2022

Exploring the Influence of Family History Before and After Type 2 Diabetes Development Through Statistical Analysis of Biomarkers and an Educational Intervention

Jessica Johnson Denton
University Of Alabama At Birmingham

EXPLORING THE INFLUENCE OF FAMILY HISTORY BEFORE AND AFTER TYPE 2 DIABETES DEVELOPMENT THROUGH STATISTICAL ANALYSIS OF BIOMARKERS AND AN EDUCATIONAL INTERVENTION

by

JESSICA JOHNSON DENTON

JOSÉ R. FERNÁNDEZ, COMMITTEE CHAIR
BRENDA BERTRAND
PAULA CHANDLER-LANEY
ANNA C.E. HURST
FERNANDO OVALLE

A DISSERTATION

Submitted to the graduate faculty of The University of Alabama at Birmingham,
in partial fulfillment of the requirements for the degree of
Doctor of Philosophy

BIRMINGHAM, ALABAMA

2022

EXPLORING THE INFLUENCE OF FAMILY HISTORY BEFORE AND AFTER TYPE 2 DIABETES DEVELOPMENT THROUGH STATISTICAL ANALYSIS OF BIOMARKERS AND AN EDUCATIONAL INTERVENTION

JESSICA JOHNSON DENTON

NUTRITION SCIENCES

ABSTRACT

The prevalence of type 2 diabetes is increasing at an alarming rate in both children and adults worldwide. Timely identification of those at risk for type 2 diabetes is essential to reduce morbidity and mortality and to mitigate the toll on families and the healthcare system. Family history is an effective, universal tool that can be used to identify individuals at risk for type 2 diabetes before they acquire additional risk factors. Understanding how family history contributes to biomarkers associated with diabetes in healthy individuals could facilitate the creation of early screening and prevention strategies designed for this specific at-risk population. In addition, educational interventions with an accurate portrayal of the genetic and environmental contributions to type 2 diabetes could increase knowledge of diabetes development and motivation to engage in healthy lifestyle behaviors to prevent the diagnosis or progression of the disease. We utilized multiple regression models to investigate whether family history is a predictor of insulin and glucose biomarkers for type 2 diabetes after adjusting for relevant covariates in healthy weight children and adults. We also created and tested a genetics-focused educational intervention designed to increase knowledge of the multifactorial etiology of type 2 diabetes and motivation to engage in healthy lifestyle behaviors. Our multiple regression model found that family history was a significant predictor of fasting insulin in children (p=0.0372) in addition to waist circumference, sex, and grams of

carbohydrate. In adults, family history was a significant predictor of fasting glucose (p=0.0193) in addition to age, gender, non-Hispanic Black ethnicity, waist circumference, and fat intake. The educational intervention increased knowledge of type 2 diabetes (p<0.0001) and motivation to engage in healthy lifestyle behaviors (p<0.0001). The findings from the multiple regression analyses contribute to the conflicting literature on how family history of diabetes affects diabetes development. Despite the limitations in understating the exact contributions of family history at a biomarker level, knowledge that type 2 diabetes is a multifactorial condition with both genetic and environmental influences can have positive effects on motivation to engage in lifestyle behaviors that reduce the risk for diabetes diagnosis and complications.

Keywords: family history, type 2 diabetes, fasting insulin, fasting glucose, educational intervention, behavior change

DEDICATION

To my husband, William, for his unfailing faith in my ability to accomplish my goals and his sacrifices to help me get there.

ACKNOWLEDGEMENTS

Many people have assisted me on the long journey to earning this degree. First, I would like to acknowledge my family and friends, who have been encouraging, patient, and dedicated to my success throughout the entire process. I especially want to thank my children, Kenley, Josephine, and Liam, for their patience and understanding. All three were born during the course of my time as a PhD student, and we are all looking forward to life on the other side. Second, I would like to acknowledge my past and present colleagues and students within the UAB Genetic Counseling Program and Department of Clinical and Diagnostic Sciences, who have allowed me to pursue this opportunity while keeping my day job. I would also like to thank my committee for providing immense guidance and support, especially my mentor, José Fernández. Finally, I would like to acknowledge the research participants who have made this work possible for their dedication to the future of scientific discovery.

TABLE OF CONTENTS

Page

LIST OF TABLES

Table *Page*

LIST OF TABLES (CONTINUED)

LIST OF FIGURES

Figure *Page*

THE ROLE OF FAMILY HISTORY OF DIABETES AS A PREDICTOR OF INSULIN ACTIVITY IN A SAMPLE OF DIVERSE, NORMAL WEIGHT CHILDREN

INVESTIGATING FAMILY HISTORY OF DIABETES AS A PREDICTOR OF FASTING INSULIN AND FASTING GLUCOSE IN A SAMPLE OF HEALTHY WEIGHT ADULTS

INTRODUCTION

Pathophysiology of Type 2 Diabetes

Type 2 diabetes is a chronic, multisystemic health condition that affects millions of people worldwide. Type 2 diabetes is characterized by elevated levels of blood glucose, or hyperglycemia, which result from reduced cellular responses to insulin and defects in insulin production.[1,2] In healthy individuals, insulin is a hormone secreted by the β-cells of the pancreas in response to elevated blood glucose after nutrient intake.[2,3] When insulin binds to its cellular receptors, it results in the recruitment of glucose transport proteins to the cell membrane, allowing glucose to enter adipose, skeletal muscle and cardiac muscle cells to be utilized for energy.[4-6]

In individuals with type 2 diabetes, cells have a reduced response to insulin, meaning glucose is not effectively transported from the blood into cells, resulting in hyperglycemia.[2,7] Sustained high blood glucose levels signal the β-cells to produce more insulin to compensate, causing elevated fasting insulin in addition to high fasting glucose.[2,7] Eventually, chronic hyperglycemia, along with insulin resistance, chronic inflammation, and increased metabolic load, cause damage to the β-cells through various stress-induced mechanisms.[8] Progressive decline of β-cell function decreases insulin production and eventually necessitates exogenous insulin therapy to avoid the damaging effects of hyperglycemia.[9]

Adult-Onset Type 2 Diabetes

The number of people with type 2 diabetes is increasing worldwide. Between 1990 and 2019, there was a 49% growth in the prevalence of type 2 diabetes.[10] By 2030, it is estimated that 578 million people will have type 2 diabetes, and by 2045, 700 million, or 10.9% of the population, will have type 2 diabetes.[11] This increasing prevalence coincides with increased morbidity and mortality due to diabetes-related complications.[10,12]

Common health complications and comorbidities due to prolonged hyperglycemia in individuals with type 2 diabetes include chronic kidney disease, diabetic retinopathy, peripheral neuropathy, and cardiovascular disease.[13] The downstream effects of these complications result in dialysis, blindness, amputations, heart failure, and stroke, which place a tremendous care and financial burden on healthcare systems across the world.[14-17] Mitigating the burden caused by type 2 diabetes is a universal goal that must begin by identifying at-risk individuals to engage them in prevention strategies.

Risk factors for adult-onset diabetes are multifaceted and have been extensively studied in the literature. Family history of diabetes, genetic variants, ethnicity, exposure to gestational diabetes, socioeconomic status, and aging are unavoidable components that contribute to type 2 diabetes risk, whereas lifestyle choices involving decreased physical activity and unhealthy dietary habits can lead to the development of obesity, increased visceral fat, and other health conditions such as hypertension and hyperlipidemia, all of which increase the risk for type 2 diabetes in adults.[18,19]

Childhood-Onset Type 2 Diabetes

Type 2 diabetes has traditionally been considered an adult-onset condition; however, the prevalence of type 2 diabetes in children is rising at an alarming rate. In the mid-1990s, 1–2% of all children with diabetes had type 2 diabetes, but by the mid-2010s, 45% of children with diabetes had type 2 diabetes.[20] From 2001 to 2017, there was a 95.3% relative increase in type 2 diabetes among children 10–19 years old[21], and by 2050, the incidence of type 2 diabetes in children is predicted to increase four-fold.[22] As more children are diagnosed with type 2 diabetes, managing the number of individuals with type 2 diabetes–related health complications will become exceedingly challenging.

Children with type 2 diabetes are at an increased risk to develop earlier onset and more treatment-resistant complications of type 2 diabetes.[23,24] The longer the body is in a hyperglycemic state, the greater the risk for microvascular complications such as diabetic retinopathy, nephropathy, and neuropathy and macrovascular complications including cardiovascular disease.[24-26] Not only will children with type 2 diabetes experience heightened morbidity, but due to their young age, the diagnosis will also affect the child's family unit, intensifying the overall impact of this disease.[27,28] Managing these detrimental effects of childhood-onset type 2 diabetes is crucial for the health of our society. Therefore, it is essential to identify which children are at risk for type 2 diabetes to implement early prevention strategies.

Risk factors for childhood-onset type 2 diabetes can be categorized into congenital risk factors and acquired risk factors. Certain racial/ethnic backgrounds (Asian, Black, Hispanic/Latino, Native American/Alaskan Native, or Pacific Islander)[21,29,30], exposure to gestational diabetes *in utero*[31], and having a family history of

diabetes[32-34] are risk factors established before birth, whereas other risk factors, such as dyslipidemia, depression, and especially obesity[29,32-34], largely arise from the nutritional intake, dietary behaviors, psychosocial, and social factors children experience throughout their lives.[29]

Type 2 Diabetes Prevention Efforts

Understanding which factors increase the risk for children and adults to develop type 2 diabetes has led to the development of prevention strategies that target modifiable risk factors. Multiple large-scale type 2 diabetes prevention trials have focused on diet, physical activity, and the use of certain medications. The Diabetes Prevention Program (DPP) is one of the more successful trials and showed that, after 15 years, those in the lifestyle intervention group had a 27% reduced incidence rate of diabetes compared to the placebo group.[35] Other lifestyle intervention programs have shown varied success based on duration of the study and study design.[19] Although some clinical trial results are promising, translating trial methodology into the community setting is challenging and would require the collaborative efforts of governmental policies, public health programs, and the clinical workforce.[36,37]

Compared to the adult population, prevention of childhood-onset type 2 diabetes is not as well studied. Most prevention strategies for children have focused on reducing childhood obesity through dietary and physical activity interventions.[38] Unfortunately, these efforts have seen little cumulative success. A meta-analysis of 34 lifestyle intervention trials with outcome targets including increasing physical activity and healthy eating and decreasing sedentary behavior and unhealthy eating found an insignificant

pooled effect on body mass index (BMI).[39] A more recent and extensive meta-analysis of 359 studies targeting child and adolescent obesity prevention found that a combination of diet and exercise interventions might reduce BMI z-score, BMI, and body weight, though there was significant statistical heterogeneity among studies and low-quality evidence grading given to each of these three claims.[40]

In summary, prevention programs for children have been moderately successful at best, and adult prevention programs have been variably successful in the trial setting, but application to large-scale populations is a significant obstacle. Therefore, there is still a need for additional strategies to improve type 2 diabetes prevention efforts.

Utility of Type 2 Diabetes Screening Recommendations

If prevention strategies are going to be effective, at-risk individuals must be identified early enough to benefit from the intervention. Weight status is currently the main method of identifying individuals at risk for type 2 diabetes[41,42]; therefore, individuals who are overweight or obese are primarily targeted for prevention strategies. However, people who are normal weight could also be at risk for diabetes, and they do not benefit from prevention programs focused solely on individuals who are overweight or obese.[43]

Furthermore, type 2 diabetes screening recommendations for asymptomatic children and adults are also based on weight status.[41,42] Guidelines state that individuals who are considered overweight (defined by BMI or BMI percentile for adults and children, respectively) should be screened for type 2 diabetes. However, BMI is a flawed measurement for many reasons. BMI is highly variable depending on biological sex, age,

and ethnicity.[44-46] In addition, BMI is a measurement of height and weight, but the weight component does not distinguish fat mass from fat-free mass. Therefore, it cannot be assumed that individuals with the same BMI have the same body composition and, subsequently, the same health risks.[47]

BMI measurements do not fully describe body fat percentage or location of fat deposition, yet these are the elements of body composition that increase risk for type 2 diabetes.[48-50] Visceral fat, fat in the abdominal region, and ectopic fat (fat deposited in non-adipose tissues) increase the risk for type 2 diabetes by promoting insulin resistance via mechanisms that increase inflammation.[48,51,52] Is has also been proposed that individuals with a healthy BMI who have exceeded their personal fat threshold may be at an increased risk for developing type 2 diabetes.[53]

In addition to the inability to describe percent body fat and fat distribution, the use of BMI as a diabetes screening tool discounts other pertinent risk factors for insulin resistance such as dietary intake, lifestyle factors, and genetic variants that could be present in individuals with a healthy BMI.[1,54] If the goal is to prevent or delay progression from insulin resistance to type 2 diabetes, then using a different method of risk stratification is warranted, especially in normal weight individuals. Additionally, to be more equitable, methods identifying individuals at risk for type 2 diabetes should strive to be universally accessible, simple, and inexpensive. Identifying at-risk individuals based on family history of diabetes is one such method that meets these criteria.

Family History of Diabetes for Risk Stratification

Family History–Based Risks

It has long been recognized that family history of diabetes is a strong risk factor for diabetes development. Past studies have reported lifetime risks to develop type 2 diabetes approach 40% if an individual has one affected parent and 60% with two affected parents.[55,56] Similarly, the Framingham Offspring Study determined an odds ratio to develop type 2 diabetes of up to 3.0 (1.9–4.5) and 6.0 (2.8–12.7) for individuals with one or two affected parents respectively after adjusting for age and BMI.[57] Additional studies have also found that a family history of type 2 diabetes increases diabetes risk regardless of BMI and waist circumference.[58] The association of family history with type 2 diabetes risk is especially evident in children, with greater than 75% of children with type 2 diabetes in the United States have an affected relative.[59] Given its strong association with disease risk, family history assessment could be a clinically easy and effective means of identifying individuals at risk for type 2 diabetes.

Family History as a Screening Tool

Family history has been proposed as a useful tool to assess risk for multifactorial conditions, including diabetes.[60,61] One study utilizing National Health and Nutrition Examination Survey (NHANES) data from 1999 to 2004 showed that adding family history to other known risk factors (age, gender, BMI, hypertension, low high-density lipoprotein cholesterol, and/or elevated triglycerides) would identify an additional 620,000 individuals with undiagnosed diabetes.[62] Another study showed that, compared to having a BMI of ≥25, a high familial risk (two affected first-degree relatives) for

diabetes has greater positive predictive value and specificity for identifying individuals with undiagnosed diabetes.[63] Because of its ability to identify individuals at risk for undiagnosed type 2 diabetes, family history of diabetes is one of the factors included in most noninvasive diabetes screening tools.[64,65]

The Effect of Family History on Type 2 Diabetes Risk

Although family history is valuable for identifying individuals with undiagnosed type 2 diabetes, once people already have a diagnosis, prevention efforts are a moot point. To halt or delay progression to type 2 diabetes, targeting at-risk individuals who have not developed prediabetes, diabetes, or other significant risk factors for prevention programs is preferable. Family history could help identify these individuals due to its previously described characteristics of being easily ascertainable at any stage of life. Once these at-risk individuals are identified, prevention programs designed specifically for healthy individuals with a family history of diabetes could be implemented. To optimize their effectiveness, these programs would need to be informed by how family history and other risk factors contribute to the biological processes that lead to diabetes development. However, knowledge of how family history relates to biomarkers associated with type 2 diabetes in healthy children and adults is limited.

Family History and Type 2 Diabetes Biomarkers

Understanding if and how family history influences type 2 diabetes biomarkers in healthy weight individuals would help decipher how family history contributes to type 2 diabetes development at a biological level. Previous studies have shown that individuals

with a family history of type 2 diabetes have significant differences in diabetes biomarkers compared to those without a family history. Individuals with a family history of type 2 diabetes have higher hemoglobin A1c (HbA1c)[66], fasting glucose[66-68], impaired glucose tolerance[66], fasting insulin[69-71], and fasting C-peptide[69]; while they have lower insulin-stimulated glucose disposal[70,72], insulin sensitivity[73-75], insulin clearance[73], insulin secretion[76,77], and β-cell function.[74]

However, many of these studies were not exclusively conducted in healthy weight individuals, so variables related to body composition could explain these biomarker differences either by confounding or mediating effects. Other limitations include small sample sizes and varying methods of measuring biomarkers and determining statistical relationships. Some utilized simple comparisons of biomarkers between groups, which provides a limited understanding of the role of family history. For those that did use multiple regression analyses, there was no collective consensus in the choice of covariates, and very few incorporated elements of dietary intake as possible independent variables. Likely due to these inconsistencies in study populations and designs, there have also been studies that show individuals with a family history of diabetes do not have differences in certain biomarkers.[71,72,75,76,78,79]

Because of limitations and discrepancies in previous studies, more work is needed to understand the link between family history of diabetes and diabetes biomarkers in larger, healthy weight populations. In addition, investigating how family history predicts the activity of diabetes biomarkers in the presence of other known risk factors, including dietary intake, would provide a more sophisticated and clinically valuable understanding of the relationship between family history and type 2 diabetes.

Educational Opportunities

Improved awareness of how family history predicts diabetes biomarkers could ultimately lead to more effective screening and prevention strategies designed specifically for individuals with a family history of type 2 diabetes. Moreover, this information could also be beneficial to individuals with a diagnosis of type 2 diabetes. In general, people with type 2 diabetes have a poor understanding of diabetes development and management strategies.[80-83] Individuals with a family history of diabetes may think their diagnosis is solely due to a genetic predisposition, creating a reduced sense of personal control over their disease.[84,85] Studies have shown that adults with a family history of diabetes have lower perceived benefits of diabetes treatments and lifestyle changes.[86-88] Consequently, lower perceived benefits result in decreased motivation to engage in practices that prevent diagnosis or progression of diabetes.[89,90]

Evidence-based information about the contributions of inherited and environmental factors to type 2 diabetes could provide individuals with a more accurate explanation of their condition and highlight the benefits of implementing healthy lifestyle behaviors. However, previous educational efforts designed to explain how a hereditary predisposition for type 2 diabetes effects diabetes risk and development have shown mixed outcomes related to behavior change. While some found their educational intervention increased perception of control to prevent or treat type 2 diabetes[91-93], others found that these perceptions do not persist long-term[94] or did not result in positive lifestyle changes.[95-97] These varying results emphasize the need for continued research and design of educational interventions to increase diabetes knowledge with the purpose of encouraging engagement in healthy lifestyle practices.

Objectives and Aims

The objective of this dissertation was to explore how family history of diabetes influences diabetes biomarkers in healthy, normal weight individuals and to understand how an educational intervention impacts knowledge of diabetes and motivation to engage in healthy lifestyle behaviors.

Aim 1: To investigate the ability of family history of diabetes to predict insulin activity in healthy, normal weight children after adjusting for relevant covariates. We hypothesize that family history of diabetes will be a significant predicator of fasting insulin, insulin sensitivity, and acute insulin response to glucose (AIRg) in healthy children.

Aim 2: To test the ability of family history of diabetes to predict fasting insulin and fasting glucose activity in healthy, normal weight adults after adjusting for relevant covariates. We hypothesize that family history of diabetes will be a significant predicator of fasting insulin and fasting glucose in healthy adults.

Aim 3: To determine whether an educational intervention for individuals with type 2 diabetes changes knowledge of the multifactorial etiology of diabetes and motivation to engage in healthy lifestyle behaviors. We hypothesize that the intervention will increase knowledge of type 2 diabetes and motivation to engage in healthy lifestyle behaviors.

THE ROLE OF FAMILY HISTORY OF DIABETES AS A PREDICTOR OF INSULIN ACTIVITY IN A SAMPLE OF DIVERSE, NORMAL WEIGHT CHILDREN

by
JESSICA J. DENTON AND JOSÉ R. FERNÁNDEZ

In preparation for *Endocrine and Metabolic Science*

Format adapted for dissertation

Abstract

This study aimed to examine the relationship between family history of type 2 diabetes and insulin activity in a diverse sample of normal weight children. Measures of fasting insulin, insulin sensitivity, and acute insulin response to glucose (AIRg) were obtained from a multiethnic sample of normal weight children ages 7–12 years (n=199). Multiple linear regression was used to determine the effect of family history of type 2 diabetes on the variables of interest. All models were adjusted for age, sex, pubertal status, ethnicity, waist circumference, and total grams of carbohydrates. Family history of type 2 diabetes was a significant predictor of fasting insulin (p=0.04). There were no significant differences in age, sex, ethnicity, body mass index percentile, pubertal stage, or body composition between children with and without a family history of diabetes. Family history of diabetes is a significant predictor of fasting insulin in a cross-sectional group of children who are normal weight. These results contribute to the further understanding of the relationship between family history and type 2 diabetes risk, which could be utilized to develop earlier detection of dysglycemia and unique disease prevention strategies for at-risk children.

Introduction

Type 2 diabetes can no longer be considered an adult-onset condition. The incidence of type 2 diabetes has been increasing at an alarming rate in children and adolescents[1] and is predicted to increase four-fold between 2010 and 2050.[2] This growing prevalence of pediatric type 2 diabetes is a concerning fact of public health relevance. Children with type 2 diabetes are at an increased risk to develop micro- and macrovascular dysfunction, especially renal and neurologic complications.[3,4] Although the long-term repercussions of pediatric type 2 diabetes are not well established, this disease will likely place an immense burden on the healthcare system, leading to exorbitant medical costs.[5] Therefore, it is essential to identify at-risk children and implement prevention strategies in order to halt a potential epidemic.

Most childhood preventive and treatment interventions have focused on reducing type 2 diabetes risk through weight loss and obesity management.[6] However, despite arduous efforts, success rates of these programs are typically below 10%.[7,8] Although the reasons for this frustrating success rate are not clear, perhaps at-risk children are not identified early enough for these interventions to achieve greater effectiveness.

Reports of undiagnosed pediatric type 2 diabetes are estimated to be low.[9] However, according to the National Health and Nutrition Examination Survey, between 1999 and 2014, the prevalence of individuals with pre-diabetes fasting glucose levels (100-125mg/dL) was 15.5%. In addition, in adolescents, hemoglobin A1c increased from 5.03% to 5.16% ($p<0.0001$) and fasting insulin increased from 10.6mIU/L to 14.6mIU/L ($p<0.0001$) over this time period.[10] Early detection of impaired glucose and insulin

function before the onset of type 2 diabetes is essential to potentially prevent or delay disease onset.

