# Investigation of the Relationship of Statin Medication Use, Fasting Blood Glucose Levels and Type 2 Diabetes Mellitus

**by**

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**Acknowledgements**

To my family, friends and teachers of whom have supported and enabled my education.

"I dreamt of a country where education would prevail"

Malala Yousafzai, Nobel Peace Prize Winner, October 2014

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## List of Abbreviations

| | |
|---|---|
| ACC | American College of Cardiology |
| ACE | Angiotensin converting enzyme |
| AHA | American Heart Association |
| ARIC | Atherosclerosis Risk in Communities |
| BMI | Body mass index |
| CDC | Centers for Disease Control and Prevention |
| CHD | Coronary heart disease |
| CI | Confidence interval |
| DGI | Diabetes Genetics Initiative |
| FBPP | Family Blood Pressure Program |
| FDA | Food and Drug Administration |
| FDR | False Discovery Rate |
| FUSION | Finland-United States Investigation of Non-Insulin Dependent Diabetes Mellitus Genetics |
| GENOA | Genetic Epidemiology Network of Arteriopathy |
| GIPR | Gastric inhibitory polypeptide receptor |
| GRS | Genetic risk score |
| GWA | Genome wide association |
| HbA1C | Glycosylated hemoglobin |
| HDL | High-density lipoprotein |
| HMG20 | High mobility group 20 |
| HMG-CoA | Hydroxymethylglutaryl coenzyme A |
| HR | Hazard ratio |
| IGF2 | Insulin-like growth factor 2 |
| LDL | Low-density lipoprotein |
| MAF | Minor Allele Frequency |
| MI | Myocardial infarction |
| NCBI | National Center for Biotechnology Information |
| NHLBI | National Heart, Lung and Blood Institute |
| OGTT | Oral glucose tolerance test |
| OR | Odds ratio |
| PC | Principal component |
| PTPRD | Protein tyrosine phosphatase receptor type D |
| RAF | Risk Allele Frequency |
| SAS | Statistical Analysis System |
| SD | Standard deviation |
| SES | Socioeconomic status |

| | |
|---|---|
| SIGMA | Slim Initiative in Genomic Medicine for the Americans |
| SNP | Single nucleotide polymorphism |
| T2DM | Type 2 diabetes mellitus |
| TG | triglyceride |
| US | United States |
| WTCCC | Wellcome Trust Case Control Consortium |
| ZBED3 | Zinc-finger BED domain-containing 3 |

**Abstract**

The ongoing surveillance of safety issues and adverse reactions associated with medication use extends beyond the completion of a clinical trial or drug development program. In February 2012, decades post the first authorization by the US Food and Drug Administration (FDA) of the first statin medication, a public safety announcement was disseminated by the FDA that warned of the potential increases in blood glucose and risk of type 2 diabetes mellitus with the use of statin therapy. This research program provides evidence of statin use and T2DM in naturalistic setting that represents actual practice patterns and 'real life' evidence of a treatment effect. Furthermore, biomarkers such as fasting blood glucose, fasting insulin and HOMA-IR were examined as parameters along the disease pathway.

Genetic research along with the field of pharmacogenomics has also rapidly emerged and deepened our insight into an individual's genetic architecture, interaction with medication exposure and predictability of safety or efficacy at the individual patient level. Previously identified T2DM single nucleotide polymorphism (SNPs) on glucose levels and T2DM risk before and after considering interactions with statin medication use was also investigated to identify genetically susceptible individuals who may be at higher risk of developing T2DM when prescribed statin medications.

This research program was conducted in the African American, Non-Hispanic White and Hispanic populations in order to the effects of statin medication in these ethnicities and across different environmental and cultural differences providing further characterization of the safety profile for statin medications in various populations.

Results from GENOA demonstrated an approximately 1.5-2-fold increase in T2DM with statin use across populations and changes in fasting blood glucose based upon different

levels of education, menopause, use of antihypertensive medications and increasing age in the GENOA non-T2DM and T2DM populations. Furthermore, new discoveries of statin-by-GRS interactions resulted in increased odds of T2DM in genetically susceptible individuals. The GENOA results demonstrate the need to understand the safety of statin medications in different populations across different regions and contribute to the ongoing characterization of the safety profile for statin medications.

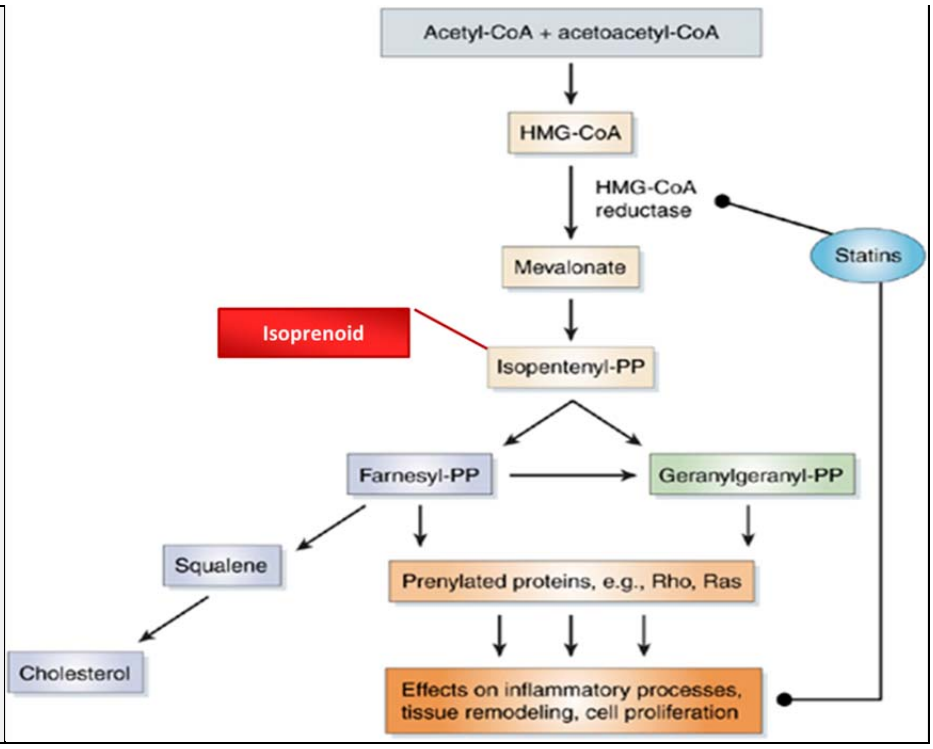
## Chapter 1 Introduction

Coronary heart disease (CHD) is recognized as a leading cause of morbidity and mortality associated with myocardial infarction or ischemic stroke in the United States (US) [National Center of Health Statistics, 2011; Wilson *et al.*, 1998]. Coronary heart disease is characterized by narrowing of the coronary arteries resulting in decreased perfusion of the coronary vasculature. Atherosclerosis is the accumulation of plaque due to excess lipid and/or cholesterol in the arteries and is believed to be the primary underlying cause of CHD; however, other theories including inflammatory processes have emerged as a primary mechanism underlying multiple stages of atherosclerosis [Libby & Theroux, 2005].

### *History of Statin Medications and Public Health Impact*

In 1987, the US Food and Drug Administration (FDA) granted authorization of the first statin medication, lovastatin, for treatment of hypercholesterolemia, primary prevention of CHD and delay of coronary atherosclerosis progression [Food and Drug Law Institute, 2009; Mevacor US package insert, 2014]. Lovastatin is a specific inhibitor of hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase, the enzyme involved in early steps of the cholesterol synthesis pathway [Figure 1]. Since this initial approval, other medications (pravastatin, simvastatin, fluvastatin, atorvastatin, rosuvastatin) within the statin pharmacological drug class have also achieved FDA approval.

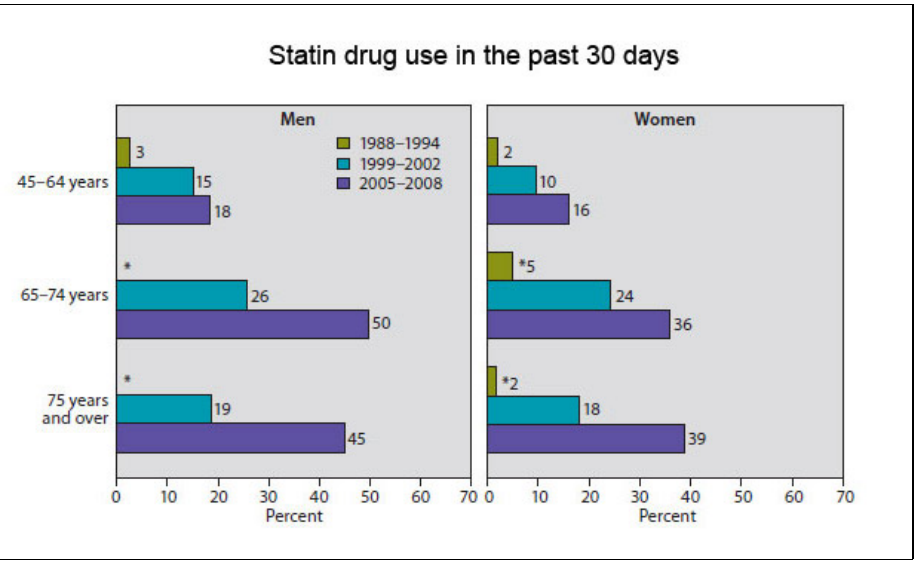
**Figure 1: Statin Inhibition of HMG-CoA Reductase and Cholesterol Synthesis**




CoA: coenzyme A; HMG-CoA: hydroxymethyl glutaryl coenzyme A; PP: pyrophosphate.
Source (edited): [www.nature.com, 2014].

The availability of these medications provided 'breakthrough' treatment for individuals at risk for CHD who required interventions beyond exercise and diet. The Centers for Disease Control and Prevention (CDC) reports that a substantial percentage of men (50% in 65-74 years; 45% in 75 years and over) and women (36% in 65-74 years; 39% in 75 years and over) have used statin medications in 2005-2008 as compared to < 2% and 5% for men and women, respectively, in the same age range in 1988-1994 [Figure 2] [National Center of Health Statistics, 2011].

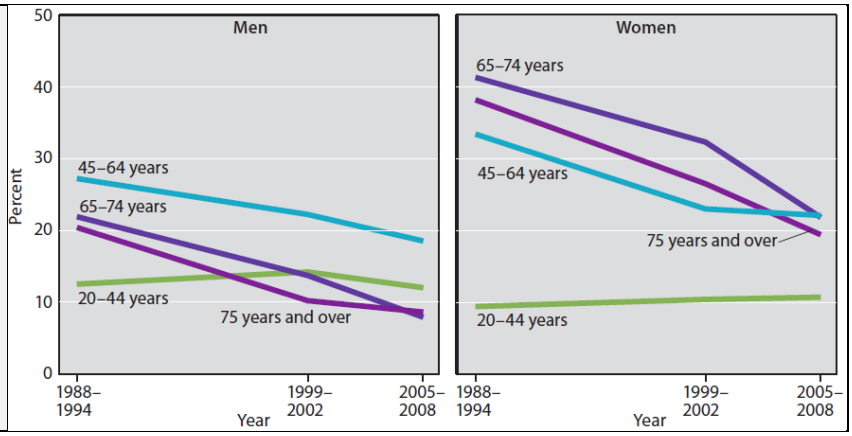
**Figure 2: Statin Drug Use by Gender and Age, 1988-1994; 1999-2002; 2005- 2008**




* Estimates are considered unreliable. Data preceded by an asterisk have a relative standard error of 20%-30%.
Source: [National Center of Health Statistics, 2011].

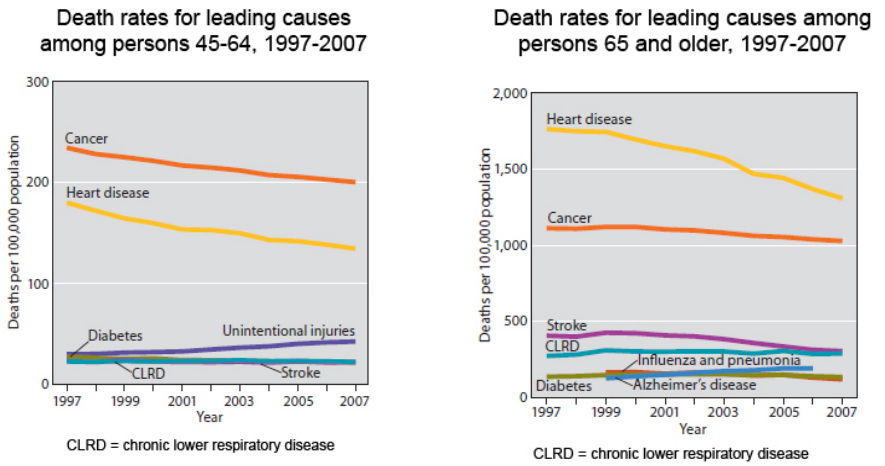
The CDC also reports declines in hypercholesterolemia (total cholesterol ≥ 240 mg/dL) in adult males and females since 1988, a trend that appears to correlate with the widespread use of statin medications. Furthermore, the decline in high total cholesterol parallels the decreasing mortality due to heart disease observed since 1997 [Figure 3 and Figure 4].

**Figure 3: Percentage with High Total Cholesterol (>240 mg/dL) by Gender and Age, 1988-1994; 1999-2002; 2005-2008, 1998-2008**




Source: [National Center of Health Statistics, 2011].

**Figure 4: Leading Causes of Death in the United States, 1997-2007**




Source: [National Center of Health Statistics, 2011].

In February 2012, decades after the first statin medication authorization in the US, a public announcement was disseminated by the FDA that warned of the potential increases in blood glucose and risk of type 2 diabetes mellitus (T2DM) with the use of statin therapy [FDA News Release, 2012]. Manufacturers of statin medications were required to communicate details of this potential risk to healthcare professionals and patients through updates of the US package inserts. The basis for the concern stemmed from data that emerged from a double-blind, randomized study, "Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER)" (n=17,603), in which a 27% increase in investigator diagnosis of T2DM in rosuvastatin-treated patients compared to placebo-treated patients was reported [FDA News Release, 2012; FDA Drug Safety Communication, 2012; Ridker *et al.*, 2008]. In another double-blind, randomized study, "Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE-IT TIMI 22)," high-dose statin therapy was also associated with worsening glycemic control [Sabatine *et al.*, 2004]. Subsequent to the availability of these results, meta-analyses were conducted, providing a mixture of results. For example, Rajpathak *et al.* analyzed data from 6 trials (n=57,593) and concluded that the association of statins and incident T2DM was uncertain, warranting further study [Rajpathak *et al.*, 2009]. Sattar *et al.* analyzed data from 13 interventional trials (n=91,140) and reported that statin therapy was associated

with a 9% increased risk for incident T2DM (odds ratio [OR] 1.09; 95% confidence interval [CI] 1.02-1.17) [Sattar *et al.*, 2010]. It should be noted that this latter meta-analysis of incident T2DM was based upon non-standardized definitions across the individual studies that ranged from physician reported diagnoses to single or multiple measures of blood glucose (fasting or non-fasting).

Prior to the availability of results from the JUPITER and PROVE-IT TIMI 22 studies, findings of incident T2DM had not been observed since the initial FDA approval in 1987, despite the active collection of adverse event and/or laboratory parameters that are required to be evaluated during interventional studies (> 1,600 studies) [www.clinicaltrial.gov, 2014]. It has been suggested that the findings in the JUPITER study may have been attributed to the unique study population of patients with high C-reactive protein, a risk factor for T2DM. However, this does not explain the findings observed in the PROVE-IT TIMI 22 study.

*Observational Studies of Statin Relationship and T2DM*

To date, few published non-interventional studies regarding the use of statins and risk of T2DM have been identified. Culver *et al.* evaluated the use of statins in postmenopausal women (n=161,808) participating in the Women's Health Initiative. Results of this study indicated that statin use was associated with an increased risk of incident T2DM in postmenopausal women (hazard ratio [HR] 1.71, 95% CI 1.61 - 1.83), noting that the effect appeared to be consistent across all statins with no specific observations regarding potency or individual statin use [Culver *et al.*, 2012]. Carter *et al.* conducted a population-based cohort study to evaluate the risk of statin use and incident T2DM during the time period of 1997–2010 [Carter *et al.*, 2012]. Participants aged 66 years or older without a diagnosis of T2DM were enrolled in the study. Pravastatin was assigned as the reference treatment arm. Results based upon Cox proportional hazard modeling demonstrated a 22%, 18% and 10% increased risk of incident T2DM with atorvastatin (95% CI 1.15-1.29), rosuvastatin (95% CI 1.10-1.26) and simvastatin (95% CI 1.04-1.17), respectively, as compared to pravastatin. No significant

increased risk was observed in patients who received fluvastatin or lovastatin [Carter *et al.*, 2013].

*Type 2 Diabetes Mellitus and Public Health Implications*

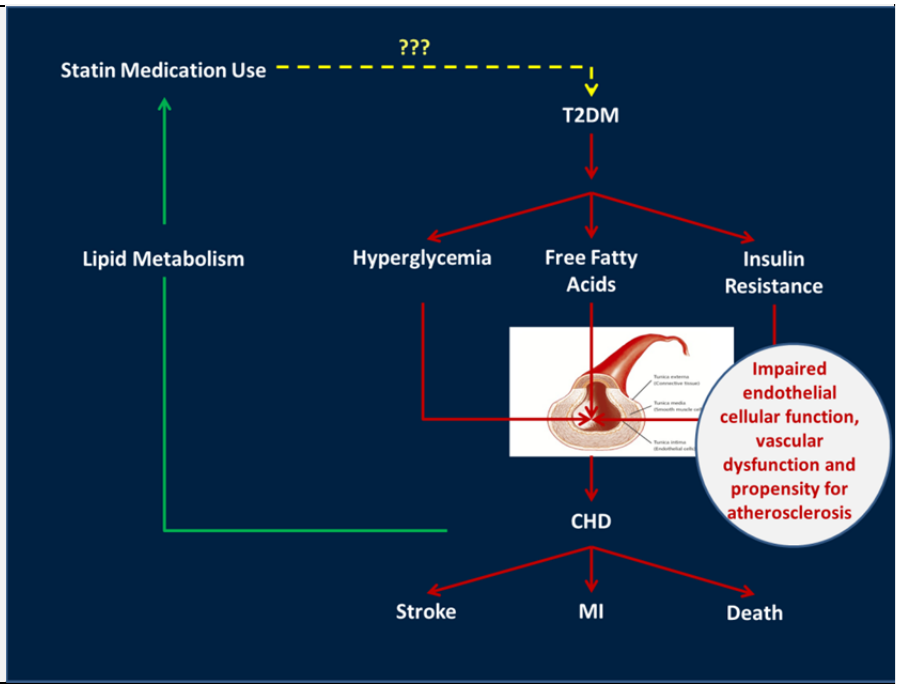
The pathophysiology of T2DM (previously termed noninsulin-dependent diabetes mellitus) is characterized by an initial deficiency in insulin secretion due to β-cell decline and ultimately β-cell failure as well as peripheral insulin resistance [Reaven, 1998; Olefsky, 1989]. In 1980, the number of Americans diagnosed with diabetes (type 1 or type 2) was approximately 5.6 million and in 2011, this number rose to approximately 21 million [CDC, 2013]. The prevalence of T2DM is relatively higher in the elderly and the African American, Hispanic American, and Native American populations [Ahmad & Crandall, 2010; Dall *et al*, 2007]. Individuals with T2DM are at risk of multi-organ damage over the course of this disease and as a result, complications such as peripheral neuropathy, nephropathy and ocular damage need to be managed. In addition to these prominent co-morbid conditions, cardiovascular complications may occur and represent the leading cause of mortality associated with T2DM [Tuomilehto *et al,* 2001; Lindström *et al*, 2006].

The diagnosis of T2DM is based upon several criteria including a) oral glucose tolerance test with a 2-h value of 200 mg/dL or more, b) fasting plasma glucose of 126 mg/dL or more, or c) non-fasting plasma glucose of 200 mg/dL or more with typical symptoms of T2DM such as increased thirst, weight loss, fatigue, frequent urination and/or blurry vision [Wingard & Barrett-Connor, 1995]. Glucose impairment is defined as fasting plasma glucose of 110-125 mg/dL and is considered to be on the causal pathway for T2DM given that approximately one-third of individuals with impaired fasting glucose are at risk for the development of T2DM [Wingard & Barrett-Connor, 1995; Antonucci *et al*., 1998; Alberti *et al*., 1996; Knowler *et al*., 1997]. Fasting insulin levels are also assessed as surrogate measures for insulin resistance and furthermore, there is evidence to believe that fasting insulin levels may be involved in the pathophysiology of T2DM through mechanisms independent of insulin resistance [Weyer *et al*., 2000]. The

composite measure of HOMA-IR is a model that has been widely utilized in research as endpoints for examining insulin resistance and beta-cell function [Wallace]. Alterations in the biomarkers are representative of the physiological processes underlying T2DM.

The public health implications of the emerging safety observation of statin use and possible association with T2DM are important. It is known that individuals with dyslipidemia, concomitant T2DM, and contributing lifestyle factors (i.e., obesity, smoking) develop accelerated progression of coronary atherosclerosis [Garg & Grundy, 1990]. This evidence is supported by the reported two-fold increase in the manifestations of CHD such as myocardial infarction, cerebrovascular accident and/or sudden death in T2DM individuals compared to individuals without T2DM [Laakso & Lehto, 1997]. Suggested molecular mechanisms underlying this pathway involve the metabolic disorders that characterize T2DM such as hyperglycemia, excess free fatty acids, and insulin resistance. These metabolic disorders can cause impairment of the endothelial layer leading to vascular dysfunction and a higher propensity for the atherosclerotic process [Creager *et al.*, 2003] [Figure 5]. Thus, individuals who receive statin medications for management of elevated cholesterol or CHD may, in fact, be at increased risk of developing T2DM, which could result in the downstream potential for exacerbation of their underlying cardiovascular disease and accompanying comorbid consequences [Figure 5].

**Figure 5: Potential Pathway for Statin Medication Use and Treatment Emergent T2DM Leading to CHD**




CHD: coronary heart disease; MI: myocardial infarction; T2DM: type 2 diabetes mellitus.

The additional public health concern lies with the steadily increasing rates of T2DM in the US, which pose a primary threat to public health [Laakso & Lehto, 1997]. The concerns are further enhanced given the anticipated increased statin medication use prompted by the most recent American College of Cardiology/American Heart Association (ACC/AHA) recommendations that now encourage use of these medications earlier in the disease process and in high risk individuals with or without evidence of atherosclerotic cardiovascular disease [Stone *et al.,* 2013]. Thus, the widespread use of statin medications and the potential for treatment emergent T2DM could imply even further increases in incident T2DM and the accompanying disease burden.

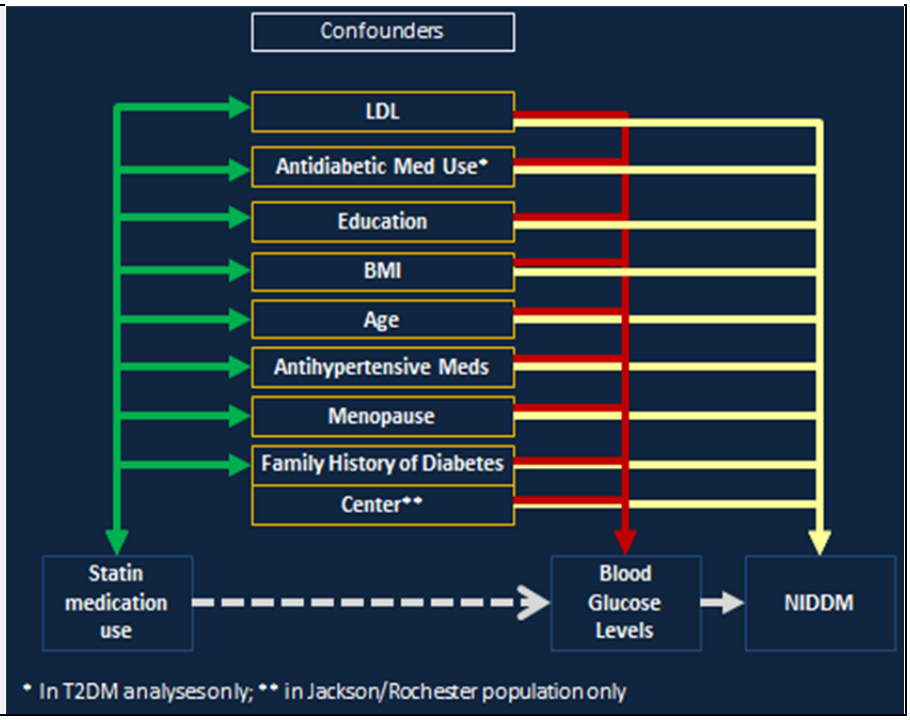
*Risk Factors for Type 2 Diabetes Mellitus*

Type 2 diabetes mellitus is a heterogeneous disorder that is influenced by multiple factors involving environmental, genetic, social, economic, demographic and pharmacological stressors.

