reinitiation (OR=4.41; 95% CI: 3.55, 5.47). As a secondary analysis, we assessed the sensitivity of the control and hazard periods by decreasing each period to 15 days. The results were qualitatively similar; however, the effect estimates for A1c and LDL testing were attenuated and the estimates related to T2DM complications were intensified (Table 3). Results were largely similar in the sensitivity analysis when discontinuation was redefined as 180 days.

4.2.1 Tables

Table 6. Baseline Characteristics of New User Cohort

	Total Cohort
No. of Subjects	15270
Age (%)	
8-12	3221 (21.1)
13-15	4850 (31.8)
16-18	7199 (47.1)
Gender (%)	
Female	11132 (72.9)
Index Drug Type	
Metformin	14102 (92.4)
Sulfonylurea	401 (2.6)
TZD	308 (2.0)
Other Drug Classes[a]	459 (3.0)
Physician Specialty[b]	
Family Practice	3185 (20.9)
Pediatrician	3133 (20.5)
Both	373 (2.4)
Unknown	8579 (56.2)
Copay of Index Drug	
$0	3264 (22.4)
$1-5	5251 (36.0)
$6-10	4083 (28.0)
$11-15	713 (4.9)
>$15	1270 (8.7)
Region	
NE	1384 (9.1)
NC	4125 (27.0)
South	7253 (47.5)
West	2399 (15.7)
Index Drug Calendar Period	
2002-2005	2561 (16.8)
2006-2009	6044 (39.6)
2010-2012	6665 (43.7)

[a] Includes alpha-glucosidase, meglitinide analogs, dipeptidyl peptidase-4 inhibitors, and drug combinations
[b]Based on outpatient medical encounters in the 3-months prior to index drug date

Table 7. Cumulative Risk (30-Days, 180-Days, and 360-Days Non-Persistence) and Predictors of Discontinuation

	30-D Non-Persistence (%)	180-D Non-Persistence (%)	360-D Non-Persistence (%)	Hazard Ratio at Day 360 (95% CI)
Overall	28.5 (27.7, 29.2)	65.1 (64.3, 65.9)	83.3 (82.7, 84.0)	
Age Group				
8-12	43.9 (42.2, 45.7)	78.0 (76.6, 79.4)	85.5 (84.3, 86.7)	0.89 (0.85, 0.93)
13-15	43.1 (41.7, 44.5)	77.5 (76.3, 78.7)	83.9 (82.8, 84.9)	0.88 (0.85, 0.91)
16-18	45.7 (44.5, 46.8)	80.5 (79.6, 81.4)	86.8 (86.0, 87.6)	1.0
Gender				
Female	44.5 (43.6, 45.4)	79.2 (78.5, 80.0)	85.6 (84.9, 86.2)	1.04 (1.00, 1.08)
Male	44.5 (43.0, 46.0)	78.6 (77.3, 79.8)	85.6 (84.6, 86.8)	1.0
Physician Specialty				
Family Practitioner	46.6 (44.8, 48.3)	83.1 (81.8, 84.4)	89.8 (88.8, 90.9)	1.0
Pediatrician	43.1 (41.3, 44.8)	78.5 (77.0, 79.9)	87.0 (85.8, 88.2)	0.87 (0.82, 0.91)
Unknown	44.4 (43.4, 45.5)	77.8 (76.9, 78.7)	83.5 (82.7, 84.3)	-----
Copay				
$0	45.2 (43.4, 46.9)	86.9 (85.7, 88.1)	95.4 (94.7, 96.2)	1.0
$1-5	47.0 (45.6, 48.3)	85.1 (84.1, 86.1)	94.2 (93.5, 94.8)	0.98 (0.93, 1.02)
$6-10	49.7 (48.2, 51.3)	86.5 (85.5, 87.6)	94.7 (94.0, 95.4)	1.03 (0.98, 1.08)
$11-15	40.7 (37.0, 44.3)	84.3 (81.5, 87.1)	94.7 (93.0, 96.4)	0.92 (0.84, 1.00)
>$15	34.6 (32.0, 37.3)	85.6 (83.6, 87.6)	95.1 (93.8, 96.3)	0.89 (0.83, 0.95)

Table 8. Case-Crossover Results: Unadjusted Conditional Odds Ratios Predicting Reinitiation of Therapy