The current guidelines for clinical type 2 diabetes screening in asymptomatic children and adolescents set forth by the American Diabetes Association suggest that children be screened if they are overweight (defined as body mass index, or BMI, greater than 85th percentile for age and sex, weight for height above the 85th percentile, or weight greater than 120% of ideal for height) and have one or more of the following criteria: maternal history of gestational diabetes, family history of type 2 diabetes in a first or second degree relative, are Native American, African American, Latino, Asian American, or Pacific Islander, or show signs of insulin resistance or conditions associated with insulin resistance (hypertension, dyslipidemia, polycystic ovarian syndrome, small for gestational age birth weight, or acanthosis nigricans).[11]

These guidelines rely heavily on weight status as determined by BMI; however, BMI is a flawed measurement, especially in certain ethnic groups. The use of a BMI measurement to determine which children are screened for diabetes discounts the potential relevance of other risk factors that could be present in children despite their BMI classification. Insulin resistance, which is present in children prior to diagnosis of type 2 diabetes, is influenced by multiple factors not captured in a BMI measurement, including diet, lifestyle, ectopic fat distribution, and genetics.[12] If the goal is to prevent or delay progression from insulin resistance to type 2 diabetes in children, these pre-diabetes risk factors must also be considered.

Family history is widely recognized as a strong predictor for risk to develop type 2 diabetes.[13] The effect of family history on type 2 diabetes risk seems to be an especially

potent factor in children. Seventy-five percent of children in the United States diagnosed with type 2 diabetes have a first- or second-degree relative with type 2 diabetes.[14] A study from Japan found that many children with normal weight and type 2 diabetes had a family history of diabetes (62.5%), which was not significantly different from the prevalence of family history in children with type 2 diabetes and obesity (58.5%).[15] Moreover, family history of type 2 diabetes has been determined as an independent predictor of impaired fasting glucose in normal weight Mexican children.[16]

The latter two studies demonstrate efforts to understand family history as a risk factor for type 2 diabetes in a normal weight population. Normal weight children are not being screened for type 2 diabetes based on the current guidelines, but if a normal weight child has a family history of type 2 diabetes, the child could still be at significant risk. However, further data on how family history contributes to type 2 diabetes risk is sparse, and no studies have been done in an ethnically diverse sample of normal weight children. Improved characterization of how family history influences type 2 diabetes risk without the confounding variable of obesity is vital in order to provide guidelines to identify the greatest number of children at risk for type 2 diabetes. This study aims to investigate the ability of family history of diabetes to predict insulin activity in a diverse group of children who are normal weight. We hypothesize that family history of diabetes will be a significant predicator of fasting insulin, insulin sensitivity, and acute insulin response to glucose (AIRg) in healthy children.

Methods

Study Population

A total of 322 participants were recruited from the Birmingham, Alabama, United States, area as part of a study to evaluate genetic and environmental factors influencing pediatric health, as described elsewhere.[17] Children were recruited through advertisements in newspapers, churches, community centers, and flyers that children took home from school. A phone interview with potential participants' parents/guardians was performed to ensure children met the study criteria. Children were excluded from the study if they were under age 7 or over age 13, had a diagnosis of type 1 diabetes, type 2 diabetes, polycystic ovary disease, or glucose or lipid metabolism disturbances or if they had a condition or used medication that alters physical activity or body composition.[17] Children and parents provided informed assent and consent, respectively. This study was approved by the University of Alabama at Birmingham Institutional Review Board.

Data Collection and General Measurements

Data were collected during two in-person visits. The first was an outpatient visit, which consisted of dual-energy x-ray absorptiometry (DXA) scans (GE Lunar Prodigy Radiation Corp., Madison, WI; software version 1.5e), assessment of pubertal status according to the criteria of Marshall and Tanner[18, 19], and a 24-hour dietary recall. Anthropometric measures obtained included weight in light clothing to the nearest 0.1 kg (Scale-tronix 6702W; Scale-tronix, Carol Stream, IL) and height without shoes to the nearest 0.1 cm (digital stadiometer; Heightronic 235; Measurement Concepts). Body mass index (BMI) percentiles were assigned using the Centers for Disease Control and

Prevention (CDC) guidelines and were age, sex, and ethnicity specific for the time of data collection.[20] The second study visit was an overnight stay at the UAB General Clinical Research Center (GCRC). All children were given the same meals and snacks and received water only after 8:00 p.m. In the morning, resting energy expenditure measurements, blood tests, and blood pressure tests were completed. A 24-hour dietary recall was also performed at this visit.

Dietary Recalls

A total of two 24-hour dietary recalls were overseen and analyzed by a registered dietitian nutritionist using the triple-pass method.[21] The child's parent or guardian was in attendance during and assisted with both recalls. All recalls were conducted on weekdays, and visual images were used to determine portion size. The same registered dietitian nutritionist who performed the recalls entered data from the recalls into the Nutrition Data System for Research (software version 2006; Nutrition Coordinating Center, University of Minnesota, Minneapolis, MN). The two recalls were averaged to provide an average intake of carbohydrates in grams, which was used as a covariate in the regression analyses. Grams of carbohydrate was included as a covariate to account for the variation in insulin activity that could result from total carbohydrate intake.

Analysis of Glucose and Insulin

Glucose and insulin analyses were performed in the GCRC Physiology and Metabolism Core Laboratory after a 12-hour overnight fast. An intravenous glucose tolerance test was used to determine measures of insulin secretion and sensitivity. A

topical anesthetic (Emla cream, AstraZeneca, Wilmington, DE) was applied to the antecubital space of both arms before placing flexible intravenous catheters. Glucose was measured in 10 µl sera using an Ektachem DT System (Johnson and Johnson Clinical Diagnostics). The intra-assay coefficient of variation (c.v.) for this analysis is 0.61% and the mean inter-assay c.v. is 1.45%. Insulin was assayed in 100 µl aliquots with reagents obtained from LINCO Research, Inc. (St. Charles, MO). The intra-assay c.v. for this analysis is 3.59%, and the mean inter-assay c.v. is 5.64%. Fasting insulin and glucose values were determined by the average of two baseline blood samples (2 ml/each). Values of glucose and insulin were entered into the MINMOD computer program for determination of insulin sensitivity as described elsewhere.[22-24] Calculation of acute insulin response to glucose (AIRg) was determined by the area above baseline insulin concentration during 0 to 10 minutes, calculated by the trapezoidal method.[25]

Family History of Diabetes

Family history of diabetes was determined by a questionnaire completed by the child's parent or guardian. The parent/guardian checked "yes" or "no" in response to the question "have any of the following relatives been diagnosed with high blood sugar/diabetes?" The relatives listed included paternal grandparents, maternal grandparents, parents, and siblings. It was not within the scope of this study to confirm whether the child's family members had a diabetes diagnosis; self-reported family history of diabetes was accepted as true.

Statistics

To avoid confounding results attributed to the presence of overweight or obese children, participants with a BMI percentile of 85% and above, as defined by the CDC at the time of the study, were removed from the data set prior to analysis. Descriptive and frequency statistics were completed for the remaining individuals with and without a family history of diabetes (family history=1, no family history=0). A new, dichotomous variable was created to capture whether children had a fasting glucose of greater than or equal to 100 mg/dl (highriskdiab=1). Independent sample t-tests were performed to determine significant differences in continuous variables, and chi-square analysis was used to determine significant differences in categorical variables between children with and without a family history of diabetes.

Four different multiple regression models were analyzed to test whether family history of type 2 diabetes predicted the main outcomes of interest, which were fasting insulin, insulin sensitivity, AIRg, and glucose tolerance. Covariates used in each model included age, sex, pubertal status, ethnicity, waist circumference, and total grams of carbohydrates. The model using AIRg as the dependent variable also included insulin sensitivity as a covariate since insulin sensitivity is a known determinant of AIRg. Residuals above and below three standard deviations were removed. All statistics were performed using SAS version 9.4 (SAS Institute Inc.).

Results

Demographics

The derivation of the final sample included in the statistical analysis is described in Figure 1. The original sample comprised 322 children. Children who were overweight or obese, defined by the CDC as having a BMI percentile of 85 or above at the time of this study, were excluded from the study to focus the study on non-overweight children. This exclusion reduced the sample to 217 children. An additional individual was removed who did not have a data point for BMI percentile, resulting in 216 individuals. Of these 216 children, 17 were excluded from analysis because the family history of diabetes section was not completed on their questionnaires. This exclusion resulted in a final sample of 199 children who were not overweight or obese and who had complete information about their family history of diabetes for final analysis.

This sample of 199 children contained a relatively equal number of males (50.75%) and females (49.25%) 7–12 years old, with an average age of 9.66 years. Most children were in Tanner stages 1–2 (76.86%). Children in this sample were ethnically diverse and consisted of Caucasians (45.72%), African Americans (31.16%), Hispanics (19.60%), or an unspecified other ethnicity (3.52%). On average, children were in the 53–55th BMI percentile with an average fat mass of 6.63 kg and an average lean mass of 25.08 kg. Family history of diabetes was common, with 43.72% (n=87) of children reporting a parent, sibling, or grandparent with diabetes.

Differences in demographic characteristics of children with a family history of diabetes (n=87) and without a family history of diabetes (n=112) are displayed in Table 1. There were no significant differences in sex, age, ethnicity, socioeconomic status,

resting energy expenditure, BMI percentile, or body composition between the two groups. There were also no significant differences in measures of fasting glucose, fasting insulin, insulin sensitivity, or acute insulin response to glucose.

Regression Analysis

Multiple linear regression analysis was used to determine the influence of family history of diabetes on insulin measures (fasting insulin, insulin sensitivity, and AIRg). All models were adjusted for sex, age, pubertal status, ethnicity, waist circumference, and grams of carbohydrates. Family history was a significant predictor of higher fasting insulin (p=0.0372) along with sex (p=0.0034), waist circumference (p=<0.0001), and carbohydrate intake (0.0075). Ethnicity, age, and Tanner stages were not significant predictors of fasting insulin. Table 2 provides details from this analysis. Family history was not a significant predictor of insulin sensitivity or AIRg (p=0.32, p=0.13, respectively).

Discussion

This study evaluated how a family history of diabetes could influence various measures of insulin activity in children who are not overweight or obese. Our results found that family history of diabetes significantly predicts fasting insulin levels in normal weight children. . In addition, having a family history of diabetes contributes to the variability of fasting insulin when accounting for the contributions of age, sex, pubertal status, ethnicity, waist circumference, and carbohydrate intake.

In addition to family history of diabetes, grams of carbohydrates consumed, sex, and waist circumference were also significant predictors of fasting insulin in this cohort of normal weight children. Although previous studies demonstrate that insulin resistance increases during puberty[26 27], Tanner stage was not a significant predictor of fasting insulin in this analysis (p=0.0583). In our cohort, 74/87 (85.1%) of children with a family history of diabetes and 96/112 (85.7%) of children without a family history of diabetes were in Tanner stages 1 or 2. Therefore, the uniformity of this categorical variable within our sample likely reduced its effect. Similarly, the narrow age range (7–12 years) and similar ages of children with a family history of diabetes (average=9.72 years, standard deviation=1.57 years) and without a family history of diabetes (average=9.62 years, standard deviation=1.51 years) likely prevented age from being a significant predictor of fasting insulin, as seen previously.[28] Ethnicity was also not a significant predicator of fasting insulin in this analysis. It has been shown that African American children have higher fasting insulin levels compared to white children; however, it is recognized that the contributions of race/ethnicity to insulin-related outcomes can be mediated by factors such as body composition.[29] Our analysis excluded children who were overweight or obese, so there were minimal differences in body composition among the children in this sample, which could have modified the effect of ethnicity in this study.

Previous research has shown that fasting insulin levels in children can be predictive of future risk for developing type 2 diabetes. A study of Pima Indians ages 5–19 showed that high levels of fasting insulin were predictive of type 2 diabetes after an 8.4 year follow-up period.[30] High fasting insulin in childhood was also a significant predictor of adult type 2 diabetes in a study of African American and Caucasian girls.[31]

Nguyen et al. (2010) concluded that children in the top decile for fasting insulin were 2.85 times more likely to develop pre-diabetes and 5.54 times more likely to develop diabetes, regardless of weight.[32] Findings from the Bogalusa Heart Study, a longitudinal study of children ages 4–17, showed higher fasting insulin levels in children with a parental history of diabetes.[33] Importantly, parental history of diabetes was an independent predictor of hyperinsulinemia, hyperglycemia, and other risk factors associated with metabolic syndrome in adulthood.[33] These studies demonstrate the importance of identifying children with high fasting insulin at an early age in order to potentially decrease their risk of type 2 diabetes through intervention and prevention programs.

Our results and others demonstrate that family history of diabetes is one way to help identify children who might eventually develop hyperinsulinemia and be at an increased risk for insulin resistance. The heritability of fasting insulin is estimated to be 49%[34-36], meaning the variability in fasting insulin is equally due to genetic and environmental influences. According to our results, having a family member with diabetes is an independent predictor of fasting insulin in normal weight children when considering multiple environmental covariates. This finding suggests that perhaps the genetic influences on fasting insulin are more contributory to its variability in normal weight children. Therefore, family history of diabetes could be used as a simple screening tool to identify normal weight children who are potentially at risk for high levels of fasting insulin and, later, type 2 diabetes.

This study was limited by sample size and missing information for some participants. Furthermore, the question “is there a family history of high blood

sugar/diabetes" could have captured children with a family history of both type 1 and type 2 diabetes, but we anticipate the number of individuals with a family history of type 1 diabetes to be much less than those with a family history of type 2 diabetes because type 2 diabetes has a much higher population prevalence compared to type 1 diabetes. In addition, the association with grams of carbohydrate and fasting insulin could be confounded by total caloric intake, which was not accounted for in the regression models.

Despite these limitations, this study population was ethnically diverse, and all variables studied were obtained under a strictly controlled environment, which increases the reliability and generalizability of the results. Future studies could evaluate the relationship between family history and additional insulin and glucose measurements such as HOMA and insulin secretion to better understand insulin resistance and beta-cell function, respectively. The impact of family history could also be further explored by determining if paternal or maternal family history is more influential on biomarker activity.

Performing type 2 diabetes screening for all children with a family history of diabetes using the current methods would be an expensive endeavor, given the current direct and indirect costs of diabetes screening per case identified.[37] However, the potential impact of introducing prevention programs to normal weight children based on their family history of diabetes has yet to be investigated. As discussed, type 2 diabetes prevention programs for children have had low success rates, and they have typically focused on diet and physical activity behaviors in overweight children. Prevention programs for children with a family history of diabetes who are *normal weight* could have numerous benefits, such as reducing the risk for unhealthy weight gain, which

would not only decrease the risk for type 2 diabetes but also for other obesity-related comorbidities. The efficacy of such programs would be an important contribution to the knowledge of how family history of diabetes can be used as a tool for disease prevention.

REFERENCES

1. Dabelea D, Mayer-Davis EJ, Saydah S, et al. Prevalence of type 1 and type 2 diabetes among children and adolescents from 2001 to 2009. JAMA 2014;311(17):1778-86 doi: 10.1001/jama.2014.3201.

2. Imperatore G, Boyle JP, Thompson TJ, et al. Projections of type 1 and type 2 diabetes burden in the U.S. population aged <20 years through 2050: dynamic modeling of incidence, mortality, and population growth. Diabetes Care 2012;35(12):2515-20 doi: 10.2337/dc12-0669.

3. Dart AB, Martens PJ, Rigatto C, Brownell MD, Dean HJ, Sellers EA. Earlier onset of complications in youth with type 2 diabetes. Diabetes Care 2014;37(2):436-43 doi: 10.2337/dc13-0954.

4. Amutha A, Mohan V. Diabetes complications in childhood and adolescent onset type 2 diabetes—a review. Journal of Diabetes and Its Complications 2016;30(5):951-7 doi: 10.1016/j.jdiacomp.2016.02.009.

5. Yeaw J, Halinan S, Hines D, et al. Direct medical costs for complications among children and adults with diabetes in the US commercial payer setting. Applied Health Economics and Health Policy 2014;12(2):219-30 doi: 10.1007/s40258-014-0086-9.

6. Wu Y, Ding Y, Tanaka Y, Zhang W. Risk factors contributing to type 2 diabetes and recent advances in the treatment and prevention. International Journal of Medical Sciences 2014;11(11):1185-200 doi: 10.7150/ijms.10001.

7. Arenaza L, Medrano M, Amasene M, et al. Prevention of diabetes in overweight/obese children through a family-based intervention program including supervised exercise (PREDIKID project): study protocol for a randomized controlled trial. Trials 2017;18(1):372 doi: 10.1186/s13063-017-2117-y.

8. Onge ES, Miller SA, Motycka C, DeBerry A. A review of the treatment of type 2 diabetes in children. Journal of Pediatric Pharmacology and Therapeutics 2015;20(1):4-16 doi: 10.5863/1551-6776-20.1.4.

9. Liese AD, D'Agostino RB, Jr., Hamman RF, et al. The burden of diabetes mellitus among US youth: prevalence estimates from the SEARCH for Diabetes in Youth Study. Pediatrics 2006;118(4):1510-8 doi: 10.1542/peds.2006-0690.

10. Lee AM, Fermin CR, Filipp SL, Gurka MJ, DeBoer MD. Examining trends in prediabetes and its relationship with the metabolic syndrome in US adolescents, 1999-2014. Acta Diabetologica 2017;54(4):373-81 doi: 10.1007/s00592-016-0958-6.

11. Standards of Medical Care in Diabetes—2017 Abridged for Primary Care Providers. Clinical Diabetes: a publication of the American Diabetes Association 2017;35(1):5-26 doi: 10.2337/cd16-0067.

12. Valaiyapathi B, Gower B, Ashraf AP. Pathophysiology of Type 2 Diabetes in Children and Adolescents. Current Diabetes Reviews 2020;16(3):220-29 doi: 10.2174/1573399814666180608074510.

13. Xue Y, Gao M, Gao Y. Childhood type 2 diabetes: Risks and complications. Experimental and Therapeutic Medicine 2016;12(4):2367-70 doi: 10.3892/etm.2016.3654.

14. Rosenbloom AL, Silverstein JH, Amemiya S, Zeitler P, Klingensmith GJ. ISPAD Clinical Practice Consensus Guidelines 2006-2007. Type 2 diabetes mellitus in the child and adolescent. Pediatric Diabetes 2008;9(5):512-26 doi: 10.1111/j.1399-5448.2008.00429.x.

15. Urakami T, Kuwabara R, Habu M, et al. Clinical characteristics of non-obese children with type 2 diabetes mellitus without involvement of beta-cell autoimmunity. Diabetes Research and Clinical Practice 2013;99(2):105-11 doi: 10.1016/j.diabres.2012.11.021.

16. Rodriguez-Moran M, Guerrero-Romero F, Aradillas-Garcia C, et al. Obesity and family history of diabetes as risk factors of impaired fasting glucose: implications for the early detection of prediabetes. Pediatric Diabetes 2010;11(5):331-6 doi: 10.1111/j.1399-5448.2009.00590.x.

17. Casazza K, Dulin-Keita A, Gower BA, Fernandez JR. Differential influence of diet and physical activity on components of metabolic syndrome in a multiethnic

sample of children. Journal of the American Dietetic Association 2009;109(2):236-44 doi: 10.1016/j.jada.2008.10.054.

18. Marshall WA, Tanner JM. Variations in pattern of pubertal changes in girls. Archives of Disease in Childhood 1969;44(235):291-303.

19. Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in boys. Archives of Disease in Childhood 1970;45(239):13-23.

20. Kuczmarski RJ, Ogden CL, Guo SS, et al. 2000 CDC Growth Charts for the United States: methods and development. Vital and Health Statistics. Series 11, Data from the National Health Survey 2002(246):1-190.

21. Johnson RK, Driscoll P, Goran MI. Comparison of multiple-pass 24-hour recall estimates of energy intake with total energy expenditure determined by the doubly labeled water method in young children. Journal of the American Dietetic Association 1996;96(11):1140-4 doi: 10.1016/s0002-8223(96)00293-3.

22. Bergman RN, Phillips LS, Cobelli C. Physiologic evaluation of factors controlling glucose tolerance in man: measurement of insulin sensitivity and beta-cell glucose sensitivity from the response to intravenous glucose. The Journal of Clinical Investigation 1981;68(6):1456-67.

23. Pacini G, Bergman RN. MINMOD: a computer program to calculate insulin sensitivity and pancreatic responsivity from the frequently sampled intravenous glucose tolerance test. Computer Methods and Programs in Biomedicine 1986;23(2):113-22.

24. Yang YJ, Youn JH, Bergman RN. Modified protocols improve insulin sensitivity estimation using the minimal model. The American Journal of Physiology 1987;253(6 Pt 1):E595-602 doi: 10.1152/ajpendo.1987.253.6.E595.

25. Matthews DR, Edge JA, Dunger DB. An unbiased glucose clamp method using a variable insulin infusion: its application in diabetic adolescents. Diabetic Medicine: a journal of the British Diabetic Association 1990;7(3):246-51.

26. Goran MI, Gower BA. Longitudinal study on pubertal insulin resistance. Diabetes 2001;50(11):2444-50 doi: 10.2337/diabetes.50.11.2444.

27. Hannon TS, Janosky J, Arslanian SA. Longitudinal study of physiologic insulin resistance and metabolic changes of puberty. Pediatric Research 2006;60(6):759-63 doi: 10.1203/01.pdr.0000246097.73031.27.

28. Moran A, Jacobs DR, Jr., Steinberger J, et al. Changes in insulin resistance and cardiovascular risk during adolescence: establishment of differential risk in males and females. Circulation 2008;117(18):2361-8 doi: 10.1161/circulationaha.107.704569.

29. Gower BA, Nagy TR, Trowbridge CA, Dezenberg C, Goran MI. Fat distribution and insulin response in prepubertal African American and white children. The American Journal of Clinical Nutrition 1998;67(5):821-7 doi: 10.1093/ajcn/67.5.821.

30. McCance DR, Pettitt DJ, Hanson RL, Jacobsson LT, Bennett PH, Knowler WC. Glucose, insulin concentrations and obesity in childhood and adolescence as predictors of NIDDM. Diabetologia 1994;37(6):617-23.

31. Morrison JA, Glueck CJ, Umar M, Daniels S, Dolan LM, Wang P. Hyperinsulinemia and metabolic syndrome at mean age of 10 years in black and white schoolgirls and development of impaired fasting glucose and type 2 diabetes mellitus by mean age of 24 years. Metabolism: Clinical and Experimental 2011;60(1):24-31 doi: 10.1016/j.metabol.2009.12.013.