Specific covariates that are expected to have an important influence on the primary exposure variable, statin medications, and also known to be a risk factors for the

outcomes of interest were considered for this research. [Figure 6] provides graphical representation of the primary variable, outcome, and confounders. The rationale for each confounder is provided next.

**Figure 6: Graphical Representation of the Relationship between the Primary Exposure Variable, Outcomes and Confounders that were considered in the Analyses**




BMI: body mass index; T2DM: type 2 diabetes mellitus.

*Rationale for Confounders*

a) Body mass index (BMI, kg/m$^2$): In age adjusted analysis, increasing BMI has been positively and linearly associated with fasting glucose blood levels [Lamon-Fava *et al.*, 1996] and T2DM [CDC, 2014]. The CDC has defined subjects with BMI between 25.0-29.9 as overweight and BMI with ≥30.0 as obese [CDC, 2014]. Obesity has been shown to be a determinant for high levels of low-density lipoprotein (LDL) and triglycerides (TG) through a strong effect upon lipoprotein metabolism [Krauss *et al.*, 1998] and therefore, a higher use of statins is anticipated in this population. For purposes of these analyses, BMI was defined as a continuous variable.

b) Age (years): Age related impairment of glucose tolerance has been documented [Rhee *et al.*, 2006]. Analysis of the relationship between age and cholesterol levels has demonstrated decreased LDL and TG with older age. However, recent publications have shown the benefits of lipid lowering medications and prevention of cardiovascular disease and mortality in the aging population and therefore, it is believed that the use of statin medications is higher in the elderly as compared to the younger population. For purposes of these analyses, age was defined as a continuous variable.

c) Low-density lipoprotein (mg/dL): A higher use of statin medications is indicated for treatment of dyslipidemia and dyslipidemia is a well-recognized risk factor for T2DM. Low-density lipoprotein was defined as a continuous variable

d) Antidiabetic medication use: In the GENOA study, different percentages of antidiabetic medication and concomitant medication use were observed across the Jackson/African American, Rochester/Non-Hispanic Whites and Starr County/Hispanics (Phase 1 Jackson: 2.45%; Phase 1 Rochester 2.17%; Starr County Hispanic Phase 1 8.03%). Antidiabetic medication use was considered for the T2DM population analyses only and categorically defined as 0=no antidiabetic medication use and 1=antidiabetic medication use.

e) Antihypertensive medications: Various medications that are used in the medical management of hypertension have been associated with a higher risk of T2DM [Taylor *et al*., 2006]. Concomitant use of antihypertensive and statin medications has also been documented among patients with CHD or CHD risk factors [Chapman *et al.*, 2009]. For purposes of these analyses, antihypertensive medications was categorically defined as 0 = no medication and 1 = medication.

f) Menopause status: Goodarzi *et al*. conducted a meta-analysis to evaluate the relationship between the proportion of women in statin placebo-controlled clinical trials and the risk of T2DM through review of published literature and concluded a significant relationship [Goodarzi *et al*., 2013]. However, these differences in fasting blood glucose for females as compared to males in the Genetic Epidemiology Network of Arteriopathy (GENOA) population were not observed ($p \geq 0.05$). In the GENOA population, differences in fasting blood glucose were observed for menopause status. Endogenous hormones in postmenopausal females have been positively associated with glucose intolerance and T2DM [Golden *et al.*, 2007]. It has been demonstrated that increases in LDL and TG alongside decreases in high-density lipoprotein (HDL) occur during the premenopausal to postmenopausal phase suggesting that the use of statin medication may be higher in the postmenopausal population [Stevenson *et al*., 1993]. For purposes of these analyses, menopause status was included in the Aim 1 and Aim 2 analyses categorically defined as 0 = no menopause (males and females) and 1 = menopause. For Aim 3, the analyses included gender which was consistent with the approach from prior studies giving rise to the index T2DM single nucleotide polymorphism (SNPs).

g) Family History of Diabetes: A family history of diabetes (type 1 or type 2 diabetes) is a strong predictor for the development of T2DM. It is likely that this is elevated risk is mediated partially by genetic components (genetic factors in T2DM discussed below) and/or shared environmental factors [InterAct Consortium, 2013]. Therefore, it is anticipated that the use of statin medications is differential across the groups of participants with family history of diabetes as compared to no family history of diabetes. For purposes of these analyses, family history was categorically defined as 0 = no reported family history of diabetes and 1 = reported family history of diabetes.

h) Education: The characteristics of social and economic status (SES) are influential upon the risk of T2DM [Williams *et al.*, 2012]. Education is considered a stable proxy for SES and, theoretically, varying levels of education could result in differential use of statin medications. For purposes of this analysis, education was categorically defined as 0 = ≤ 12 years and 1 = > 12 years.

i) Center: The percentage of statin medication use was different across the centers in the GENOA study. Also, the prevalence of T2DM was different across populations enrolled in each center. Therefore, the variable 'center' was included in the analyses and categorically defined as 0=Jackson, 1=Rochester.

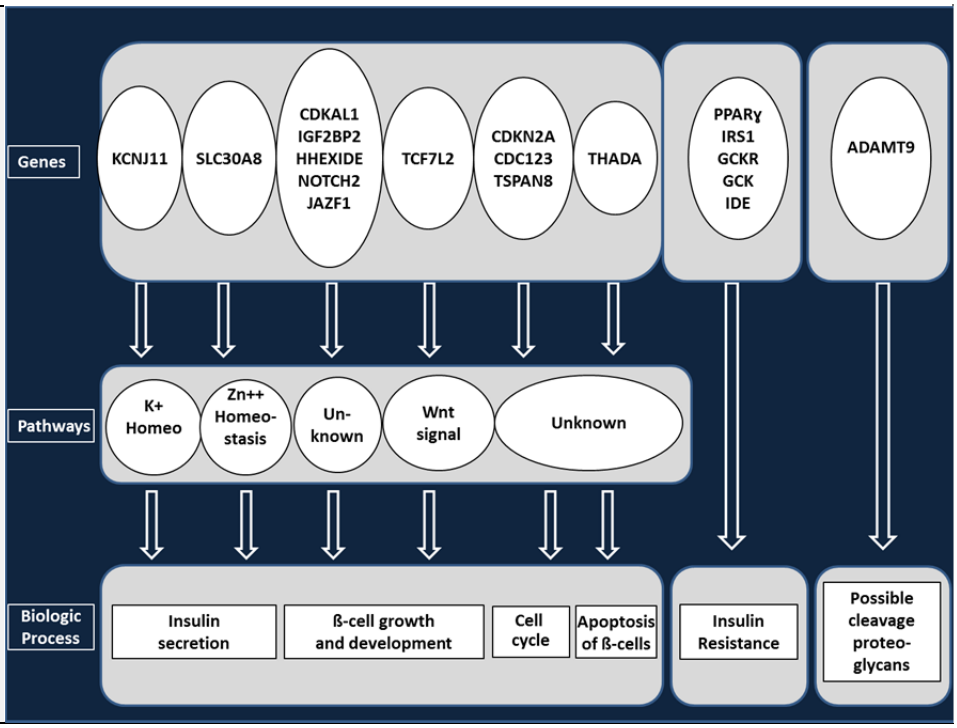
*Genetic Factors in T2DM*

An understanding of genetic determinants that are associated with disease pathogenesis, especially for complex diseases, and the potential for drug interaction may also provide insight to the underlying causal pathway between drug exposure and drug safety concerns. [Figure 7] provides a description for some of the major genetic factors and mapping to various pathways involved in the T2DM disease process. McCarthy and Zeggini [McCarthy & Zeggini, 2009] reviewed the substantial evidence that has emerged over the past decade regarding the genetic predisposition to T2DM and have collated the most significant and replicated T2DM genetic susceptibility loci derived from genome wide association (GWA) studies. Sladek *et al.* discovered variations in the *SLC30A8* gene that encodes for zinc transporters expressed exclusively in β-cells and are involved in final stages of insulin synthesis; variations near the *HHEX* gene that is involved with pancreatic β-cell development and function [Sladek *et al.*, 2007]; and, also confirmed a well-known variation within the *TCF7L2* gene that plays a role in Wnt signaling and has been implicated in decreased β-cell proliferation and insulin secretion. The *TCF7L2* gene is the most significant genetic determinant for T2DM and it has been replicated across multiple ethnicities [SIGMA, 2014; Palmer *et al.*, 2012; Grant *et al.*, 2006; Florez *et al.*, 2006; Saxena *et al.*, 2006; Chang *et al.*, 2007]. Other genetic factors were discovered through the Diabetes Genetics Initiative (DGI), in

collaboration with the Finland-United States Investigation of Non-Insulin Dependent Diabetes Mellitus Genetics (FUSION) initiative and Wellcome Trust Case Control Consortium (WTCCC), include the *IGF2BP2* and *CDKN2A/2B* genes that are believed to be involved with insulin secretion through influence upon insulin signaling and decreased pancreatic β-cell mass, respectively [WTCCC, 2007; Scott *et al*., 2007; Saxena *et al.*, 2007]. These investigators also identified the *CDKAL1* gene which, if impaired, may lead to reduced insulin gene expression and impaired response to glucotoxicity; the identification of *CDKAL1* was later corroborated by results from the deCODE study that also suggested that the genotype OR for the variant was substantially greater in homozygous carriers (OR 1.5; 95% CI 1.31 – 1.72) compared to heterozygous carriers (OR 1.15; 95% CI 1.06–1.24) [Steinthorsdottir *et al.*, 2007]. The *PPARɣ* and *KCNJ11* genes were discovered through prior candidate gene studies and were also confirmed in the DGI study; both genes have become the target for T2DM treatment. The *PPARɣ* gene plays a fundamental role in adipogenesis and insulin resistance and the *KCNJ11* gene encodes $K^+$-channels that are involved with β-cell insulin secretion [Altshuler *et al.*, 2000].

Subsequent to these initial GWA studies, researchers from the DGI, FUSION and WTCCC consortiums also collaborated to perform a GWA scan meta-analysis that identified additional genetic loci associated with T2DM. These included variations in or near *JAZF1, CDC123-CAMK1D, TSPAN8-LGR5, THADA, ADAMTS9, NOTCH2* genes [Zeggini *et al.*, 2008].

**Figure 7 Major Genetic Factors Involved in Type 2 Diabetes Mellitus Disease Process (US/EU Populations)**




Of recent, 65 distinct genetic loci associated with T2DM have been reported by the DIAbetes Genetics Replication and Meta-Analysis (DIAGRAM) consortium [Morris *et al.*, 2012] and are presented in [Appendix 1]. Furthermore, as T2DM genetic variants have become known, researchers examined the aggregation of genetic information into a genetic risk score (GRS) and the ability to prospectively predict incident cases of disease. These GRSs represent a collection of information from greater than one variant at different genetic loci associated with a particular disease [Hivert *et al.*, 2014]. The individual 65 genetic variants as well as the GRS are in scope of this research.

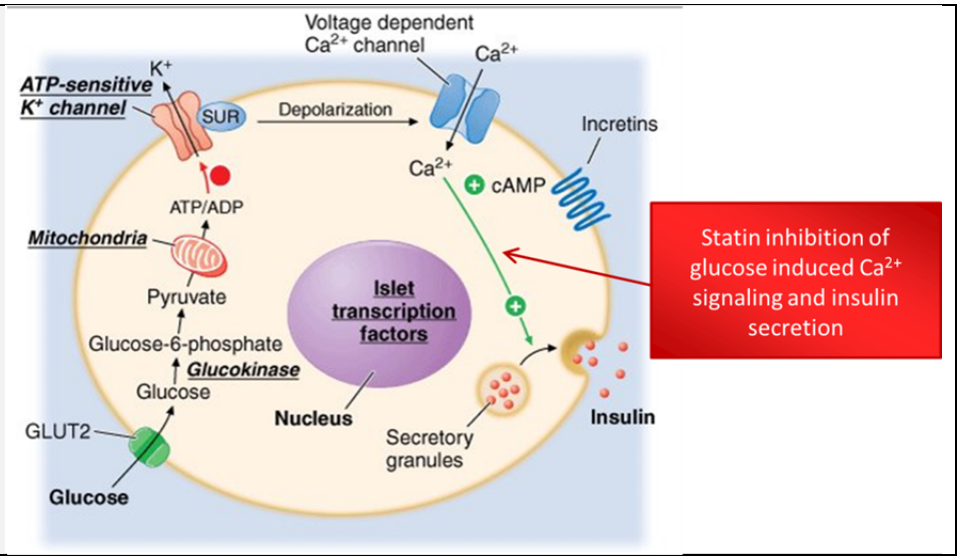
*Statin Use and Potential Physiological Mechanisms Leading to T2DM*

The underlying pathogenesis of T2DM primarily involves alterations in pancreatic β-cell function leading to impaired insulin secretion as well as mechanisms associated with peripheral insulin resistance. The influence of medication use on these pathways is not a novel concept. For example, antihypertensive medications inhibit insulin secretion through β-receptor blockade [Mills & Horn, 1985; Taylor *et al.*, 2006]; glucocorticoid medications are predominately involved with impaired hepatic insulin receptor

resistance and anti-psychotic medications are known to be associated with both insulin resistance and impaired insulin sensitivity [Ferris & Kahn, 2012].

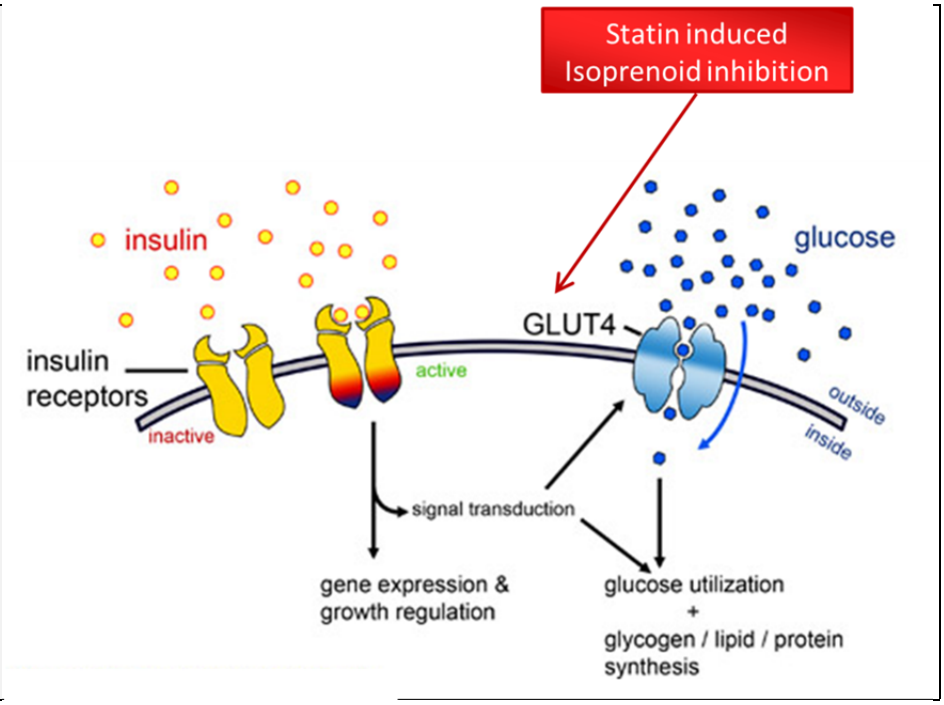
*In vivo* and *in vitro* studies have raised potential cellular mechanisms to explain the pathway between statin exposure leading to impaired glucose and T2DM. Yada *et al.* demonstrated the effects of statins on pancreatic β-cell function and impaired insulin secretion through inhibition of glucose mediated cytosolic $Ca^{2+}$-signaling [Figure 8; Yada *et al.*, 1999]. Impaired insulin sensitivity with statin exposure has also been observed as a result of inhibition of isoprenoid, an intermediate product in the cholesterol formation pathway [Figure 1], leading to down regulation of glucose transporters [Figure 9; Nakata *et al.*, 2006; Chamberlain, 2001]. To understand this pathway in a diabetic model, Kanda *et al.* demonstrated that statin medications may affect glucose tolerance in rats, without influencing insulin secretion [Kanda *et al.*, 2003]. Although multiple theories regarding the biological mechanisms of statin use and potential for T2DM have been postulated, no specific biologic pathway has been elucidated in humans.

**Figure 8: Proposed Glucose Induced Cytosolic $Ca^{2+}$ Signaling and Statin Inhibition**




ATP: adenosine triphosphate; AcylCoA: acetyl coenzyme A; GLUT2: Glucose transporter type 2;
$PIP_2$: phosphatidylinositol 4,5-bisphosphates;
Source (edited): [Fauci *et al.*, 2014].

**Figure 9: Statin Influence Upon General Insulin Signaling Pathway in Peripheral Tissue**




GLUT-4 : Glucose transporter type 4.
Source (edited): [Beta Cell Biology Consortium, 2014].

*Rationale for this Research Program*

The limited availability of evidence to evaluate the association of statin medication use and risk of T2DM from observational research gave rise to the rationale for this research program. Although some would argue that the treatment effect estimates generated from randomized clinical trials and observational studies are generally comparable, others would suggest that the estimates from non-randomized studies are likely to demonstrate greater magnitude of treatment effects [Chalmers *et al*., 1977; Sacks *et al*., 1982; Colditz *et al*., 1989; Miller *et al*., 1989]. For the most part, researchers would agree that randomized clinical trials and observational studies act synergistically to provide more in depth information regarding a treatment effect. More specifically, the observational study design serves to evaluate a treatment or intervention in a broader population and, in contrast to the randomized clinical trial, patients tend to be relatively less healthy, less educated and of lower socioeconomic status. Further, in randomized clinical trials, patients are more likely to adhere to the treatment regimen due to their awareness that participation is dependent upon this factor. Therefore, results from

observational studies provide evidence of actual practice patterns, 'real life' evidence of a treatment effect, and provide appropriate contextualization of the conclusions drawn from controlled randomized clinical trials.

The study population for this dissertation research is comprised of Non-Hispanic Whites, African American and Hispanic participants enrolled in the Genetic Epidemiology Network of Arteriopathy (GENOA) study. The difference in ethnic composition of this study population provides the ability to evaluate statin medication use in these distinct populations. The study was conducted at field centers located in Rochester, MN; Jackson, MS and Starr County, TX, respectively, and therefore, potential differences observed across ethnicities could be confounded by environmental differences.

The Specific Aims of this research are described below:

- Specific Aim 1: To examine the relationship between statin medication use and fasting blood glucose levels, insulin levels and HOMA-IR at baseline and follow-up in the GENOA participants.

  Rationale: Changes in fasting blood glucose, fasting insulin, β-cell function and/or insulin resistance are on the causal pathway for T2DM and may be indicative of a pre-diabetic state, or precursor to T2DM. Analyses in Phase 1 non-T2DM participants and changes in fasting blood glucose in Phase 2 non-T2DM as well as T2DM participants will be conducted. If statin use is associated with increased risk of T2DM, changes in these various biomarkers along the causal pathway should be apparent.

- Specific Aim 2: To examine the prevalence and incidence of T2DM in participants exposed to statin medications compared to participants not exposed to statin medications.

Rationale: The observational study design provides results from 'real life' setting to examine the association of statin use and T2DM. Results from this study will serve as complimentary evidence to results that have been published from controlled, interventional clinical trials.

- Specific Aim 3: To investigate the influence of previously identified SNPs (in T2DM genes) on GENOA glucose levels and T2DM risk before and after considering interactions with statin medication use.

  Rationale: Given the widespread use of statin medications in the US, genetically susceptible individuals may be at higher risk of developing T2DM when prescribed statin medications.

# Chapter 2 AIM 1: Investigation of the Relationship of Statin Medication Use, Fasting Blood Glucose Levels and Fasting Insulin Levels

## 2.1 Introduction

Decades post the initial regulatory approval of lovastatin, the first medication within the statin pharmacological class, the FDA disseminated warnings to healthcare providers regarding the potential increases in blood glucose and risk of T2DM associated medications within the statin class of medications. The primary source of evidence underlying the potential association of treatment emergent changes in blood glucose and/or T2DM was data generated within the context of randomized, clinical trials (Ridker *et al.*, 2008; Sabatine *et al.*, 2004].

To date, few non-interventional studies regarding the use of statins and risk of changes in fasting blood glucose or T2DM have been published. Furthermore, results from studies have been conflicting with regard to statin use and incident T2DM or deterioration of glycemic control with use in the diabetic population [Sabatine *et al.*, 2004]. In the JUPITER study, incident T2DM was associated with rosuvastatin use however, *post hoc* analysis demonstrated that approximately 80% of these patients actually presented with impaired fasting glucose at the time of entry into the study. These data suggest that the relationship could be attributed to exacerbation of the pre-diabetic state or other risk factors such as metabolic syndrome that may be uncovered while monitoring patients who receive statin treatment [Rocco, 2012]. Zhou *et al.* conducted meta-analysis of randomized clinical trials to investigate whether statins deteriorate glycemic control in diabetic patients and found no significant influence on glycosylated hemoglobin (HbA1c), fasting plasma glucose or fasting insulin [Zhou *et al.*, 2013]. In contrast, Sukhija *et al.* examined statin use in patients with and without T2DM and observed increases in fasting blood glucose in the non-diabetics (7 mg/dL in statin

users, versus 5 mg/dL in non-statin users, $p < 0.0001$) and even greater increases in the diabetic population (39 mg/dL, versus 32 mg/dL in non-statin users, $p < 0.0001$), independent of age, use of aspirin, and antihypertensive medications [Sukhija *et al.*, 2009].

Kanda *et al.* examined the effects of atorvastatin (8 mg/kg/d), pravastatin (8 mg/kg/d), and control vehicle in non-diabetic and mildly induced diabetic rats (streptozotocin induced) by measuring blood glucose and insulin at 1, 2, 3 and 6 week time points. Increases in blood glucose in the diabetic rats were higher than in the non-diabetic rats, and the magnitude of change was even greater with administration of atorvastatin as compared to pravastatin. No changes in blood insulin levels were observed with administration of statins or control [Kanda *et al.*, 2003].

*In vitro* and *in vivo* (in animals) evidence indicates multiple cellular mechanisms in the microbiologic pathway of glucose transportation or insulin secretion and involvement with statin induced inhibition of isoprenoid synthesis, an intermediate product in the cholesterol formation pathway, or inhibition of glucose mediated cytosolic $Ca^{2+}$-signaling. However, no mechanism has been elucidated in humans.

The main goal of this study was to examine the relationship between statin medication use and fasting blood glucose levels at baseline and follow-up in Non-Hispanic White, African American and Hispanic participants enrolled in the GENOA study. Further, insulin resistance was examined using measures of fasting insulin levels and HOMA-IR, the latter being a widely recognized composite measure of fasting insulin and fasting glucose [Wallace *et al*., 2005]. Examination of the association was performed in the non-T2DM population as well T2DM population.

Given the multitude of social and psychological determinants that are dependent upon the environment and also influence the disease pathway, potential outcome differences in the GENOA African American, Non-Hispanic White and Hispanic populations are confounded with environmental differences among the Jackson, Rochester and Starr

County field centers, respectively. The limited availability of evidence to evaluate the association of statin medication use and risk of elevations in fasting glucose, fasting insulin and HOMA-IR from observational research is the rationale for this study and will provide evidence of actual practice patterns, 'real life' evidence of a treatment effect, and contextualization of the conclusions drawn from controlled randomized clinical trials.

## 2.2 Methods

### 2.2.1 Study Design

The Family Blood Pressure Program (FBPP), supported by the National Heart, Lung and Blood Institute (NHLBI), is a collaboration that serves to identify genetic determinants that influence blood pressure, hypertension and associated target-organ damage. The FBPP offers a robust scientific resource comprised of four multicenter networks. Each network is a family based study, originally intended to well characterize genetic associations and hypertension [FBPP Investigators, 2002]. Since FBPP was established, further research has been conducted to evaluate disease states beyond the initial focus of hypertension.

To address the main goals, this study was conducted in GENOA, one of the individual networks of the FBPP. GENOA is a sibship-based study, originally designed to investigate the genetic linkage of hypertension in sibships with at least two hypertensives diagnosed prior to age 60 years old (for African Americans and Non-Hispanic Whites) and T2DM (in Hispanics). The GENOA study consisted of two phases: the initial phase (Phase 1) and the second follow-up phase (Phase 2).

In this study, three analyses were conducted using different design attributes of the GENOA study:

- A cross-sectional study of participants enrolled in the Jackson, Rochester and Starr County field centers enrolled in Phase 1 during the period of 1996 – 2000;

- A cross-sectional study of participant enrolled in the Jackson, Rochester and Starr County field centers enrolled in Phase 2 during the period of 2000 – 2004;
- A longitudinal study of participants in Phase 1 who were also enrolled in Phase 2. [Figure 12] provides a graphical illustration of the planned longitudinal analyses.

The study protocol was approved by the Human Studies Review Boards of the Mayo Clinic, the University of Mississippi, and the University of Texas. The study protocol was also approved by the University of Michigan Investigational Review Board.