	15-Day Hazard and Control Periods*	30-Day Hazard and Control Periods**
Outpatient Medical Encounter	3.29 (2.91, 3.71)	2.88 (2.58, 3.22)
T2DM Complications[a]	3.08 (2.14, 4.44)	3.00 (2.16, 4.16)
LDL Test	2.58 (2.04, 3.26)	3.75 (2.98, 4.72)
HbA1c Test	3.19 (2.62, 3.88)	4.13 (3.41, 5.01)
Complications[a] + Med Enc	3.96 (2.60, 6.04)	3.22 (2.27, 4.57)
LDL + Med End	3.19 (2.37, 4.30)	4.36 (3.30, 5.76)
HbA1c + Med Enc	4.20 (3.29, 5.35)	4.41 (3.55, 5.47)

Enc, Encounter

*Sensitivity analysis; **Primary analysis

[a]T2DM-related complications include hypertension, hyperlididemia, acanthosis nigricans, polyuria, polydipsia, nocturia, and hyperosmolar hyperglycemic state

CHAPTER 5: DISCUSSION

5.1 Study 1 discussion: trends and determinants of oral anti-diabetic initiation in youth with suspected type 2 diabetes

The incidence of filled OAD prescriptions among children and adolescents increased substantially from 2002 to 2012, especially among females and individuals treated by FPs. Temporal trends demonstrate a decline in new prescriptions starting in 2008, counterbalancing the sharp increase in new prescriptions from 2002 to 2008. We estimated similar trends of increasing use followed by gradual declines in treatment initiation for all sub-group specific analyses. The off-label usage of all other OAD drug classes decreased in this population over time as nearly all patients were on metformin by 2008. Conversely, off-label prescriptions for children aged 8-10 increased during the study period.

To our knowledge very little has been published on the incidence of pharmacy dispensed OAD prescriptions in children and adolescents, which makes comparisons with other studies difficult. Two studies were identified that evaluated prevalence trends in OAD prescriptions amongst youth in the US over a period spanning from 2002 to 2007. Conclusions drawn from both studies were consistent and illustrated an approximate doubling in prevalence with the highest prevalence amongst females and adolescents (54)' (51). The results from our study are consistent with this earlier work, as we reported increasing incidence of use from 2002-2008, with the highest incidence observed in females and patients 15-18 year olds. However, we were unable to contrast our observed decrease in incidence between 2008 and 2012 with the prevalence trends during the same time frame because both aforementioned studies were completed by 2007. Our study significantly

extends this prior work by providing estimates for the number of new users of OAD therapies, which allowed us to examine factors influencing treatment initiation.

The trend in T2DM disease incidence and prevalence has been well documented by the SEARCH for Diabetes in Youth Research group (71, 75, 76). Based on their reports, the prevalence and incidence of T2DM has increased by 30.5% and 37.5%, respectively, between the years 2001 and 2009 with the most substantial subgroup increases seen in females, late-teens between 15-19 years of age, and racial minorities (71). The estimated increase in T2DM disease incidence is aligned with our findings on OAD incidence; however, we are unable to correlate our findings with theirs after the year 2009 where we observed a decrease in new OAD fills.

Obesity is the primary risk factor for T2DM, with over 50% of all obese adolescents having clinical markers for the condition (17). Therefore, the decreasing trend in new prescriptions beginning in 2008 reported by this study may be partially attributed to the fact that the prevalence of obesity has not increased in this population since 2007 (77). However, gender-specific trends are not consistent with obesity trends. Our study found that initiators were more likely to be females, whereas gender-specific obesity rates consistently show higher rates among males (77), making it unlikely that obesity is the only factor explaining the observed trends. It is well-documented in the literature that T2DM rates are consistently higher in females compared with males during adolescence (75, 78). However, one factor that may erroneously inflate the rate of female initiators is PCOS, which is a known risk factor for T2DM and is often treated with metformin. We therefore attempted to exclude all patients with a diagnosis for PCOS and PCOS-related symptoms in order to achieve a more homogenous population. Furthermore, we compared the trends in PCOS and symptom-

related diagnoses with female initiators over the same calendar period, and established that PCOS was unlikely to impact the observed female trend. We recognize that by excluding PCOS, our study may have somewhat underestimated the true rate of OAD initiation.