32. Nguyen QM, Srinivasan SR, Xu JH, Chen W, Kieltyka L, Berenson GS. Utility of childhood glucose homeostasis variables in predicting adult diabetes and related cardiometabolic risk factors: the Bogalusa Heart Study. Diabetes Care 2010;33(3):670-5 doi: 10.2337/dc09-1635.

33. Srinivasan SR, Frontini MG, Berenson GS. Longitudinal changes in risk variables of insulin resistance syndrome from childhood to young adulthood in offspring of parents with type 2 diabetes: the Bogalusa Heart Study. Metabolism: Clinical and Experimental 2003;52(4):443-50; discussion 51-3 doi: 10.1053/meta.2003.50065.

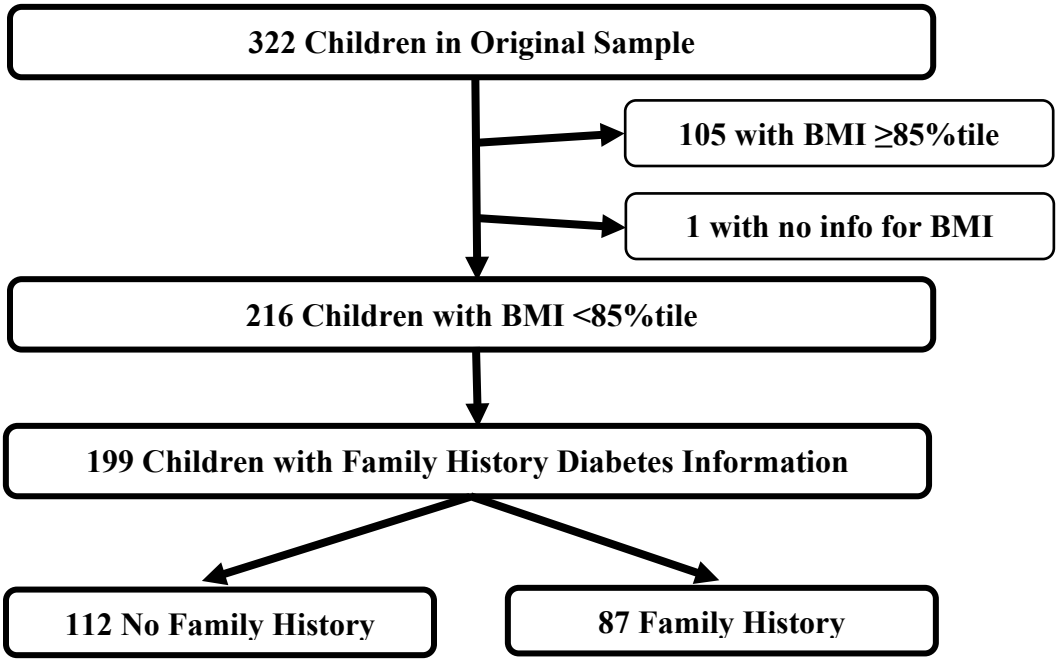
34. Lehtovirta M, Kaprio J, Forsblom C, Eriksson J, Tuomilehto J, Groop L. Insulin sensitivity and insulin secretion in monozygotic and dizygotic twins. Diabetologia 2000;43(3):285-93 doi: 10.1007/s001250050046.

35. Hong Y, Pedersen NL, Brismar K, Hall K, de Faire U. Quantitative genetic analyses of insulin-like growth factor I (IGF-I), IGF-binding protein-1, and insulin levels in middle-aged and elderly twins. The Journal of Clinical Endocrinology and Metabolism 1996;81(5):1791-7 doi: 10.1210/jcem.81.5.8626837.

36. Souren NY, Paulussen AD, Loos RJ, et al. Anthropometry, carbohydrate and lipid metabolism in the East Flanders Prospective Twin Survey: heritabilities. Diabetologia 2007;50(10):2107-16 doi: 10.1007/s00125-007-0784-z.

37. Wu EL, Kazzi NG, Lee JM. Cost-effectiveness of screening strategies for identifying pediatric diabetes mellitus and dysglycemia. JAMA Pediatrics 2013;167(1):32-9 doi: 10.1001/jamapediatrics.2013.419.

Figure 1. Study sample procurement



Of the 322 children in the original study, 199 children met the requirements for inclusion in this analysis due to being normal weight and having information about their family history of type 2 diabetes. Family history of diabetes was present in approximately 44% of the children in this procured sample.

Table 1. Differences in participant demographic information according to family history of diabetes

Variable	No Family History of Type 2 Diabetes	Family History of Type 2 Diabetes	*P* value
	Mean (N)	Mean (N)	
Male (%)	54.46 (61)	45.98 (40)	0.2349
Female (%)	45.54 (51)	54.02 (47)	
Age	9.62 (112)	9.72 (87)	0.6516
Tanner Stage 1	68.47 (76)	65.12 (56)	0.9419
Tanner Stage 2	18.02 (20)	20.93 (18)	
Tanner Stage 3	12.61 (14)	12.79 (11)	
Tanner Stage 4	0.9 (1)	1.16 (1)	
Caucasian (%)	49.11 (55)	41.38 (36)	0.6852
African American (%)	29.46 (33)	33.33 (29)	
Hispanic (%)	18.75 (21)	20.69 (18)	
Other Ethnicity (%)	2.68 (3)	4.6 (4)	
BMI Percentile	55.88 (112)	52.84 (87)	0.3590
Total Fat Mass (kg)*	6.68 (110)	6.57 (82)	0.7878
Total Lean Mass (kg)*	25.08 (110)	25.08 (82)	0.9979
Fasting Insulin*	10.41 (101)	11.79 (78)	0.0678
Insulin Sensitivity*	6.22 (99)	6.43 (76)	0.6884
AIRg*	728.92 (99)	820.96 (77)	0.2926
Fasting glucose (mg/dL)*	96.98 (101)	97.92 (77)	0.3419
Fasting Glucose ≥100 mg/dl (%)*	32.14 (36)	40.23 (35)	0.2375

*Indicates variables with missing data for some children.
Children with a family history of diabetes were compared to children without a family history of diabetes. All children were below the 85th and above the 5th BMI percentile.

Table 2. Statistical output from the regression model using fasting insulin as the outcome variable

Variable	F Value	*P* Value
Waist Circumference	19.46	<0.0001*
Sex	8.84	0.0034*
Grams of Carbohydrates	7.35	0.0075*
Family History of Diabetes	4.42	0.0372*
Tanner Stage	2.54	0.0583
Ethnicity	1.37	0.2529
Age	0.14	0.7047

Model: fasting insulin = sex Tanner stage age ethnicity waist circumference grams of carbohydrates family history diabetes
*P<0.05

INVESTIGATING FAMILY HISTORY OF DIABETES AS A PREDICTOR OF FASTING INSULIN AND FASTING GLUCOSE IN A SAMPLE OF HEALTHY WEIGHT ADULTS

by
JESSICA J. DENTON, YENNI E. CEDILLO, JOSÉ R. FERNÁNDEZ

In preparation for *Preventative Medicine*

Format adapted for dissertation

Abstract

Type 2 diabetes is a major public health problem for the global community. Having a family history of diabetes significantly increases the risk for diabetes development. A better understanding of how family history contributes to diabetes risk could lead to more effective prevention efforts for these at-risk individuals. In a previous study, we showed that family history of diabetes is a significant predictor of fasting insulin in healthy weight children. To build on this finding, the present study utilized the National Health and Nutrition Examination Survey (NHANES, 2017) to determine if family history of diabetes could also predict fasting insulin, and fasting glucose, in a population of healthy weight adults. Fasting glucose (mg/dL) and fasting insulin (pmol/L) were used as dependent variables in each model respectively, with family history of diabetes as the independent variable. Covariates for each model included age, gender, race/ethnicity, waist circumference, and macronutrient intake. The model significantly predicted the variance of fasting glucose [($F(11,364)=34.80$, $p<0.001$, $R^2=0.2342$] and fasting insulin [$F(11,343)=17.58$, $p<0.001$, $R^2=0.1162$]. After adjusting for covariates, family history was a significant predicator of fasting glucose ($p=0.0193$), as were age, gender, non-Hispanic Black ethnicity, waist circumference, and fat intake. Significant predictors of fasting insulin included gender and waist circumference, but not family history ($p=0.8264$). In addition, fasting plasma glucose was higher in individuals with a family history of diabetes ($p=0.033$). These results add to the understanding of how family history of diabetes contributes to the crucial components of diabetes development. Knowledge of how family history of diabetes relates to fasting insulin and glucose

activity in healthy weight individuals can be used to design personalized screening and early prevention strategies.

Introduction

Type 2 diabetes prevention is a necessary but challenging priority of public health organizations worldwide. Globally, 537 million people have type 2 diabetes, and this is expected to rise to 643 million in 2030 and reach 782 million in 2045, which will have major economic and health consequences, especially for low- and middle-income countries where diabetes rates are highest.[1] The increasing prevalence of type 2 diabetes emphasizes the need for prevention strategies but also diverts limited resources from prevention efforts to the treatment of diabetes. Therefore, prevention strategies must consider how to make a significant impact while also being simple and cost-effective. Identifying individuals at risk for type 2 diabetes is essential for establishing effective prevention efforts. Multiple large population studies have found that family history of diabetes significantly increases the risk to develop diabetes regardless of other risk factors such as body mass index (BMI), age, ethnicity, socioeconomic status, physical inactivity, and biological sex.[2] Utilizing family history of diabetes for identification of at-risk individuals is simple, universally accessible, and inexpensive. Furthermore, these individuals could be targeted for early diabetes prevention efforts, which could also prevent the development of additional risk factors for diabetes, such as obesity and cardiovascular disease.

Prevention strategies for individuals with a family history of diabetes should be informed by how family history contributes to diabetes development. However, understanding how family history increases diabetes risk is complicated by overlapping genetic, behavioral, and environmental influences shared by families.[3] Identifying genetic variants associated with type 2 diabetes has been a major research focus, but, to date, common genetic variants explain only approximately half of the heritability of diabetes.[4]

Through these research efforts, genetic loci that affect glucose and insulin function have been discovered and linked to type 2 diabetes risk.[5,6] While understanding how genetic variation influences glucose and insulin activity at a molecular level is important, it will take time and additional large, more diverse research cohorts to apply this information in a cost-effective and equitable manner clinically.[4] In the meantime, readily available tools to understand how family history affects diabetes risk must be explored.

Measuring fasting plasma glucose is a clinically available and effective method for the diagnosis of diabetes (≥126 mg/dL) and prediabetes (100–125 mg/dL).[7] High levels of fasting glucose are caused by reduced cellular responses to insulin and defects in insulin production.[8] The body's response to decreased insulin sensitivity is to produce more insulin, which can result in increased levels of fasting insulin in addition to high levels of fasting glucose.[9] Understanding fasting glucose and insulin levels in individuals with a family history of diabetes will help illuminate the contribution of family history to diabetes risk. Studying those with a family history of diabetes who have not yet developed diabetes or acquired additional risk factors is necessary to isolate the contribution of family history to fasting glucose and insulin in these at-risk individuals.

In a previous study, we demonstrated that family history of diabetes is a significant predictor of fasting insulin in a sample of diverse, healthy weight children after adjusting for age, sex, pubertal status, ethnicity, waist circumference, and total grams of carbohydrates consumed per day.[10] To further understand how family history influences fasting glucose and insulin, this analysis explores whether family history of diabetes is a significant predictor of fasting glucose and fasting insulin in a population of

healthy weight adults. We hypothesize that family history of type 2 diabetes will be a significant predicator of fasting insulin and fasting glucose in healthy adults.

Methods

Participants

Data from the public National Health and Nutrition Examination Survey (NHANES) collected from 2017 to 2018 were included for this study (n=970). For this research, the analyses focused on adult participants (>19 years) who were healthy weight (BMI ≥18.5 and ≤24.9) with and without family history of diabetes. Any participants who were pregnant, were younger than 20 years old, had a fasting glucose >126 mg/dL, or had a diagnosis of liver disease, cancer, or diabetes were excluded from analyses. The NHANES data were adjusted for person weights (two-year sample weights) from NHANES 2017–2018 (WTMEC2YR), as is recommended by the National Center for Health Statistics (NCHS). NHANES Institutional Review Board (IRB) approval and documented consent were obtained from the participants. This study was exempt from IRB review. This exemption complied with the policy of the University of Alabama at Birmingham IRB related to the use of public available data for research and publication.

NHANES Variables

Variables from the demographics, examination, laboratory, dietary, and questionnaire data of NHANES were used in the statistical models. Demographic variables included participant age in years (RIDAGEYR), gender (RIAGENDR), and race and Hispanic origin information (RIDRETH1). Gender was defined as male or

female. Race and Hispanic origin information included Mexican American, other Hispanic, non-Hispanic white, non-Hispanic Black, and other race including multiracial. The examination variable included participant waist circumference in centimeters (BMXWAIST). Laboratory variables included fasting glucose in mg/dL (LBXGLU) and fasting insulin in pmol/L (LBDINSI). Dietary variables included percent intake of carbohydrates, fat, and protein. Percent intake was calculated by averaging intake over the course of two successive days. The questionnaire variables included whether the participant had a family history of diabetes and whether they felt at risk for diabetes/prediabetes. Participants could provide a yes or no answer to the following questions: "Including living and deceased, were any of your close biological relatives...including father, mother, sisters, or brothers, ever told by a health professional that they had diabetes?" (MCQ300c). "Do you feel you could be at risk for diabetes or prediabetes?" (DIQ172).

Statistical Analysis

Descriptive statistics (means and frequencies) were calculated to summarize age, gender, race, examination, laboratory, and dietary information by family history of diabetes. Independent-sample t-tests and chi-squared tests were performed to detect differences in sociodemographic characteristics by family history of diabetes. The Rao-Scott x2 p-values were reported in the results as recommended by NHANES survey. Separate multiple regression models were tested using fasting glucose or fasting insulin as the dependent variable and family history of diabetes as the independent variable. For each model, covariates included age, gender, race, waist circumference, and percent

macronutrient intake (carbohydrates, fat, and protein). Dietary intake was included to investigate which, if any, macronutrient categories were predictive of biomarkers, and if so, the direction of the relationship between macronutrients and biomarkers. Whether macronutrients predict decreased or increased biomarker concentration could inform dietary strategies to prevent diabetes. All residuals were tested for normality, and significance level was considered $\alpha=0.05$ for all statistical analyses. All analyses were performed with SAS statistical software (version 9.4, 2002–2012 by SAS Institute Inc., Cary, NC).

Results

Participants

Of the 9,254 individuals who completed the 2017–2018 NHANES, 970 met the inclusion and exclusion criteria for this analysis (Figure 1). Given that the focus of this research is on family history of diabetes and how it impacts risk for developing type 2 diabetes, only individuals with family history information provided who did not have diabetes or a fasting glucose that indicates diabetes were included. Individuals with a BMI $\leq$18.5 and $\geq$24.9 were removed from the sample to prevent factors associated with being over or under weight to confound the impact of family history of diabetes.

Among the 970 participants, approximately 34.8% had a family history of diabetes in a parent or sibling. Demographic information was compared between participants with and without a family history of diabetes (Table 1). There were no differences in age, gender, or race. Participants were, on average, 42.12 years old (CL 40.38–43.85), and 59.14% identified as female. The majority of participants identified as

non-Hispanic white (33.5%) or selected other race including multiracial (31.3%). There were no differences in BMI or waist circumference between participants with and without a family history of diabetes. On average, participant BMI was 22.25 kg/m^2 (CL 22.10–22.39) and waist circumference was 81.82 cm (CL 80.90–82.73). There were no differences in average macronutrient intake between groups. Individuals with a family history of diabetes had a macronutrient distribution of 47.39%kcals from carbs, 34.54%kcal from fat, and 16.03%kcal from protein; those without a family history had a distribution of 47.04%kcal from carbs, 35.29%kcal from fat, and 15.24%kcal from protein. Participants with a family history had higher fasting glucose (average=99.30 mg/dL, p=0.03, CL 97.75–100.85). Average fasting insulin was not different between those with and without a family history of diabetes (p=0.6708). When participants were asked if they felt at risk for prediabetes/diabetes, 32.5% of individuals with a family history answered "yes" compared to 7.2% of individuals without a family history (p<0.0001).

Regression Analysis

Separate multivariate regression analyses were carried out to assess whether family history of diabetes predicts the variance of fasting glucose and fasting insulin, respectively. We began by testing the model used in our previous study, which included age, gender, race, waist circumference, and grams of carbohydrate consumed as covariates. To better investigate the effects of race and dietary intake on fasting glucose and fasting insulin, the final models included age, gender, race (divided into five subgroups – Mexican American, other Hispanic, non-Hispanic white, non-Hispanic

Black, and other race including multiracial), waist circumference, and percent intake of carbohydrate, fat, and protein as covariates.

The model significantly predicted the variance of fasting glucose [$F(11,364)=34.80$, $p<0.001$, $R^2=0.2342$] with age, gender, non-Hispanic Black ethnicity, waist circumference, fat intake, and family history of diabetes as significant predictors. Age ($p=0.0394$), waist circumference ($p=0.0010$), and percent fat intake ($p=0.0216$) were all significant predictors of increased fasting glucose (Table 2). Fasting glucose was predicted to be higher in males ($p=0.0029$) and lower in Non-Hispanic Blacks ($p=0.0216$). Family history of diabetes was a significant predictor of increased fasting glucose when adjusting for all other variables in the model ($p=0.0193$).

The model significantly predicted the variance of fasting insulin [$F(11,343)=17.58$, $p<0.001$, $R^2=0.1162$] with gender and waist circumference as the significant predictors. Waist circumference predicted increased fasting insulin ($p=0.0020$), and fasting insulin was predicted to be lower in males ($p=0.0359$). Neither family history of diabetes nor any other covariate was a significant predictor of fasting insulin in the model (Table 3).

Discussion

The purpose of this study was to investigate whether a family history of diabetes is a significant predictor of fasting glucose and fasting insulin levels in healthy weight adults. Our results showed that family history was a significant predictor of fasting glucose, but not fasting insulin, after adjusting for age, gender, race, waist circumference, and percent daily macronutrient intake. Age, gender, waist circumference, non-Hispanic Black ethnicity, and percent fat intake were significant predictors of fasting glucose in

addition to family history of diabetes. Gender and waist circumference were significant predictors of fasting insulin. The relationships between the covariates and fasting glucose were mostly anticipated based on previously identified associations, but the results from the fasting insulin model were somewhat surprising.

Our analysis showed that age and male sex predicted increased fasting glucose, which was expected given prior conclusions from the literature. As individuals age, decreased insulin sensitivity and insulin production in addition to changes in body composition and metabolism result in elevated fasting plasma glucose, even in individuals without diabetes.[11-14] Regardless of age, males with and without diabetes have higher fasting glucose compared to females, which is thought to be due to hormonal, body composition, and energy utilization differences; however, the relationship between fasting glucose and biological sex is not fully understood.[15-19]

Conversely, our analysis indicated that male sex significantly predicted decreased fasting insulin. In individuals with normal glucose levels, it has been shown that women are more insulin sensitive compared to men, likely due to hormonal differences.[18,20] However, the differences in fasting insulin according to biological sex have been mixed. In one healthy adult sample, there were no differences in the fasting insulin levels of men and women[20], but another study showed that female adolescents have higher fasting insulin compared to males.[21] One study examining fasting insulin candidate genes found differences in gene expression by sex[22], adding another layer of complexity to the impact of biological sex on fasting insulin.

This analysis found that non-Hispanic Black ethnicity significantly predicts lower levels of fasting glucose. Although multiple studies have found higher hemoglobin A1c

(HbA1c) levels in Blacks compared with other ethnicities[23-28], knowledge of ethnic differences in fasting glucose among healthy weight individuals is limited and conflicting. One study showed no differences in fasting glucose levels between Blacks and non-Hispanic whites or between Hispanics and non-Hispanic whites without diabetes.[29] However, in studies of non-diabetic individuals with a family history of diabetes, Blacks have lower fasting glucose levels compared to whites[24,28,30], which is consistent with our results. More understanding of how ethnicity impacts glucose activity in healthy individuals is needed to fully appreciate the relationship between ethnicity and fasting glucose.

Age, biological sex, and ethnicity are unavoidable components of type 2 diabetes risk, but additional factors contribute significantly to diabetes development. Therefore, we also investigated how modifiable components such as diet and waist circumference contribute to the variability of fasting glucose and fasting insulin in the presence of innate risk factors. We found percentage intake of fat predicted higher fasting glucose, and waist circumference predicted higher fasting glucose and fasting insulin in our sample population.

Previous studies have also shown that increases in waist circumference are associated with higher fasting glucose and fasting insulin levels.[31-33] Waist circumference is utilized as a noninvasive measure of abdominal fat, including visceral fat[34], which, in excess, promotes insulin resistance through cellular processes that lead to chronic inflammation.[35-37] It has been demonstrated that waist circumference is a stronger predictor of type 2 diabetes risk compared to BMI in certain ethnic groups and for individuals with a low or healthy weight.[38,39] Our analysis of individuals with a healthy

BMI demonstrates waist circumference is a significant predictor of fasting insulin and fasting glucose activity, further emphasizing the utility of this measurement in this population.

Even when accounting for waist circumference, dietary fat intake was found to predict increased fasting glucose in this analysis. Excessive intake of fat is clearly linked to obesity and insulin resistance[40-42], and it has been shown that a low carbohydrate/high fat diet increases fasting glucose in healthy weight adults.[43] Yet others have found diets consisting of a greater percentage of carbohydrate to be associated with higher fasting insulin levels in individuals without diabetes.[44,45] On the other hand, studies have also shown that replacing intake of carbohydrates or saturated fats with polyunsaturated fats has led to improvement in fasting insulin and blood glucose regulation.[46,47] These studies demonstrate that the relationship between dietary fat and diabetes biomarkers is complex because different types of fat have varying effects. Of note, total percent fat intake was used as a variable in the model, which did not distinguish between saturated and unsaturated fats.