### 2.2.2 Study Eligibility

#### 2.2.2.1 Inclusion Criteria

ROCHESTER AND JACKSON FIELD CENTERS

In the Rochester, MN field center, the Mayo Clinic diagnostic index and medical record linkage system of the Rochester Epidemiology Project were used to identify Non-Hispanic White Olmsted County residents who had the diagnosis of essential hypertension prior to age < 60 years or who had the diagnosis of essential hypertension and received care in the county during the previous 3 years [Daniels *et al.*, 2004]. In Jackson, sibships were recruited through hypertensive probands who had participated in the Atherosclerosis Risk in Communities (ARIC) study [ARIC Investigators, 1989]. The ARIC cohort in Jackson was a probability sample of 45- to 64-year-old African American residents of that community. In both field centers, eligible probands were asked whether they had any siblings living in the area and if so, the siblings were contacted. If at least one additional sibling reported the previous diagnosis of hypertension prior to age 60 years old, all available members of the sibship were invited to the study center. Additional criteria included the requirement for all sibships to express willingness to participate in the study through provision of informed consent.

STARR COUNTY FIELD CENTER

In Starr County, sibships were identified from Hispanic White adults less than 60 years of age who were participants in the Starr County Health Studies. Due to the frequency of T2DM among Mexican Americans, subjects were recruited as members of families in which at least two siblings had a diagnosis of T2DM prior to age 60 years old. Type 2 diabetes mellitus was defined by one of the following: current use (within the last month) or prior use (for at least 1 year in lifetime) of anti-diabetic medications; or, two 10-hour fasting blood glucose assessments at least 24 hours apart with results ≥ 120 mg/dL using whole blood or ≥ 140 mg/dL using venous plasma; or, oral glucose tolerance test (OGTT) with results ≥ 200 mg/dL at 120 minutes and also ≥ 200 mg/dL at one prior time point (30, 60 or 90 minutes). When two such full siblings were identified, all members of the sibship were invited to participate. Additional criteria for inclusion in the study involved the requirement for all sibships to express willingness to participate in the study through provision of informed consent.

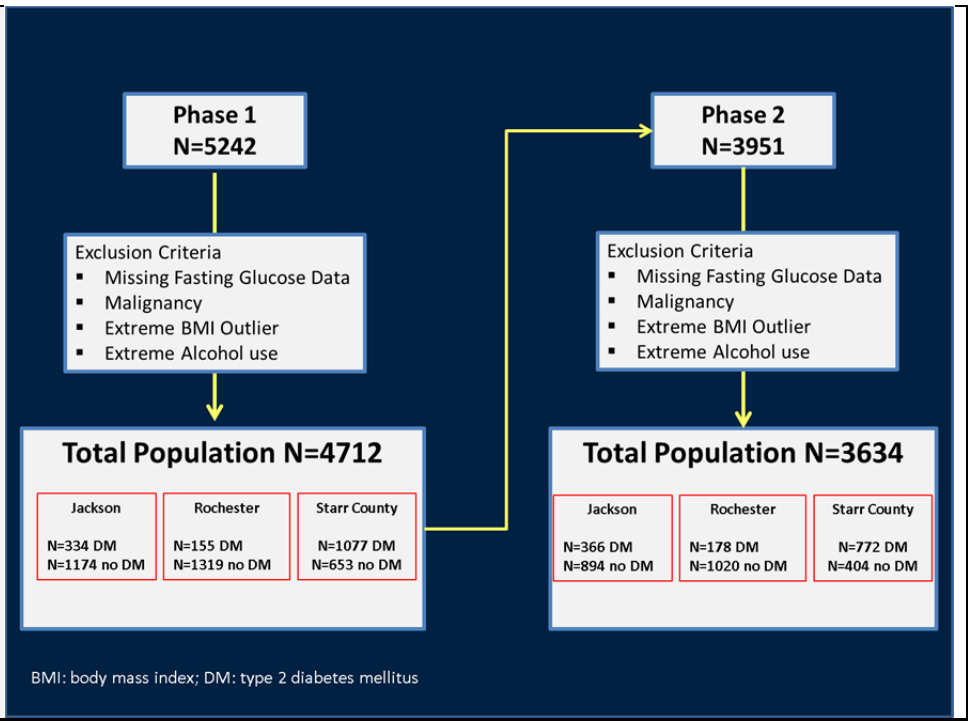
Recruitment methods for the second phase of the study involved contact of all sibships enrolled in Phase 1 with requests to participate in a follow up exam.

#### 2.2.2.2 Exclusion Criteria

Participants with a diagnosis of secondary hypertension, serum creatinine levels >2.5 mg/dL, alcoholism, drug abuse, pregnancy or Type 1 insulin-dependent diabetes mellitus were excluded from the GENOA study. All participants from the Rochester field center study were self-reported as being Non-Hispanic Whites. One participant underwent surgical sex reassignment and was excluded.

Additional exclusion criteria were applied for this study, which included missing fasting blood glucose levels (Phase 1 n=433; Phase 2 n=236), active malignancy (Phase 1 n=20; Phase 2 n=23), extreme BMI values (values > mean gender specific BMI + [4 x SD]; Phase 1 n=13; Phase 2 n=6) and extreme alcohol use (values > mean center specific number drinks/week + [4 x SD]; Phase 1 n=64; Phase 2 n=52) [Figure 10].

**Figure 10: Study Eligibility Criteria for Phase 1 and Phase 2**




### 2.2.3 Data Collection

Study visits were conducted in the morning after an overnight fast of at least 8 hours. Participant interview, physical exam and laboratory blood sampling were the primary methods of data collection. Participants were queried for demographic information which included gender and date of birth. Medical history was obtained through participant report of prior diagnosis by a physician, date of diagnosis and treatment of diagnosis. Height and weight were collected during physical exam. Prescription information for medications used in the past $\geq$1 month was collected from pharmacy sources provided by the participant (i.e., label on prescription vial). Lifestyle factors were collected which included a series of questions regarding physical activity, use of tobacco products, use of alcoholic beverages, completed educational years, and employment status.

[Table 1] provides details of data collected in Phase 1 and Phase 2 of the study that are most relevant for the analysis of this research.

**Table 1: Relevant Data Collected in Phase 1 and Phase 2 of the GENOA Study**

| Variable | Phase 1 | Phase 2 |
|---|---|---|
| Demographics, Intrinsic/Extrinsic Factors | | |
| Gender | X | X |
| Ethnicity | X | X |
| Date of birth | X | X |
| Completed educational years | X | X |
| Health History | | |
| Diagnosis of T2DM | X | X |
| Year of diagnosis for T2DM | X | X |
| Family history of diabetes | X | X |
| Menopause status | X | X |
| Medications Administered ≥ 1 month | | |
| Statin medications | X | X |
| Medications to treat hypertension | X | X |
| Anti-diabetic medications | X | X |
| Hormone replacement therapy | X | X |
| Physical Exam | | |
| Height | X | X |
| Weight | X | X |
| Laboratory Data (and draw time) | | |
| Fasting blood glucose | X | X |
| Fasting insulin | X | X |
| Total cholesterol, HDL, LDL (calculated), TG | X | X |

GENOA: Genetic Epidemiology Network of Arteriopathy; HDL: high-density lipoprotein; LDL: low-density lipoprotein; TG: triglycerides.

### 2.2.4 Exposure Classification and Outcome Measures

EXPOSURE CLASSIFICATION

The Medispan Generic Product Identifier drug dictionary was utilized to codify the first six digits that correspond to individual medications. The first six digits identified medications within the same pharmacological class. The primary exposure of interest, STATIN, represents a composite variable of individual medications within the statin pharmacological class (code 394000).

Case definition for STATIN was the participant-reported use of at least one of the following medications at the time of Phase 1 and Phase 2 exam:

- Atorvastatin
- Lovastatin
- Pravastatin
- Cerivastatin
- Fluvastatin
- Simvastatin

OUTCOME MEASURES

Fasting plasma glucose levels (collected in the morning) were evaluated as a continuous variable. Samples were assayed in duplicate and fasting blood glucose was measured using Elan Glucose reagent. The sensitivity range was 2–450 mg/dL, with the observed detection limit of 1.02 mg/dL and fasting is defined as ≥ 8 hours of no oral food or fluid intake.

Fasting insulin levels (uU/mL) were evaluated as a continuous variable. Fasting insulin levels were collected in the morning from all subjects. Samples were assayed using the Beckman Instrument Access Immunoassay which has a linear range from very low (1 uU/mL) to relatively high (300 uU/mL). This assay system has minimal cross-reactivity with proinsulin or c-peptide.

HOMA-IR was evaluated as a continuous variable utilizing the formula of HOMA1-IR = [(FPI x FPG) / 22.5], where FPI is fasting plasma insulin concentration (mU/l) and FPG is fasting plasma glucose (mg/dL).

## 2.3 Statistical Analysis Plan

### 2.3.1 Covariates

Covariates that were expected to have an important influence on the primary exposure variable and identified as a risk factor for the outcomes of interest were considered (detailed rationale for each covariate provided in Chapter 1). Covariates were categorized as quantitative or qualitative and were based upon data collected at the

time of Phase 1 and Phase 2 study visits. Continuous variables included BMI (kg/$m^2$), LDL (mg/dL) and age (years); and categorical variables included antihypertensive medications (i.e. β-blockers, $Ca^{2+}$-channel blockers, angiotensin converting enzyme (ACE) inhibitors, angiotensin-II receptor antagonist, reserpine, diuretics), menopause status, family history of diabetes, and education (≤ 12 years vs > 12 years). The categorical variable for antidiabetic medication use was also considered in the analyses conducted in T2DM populations only and, in the combined Jackson and Rochester analysis, 'center,' as well as the interaction term for 'statin x center' was included in order to examine the potential differences of statin effects in the African American and Non-Hispanic White populations.

### 2.3.2 General Statistical Approach

Demographic characteristics and intrinsic/extrinsic factors were summarized using descriptive statistics. Sample mean, median and interquartile range were examined for continuous variables of interest and, to meet model assumptions, continuous variables were also evaluated for normality through examination of histograms and determination of skewness.

Cross-sectional investigations were conducted separately in Phase 1 (1996 – 2000) and Phase 2 (2000 – 2004) as described in [Figure 11]. Using Statistical Analysis System (SAS) 9.3, univariate and multivariable linear mixed models were utilized to evaluate the relationship of statin medication use and fasting blood glucose, fasting insulin levels and HOMA-IR, by use of random intercept, accounting for the familial relationships within the study population. These examinations were conducted across ethnicities while recognizing the environmental and cultural differences between these field centers may be confounded with ethnicity in this examination. Thus, cross-sectional statistical analyses were conducted separately in the following four populations:

- African American enrolled in Jackson field center;
- Non-Hispanic Whites enrolled in Rochester field center;

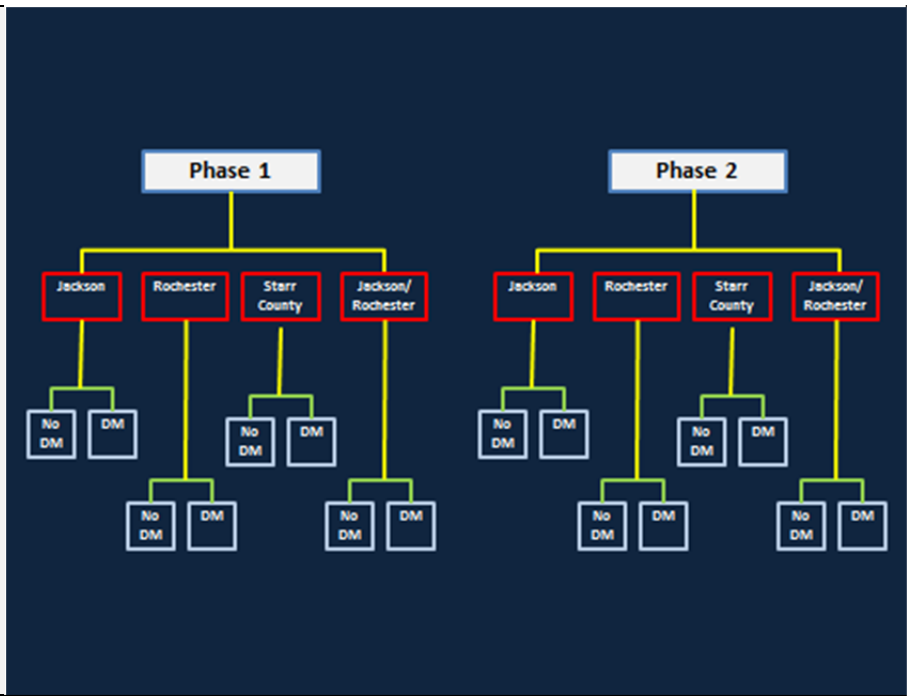
- Hispanics enrolled in Starr County field center;
- Combined African American and Non-Hispanic White populations given the similar methods of recruitment for sibships with a diagnosis of hypertension. Given that recruitment of Hispanic participants in the Starr County center was based upon a diagnosis of T2DM, this population was not integrated with the African American and Non-Hispanic White populations.

Furthermore, for cross sectional analyses, all examinations were conducted in non-T2DM participants separately from T2DM participants.

To select covariates for the analyses of fasting blood glucose and fasting insulin, stepwise linear regression was conducted for each of the above described populations [Figure 11]. Specifically, stepwise linear regression was performed with the main effects of the covariates using entrance p-value criteria of 0.05 and exit criteria of 0.10 (all covariates that were considered in the stepwise procedures are described in [Section 2.3.1]) in Phase 1 and Phase 2 for non-T2DM and T2DM participants in each of the four populations. The covariates selected for the fasting insulin analyses were applied for the HOMA-IR analyses.

Once main effects were selected via the stepwise linear regression, these covariates were included in linear mixed models (described in [Section 2.3.1]) to assess the association of statin use and the outcomes. Pairwise interactions of the primary exposure variable, statin medications, and the covariates that were selected via the stepwise procedure were also examined in the linear mixed models.

**Figure 11 Graphical Illustration for Cross Sectional Analyses**




DM: diabetes mellitus.

Longitudinal investigations were conducted to examine the association between statin use in Phase 1 and prediction of fasting blood glucose and fasting insulin in Phase 2. [Figure 12] provides a graphical illustration of this longitudinal analysis. In addition, the difference in fasting blood glucose between Phase 1 and Phase 2 was also examined, while adjusting for the changes in values for covariates in Phase 1 and Phase 2 as well as the baseline values of the covariates collected in Phase 1. The longitudinal statistical analyses were also conducted separately in the following four populations:

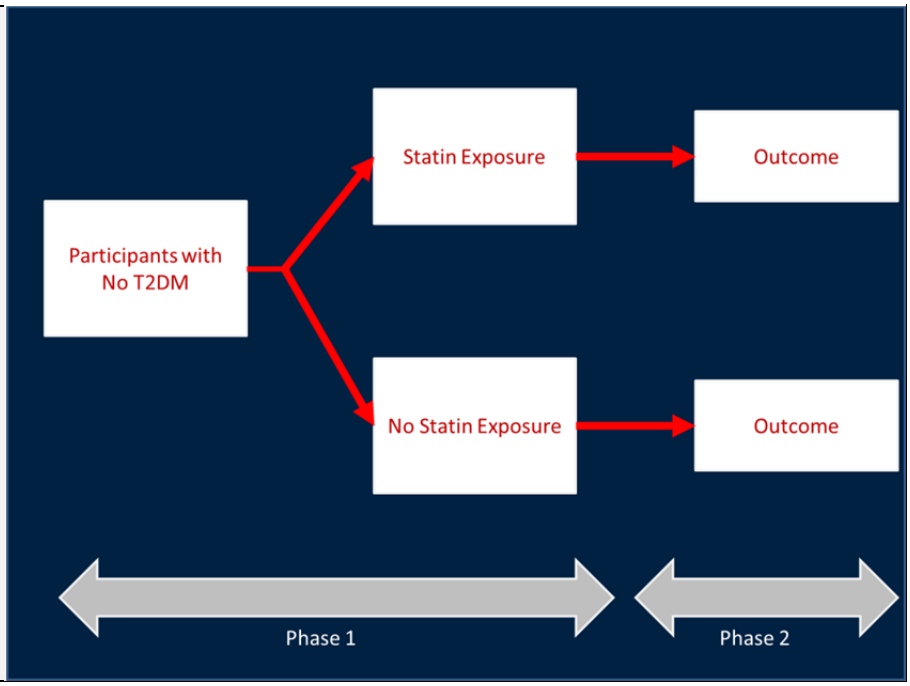
- African American enrolled in Jackson field center;
- Non-Hispanic Whites enrolled in Rochester field center;
- Hispanics enrolled in Starr County field center;
- Combined African American and Non-Hispanic White populations given the similar methods of recruitment for sibships with a diagnosis of hypertension. Given that recruitment of Hispanic participants in the Starr County center was based upon a diagnosis of T2DM, this population was not integrated with the African American and Non-Hispanic White populations.

Furthermore, for the longitudinal examination, statistical analyses were conducted in Phase 1 non-T2DM participants (and outcomes were assessed in Phase 2 or outcomes were assessed as the difference between Phase 1 and Phase 2). Longitudinal examination of fasting blood glucose was also conducted in Phase 2 non-T2DM separately from T2DM participants.

To determine the covariate selection for the longitudinal analyses in each population, stepwise linear regression was conducted with the main effects of the covariates using entrance p-value criteria of 0.05 and exit criteria of 0.10 (all covariates that were considered in the stepwise procedures are described in [Section 2.3.1]) in each of the four populations; Jackson African Americans, Rochester Non-Hispanic Whites, Starr County Hispanics, as well as the combined African American/Non-Hispanic White populations. The covariates selected for the longitudinal analyses of Phase 1 statin use and prediction of Phase 2 fasting blood glucose were applied in the longitudinal analyses of Phase 1 statin use and differences in Phase 1 and Phase 2 fasting blood glucose. The stepwise procedures for covariate selection were conducted separately for each outcome, fasting blood glucose and fasting insulin.

Once main effects were selected via the stepwise linear regression, these covariates were included in linear mixed models (described in [Section 2.3.1]) to assess the association of statin use and the outcomes. Pairwise interactions of the primary exposure variable, statin medications, and the covariates that were selected via the stepwise procedure were also examined in the linear mixed models.

**Figure 12: Graphical Illustration for Longitudinal Analysis**




T2DM: type 2 diabetes mellitus.
Note: Outcome for fasting blood glucose was conducted in non-T2DM and T2DM participants.

### 2.3.3 Cross Sectional Analyses

To examine the cross sectional relationship between statin medication use and fasting blood glucose, fasting insulin and HOMA-IR, univariate linear mixed models were performed [Model A1]; the adjusted analyses included covariates that were selected from the stepwise procedures [Model A2]; examination of pairwise interactions for the main exposure variable, statin medication use, and the covariates selected via the stepwise procedure were also examined [Model A3].

| |
|---|
| Model A1: $Y_{ij} = \beta_0 + \beta_1(statin_{ij}) + W_{0j} + \varepsilon_{ij}$ , for participant i in sibship j. |
| Model A2: $Y_{ij} = \beta_0 + \beta_1(statin_{ij}) + \beta_2(x_{ij}) + \ldots. + \beta_k(x_k) + W_{0j} + \varepsilon_{ij}$ , for participant i in sibship j |
| ▪ $Age_{ij}$<br>▪ $BMI_{ij}$<br>▪ $LDL_{ij}$<br>▪ $Menopause\ status_{ij}$<br>▪ $Family\ History_{ij}$<br>▪ $Education_{ij}$<br>▪ $Antihypertensive\ medication_{ij}$<br>▪ $Antidabetic\ medication_{ij}$ (for T2DM populations only)<br>▪ Center x $statin_{ij}$ [combined Jackson/Rochester population only] |

| Model A3: $Y_{ij} = \beta_0 + \beta_{1(}\text{statin}_{ij)} + \beta_2(x_{ij}) + \ldots \beta_k(x_k) + \beta_{k+1(}\text{statin x}_{xk1+1)} + W_{0j} + \varepsilon_{ij}$, for participant i in sibship j. | |
|---|---|
| ▪ $\text{Age}_{ij}$ x $\text{statin}_{ij}$<br>▪ $\text{BMI}_{ij}$ x $\text{statin}_{ij}$<br>▪ $\text{LDL}_{ij}$ x $\text{statin}_{ij}$ | ▪ $\text{Menopause status}_{ij}$ x $\text{statin}_{ij}$<br>▪ $\text{Family History}_{ij}$ x $\text{statin}_{ij}$<br>▪ $\text{Education}_{ij}$ x $\text{statin}_{ij}$<br>▪ $\text{Antihypertensive medication}_{ij}$ x $\text{statin}_{ij}$<br>▪ $\text{Antidiabetic medication}_{ij}$ x $\text{statin}_{ij}$<br>▪ Center x $\text{statin}_{ij}$ [combined Jackson/Rochester population only] |

In [Model A1-3], $\text{variables}_{ij}$ are represented by participant i in sibship j and are based upon data collected during Phase 1 or Phase 2 for the respective analyses; $Y_{ij}$ is the value of fasting plasma glucose level, fasting insulin level or HOMA-IR; and $W_{0j}$ is the random intercept for each sibship. The error term, $\varepsilon_{ij}$, is the residual variation unexplained by the model. The primary coefficient of interest, $\beta(\text{statin}_{ij})$ is the overall effect of statin use upon the fasting blood glucose, insulin levels or HOMA-IR, adjusting for the fixed effects of the other covariates and random intercept for sibships.

### 2.3.4 Longitudinal Statistical Analyses

To examine the longitudinal relationship between statin medication use and fasting blood glucose and fasting insulin, univariate linear mixed models were performed [Model B1] and the adjusted analyses included covariates that were selected from the stepwise procedures [Model B2]; examination of pairwise interactions for the main exposure variable, statin medication use, and the covariates selected via the stepwise procedure were also examined [Model B3].

| Model B1: $Y_{ij2} = \beta_0 + \beta_1(\text{statin}_{ij1}) + W_{0j} + \varepsilon_{ij}$, for participant i in sibship j across k time points | |
|---|---|
| Model B2: $Y_{ij2} = \beta_0 + \beta_{1(}\text{statin}_{ij1)} + \beta_2(x_{ij1}) + \ldots \beta_k(x_{k1}) + \beta_{k+1(}\text{statin x}_{xk1+1)} + W_{0j} + \varepsilon_{ij}$, for participant i in sibship j across k time points | |
| ▪ $\text{Age}_{ij1}$<br>▪ $\text{BMI}_{ij1}$<br>▪ $\text{LDL}_{ij1}$ | ▪ $\text{Menopause status}_{ij1}$<br>▪ $\text{Family History}_{ij1}$<br>▪ $\text{Education}_{ij1}$<br>▪ $\text{Antihypertensive medication}_{ij1}$<br>▪ $\text{Antidabetic medication}_{ij1}$ (for T2DM populations only)<br>▪ Center x $\text{statin}_{ij1}$ [combined Jackson/Rochester population only] |

| | |
|---|---|
| ▪ Model B3: $Y_{ij2} = \beta_0 + \beta_1(statin_{ij1}) + \beta_2(x_{ij1}) + \ldots \beta_k(x_{k1}) + \beta_{k+1}(statin \times x_{xk1+1}) + W_{0j} + \varepsilon_{ij}$, for participant i in sibship j. | |
| ▪ $Age_{ij1}$ x $statin_{ij1}$<br>▪ $BMI_{ij1}$ x $statin_{ij1}$ | ▪ Menopause status$_{ij1}$ x $statin_{ij1}$<br>▪ Family History$_{ij1}$ x $statin_{ij1}$<br>▪ Education$_{ij1}$ x $statin_{ij1}$<br>▪ Antihypertensive medication$_{ij1}$ x $statin_{ij1}$<br>▪ Center x $statin_{ij}$ [combined Jackson/Rochester population only] |

In [Models B1-B3], variables$_{ij1}$ are represented by participant i in sibship j and are based upon data collected during Phase 1; fasting blood glucose level and fasting insulin level are represented by $Y_{ij2}$ and based upon data collected in Phase 2; and $W_{0j}$ is the random intercept for each sibship. The error term, $\varepsilon_{ij}$, is the residual variation unexplained by the model. The primary coefficient of interest, $\beta(statin_{ij1})$, is the overall effect of statin exposure during Phase 1 upon fasting plasma glucose and fasting insulin levels in Phase 2, adjusting for the fixed effects of the other covariates and random intercept for sibships.