Our observation that initiators were twice as likely to have visited a FP compared with a general pediatrician is of particular interest. Obesity and obesity-related comorbidities are difficult to manage, contributing to the low self-perceived competence level to treat such disease states by physicians (79, 80). Differences in attitudes and management of T2DM have been seen to vary by physician characteristics (81). Results from survey data showed that younger providers and female physicians were more inclined to be aggressive with screening and monitoring practices (81). Less is known about how provider specialty impacts treatment decisions regarding OADs. However, as FPs frequently manage adult patients with T2DM and pre-diabetes (82, 83), they may be more comfortable with prescribing OADs than general pediatricians. Therefore, it may not be surprising that our study reported differences in prescribing rates by provider type. Nevertheless, this high degree of variation by provider may indicate overuse and/or underuse, and suggests opportunities for improvement in education, training, and care.

Our study has several limitations. First, our results are not representative of the lower social economic status (SES) population as all of our study subjects were commercially insured and represent only 10% of the national youth population. Moreover, by requiring continuous enrollment prior to treatment initiation, our study further excluded lower income patients who may be more likely to have gaps in healthcare coverage. It has been widely reported that the burden of obesity, pre-diabetes, and T2DM excessively affects children from lower SES families (5, 12, 39, 40, 84). Because lower SES communities are

underrepresented in our study, we are unable to extrapolate our results to the general population but can assume our reported rates of treatment initiation are an underestimation of the rates in the overall population. Second, we were unable to analyze additional patient characteristics that may impact OAD prescribing, such as race/ethnicity, family SES status and BMI, as these data are not routinely collected by health insurance plans. Third, outpatient pharmacy claims do not include the identity or specialty of the provider that ordered the filled prescription. Thus, we employed a method that included using a 3-month look-back window in outpatient claims files to classify patients who visited either a family practitioner or pediatrician and separately considered those patients who visited both or other specialties. Although this method does not guarantee the correct classification of the prescribing provider, using a 6-month look back window resulted in consistent findings with the 3-month window. Lastly, prescription claims data do not capture medications obtained without insurance, such as drugs paid out-of-pocket and is of particular concern to our study given that $4 generic drug programs launched in late 2006, offering metformin at discounted prices (not resulting in insurance claims). Although the impact of these low-cost, out-of-pocket programs on claims for OADs is unknown (85), it has been reported that at least 1 in 10 warfarin prescriptions are filled in this manner (86). This may partially explain the observed decrease in OAD usage from 2008 to 2012.

In conclusion, the results from our study demonstrated an increase in OAD initiation among children and adolescents between 2002 and 2008. Furthermore, time trends from 2002 to 2012 consistently showed higher rates of prescriptions by FPs compared to general pediatricians. We observed a decrease in OAD initiators beginning 2008, which is likely multi-factorial, reflecting a decreased burden of obesity in the population along with

prescriptions filled without health insurance coverage. Continued efforts to educate and support physicians treating these patients are necessary in order to address the emerging epidemic of T2DM and its consequences in youth.

5.2 Study 2 discussion: persistence and re-initiation following discontinuation of oral anti-diabetic agents in children and adolescents

These results are from one of the largest population-based cohort on pediatric new users of OADs that we are aware of, and demonstrate that sub-optimal OAD use is common. We saw a rapid decline in persistence after initiation where over three-quarters of patients were non-adherent by 6-months of follow-up. However, almost one in three patients who had at least 1 extended period of without drug supply during the study subsequently restarted therapy, with more than half of these patients restarting within six months of discontinuation. Follow-up care of different forms were associated with reinitiation, particularly the dual occurrence of a laboratory test with an outpatient visit.

The magnitude of poor persistence in the pediatric OAD population has been previously reported in only one other study. Although the study population was drawn from Medicaid and consisted of families of generally lower socioeconomic status than the Marketscan population, our rates and predictors of non-persistence are consistent with this earlier work (62). Results from both studies demonstrate that age is a strong predictor of persistence with adolescents consistently demonstrating the poorest persistence. In the pediatric population, factors influencing persistence can vary between younger children and adolescents. Adherence by younger children are generally affected by parental motivation (73) while adolescents' adherence is less swayed by parental influence but more so by the mental and emotional challenges that occur during the transitional period into early adulthood (59). For these reasons, adolescent adherence levels have generally been the

lowest compared with all other age groups for numerous therapies with reported treatment compliance rates varying from 10-56% (73). Further research is clearly needed to identify effective strategies for overcoming the unique adherence barriers faced by adolescents with T2DM and other chronic conditions.