Diets low in fat have been shown to induce weight loss and therefore reduce the risk for type 2 diabetes, but other diets (Mediterranean, low-carbohydrate, low energy, intermittent fasting) can also achieve similar outcomes.[43] However, if weight loss is not necessary or desired, perhaps an approach of avoiding certain food groups known to increase the risk for type 2 diabetes, such as red and processed meats and sugar-sweetened beverages, is advisable.[44,45] Individuals who are a normal weight but who are at risk for type 2 diabetes based on their family history may find it beneficial to reduce

their intake of certain fats, given the association of those fats with increased fasting glucose shown in multiple studies.

Understanding how macronutrient intake is related to diabetes risk for normal weight individuals with a family history of diabetes has many potential benefits. In our sample, those with a family history of diabetes were more likely to feel at risk for diabetes ($p<0.0001$). Providing these individuals with established dietary strategies to reduce diabetes risk could allow them to feel more in control of their health.

Another significant finding of this analysis was that individuals with a family history of diabetes had higher fasting glucose levels compared to those without a family history. Having a family history of diabetes has been shown to significantly increase hemoglobin A1C (HbA1C) in individuals with and without a diagnosis of diabetes[48] and has also been associated with poor glycemic control in multiple populations.[49-53] Previous studies comparing fasting glucose levels between individuals with and without a family history of diabetes have been inconsistent. Some have found significant differences[48,54-56], while others have not found significant differences in fasting glucose based on family history.[57-59]

Current recommendations from the U.S. Preventive Services Task Force (USPSTF) are to screen adults for type 2 diabetes by measuring fasting plasma glucose only if they are overweight or obese.[7] In our sample, the average fasting glucose for individuals with a family history of diabetes was 99.30±0.72mg/dL, which intersects prediabetes levels (defined as 100–125 mg/dL).[60] Therefore, individuals who are a healthy weight and have a family history of diabetes could potentially benefit from diabetes screening to identify borderline or undetected dysglycemia. These individuals

could then engage in prevention strategies that serve the dual purpose of preventing diabetes and unhealthy weight gain, thus improving the overall health of this population.

Unexpectedly, our results found that family history was not a significant predictor of fasting insulin. Previous studies have shown that individuals with a family history of diabetes tend to have higher fasting insulin levels[57,59,61,62], however, not all these studies were conducted in healthy weight individuals, which was a characteristic of our sample. For this and other reasons such as differences in study population and design, other studies have not found higher fasting insulin levels in those with a family history of diabetes.[56,63,64] Healthy weight individuals could have less variation in their fasting insulin levels because they do not have the insulin resistance that is commonly associated with excess weight gain. Further, it is possible that, for adults with normal weight, the diabetes in their family is consequent to excess weight gain rather than to any genetic impairment in insulin resistance or beta cell function.

Interestingly, individuals with a family history of diabetes in our sample had higher fasting glucose, but on average, it was below prediabetic levels. Perhaps, in individuals with a family history of diabetes who are normoglycemic and normal weight, it is their cellular response to insulin that is impaired, causing slightly elevated fasting glucose compared to those without a family history. However, their elevated plasma glucose is below the threshold that would signal increased insulin secretion and subsequent elevated fasting insulin. Therefore, individuals with and without a family history have similar fasting insulin levels in our sample. If there is minimal variance in fasting insulin between those with and without a family history, it would make sense that family history is not a significant predictor of the variance in fasting insulin in this model.

The sequence of insulin defects that lead to diabetes development have long been debated[65,66] and perhaps vary based on accompanying genetic variants that may be passed down through families. Future studies could investigate whether family history is predictive of other biomarkers that contribute to diabetes development, such as glucose disposal rate or insulin sensitivity, and whether these biomarkers enact a mediating effect between fasting insulin and family history.

This study was able to utilize a population of healthy weight adults to investigate how relevant risk factors influence fasting glucose and fasting insulin activity. However, the study sample from this adult cohort consisted of primarily non-Hispanic white individuals in their early 40s, which limits the generalizability of the results. In addition, the 970 individuals who met study criteria did not all have laboratory values for fasting glucose and/or fasting insulin, which reduced the sample size for the separate statistical analyses. In addition, the question determining positive family history of diabetes did not specify a family history of type 1 or type 2 diabetes; however, we expect most individuals had a family history of type 2 diabetes given its great population prevalence. We did not investigate other measures of glucose and insulin activity (glucose tolerance, insulin sensitivity, etc.) in our population, though this is a potential area for future study. Our finding that family history did not predict fasting insulin was unexpected, though it perhaps reveals insight into the early biological mechanisms of diabetes development in the absence of factors associated with overweight and obesity.

Conclusion

Family history of diabetes was a significant predictor of fasting glucose, but not fasting insulin, in a sample of healthy weight adults without diabetes after controlling for innate and modifiable risk factors. Further research is needed to better understand how family history contributes to the biological processes responsible for type 2 diabetes development in order to design individualized prevention strategies for at-risk individuals.

REFERNCES

1. Federation ID. IDF Diabetes Atlas, 10th edn. https://www.diabetesatlas.org

2. Ismail L, Materwala H, Al Kaabi J. Association of risk factors with type 2 diabetes: A systematic review. *Comput Struct Biotechnol J*. 2021;19:1759-1785. doi:10.1016/j.csbj.2021.03.003

3. Claassen L, Henneman L, Janssens AC, et al. Using family history information to promote healthy lifestyles and prevent diseases; a discussion of the evidence. *BMC Public Health*. May 13 2010;10:248. doi:10.1186/1471-2458-10-248

4. Udler MS, McCarthy MI, Florez JC, Mahajan A. Genetic Risk Scores for Diabetes Diagnosis and Precision Medicine. *Endocr Rev*. Dec 1 2019;40(6):1500-1520. doi:10.1210/er.2019-00088

5. Dupuis J, Langenberg C, Prokopenko I, et al. New genetic loci implicated in fasting glucose homeostasis and their impact on type 2 diabetes risk. *Nat Genet*. Feb 2010;42(2):105-16. doi:10.1038/ng.520

6. Saxena R, Hivert MF, Langenberg C, et al. Genetic variation in GIPR influences the glucose and insulin responses to an oral glucose challenge. *Nat Genet*. Feb 2010;42(2):142-8. doi:10.1038/ng.521

7. Force UPST. Screening for Prediabetes and Type 2 Diabetes: US Preventive Services Task Force Recommendation Statement. *JAMA*. 2021;326(8):736-743. doi:10.1001/jama.2021.12531

8. Galicia-Garcia U, Benito-Vicente A, Jebari S, et al. Pathophysiology of Type 2 Diabetes Mellitus. *Int J Mol Sci*. Aug 30 2020;21(17)doi:10.3390/ijms21176275

9. Petersen MC, Shulman GI. Mechanisms of Insulin Action and Insulin Resistance. *Physiol Rev*. Oct 1 2018;98(4):2133-2223. doi:10.1152/physrev.00063.2017

10. Denton JJ, Fernandez JR. The role of family history of diabetes as a predictor of insulin activity in a sample of diverse, normal weight children. *Endocrine and*

Metabolic Science. 2021/06/30/ 2021;3:100090. doi:https://doi.org/10.1016/j.endmts.2021.100090

11. Chia CW, Egan JM, Ferrucci L. Age-Related Changes in Glucose Metabolism, Hyperglycemia, and Cardiovascular Risk. *Circ Res*. Sep 14 2018;123(7):886-904. doi:10.1161/circresaha.118.312806

12. Zavaroni I, Dall'Aglio E, Bruschi F, et al. Effect of age and environmental factors on glucose tolerance and insulin secretion in a worker population. *J Am Geriatr Soc*. Apr 1986;34(4):271-5. doi:10.1111/j.1532-5415.1986.tb04223.x
13. Zamboni M, Armellini F, Harris T, et al. Effects of age on body fat distribution and cardiovascular risk factors in women. *Am J Clin Nutr*. Jul 1997;66(1):111-5. doi:10.1093/ajcn/66.1.111

14. Ko GT, Wai HP, Tang JS. Effects of age on plasma glucose levels in non-diabetic Hong Kong Chinese. *Croat Med J*. Oct 2006;47(5):709-13.

15. Mauvais-Jarvis F. Gender differences in glucose homeostasis and diabetes. *Physiol Behav*. Apr 1 2018;187:20-23. doi:10.1016/j.physbeh.2017.08.016

16. Williams JW, Zimmet PZ, Shaw JE, et al. Gender differences in the prevalence of impaired fasting glycaemia and impaired glucose tolerance in Mauritius. Does sex matter? *Diabet Med*. Nov 2003;20(11):915-20. doi:10.1046/j.1464-5491.2003.01059.x

17. Sicree RA, Zimmet PZ, Dunstan DW, Cameron AJ, Welborn TA, Shaw JE. Differences in height explain gender differences in the response to the oral glucose tolerance test- the AusDiab study. *Diabet Med*. Mar 2008;25(3):296-302. doi:10.1111/j.1464-5491.2007.02362.x

18. Tramunt B, Smati S, Grandgeorge N, et al. Sex differences in metabolic regulation and diabetes susceptibility. *Diabetologia*. Mar 2020;63(3):453-461. doi:10.1007/s00125-019-05040-3

19. Menke A, Rust KF, Savage PJ, Cowie CC. Hemoglobin A1c, fasting plasma glucose, and 2-hour plasma glucose distributions in U.S. population subgroups: NHANES 2005-2010. *Ann Epidemiol*. Feb 2014;24(2):83-9. doi:10.1016/j.annepidem.2013.10.008

20. Kautzky-Willer A, Brazzale AR, Moro E, et al. Influence of increasing BMI on insulin sensitivity and secretion in normotolerant men and women of a wide age span. *Obesity (Silver Spring)*. Oct 2012;20(10):1966-73. doi:10.1038/oby.2011.384

21. DeBoer MD, Dong L, Gurka MJ. Racial/ethnic and sex differences in the ability of metabolic syndrome criteria to predict elevations in fasting insulin levels in

adolescents. *J Pediatr*. Dec 2011;159(6):975-81.e3. doi:10.1016/j.jpeds.2011.05.023

22. Lagou V, Mägi R, Hottenga JJ, et al. Sex-dimorphic genetic effects and novel loci for fasting glucose and insulin variability. *Nat Commun*. Jan 5 2021;12(1):24. doi:10.1038/s41467-020-19366-9

23. Carson AP, Muntner P, Selvin E, et al. Do glycemic marker levels vary by race? Differing results from a cross-sectional analysis of individuals with and without diagnosed diabetes. *BMJ Open Diabetes Res Care*. 2016;4(1):e000213. doi:10.1136/bmjdrc-2016-000213

24. Chapp-Jumbo E, Edeoga C, Wan J, Dagogo-Jack S. Ethnic disparity in hemoglobin A1c levels among normoglycemic offspring of parents with type 2 diabetes mellitus. *Endocr Pract*. May-Jun 2012;18(3):356-62. doi:10.4158/ep11245.

25. Kirk JK, D'Agostino RB, Jr., Bell RA, et al. Disparities in HbA1c levels between African-American and non-Hispanic white adults with diabetes: a meta-analysis. *Diabetes Care*. Sep 2006;29(9):2130-6. doi:10.2337/dc05-1973

26. Ziemer DC, Kolm P, Weintraub WS, et al. Glucose-independent, black-white differences in hemoglobin A1c levels: a cross-sectional analysis of 2 studies. *Ann Intern Med*. Jun 15 2010;152(12):770-7. doi:10.7326/0003-4819-152-12-201006150-00004

27. Herman WH, Ma Y, Uwaifo G, et al. Differences in A1C by race and ethnicity among patients with impaired glucose tolerance in the Diabetes Prevention Program. *Diabetes Care*. Oct 2007;30(10):2453-7. doi:10.2337/dc06-2003

28. Razavi LN, Ebenibo S, Edeoga C, Wan J, Dagogo-Jack S. Five-Year Glycemic Trajectories Among Healthy African-American and European-American Offspring of Parents With Type 2 Diabetes. *Am J Med Sci*. May 2020;359(5):266-270. doi:10.1016/j.amjms.2020.03.005

29. Haffner SM, D'Agostino R, Saad MF, et al. Increased insulin resistance and insulin secretion in nondiabetic African-Americans and Hispanics compared with non-Hispanic whites. The Insulin Resistance Atherosclerosis Study. *Diabetes*. Jun 1996;45(6):742-8. doi:10.2337/diab.45.6.742

30. Dagogo-Jack S, Edeoga C, Ebenibo S, Nyenwe E, Wan J. Lack of racial disparity in incident prediabetes and glycemic progression among black and white offspring of parents with type 2 diabetes: the pathobiology of prediabetes in a biracial cohort (POP-ABC) study. *J Clin Endocrinol Metab*. Jun 2014;99(6):E1078-87. doi:10.1210/jc.2014-1077

31. Veghari G, Sedaghat M, Joshaghani H, et al. The association of fasting blood glucose (FBG) and waist circumference in northern adults in Iran: a population based study. *J Diabetes Metab Disord*. Jan 6 2014;13(1):2. doi:10.1186/2251-6581-13-2

32. Farin HM, Abbasi F, Reaven GM. Body mass index and waist circumference both contribute to differences in insulin-mediated glucose disposal in nondiabetic adults. *Am J Clin Nutr*. Jan 2006;83(1):47-51. doi:10.1093/ajcn/83.1.47

33. Pang SJ, Man QQ, Song S, et al. Relationships of Insulin Action to Age, Gender, Body Mass Index, and Waist Circumference Present Diversely in Different Glycemic Statuses among Chinese Population. *J Diabetes Res*. 2018;2018:1682959. doi:10.1155/2018/1682959

34. Pouliot MC, Després JP, Lemieux S, et al. Waist circumference and abdominal sagittal diameter: best simple anthropometric indexes of abdominal visceral adipose tissue accumulation and related cardiovascular risk in men and women. *Am J Cardiol*. Mar 1 1994;73(7):460-8. doi:10.1016/0002-9149(94)90676-9

35. Snel M, Jonker JT, Schoones J, et al. Ectopic Fat and Insulin Resistance: Pathophysiology and Effect of Diet and Lifestyle Interventions. *International Journal of Endocrinology*. 2012/05/24 2012;2012:983814. doi:10.1155/2012/983814

36. Ritchie SA, Connell JM. The link between abdominal obesity, metabolic syndrome and cardiovascular disease. *Nutr Metab Cardiovasc Dis*. May 2007;17(4):319-26. doi:10.1016/j.numecd.2006.07.005

37. Olefsky JM, Glass CK. Macrophages, inflammation, and insulin resistance. *Annu Rev Physiol*. 2010;72:219-46. doi:10.1146/annurev-physiol-021909-135846

38. Feller S, Boeing H, Pischon T. Body mass index, waist circumference, and the risk of type 2 diabetes mellitus: implications for routine clinical practice. *Dtsch Arztebl Int*. Jul 2010;107(26):470-6. doi:10.3238/arztebl.2010.0470

39. Fan Y, Wang R, Ding L, et al. Waist Circumference and its Changes Are More Strongly Associated with the Risk of Type 2 Diabetes than Body Mass Index and Changes in Body Weight in Chinese Adults. *J Nutr*. May 1 2020;150(5):1259-1265. doi:10.1093/jn/nxaa014

40. Ahmed B, Sultana R, Greene MW. Adipose tissue and insulin resistance in obese. *Biomed Pharmacother*. May 2021;137:111315. doi:10.1016/j.biopha.2021.111315

41. Lionetti L, Mollica MP, Lombardi A, Cavaliere G, Gifuni G, Barletta A. From chronic overnutrition to insulin resistance: the role of fat-storing capacity and

inflammation. *Nutr Metab Cardiovasc Dis*. Feb 2009;19(2):146-52. doi:10.1016/j.numecd.2008.10.010

42. Boushey C, Ard J, Bazzano L, et al. USDA Nutrition Evidence Systematic Reviews. *Dietary Patterns and Growth, Size, Body Composition, and/or Risk of Overweight or Obesity: A Systematic Review*. USDA Nutrition Evidence Systematic Review; 2020.

43. Parry SA, Smith JR, Corbett TR, Woods RM, Hulston CJ. Short-term, high-fat overfeeding impairs glycaemic control but does not alter gut hormone responses to a mixed meal tolerance test in healthy, normal-weight individuals. *Br J Nutr*. Jan 2017;117(1):48-55. doi:10.1017/s0007114516004475

44. Gower BA, Pearson K, Bush N, et al. Diet pattern may affect fasting insulin in a large sample of black and white adults. *Eur J Clin Nutr*. Apr 2021;75(4):628-635. doi:10.1038/s41430-020-00762-9

45. Schwingshackl L, Hoffmann G. Long-term effects of low glycemic index/load vs. high glycemic index/load diets on parameters of obesity and obesity-associated risks: a systematic review and meta-analysis. *Nutr Metab Cardiovasc Dis*. Aug 2013;23(8):699-706. doi:10.1016/j.numecd.2013.04.008

46. Imamura F, Micha R, Wu JH, et al. Effects of Saturated Fat, Polyunsaturated Fat, Monounsaturated Fat, and Carbohydrate on Glucose-Insulin Homeostasis: A Systematic Review and Meta-analysis of Randomised Controlled Feeding Trials. *PLoS Med*. Jul 2016;13(7):e1002087. doi:10.1371/journal.pmed.1002087

47. Wanders AJ, Blom WAM, Zock PL, Geleijnse JM, Brouwer IA, Alssema M. Plant-derived polyunsaturated fatty acids and markers of glucose metabolism and insulin resistance: a meta-analysis of randomized controlled feeding trials. *BMJ Open Diabetes Res Care*. 2019;7(1):e000585. doi:10.1136/bmjdrc-2018-000585

48. Lee YH, Shin MH, Nam HS, et al. Effect of Family History of Diabetes on Hemoglobin A1c Levels among Individuals with and without Diabetes: The Dong-gu Study. *Yonsei Med J*. Jan 2018;59(1):92-100. doi:10.3349/ymj.2018.59.1.92

49. Kuo CK, Lin LY, Yu YH, Chang CH, Kuo HK. A family history of diabetes mellitus is associated with poor glycemic control and increased metabolic risks among people with diabetes: data from the National Health and Nutrition Examination Survey 1999-2004. *Intern Med*. 2010;49(6):549-55. doi:10.2169/internalmedicine.49.2880

50. Gong L, Kao WH, Brancati FL, Batts-Turner M, Gary TL. Association between parental history of type 2 diabetes and glycemic control in urban African Americans. *Diabetes Care*. Sep 2008;31(9):1773-6. doi:10.2337/dc08-0618

51. Hilding A, Eriksson AK, Agardh EE, et al. The impact of family history of diabetes and lifestyle factors on abnormal glucose regulation in middle-aged Swedish men and women. *Diabetologia*. Nov 2006;49(11):2589-98. doi:10.1007/s00125-006-0402-5

52. Xiong X, Wei L, Xiao Y, et al. Effects of family history of diabetes on pancreatic β-cell function and diabetic ketoacidosis in newly diagnosed patients with type 2 diabetes: a cross-sectional study in China. *BMJ Open*. Jan 11 2021;11(1):e041072. doi:10.1136/bmjopen-2020-041072

53. Alzaheb RA, Altemani AH. The prevalence and determinants of poor glycemic control among adults with type 2 diabetes mellitus in Saudi Arabia. *Diabetes Metab Syndr Obes*. 2018;11:15-21. doi:10.2147/dmso.S156214

54. Shahid A, Saeed S, Rana S, Mahmood S. Family history of diabetes and parental consanguinity: important risk for impaired fasting glucose in south east Asians. *West Indian Med J*. Jun 2012;61(3):219-23. doi:10.7727/wimj.2011.072

55. Rodríguez-Moran M, Guerrero-Romero F, Aradillas-García C, et al. Obesity and family history of diabetes as risk factors of impaired fasting glucose: implications for the early detection of prediabetes. *Pediatr Diabetes*. Aug 2010;11(5):331-6. doi:10.1111/j.1399-5448.2009.00590.x

56. Lopez X, Bouché C, Tatro E, Goldfine AB. Family history of diabetes impacts on interactions between minimal model estimates of insulin sensitivity and glucose effectiveness. *Diabetes Obes Metab*. Feb 2009;11(2):123-30. doi:10.1111/j.1463-1326.2008.00913.x

57. Vauhkonen I, Niskanen L, Vanninen E, Kainulainen S, Uusitupa M, Laakso M. Defects in insulin secretion and insulin action in non-insulin-dependent diabetes mellitus are inherited. Metabolic studies on offspring of diabetic probands. *J Clin Invest*. Jan 1 1998;101(1):86-96. doi:10.1172/jci716

58. Danadian K, Balasekaran G, Lewy V, Meza MP, Robertson R, Arslanian SA. Insulin sensitivity in African-American children with and without family history of type 2 diabetes. *Diabetes Care*. Aug 1999;22(8):1325-9. doi:10.2337/diacare.22.8.1325

59. Perseghin G, Ghosh S, Gerow K, Shulman GI. Metabolic defects in lean nondiabetic offspring of NIDDM parents: a cross-sectional study. *Diabetes*. Jun 1997;46(6):1001-9. doi:10.2337/diab.46.6.1001

60. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2020. *Diabetes Care*. Jan 2020;43(Suppl 1):S14-s31. doi:10.2337/dc20-S002

61. Gulli G, Ferrannini E, Stern M, Haffner S, DeFronzo RA. The metabolic profile of NIDDM is fully established in glucose-tolerant offspring of two Mexican-American NIDDM parents. *Diabetes*. Dec 1992;41(12):1575-86. doi:10.2337/diab.41.12.1575

62. Warram JH, Martin BC, Krolewski AS, Soeldner JS, Kahn CR. Slow glucose removal rate and hyperinsulinemia precede the development of type II diabetes in the offspring of diabetic parents. *Ann Intern Med*. Dec 15 1990;113(12):909-15. doi:10.7326/0003-4819-113-12-909

63. Sakurai M, Nakamura K, Miura K, et al. Family history of diabetes, lifestyle factors, and the 7-year incident risk of type 2 diabetes mellitus in middle-aged Japanese men and women. *J Diabetes Investig*. May 6 2013;4(3):261-8. doi:10.1111/jdi.12033

64. Mbanya JC, Pani LN, Mbanya DN, Sobngwi E, Ngogang J. Reduced insulin secretion in offspring of African type 2 diabetic parents. *Diabetes Care*. Dec 2000;23(12):1761-5. doi:10.2337/diacare.23.12.1761

65. Abdul-Ghani M, DeFronzo RA. Insulin Resistance and Hyperinsulinemia: the Egg and the Chicken. *J Clin Endocrinol Metab*. Mar 25 2021;106(4):e1897-e1899. doi:10.1210/clinem/dgaa364

66. Weir GC. Which comes first in non-insulin-dependent diabetes mellitus: insulin resistance or beta-cell failure? Both come first. *Jama*. Jun 21 1995;273(23):1878-9.