To examine the difference in plasma fasting blood glucose levels between Phase 1 and Phase 2 and use of statin medications in Phase 1, univariate models were performed [Model B4]; adjusted analyses were conducted for the differences in the continuous and categorical variables (described in [Section 2.3.1]) as well as the baseline values of these variables [Model B5]. The difference in fasting glucose level is calculated as Phase 2 - Phase 1; the other variables are represented by the differences in values for each variable collected at the time of enrollment in Phase 2 compared to Phase 1 (variable$_{ij2}$ - variable$_{ij1}$); variables$_{ij1}$ are included in the model to adjust for baseline values collected in Phase 1 (including baseline glucose collected in Phase 1); $\beta(statin_{ij1})$ is the overall effect of statin exposure during Phase 1 upon the change in fasting plasma glucose level over time, adjusting for the fixed effects of the other covariates; and $W_{0j}$ is the random intercept for each sibship.

| | |
|---|---|
| Model B4: E ($Y_{ij2}$ - $Y_{ij1}$) = $\beta_0$ + $\beta_1$ ($statin_{ij1}$) +$W_{0j}$ + $\varepsilon_{ij}$, for participant *i,* in sibship j across k timepoints (k=1 for Phase 1; k=2 for Phase 2). | |
| Model B5: E ($Y_{ij2}$ - $Y_{ij1}$) = $\beta_0$ + $\beta_1$($x_{ij2}$ -$x_{ij1}$) + …. + $\beta_7$($statin_{ij1}$) + $\beta_8$($glucose_{ij1}$) ++ $\beta_k$($x_{ij1}$) + $W_{0j}$ + $\varepsilon_{ij}$, for participant *i,* in sibship j across k timepoints (k=1 for Phase 1; k=2 for Phase 2). | |
| ▪ $Age_{ij1}$<br>▪ $BMI_{ij1}$<br>▪ $LDL_{ij1}$ | ▪ Menopause $status_{ij1}$<br>▪ Family $History_{ij1}$<br>▪ $Education_{ij1}$<br>▪ Antihypertensive $medication_{ij1}$<br>▪ Antidabetic $medication_{ij1}$ (for T2DM populations only)<br>▪ Center x $statin_{ij1}$[combined Jackson/Rochester population only] |

## 2.4 Results

### 2.4.1 Demographics, Intrinsic and Extrinsic Factors

In the initial phase of the GENOA study (1996-2001), a total of 4712 participants met the inclusion and exclusion criteria for this study; of which, 1508 were African American, 1474 were Non-Hispanic White and 1730 were of Hispanic ethnicity. Of the total number of Phase 1 participants, approximately 72%, 57% and 60% were female in the African American, Non-Hispanic White and Hispanic populations, respectively. In Phase 2 of the GENOA study (2000-2004), a total of 3634 participants met the inclusion and exclusion criteria for this study of which 1260 were African American, 1198 were Non-Hispanic Whites and 1176 were of Hispanic ethnicity. Of the total number of Phase 2 participants, approximately 72% African American, 58% Non-Hispanic White and 61% Hispanic were female.

In Phase 1, the mean ages of African American, Non-Hispanic White, and Hispanic participants were 58.4 years, 55.3 years and 55.5 years, respectively. In Phase 2, the mean ages of African American, Non-Hispanic White, and Hispanic participants were 63.4 years, 58.9 years and 58.8 years, respectively.

Of the total number of participants recruited during Phase 1, the highest use of statin medications was reported in the Non-Hispanic White population (15.9%) and lowest in

the African American population (5.3%). The prevalence of statin use increased in Phase 2 of the study, and continued to be highest in Non-Hispanic Whites (29.2%) and lowest in the African American (18.8%) participants.

[Table 2] summarizes demographic, intrinsic and extrinsic factors as well as mean fasting glucose levels and percent of T2DM for the individual centers across Phase 1 and Phase 2 of the study. Mean, median, and interquartile ranges are provided in [Appendix 2 and Appendix 3].

**Table 2: Demographics, Intrinsic and Extrinsic Factors across Centers in Phase 1 and Phase 2**

| | | Total N=4712 | | |
|---|---|---|---|---|
| | | **African American Jackson** | **Non-Hispanic White Rochester** | **Hispanic Starr County** |
| **PHASE 1** | | N=1508 | N=1474 | N=1730 |
| Gender | % Female | 72.08 | 56.85 | 59.65 |
| | % Male | 27.92 | 43.15 | 40.35 |
| Age, years | Mean (SD) | 58.41 (10.31) | 55.30 (10.91) | 55.54 (11.8) |
| Statin use | % | 5.31 | 15.94 | 10.69 |
| Glucose, mg/dL | Mean (SD) | 111.05 (45.66) | 98.97 (27.31) | 153.05 (72.16) |
| T2DM | % | 22.15 | 10.52 | 62.25 |
| Education (> 12 years) | % | 36.14 | 51.29 | 10.92 |
| Anti-HTN medication use | % | 62.67 | 64.04 | 34.91 |
| Family history diabetes | % | 57.29 | 43.03 | 99.83 |
| | | **Total N=3634** | | |
| **PHASE 2** | | N=1260 | N=1198 | N=1176 |
| Gender | % Female | 72.30 | 57.76 | 61.39 |
| | % Male | 27.70 | 42.24 | 38.61 |
| Age, years | Mean (SD) | 63.40 (9.45) | 58.85 (10.19) | 58.78 (11.21) |
| Statin use | % | 18.81 | 29.22 | 25.85 |
| Glucose, mg/dL | Mean (SD) | 111.67 (43.44) | 104.80 (24.37) | 152.26(65.63) |
| T2DM | % | 29.05 | 14.86 | 65.65 |
| Education (>12 years) | % | 38.25 | 52.59 | 13.1 |
| Anti-HTN medication use | % | 72.30 | 69.03 | 46.51 |
| Family history diabetes | % | 62.06 | 44.99 | 98.89 |

T2DM: Type 2 diabetes mellitus; SD: standard deviation.
Note: Based upon available observations.

### 2.4.2 Phase 1 Mixed Model Results in Non-T2DM versus T2DM Populations Across All Field Centers

**EXAMINATION OF FASTING BLOOD GLUCOSE, FASTING INSULIN AND HOMA-IR IN NON-T2DM POPULATIONS ACROSS FIELD CENTERS**

[Table 3] presents Phase 1 results of the linear mixed model for fasting blood glucose levels and statin use and the specific covariates identified through stepwise selection modeling in the African American (n=1174), Non-Hispanic White (n=1319), Hispanic (n=653), and combined African American/Non-Hispanic White (n=2493) non-T2DM populations.

*Univariate Analysis of Statin Use and Fasting Blood Glucose*

Based upon the univariate analyses, significantly increased fasting blood glucose was observed with statin use compared to no statin use in the Non-Hispanic White population (fasting blood glucose 1.80 mg/dL; $0.01 \geq p > 0.001$); positive increases were also observed in the remaining populations but these results were not significant ($p \geq 0.05$) [Table 3].

*Multivariable Analysis of Statin Use and Fasting Blood Glucose*

When adjusting for other covariates, the value of fasting glucose comparing statin exposure to no statin exposure was 0.33 mg/dL in the African American population in Jackson, -0.28 mg/dL in Non-Hispanic Whites in Rochester, 2.01 mg/dL in the Hispanic population in Starr County, and 0.19 mg/dL in the combined African American/Non-Hispanic White population. Overall, these results for the multivariable analysis in the non-diabetic population did not achieve statistical significance ($p \geq 0.05$) [Table 3].

*Analysis of Pre-specified Covariates and Fasting Blood Glucose*

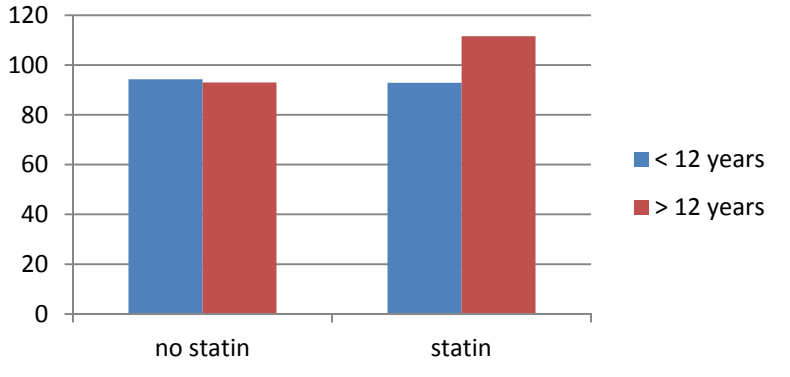
In the non-T2DM population, regardless of field center, the significant predictors of fasting plasma glucose were BMI, age, and hypertension medication [Table 3]. In both the Jackson African-Americans and Rochester Non-Hispanic Whites, menopause status was also a significant predictor of fasting plasma glucose levels in Phase 1. In the combined African American/Non-Hispanic White analysis, family history of diabetes and field center were additional predictors in all the populations.

*Effect Modification of Statin Use and Fasting Blood Glucose*

Additional examination of potential interactions between statins and the pre-specified covariates identified a statin-by-education interaction in Starr county Hispanic-Americans. For those with lower education (≤ 12 years), the difference in fasting blood glucose between statin use and no statin use was -1.39 mg/dL while with higher education (> 12 years), the difference between statin use and no statin use was 18.60 mg/dL [Figure 13]. This difference is reflected by the significant statistical interaction for statin-by-education (19.9 mg/dL; p=0.02).

**Figure 13:**
**Fasting Blood Glucose for Statin Use Compared to No Statin Use in Phase 1 Hispanic Non-T2DM Population, for Higher Education (> 12 Years) Compared to Lower Education (≤ 12 Years) When Adjusting for Age and Anti-Hypertensive Medications**

| Education | Fasting Blood Glucose | |
|---|---|---|
| | No Statin | Statin |
| ≤ 12 years | 94.26 | 92.87 |
| > 12 years | 92.98 | 111.58 |




T2DM: type 2 diabetes mellitus.

Results for the interaction of statin and center in the combined African American and Non-Hispanic White population were not significant.

*Univariate and Multivariable Analysis of Statin Use and Fasting Insulin Levels and HOMA-IR*

[Appendix 4] provides results from the Phase 1 univariate and adjusted regression analyses for fasting insulin levels when comparing statin use to no statin use in the non-T2DM population. None of these results were statistically significant ($p \geq 0.05$).

[Appendix 5] provides results for the adjusted regression analyses for HOMA-IR when comparing statin use as compared to non-use in the Phase 1 non-T2DM population. None of these results were statistically significant ($p \geq 0.05$).

*Effect Modification of Statin Use and Changes in Fasting Insulin Levels and HOMA-IR*

A statistically significant effect was observed in fasting insulin levels (interaction value of 1.1 mg/dL; $p < 0.05$) and HOMA-IR (interaction value of 5.34 mg/dL; $0.01 \geq p > 0.001$) for the interaction of statin-by-menopause in the Non-Hispanic White population enrolled in Rochester field center.

## EXAMINATION OF FASTING BLOOD GLUCOSE, FASTING INSULIN AND HOMA-IR IN T2DM POPULATIONS ACROSS FIELD CENTERS

[Table 3] presents Phase 1 results of the linear mixed model for fasting blood glucose levels on statin use and the specific covariates identified through stepwise linear regression in the in the African American (n=334), Non-Hispanic White (n=155), Hispanic (n=1077) and combined African American/Non-Hispanic White (n=489) T2DM populations.

*Univariate Analysis of Statin Use and Fasting Blood Glucose*

Based upon the univariate analyses, the fasting blood glucose with statin use compared to no statin use in the African American, Hispanic and combined African American/Non-Hispanic White populations (African American value of -26.21 mg/dL; Hispanic value of -29.50 mg/dL; African American/Non-Hispanic White value of -23.61 mg/dL; $p<0.05$); a decrease was also observed in the Non-Hispanic White population but not considered significant (-16.17 mg/dL; $p \geq 0.05$) [Table 3].

*Multivariable Analysis of Statin Use and Fasting Blood Glucose*

When adjusting for other covariates, the estimated fasting blood glucose comparing statin exposure to no statin exposure was significantly decreased in the Starr County Hispanic population (-19.55; $p < 0.05$). This estimate was also decreased in the Non-Hispanic White population, however, not significant (-14.34; $p \geq 0.05$). The estimated value for fasting blood glucose was not significant in the African American population (0.07; $p \geq 0.05$) or combined African American/Non-Hispanic White population (-0.02; $p \geq 0.05$) [Table 3].

*Analysis of Covariates and Fasting Blood Glucose*

In the T2DM population, regardless of field center, the significant predictors of fasting plasma glucose were BMI, age, and hypertension medication [Table 3]. In the combined Jackson African-Americans and Rochester Non-Hispanic Whites, menopause status was also a significant predictor of fasting plasma glucose levels in Phase 1. In the combined African American/Non-Hispanic White analysis, education and field center were additional predictors.

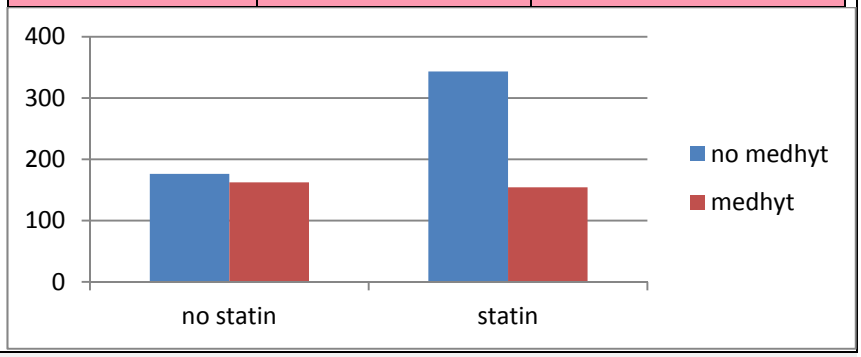
*Effect Modification of Statin Use and Fasting Blood Glucose*

Additional examination of potential interactions between statins and the pre-specified covariates identified a statin-by-antihypertensive medication interaction and statin-by-age interaction in the African American population.

For those not using antihypertensive medication, the difference in fasting blood glucose between statin use and no statin use was 167.23 mg/dL while for those using antihypertensive medications, the difference between statin use and no statin use was -8.19 mg/dL [Figure 14]. This difference is reflected by a significant statistical interaction for statin-by-education (-175.40; p=0.0002).

**Figure 14: Fasting Blood Glucose for Statin Use Compared to No Statin Use in Phase 1 for Antihypertensive Use in the African American T2DM Population Adjusting for Age and Menopause**

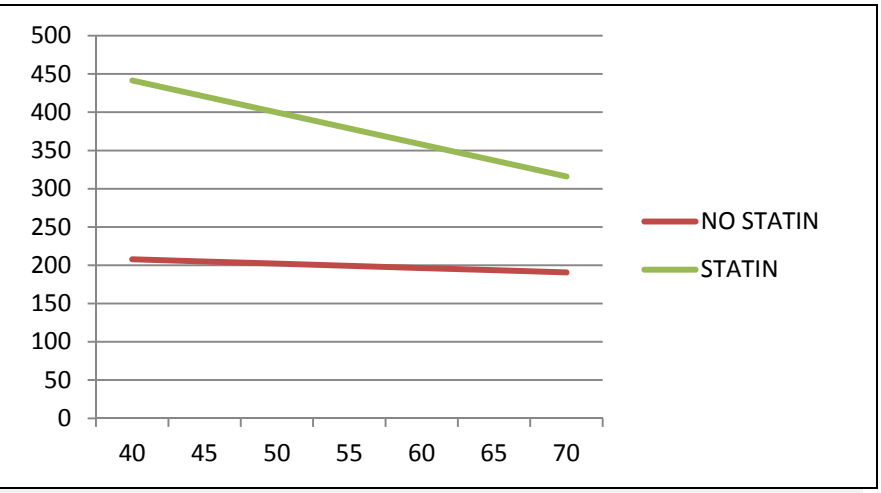
| Antihypertensive Medication | Fasting Blood Glucose | |
|---|---|---|
| | No Statin | Statin |
| No | 176.14 | 343.37 |
| Yes | 162.45 | 154.26 |




Medhyt: antihypertensive use; T2DM: type 2 diabetes mellitus.

The difference in fasting blood glucose decreased as age increased; this estimate was greater for statin use as compared to no statin use. For example, the difference in fasting blood glucose for age 70 and age 40 with statin use was -125.37 mg/dL while the difference in fasting blood glucose for age 70 compared to age 40 with no statin use was -17.15 mg/dL [Figure 15]. This difference is reflected by a significant statistical interaction for statin-by-age (-3.60; p=0.03).

**Figure 15: Fasting Blood Glucose for Statin Use Compared to No Statin Use with Increasing Age in Phase 1 African American T2DM Population While Adjusting for Menopause and Anti-Hypertensive Medication**




T2DM: type 2 diabetes mellitus.

The statin-by-menopause interaction was selected via the stepwise linear regression in the Hispanic T2DM population but was not considered significant in the linear mixed model analysis. Results for the interaction of statin and center in the combined African American and Non-Hispanic White population were not significant ($p \geq 0.05$) [Table 3].

*Analysis of Statin Use and Fasting Insulin and HOMA-IR*

[Appendix 4] provides results from univariate and adjusted analyses for fasting insulin when comparing statin use as compared to non-use in the Phase 1 T2DM population. None of these results were considered statistically significant ($p \geq 0.05$).

[Appendix 5] provides results for the adjusted analyses for HOMA-IR when comparing statin use as compared to non-use in the Phase 1 T2DM population. None of these results were considered statistically significant ($p \geq 0.05$).

Pearson correlation coefficients for the continuous variables included as [Appendix 6].

**Table 3: Phase 1 Univariate and Multivariable Mixed Model Analyses for Statin Use and Fasting Blood Glucose (mg/dL)**

| | No T2DM | | | | T2DM | | | |
|---|---|---|---|---|---|---|---|---|
| **Phase 1** | **African American Jackson** | **Non-Hispanic White Rochester** | **Hispanic Starr County** | **African American/Non-Hispanic White Jackson/ Rochester** | **African American Jackson** | **Non-Hispanic White Rochester** | **Hispanic Starr County** | **African American/ Non-Hispanic White Jackson/ Rochester** |
| | **UNIVARIATE** | | | | **UNIVARIATE** | | | |
| **# Obs Used** | **1174** | **1319** | **653** | **2493** | **334** | **155** | **1077** | **489** |
| Statin | 0.80 | 1.80** | 0.68 | 1.22 | -26.21* | -16.17 | -29.50*** | -23.61** |
| | **MULTIVARIABLE** | | | | **MULTIVARIABLE** | | | |
| **# Obs Used** | **1170** | **1318** | **652** | **2488** | **333** | **155** | **1075** | **488** |
| Intercept | 74.1*** | 66.32*** | 69.32*** | 70.59*** | 240.6*** | 201.65*** | 305.10*** | 85.77*** |
| BMI | 0.39*** | 0.42*** | 0.54*** | 0.42*** | --- | -0.76 | -0.77* | --- |
| Age | 0.13** | 0.25*** | 0.19*** | 0.19*** | -0.69 | --- | -1.40*** | 0.14*** |
| HTN med | 1.79** | 2.05** | -2.36* | 1.95*** | -19.01 | -15.99 | -9.96* | 3.20*** |
| Menopause | -0.96** | -2.23*** | --- | -1.66*** | -6.41 | --- | -2.98 | -1.28*** |
| Family history of diabetes | 1.18 | 0.93 | --- | 1.10** | --- | --- | -- | --- |
| Education | -1.28 | --- | 1.38 | -0.67 | --- | --- | -20.66** | -1.01* |
| Center | NA | NA | NA | -1.38** | NA | NA | NA | -1.73*** |
| Statin | 0.33 | -0.28 | 2.01 | 0.19 | 0.07 | -14.34 | -19.55** | -0.02 |

*0.05 > p > 0.01; **0.01≥ p > 0.001; ***p ≤ 0.001; --- covariate excluded via stepwise selection.

BMI: body mass index; HTN med: antihypertensive use; Obs : observation; T2DM: type 2 diabetes mellitus; NA: Not applicable

### 2.4.3 Phase 2 Mixed Model Results in Non-T2DM versus T2DM Populations Across All Field Centers

Results in the Phase 2 non-T2DM populations for the pre-specified covariates were generally similar to the results observed in the Phase 1 non-T2DM populations. [Table 4] presents Phase 2 results of the linear mixed modeling for fasting blood glucose levels on statin use and the specific covariates identified through stepwise linear regression in the African American (n=894), Non-Hispanic White (n=1020), Hispanic (n=404), and combined African American/Non-Hispanic White (n=1914) non-T2DM populations.

**EXAMINATION OF FASTING BLOOD GLUCOSE, FASTING INSULIN AND HOMA-IR IN NON-T2DM POPULATION ACROSS FIELD CENTERS**

*Univariate Analysis of Statin Use and Fasting Blood Glucose*

Based upon the univariate analyses, significant fasting blood glucose with statin use compared to no statin use was observed in the Non-Hispanic White and combined African American/Non-Hispanic White populations (2.64 mg/dL and 2.04 mg/dL, respectively; $0.01 \geq p > 0.001$); increases were also observed in the African American and Hispanic populations but these results were not significant (0.61 mg/dL and 2.04 mg/dL, respectively; $p \geq 0.05$) [Table 4]

*Multivariable Analysis of Statin Use and Fasting Blood Glucose*

When adjusting for other covariates, the estimated value of fasting glucose comparing statin exposure to no statin exposure was not significant in all non-T2DM populations (-0.36 mg/dL for the African American population; 0.71 mg/dL for the Non-Hispanic White population; 0.22 mg/dL for the Hispanic population; -0.27 mg/dL for the combined African American/Non-Hispanic White population) [Table 4].

*Analysis of Pre-specified Covariates and Fasting Blood Glucose*

In the non-T2DM population, regardless of field center, the significant predictors of fasting plasma glucose were BMI, age, and hypertension medication [Table 4]. In both the Jackson African-Americans and Rochester Non-Hispanic Whites, menopause status was also a significant predictor of fasting plasma glucose and in the combined Jackson/Rochester analysis, field center was an additional predictor.

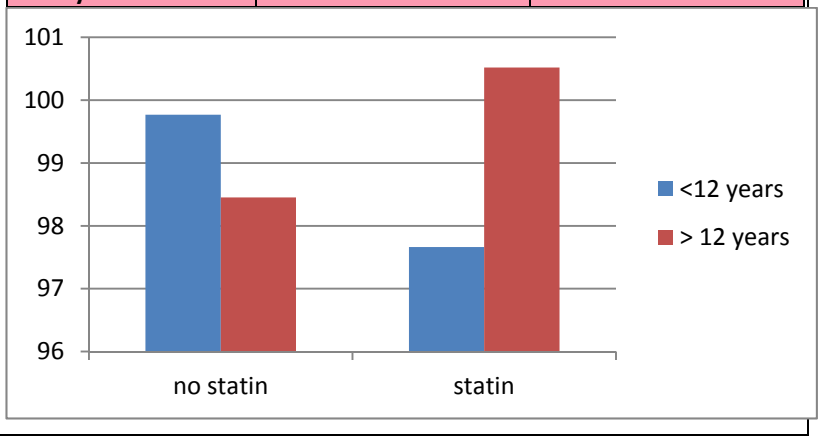
*Effect Modification of Statin Use and Fasting Blood Glucose*

Additional examination of potential interaction between statins and the pre-specified covariates identified a significant statin-by-education interaction in the Non-Hispanic White population and significant statin-by-education interaction in the Hispanic population in Rochester and Starr County, respectively. A significant statin-by-menopause interaction was also identified in the African American population in Jackson.

For Non-Hispanic Whites with lower education (≤ 12 years), the difference in fasting blood glucose between statin use and no statin use was -2.10 mg/dL while with higher education (> 12 years), the difference between statin use and no statin use was 2.06 mg/dL [Figure 16]. This difference is reflected by the significant statistical interaction for statin-by-education (4.17 mg/dL; p = 0.002).

**Figure 16:**
**Fasting Blood Glucose for Statin Use Compared to No Statin Use in Phase 2 Non-Hispanic White Non-T2DM Population, for Higher Education (> 12 Years) Compared to Lower Education (≤ 12 Years) when Adjusting for BMI, Age and Anti-Hypertensive Medications, Menopause and Family History of Diabetes**

| Education | Fasting Blood Glucose | |
|---|---|---|
| | No statin | Statin |
| ≤ 12 years | 99.76 | 97.66 |
| > 12 years | 98.45 | 100.51 |

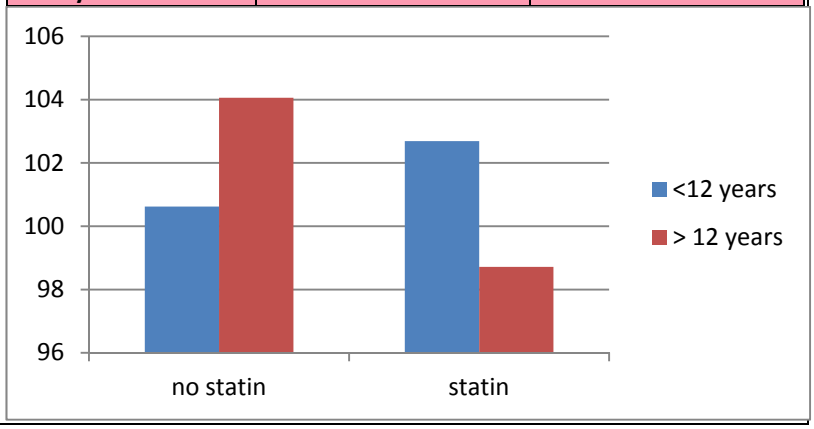



BMI: body mass index; T2DM: type 2 diabetes mellitus.