Our study found that many non-adherent patients subsequently restarted therapy, suggesting that OAD persistence is not quite as bad as it appears. Comparable paradigms have been previously reported in adult chronic medication users. Reinitiation rates following a period of discontinuation among OAD users in the adult population are between 60% and 80.6% (64, 65). These rates are much higher compared to what was observed in the current study and can largely be attributed to higher disease severity of T2DM in the adult population. Similar research conducted in the adult statin and antihypertensive user populations have also demonstrated high rates of reinitiation following a period of non-adherence (87, 88).

A major strength of using a case-crossover design in the current study is that it helps to adjust for confounding by an individual's health-seeking attitudes, which should not change over a short period of time. In other study designs, such as a standard cohort study, it would be difficult to determine if it was the occurrence of follow-up care or if it was the patient's health-seeking tendencies that played the key role in restarting therapy. By adjusting for these patient characteristics, we are better equipped to examine the events that are associated with restarting therapy. Based on the results of our case-crossover analysis, we found that the process of restarting OAD therapy was strongly linked to the dual occurrence of a laboratory test along with a physician visit. We anticipated that physician visits and

follow-up care would be associated with reinitiation of OADs but the degree of the effect is still striking.

Our finding that a physician visit along with a glucose test was strongly associated with reinitiation of OAD therapy is consistent with previous research in adult statin users that found that non-adherent patients who visited the same physician who initiated their statin regimen and had a cholesterol test were more likely to restart statin therapy. Their study concluded that regular follow-up and continuity of care were likely important determinants of long-term medication adherence among statin users (87). Relatively little research has been conducted on the influence of health care-related factors on medication adherence in children and adolescents. However, the benefits of these factors have been linked to other outcome measures. High continuity of care in infants has been associated with decreased emergency department visits during early childhood and increased receipt of dental, nutritional, and developmental advice (89, 90). Furthermore, children with over one-year of follow-up care, regardless of whether they remained with one provider, were up to 17 times more likely to be up-to-date with immunization compared to children with less than 6-months of follow-up care (91). Our study extends on this previous work and supports the validity of these findings by demonstrating that follow-up care of different forms is also associated with improved medication adherence.

Results from this study suggest that greater follow-up care may improve the likelihood that a patient will restart therapy. It is conceivable that had the physician visit and testing occurred earlier, the length of the treatment gap may have been shorter. Furthermore, it is possible that if patients who did not restart OAD therapy in our study had visited a physician, they may have reinitiated therapy as well. However, these are conjectures that

require additional research. The improper use of chronic medications likely stems from a lack of appreciation for the long-term implications of ineffective management of these conditions. Consequentially, adherence becomes a dynamic process where treatment gaps of varying lengths of time are common. Management strategies aimed at improving adherence should focus on approaches that can decrease the frequency and length of these gaps in these different patient populations. Quality improvement approaches should focus on identifying and recalling patients with poor persistence, assessing their adherence, providing education to both the patient and provider, and performing appropriate diagnostic testing before patients develop short- and long-term disease related complications.

Our study has several limitations. First, it is important to note that the re-initiation analysis only assessed a population of kids who restarted therapy. We are unable to say anything about the population of children who discontinued and did not subsequently restart therapy. Second, despite the aforementioned strengths of a case-crossover design, the study may be confounded by time-varying patient characteristics. An individual patient's views on their health status and the benefits of OAD therapy is difficult to predict and may change over time, especially by influences at the doctor's office or factors outside of the healthcare setting. Therefore, the study is unable to remove confounding by these factors and cannot eliminate these additional explanations when interpreting our results. Third, we are unable to determine the reasons behind the gaps in treatment. It is possible that the patient experienced lack of effectiveness or an adverse reaction to the drug, which prompted the treating physician to discontinue the drug. However, as most patients who reinitiated therapy in our study restarted the same drug as their index drug, this is an unlikely explanation for most of the observed gaps. Fourth, administrative claims databases such as Marketscan have inherent