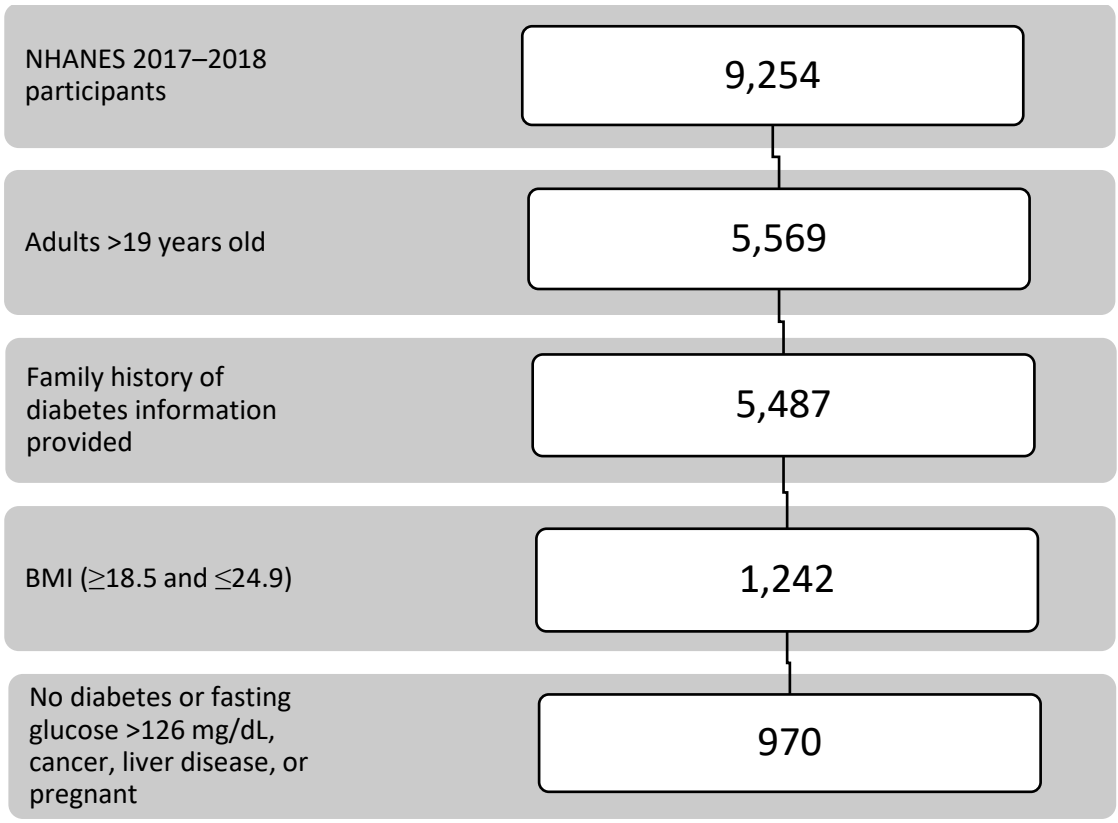


Figure 1: Study sample creation

Table 1. Comparison of participant factors based on family history of diabetes

Variable	No Family History of Diabetes (n=616)	Family History of Diabetes (n=354)	*p*-value
Demographic Data			
Age (years)	41.64±0.99	43.01 ±1.18	0.3564
Gender			
Male (%)	27.94%(n=282)	12.91%(n=144)	0.1322
Female (%)	37.20%(n=334)	21.94%(n=210)	
Race			
Mexican American (%)	2.53% (n=38)	2.35% (n=32)	0.2535
Other Hispanic (%)	3.66% (n=43)	1.80%(n=19)	
Non-Hispanic White (%)	43.90%(n=218)	21.52%(n=107)	
Non-Hispanic Black (%)	6.69% (n=127)	3.91%(n=82)	
Other Race – Including Multiracial (%)	8.34% (n=190)	5.25%(n=114)	
Feel at risk for prediabetes/diabetes (%)			
Yes	4.72%(n=50)	11.27% (n=132)	<0.0001*
No	60.58%(n=564)	23.41%(n=215)	
Examination Data			
BMI (kg/m^2)	22.21±0.10	22.33±0.13	0.5626
Waist Circumference (cm)	81.79±0.51	81.88±0.55	0.8943
Laboratory Data			
Fasting Glucose (mg/dL)	97.55±0.58	99.30±0.72	0.0330*
Fasting Insulin (pmol/L)	39.10±2.50	41.22±4.77	0.6708
Dietary Data			
Energy Intake (kcal)	2103.33±45.18	2025.03±80.77	0.4320
Daily Carbohydrate Intake (gm)	247.75±6.83	238.94±9.13	0.4624
Protein Intake (gm)	78.74±1.93	77.73±3.27	0.7893
Fat Intake (gm)	82.57±2.24	78.25±3.54	0.3714

*$p<0.05$; Values are reported as either means and standard deviations or as percentages.

Table 2. Multiple regression analysis exploring the relationship between fasting glucose (mg/dL) and family history of diabetes NHANES (2017) (n=364)

Variable	β	*p*-value	Standard error
Age	0.1172	0.0094*	0.0394
Gender (males)	3.3813	0.0029*	0.9505
Race			
Mexican American	0.7387	0.7396	2.1919
Other Hispanic	0.2148	0.9127	1.9270
Non-Hispanic White	-1.7130	0.2067	1.2979
Non-Hispanic Black	-3.9838	0.0216*	1.5544
Waist Circumference (cm)	0.2854	0.0010*	0.0703
Percent Carbohydrates	0.1349	0.2179	0.1049
Percent Protein	0.1424	0.1728	0.0995
Percent Fat	0.1894	0.0216*	0.0738
Family History of Diabetes	2.5592	0.0193*	0.9764

* Significant differences were denoted at $p<0.05$

Table 3. Multiple regression analysis exploring the relationship between fasting insulin (pmol/L) and family history of diabetes NHANES (2017) (n=343)

Variable	β	*p*-value	Standard error
Age	-0.103	0.1184	0.0627
Gender (male)	-6.1957	0.0359*	2.6890
Race			
Mexican American	-0.7771	0.8797	5.0464
Other Hispanic	-4.6764	0.3420	4.7657
Non-Hispanic White	-6.6309	0.0578	3.2271
Non-Hispanic Black	0.1749	0.9689	4.405
Waist Circumference	0.6424	0.0020*	0.1726
Percent Carbohydrate	0.3552	0.1306	0.2220
Percent Protein	-0.2955	0.3318	0.2946
Percent Fat	0.3348	0.0851	0.1816
Family History of Diabetes	-0.6296	0.8264	2.9970

*Significant differences were denoted at $p<0.05$

INCORPORATION OF A GENETICS-BASED INFORMATION MODULE INTO STANDARDIZED DIABETES PATIENT EDUCATION

by
KATHRYN T. DRAZBA, JESSICA JOHNSON DENTON, CHRISTINA BARGER HURST, GERALD MCGWIN, PAUL A. MACLENNAN, FERNANDO OVALLE

In preparation for *Primary Care Diabetes*

Format adapted for dissertation

Abstract

The purpose of this study is to investigate the effectiveness of a genetics educational module created to improve understanding about the genetics of diabetes, assess motivation to engage in healthy lifestyle behaviors, and gauge interest in genetic testing for diabetes. Participants were recruited from the Multidisciplinary Comprehensive Diabetes Clinic at the University of Alabama at Birmingham. Participants completed a pre-survey to assess three domains: 1) knowledge about diabetes etiology and testing, 2) healthy lifestyle behaviors, and 3) interest in genetic testing. Participants viewed a short, recorded educational module and then completed a post-survey to reassess the domains. Participants increased knowledge about genetics of diabetes ($p<0.0001$) and genetic testing ($p=0.0184$), demonstrated motivation to adopt healthy behaviors ($p<0.0001$), and decreased interest in genetic testing ($p=0.0833$) after viewing the module. The educational module increased understanding of diabetes and increased motivation to adopt healthy behaviors. The need for patient-friendly educational modules explaining the genetics of diabetes will likely increase with continued discoveries of how genetics contributes to diabetes risk and outcomes. This short, educational module has the potential to provide genetic information in an effective way that is easily adapted in a routine clinic setting.

Introduction

Type 2 diabetes is a serious health condition, and the significant increase in prevalence in recent decades has led public health officials to declare diabetes a global crisis. It is estimated that by 2050, one in three Americans will have diabetes.[1] Reducing the incidence and prevalence of diabetes to circumvent the predicted healthcare and economic impacts is a major national and global public health goal.[2] Currently, diabetes imposes a substantial burden on the healthcare system due to the associated direct and indirect costs of medical treatment.

The current and projected prevalence of diabetes and the anticipated burden on the healthcare system demonstrate the immediate need for cost-effective and prevention-based interventions. Because of the scale of diabetes diagnoses and the anticipated costs, primary prevention at the population level is thought to be the most cost-effective approach in reducing diabetes incidence.[3]

Research focused on the development of effective diabetes prevention interventions is ongoing; however, preventing the upward trend of diabetes prevalence in the population continues to be a significant challenge. It has been demonstrated that lifestyle interventions such as the Diabetes Prevention Program can successfully reduce diabetes incidence for up to 15 years, but longer-term/permanent efficacy for a lifestyle-based intervention has not been achieved.[4] Therefore, researchers must continue the necessary and meaningful investigations into novel, multidisciplinary, and effective diabetes prevention approaches.[5]

Many health professionals believe that genomics-based tools for risk assessment for the management and prevention of diabetes are promising.[6] However, healthcare

providers recognize that incorporating genetic risk information for chronic diseases into patient care is challenging, and they have expressed uncertainty about when, why, and how to incorporate genetics information into their clinical care and practice. Recent emphasis on translational research aims to close the gap between genetic risk assessment and clinical care will allow for more useful incorporation of genetics knowledge into both the primary care and prevention settings.[7]

Increased knowledge about the genetic associations and implications of chronic health conditions has led to an increase in the development of interventions that aim to effectively communicate diabetes risk and motivate patients to adopt healthier lifestyle behaviors. However, education regarding genetic contributions and the role of family history as a risk factor has been used in diabetes prevention and management interventions with mixed results.

Some studies have shown that informing patients about their genetic risk to develop diabetes did not lead to significant positive behavior changes.[8-10] One study showed that adults who were at high risk for developing type 2 diabetes were motivated to make healthy lifestyle choices only if they were to receive genetic risk information that demonstrated they were at high risk.[11] Other studies have demonstrated that education about genetic risk can increase perception of control with respect to preventing or treating diabetes.[12-14] One study demonstrated short-term feelings of controllability, but the intended effects were negligible after just three months.[15] More research about the effects of genetic risk assessment and education is currently underway, and additional research is necessary to determine the most effective methods of communicating diabetes risk and instilling long-term behavioral changes.[16,17]

Study Rationale

Because previous research has shown mixed results in producing long-term prevention of type 2 diabetes, more research is necessary to determine if genetics-based education is useful in prevention efforts, as well as in the management of diabetes. If individuals understood that diabetes development and progression were not due solely to either genetics or lifestyle, but a combination of the two, it could help them understand what behavior changes would be most beneficial in preventing or managing their diabetes.

This study aimed to determine whether an educational module about the genetics of diabetes would affect knowledge about diabetes etiology and the current state of genetic testing for type 2 diabetes, patient motivation to make healthy lifestyle changes, and patient interest in genetic testing for diabetes. We hypothesize that the intervention will increase knowledge of type 2 diabetes and motivation to engage in healthy lifestyle behaviors.

Methods

Study Design

This was a cross-sectional study that assessed four primary outcomes within three overarching domains (Table 1) using an educational intervention. This study aimed to 1) increase patient knowledge about the genetic contributions of diabetes, 2) increase patient knowledge about the current clinical utility of genetic testing for diabetes, 3) assess patient motivation to change lifestyle/behaviors, and 4) assess patient interest in genetic

testing for diabetes. The Institutional Review Board of the University of Alabama at Birmingham (UAB) reviewed this study and granted it exempt status.

Recruitment and Participants

Data collection occurred from December 2015 through February 2016. Convenience sampling was employed by recruiting participants from the educational classes offered by the UAB Multidisciplinary Comprehensive Diabetes Clinic (MCDC) located in the UAB Kirklin Clinic in Birmingham, Alabama. Classes were taught by diabetes education and care specialists. The patients attending this clinic had an active diagnosis of type 1 or type 2 diabetes. This research opportunity was presented to all patients who attended the educational sessions on days when data collection occurred.

Implementation

A folder containing all study materials was given to the education class attendees. The study folder contained: 1) an informational letter describing the study, 2) instructions for the study, 3) the demographic questionnaire, 4) the pre-survey, and 5) the post-survey. Education class attendees who did not desire to be a participant in the study were instructed to return their study folders without completing the demographic questionnaire and the surveys. Attendees who elected to participate were instructed to complete the demographic questionnaire and the pre-survey before the educational intervention was presented. The 10-minute-long genetics-based educational module was then shown to the participants. After the conclusion of the educational module, the participants completed

the post-survey. The implementation of the study protocol was overseen by the same individuals each recruitment day to ensure consistency among participants.

No identifying patient information was collected or recorded during the course of the study. Therefore, all survey responses were anonymous. Participants created their own unique identifier of three numbers and three letters, which were used to link the demographic questionnaire and the pre- and post-surveys to facilitate statistical analysis.

Study Materials

Surveys

The pre- and post-surveys were developed by the Principal Investigator (PI; a UAB genetic counseling graduate student) after reviewing and evaluating existing knowledge-based diabetes education surveys, such as those available from the Michigan Diabetes Research Center at the University of Michigan (Michigan Diabetes Research Center, 2015; Gateway Community Health Center, 2003). A validated survey that fulfilled the needs for this particular study was not identified, but the survey examples available provided guidance in terms of the development of educational content and survey questions related to diabetes knowledge. The survey instruments were reviewed by a certified genetic counselor, the medical director of the MCDC, and a certified diabetes care and education specialist. The surveys each contained 12 “agree or disagree” questions written at an eighth grade reading level. Pre- and post-survey questions were matched in the sense that Question 1 for both the pre- and post-survey assessed the same information, but each survey utilized different wording to prevent recall bias.

Educational Presentation

The presentation entitled "Genetics of Diabetes" was developed by the PI as an educational module to describe what is known and what is not currently known about the genetics of diabetes. The presentation was recorded using PowerPoint slides and contained the following information: a brief discussion of monogenic diabetes (neonatal diabetes mellitus and maturity-onset diabetes of the young) and type 1 diabetes, genetic contributions to type 2 diabetes including a discussion of family history as an important risk factor for type 2 diabetes and the contributions of lifestyle factors, and a statement on how current genetic testing for type 2 diabetes is not clinically actionable. The educational module was shown to all attendees of the diabetes education classes regardless of their study participation status.

Analysis

Data from the demographic questionnaire and the pre- and post-surveys were inputted and managed in a study-specific project database within the Research Electronic Data Capture (REDCap) database. Participant responses were coded, indexed, and analyzed with SAS (SAS Institute Inc.; Cary, NC). Pre- and post-survey data were compared for the four primary outcomes: 1) patient knowledge about the genetic contributions of diabetes, 2) patient knowledge about the clinical utility of genetic testing for diabetes, 3) patient motivation to change lifestyle/behaviors, and 4) interest in genetic testing for diabetes.

For three of the four primary outcomes, a pre- and post-survey summary score was calculated. In addition, for each outcome it was determined whether the participant

received a “high score,” which was determined as follows. Four questions on the pre- and post-surveys assessed participant knowledge about the genetic contributions of diabetes. A high score equated to answering at least three out of four questions correctly. Two questions on the pre- and post-surveys assessed participant knowledge about the clinical utility of genetic testing for diabetes. A high score equated to answering two out of two questions correctly. Five questions on the pre- and post-surveys assessed the current practice of and intent to practice healthy lifestyle behaviors, respectively. A high score equated to selecting “Agree” (reflecting motivation to participate in the specific behavior) for at least four of the five questions. One question on the pre- and post-surveys assessed interest in genetic testing. Participants selected either “Agree” or “Disagree” to reflect his/her interest in testing, and no summary score was calculated because the question produced a dichotomous variable.

The frequency of high scores pre- and post-survey were examined using McNemar’s test with alpha <0.05 considered statistically significant. Furthermore, significant differences in the pre- and post-survey proportion of participant interest in genetic testing were also assessed using McNemar’s test. Because domain scores were not normally distributed, differences in pre- and post-survey domain scores were assessed overall and within demographic characteristics using non-parametric methods, specifically, the Wilcoxon signed rank test. Repeated measures logistic regression was used to examine significance within group differences for pre- and post-survey domain high knowledge (binary outcome) for demographic characteristics. The model produced p-values for z-scores and assessed whether pre- and post-survey differences were significant.

Results

Participant Demographics

All patients who attended the diabetes education classes during recruitment days agreed to participate in the study and completed the demographics questionnaire and the pre-survey. However, one participant did not complete the post-survey and was excluded from the study, resulting in a total of 49 participants. Participant demographics are listed in Table 2. Two-thirds of the participants were female (n=30; 61.2%), and participants ranged in age from 24 to 83 years with a mean age of 58 years. The majority of the sample included African American (n=24; 49.0%) and Caucasian (n=20; 40.8%) participants. Slightly more than half the participants (51.0%; n=25) who responded had an annual income that was $50,000 or less. Approximately 43% of participants (n=21) completed a high school education or less, and 40.8% (n=20) completed college or had obtained a graduate/professional degree.

Survey Responses

For the three primary outcomes within the knowledge of genetics, knowledge of testing, and healthy behaviors domains, the proportion of high scores and average scores increased significantly from pre- to post-survey. Participants also decreased their overall interest in genetic testing for type 2 diabetes, although not significantly (Table 3). Overall summary scores increased for the knowledge of genetics, knowledge of testing, and healthy behaviors domains within demographic groups, with some demographic characteristics having statistically significant increases in knowledge and/or healthy behavior motivation. Table 4 presents the mean differences of the pre- and post-survey

scores of the two knowledge domains and the healthy behaviors domain stratified by demographic characteristics. Table 5 presents the differences in interest in genetic testing for diabetes stratified by demographic characteristics.

Knowledge of Genetics of Diabetes

Participants answered an average of 2.3 (out of 4) questions correctly in the pre-survey and an average of 3.5 questions correctly in the post-survey. High knowledge (≥3 correct answers of 4) about the genetics of diabetes increased from 40.8% pre-survey to 85.7% post-survey ($p<0.0001$). Participants averaged an increase of 1.12 correct answers, which corroborates that a significant increase ($p<0.01$) in knowledge was demonstrated. Of the characteristics examined, several demographic groups had significant increases in knowledge after viewing the education module ($p<0.01$), including: both genders, both age groups, Caucasians and African Americans, married, have children, employed full-time and retired, <$50,000 annual income, both under a high school level attainment and college graduates, and those who are not taking insulin.

Knowledge of Genetic Testing for Type 2 Diabetes

Participants answered an average of 0.7 (out of 2) questions correctly in the pre-survey and an average of 1.1 questions correctly in the post-survey. The proportion of people with high knowledge (2 of 2 correct answers) of genetic testing for diabetes increased from 26.6% pre-survey to 46.9% post-survey ($p=0.0184$). Overall, the mean number of questions answered correctly about genetic testing significantly increased ($p<0.01$) by 0.45 points. Knowledge of genetic testing significantly increased ($p<0.05$)

for the following participants after viewing the education module: female, <60 years old, Caucasian, and employed full-time.

Healthy Behaviors

In the pre-survey, 44.9% of participants reported a high level of healthy behaviors with an average of 3.1 (out of 5) positive behaviors reported. In the post-survey, most participants demonstrated a high level of motivation to adopt healthy behaviors with an average of 4.5 positive healthy behaviors they were willing to adopt. High motivation for healthy behaviors increased from 44.9% pre-survey to 87.8% post-survey ($p<0.0001$). In addition, motivation significantly increased ($p<0.01$) by 1.38 points overall. For the demographic characteristics examined, the following participant groups had significant increases ($p<0.01$) in willingness to adopt healthy behaviors after viewing the education module: both genders, both age categories, Whites and African Americans, married, have children, less than high school educational attainment, and family history of diabetes.

Interest in Genetic Testing for Type 2 Diabetes

In the pre-survey, 79.2% (n=38) of participants demonstrated an interest in genetic testing for diabetes. Interest decreased in the post-survey, with 66.7% (n=32) reporting interest in genetic testing for diabetes ($p=0.0833$). Table 5 shows the proportion of subjects interested in genetic testing pre- and post-survey by demographic characteristics. For most of the demographic characteristics examined, post-survey interest decreased. Participants who were female, ≥60 years, retired, and had a college

education each demonstrated a significant decrease ($p<0.05$) in interest in genetic testing for diabetes.

Discussion

The purpose of this study was to investigate whether patients attending standardized diabetes education classes were receptive to learning about the genetics of diabetes and the current status of the clinical utility of genetic testing. An educational module was developed to provide accurate information about current knowledge of genetics in relation to diabetes, as well as inform participants about healthy lifestyle behaviors. The results of this study suggest that the educational module was effective in achieving its goals.

Participants' knowledge about the genetics of diabetes and the inability of a genetic test to diagnose or predict risk for diabetes at this time increased. Validation of these hypotheses demonstrates that the purpose of the educational module in increasing knowledge was achieved. Previous studies have shown receipt of information about type 2 diabetes resulting from both genetic and environmental influences has provided individuals with a greater sense of control over diabetes development.[13,15] Evidence of healthy behavior change after incorporating genetic risk information has also been demonstrated in previous studies focused on smoking cessation due to lung cancer risk, and positive changes in diet, exercise, smoking, and adherence to medical screening guidelines after learning about increased risk conditions such as cancer or Alzheimer's disease.[18-20] This led us to hypothesize that participants' motivation to adopt healthy lifestyle behaviors would increase after viewing the educational module, and there was a

statistically significant increase in participants who scored high on the healthy behaviors domain. This result shows promise that increased knowledge about the dual roles of genetics and lifestyle factors may inspire individuals to act on their motivation and adopt healthy behaviors as shown in these previous studies. It was also hypothesized that interest in genetic testing would decrease after watching the presentation due to increased knowledge about the limitations of genetic testing for diabetes. Interest in genetic testing did decrease post-module; however, the results did not achieve statistical significance. This may be due to an overall interest in genetic testing and desire for health-related personal information, even if the desired knowledge is not currently clinically useful or immediately applicable.