For the Hispanic population in Starr County with lower education (≤ 12 years), the difference in fasting blood glucose between statin use and no statin use was 2.07 mg/dL while with higher education (> 12 years), the difference between statin use and no statin use was -5.34 mg/dL [Figure 17]. This difference is reflected by the significant statistical interaction for statin-by-education (-7.41 mg/dL; p = 0.04).

**Figure 17:**
**Fasting Blood Glucose for Statin Use Compared to No Statin Use in Phase 2 for Higher Education (> 12 Years) in Hispanic Non-T2DM Population Compared to Lower Education (≤ 12 Years) when Adjusting for Age, Anti-Hypertensive Medications, Menopause and Family History of Diabetes**

| Education | Fasting Blood Glucose | |
|---|---|---|
| | No Statin | Statin |
| ≤ 12 years | 100.62 | 102.69 |
| > 12 years | 104.06 | 98.72 |

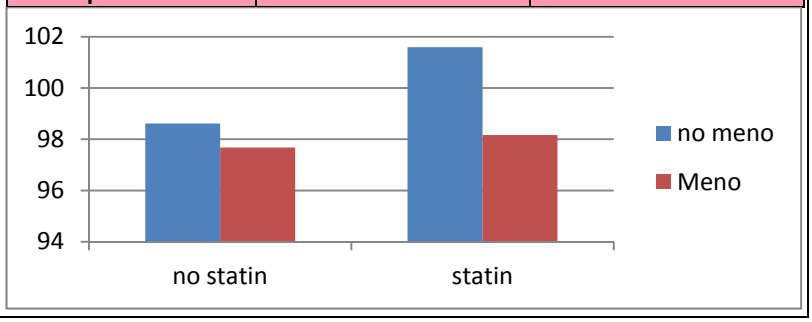



T2DM: type 2 diabetes mellitus.

For the African Americans in Jackson with no menopause, the difference in fasting blood glucose between statin use and no statin use was 2.98 mg/dL while with menopause, the difference between statin use and no statin use was 0.49 mg/dL [Figure 18]. This difference is reflected by the significant statistical interaction for statin-by-menopause (-2.50 mg/dL; p = 0.03).

**Figure 18:**
**Fasting Blood Glucose for Statin Use Compared to No Statin Use in Phase 2 for Menopause Status in African American Non-T2DM Population Compared to Non Menopause When Adjusting for Age, BMI, Menopause and Family History of Diabetes**

| Menopause Status | Fasting Blood Glucose | |
|---|---|---|
| | No Statin | Statin |
| No Menopause | 98.61 | 101.59 |
| Menopause | 97.67 | 98.16 |




BMI: body mass index; meno: menopause; T2DM: type 2 diabetes mellitus.

The interaction of statin-by-age in the African American and Non-Hispanic White populations were selected via the stepwise linear regression but not significant in the linear mixed model. The statin-by-center in the combined African/American population was not considered significant (p ≥ 0.05) [Table 4].

*Analysis of Statin Use and Fasting Insulin and HOMA-IR*

[Appendix 7] provides results from univariate and adjusted analyses for fasting insulin when comparing statin use to non-use in the non-T2DM population. Based upon the univariate analyses, statistical significance was observed in the combined African American/Non-Hispanic White population (0.72 uU/mL; p < 0.05). After adjusting for other covariates, statistical significance was not achieved in any of the populations.

[Appendix 8] provides results for the adjusted analyses for HOMA-IR when comparing statin use to non-use in the Phase 2 non-T2DM population. No significant changes in HOMA-IR were achieved in the Phase 2 non-T2DM populations.

*Effect Modification of Statin Use and Changes in Fasting Insulin and HOMA-IR*

A significant statin-by-antihypertensive medication interaction was observed for fasting insulin (-7.59 uU/mL; $p < 0.05$) and HOMA-IR (-37.99; $p < 0.05$) in the Hispanic population.

## EXAMINATION OF FASTING BLOOD GLUCOSE, FASTING INSULIN AND HOMA-IR IN T2DM POPULATION ACROSS FIELD CENTERS

[Table 4] presents Phase 2 results of linear mixed model for fasting blood glucose levels on statin use and specific covariates identified through stepwise linear regression in the African American (n=336), Non-Hispanic White (n=178), Hispanic (n=772), and combined African American/Non-Hispanic White (n=544) T2DM populations.

*Univariate Analysis of Statin Use and Fasting Blood Glucose*

Based upon the univariate analyses for statin use compared to no use, decreased fasting blood glucose was observed in all populations (African American value of -10.10 mg/dL; Non-Hispanic White value of -0.20 mg/dL; African American/Non-Hispanic White value of -6.63 mg/dL; $p \geq 0.05$); however, significance was achieved in the Hispanic population only (value of -23.43 mg/dL; $p \leq 0.001$).

*Multivariable Analysis of Statin Use and Fasting Blood Glucose*

Adjusting for other covariates, the estimated value of fasting blood glucose comparing statin use to no statin use was significantly decreased in the Hispanic population (value of -14.99 mg/dL; $p < 0.05$); similar trends were observed in the African American T2DM population (value of -10.10 mg/dL) and combined African American/Non-Hispanic White populations (value of -6.37 mg/dL); however, these latter observations were not statistically significant ($p \geq 0.05$). A slight increase in mean fasting blood glucose was observed in the Non-Hispanic White population (value of 0.54 mg/dL) that was not significant ($p \geq 0.05$) [Table 4].

*Analysis of Pre-specified Covariates and Fasting Blood Glucose*

In the T2DM population, regardless of field center, the significant predictors of fasting blood glucose were BMI, age and education [Table 4].

*Effect Modification of Statin Use and Fasting Blood Glucose*

No statistically significant results were observed across field centers.

*Analysis of Statin Use and Fasting Insulin and HOMA-IR*

[Appendix 7] provides results from the adjusted analyses for fasting insulin levels when comparing statin use as compared to non-use in the Phase 2 T2DM population. None of these results were considered statistically significant ($p \geq 0.05$).

[Appendix 8] provides results for the adjusted analyses for HOMA-IR when comparing statin use as compared to non-use in the Phase 2 T2DM population. None of these results were considered statistically significant ($p \geq 0.05$).

*Effect Modification of Statin Use and Fasting Insulin and HOMA-IR*

The statin-by-menopause interaction was statistically significant (value of -4.9 uU/mL; $p < 0.05$) and HOMA-IR (value of -31.13 uU/mL; $p < 0.05$) in the combined African American/Non-Hispanic White population.

Pearson correlation coefficients for the continuous variables included as [Appendix 9].

**Table 4: Phase 2 Univariate and Multivariable Mixed Model Analyses for Statin Use and Fasting Blood Glucose (mg/dL)**

| Phase 2 | No T2DM | | | | T2DM | | | |
|---|---|---|---|---|---|---|---|---|
| | African American Jackson | Non-Hispanic White Rochester | Hispanic Starr County | African American/Non-Hispanic White Jackson/Rochester | African American Jackson | Non-Hispanic White Rochester | Hispanic Starr County | African American/Non-Hispanic White Jackson/Rochester |
| | **UNIVARIATE** | | | | **UNIVARIATE** | | | |
| **# Obs Used** | **894** | **1020** | **404** | **1914** | **336** | **178** | **772** | **544** |
| Statin | 0.61 | 2.64** | 2.04 | 2.04** | -10.10 | -0.20 | -23.43*** | -6.63 |
| | **MULTIVARIABLE** | | | | **MULTIVARIABLE** | | | |
| **# Obs Used** | **891** | **1019** | **400** | **1910** | **366** | **178** | **765** | **544** |
| Intercept | 66.29*** | 67.50*** | 73.89*** | 66.70*** | 206.65* | 153.20*** | 282.02*** | 156.67*** |
| BMI | 0.39*** | 0.45*** | 0.49*** | 0.28*** | --- | --- | -1.24** | -0.12 |
| Age | 0.28*** | 0.28*** | 0.18** | 0.27*** | -0.69 | --- | -1.74*** | --- |
| HTN med | --- | 1.83* | --- | 1.45** | --- | --- | --- | --- |
| Menopause | -1.28* | -2.09*** | -1.11 | -1.75*** | -5.57 | --- | --- | --- |
| Family history of diabetes | 1.85* | 1.25 | 0.05 | --- | --- | --- | 50.58 | --- |
| Education | --- | -0.18 | 2.15 | --- | --- | -10.6* | -17.09* | --- |
| Center | NA | NA | NA | -2.18** | NA | NA | NA | -0.22 |
| Statin | -0.36 | 0.71 | 0.22 | -0.27 | -10.10 | 0.54 | -14.99** | -6.37 |

*0.05 > p > 0.01; **0.01≥ p > 0.001; ***p ≤ 0.001; --- covariate excluded via stepwise selection.
BMI: body mass index; HTN med: antihypertensive use; Obs: observation; NA: not applicable

### 2.4.4 Longitudinal Examination of Statin Use in Phase 1 Non-T2DM Participants and Prediction of Phase 2 Fasting Blood Glucose and Fasting Insulin Levels

[Table 5] presents of fasting blood glucose based upon longitudinal analyses across the specific variables identified through stepwise linear regression in the African American (n=840), Non-Hispanic White (n=1008), Hispanic (n=475) and combined African American/Non-Hispanic White (n=1848) populations.

*Univariate Analysis of Statin Use and Fasting Blood Glucose*

Based upon the univariate analyses of statin use compared to non-use, non-significant decreases in fasting blood glucose were observed in the African American population (value of -3.25 mg/dL; $p \geq 0.05$); however, in the remaining populations, increases were observed of which were only statistically significant in the Non-Hispanic White population (Non-Hispanic White value of 3.11 mg/dL; $p < 0.05$; Hispanic value of 4.07 mg/dL; $p \geq 0.05$; African American/Non-Hispanic White value of 1.59 mg/dL; $p \geq 0.05$) [Table 5].

*Multivariable Analysis of Statin Use and Fasting Blood Glucose*

Adjusting for other covariates, the predicted value of fasting blood glucose based upon longitudinal analyses comparing statin use to no statin use was increased in all field centers (value of 2.49 mg/dL for African American population; 0.16 mg/dL for Non-Hispanic White population; 4.71 mg/dL for Hispanic population; 0.27 mg/dL for combined African American/Non-Hispanic White population); these results were not statistically significant ($p \geq 0.05$) [Table 5].

For the analyses of fasting blood glucose in Phase 2 non-T2DM, adjusting for other covariates, the predicted value of fasting blood glucose based upon longitudinal analyses comparing statin use to no statin use was decreased in the African American (-1.82 mg/dL; p=0.35; n=730), Non-Hispanic White (-1.60 mg/dL; p=0.08; n=938), and combined African American/Non-Hispanic White populations field centers (-0.72 mg/dL;

p=0.39; n=1668). In the Hispanic population, the predicted value of fasting blood glucose was increased (3.29 mg/dL; p=0.18; n=217); these results were not statistically significant ($p \geq 0.05$).

*Analysis of Pre-specified Covariates and Fasting Blood Glucose*

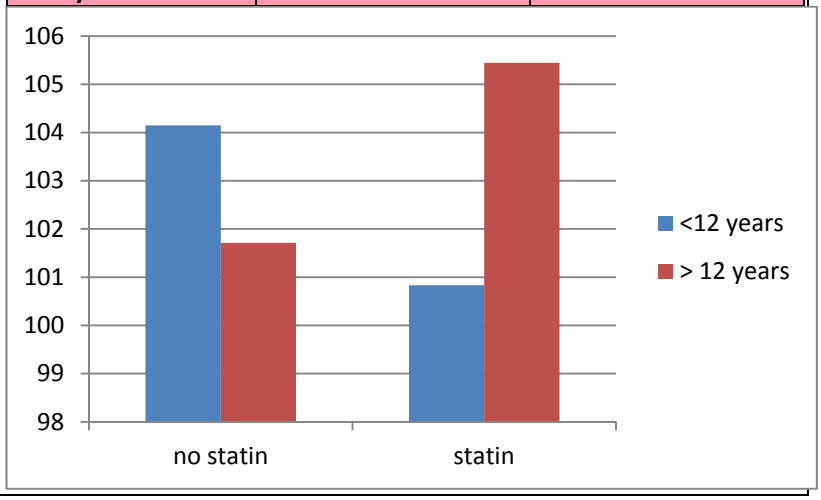
In the longitudinal analyses, regardless of field center, BMI and age were predictors of fasting blood glucose [Table 5]. Menopause and family history of diabetes were additional predictors in the combined African American/Non-Hispanic White population and education was a predictor of fasting blood glucose in the Non-Hispanic White population.

*Effect Modification of Statin Use and Fasting Blood Glucose*

Additional examination of potential interaction between statins and the pre-specified covariates identified a significant statin-by-education interaction in the Non-Hispanic White population. For those with lower education (≤ 12 years), fasting blood glucose between statin use and no statin use was -3.31 mg/dL while with higher education (> 12 years), the difference between statin use and no statin use was 3.73 mg/dL [Figure 19]. This difference is reflected by the significant statistical interaction for statin-by-education (7.05 mg/dL; p = 0.01).

**Figure 19: Longitudinal Analysis of Fasting Blood Glucose for Statin Use Compared to No Statin Use for Higher Education (> 12 Years) in Non-Hispanic White Non-T2DM Population Compared to Lower Education (≤ 12 Years) when Adjusting for BMI, Age, Anti-Hypertensive Medications, Menopause and Family History of Diabetes**

| Phase 1 Education | Phase 1 No Statin | Phase 1 Statin |
|---|---|---|
| | Phase 2 Fasting Blood Glucose Levels | |
| ≤ 12 years | 104.14 | 100.83 |
| > 12 years | 101.71 | 105.44 |




BMI: body mass index; T2DM: type 2 diabetes mellitus.

The interaction of statin use and center in the combined African/American population was not considered significant ($p \geq 0.05$).

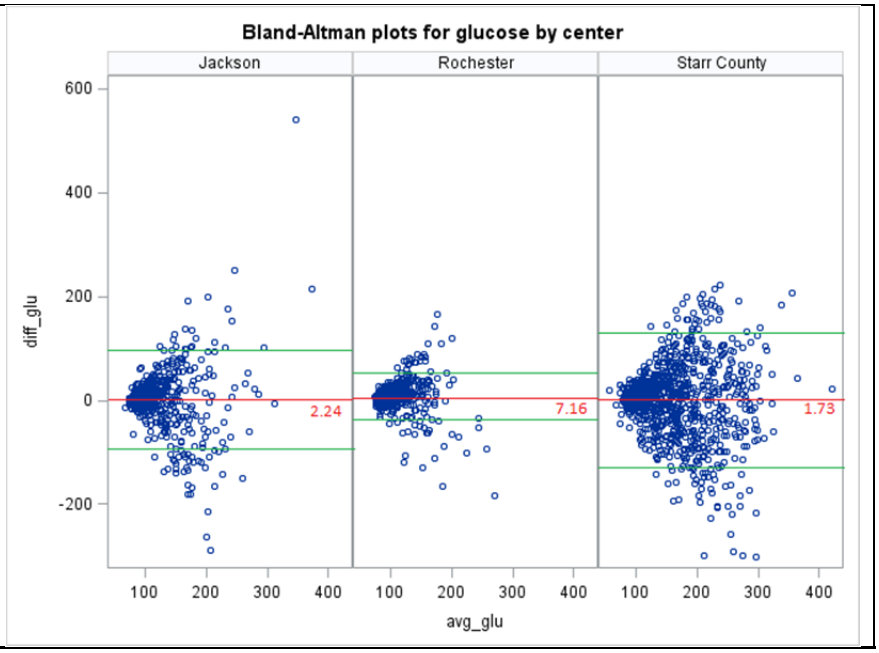
*Examination of the Differences in Changes in Fasting Blood Glucose in Phase 2 Compared to Phase 1 Non-T2DM Population Across Field Centers*

The mixed model results are provided in [Appendix 10]. No statistical association was observed in fasting blood glucose for Phase 2 compared to Phase 1 with statin use compared to non-use in the non-T2DM population across field centers ($p \geq 0.05$).

The Bland-Altman scatterplot [Bland Altman Analysis, 2009] was generated for mean fasting blood glucose in Phase 1 minus Phase 2 (horizontal axis) and difference in fasting blood glucose. The Bland-Altman scatterplot allows for a visual confirmation of agreement between two measures. Agreement implies that approximately 95% of the mean values for fasting blood glucose reside within the center specific 95% confidence interval for the difference in fasting blood glucose for Phase 2 minus Phase 1 values.

The plots were generated separately for each center (Jackson, Rochester and Starr County) [Figure 20]. Overall, there was agreement whereby approximately 94%, 95% and 93% of the mean fasting blood glucose values were within the center specific 95% CI for differences in fasting blood glucose for Phase 2 minus Phase 1 values. It is important to note that within all three field centers, higher mean fasting glucose scores have more variability in fasting glucose difference values.

**Figure 20 Bland-Altman Plot for Mean Fasting Blood Glucose and Difference in Fasting Blood Glucose Across the Centers**




diff_glu: difference in fasting blood glucose; avg_glu: mean fasting blood glucose.

*Analysis of Statin Use and Changes in Fasting Insulin*

[Appendix 11] provides results from univariate and adjusted analyses for fasting insulin when comparing statin use as compared to no statin use. Results were not considered statistically significant ($p \geq 0.05$), with the exception of a significant decreased fasting insulin observed for the univariate analysis in the Hispanic population (value of -3.21 uU/mL, $p < 0.05$).

**Table 5: Prediction of Phase 2 Fasting Blood Glucose (mg/dL) in Non-T2DM from Phase 1**

| | No T2DM in Phase 1 | | | |
|---|---|---|---|---|
| | **African American Jackson** | **Non-Hispanic White Rochester** | **Hispanic Starr County** | **African American/Non-Hispanic White Jackson/Rochester** |
| | **UNIVARIATE** | | | |
| **# Obs Used** | **840** | **1008** | **475** | **1848** |
| Statin | -3.25 | 3.11* | 4.07 | 1.59 |
| | **MULTIVARIABLE** | | | |
| **# Obs Used** | **838** | **1007** | **475** | **1845** |
| Intercept | 71.19*** | 62.93*** | 88.26*** | 65.76*** |
| BMI | 0.54** | 0.77*** | 0.79** | 0.67*** |
| Age | 0.21* | 0.28* | --- | 0.27*** |
| HTN med | --- | 1.76 | --- | --- |
| Menopause | -1.82 | -2.51* | -2.43 | -2.36*** |
| Family history of diabetes | 6.39** | 2.38* | --- | 4.23*** |
| Education | --- | -1.35* | -3.22 | --- |
| Center | NA | NA | NA | -0.60 |
| Statin | 2.49 | 0.16 | 4.71 | 0.27 |

*0.05 > p > 0.01; **0.01≥ p > 0.001; ***p ≤ 0.001; --- covariate excluded via stepwise selection.

BMI: body mass index; HTN med: antihypertensive use; Obs: observations; T2DM: type 2 diabetes mellitus. NA: not applicable

## 2.5 Discussion

Published results from clinical trials have been conflicting with regard to statin use and incident T2DM or deterioration of glycemic control with use in the T2DM population [Sabatine *et al.*, 2004]. Results have suggested that changes in fasting blood glucose could be attributed to underlying risk factors such as metabolic syndrome that are uncovered through patient monitoring once a statin medication is prescribed [Rocco, 2012]; some researchers have observed no appreciable deterioration of glycemic control or insulin levels [Zhou *et al.*, 2013]*;* and other researchers have observed greater increases of fasting blood glucose with statin use in the T2DM population as compared to the non-T2DM population [Sukhija *et al.*, 2009]*.* Furthermore, results from *in vivo* experiments have demonstrated changes in fasting blood glucose in the T2DM rat model but not in the non-T2DM rat model [Kanda *et al.*, 2003]. Researchers have postulated various biological mechanisms of statin use and potential for T2DM however, these theories are based upon *in vitro* experimentation and no specific pathway has been elucidated in humans.

In this study, fasting blood glucose levels were generally not significant in the T2DM or non-T2DM populations with the main effect of statin use, after adjustment of specific covariates. Moreover, adjusted analyses of the interaction for statin use and 'center' in the combined Jackson/Rochester population was not significant in the non-T2DM and T2DM populations signifying that the prediction of fasting blood glucose with statin use as compared to no statin use was no different among the African American population as compared to the Non-Hispanic White population. Although the statin-by center interaction was not significant in this combined population, examination in the individual populations did yield significant results for statin use and fasting blood glucose with varying levels of education, presence of menopause, use of concomitant antihypertensive medications or increasing age. The GENOA observations with the interactions of statin use and menopause were opposite in effect to results from published observational studies for sub-populations of post-menopausal females;

however, the GENOA results were similar to prior results in elderly males (>65 years) [Culver *et al.*, 2012; Carter *et al.*, 2013].

Type 2 diabetes mellitus is a complex disease influenced by a multitude of biological, genetic, psychological, social and/or environmental factors that may impact the onset or progression of disease [Glasgow, 1994]. The complex interplay amongst these determinants creates challenges when considering treatment regimens or interventions for management of this disease at the individual patient or population level. These challenges also present during the conduct of T2DM research where the concepts of confounding and/or effect modification are amplified given the various levels for each determinant. This, in turn, raises the importance of collecting a voluminous amount of data, a virtually impossible task whether in the context of randomized or observational studies. Thus, in reality, the results generated in T2DM research must be contextualized against the potential for residual confounding due to the lack of ability to measure and/or adjust for every determinant that may influence the disease or outcome.

In this study, the objective was to examine statin use and fasting blood glucose across the African American, Non-Hispanic White and Hispanic populations and, although interesting trends were observed across these various ethnicities, it is important that these results are considered while recognizing the environmental and cultural differences between field centers are confounded with ethnicity. More specifically, it is not possible to generalize these results as simply ethnic differences but instead, the observation should be attributed to ethnic effects combined with potential social and environmental effects that may have influenced the results of this study. Furthermore, the differences in ascertainment of T2DM status across the populations should be considered.

The following provides a discussion of the results for statin use in the Phase 1 and Phase 2 non-T2DM and T2DM populations. Other factors such as pharmacology and potential confounding that may have influenced results of this study are also discussed.

*Statin Utilization in the United States Compared to the GENOA Study*

The CDC reported that a greater percentage of men (50% in 65-74 years; 45% in 75 years and over) and women (36% in 65-74 years; 39% in 75 years and over) used statin medications in 2005-2008 as compared to men (~15-26%) and women (~10-24%), in the same age ranges in 1999-2002 [Figure 2] [National Center of Health Statistics, 2011].

In Phase 1 of the GENOA study [1996-2000], the use of statin medications in males and females across all age categories was relatively less compared to the CDC reported gender specific rates during a similar time period [Table 6, Figure 2].

**Table 6: Statin Use in Each Cohort by Age Category in Phase 1 [1996-2000]**

| Age | African American Jackson | Non-Hispanic White Rochester | Hispanic Starr County |
|---|---|---|---|
| 45-64 years | F: 2%<br>M: 0% | F: 4%<br>M: 6% | F: 3%<br>M: 2% |
| 65-74 years | F: 1%<br>M: 1% | F: 2%<br>M: 3% | F: 2%<br>M: 2% |
| ≥75 years | F: 0%<br>M: 0% | F: 0%<br>M: 1% | F: 1%<br>M: 0% |

Total N for each center used as denominator.
F: female; M: male.

As anticipated, with time, statin use generally increased across the field centers in Phase 2 [2000-2004], which was parallel to the temporal trends of increased use of statins in the US [Table 7]. Overall, statin medication use in Phase 2 of the GENOA study [2000-2004] was relatively less compared to CDC reported rates.

| Table 7: Statin Use in Each Cohort by Age Categories in Phase 2 [2000-2004] | | | |
|---|---|---|---|
| **Age** | **African American Jackson** | **Non-Hispanic White Rochester** | **Hispanic Starr County** |
| 45-64 years | F: 7%<br>M: 3% | F: 7%<br>M: 9% | F: 8%<br>M: 5% |
| 65-74 years | F: 5%<br>M: 2% | F: 5%<br>M:5% | F: 6%<br>M: 3% |
| ≥75 years | F: 1%<br>M: 1% | F: 1%<br>M: 1% | F: 2%<br>M: 1% |

Total N for each center used as denominator.
F: female; M: male.

GENOA participants were selected based upon a diagnosis of hypertension or diabetes and therefore, one would anticipate greater concomitant statin medication use in this population. Therefore, reasons for the apparent lower statin use in the GENOA study are not clear. It could be speculated that participants residing in relatively less affluent regions such as Jackson and Starr County, may have less access to medical care and prescription medications; however, this theory does not explain the lower use in Rochester which is a relatively more affluent region with theoretically greater access to medical care. It should be noted that use of statins in the GENOA study was based upon participant information collected from prescription vials that were provided by the participant at the time of Phase 1 and Phase 2 enrollment.

The increased use of statin medications over time assumes greater availability, access and/or acceptance by participants; this 'time dimension effect' may influence epidemiologic inferences. More specifically, trends of increased usage could parallel trends of increased differences in outcome. Alternatively, trends of increased usage could result in greater health awareness and disease monitoring which could result in decreased risk for the outcome of interest. Lastly, as age increases, the overall disease burden increases. Therefore, this 'age effect' may also influence the trends observed of statin medication use and outcome in this study.