limitations in terms of their capabilities and usefulness including inconsistencies and oversights in coding practices. CPT procedure codes are present in over 85% of all physician claims in Marketscan (92); however, the consistency between documentation and actual performance is unknown. . This may be particularly relevant for some of the laboratory testing such as HbA1C and lipid levels, which may have been coded as miscellaneous laboratory or bundled services rather than through discrete CPT codes. Similarly, the prescription fill data in Marketscan only signifies availability of that drug to the patient. It does not provide complete information on actual drug consumption so it is possible that during the perceived gaps in treatment, patients were taking the drug but on an inconsistent basis. However, numerous studies have examined the relative validity of a prescription drug claim compared to a patient's self-reported drug use and consistently found high agreement between the two sources (93-96). Furthermore, in terms of utilizing claims data for compliance research, prescription claims data have been shown to be highly concordant with pill counts (96). Lastly, prescription claims data do not capture medications obtained without insurance, such as drugs paid out-of-pocket and is of particular concern to our study given that $4 generic drug programs launched in late 2006, offering metformin at discounted prices. Although the impact of these low-cost, out-of-pocket programs on claims for OADs is unknown (85), it has been reported that at least 1 in 10 warfarin prescriptions are filled in this manner (86). It is possible that some of the observed patients who discontinued therapy had in fact switched to a lower cost generic that did not result in an insurance claim.

In conclusion, our study reports that non-persistence to OADs in the pediatric population is prevalent and typically occurs within the first few months of treatment initiation, although many of those who discontinued therapy subsequently restarted

treatment. Our findings suggest that reinitiation of treatment is strongly related to different modes of follow-up care, suggesting that physicians can play an important role in promoting long-term patient adherence. Continued efforts to educate and support physicians treating these patients are necessary in order to address the T2DM epidemic and its consequences in the youth population.

CHAPTER 6: CONCLUSIONS

The overall purpose of this dissertation was to explore the trends in filled oral anti-diabetic (OAD) agents in youth with suspected T2DM and to understand factors specific to this population that are influencing the effectiveness of these drugs. Results from the three aims have been presented in the previous chapter. In study aim 1, we sought to describe the temporal trends in treatment initiation from years 2002 to 2012 as well as identify predictors of initiation. Aim 2 depicted the degree of adherence on index drug and explored the frequency and predictors of re-initiation among patients with extended periods of discontinuation. This chapter will summarize the results from the three studies, discuss the implications of these results in consideration of the strengths and limitations of each study design, and propose recommendations for additional research.

6.1 Summary of findings

In study 1, we identified a total of 13,824 initiators between 2002 and 2012 with a mean monthly incidence of 4.6 (95% CI: 3.6, 5.5) per 100,000 youths. Initiators were more likely to be females, age 15-18, and from the southern region. Furthermore, we found that initiators were twice as likely to have visited a family practitioner compared to a pediatrician in the 3-months prior to their index date (RR=2.00; 95% CI=1.02, 5.02). It is well documented that differences in attitudes and management of T2DM have been seen to vary by physician characteristics (81) but less is known on how provider specialty impacts treatment decisions regarding OADs. However, as FPs frequently manage adult patients with T2DM and pre-diabetes (82, 83), they may be more comfortable with prescribing OADs than

general pediatricians. Therefore, it is not surprising that this study reported differences in prescribing rates by provider type.

Time trends demonstrated a 43% increase in initiation during the study period, with a gradual decrease starting from early 2008. The observed decrease is likely multi-factorial, reflecting the decreasing burden of obesity in the population and the increase in use of $4 generic programs, which allows patients to obtain medications without using their health insurance.

In study 2, we determined that pediatric persistence to index OAD was very low, with 44.5% (95% CI: 43.7, 45.3%) non-persistent at 30 days and 85.6% (95% CI: 85.1, 86.2%) non-persistent at 360 days. The improper use of chronic medications likely stems from a lack of appreciation for the long-term implications of ineffective management of these conditions. Consequentially, drug-taking habits become a dynamic process where treatment gaps of varying lengths of time are common. Management strategies aimed at improving adherence should focus on approaches that can decrease the frequency and length of these gaps through identifying predictors of treatment re-initiation in these different young patient populations.

Although persistence to index drug was short, we found that drug-taking behaviors in this population is not as bad as it seemed. Our results demonstrate that almost one in three patients who had at least one extended period of non-adherence during the study subsequently restarted therapy, with more than half of these restarting within 6-months of discontinuation. Furthermore, we found that the combination of having an HbA1c and related test plus evidence of an outpatient medical encounter was the strongest predictor of re-initiation (OR=4.41; 95% CI: 3.55, 5.47). We anticipated that physician visits and follow-up

care of different forms would be associated with re-initiation of OADs but the degree of the effect is very striking.