Repeated measures logistic regression was used to analyze characteristics of individuals who increased their knowledge of diabetes and genetic testing for diabetes and increased motivation to adopt healthy lifestyle behaviors. The educational module was successful in increasing knowledge of diabetes across multiple participant characteristics. The only demographic categories that did not demonstrate an increase in this area were the categories with less than eight individuals; therefore, it is possible that the educational intervention could still be effective in these subgroups if more of these individuals were included in the study. Groups that increased in high scores for motivation to adopt healthy lifestyle behaviors were similar to those that increased in knowledge of diabetes. Interestingly, individuals who were currently on insulin therapy did not increase their motivation, but they did increase their knowledge. It has been shown previously that individuals with a family history of diabetes have lower perceived benefits of type 2 diabetes treatment.[12] The majority of participants in our study

population had a family history of diabetes, and it is possible that because individuals require insulin to manage their type 2 diabetes, they have lower perceived benefits of lifestyle changes, and therefore, less motivation to change their current habits.

In contrast, the fewest number of demographic subgroups increased their high score for knowledge of genetic testing for diabetes. For this section, there were only two questions, and a high score was defined as answering both questions correctly. This definition of a high score could be masking score increases, for example individuals may have answered no questions correctly on the pre survey but one question correctly on the post survey, which would not be considered a high score. However, these results could also indicate that the intervention was not successful in increasing knowledge of genetic testing for diabetes. Genetic testing concepts are complicated, and multiple studies have demonstrated that knowledge of genetic testing is low among patients and physicians.[21-23] Furthermore, to reduce the length of the surveys, prior knowledge of genetic testing and healthy literacy were not accessed, which have been shown to be predictive of genetic testing knowledge.[23] Improving the intervention's ability to convey information about the capability of genetic testing may need to include more information about genetic testing in general in order to build a better foundation for individuals to understand the utility of genetic testing in type 2 diabetes specifically.

Limitations of this study include a sample that did not provide enough participants for each demographic characteristic to achieve statistical significance when the data were analyzed within demographic groups. Having a more diverse group of participants and a larger overall sample to provide more participants in each demographic group may have provided additional insight about which groups of participants were better able or less

likely to comprehend the information in the educational module. Extending the recruitment time for the study would have assisted in this area.

Additionally, the study recruited from participants attending optional diabetes education classes. Therefore, the sample comprised individuals who presumably have a higher level of motivation to manage diabetes than a random sample of individuals with diabetes. In addition, we did not ask demographic questions regarding genetics background knowledge, including whether participants studied life sciences. These individuals may have a higher knowledge of genetics or a higher capacity to understand genetics concepts. Offering this intervention in a primary care setting and specifically asking about science education background could provide information about how a more typical patient population would respond to the intervention. In addition, the information provided in this module could be adapted to a particular patient population based on their educational level and understanding of genetics concepts to optimize its effectiveness.

Furthermore, this study was a cross-sectional study and did not investigate long-term knowledge recall/retention, assessment of whether individuals would or did act on their motivation to adopt healthier lifestyle behaviors, or whether participants decided to talk to their family members and physicians about their family history of diabetes, if applicable. Future studies could survey participants longitudinally to evaluate knowledge retention and behavioral outcomes.

Practice Implications

Introducing discussions about the genetics of diabetes and the importance of family history as a risk factor for type 2 diabetes was a novel approach for the UAB

MCDC because the standardized diabetes education classes did not previously address the genetics of diabetes or family history. Our study suggests that patients can understand basic information about the importance of genetics and family history with respect to diabetes and that adding information about these topics to the standardized diabetes education classes and informational booklets may not only be a topic of interest to patients but would provide a more comprehensive approach to educating patients about how one develops diabetes. In addition, given its short length and recorded content, this educational module could be integrated into traditional diabetes education within other diabetes care centers and other providers' practices, including primary care/family medicine clinics, which are often sites to treat and diagnose patients with diabetes. With increased knowledge about the multifactorial nature of diabetes, patients may learn or be reminded that genetics are not fate for those at risk for developing type 2 diabetes, and that adjustment of one's diet and activity levels can increase an individual's chances of experiencing better health outcomes.

REFERENCES

1. J.P. Boyle, T.J. Thompson, E.W. Gregg, et al. Projection of the year 2050 burden of diabetes in the US adult population: dynamic modeling of incidence, mortality, and prediabetes prevalence. Popul Health Metr. 8 (2010) 1-12. https://doi.org/ 10.1186/1478-7954-8-29.

2. M.J. Khoury, M.S. Bowen, W. Burke, et al. Current priorities for public health practice addressing the role of human genomics in improving population health, Am J Prev Med. 40 (2011) 486-93. https://doi.org/10.1016/j.amepre.2010.12.009.

3. L.W. Green, F.L. Brancati, A. Albright. Primary Prevention of Diabetes Working Group, Primary prevention of type 2 diabetes: integrative public health and primary care opportunities, challenges and strategies, Fam Pract. 29 (2012) i13-i23. https://doi.org/ 10.1093/fampra/cmr126.

4. Diabetes Prevention Program Research Group, Long-term effects of lifestyle intervention or metformin on diabetes development and microvascular complications over 15-year follow-up: the Diabetes Prevention Program Outcomes Study, Lancet Diabetes Endocrinol. 3 (2015) 866-75. https://doi.org/10.1016/S2213-8587(15)00291-0.

5. A.A. Vorderstrasse, A. Cho, C.I. Voils, et al. Clinical utility of genetic risk testing in primary care: the example of Type 2 diabetes, Per Med. 10 (2013) 549-63. https://doi.org/10.2217/pme.13.47.

6. K.A.J. Taber, B.D. Dickinson. Genomic-based tools for the risk assessment, management, and prevention of type 2 diabetes, Appl Clin Genet. 8 (2015) 1-8. https://doi.org/10.2147/TACG.S75583.

7. M.T. Scheuner, P. Sieverding, P.G. Shekelle. Delivery of genomic medicine for common chronic diseases: a systematic review, JAMA. 299 (2008) 1320-34. https://doi.org/10.1001/jama.299.11.1320.

8. M. Hivert, J.L. Vassy, J.B. Meigs. Susceptibility to type 2 diabetes mellitus – from genes to prevention, Nat Rev Endocrinol. 10 (2014) 198-205. https://doi.org/10.1038/nrendo.2014.11

9. R.W. Grant, K.E. O'Brien, J.L. Waxler, et al. Personalized genetic risk counseling to motivate diabetes prevention: a randomized trial, Diabetes Care. 36 (2013) 13-19. https://doi.org/10.2337/dc12-0884.

10. C.I. Voils, C.J. Coffman, J.M. Grubber, et al. Does type 2 diabetes genetic testing and counseling reduce modifiable risk factors? A randomized controlled trial of veterans, J Gen Intern Med. 30 (2015) 1591-8. https://doi.org/10.1007/s11606-015-3315-5.

11. S.M. Markowitz, E.R. Park, L.M. Delahant, et al. Perceived impact of diabetes genetic risk testing among patients at high phenotypic risk for type 2 diabetes, Diabetes Care. 34 (2011) 568-73. https://doi.org/10.2337/dc10-1960.

12. L.E. Davies, K. Thirlaway. The influence of genetic explanation of type 2 diabetes on patients' attitudes to prevention, treatment and personal responsibility for health, Public Health Genomics. 16 (2013) 199-207. https://doi.org/10.1159/000353459.

13. M. Nishigaki, Y. Tokunaga-Nakawatase, Y. Nishida, K. Kazuma. The effect of genetic counseling for adult offspring of patients with type 2 diabetes on attitudes toward diabetes and its heredity: a randomized controlled trial, J Genet Couns. 23 (2014) 762-9. https://doi.org/10.1007/s10897-013-9680-5.

14. M. Nishigaki, Y. Tokunaga-Nakawatase, J. Nishida, et al. Randomized controlled trial of the effectiveness of genetic counseling and a distance, computer-based, lifestyle intervention program for adult offspring of patients with type 2 diabetes: background, study protocol, and baseline patient characteristics, J Nutr Metab. (2012) 1-13. https://doi.org/10.1155/2012/831735.

15. M.A. McVay, C. Beadles, R. Wu, et al. Effects of provision of type 2 diabetes genetic risk feedback on patient perceptions of diabetes control and diet and physical activity self-efficacy, Patient Educ Couns. 98 (2015) 1600-7. https://doi.org/10.1016/j.pec.2015.06.016.

16. C.S. Bloss, L. Madlensky, N.J. Schork, E.J. Topol. Genomic information as a behavioral health intervention: can it work? Per Med. 8 (2011) 659-67. https://doi.org/10.2217/pme.11.73.

17. J. Austin, The effect of genetic test-based risk information on behavioral outcomes: a critical examination of failed trials and a call to action, Am J Med Genet. 167A (2015) 2913-5. https://doi.org/10.1002/ajmg.a.37289

18. C.M. McBride, G. Bepler, I.M. Lipkus, et al. Incorporating genetic susceptibility feedback into a smoking cessation program for African-American smokers with low income. Cancer Epidemiol Biomarkers Prev. 11 (2002) 521-8.

19. J.T. Heshka, C. Palleschi, H. Howley, B. Wilson, P.S. Wells. A systematic review of perceived risks, psychological and behavioral impacts of genetic testing. Genet Med. 10 (2008) 19-32. https://doi.org/10.1097/GIM.0b013e31815f524f

20. S. Chao, J.S. Roberts, T.M. Marteau, R. Silliman, L.A. Cupples, R.C. Green. Health behavior changes after genetic risk assessment for Alzheimer disease: The REVEAL Study. Alzheimer Dis Assoc Disord. 22 (2008) 94-97. https://doi.org/10.1097/WAD.0b013e31815a9dcc.

21. E.W. Dekanek, D.L. Thull, M. Massart, et al. Knowledge and opinions regarding BRCA1 and BRCA2 genetic testing among primary care physicians, J Genet Couns. 29 (2020) 122-130. https://doi.org/10.1002/jgc4.1189

22. S.B. Haga, W. Burke, G.S. Ginsburg, R. Mills, R. Agans. Primary care physicians' knowledge of and experience with pharmacogenetic testing. Clin Genet. 82 (2012) 388-94. https://doi.org/10.1111/j.1399-0004.2012.01908.x

23. S. Veilleux and M. Bouffard. Knowledge and understanding of pharmacogenomic testing among patients and health care professionals: A scoping review. Patient Educ Couns. 102 (2019) 2001-2009. https://doi.org/10.1016/j.pec.2019.06.008

Table 1. Study domains, primary outcomes, and score categorizations

Domain	Primary Outcome	Number of Survey Questions	Score Categorization
Knowledge	Genetics of Diabetes	4	Possible score range: 0–4 High score: 3–4 correct answers
	Genetic Testing	2	Possible score range: 0–2 High score: 2 correct answers
Healthy Behaviors	Currently practicing (Pre-survey) Motivation to adopt (Post-survey)	5	Possible score range: 0–5 High score: 4–5 “Agree” responses
Interest in Genetic Testing	Have an Interest	1	Agree Disagree

Table 2. Participant demographics (n=49)

	N (%)
Gender	
Female	30 (61.2)
Male	19 (38.8)
Age in years	
Average (SD)	58 (12.9)
Median (Min, Max)	60 (24, 83)
Race/Ethnicity	
African American	24 (49.0)
Asian	3 (6.1)
Native American/Alaska Native	2 (4.1)
Caucasian	20 (40.8)
Marital Status	
Single/Never Married	6 (12.2)
Married	30 (61.2)
Domestic Partnership	1 (2.0)
Separated/Divorced	7 (14.3)
Widowed	5 (10.2)
Children	
Yes	42 (85.7)
No	7 (14.3)
Employment Status	
Employed Full-time	20 (40.8)
Retired	23 (46.9)
Unemployed	6 (12.2)
Annual Income	
Less than $25,000	14 (38.6)
$25,001–50,000	11 (22.5)
$50,001–75,000	7 (14.3)
$75,001–100,000	5 (10.2)
Greater than $100,000	8 (16.3)
Declined to Answer	4 (8.2)
Educational Attainment	
High School or Less	21 (42.9)
Trade or Technical School	2 (4.1)
Community College/Associate Degree	6 (12.2)
College/Bachelor's Degree	14 (28.6)
Graduate or Professional Degree	6 (12.2)
Family History of Diabetes	
Yes	41 (83.7)
No	7 (14.3)
Don't Know	1 (2.0)
Type of Diabetes	
Type 2	42 (85.7)
Type 1	2 (2.0)
Don't Know	4 (8.2)
Declined to Answer	1 (2.0)
Insulin Treatment	
Yes	13 (26.5)
No	36 (73.5)

Table 3. A comparison of high scores and average participant scores across the primary study outcomes before and after an educational intervention

A. A comparison of high scores before and after an educational intervention.

Domain	**Primary Outcome**	**High Score Definition**	**% High Score (n)**		***p*-value**
			Pre-survey	**Post-survey**	
Knowledge	Genetics of Diabetes	3–4 correct answers	40.8 (20)	85.7 (42)	<0.0001
	Genetic Testing	2 correct answers	26.6 (13)	46.9 (23)	0.0184
Healthy Behaviors	Currently Practicing (pre) Motivation to Adopt (post)	4–5 "agree" responses	44.9 (22)	87.8 (43)	<0.0001
Interest in Genetic Testing	Have an Interest	"yes" response	79.2 (38)	66.7 (32)	0.0833

B. A comparison of average scores before and after an educational intervention.

Domain	**Primary Outcome**	**Number of Questions**	**Average Score**		***p*-value**
			Pre-survey	**Post-survey**	
Knowledge	Genetics of Diabetes	0–4	2.3	3.5	<0.01
	Genetic Testing	0–2	0.7	1.1	<0.01
Healthy Behaviors	Currently Practicing (pre) Motivation to Adopt (post)	0–5	3.1	4.5	<0.01

Table 4. Mean difference (change +/-) in pre- and post-survey scores for knowledge about genetics of diabetes, knowledge about genetic testing, and motivation to adopt healthy behaviors stratified by demographic characteristics (*p<0.05, **p<0.01)

	Change in Knowledge of Diabetes	Change in Knowledge of Genetic Testing	Change in Motivation to Adopt Healthy Behaviors
Overall	+1.12**	+0.45**	+1.38**
Gender			
Female	+1.03**	+0.46*	+0.50**
Male	+1.26**	+0.42	+1.21**
Age			
<60 years	+1.13**	+0.52*	+1.17**
≥60 years	+1.12**	+0.38	+1.57**
Race/Ethnicity			
African American	+0.88**	+0.46	+1.46**
Caucasian	+1.55**	+0.65*	+1.40**
Asian	+0.67	0.00	+0.67
American Indian/Alaska Native	+0.50	-1.00	+1.50
Marital Status			
Single/Never Married	+1.16	+0.33	+0.67
Married	+1.20**	+0.37	+1.26**
Domestic Partnership	+1.00	+1.00	0.00
Separated/Divorced	+1.14*	+0.86	+2.42*
Widowed	+0.60	+0.40	+1.80
Children			
Yes	+1.19**	+0.52	+1.43**
No	+0.71	0.00	+1.14
Employment Status			
Employed Full-time	+1.30**	+0.65*	+1.25**
Retired	+1.04**	+0.21	+1.43**
Unemployed	+0.83	+0.67	+1.67
Annual Income			
Less than $25,000	+0.86**	+0.14	+1.36*
$25,001–50,000	+1.27**	+0.55	+1.55*
$50,001–75,000	+0.71	0.00	+1.86*
$75,001–100,000	+1.80	+0.60	+1.60
Greater than $100,000	+1.25*	+1.07	+0.88
Declined to Answer	+1.25	+0.80	+1.83
Educational Attainment			
High School or Less	+1.00**	+0.10	+1.33**
Trade or Technical School	+1.00	+0.50	+0.50
Community College/Associate degree	+1.33*	+1.33	+2.17*
College/ Bachelor's Degree	+1.29**	+0.29	+1.21*
Graduate or Professional Degree	+1.00	+1.17	+1.50
Family History of Diabetes			
Yes	+1.12*	+0.44*	+1.46**
No	+1.00	+0.29	+1.00
Don't know	+2.00	+2.00	+1.00
Type of Diabetes			
Type 2	+1.14*	+0.40*	+1.43**
Type 1	+2.00	0.00	+0.50
Don't Know	+0.80	+1.15	+1.50
Declined to Answer	0.00	+1.00	+1.00
Insulin Treatment			
Yes	+0.85*	+0.08	+1.15
No	+1.22**	+0.58**	+1.47**

Table 5. Pre- and post-survey interest in genetic testing for diabetes stratified by demographic characteristics (*p<0.05)

	Interest in Genetic Testing		
	Pre-survey N (%)	**Post-survey N (%)**	***p*-value**
Overall	39 (79.6)	32 (65.3)	0.0522
Gender			
Female	21 (70.0)	23 (76.7)	0.0253*
Male	16 (84.2)	11 (57.9)	0.4795
Age			
<60 years	17 (73.9)	16 (69.6)	0.6547
≥60 years	22 (84.6)	16 (61.5)	0.0339*
Race/Ethnicity			
African American	22 (91.7)	19 (79.2)	0.1797
Caucasian	14 (70.0)	9 (45.0)	0.0588
Asian	2 (66.7)	2 (66.7)	--
American Indian/Alaska Native	1 (50.0)	2 (100)	0.3173
Marital Status			
Single/never married	5 (83.3)	4 (66.7)	0.3173
Married	23 (76.7)	20 (66.7)	0.3173
Domestic Partnership	1 (100)	1 (100)	--
Separated/Divorced	6 (85.7)	4 (57.1)	0.1573
Children			
Yes	34 (81.0)	27 (64.3)	0.0522
No	5 (71.4)	5 (71.4)	--
Employment Status			
Employed Full-time	13 (65.5)	14 (70.0)	0.5637
Retired	20 (87.0)	13 (56.5)	0.0196*
Unemployed	6 (100)	5 (83.3)	0.3173
Annual Income			
Less than $25,000	12 (85.7)	12 (85.7)	--
$25,001 – 50,000	10 (90.0)	7 (63.4)	0.0833
$50,001 – 75,000	6 (85.7)	6 (85.7)	--
$75,001 – 100,000	4 (80.0)	3 (60.0)	0.3173
Greater than $100,000	5 (62.5)	3 (37.5)	0.4142
Declined to answer	2 (50.0)	1 (25.0)	0.3173
Educational Attainment			
High School or less	19 (90.5)	18 (85.7)	0.5637
Trade or Technical School	2 (100)	2 (100)	--
Community College/Associate's degree	5 (83.3)	4 (66.7)	0.5637
College/ Bachelor's degree	10 (71.4)	6 (42.9)	0.0455*
Graduate or Professional degree	3 (50.0)	2 (33.3)	0.5637
Family History of Diabetes			
Yes	32 (78.1)	28 (68.3)	0.2059
No	6 (85.7)	4 (57.1)	0.1573
Don't know	1 (100)	0 (0)	--
Type of Diabetes			
Type 2	33 (78.6)	28 (66.7)	0.1317
Type 1	2 (100)	2 (100)	--
Don't know	3 (75.0)	1 (25.0)	0.1573
Declined to answer	1 (100)	1 (100)	--
Insulin Treatment			
Yes	11 (84.6)	10 (76.9)	0.5637
No	28 (77.8)	22 (61.1)	0.0578

DISCUSSION

Family History and Type 2 Diabetes Biomarkers

Family history is a useful tool for identifying individuals at risk for type 2 diabetes. Understanding how family history contributes to type 2 diabetes development in at-risk individuals could be utilized for building targeted screening and early prevention strategies; however, the exact mechanisms by which family history increases the risk for diabetes remain unknown. Therefore, one goal of this dissertation was to investigate how family history of diabetes influences biomarkers associated with type 2 diabetes development in healthy weight children and adults. Our research found that family history of diabetes was a significant predictor of fasting insulin in a population of healthy weight children when controlling for age, sex, pubertal status, ethnicity, waist circumference, and carbohydrate intake. However, family history was a significant predictor of fasting glucose, not fasting insulin, in a population of healthy weight adults when controlling for age, sex, ethnicity, waist circumference, and percent macronutrient intake.

Understanding the exact progression of the biological processes responsible for type 2 diabetes would be revolutionary for screening, prevention, and therapeutic efforts. It is well established that type 2 diabetes results from defects in insulin production and insulin sensitivity[1,2], but the essential question of whether insulin resistance precedes hyperinsulinemia, or vice versa is still unanswered today.[98,99] Studying the influence of

family history on diabetes biomarkers in both healthy children and adults is one strategy for investigating this question because it could reveal information about the first events that occur in the progression of diabetes development.

In our population of children, family history was a significant predictor of fasting insulin, but in our population of adults, family history does not predict fasting insulin activity; it predicts increased fasting glucose, which is typically due to insulin resistance.[1] If these findings were viewed independently, it could be suggested either 1) that hyperinsulinemia occurs first in the biological progression of type 2 diabetes because family history predicted increased fasting insulin, not insulin sensitivity in healthy weight children, OR 2) that defects in insulin action are the starting point for diabetes development because family history was not a predictor of fasting insulin but did predict increased fasting glucose in healthy weight adults. Viewing the findings together, it is possible family history is more influential on fasting insulin in children because they have not developed additional risk factors, which are stronger predictors of fasting insulin in adults and therefore lessen the effect of family history. This conclusion could indicate that the timing of genetic influences on diabetes biomarkers is variable and dependent on outside factors, suggesting the biological progression to type 2 diabetes is not a straightforward series of events.

The ability of family history to predict fasting insulin in a population of children, but not in adults could also be due to differences in the specific populations studied. Though NHANES is meant to be a representative sample, this particular NHANES dataset (2017-2018) was oversampled for certain ethnic minority groups, individuals significantly below the poverty line, and individuals over 80 years old. Differences in the

frequency of certain ethnic backgrounds, age, hormonal differences (which were not accounted for in either study other than the use of biological sex as a covariate), and body composition differences exist between the two samples utilized for the first two aims, which could explain the differences in regression results for each study. In addition, for the adult sample, we included percent intake of carbohydrates, fat, and protein, but only the intake of carbohydrates in the pediatric sample. Adjusting the models with different covariates for each population complicates the comparison of regression models results from each sample.