*Phase 1: Relationship of Statin Use and Fasting Blood Glucose, Fasting Insulin and HOMA-IR in the Non-T2DM and T2DM Populations*

In the GENOA Phase 1 non-T2DM African American, Hispanic and combined African American/Non-Hispanic White population, non-significant increases in fasting blood glucose were associated with statin use compared to no statin use, after adjustment. This trend was opposite to the decreases in fasting blood glucose generally observed in the Phase 1 T2DM population across the field centers; significance was achieved in the Phase 1 T2DM Hispanic population only. The cross sectional study design may have limited ability to detect changes in fasting blood glucose as the analyses are carried out at one point in time. In the case of statin medication use and influence upon fasting blood glucose, prior evidence suggests that approximately 24 months of chronic statin medication use was associated with changes in fasting blood glucose [Ridker *et al.*, 2008]. Thus, it is possible that perturbations in fasting blood glucose may have gone undetected given the GENOA study design of one distinct data collection time point in Phase 1.

In the Phase 1 Hispanic T2DM population, a statistically significant and clinically meaningful decrease in fasting blood glucose of -19.55 ($p < 0.05$) was observed with statin use compared to non-use, after adjustment for other covariates. This decreased effect was also observed in the Non-Hispanic White and combination African American/Non-Hispanic population, albeit not significant. Thus, if statins influence fasting blood glucose in the Hispanic population, it is possible to be more likely detected given the relatively higher percentage of Hispanic T2DM participants in Starr County (62.5%) as compared to African American (22.15%) and Non-Hispanic White populations (10.5%).

Additionally, in the Phase 1 T2DM population, baseline fasting blood glucose was higher than the normal clinical range across field centers (normal range 60-120 mg/dL; African American 240.6 mg/dL; Non-Hispanic White 201.65mg/dL; Hispanic 305.1) [Table 3]. Thus, this effect of decreased fasting blood glucose with statin use is contrary to results

from prior studies which have suggested the possibility of a pronounced risk with statin use in patients with impaired fasting glucose [Zhou *et al.*, 2013; Rocco *et al.*, 2012; Sabatine *et al.*, 2004; Sukhija *et al*., 2009].

Statin use and the relatively greater effect of decreased fasting blood glucose observed in the Hispanic population may also be explained by the increased use of antidiabetic medication in this population as compared to the African American and Non-Hispanic White populations. To build upon this reasoning, concomitant use of statin medication and antidiabetic medication was also higher in the Hispanic population [Table 8].

**Table 8: Phase 1 Percentage of Antidiabetic Medication Use and Concomitant Antidiabetic Medication-Statin Use**

| Population | Overall Antidiabetic Medication Use | Concomitant Antidiabetic and Statin Medication Use |
|---|---|---|
| Jackson African American | 17.64% | 2.45% |
| Rochester Non-Hispanic White | 6.65% | 2.17% |
| Starr County Hispanic | 51.79% | 8.03% |

Thus, if statins influence a decreasing effect of fasting blood glucose in the Hispanic population, this effect may be amplified due to the greater percentage of T2DM and the relatively greater use of antidiabetic medications in this population. Again, it should be mentioned that the GENOA results for statin use and decreased fasting blood glucose in the Hispanic population contrast the results of prior studies which demonstrated increase fasting blood glucose in T2DM individuals [Rocco *et al.*, 2012; Sukhija *et al*., 2009].

Fasting hyperinsulinemia is typically associated with glucose intolerance and some researchers even believe that fasting hyperinsulinemia is in fact a primary contributor in the pathogenesis of T2DM, independent of insulin resistance [Weyer *et al*., 2000]. Many factors are capable of increasing insulin secretion such as increased free fatty acids, certain amino acids, gastrointestinal hormones, and/or parasympathetic stimulation; other factors are capable of decreasing insulin secretion such as the fasting state and/or increased adrenergic activity [Aronoff *et al*., 2004; Brunetti *et al*., 2014].

In the GENOA Phase 1 non-T2DM population, no statistically significant findings were observed with statin use and fasting insulin levels which corroborate the general observations of non-significant findings of statin use and fasting blood glucose in the non-T2DM population. Similar results were observed for HOMA-IR. In the GENOA Phase 1 T2DM population, the overall results for slightly elevated fasting insulin levels may have contributed to the observed decreased fasting blood glucose levels, however the results for fasting insulin were generally not significant. Fasting insulin levels could be influenced by multiple biological and/or environmental factors that were not controlled in the analyses. Results for HOMA-IR were generally corroborative of fasting blood glucose levels in the GENOA Phase 1 T2DM population which is anticipated given fasting blood glucose is a component of this composite measure.

*Phase 2: Relationship of Statin Use and Fasting Blood Glucose and Fasting Insulin in the Non-T2DM and T2DM Populations*

Overall, a total of 3634 participants (approximately 76%) were re-recruited for enrollment in Phase 2 of this study across all field centers. In general, non-significant changes in fasting blood glucose were observed after adjustment with statin use compared to no statin use in the non-T2DM populations. When also considering the non-significant statistical findings in the Phase 1 non-T2DM population, these results would suggest that statins are not predictive of fasting blood glucose levels in the non-T2DM GENOA population. The same explanation for the undetected changes in fasting blood glucose may be attributed to the cross sectional study design which may have limited ability to detect changes in fasting blood glucose as the analyses are carried out at 1 distinct time point in Phase 2.

Similar to Phase 1 T2DM populations, decreases in fasting blood glucose were generally observed across ethnicities that were statistically non-significant, with the exception of a significant association in the Hispanic population. In the Hispanic population, a clinically and statistically significant decrease in fasting blood glucose was observed

(value of -14.99 mg/dL; $p < 0.05$). As in Phase 1, concomitant use of antidiabetic and statin medication use was greater in the Hispanic Population [Table 9].

**Table 9: Phase 2 Percentage of Antidiabetic Use and Concomitant Antidiabetic–Statin Medication Use**

| Population | Phase 2 Overall Antidiabetic Medication Use | Phase 2 Concomitant Antidiabetic and Statin Medication Use |
|---|---|---|
| Jackson African American | 24.60% | 8.65% |
| Rochester Non-Hispanic White | 9.93% | 5.09% |
| Starr County Hispanic | 56.89% | 19.81% |

In the GENOA Phase 2 population, fasting insulin was generally increased but non-significant across the non-T2DM and T2DM populations. The increases in fasting insulin levels may be compensatory to overcome peripheral resistance to glucose uptake. Non-significant changes in fasting insulin and HOMA-IR were observed which corroborated the non-significant changes in fasting glucose results described above. As mentioned above, fasting insulin may be influenced by multiple environmental and social factors that were not measured in the GENOA study.

*Longitudinal Relationship of Phase 1 Statin Use in the Non-T2DM Population and Fasting Blood Glucose and Fasting Insulin Collected in Phase 2*

Results from the longitudinal analyses for statin use compared to no statin use did not reveal significance for fasting blood glucose or insulin levels in the GENOA study [Table 5 and Appendix 11]. The same is true for the examination of fasting blood glucose in Phase 2 as compared to Phase 1 [Appendix 10]. These data suggest that a temporal association of statin use and changes in fasting blood glucose or insulin levels in the GENOA study was not detected. The lack of detection of a temporal relationship could be attributed to the time points of data collection in relation to the general time for onset of T2DM. More specifically, the time to onset of T2DM has been determined to be an average of approximately 29.0 months [Nichols *et al.*, 2007]. Furthermore, disease progression and time to onset is more predictable with higher BMI, blood pressure and

TG [Nichols *et al.*, 2007; Fonseca, 2009]. Other researchers have determined that the conversion from a non-diabetic to diabetic state is abrupt, as opposed to gradual, and increases in fasting blood glucose generally occur within a 3-year time period [Ferrannini *et al*, 2004; Fonseca, 2009].

In the GENOA study, measures of fasting blood glucose were collected on two distinct occasions; time of Phase 1 enrollment and Phase 2 enrollment. Thus, given the disease latency, it is possible that onset of T2DM, or signs thereof, was not captured in the time period between participant enrollment in Phase 1 and Phase 2, which may explain the lack of detection of a clinical or statistical association in the longitudinal analysis. In addition, prior studies have demonstrated significant evidence of incident T2DM after 24 months of chronic statin use. Use of statin medication in the GENOA study was collected by participant-report during the time of enrollment in Phase 1 and Phase 2 of this study. The total duration of statin medication use was unknown because the exact date of initial treatment was not available. Thus, participants may have initiated therapy just after Phase 1 and prior to Phase 2 enrollment, however, it is possible that some participants developed T2DM after completion of the Phase 2 study. It should be noted that given the nature of chronic use of statin medication, it can be assumed that a statin regimen continued, once initiated.

*Effect Modification of Statin Use and Education in the Non-T2DM Population*

Although the changes in fasting blood glucose were not consistently significant with the main effect of statin use, results demonstrated significant statin-by-education interaction in the Phase 1 Hispanic Non-T2DM population (value of 19.9 mg/dL; $p < 0.05$), which were further examined in [Figure 13]. Similar significant statin-by-education interactions were identified in the Phase 2 Non-Hispanic White non-T2DM population (4.17 mg/dL; $p < 0.05$) and longitudinal analyses (7.04 mg/dL; $p < 0.05$), which were further examined in [Figure 16] and [Figure 19], respectively. The explanation for the increased effect with higher education could be attributed to multiple social or environmental factors. For example, given that education is a proxy

for SES, one could interpret these findings in a manner such that participants who need statin medications and are of a higher SES strata enjoy a richer, higher calorie diet as opposed to their counterparts who do not require statin medication therapy. Thus, the effect of statin medications in the higher educated T2DM population may be amplified if those participants have more complex metabolic risks. It should be noted that these observations are contrary to published results which demonstrate that factors such as low SES alongside with low levels of education have been associated with lower T2DM regimen adherence and greater T2DM-related morbidity [Delamater *et al*., 2001; Williams *et al.*, 2012].

In the Phase 2 Hispanic non-T2DM population, an opposite effect was observed such that the statin-by-education interaction was significantly decreased (value of -7.41 mg/dL; $p < 0.05$). These results were further examined in [Figure 17]. The observations in the Phase 2 Hispanic population are consistent with the aforementioned published literature.

These Phase 2 results in the Hispanic population were in the opposite direction of the Phase 1 results in the Hispanic population. In Phase 2, statin use in the higher education group (24%) was comparable to use in the lower education group (26%) and therefore, not considered to be influential upon these results. An alternative factor to consider is that patient awareness of health risks may be enhanced as a result of the information exchange in the research environment. Therefore, for those higher educated participants who were on a statin medication, the awareness of good health practices to manage their disease as well as the importance of continuous clinical monitoring may have played a role. This 'learning bias' may have occurred from the time period of Phase 1 to Phase 2 in the higher education non-T2DM Hispanic population resulting in lower differences in fasting blood glucose in statin use versus no statin use.

*Effect Modification of Statin Use and Menopause in the Non-T2DM and T2DM Populations*

The results for the interaction of statin-by-menopause were significant in the Phase 2 African American non-T2DM population (Jackson value of -2.5 mg/dL; $p < 0.05$). Further examination of these results are illustrated in the interaction plot where fasting blood glucose for statin use compared to no statin use are presented across different menopause status in when adjusting for other covariates in [Figure 18].

These results are contrary to evidence published by Culver *et al.* who recruited postmenopausal women in 40 clinical sites across the US during the time period of 1993-1998 [Culver *et al.*, 2012]. These researchers observed increased risk of T2DM in non-T2DM African American post-menopausal women (adjusted HR 1.18 (95% CI, 0.96-1.45) [Culver *et al.*, 2012]. The distinction between the Culver and GENOA results could be attributed to other influencing factors associated with regional differences of the multiple clinical sites included in the Culver study as compared to the specific environmental influencers in the GENOA Jackson field center. More specifically, the results from the Culver study represented the overall observations across multiple US clinical sites; specific site results were not reported and therefore, it is difficult to determine comparability of regions in the Culver study versus the GENOA study. For example, given the disparate regional factors in Jackson MS, initiatives for peri- and post menopause females have been established for purposes of education and enhancement of management of personal health status [Baptist Health Systems, 2013]. Thus, it is quite possible that the awareness of disease management was enhanced even more so in those menopausal females who also experienced metabolic disorders (i.e., dyslipidemia) requiring statin medications. Thus, the environmental differences across the clinical sites in the Culver study as compared to the GENOA Jackson, MS field center could explain the differences in the results reported from these two studies.

The analyses for fasting insulin and HOMA-IR provided different effects. In the Phase 2 T2DM African American/Non-Hispanic White population, significant statin-by-

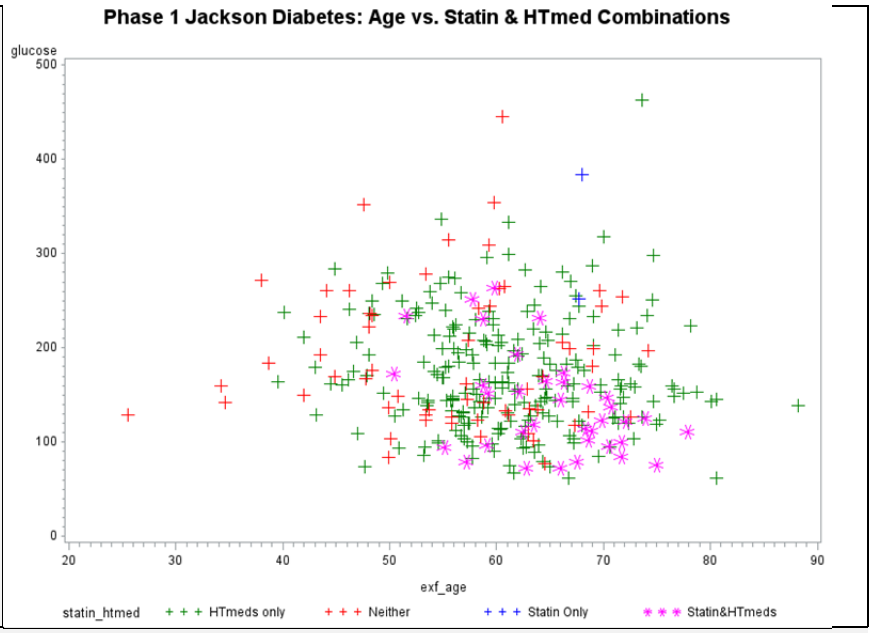
menopause for fasting insulin levels (value of -4.9uU/mL; $p < 0.05$) and HOMA-IR (value of -30.13; $p < 0.05$) were observed. These results were also contrary to the results of Culver *et al*. The effect observed in the Phase 1 non-T2DM Hispanic population whereby the statin-by-menopause interaction for fasting insulin levels (value of 5.34 uU/mL; $0.001 \geq p > 0.01$) and HOMA-IR (value of 1.1; $p < 0.05$) was in the opposite direction for statin use as compared to no statin use in participants with menopause as compared to no menopause. These results are corroborative of the results published by Culver *et al*. [Culver *et al.*, 2012].

Given the sensitive nature of fasting insulin levels (and also HOMA-IR) and ability to be influenced by a multitude of external factors that were likely not measured in the GENOA study, these mixed effects should be further investigated while controlling for the multiple determinants.

*Effect Modification of Concomitant Statin Use, Antihypertensive Medication Use and Increasing Age in the T2DM population*

Significant statin-by-antihypertensive medication interaction was observed in the Phase 2 African American T2DM population (value of -175.4 mg/dL; $p < 0.05$). The same is true for the statin-by-age interaction (value of -3.6 mg/dL; $p < 0.05$). Further examinations of these results are illustrated in [Figure 14] and [Figure 15], respectively. It should be noted that 36 of 38 statin users in the Phase 1 African American population (approximately 94%) were concomitantly exposed to antihypertensive medications and the trend of concomitant use appears to be higher in the elderly population, which may explain this observation [Figure 21].

**Figure 21: Concomitant use of Antihypertensive and Statin Medications across Age in the Phase 1 Jackson Population**



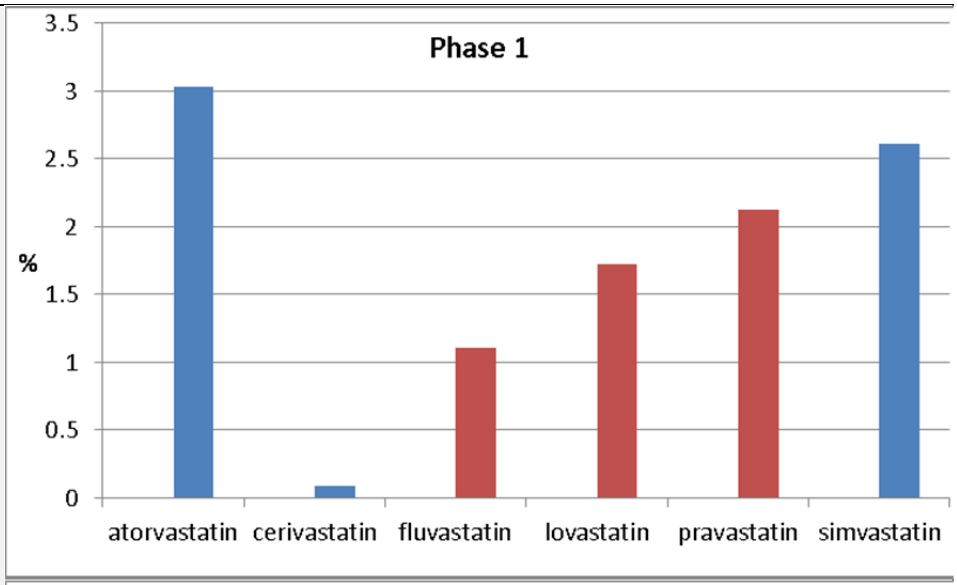

HTmed: antihypertensive use.

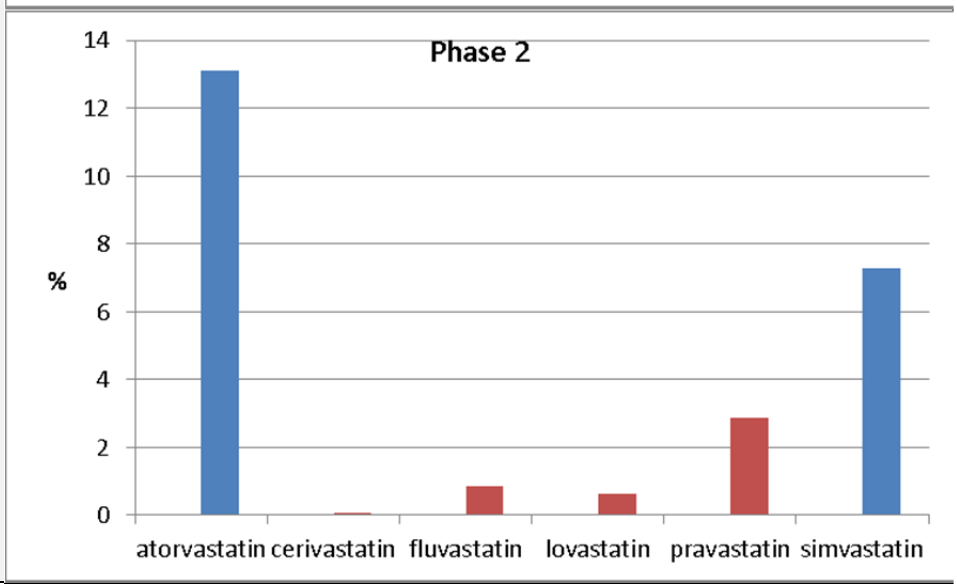
*Statin Pharmacology and Theoretical Impact on Risk for Elevated Blood Glucose Levels or T2DM*

Experimental evidence would suggest a differential potency for the individual statin medications and HMG-CoA reductase inhibition. This has led to the possible link of a differential effect for the individual statins and impact on the diabetic pathway. Although the pharmacodynamic effects of these medications are similar, atorvastatin, simvastatin, and cerivastatin exhibit greater inhibitory effects on HMG-CoA reductase whereas lovastatin, pravastatin and fluvastatin exhibit lower potency [Koh *et al*., 2011]. Examination of pravastatin in humans has shown enhanced insulin sensitivity and other studies have demonstrated increased risk of incident T2DM associated with atorvastatin, rosuvastatin and simvastatin [Koh *et al*., 2010; Collins *et al.*, 2003; Sever *et al.*, 2003; Coleman *et al*, 2008; Ridker *et al.*, 2008]. The different inhibitory effects of the individual statin medications upon HMG-CoA reductase need to be further explored with respect to the proposed mechanistic links of statin induced impaired glucose or T2DM such as influence upon isoprenoid synthesis, $Ca^{2+}$ release, insulin secretion, and/or insulin resistance to gain further insight into the potential effects of the distinct statin medications.

In this study, increased fasting blood glucose was observed across the populations however, results were not consistently significant in the T2DM or the non-T2DM populations. The primary exposure variable in this study was a composite of the individual statin medications and the evaluation was based upon a pharmacological class effect. Therefore, it is uncertain if statins with lower potency could be 'masking' the effects of statins with higher potency [Figure 22]. The temporal effect of increased statin use, particularly with the high potency statin medications over time may also explain the different results observed in Phase 1 as compared to Phase 2.

**Figure 22: Percentage of Individual Statin Use in Phase 1 and 2 Across All Populations**




High potency statin
Low potency statin

*Social and Environment Factors and Impact on Risk for Changes in Fasting Blood Glucose*

Social and environmental factors are on the causal pathway for changes in blood glucose levels. For example, the analyses in this study accounted for educational status (> 12 years vs ≤ 12 years) as a stable proxy for SES; however, the concept of residual confounding cannot be excluded. For example, stress as a manifestation of physical factors (i.e. injuries) or psychosocial factors (i.e., unresolved work issues, bereavement) is a known risk factor for T2DM however, these factors were not collected in this study. Access and usage of medical services within the environment of each center was also not measured. Thus, the concept of residual confounding is particularly important in the examination of statin use across ethnicities, given the different environmental conditions surrounding each center. As such, it should be stressed that all social or environmental factors associated with the surroundings of each center were not measured but could influence the results and explain the any differences across the ethnicities included in the examination of this study.

*Strengths and Limitations*

This study had several major strengths. One is the large, multiethnic source population that provides a strong population base to investigate the association of statin medication use and changes in fasting blood glucose levels in real world clinical practice settings. Although this program included cross sectional analyses giving rise to challenges in assessing temporal associations, this program also included longitudinal analyses to overcome these challenges and allowed for the examination of temporal association between the planned exposure and outcome variables. Longitudinal analyses of the exposure variable were based upon data collected at the time of participant enrollment; however, exact duration of statin medication use was not collected during the participant interview. Therefore, characterization of the onset for changes in fasting blood glucose levels or fasting insulin would not have been possible in this research program.

## 2.6 Conclusions

Currently, use of statins is widespread and even greater use is anticipated to the recent ACC/AHA recommendations which now encourage use of these medications earlier in the disease process and in high risk individuals with or without evidence of atherosclerotic cardiovascular disease [Stone *et al.*, 2013]. Although results of this study did not generally demonstrate significant changes in fasting blood glucose with the main effect of statin use across all populations, effect modification was observed, suggesting decreases in fasting blood glucose with concomitant antihypertensive medication use and increases in age in the African American population enrolled in the Jackson, MS field center. Furthermore, increases as well as decreases in fasting blood glucose were associated with educational status in all populations. The changes in fasting blood glucose were corroborated by changes in fasting insulin and HOMA-IR. These data support the need for further research to understand the risks of statin use and changes in blood glucose in particular populations at potentially greater risk.

This study examined the overall pharmacological class effect of statin use and changes in fasting glucose and fasting insulin however, the different inhibitory effects upon HMG-CoA reductase also need to be further explored in order to understand the relative risk of the outcome with respect to individual statin medications.

Lastly, the results in the study are in contrast to the evidence generated in randomized clinical trials which stresses the importance of research in a naturalistic setting as complimentary evidence to support fully informed public health decisions.

# Chapter 3 AIM 2: Investigation of the Relationship of Statin Medication Use and Type 2 Diabetes Mellitus

## 3.1 Introduction

Type 2 diabetes mellitus is a chronic and progressive disease, primarily characterized by the process of β-cell dysfunction and/or worsening of peripheral insulin resistance which commonly manifests as deterioration of glycosylated hemoglobin (HbA1C), fasting blood glucose, and/or fasting insulin levels. Primary modulators such as elevated BMI, dyslipidemia, medications (thiazides or β-blockers that are used to treat cardiovascular disease), inflammatory mediators, and/or decreased HDL have been identified as influencers of decreased insulin secretion or inhibition of peripheral glucose uptake, ultimately leading to onset of disease [Ferrannini *et al.*, 2004; Fonseca, 2009; Kautzky-Willer *et al.*, 2012; Sandström, 1993; Sarafidis *et al.*, 2007; Schenk *et al*., 2008]. Once T2DM is established, progression of disease is primarily modulated by the loss of glycemic control with antidiabetic medications, patient non-compliance with antidiabetic therapy and/or the aforementioned factors that influence persistent elevated fasting blood glucose levels [Riedel *et al*, 2007; Sharma *et al*, 2014]. Although the majority of research has been focused upon predictors of T2DM, information regarding rate of onset also exists which would suggest that individuals with one or more of the aforementioned modulators would experience decreased time to onset of 'overt' disease as compared to patients with normal levels of these factors [Fonseca, 2009].