6.2 Clinical and public health implications

Trends in OAD initiation and utilization in youth have changed as a reflection of the growing number of T2DM cases in this population as well as advancements in treatment practices and guidelines. Recognizing the patient population that is being treated helps form the basis of future pharmacoepidemiologic research conducted in this field. Our study found a high degree of variation by provider type (family practitioner versus general pediatrician), which may indicate overuse and/or underuse of these medications by specialties. These results suggest opportunities for improvement in education, training, and care among providers treating these patients.

Our evaluation into persistence demonstrated that non-persistence to OADs in the pediatric population is common and typically occurs within the first few months of treatment initiation, although many of those who discontinued therapy subsequently restarted treatment. Furthermore, using case-crossover analysis, we found that re-initiation was strongly related to different modes of follow-up care, which indicates that physicians play an important role in recognizing and maintaining long-term patient adherence. It is conceivable that had the physician visit and testing occurred earlier, the length of the treatment gap may have been shorter. It is also possible that had the patients who did not restart OAD therapy in our study visited a physician, they may have reinitiated therapy as well. However, these are speculations that will require further research.

6.3 Strengths

T2DM continues to be a rare condition in children and adolescents causing practitioners to be fairly inexperienced when it comes to caring for patients in this population with this disease. From a public health perspective, the results from this research can serve as a reference in the management of T2DM by providing a comprehensive evaluation of various trends and patient-based issues unique to this population.

A central strength of this research design is the database utilized. Marketscan captures real-world treatment patterns for a large and diverse sample of the U.S. commercially insured population. It provides an easy and cost-effective way of accessing a large sample size, which is exceptionally beneficial for studies of rare exposures and/or outcomes. OAD usage in children and adolescents is one such example given the overall low prevalence of OAD prescriptions (0.31 per 1000) (54) in the U.S.

In study 2, we used a case-crossover analysis to explore predictors of treatment re-initiation. In a case-crossover analysis, a patient's own past history serves as their "control" allowing for within subject comparisons, which provides effective control of confounding by measured and unmeasured patient characteristics that are constant over time (74). A major strength of using a case-crossover design is that it helps to adjust for confounding by an individual's health-seeking attitudes, which should not change over a short period of time. In other study designs, such as a standard cohort study, it would be difficult to determine if it was the occurrence of follow-up care or if it was the patient's health-seeking tendencies that played the key role in restarting therapy.

6.4 Limitations

6.4.1 Limitations of Marketscan database

Insurance claims databases have inherent limitations in terms of their capabilities and usefulness, as these resources were created for insurance billing purposes and not for clinical practice or research (97). Inconsistencies and oversight in coding practices and data input are potential weaknesses of claims-based data.

Important covariates of interest may not be completely or even partially captured in claims databases. One covariate of interest that is not captured in Marketscan but would be extremely useful to include is socioeconomic status (SES). It has been established from countless observational studies that the burden of T2DM excessively affects children from lower SES families since the prevalence of numerous T2DM risk factors is higher in this population (5, 12, 39, 40, 84). Additionally, research conducted in adults has suggested that there are substantial differences in health care utilization (98, 99)and compliance patterns by an individual's SES (100). The inability to incorporate SES is a limitation of this research. However, Marketscan is comprised of commercially insured individuals where the range of SES is probably not as wide compared to the general population. This is reassuring since observed discrepancies by SES are most pronounced between the very low and very high SES (98). By underrepresenting the lower SES communities, we can assume that the rates estimated from aim 1 are an underestimation of the overall population. Another important variable of interest that is not readily available in most claims-based datasets is BMI. As was described in chapter 1, obesity is the strongest predictor of insulin resistance and T2DM onset for all age groups. Although it would be informative to examine associations by BMI or obesity status, the absence of this variable should not compromise the integrity of study

results since obesity status will not vary dramatically within a youth T2DM population – 93% of children diagnosed with T2DM had a BMI>=95th percentile (41).

Lastly, prescription claims data do not capture medications obtained without insurance, such as samples from the doctor's office or drugs paid out-of-pocket and is of particular concern to this dissertation given that $4 generic drug programs launched in late 2006, offering metformin at discounted prices (not resulting in insurance claims). Although the impact of these low-cost, out-of-pocket programs on claims for OADs is unknown (85), it has been reported that at least 1 in 10 warfarin prescriptions are filled in this manner (86). This particular limitation likely affected results from both studies and led to underestimations of incidence and persistence calculations. However, results from our researched showed that over 58% of patients had an index drug copay that was $5 or less (Section 4.2), which may indicate that low-cost generic programs may not be especially appealing for these users.