Discovering which factors interact with genetic influences and when in development these factors emerge and exert their effects could reveal new directions to explore and then harness for type 2 diabetes prevention efforts. These factors could be more strongly related to the activity of certain biomarkers at particular points in diabetes development and could either enhance or weaken the effect of family history when included in statistical models, depending on the characteristics of the population. Factors such as age and pubertal status were included as covariates in our multiple regression models as surrogates for developmental change. However, if these factors regulating genetic influences were also included, it could explain why the ability of family history to predict the variance of biomarkers was different in children and adults. The need to account for complicated variable interactions and timing of effect to understand biomarker activity emphasizes the likelihood that there is no simple stepwise biological pathway responsible for the development of diabetes.

In fact, there are probably multiple intertwined mechanisms that contribute to diabetes development, and these processes could differ at an individual level based on a

person's unique genetic and environmental risk factors.[98-100] As an example, one study showed that BMI was the main determinant of insulin response to glucose in a group of individuals without a family history of diabetes, but not in those with a family history, which supports the idea that the progression of diabetes development is different in those with varying risk factors.[76] Therefore, family history may have a stronger association with other diabetes biomarkers that were not the focus of our analyses.

Studies of other diabetes biomarkers propose that β-cell dysfunction and subsequent insulin secretion are key for diabetes development in those with a family history.[74,77,101] Others have demonstrated that family history is a significant predicator of insulin-dependent glucose disposal in healthy children[72] and adults.[78] These findings, in addition to our own, support the notion that family history is influential in both insulin action and secretion processes, but the degree of its influence is likely dependent on how additional risk factors uniquely interact with one another in the at-risk individual. Future research could benefit from approaching the interrelatedness of these risk factors as a variable in itself rather than dissecting the individual contribution of each component.

Although the conclusions and future research directions developed by this dissertation are plausible, they must be viewed with important caveats. Understanding family history as a predictor for diabetes biomarkers is not going to provide a complete answer because other risk factors are clearly also contributing to biomarker variability. Moreover, family history is a proxy for both the shared genetic and environmental risk factors that can be present in families, so determining whether the genetic component or the environmental component influences the biomarkers is difficult. Furthermore, none of the research participants had hyperinsulinemia or hyperglycemia, so learning about the

influence of family history in individuals where insulin section and action are functional means assumptions must be made about what our conclusions mean for future dysfunctionality of these processes.

A Potential Framework for Diabetes Development

The answer to the question of "which insulin process initiates the development of type 2 diabetes" is complicated and will require investigations of other insulin related processes not included in this dissertation work to fully understand. Our conclusions might suggest the progression of type 2 diabetes development is influenced by how an individual's genetic makeup interacts with the timing of their environmental exposures to activate the biological processes that result in diabetes, such as the accrual of excess body weight. Similar mechanisms for disease development have been proposed in other areas where both genetic and environmental factors are important considerations. For example, in the field of cancer genetics, Knudson's two-hit hypothesis states both alleles of a tumor suppressor gene must become inactive for cancer to develop.[102] The inactivation typically occurs through progressive damaging somatic events caused by environmental exposures. This process is the same, but accelerated in individuals with a genetic predisposition to cancer because they are born with one non-working allele due to a germline pathogenic variant; therefore, it takes less time for the second allele to become damaged through a somatic event, resulting in cancer development at an earlier age.[102,103] Individuals with a family history of diabetes also develop type 2 diabetes earlier in life.[104-107] Possibly, this earlier development is due to a predisposing "first hit" that is either acquired through an inherited genetic variant or an early somatic insult due to

shared family environmental exposures. Regardless of the underlying cause, understanding the influences of family history on diabetes biomarkers could reveal information about the early processes that occur in diabetes development, which could be used as a framework for designing successful prevention strategies.

Educational Interventions to Promote Behavior Change

While the information upon which prevention efforts are built is of utmost importance, the success of any prevention program will rely on how well the information is understood by its participants. Effective communication of the contributions of genetic and environmental factors associated with diabetes development has the potential to improve knowledge and health outcomes. Therefore, the second goal of this dissertation's research was to evaluate whether an educational intervention could increase knowledge of the multifactorial etiology of type 2 diabetes and, as a result, increase motivation to adopt healthy lifestyle changes. We found that the educational intervention significantly increased knowledge of type 2 diabetes and motivation to adopt healthy lifestyle behaviors in a population of adult individuals with type 2 diabetes. We also discovered which demographic variables were predictive of increased knowledge and motivation, which could assist with further refinement of the intervention.

Previous studies have shown that the ability of educational interventions to promote behavior change is enhanced when the interventions are personalized.[108,109] Therefore, adjusting and reevaluating the content for specific groups could personalize the intervention and provide more equitable benefit. To make these adjustments and increase motivations for behavior change, content could be developed by engaging with

individuals for which the intervention is designed and understanding community-based resources.[110,111] One-on-one or group counseling could increase healthy behaviors by acknowledging and addressing personal barriers to behavior change.

Strengths, Limitations, and Future Directions

Aims 1 and 2

Previous studies aimed at understanding the influence of family history on type 2 diabetes biomarkers have been limited by sample size, homogeneous populations, varying statistical methods, and potential confounding characteristics of selected patient populations. Our studies consisted of comparably large populations of individuals from diverse ethnic backgrounds. In addition, we purposefully included only individuals who were of healthy weight. We did this to exclude any potential confounding contributions of the biological consequences that can result from being underweight, overweight, or obese. Rather than comparing biomarkers between groups with and without a family history of diabetes, we chose multiple regression as the main statistical approach, so we could evaluate not only if, but how family history predicted diabetes biomarkers. Multiple regression also allowed us to understand family history's influence on biomarkers when accounting for relevant covariates. An additional strength of our statistical models was including dietary intake information as covariates to better understand how macronutrients contribute to diabetes biomarkers in the presence of additional risk factors.

However, these studies also had limitations that could be addressed in future work. For both studies, the original sample size was reduced during statistical analysis

due to missing data for certain variables. Furthermore, we did not study all biomarkers associated with type 2 diabetes in either analysis due to the limitations of the data collected from participants. Similarly, the utility of family history information was limited by survey question format, which asked about family history of diabetes with a yes/no answer choice. It would have been interesting to understand whether family history influences diabetes biomarkers differently based on the number of affected relatives or whether the family history was maternal or paternal. In the future, we would like to investigate the performance of our statistical models in larger, diverse populations and with additional biomarkers for type 2 diabetes, specifically, markers associated directly with β-cell function and insulin-mediated glucose disposal. It would also be interesting to evaluate which aspects of the family history (genetic, social) are most influential on diabetes biomarkers by incorporating polygenic risk scores, whether the participant lived with their affected relative(s), and more detailed information about the construct of the family history of diabetes, as mentioned above.

Aim 3

For the educational intervention, strengths included multidisciplinary development and delivery of the intervention and the ability to test the intervention in an actual clinical setting for which it could be used in the future. We also performed a detailed analysis of demographic characteristics associated with each main outcome, which could assist in tailoring the intervention to specific populations in the future. However, the sample size was small, which limits the generalizability of the results. Furthermore, since the study took place in a diabetes education clinic, the results could be

biased by participants who were already motivated to learn about diabetes and healthy lifestyle changes. We also did not follow up with participants to see if their increased motivation resulted in actual behavior change. Conducting the educational intervention in a primary care setting for a longer period could assist in increasing the number and diversity of participants. In addition, measuring knowledge, motivation, and behavior changes over time would provide stronger conclusions regarding the utility of the intervention. Finally, although the intervention was designed for those with a diagnosis of type 2 diabetes, the content could be adjusted and explored in specific populations at risk for type 2 diabetes to evaluate its effectiveness as a prevention strategy.

Future Clinical Applications in Precision Nutrition

Underlying the design and conclusions of this dissertation research is the theme of personalization. We questioned how exactly family history influences specific diabetes biomarkers in hopes that this information could contribute to screening and prevention strategies intended especially for those with a family history of diabetes. Furthermore, we sought not only to develop and implement an educational intervention, but to understand who did and, even more important, who did *not* benefit from the information, with the goal of refining the content for specific audiences.

Developing educational and prevention programs for individuals based on personal characteristics and risk factors is a main objective of precision medicine. Precision medicine is an evolving practice that aims to tailor prevention and treatment of disease by considering an individual's unique genetic, environmental, and lifestyle influences. For precision nutrition, these influences include a combination of

nutrigenomics, deep phenotyping, metabolomics, microbiota, dietary habits, food behavior, and physical activity.[112] Each of these components is a robust area of research unto itself, so interdisciplinary collaborations are needed to make meaningful progress.[112,113] Fortunately, the field is motivated to engage in these efforts, for precision nutrition has great potential in the future of healthcare.[114,115]

Given concerning increases in its prevalence and its multifactorial nature, type 2 diabetes is an obvious target of precision nutrition research. Reviews of precision nutrition for type 2 diabetes highlight promising progress from studies testing various interactions between genetic risk scores or circulating metabolites with dietary and lifestyle interventions.[112,116] Yet problems with reproducing results and implementation of study designs in clinical settings are common. Suggestions for improving precision medicine studies for type 2 diabetes include prioritizing prospective, large, randomized control trials with sufficient power, incorporating pharmacogenomics for common diabetes medications, and dividing individuals with type 2 diabetes into diagnostic subcategories for better understanding of how interventions affect individuals at varying points of disease progression.[116-119] In theory, with suggested improvements, precision nutrition efforts could inform multiple processes, including identifying at-risk individuals and the development of personalized prevention and treatment programs. However, the effectiveness of these efforts will depend on how information is delivered to and understood by at-risk and affected individuals.

The conclusions of this dissertation clearly communicate that family history is neither necessary nor sufficient to develop type 2 diabetes. Explaining the multifactorial etiology of type 2 diabetes, helping individuals understand the contribution of their innate

and acquired risk factors to diabetes risk and development, and motivating individuals to make lifestyle changes based on this knowledge are tremendous tasks. Strategies for how to best accomplish these educational and behavioral goals in a clinical setting are needed if the potential of precision nutrition for type 2 diabetes is to be realized.

The breadth of these goals precipitates the need for multidisciplinary collaborations among researchers and clinicians. Involving genetic counselors in these efforts could be particularly beneficial given their expertise in risk assessment, education, and counseling techniques to help individuals integrate genetic information into their lives and the lives of their families.[120] Genetic counselors with an interest in and understanding of the nutritional, behavioral, and genetic mechanisms that predispose one to common disease development would be particularly well suited for counseling individuals at risk for type 2 diabetes. As a genetic counselor with such interests and understanding (afforded her by the process of earning this doctoral degree in nutrition sciences), this author hopes to increase inclusion of genetic counselors in the design and implementation of precision nutrition initiatives with the goal of furthering our contributions to the future of personalized medicine.

GENERAL REFERENCES

1. Stumvoll M, Goldstein BJ, van Haeften TW. Type 2 diabetes: principles of pathogenesis and therapy. *Lancet*. Apr 9-15 2005;365(9467):1333-46. doi:10.1016/s0140-6736(05)61032-x

2. Galicia-Garcia U, Benito-Vicente A, Jebari S, et al. Pathophysiology of Type 2 Diabetes Mellitus. *Int J Mol Sci*. Aug 30 2020;21(17)doi:10.3390/ijms21176275

3. Roden M, Shulman GI. The integrative biology of type 2 diabetes. *Nature*. Dec 2019;576(7785):51-60. doi:10.1038/s41586-019-1797-8

4. Pessin JE, Saltiel AR. Signaling pathways in insulin action: molecular targets of insulin resistance. *J Clin Invest*. Jul 2000;106(2):165-9. doi:10.1172/jci10582

5. Chadt A, Al-Hasani H. Glucose transporters in adipose tissue, liver, and skeletal muscle in metabolic health and disease. *Pflugers Arch*. Sep 2020;472(9):1273-1298. doi:10.1007/s00424-020-02417-x

6. Leto D, Saltiel AR. Regulation of glucose transport by insulin: traffic control of GLUT4. *Nat Rev Mol Cell Biol*. May 23 2012;13(6):383-96. doi:10.1038/nrm3351

7. Petersen MC, Shulman GI. Mechanisms of Insulin Action and Insulin Resistance. *Physiol Rev*. Oct 1 2018;98(4):2133-2223. doi:10.1152/physrev.00063.2017

8. Halban PA, Polonsky KS, Bowden DW, et al. β-cell failure in type 2 diabetes: postulated mechanisms and prospects for prevention and treatment. *J Clin Endocrinol Metab*. Jun 2014;99(6):1983-92. doi:10.1210/jc.2014-1425

9. Home P, Riddle M, Cefalu WT, et al. Insulin therapy in people with type 2 diabetes: opportunities and challenges? *Diabetes Care*. Jun 2014;37(6):1499-508. doi:10.2337/dc13-2743

10. Safiri S, Karamzad N, Kaufman JS, et al. Prevalence, Deaths and Disability-Adjusted-Life-Years (DALYs) Due to Type 2 Diabetes and Its Attributable Risk Factors in 204 Countries and Territories, 1990-2019: Results From the Global Burden of Disease Study 2019. *Front Endocrinol (Lausanne)*. 2022;13:838027. doi:10.3389/fendo.2022.838027

11. Saeedi P, Petersohn I, Salpea P, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes

Federation Diabetes Atlas, 9(th) edition. *Diabetes Res Clin Pract*. Nov 2019;157:107843. doi:10.1016/j.diabres.2019.107843

12. Yu M, Zhan X, Yang Z, Huang Y. Measuring the global, regional, and national burden of type 2 diabetes and the attributable risk factors in all 194 countries. *J Diabetes*. Aug 2021;13(8):613-639. doi:10.1111/1753-0407.13159

13. Avogaro A, Fadini GP. Microvascular complications in diabetes: A growing concern for cardiologists. *Int J Cardiol*. Sep 15 2019;291:29-35. doi:10.1016/j.ijcard.2019.02.030

14. Melzer Cohen C, Hallén N, Chodick G, Bourvine L, Waner T, Karasik A. Elevated Costs and Healthcare Resource Utilization in Patients With Type 2 Diabetes and Established Cardiovascular Disease in Israel. *Value Health Reg Issues*. Sep 2020;22:83-92. doi:10.1016/j.vhri.2020.05.003

15. Wu JH, Wu Y, Wang ZJ, et al. Healthcare Costs Associated with Complications in Patients with Type 2 Diabetes among 1.85 Million Adults in Beijing, China. *Int J Environ Res Public Health*. Apr 1 2021;18(7)doi:10.3390/ijerph18073693

16. Jacobs E, Hoyer A, Brinks R, Icks A, Kuß O, Rathmann W. Healthcare costs of Type 2 diabetes in Germany. *Diabet Med*. Jun 2017;34(6):855-861. doi:10.1111/dme.13336

17. Einarson TR, Acs A, Ludwig C, Panton UH. Economic Burden of Cardiovascular Disease in Type 2 Diabetes: A Systematic Review. *Value Health*. Jul 2018;21(7):881-890. doi:10.1016/j.jval.2017.12.019

18. Kyrou I, Tsigos C, Mavrogianni C, et al. Sociodemographic and lifestyle-related risk factors for identifying vulnerable groups for type 2 diabetes: a narrative review with emphasis on data from Europe. *BMC Endocr Disord*. Mar 12 2020;20(Suppl 1):134. doi:10.1186/s12902-019-0463-3

19. Weisman A, Fazli GS, Johns A, Booth GL. Evolving Trends in the Epidemiology, Risk Factors, and Prevention of Type 2 Diabetes: A Review. *Can J Cardiol*. May 2018;34(5):552-564. doi:10.1016/j.cjca.2018.03.002

20. Pulgaron ER, Delamater AM. Obesity and type 2 diabetes in children: epidemiology and treatment. *Current diabetes reports*. 2014;14(8):508-508. doi:10.1007/s11892-014-0508-y

21. Lawrence JM, Divers J, Isom S, et al. Trends in Prevalence of Type 1 and Type 2 Diabetes in Children and Adolescents in the US, 2001-2017. *Jama*. Aug 24 2021;326(8):717-727. doi:10.1001/jama.2021.11165

22. Imperatore G, Boyle JP, Thompson TJ, et al. Projections of type 1 and type 2 diabetes burden in the U.S. population aged <20 years through 2050: dynamic modeling of incidence, mortality, and population growth. *Diabetes care*. Dec 2012;35(12):2515-20. doi:10.2337/dc12-0669

23. Dart AB, Martens PJ, Rigatto C, Brownell MD, Dean HJ, Sellers EA. Earlier onset of complications in youth with type 2 diabetes. *Diabetes care*. Feb 2014;37(2):436-43. doi:10.2337/dc13-0954

24. Amutha A, Mohan V. Diabetes complications in childhood and adolescent onset type 2 diabetes-a review. *J Diabetes Complications*. Jul 2016;30(5):951-7. doi:10.1016/j.jdiacomp.2016.02.009

25. Donaghue KC, Wadwa RP, Dimeglio LA, et al. ISPAD Clinical Practice Consensus Guidelines 2014. Microvascular and macrovascular complications in children and adolescents. *Pediatr Diabetes*. Sep 2014;15 Suppl 20:257-69. doi:10.1111/pedi.12180

26. Dart AB, Martens PJ, Rigatto C, Brownell MD, Dean HJ, Sellers EA. Earlier Onset of Complications in Youth With Type 2 Diabetes. *Diabetes Care*. 2014;37(2):436-443. doi:10.2337/dc13-0954

27. Helgeson VS, Becker D, Escobar O, Siminerio L. Families with children with diabetes: implications of parent stress for parent and child health. *J Pediatr Psychol*. May 2012;37(4):467-78. doi:10.1093/jpepsy/jsr110

28. Butler AM. Social Determinants of Health and Racial/Ethnic Disparities in Type 2 Diabetes in Youth. *Curr Diab Rep*. Aug 2017;17(8):60. doi:10.1007/s11892-017-0885-0

29. Dabelea D, Sauder KA, Jensen ET, et al. Twenty years of pediatric diabetes surveillance: what do we know and why it matters. *Ann N Y Acad Sci*. Jul 2021;1495(1):99-120. doi:10.1111/nyas.14573

30. Golden SH, Yajnik C, Phatak S, Hanson RL, Knowler WC. Racial/ethnic differences in the burden of type 2 diabetes over the life course: a focus on the USA and India. *Diabetologia*. Oct 2019;62(10):1751-1760. doi:10.1007/s00125-019-4968-0

31. Pettitt DJ, Lawrence JM, Beyer J, et al. Association between maternal diabetes in utero and age at offspring's diagnosis of type 2 diabetes. *Diabetes Care*. Nov 2008;31(11):2126-30. doi:10.2337/dc08-0769

32. Ismail L, Materwala H, Al Kaabi J. Association of risk factors with type 2 diabetes: A systematic review. *Comput Struct Biotechnol J*. 2021;19:1759-1785. doi:10.1016/j.csbj.2021.03.003

33. Lascar N, Brown J, Pattison H, Barnett AH, Bailey CJ, Bellary S. Type 2 diabetes in adolescents and young adults. *Lancet Diabetes Endocrinol*. Jan 2018;6(1):69-80. doi:10.1016/s2213-8587(17)30186-9

34. Pulgaron ER, Delamater AM. Obesity and type 2 diabetes in children: epidemiology and treatment. *Curr Diab Rep*. Aug 2014;14(8):508. doi:10.1007/s11892-014-0508-y

35. Long-term effects of lifestyle intervention or metformin on diabetes development and microvascular complications over 15-year follow-up: the Diabetes Prevention Program Outcomes Study. *Lancet Diabetes Endocrinol*. Nov 2015;3(11):866-75. doi:10.1016/s2213-8587(15)00291-0

36. Bergman M, Buysschaert M, Schwarz PE, Albright A, Narayan KV, Yach D. Diabetes prevention: global health policy and perspectives from the ground. *Diabetes Manag (Lond)*. 2012;2(4):309-321. doi:10.2217/dmt.12.34

37. Narayan KM, Echouffo-Tcheugui JB, Mohan V, Ali MK. Analysis & commentary: Global prevention and control of type 2 diabetes will require paradigm shifts in policies within and among countries. *Health Aff (Millwood)*. Jan 2012;31(1):84-92. doi:10.1377/hlthaff.2011.1040

38. Serbis A, Giapros V, Kotanidou EP, Galli-Tsinopoulou A, Siomou E. Diagnosis, treatment and prevention of type 2 diabetes mellitus in children and adolescents. *World J Diabetes*. Apr 15 2021;12(4):344-365. doi:10.4239/wjd.v12.i4.344

39. Kamath CC, Vickers KS, Ehrlich A, et al. Clinical review: behavioral interventions to prevent childhood obesity: a systematic review and metaanalyses of randomized trials. *J Clin Endocrinol Metab*. Dec 2008;93(12):4606-15. doi:10.1210/jc.2006-2411

40. Salam RA, Padhani ZA, Das JK, et al. Effects of Lifestyle Modification Interventions to Prevent and Manage Child and Adolescent Obesity: A Systematic Review and Meta-Analysis. *Nutrients*. Jul 24 2020;12(8)doi:10.3390/nu12082208

41. Davidson KW, Barry MJ, Mangione CM, et al. Screening for Prediabetes and Type 2 Diabetes: US Preventive Services Task Force Recommendation Statement. *Jama*. Aug 24 2021;326(8):736-743. doi:10.1001/jama.2021.12531

42. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2020. *Diabetes Care*. Jan 2020;43(Suppl 1):S14-s31. doi:10.2337/dc20-S002

43. Barry E, Roberts S, Oke J, Vijayaraghavan S, Normansell R, Greenhalgh T. Efficacy and effectiveness of screen and treat policies in prevention of type 2 diabetes: systematic review and meta-analysis of screening tests and interventions. *BMJ*. 2017;356:i6538. doi:10.1136/bmj.i6538

44. Deurenberg P, Deurenberg Yap M, Wang J, Lin FP, Schmidt G. The impact of body build on the relationship between body mass index and percent body fat. *Int J Obes Relat Metab Disord*. May 1999;23(5):537-42. doi:10.1038/sj.ijo.0800868

45. Deurenberg P, Deurenberg-Yap M, Foo LF, Schmidt G, Wang J. Differences in body composition between Singapore Chinese, Beijing Chinese and Dutch children. *Eur J Clin Nutr*. Mar 2003;57(3):405-9. doi:10.1038/sj.ejcn.1601569