In 2012, FDA warned of the potential increases in blood glucose and risk of T2DM with the use of statin therapy [FDA News Release, 2012]. Manufacturers of statin medications were required to communicate details of this potential risk to healthcare professionals and patients through updates of the US package inserts. The primary basis

for the concern stemmed from data that emerged from a double-blind, randomized study, “Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER)”, in which a 27% increase in investigator diagnosis of T2DM in rosuvastatin-treated patients compared to placebo-treated patients was reported [FDA News Release, 2012; FDA Drug Safety Communication, 2012; Ridker *et al.*, 2008]. In another double-blind, randomized study, “Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE-IT TIMI 22),” high-dose statin therapy associated with worsening glycemic control [Sabatine *et al.*, 2004]. Subsequent to the availability of these results, meta-analyses were conducted, providing a mixture of results (Rajpathak *et al.*, 2009; Sattar *et al.*, 2010).

To date, few published non-interventional studies regarding the use of statins and risk of T2DM were identified. Culver *et al.* evaluated the use of statins in postmenopausal women participating in the Women’s Health Initiative. Results of this study indicated that statin use was associated with an increased risk of incident T2DM in postmenopausal women (HR 1.71, 95% CI 1.61 - 1.83), noting that the effect appeared to be consistent across all statins with no specific observations regarding potency or individual statin use [Culver *et al.*, 2012]. Carter *et al.* conducted a population-based cohort study to evaluate the risk of statin use and incident T2DM during the time period of 1997–2010 [Carter *et al.*, 2013]. Participants aged 66 years or older without a diagnosis of T2DM were enrolled in the study. Pravastatin was assigned as the reference treatment arm. Results based upon Cox proportional hazard modeling demonstrated an increased risk of incident T2DM with atorvastatin, rosuvastatin and simvastatin as compared to pravastatin. No significant increased risk was observed in patients who received fluvastatin or lovastatin [Carter *et al.*, 2013].

In addition to results from randomized and observational research, statin use and fasting blood glucose has been examined in the GENOA study and results demonstrated trends in changes in fasting blood glucose with statin use, albeit generally not significant

[see Chapter 2]. Analyses of pairwise interactions in the GENOA population did suggest significant changes in fasting blood glucose with statin use and varying degrees of education or concomitant antihypertensive medication use; the same is true with presence of menopause however, GENOA results demonstrated decreases in fasting blood glucose which contrast published results of Culver *et al*. (Culver *et al*., 2013).

The main goal of this study was to examine the relationship between statin medication use and T2DM at baseline and follow-up in Non-Hispanic White, African American and Hispanic participants enrolled in the Rochester, Jackson and Starr County field centers of the GENOA study, respectively. Given the multitude of social and psychological determinants that are environment dependent and also influence the disease pathway, potential outcome differences in risk of T2DM in the GENOA Non-Hispanic White, African American and Hispanic populations are confounded with environmental differences among the Rochester, Jackson, and Starr County field centers, respectively. The limited availability of evidence to evaluate the association of statin medication use and risk of T2DM from observational research is the rationale for this research and will provide evidence of actual practice patterns, 'real life' evidence of a treatment effect, and contextualization of the conclusions drawn from controlled randomized clinical trials.

## 3.2 Methods

### 3.2.1 Study Design

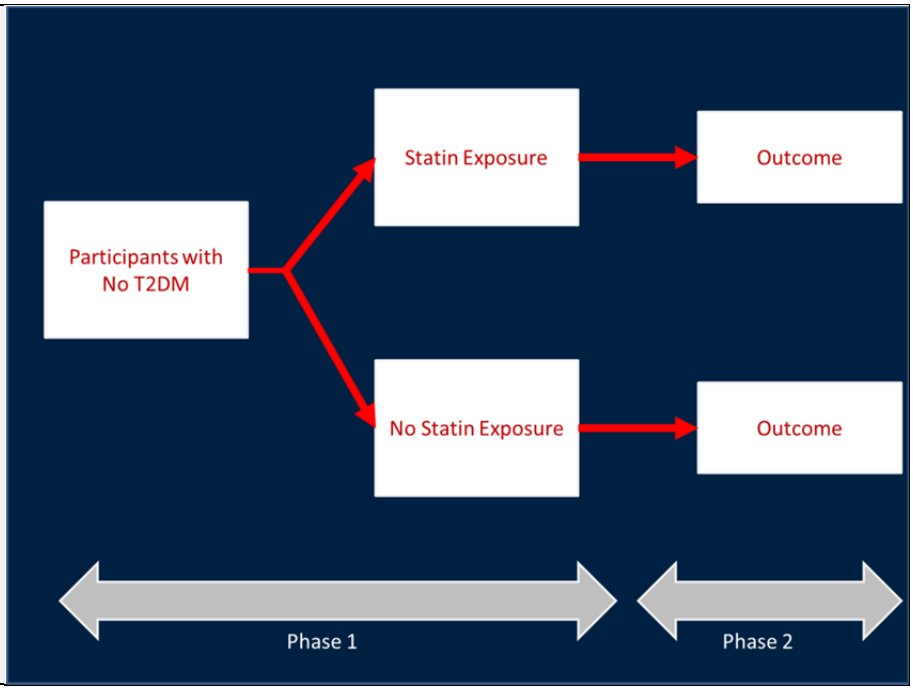
The FBPP, supported by the NHLBI, is a collaboration that serves to identify genetic determinants with possible influence on blood pressure, hypertension and associated target-organ damage. The FBPP offers a robust scientific resource comprised of four multicenter networks. Each network is a family based study, originally intended to well characterize genetic associations and hypertension [FBPP Investigators, 2002]. Since FBPP was established, further research has been conducted to evaluate disease states beyond the initial focus of hypertension.

To address the main goal, this study was conducted in GENOA, one of the individual networks of the FBPP. GENOA is a sibship-based study, originally designed to investigate the genetic linkage of hypertension and T2DM in sibships with at least two hypertensives diagnosed prior to age 60 years old. The GENOA study consisted of two phases: the initial phase (Phase 1) and the second follow-up phase (Phase 2).

In this study, three analyses were conducted using different design attributes of the GENOA study:

- A cross-sectional study of participants enrolled in the Jackson, Rochester and Starr County field centers enrolled in Phase 1 during the period of 1996 – 2000;
- A cross-sectional study of participants enrolled in the Jackson, Rochester and Starr County field centers enrolled in Phase 2 during the period of 2000 – 2004;
- A longitudinal study of participants in Phase 1 who were also enrolled in Phase 2. [Figure 23] provides a graphical illustration of the planned longitudinal analyses.

**Figure 23: Graphical Illustration for Longitudinal Analysis**




T2DM: type 2 diabetes mellitus

The study protocol was approved by the Human Studies Review Boards of the Mayo Clinic, the University of Mississippi, and the University of Texas. The study protocol was also approved by the University of Michigan Investigational Review Board.

### 3.2.2 Study Eligibility

#### 3.2.2.1 Inclusion Criteria

ROCHESTER AND JACKSON FIELD CENTERS

In the Rochester, MN field center, the Mayo Clinic diagnostic index and medical record linkage system of the Rochester Epidemiology Project were used to identify Non-Hispanic White Olmsted County residents who had the diagnosis of essential hypertension prior to age < 60 years and received care in the county during the previous 3 years [Daniels *et al.*, 2004]. In Jackson, sibships were recruited through hypertensive probands who had participated in the ARIC study [ARIC Investigators, 1989]. The ARIC cohort in Jackson was a probability sample of 45- to 64-year-old African American residents of that community. In both field centers, eligible probands were asked whether they had any siblings living in the area and if so, the siblings were contacted. If at least one additional sibling reported the previous diagnosis of hypertension prior to age 60 years old, all available members of the sibship were invited to the study center. Additional criteria included the requirement for all sibships to express willingness to participate in the study through provision of informed consent.

STARR COUNTY FIELD CENTER

In Starr County, sibships were identified from Hispanic White adults less than 60 years of age who were participants in the Starr County Health Studies. Due to the frequency of T2DM among Mexican Americans, subjects were recruited as members of families in which at least two siblings with a diagnosis of T2DM prior to age 60 years old. Type 2 diabetes mellitus was defined by one of the following: current use (within the last month) or prior use (for at least 1 year in lifetime) of anti-diabetic medications; or, two

10-hour fasting blood glucose assessments at least 24 hours apart with results ≥ 120 mg/dL using whole blood or ≥ 140 mg/dL using venous plasma; or, OGTT with results ≥ 200 mg/dL at 120 minutes and also ≥ 200 mg/dL at one prior time point (30, 60 or 90 minutes). When two such full siblings were identified, all members of the sibship were invited to participate. Additional criteria for inclusion in the study involved the requirement for all sibships to express willingness to participate in the study through provision of informed consent.

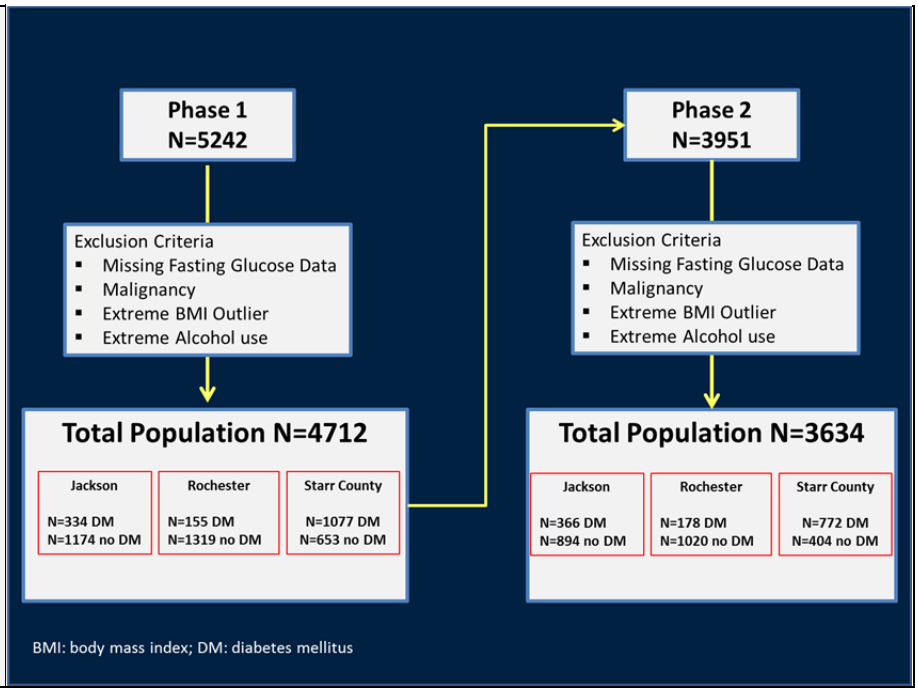
Recruitment methods for the second phase of the study involved contact of all sibships enrolled in Phase 1 with requests to participate in a follow up exam, a requirement of Phase 2 of the study.

#### 3.2.2.2 Exclusion Criteria

Participants with a diagnosis of secondary hypertension, serum creatinine levels >2.5 mg/dL, alcoholism, drug abuse, pregnancy, Type 1 insulin-dependent diabetes mellitus were excluded from the GENOA study. One participant underwent surgical gender reassignment and was excluded from the current analyses.

Additional exclusion criteria were applied for this study, which included missing fasting blood glucose levels (Phase 1 n=433; Phase 2 n=236), active malignancy (Phase 1 n=20; Phase 2 n=23), extreme BMI values (values > mean gender specific BMI + [4 x SD]; Phase 1 n=13; Phase 2 n=6) and extreme alcohol use (values > mean center specific number drinks/week + [4 x SD]; Phase 1 n=64; Phase 2 n=52) [Figure 24].

**Figure 24: Study Eligibility Criteria for Phase 1 and Phase 2**




### 3.2.3 Data Collection

Study visits were conducted in the morning after an overnight fast of at least 8 hours. Participant interview, physical exam and laboratory blood sampling were the primary methods of data collection. Participants were queried for demographic information which included gender and date of birth. Medical history was obtained through participant report of prior diagnosis by a physician, date of diagnosis and treatment of diagnosis. Height and weight were collected during physical exam. Prescription information for medications used in the past $\geq$1 month was collected from pharmacy sources provided by the participant (i.e., label on prescription vial). Lifestyle factors were collected which included a series of questions regarding physical activity, use of tobacco products, use of alcoholic beverages, completed educational years and employment status.

[Table 10] provide details of data collected in Phase 1 and Phase 2 of the study that are most relevant for the analysis of this research.

**Table 10: Relevant Data Collected in Phase 1 and Phase 2 of the GENOA Study**

| Variable | Phase 1 | Phase 2 |
|---|---|---|
| Demographics, Intrinsic/Extrinsic Factors | | |
| Gender | X | X |
| Ethnicity | X | X |
| Date of birth | X | X |
| Completed educational years | X | X |
| Health History | | |
| Diagnosis of T2DM | X | X |
| Year of diagnosis for T2DM | X | X |
| Family history of diabetes | X | X |
| Menopause status | X | X |
| Medications Administered $\geq$ 1 month | | |
| Statin medications | X | X |
| Medications to treat hypertension | X | X |
| Anti-diabetic medications | X | X |
| Hormone replacement therapy | X | X |
| Physical Exam | | |
| Height | X | X |
| Weight | X | X |
| Laboratory Data (and draw time) | | |
| Fasting blood glucose | X | X |
| Fasting insulin | X | X |
| Total cholesterol, HDL, LDL (calculated), TG | X | X |

GENOA: Genetic Epidemiology Network of Arteriopathy; HDL: high-density lipoprotein; LDL: low-density lipoprotein; TG: triglyceride; T2DM: type 2 diabetes mellitus.

### 3.2.4 Exposure Classification and Outcome Measures

EXPOSURE CLASSIFICATION

The Medispan Generic Product Identifier drug dictionary was utilized to codify the first six digits that correspond to individual medications. The first six digits identified medications within the same pharmacological class. The primary exposure of interest, STATIN, represents a composite variable of individual medications within the statin pharmacological class (code 394000).

Case definition for STATIN was the participant-reported use of at least one of the following medications at the time of Phase 1 and Phase 2 exam:

- Atorvastatin
- Lovastatin
- Pravastatin
- Cerivastatin
- Fluvastatin
- Simvastatin

OUTCOME MEASURES

T2DM will be evaluated as a binary outcome variable using the following criteria for "DEFINITE DIABETES" as defined in the GENOA study:

a) Fasting blood glucose > 126 mg/dL and/or
b) Current use of antidiabetic medication (i.e., insulin or oral hypoglycemic agents)

### 3.3 Statistical Analysis Plan

#### 3.3.1 Covariates

Pre-specified covariates that were expected to have an important influence on the primary exposure variable and considered a risk factor for the outcomes of interest were identified (detailed rationale for each covariate provided in Chapter 1). Covariates were categorized as quantitative or qualitative and were based upon data collected at the time of Phase 1 and Phase 2 examination. Covariates considered in this research analysis included BMI ($kg/m^2$), LDL (mg/dL) and age (years) that were treated as continuous variables as well as antihypertensive medications (β-blockers, $Ca^{2+}$-channel blockers, ACE inhibitors, angiotensin-II receptor antagonist, reseprine, diuretics), menopause status, family history of diabetes, and education (≤ 12 years vs. > 12 years) that were treated as categorical variables. In the combined Jackson/Rochester population, 'center' as well as the interaction term for 'statin x center' was included in order to examine the potential differences of statin effects in the African American and Non-Hispanic White populations.

### 3.3.2 General Statistical Approach

Demographic characteristics and intrinsic/extrinsic factors were summarized using descriptive statistics. Sample mean, median and interquartile range were examined for continuous variables of interest and, to meet model assumptions, continuous variables were also evaluated for normality through examination of histograms and determination of skewness.

Cross sectional investigations were conducted in Phase 1 (1996 – 2000) and Phase 2 (2000 – 2004). Longitudinal relationships for statin use were evaluated over time in non-T2DM participants enrolled in Phase 1 and subsequently in Phase 2. [Figure 23] provides a graphical illustration longitudinal analyses that were performed in this study.

Statistical analyses were conducted independently in the African American, Non-Hispanic White and Hispanic populations in order to examine the association of statin medications and T2DM in these ethnicities and in the context of the respective environments of the Jackson, Rochester and Starr County centers, respectively. In addition, analyses were conducted in the combined African American and Non-Hispanic White populations given the similar methods of recruitment for sibships with a diagnosis of hypertension. Given that recruitment of Hispanic participants in the Starr County center was based upon a diagnosis of T2DM, this population was not integrated with the African American and Non-Hispanic White populations.

Using SAS 9.3, univariate and multivariable logistic mixed models were utilized to examine the relationship of statin medication use and T2DM while accounting for the familial relationships within the study population. To determine the best model, stepwise logistic regression was performed with the main effects of covariates described in [Section 3.3.1] using entrance p-value criteria of 0.05 and exit criteria of 0.10. Stepwise logistic regression was performed in Phase 1 and Phase 2 for each individual population; African American, Non-Hispanic White, Hispanic, as well as the combined African American/Non-Hispanic White populations.

### 3.3.3 Cross Sectional Analyses

To examine the relationship between statin exposure and T2DM, univariate logistic mixed models were performed [Model A]; adjusted analyses were performed with the covariates selected via the stepwise logistic regression procedures [Model B1]. In addition to the main effects, all combinations of pairwise interaction terms between the primary exposure variable, statin, and covariates selected via the stepwise procedure were examined [Model B2].

| |
|---|
| Model A: Logit $DM_{ij} = \beta_0 + \beta_1(statin_{ij}) + W_{0j}$, for participant i in sibship j. |

| | |
|---|---|
| Model B1: Logit $DM_{ij} = \beta 0 + \beta_1(xi_j) + ....+\beta_k(x_k) + W_{0j} + \varepsilon_{ij}$ , for participant i in sibship j. | |
| ▪ $Age_{ij}$<br>▪ $BMI_{ij}$<br>▪ $LDL_{ij}$ | ▪ $Education_{ij}$<br>▪ $Antihypertensive\ medication_{ij}$<br>▪ $Menopause\ status_{ij}$<br>▪ $Family\ History_{ij}$<br>▪ $Center_{ij}$ (for combined Jackson/Rochester only) |
| Model B2: Logit $DM_{ij} = \beta_0 + \beta_1(xi_j) + ....+\beta_k(x_k) + \beta_{k+1}$(pairwise interactions including $statin_{ij1}$) … $+ W_{0j} + \varepsilon_{ij}$ , for participant i in sibship j. | |
| ▪ $Age_{ij1}$ x $statin_{ij1}$<br>▪ $BMI_{ij\ 1}$x $statin_{ij1}$<br>▪ $LDL_{ij1}$ x $statin_{ij1}$ | ▪ $Education_{ij1}$ x $statin_{ij1}$<br>▪ $Antihypertensive\ medication_{ij1}$ x $statin_{ij1}$<br>▪ $Menopause\ status_{ij1}$ x $statin_{ij1}$<br>▪ $Family\ History_{ij1}$ x $statin_{ij1}$<br>▪ $Statin_{ij1}$ x center (for combined Jackson/Rochester only) |

In [Model B1 and B2], $variables_{ij}$ are represented by participant i in sibship j and are based upon data collected during Phase 1 or Phase 2 for the respective analyses; the outcome, Logit $DM_{ij}$, is interpreted as the odds ratio of T2DM and $W_{0j}$ is the random intercept foreach sibship. The error term, $\varepsilon_{ij}$, is the residual variation unexplained by the model. The primary coefficient of interest, $e^{\beta(statinij)}$, is the odds ratio (OR) of statin use and binary outcome of T2DM, adjusting for the fixed effects of the other covariates.

### 3.3.4 Longitudinal Statistical Analyses

Univariate and multivariable logistic mixed models were performed to examine the relationship of Phase 1 statin exposure and Phase 2 outcome of T2DM [Model C]. This longitudinal relationship between statin exposure and T2DM was also performed while adjusting for those continuous and categorical variables described in [Section 3.3.1] that were selected via the stepwise procedure [Model D1]. In addition to the main effects, all combinations of pairwise interaction terms between the primary exposure variable, statin, and covariates that were selected via the stepwise procedure were also examined [Model D2]. Additional analysis was conducted by including Phase 1 fasting blood glucose levels in the model [Model D3].

| |
|---|
| Model C: Logit $DM_{ij2} = \beta_0 + \beta_1(statin_{ij}) + W_{0j}$, for participant i in sibship j. |

| | |
|---|---|
| Model D1: Logit $DM_{ij2} = \beta_0 + \beta_1(x_{ij1}) + \ldots. \beta_k(BMI_{ijk}) + W_{0j} + \varepsilon ij$, for participant i in sibship j across k time points (k=1 for Phase 1; k=2 for Phase 2) | |
| ▪ $Age_{ij}$<br>▪ $BMI_{ij}$<br>▪ $LDL_{ij}$ | ▪ $Education_{ij}$<br>▪ $Antihypertensive\ medication_{ij}$<br>▪ $Menopause\ status_{ij}$<br>▪ $Family\ History_{ij}$<br>▪ $Center_{ij}$ (combined Jackson/Rochester only) |
| Model D2: Logit $DM_{ij2} = \beta_0 + \beta_1(x_{ij1}) + \ldots. \beta_k(BMI_{ijk}) + \beta_{k+1}$(pairwise interactions including $statin_{ij1}$) + $W_{0j} + \varepsilon_{ij}$, for participant i in sibship j across k time points (k=1 for Phase 1; k=2 for Phase 2) | |
| ▪ $Age_{ij1}$ x $statin_{ij1}$<br>▪ $BMI_{ij1}$ x $statin_{ij1}$<br>▪ $Menopause\ status_{ij1}$ x $statin_{ij1}$<br>▪ $Family\ History_{ij1}$ x $statin_{ij1}$ | ▪ $Education_{ij1}$ x $statin_{ij1}$<br>▪ $Antihypertensive\ medication_{ij1}$ x $statin_{ij1}$<br>▪ $Statin_{ij1}$ x center (combined Jackson/Rochester only) |
| Model D3: Logit $DM_{ij2} = \beta_0 + \beta_1(x_{ij1}) + \ldots. \beta_k(\text{Phase 1 } FBG_{ijk}) + \beta_{k+1}$(pairwise interactions including $statin_{ij1}$) + $W_{0j} + \varepsilon_{ij}$, for participant i in sibship j across k time points (k=1 for Phase 1; k=2 for Phase 2) | |

The outcome, Logit $DM_{ij}$, is interpreted as the relative risk of T2DM and $W_{0j}$ is the random intercept for each sibship; $e^{\beta(statinij)}$ is interpreted as the odds of statin use and binary outcome of T2DM, adjusting for the fixed effects of the other covariates and random effects of the sibships.

## 3.4 Results

### 3.4.1 Demographics, Intrinsic and Extrinsic Factors

In the initial phase of the GENOA study (1996-2001), a total of 4712 participants met the inclusion and exclusion criteria for this study of which 1508 were African American, 1474 were Non-Hispanic White and 1730 were of Hispanic ethnicity. Of the total number of Phase 1 participants, approximately 72%, 57% and 60% were female in the Jackson African Americans, Rochester Non-Hispanic Whites and Starr County Hispanics populations, respectively. In Phase 2 of the GENOA study (2000-2004), a total of 3634 participants met the inclusion and exclusion criteria for this study of which 1260 were African American, 1198 were Non-Hispanic Whites and 1176 were of Hispanic ethnicity. Of the total number of Phase 2 participants, approximately 72% African American, 58% Non-Hispanic White and 61% Hispanic were female.

In Phase 1, the mean ages of African American, Non-Hispanic White, and Hispanic participants were 58.4 years, 55.3 years and 55.5 years, respectively. In Phase 2, the mean ages of African American, Non-Hispanic White, and Hispanic participants were 63.4 years, 58.9 years and 58.8 years, respectively.

Of the total number of participants recruited during Phase 1, the highest use of statin medications was reported in the Non-Hispanic White population (15.9%) and lowest in the African American population (5.3%). The prevalence of statin use increased in Phase 2 of the study and continued to be highest in Non-Hispanic White population (29.2%) and lowest in the African American population (18.8%).

[Table 11] summarizes demographic, intrinsic and extrinsic factors as well as mean fasting glucose levels and percent of T2DM for the individual centers across Phase 1 and Phase 2 of the study. Mean, median, and interquartile ranges are provided in [Appendix 2 and Appendix 3].