6.4.2 OAD exposure misclassification

The research of this dissertation based OAD exposure assessments on prescription fill data where a claim for an OAD only signifies availability of that drug to the patient. It does not provide complete information on drug-taking habits that could be determined from other sources such as self-reports and pill counts. However, it is also not prone to recall bias, which can undermine results from self-reported data susceptible to such bias. Numerous studies have examined the relative validity of a prescription drug claim compared to a patient's self-reported drug use and consistently found high agreement (Positive Predicted Value>90%) between the two sources (93-95). Furthermore, prescription claims data have been shown to be highly concordant with pill counts (96).

6.4.3 Generalizability

In 2012, Marketscan included approximately 5.5 million youth aged 6-17, equivalent to 10% of the overall population and 20% of the commercially insured population in the US for that age group (69, 70). While Marketscan is likely to be representative of the U.S. population receiving employer-based insurance, is not representative of the overall U.S. population of children and adolescents. The database does not capture the population of children whose parents are unemployed, uninsured, or receiving Medicaid. Furthermore, by requiring continuous enrollment prior to treatment initiation for all study aims, our research further excluded lower income patients who may be more likely to have gaps in healthcare coverage. Children from families that experience more job instability, i.e. layoffs and job changes, will be more likely to be omitted from these estimations. Generalizability may be compromised for all the reasons listed above; however, it does not affect the integrity of any study results as internal validity is maintained.

6.5 Future directions

Further research is necessary to expand upon the work from this dissertation. As previously mentioned, results from this study cannot be generalized to the lower-income pediatric population. As T2DM disproportionately affects children from lower SES families, it would be extremely interesting to assess trends in treatment incidence and characteristics of new users in the Medicaid population and compare those results to that from study 1 (5, 12, 39, 40, 84). It is possible that the prescriptions from the Medicaid population are less affected by the low-cost generic programs and may provide additional insight into the decrease in prescriptions starting 2008 that was observed in study 1. Furthermore, drug-taking habits have also been shown to vary by an individual's SES (100). It would also be

interesting to assess rates of discontinuation and reinitiation in the Medicaid population and compare those rates to what was observed in study 2.

Another interesting feature related to pediatric drug-taking behavior is the factors influencing persistence can vary widely from younger children and adolescents. It has been previously shown that adherence by younger children are generally affected by parental motivation (73) while adolescents' adherence is more swayed by the mental and emotional challenges that occur during the transitional period into early adulthood. Therefore, future studies should focus on the role of parental factors and the changing role of these factors as a child matures into early adulthood. In claims data this may be more difficult to do, but one can look at proxies such as the total number of family members in a household.

In conclusion, this research has added valuable insight into the utilization of OADs in youth as well as highlighting factors that are related to the effectiveness of these drugs specific to this population. We believe that additional studies using registries and electronic health records along with quality improvement approaches can significantly help to increase reliable follow-up care for these patients and hopefully delay and/or avoid the short- and long-term disease related complications.

APPENDIX

Appendix Table 1. Frequency of Events in Control & Hazard Period for Case-Crossover Analysis

	15-Day Control Period	15-Day Hazard Period	30-Day Control Period	30-Day Hazard Period
Outpatient Medical Encounter	596 (17.5)	1374 (40.4)	927 (27.2)	1714 (50.4)
T2DM Complications[a]	40 (1.2)	119 (3.5)	61 (1.8)	157 (4.6)
LDL Test	101 (3.0)	254 (7.5)	98 (2.9)	351 (10.3)
HbA1c & Related Tests	139 (4.1)	426 (12.5)	155 (4.6)	556 (16.3)
Complications[a] + Med Enc	27 (0.8)	107 (3.4)	50 (1.5)	141 (4.1)
LDL + Med End	58 (1.7)	183 (5.4)	66 (1.9)	271 (8.0)
HbA1c + Med Enc	87 (2.6)	346 (10.2)	119 (3.5)	463 (13.6)

[a]T2DM-related complications include hypertension, hyperlididemia, acanthosis nigricans, polyuria, polydipsia, nocturia, and hyperosmolar hyperglycemic state

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