46. Gallagher D, Visser M, Sepúlveda D, Pierson RN, Harris T, Heymsfield SB. How useful is body mass index for comparison of body fatness across age, sex, and ethnic groups? *Am J Epidemiol*. Feb 1 1996;143(3):228-39. doi:10.1093/oxfordjournals.aje.a008733

47. Going SB, Lohman TG, Cussler EC, Williams DP, Morrison JA, Horn PS. Percent body fat and chronic disease risk factors in U.S. children and youth. *Am J Prev Med*. Oct 2011;41(4 Suppl 2):S77-86. doi:10.1016/j.amepre.2011.07.006

48. Snel M, Jonker JT, Schoones J, et al. Ectopic Fat and Insulin Resistance: Pathophysiology and Effect of Diet and Lifestyle Interventions. *International Journal of Endocrinology*. 2012/05/24 2012;2012:983814. doi:10.1155/2012/983814

49. Piché ME, Tchernof A, Després JP. Obesity Phenotypes, Diabetes, and Cardiovascular Diseases. *Circ Res*. May 22 2020;126(11):1477-1500. doi:10.1161/circresaha.120.316101

50. Mooney SJ, Baecker A, Rundle AG. Comparison of anthropometric and body composition measures as predictors of components of the metabolic syndrome in a clinical setting. *Obesity Research & Clinical Practice*. 2013/01/01/ 2013;7(1):e55-e66. doi:https://doi.org/10.1016/j.orcp.2012.10.004

51. Neeland IJ, Ross R, Després JP, et al. Visceral and ectopic fat, atherosclerosis, and cardiometabolic disease: a position statement. *Lancet Diabetes Endocrinol*. Sep 2019;7(9):715-725. doi:10.1016/s2213-8587(19)30084-1

52. Janochova K, Haluzik M, Buzga M. Visceral fat and insulin resistance - what we know? *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub*. Feb 2019;163(1):19-27. doi:10.5507/bp.2018.062

53. Taylor R, Holman RR. Normal weight individuals who develop type 2 diabetes: the personal fat threshold. *Clin Sci (Lond)*. Apr 2015;128(7):405-10. doi:10.1042/cs20140553

54. Valaiyapathi B, Gower B, Ashraf AP. Pathophysiology of Type 2 Diabetes in Children and Adolescents. *Curr Diabetes Rev*. 2020;16(3):220-229. doi:10.2174/1573399814666180608074510

55. Pierce M, Keen H, Bradley C. Risk of diabetes in offspring of parents with non-insulin-dependent diabetes. *Diabet Med*. Jan 1995;12(1):6-13. doi:10.1111/j.1464-5491.1995.tb02054.x

56. Tattersal RB, Fajans SS. Prevalence of diabetes and glucose intolerance in 199 offspring of thirty-seven conjugal diabetic parents. *Diabetes*. May 1975;24(5):452-62. doi:10.2337/diab.24.5.452

57. Meigs JB, Cupples LA, Wilson PW. Parental transmission of type 2 diabetes: the Framingham Offspring Study. *Diabetes*. Dec 2000;49(12):2201-7. doi:10.2337/diabetes.49.12.2201

58. Scott RA, Langenberg C, Sharp SJ, et al. The link between family history and risk of type 2 diabetes is not explained by anthropometric, lifestyle or genetic risk factors: the EPIC-InterAct study. *Diabetologia*. Jan 2013;56(1):60-9. doi:10.1007/s00125-012-2715-x

59. Rosenbloom AL, Silverstein JH, Amemiya S, Zeitler P, Klingensmith GJ. ISPAD Clinical Practice Consensus Guidelines 2006-2007. Type 2 diabetes mellitus in the child and adolescent. *Pediatr Diabetes*. Oct 2008;9(5):512-26. doi:10.1111/j.1399-5448.2008.00429.x

60. Yoon PW, Scheuner MT, Peterson-Oehlke KL, Gwinn M, Faucett A, Khoury MJ. Can family history be used as a tool for public health and preventive medicine? *Genet Med*. Jul-Aug 2002;4(4):304-10. doi:10.1097/00125817-200207000-00009

61. Yoon PW, Scheuner MT, Khoury MJ. Research priorities for evaluating family history in the prevention of common chronic diseases. *Am J Prev Med*. Feb 2003;24(2):128-35. doi:10.1016/s0749-3797(02)00585-8

62. Yang Q, Liu T, Valdez R, Moonesinghe R, Khoury MJ. Improvements in ability to detect undiagnosed diabetes by using information on family history among adults in the United States. *Am J Epidemiol*. May 15 2010;171(10):1079-89. doi:10.1093/aje/kwq026

63. Hariri S, Yoon PW, Moonesinghe R, Valdez R, Khoury MJ. Evaluation of family history as a risk factor and screening tool for detecting undiagnosed diabetes in a nationally representative survey population. *Genet Med*. Dec 2006;8(12):752-9. doi:10.1097/01.gim.0000250205.73963.f3

64. Bang H, Edwards AM, Bomback AS, et al. Development and validation of a patient self-assessment score for diabetes risk. *Ann Intern Med*. Dec 1 2009;151(11):775-83. doi:10.7326/0003-4819-151-11-200912010-00005

65. Heikes KE, Eddy DM, Arondekar B, Schlessinger L. Diabetes Risk Calculator: a simple tool for detecting undiagnosed diabetes and pre-diabetes. *Diabetes Care*. May 2008;31(5):1040-5. doi:10.2337/dc07-1150

66. Lee YH, Shin MH, Nam HS, et al. Effect of Family History of Diabetes on Hemoglobin A1c Levels among Individuals with and without Diabetes: The Dong-gu Study. *Yonsei Med J*. Jan 2018;59(1):92-100. doi:10.3349/ymj.2018.59.1.92

67. Shahid A, Saeed S, Rana S, Mahmood S. Family history of diabetes and parental consanguinity: important risk for impaired fasting glucose in south east Asians. *West Indian Med J*. Jun 2012;61(3):219-23. doi:10.7727/wimj.2011.072

68. Rodríguez-Moran M, Guerrero-Romero F, Aradillas-García C, et al. Obesity and family history of diabetes as risk factors of impaired fasting glucose: implications for the early detection of prediabetes. *Pediatr Diabetes*. Aug 2010;11(5):331-6. doi:10.1111/j.1399-5448.2009.00590.x

69. Gulli G, Ferrannini E, Stern M, Haffner S, DeFronzo RA. The metabolic profile of NIDDM is fully established in glucose-tolerant offspring of two Mexican-American NIDDM parents. *Diabetes*. Dec 1992;41(12):1575-86. doi:10.2337/diab.41.12.1575

70. Warram JH, Martin BC, Krolewski AS, Soeldner JS, Kahn CR. Slow glucose removal rate and hyperinsulinemia precede the development of type II diabetes in the offspring of diabetic parents. *Ann Intern Med*. Dec 15 1990;113(12):909-15. doi:10.7326/0003-4819-113-12-909

71. Perseghin G, Ghosh S, Gerow K, Shulman GI. Metabolic defects in lean nondiabetic offspring of NIDDM parents: a cross-sectional study. *Diabetes*. Jun 1997;46(6):1001-9. doi:10.2337/diab.46.6.1001

72. Danadian K, Balasekaran G, Lewy V, Meza MP, Robertson R, Arslanian SA. Insulin sensitivity in African-American children with and without family history of type 2 diabetes. *Diabetes Care*. Aug 1999;22(8):1325-9. doi:10.2337/diacare.22.8.1325

73. Arslanian SA, Bacha F, Saad R, Gungor N. Family history of type 2 diabetes is associated with decreased insulin sensitivity and an impaired balance between insulin sensitivity and insulin secretion in white youth. *Diabetes Care*. Jan 2005;28(1):115-9. doi:10.2337/diacare.28.1.115

74. Fernández-Castañer M, Biarnés J, Camps I, Ripollés J, Gómez N, Soler J. Beta-cell dysfunction in first-degree relatives of patients with non-insulin-dependent diabetes mellitus. *Diabet Med*. Nov 1996;13(11):953-9. doi:10.1002/(sici)1096-9136(199611)13:11<953::Aid-dia257>3.0.Co;2-v

75. Vauhkonen I, Niskanen L, Vanninen E, Kainulainen S, Uusitupa M, Laakso M. Defects in insulin secretion and insulin action in non-insulin-dependent diabetes mellitus are inherited. Metabolic studies on offspring of diabetic probands. *J Clin Invest*. Jan 1 1998;101(1):86-96. doi:10.1172/jci716

76. Mbanya JC, Pani LN, Mbanya DN, Sobngwi E, Ngogang J. Reduced insulin secretion in offspring of African type 2 diabetic parents. *Diabetes Care*. Dec 2000;23(12):1761-5. doi:10.2337/diacare.23.12.1761

77. Pimenta W, Korytkowski M, Mitrakou A, et al. Pancreatic beta-cell dysfunction as the primary genetic lesion in NIDDM. Evidence from studies in normal glucose-tolerant individuals with a first-degree NIDDM relative. *Jama*. Jun 21 1995;273(23):1855-61.

78. Lopez X, Bouché C, Tatro E, Goldfine AB. Family history of diabetes impacts on interactions between minimal model estimates of insulin sensitivity and glucose effectiveness. *Diabetes Obes Metab*. Feb 2009;11(2):123-30. doi:10.1111/j.1463-1326.2008.00913.x

79. Sakurai M, Nakamura K, Miura K, et al. Family history of diabetes, lifestyle factors, and the 7-year incident risk of type 2 diabetes mellitus in middle-aged Japanese men and women. *J Diabetes Investig*. May 6 2013;4(3):261-8. doi:10.1111/jdi.12033

80. Zowgar AM, Siddiqui MI, Alattas KM. Level of diabetes knowledge among adult patients with diabetes using diabetes knowledge test. *Saudi Med J*. Feb 2018;39(2):161-168. doi:10.15537/smj.2017.2.21343

81. Sircar AR, Sircar S, Sircar J, Misra S. Patients' concepts and attitudes about diabetes. *J Diabetes Complications*. Nov-Dec 2010;24(6):398-403. doi:10.1016/j.jdiacomp.2009.07.004

82. Mann DM, Ponieman D, Leventhal H, Halm EA. Misconceptions about diabetes and its management among low-income minorities with diabetes. *Diabetes Care*. Apr 2009;32(4):591-3. doi:10.2337/dc08-1837

83. Sharma PK, Rajpal N, Upadhyay S, Shaha D, Deo N. Status of diabetes control and knowledge about diabetes in patients. *Endocrinol Diabetes Nutr (Engl Ed)*. Dec 2021;68(10):716-727. doi:10.1016/j.endien.2021.12.003

84. Wilcox AJ, Taylor JA, Sharp RR, London SJ. Genetic determinism and the overprotection of human subjects. *Nat Genet*. Apr 1999;21(4):362. doi:10.1038/7692

85. Claassen L, Henneman L, De Vet R, Knol D, Marteau T, Timmermans D. Fatalistic responses to different types of genetic risk information: exploring the role of self-malleability. *Psychol Health*. Feb 2010;25(2):183-96. doi:10.1080/08870440802460434

86. Davies LE, Thirlaway K. The influence of genetic explanations of type 2 diabetes on patients' attitudes to prevention, treatment and personal responsibility for health. *Public Health Genomics*. 2013;16(5):199-207. doi:10.1159/000353459

87. Dorman JS, Valdez R, Liu T, et al. Health beliefs among individuals at increased familial risk for type 2 diabetes: implications for prevention. *Diabetes Res Clin Pract*. May 2012;96(2):156-62. doi:10.1016/j.diabres.2011.12.017

88. Asimakopoulou KG, Skinner TC, Spimpolo J, Marsh S, Fox C. Unrealistic pessimism about risk of coronary heart disease and stroke in patients with type 2 diabetes. *Patient Educ Couns*. Apr 2008;71(1):95-101. doi:10.1016/j.pec.2007.12.007

89. Heideman WH, de Wit M, Middelkoop BJ, et al. Diabetes risk reduction in overweight first degree relatives of type 2 diabetes patients: effects of a low-intensive lifestyle education program (DiAlert) A randomized controlled trial. *Patient Educ Couns*. Apr 2015;98(4):476-83. doi:10.1016/j.pec.2014.12.008

90. Mohebi S, Sharifirad G, Feizi A, Botlani S, Hozori M, Azadbakht L. Can health promotion model constructs predict nutritional behavior among diabetic patients? *J Res Med Sci*. Apr 2013;18(4):346-59.

91. Markowitz SM, Park ER, Delahanty LM, O'Brien KE, Grant RW. Perceived impact of diabetes genetic risk testing among patients at high phenotypic risk for type 2 diabetes. *Diabetes Care*. Mar 2011;34(3):568-73. doi:10.2337/dc10-1960

92. Nishigaki M, Tokunaga-Nakawatase Y, Nishida J, Kazuma K. The effect of genetic counseling for adult offspring of patients with type 2 diabetes on attitudes toward diabetes and its heredity: a randomized controlled trial. *J Genet Couns*. Oct 2014;23(5):762-9. doi:10.1007/s10897-013-9680-5

93. Nishigaki M, Tokunaga-Nakawatase Y, Nishida J, et al. Randomized controlled trial of the effectiveness of genetic counseling and a distance, computer-based, lifestyle intervention program for adult offspring of patients with type 2 diabetes: background, study protocol, and baseline patient characteristics. *J Nutr Metab*. 2012;2012:831735. doi:10.1155/2012/831735

94. McVay MA, Beadles C, Wu R, et al. Effects of provision of type 2 diabetes genetic risk feedback on patient perceptions of diabetes control and diet and physical activity self-efficacy. *Patient Educ Couns*. Jun 30 2015;doi:10.1016/j.pec.2015.06.016

95. Hivert MF, Vassy JL, Meigs JB. Susceptibility to type 2 diabetes mellitus--from genes to prevention. *Nat Rev Endocrinol*. Apr 2014;10(4):198-205. doi:10.1038/nrendo.2014.11

96. Grant RW, O'Brien KE, Waxler JL, et al. Personalized genetic risk counseling to motivate diabetes prevention: a randomized trial. *Diabetes Care*. Jan 2013;36(1):13-9. doi:10.2337/dc12-0884

97. Voils CI, Coffman CJ, Grubber JM, et al. Does Type 2 Diabetes Genetic Testing and Counseling Reduce Modifiable Risk Factors? A Randomized Controlled Trial of Veterans. *J Gen Intern Med*. Nov 2015;30(11):1591-8. doi:10.1007/s11606-015-3315-5

98. Abdul-Ghani M, DeFronzo RA. Insulin Resistance and Hyperinsulinemia: the Egg and the Chicken. *J Clin Endocrinol Metab*. Mar 25 2021;106(4):e1897-e1899. doi:10.1210/clinem/dgaa364

99. Weir GC. Which comes first in non-insulin-dependent diabetes mellitus: insulin resistance or beta-cell failure? Both come first. *Jama*. Jun 21 1995;273(23):1878-9.

100. Corkey BE. Banting lecture 2011: hyperinsulinemia: cause or consequence? *Diabetes*. Jan 2012;61(1):4-13. doi:10.2337/db11-1483

101. Elbein SC, Hasstedt SJ, Wegner K, Kahn SE. Heritability of pancreatic beta-cell function among nondiabetic members of Caucasian familial type 2 diabetic kindreds. *J Clin Endocrinol Metab*. Apr 1999;84(4):1398-403. doi:10.1210/jcem.84.4.5604

102. Knudson AG, Jr. Mutation and cancer: statistical study of retinoblastoma. *Proc Natl Acad Sci U S A*. Apr 1971;68(4):820-3. doi:10.1073/pnas.68.4.820

103. Wang LH, Wu CF, Rajasekaran N, Shin YK. Loss of Tumor Suppressor Gene Function in Human Cancer: An Overview. *Cell Physiol Biochem*. 2018;51(6):2647-2693. doi:10.1159/000495956

104. Alharithy MK, Alobaylan MM, Alsugair ZO, Alswat KA. Impact of Family History of Diabetes on Diabetes Control and Complications. *Endocr Pract*. Sep 2018;24(9):773-779. doi:10.4158/ep-2018-0071

105. Svensson E, Berencsi K, Sander S, et al. Association of parental history of type 2 diabetes with age, lifestyle, anthropometric factors, and clinical severity at type 2 diabetes diagnosis: results from the DD2 study. *Diabetes Metab Res Rev*. Mar 2016;32(3):308-15. doi:10.1002/dmrr.2721

106. Bo S, Cavallo-Perin P, Gentile L, Repetti E, Pagano G. Influence of a familial history of diabetes on the clinical characteristics of patients with Type 2 diabetes mellitus. *Diabet Med*. Jul 2000;17(7):538-42. doi:10.1046/j.1464-5491.2000.00330.x

107. Molyneaux L, Constantino M, Yue D. Strong family history predicts a younger age of onset for subjects diagnosed with type 2 diabetes. *Diabetes Obes Metab*. May 2004;6(3):187-94. doi:10.1111/j.1462-8902.2004.00330.x

108. Heideman WH, Middelkoop BJ, Nierkens V, et al. Changing the odds. What do we learn from prevention studies targeted at people with a positive family history of type 2 diabetes? *Prim Care Diabetes*. Dec 2011;5(4):215-21. doi:10.1016/j.pcd.2011.06.004

109. Knowler WC, Fowler SE, Hamman RF, et al. 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. *Lancet*. Nov 14 2009;374(9702):1677-86. doi:10.1016/s0140-6736(09)61457-4

110. Behavioural interventions for type 2 diabetes: an evidence-based analysis. *Ont Health Technol Assess Ser*. 2009;9(21):1-45.

111. Community-based care for the management of type 2 diabetes: an evidence-based analysis. *Ont Health Technol Assess Ser*. 2009;9(23):1-40.

112. de Toro-Martín J, Arsenault BJ, Després JP, Vohl MC. Precision Nutrition: A Review of Personalized Nutritional Approaches for the Prevention and Management of Metabolic Syndrome. *Nutrients*. Aug 22 2017;9(8)doi:10.3390/nu9080913

113. Özdemir V, Kolker E. Precision Nutrition 4.0: A Big Data and Ethics Foresight Analysis--Convergence of Agrigenomics, Nutrigenomics, Nutriproteomics, and Nutrimetabolomics. *Omics*. Feb 2016;20(2):69-75. doi:10.1089/omi.2015.0193

114. Allison DB, Bassaganya-Riera J, Burlingame B, et al. Goals in Nutrition Science 2015-2020. *Front Nutr*. 2015;2:26. doi:10.3389/fnut.2015.00026

115. Camp KM, Trujillo E. Position of the Academy of Nutrition and Dietetics: nutritional genomics. *J Acad Nutr Diet*. Feb 2014;114(2):299-312. doi:10.1016/j.jand.2013.12.001

116. Wang DD, Hu FB. Precision nutrition for prevention and management of type 2 diabetes. *Lancet Diabetes Endocrinol*. May 2018;6(5):416-426. doi:10.1016/s2213-8587(18)30037-8

117. Prasad RB, Groop L. Precision medicine in type 2 diabetes. *J Intern Med*. Jan 2019;285(1):40-48. doi:10.1111/joim.12859

118. Kleinberger JW, Pollin TI. Personalized medicine in diabetes mellitus: current opportunities and future prospects. *Ann N Y Acad Sci*. Jun 2015;1346(1):45-56. doi:10.1111/nyas.12757

119. Klonoff DC, Florez JC, German M, Fleming A. The Need for Precision Medicine to be Applied to Diabetes. *J Diabetes Sci Technol*. Nov 2020;14(6):1122-1128. doi:10.1177/1932296819894295

120. Resta R, Biesecker BB, Bennett RL, et al. A new definition of Genetic Counseling: National Society of Genetic Counselors' Task Force report. *J Genet Couns*. Apr 2006;15(2):77-83. doi:10.1007/s10897-005-9014-3

APPENDIX A

INSTITUTIONAL REVIEW BOARD APPROVALS

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

Institutional Review Board for Human Use

Exemption Designation
Identification and Certification of Research
Projects Involving Human Subjects

UAB's Institutional Review Boards for Human Use (IRBs) have an approved Federalwide Assurance with the Office for Human Research Protections (OHRP). The Assurance number is FWA00005960 and it expires on January 24, 2017. The UAB IRBs are also in compliance with 21 CFR Parts 50 and 56.

Principal Investigator:	DRAZBA, KATHRYN T
Co-Investigator(s):	
Protocol Number:	**E151027006**
Protocol Title:	*"Incorporation of a Genetics-Based Information Module into Standardized Diabetes Patient Educations"*

The above project was reviewed on 12/8/15. The review was conducted in accordance with UAB's Assurance of Compliance approved by the Department of Health and Human Services. This project qualifies as an exemption as defined in 45CFR46.101(b), paragraph 2.

This project received EXEMPT review.

Date IRB Designation Issued: 12/8/15

Cari Oliver, CIP
Assistant Director, Office of the
Institutional Review Board for Human
Use (IRB)

Investigators please note:

Any modifications in the study methodology, protocol and/or consent form/information sheet must be submitted for review to the IRB prior to implementation.

470 Administration Building
701 20th Street South
205.934.3789
Fax 205.934.1301
irb@uab.edu

The University of
Alabama at Birmingham
Mailing Address:
AB 470
1720 2ND AVE S
BIRMINGHAM AL 35294-0104

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM
Office of the Institutional Review Board for Human Use

470 Administration Building
701 20th Street South
Birmingham, AL 35294-0104
205.934.3789 | Fax 205.934.1301 |
irb@uab.edu

APPROVAL LETTER

TO: Fernandez, Jose R

FROM: University of Alabama at Birmingham Institutional Review Board
Federalwide Assurance # FWA00005960
IORG Registration # IRB00000196 (IRB 01)
IORG Registration # IRB00000726 (IRB 02)

DATE: 01-Jul-2019

RE: IRB-040109007
Admixture Mapping for Insulin Complex Outcomes (AMERICO STUDY)

The IRB reviewed and approved the Continuing Review submitted on 01-Jul-2019 for the above referenced project. The review was conducted in accordance with UAB's Assurance of Compliance approved by the Department of Health and Human Services.

Type of Review: Expedited
Expedited Categories: 8c
Determination: Approved
Approval Date: 01-Jul-2019
Approval Period: One Year
Expiration Date: 30-Jun-2020

The following populations are approved for inclusion in this project:

- Children – CRL 1

Documents Included in Review:

- IPR190626.docx
- response.190626.docx