**Table 11: Demographics, Intrinsic and Extrinsic Factors across Centers in Phase 1 and Phase 2**

| | | Total N=4712 | | |
|---|---|---|---|---|
| | | **African American Jackson** | **Non-Hispanic White Rochester** | **Hispanic Starr County** |
| **PHASE 1** | | N=1508 | N=1474 | N=1730 |
| Gender | % Female | 72.08 | 56.85 | 59.65 |
| | % Male | 27.92 | 43.15 | 40.35 |
| Age, years | Mean (SD) | 58.41 (10.31) | 55.30 (10.91) | 55.54 (11.8) |
| Statin use | % | 5.31 | 15.94 | 10.69 |
| Glucose, mg/dL | Mean (SD) | 111.05 (45.66) | 98.97 (27.31) | 153.05(72.16) |
| T2DM | % | 22.15 | 10.52 | 62.25 |
| | | **Total N=3634** | | |
| **PHASE 2** | | N=1260 | N=1198 | N=1176 |
| Gender | % Female | 72.30 | 57.76 | 61.39 |
| | % Male | 27.70 | 42.24 | 38.61 |
| Age, years | Mean (SD) | 63.40 (9.45) | 58.85 (10.19) | 58.78 (11.21) |
| Statin use | % | 18.81 | 29.22 | 25.85 |
| Glucose, mg/dL | Mean (SD) | 111.67 (43.44) | 104.80 (24.37) | 152.26 (65.63) |
| T2DM | % | 29.05 | 14.86 | 65.65 |

T2DM: type 2 diabetes mellitus; SD: standard deviation.
Note: Based upon available observations.

### 3.4.2 Phase 1 Mixed Model Results of Statin Use and Type 2 Diabetes Mellitus

[Table 12] presents the univariate and multivariable Phase 1 results for the OR for T2DM with statin use and covariate effects.

*Results for Univariate and Multivariable Analysis of Statin Use and Type 2 Diabetes Mellitus*

The odds for the univariate analyses for T2DM with statin use compared to non-use was significantly increased in all populations [African American OR = 3.55 (95% CI 2.14, 5.87); Non-Hispanic White OR = 2.32 (95% CI 1.55, 3.50); Hispanic OR = 2.59 (95% CI 1.75, 3.83); African American/Non-Hispanic White OR = 2.01 (95% CI 2.21, 2.70)]. After adjusting for the pre-specified covariates (selected via stepwise logistic regression), the odds of T2DM with statin use versus no use were also significantly increased in the African American [OR = 2.68 (95% CI 1.59, 4.53), Non-Hispanic White [OR = 1.89 (95% CI

1.23, 2.90), and combined African American/Non-Hispanic White [OR = 2.51 (95% CI 1.55, 2.99)] populations; similar observations were observed in the Hispanic population however, these results were marginally significant [OR = 1.48 (95% CI 0.99, 2.22)].

*Results for Pre-specified Covariates*

The OR for T2DM with increasing BMI, age, use of antihypertensive medication and family history of diabetes were generally predictive of T2DM across all Phase 1 populations. Education and field center were also predictive of T2DM in the combined African American/Non-Hispanic White population.

*Effect Modification of Statin Use and T2DM*

No pairwise interactions with statin medication were statistically significant.

**Table 12: Phase 1 Univariate and Multivariable General Linear Mixed Model Analyses for Statin Use and Type 2 Diabetes Mellitus**

| | African American Jackson | Non-Hispanic White Rochester | Hispanic Starr County | African America/Non-Hispanic White Jackson/ Rochester |
|---|---|---|---|---|
| **UNIVARIATE** | | | | |
| # Obs Used | 1508 | 1474 | 1730 | 2982 |
| Statin OR | 3.55 (2.14, 5.87) | 2.32 (1.55, 3.50) | 2.59 (1.75, 3.83) | 2.01 (1.49, 2.70) |
| **MULTIVARIABLE** | | | | |
| # Obs Used | 1508 | 1474 | 1728 | 2982 |
| BMI | 1.06* | 1.09* | 1.01 | 1.07* |
| Age | 1.02* | 1.05* | 1.03* | 1.03* |
| HTN med | 2.15* | 1.52 | 2.37* | 1.94* |
| Menopause | --- | --- | --- | --- |
| Family history of diabetes | 3.29* | 3.07* | --- | 3.23* |
| Education | 0.75 | 0.73 | --- | 0.74* |
| Center | NA | NA | NA | 0.47* |
| Statin | 2.68* (1.59, 4.53) | 1.89* (1.23, 2.90) | 1.48 (0.99, 2.22) | 2.51* (1.55, 2.99) |

*95% confidence interval excludes 1; --- covariate excluded via stepwise selection.
BMI: body mass index; HTN med: antihypertensive use; NA: not applicable; OR: odds ratio.

### 3.4.3 Phase 2 Mixed Model Results of Statin Use and Type 2 Diabetes Mellitus

[Table 13] presents the univariate and multivariable Phase 2 results for the OR for T2DM with statin use and covariate effects.

*Univariate and Multivariable Analysis of Statin Use and Type 2 Diabetes Mellitus*

The univariate odds for T2DM with statin use compared to non-use is significantly increased in all populations [African American OR = 3.14 (95% CI 2.29, 4.30); Non-Hispanic White OR =2.63 (95% CI 1.86, 3.82); Hispanic OR = 2.81 (95% CI 2.03, 3.90); African American/Non-Hispanic White OR = 2.46 (95% CI 1.96, 3.09)]. After adjusting for the pre-specified covariates (selected via stepwise logistic regression), the odds for T2DM with statin use versus no use was also significantly increased in all populations:

African American [OR =2.41; (95% CI 1.75, 3.33)], Non-Hispanic White [OR =1.81; (95% CI 1.23, 2.66)], Hispanic [OR =1.66; (95% CI 1.16, 2.37)], combined African American/Non-Hispanic White [OR =2.22; (95% CI 1.74, 2.83)] [Table 13].

*Results for Pre-specified Covariates*

The OR for T2DM with increasing BMI, age, use of antihypertensive medication, and family history of diabetes were increased and generally significant across all Phase 2 populations. The odds of T2DM was decreased when comparing higher education ($\geq$ 12 years) to lower education in the combined African American/Non-Hispanic White population [Table 13].

*Effect Modification of Statin Use and T2DM*

Results for the pairwise interaction of statin-by-education in the Hispanic population was significantly decreased [OR = 0.38 (95% CI 0.15, 0.95)]. Results for the pairwise interactions of statin use and family history of diabetes, as well as statin use and center, were not significant (95% CI includes 1).

**Table 13: Phase 2 Univariate and Multivariable General Linear Mixed Model Analyses for Statin Use and Type 2 Diabetes Mellitus**

| | African American Jackson | Non-Hispanic White Rochester | Hispanic Starr County | African America/Non-Hispanic White Jackson/ Rochester |
|---|---|---|---|---|
| **UNIVARIATE** | | | | |
| # Obs Used | 1260 | 1198 | 1176 | 2458 |
| Statin OR | 3.14 (2.29, 4.30) | 2.63 1.86, 3.82) | 2.81 (2.03, 3.90) | 2.46 (1.96, 3.09) |
| **MULTIVARIABLE** | | | | |
| # Obs Used | 1257 | 1197 | 1166 | 2455 |
| BMI | 1.05* | 1.11* | 1.01 | 1.07* |
| Age | 1.02 | 1.04* | 1.03* | 1.03* |
| HTN med | 3.11* | 1.87* | 2.43* | 2.63* |
| Menopause | --- | 0.68 | --- | --- |
| Family history of diabetes | 3.52* | 2.75* | 5.56* | 3.22* |
| Education | 0.78 | --- | 0.78 | 0.78* |
| Center | NA | NA | NA | 0.49* |
| Statin | 2.41* (1.75, 3.34) | 1.81* (1.23, 2.66) | 1.66* (1.16, 2.37) | 2.22* (1.74, 2.83) |

*95% confidence interval excludes 1; --- covariate excluded via stepwise selection.
BMI: body mass index; HTN med: antihypertensive use; NA: not applicable; OR: odds ratio.

### 3.4.4 Longitudinal Examination of Statin Use in Phase 1 Non-T2DM participants and T2DM Outcomes in Phase 2

[Table 14] presents the univariate and multivariable results for risk of Phase 1 statin use and covariate effects on Phase 2 T2DM.

*Univariate and Multivariable Analysis of Statin Use and Type 2 Diabetes Mellitus*

Results in the univariate analyses demonstrated statistically significant increased odds for T2DM with statin use compared to no statin use in the Non-Hispanic White population; odds of T2DM with statin use compared to no statin use in the remaining populations were not significant [Table 14].

After adjusting for the pre-specified covariates selected via stepwise logistic regression, the odds of T2DM with statin use versus no use is increased in the Non-Hispanic White population [OR = 1.32 (95% CI 0.05, 3.43)], Hispanic [OR = 1.61 (95% CI 0.65, 3.93)] and combined African American/Non-Hispanic White [OR = 1.33 (95% CI 0.76, 2.33)] populations. These results were decreased in the African American population [OR = 0.41 (95% CI 0.09, 1.82)]. Overall, these results for the adjusted analyses were not significant [Table 14].

After also adjusting for Phase 1 fasting blood glucose levels, the odds of T2DM with statin use versus no use is decreased in the African American population [OR = 0.27 (95% CI 0.05, 1.42)] population. These results were increased in the Non-Hispanic White population [OR = 02.32 (95% CI 1.14, 4.71)], Hispanic [OR = 1.18 (95% CI 0.43, 3.21)] and combined African American/Non-Hispanic White [OR = 3.76 (95% CI 0.71, 20.00]. Overall, these results for the adjusted analyses were not significant.

*Results for Pre-specified Covariates*

The OR for T2DM with increasing BMI, use of antihypertensive medication and family history of diabetes was increased and statistically significant in the African American and combined African American/Non-Hispanic White Phase 2 populations. The OR for T2DM was increased with center and statistically significant in the combined African American/Non-Hispanic White population [Table 14].

*Effect Modification of Statin Use and T2DM*

The results for pairwise interaction of statin use and center were not significant.

**Table 14: Longitudinal Univariate and Multivariable General Linear Mixed Model Analyses for Phase 1 Statin Use and Phase 2 Type 2 Diabetes Mellitus**

| | Phase 1 No T2DM | | | |
|---|---|---|---|---|
| | African American Jackson | Non-Hispanic White Rochester | Hispanic Starr County | African America/Non-Hispanic White Jackson/ Rochester |
| # Obs Used | 840 | 1008 | 475 | 1848 |
| **UNIVARIATE** | | | | |
| Statin | 0.41 (0.95, 1.81) | 1.89 (1.03, 3.48) | 1.73 (0.73, 4.08) | 1.07 (0.63, 1.81) |
| **MULTIVARIABLE** | | | | |
| BMI | 1.05* | 1.11 | 1.10 | 1.07* |
| Age | --- | --- | --- | 1.00 |
| HTN med | 1.64* | --- | 1.56 | 1.55* |
| Menopause | --- | --- | --- | --- |
| Family history of diabetes | 2.12* | 1.59 | --- | 1.93* |
| Education | --- | 0.87 | --- | 0.83 |
| Center | NA | NA | NA | 1.74* |
| Statin | 0.41 (0.09, 1.82) | 1.32 (0.05, 3.43) | 1.61 (0.65, 3.93) | 1.33 (0.76, 2.33) |

*95% confidence interval excludes 1; --- covariate excluded via stepwise selection.
BMI: body mass index; HTN med: antihypertensive use; NA: not applicable; OR: odds ratio; T2DM: type 2diabetes mellitus.

## 3.5 Discussion

Type 2 diabetes mellitus is a complex disease influenced by a multitude of biological, genetic, psychological, social and/or environmental factors that may impact the onset or progression of disease. In this study, the objective was to examine risk of statin use and T2DM in three ethnically and geographically diverse populations of hypertensive sibships in African Americans from Jackson and Non-Hispanic Whites from Rochester as well as diabetic sibships in Hispanics from Starr County. Given the potential for variation of T2DM influencers across the geographical regions included in the GENOA study, it is not possible to generalize the results of this study as simple ethnic differences but instead, the observations should be attributed to ethnic effects combined with potential social and environmental effects that may have influenced the results of this study.

The following provides a discussion of the pattern of statin use in the GENOA population as compared to observed trends in the US population; results from analyses of statin use and risk of T2DM the Phase 1 and Phase 2 populations; as well as other factors such as statin pharmacology or residual confounding that may have influenced results of this study.

*Statin Utilization in the United States Compared to the GENOA Study*

The CDC reported that a greater percentage of men (50% in 65-74 years; 45% in 75 years and over) and women (36% in 65-74 years; 39% in 75 years and over) used statin medications in 2005-2008 as compared to men (~15-26%) and women (~10-24%), in the same age ranges in 1999-2002 [Figure 2] [National Center of Health Statistics, 2011].

In Phase 1 of the GENOA study [1996-2000], the use of statin medications in males and females across all age categories was relatively less compared to the CDC reported gender specific rates during a similar time period [Table 15, Figure 2].

**Table 15: Statin Use in Each Cohort by Age Category in Phase 1 [1996-2000]**

| Age | African American Jackson | Non-Hispanic White Rochester | Hispanic Starr County |
|---|---|---|---|
| 45-64 years | F: 2%<br>M: 0% | F: 4%<br>M: 6% | F: 3%<br>M: 2% |
| 65-74 years | F: 1%<br>M: 1% | F: 2%<br>M: 3% | F: 2%<br>M: 2% |
| ≥75 years | F: 0%<br>M: 0% | F: 0%<br>M: 1% | F: 1%<br>M: 0% |

Total N for each center used as denominator.
F: female; M: male.

As anticipated, with time, statin use generally increased across the field centers in Phase 2 [2000-2004], which was parallel to the temporal trends of increased use of statins in the US [Table 16]. Overall, statin medication use in Phase 2 of the GENOA study [2000-2004] was relatively less compared to CDC reported rates [Figure 2].

| Table 16: Statin Use in Each Cohort by Age Category in Phase 2 [2000-2004] | | | |
|---|---|---|---|
| Age | African American Jackson | Non-Hispanic White Rochester | Hispanic Starr County |
| 45-64 years | F: 7%<br>M: 3% | F: 7%<br>M: 9% | F: 8%<br>M: 5% |
| 65-74 years | F: 5%<br>M: 2% | F: 5%<br>M:5% | F: 6%<br>M: 3% |
| ≥75 years | F: 1%<br>M: 1% | F: 1%<br>M: 1% | F: 2%<br>M: 1% |

Total N for each center used as denominator.
F: female; M: male.

GENOA participants were selected based upon a diagnosis of hypertension or diabetes and therefore, one would anticipate greater concomitant statin medication use in this population. Therefore, reasons for the apparent lower statin use in the GENOA study are not clear. It could be speculated that participants residing in relatively less affluent regions such as Jackson and Starr County, may have less access to medical care and prescription medications; however, this theory does not explain the lower use in Rochester which is a relatively more affluent region with theoretically greater access to medical care. It should be noted that use of statins in the GENOA study was based upon participant information collected from prescription vials that were provided by the participant at the time of Phase 1 and Phase 2 enrollment.

The increased use of statin medications over time assumes greater availability, access and/or acceptance by participants; this 'time dimension effect' may influence epidemiologic inferences. More specifically, trends of increased usage could parallel trends of increased differences in outcome. Alternatively, trends of increased usage could result in greater health awareness and disease monitoring which could result in decreased risk for the outcome of interest. Lastly, as age increases, the overall disease burden, and medication use, increases. Therefore, this 'age effect' may also influence the trends observed of statin medication use and outcome in this study.

*Relationship of Statin Use and Type 2 Diabetes Mellitus in Phase 1 and Phase 2 Jackson and Rochester Field Centers*

In keeping with prior findings from interventional and observational research, the univariate analyses performed in Phase 1 and Phase 2 of this study demonstrated the odds of T2DM with statin use as compared to no statin use was significantly increased in the African American, Non-Hispanic White, Hispanic, and combined African American/Non-Hispanic White populations. After adjustment of the pre-specified covariates, similar trends were observed in Phase 1 and replication of these results was achieved in Phase 2 across all field centers. Further, the adjusted analyses for the statin-by-center interaction in the combined Jackson/Rochester population was not significant in the Phase 1 or Phase 2 populations signifying that the probability of T2DM with statin use as compared to no statin use was no different among the African American population as compared to the Non-Hispanic White population.

The results for the magnitude of effect for statin use and T2DM were similar in Phase 1 [OR = 2.51 (95% CI 1.55, 2.99)] and Phase 2 [OR = 2.22 (95% CI 1.74, 2.83)] despite the higher prevalence of T2DM in Phase 2 [Table 11] which is expected due to the progressive nature of this disease. In addition, if we consider the 'age effect' whereby disease and the overall disease burden increase over time and with age, one may have expected the magnitude of effect to increase over time.

Factors that are known to modulate β-cell dysfunction and/or insulin resistance include increasing BMI, medication use (i.e., thiazides or β-blockers used to treat cardiovascular disease), worsening dyslipidemia and/or increasing age [Ferrannini *et al.*, 2004; Fonseca, 2009; Kautzky-Willer *et al.*, 2012; Sandström, 1993; Sarafidis *et al.*, 2007; Schenk *et al*., 2008]. In this study, the odds of T2DM were similar with increasing BMI, increasing age and concomitant use of antihypertensive medications in Phase 1 compared to Phase 2 (BMI Phase 1 and Phase 2 OR = 1.07; Age Phase 1 and Phase OR =1.03; Phase 1 Antihypertensive medication OR=1.94 and Phase 2 OR= 2.63) and therefore, onset of

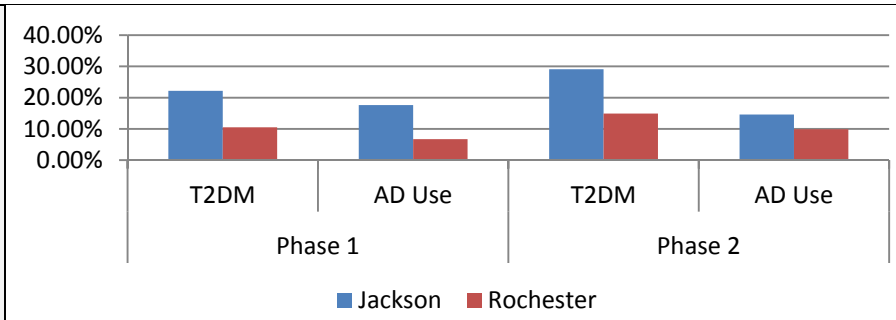
progression of disease based upon greater influence of these covariate effects over time were not apparent.

The theoretical impact of loss to follow up in the GENOA study should also be considered. Approximately 25% of participants were loss to follow up for unknown reasons and therefore, whether the loss to follow was a random or non-random effect is also not known. There are a few possibilities for which the random or non-random loss to follow up could influence the overall results in this study. For instance, if a disproportionate number of participants were loss to follow up who met the case definition of T2DM and were not receiving a statin medication, then this impact of this selective loss to follow up would positively bias the probability of T2DM with statin use in Phase 2 as compared to Phase 1. On the other hand, if the majority of participants on statin medications that were loss to follow up because of outcomes associated with T2DM (or associated co-morbid conditions), a negative bias in the Phase 2 estimate would occur due to a result in fewer cases of T2DM; that is, the magnitude of effect in Phase 2 may have been theoretically even greater than observed. Lastly, if a proportionate or disproportionate number of participants are loss to follow up for reasons that are unrelated to the disease under study (i.e. T2DM), a bias in the Phase 2 estimate may not occur. As mentioned, in the GENOA study, reasons for the loss to follow up were unknown and therefore, the potential for bias is difficult to interpret.

In Phase 1 of this study, the prevalence of T2DM in the African American and Non-Hispanic White populations was 22.2% and 10.5% which increased in Phase 2 to 29.1% and 14.9%, respectively [Table 11]. However, use of anti-diabetic medications was lower than the overall percentage of T2DM in each phase [Figure 25]. Recalling the case definition for T2DM which included use of an antidiabetic medication and/or elevated fasting blood glucose levels (> 126 mg/dL), these data would suggest that only a portion of participants were actively controlled with pharmacologic treatment and the remaining proportion of participants appear to be uncontrolled as they met the criteria of elevated fasting glucose (> 126 mg/dL); this proportion of uncontrolled participants

was greater in Phase 2 as compared to Phase 1. Despite these observations, the overall magnitude of effect for statin use and T2DM in Phase 2 was similar to Phase 1.

**Figure 25: Percent T2DM and Antidiabetic Medication Use in the Phase 1 and Phase 2 Field Centers**




T2DM: type 2 diabetes mellitus; AD: antidiabetic medications

Lastly, and as mentioned above, T2DM is a progressive disease which, in addition to persistence of the aforementioned influencers, may also be modulated by the loss of glycemic control with antidiabetic medications and/or patient non-compliance with antidiabetic therapy. In this study, the participant-reported use of antidiabetic medication was collected at the time of enrollment in Phase 1 and Phase 2; however, assessment of compliance or adherence to an individual's prescribed regimen was not performed. In addition, the concept of 'clinical inertia' may also be considered whereby the intensiveness of routine monitoring of a particular disease may diminish over time [O'Connor *et al*, 2005]. Although the GENOA results would suggest the magnitude of effect is similar over the time period from Phase 1 to Phase 2, the recommendation for routine and intensive monitoring of a patient's T2DM status should be upheld.

Taken together, similar magnitude of effect for increased odds of T2DM was observed in Phase 1 and Phase 2 of the GENOA study despite a) the potential for progression of disease due an 'age effect', b) likelihood of disease progression due to the possible lack of persistence of antidiabetic medication effects as well as c) an assumption of participant non-compliance with pharmacological treatment. The reasons for loss to follow up were not collected in GENOA study and therefore, potential impact upon the overall results is difficult to interpret.

*Effect Modification of Statin Use and Family History of Diabetes in Phase 1 and Phase 2*

The statin-by-family history of diabetes interaction for T2DM was not statistically significant. The association of a family history and T2DM is well established, irrespective of ethnic background [American Diabetes Association, 2000; Arslanian *et al*., 2005; Arslanian, 2002]. If the use of statin medications in participants with a relevant family history is associated with relatively increased risk of T2DM, this result is likely to be amplified given the potential for treatment bias such that greater use of statin medications may have occurred in participants with a family history. This theory is coupled with the potential for monitoring bias such that participants with relevant medical history may be more intensely monitored.

*Longitudinal Relationship of Statin Use in Phase 1 Non-T2DM and Phase 2 Outcome of T2DM*

Results from the longitudinal examination demonstrated increased odds of T2DM with statin use compared to non-use in the 'at-risk' Phase 1 population and assessment of T2DM in Phase 2 however, these results were not considered statistically significant, after adjustment. When adjusting for Phase 1 fasting blood glucose levels, these results were also not considered significant. This lack of significance is a similar observation to the longitudinal examination of statin use and changes in Phase 2 fasting blood glucose levels, fasting insulin levels and HOMA-IR in the Phase 1 non-T2DM GENOA population [see Chapter 2].

Although the majority of research has been focused upon identification and characterization of the predictors of T2DM, other studies have been conducted to understand the time to onset or progression of disease. Nichols *et al.* examined the progression of disease and discovered that 8.1% of subjects with slightly elevated baseline fasting glucose (100–109 mg/dl) and 24.3% of subjects with even higher initial abnormal fasting glucose (110–125 mg/dL) developed T2DM over the average duration of 29.0 months [Nichols *et al.*, 2007]. Disease progression and time to onset was more

predictable with higher BMI, blood pressure and TG [Nichols *et al.*, 2007; Fonseca, 2009]. Ferrannini *et al.* analyzed plasma glucose and insulin levels during OGTT at baseline, 3-year and 7-year timepoints. Results indicated that conversion from a normal to diabetic state was abrupt, as opposed to gradual, and increases in fasting blood glucose generally occurred within the 3-year time period [Ferrannini *et al*, 2004; Fonseca, 2009].

In the GENOA study, a diagnosis of T2DM (based upon measures of fasting blood glucose or use of antidiabetic medications) was determined on two distinct occasions, at the time of Phase 1 enrollment and Phase 2 enrollment. Thus, given the longer latency of T2DM, it is possible that onset of disease had not emerged or captured in the time period between participant enrollment in Phase 1 and Phase 2 and may explain the lack of statistical association and therefore a lack of temporal relationship observed in this study.

Prior studies have also suggested the time to onset of T2DM with chronic statin use is approximately 2 years. For example, in the JUPITER study, significant evidence of incident T2DM (changes in HbA1c levels) associated with chronic statin use was identified at 24 months. Use of statin medication in the GENOA study was collected by participant-report during the time of enrollment in Phase 1 and Phase 2 of this study. The total duration of statin medication use was unknown because the exact date of initial treatment was not available. Thus, for example, participants may have initiated therapy soon after Phase 1 enrollment (and prior to Phase 2), however, given the predicted average latency or onset of T2DM, this outcome may have occurred after completion of the Phase 2 study. Given the nature of chronic use of statin medication, it can be assumed that a statin regimen continued and therefore, limited or intermittent exposure is likely not an influential factor upon the results of the longitudinal analysis.

Taken together, the lack of a significant association for statin use and T2DM in the 'at risk' population longitudinal analysis could be attributed to the longer latency of the disease which may have not emerged during the time period in the GENOA study alongside with the unknown duration of statin medication use in the GENOA study. It

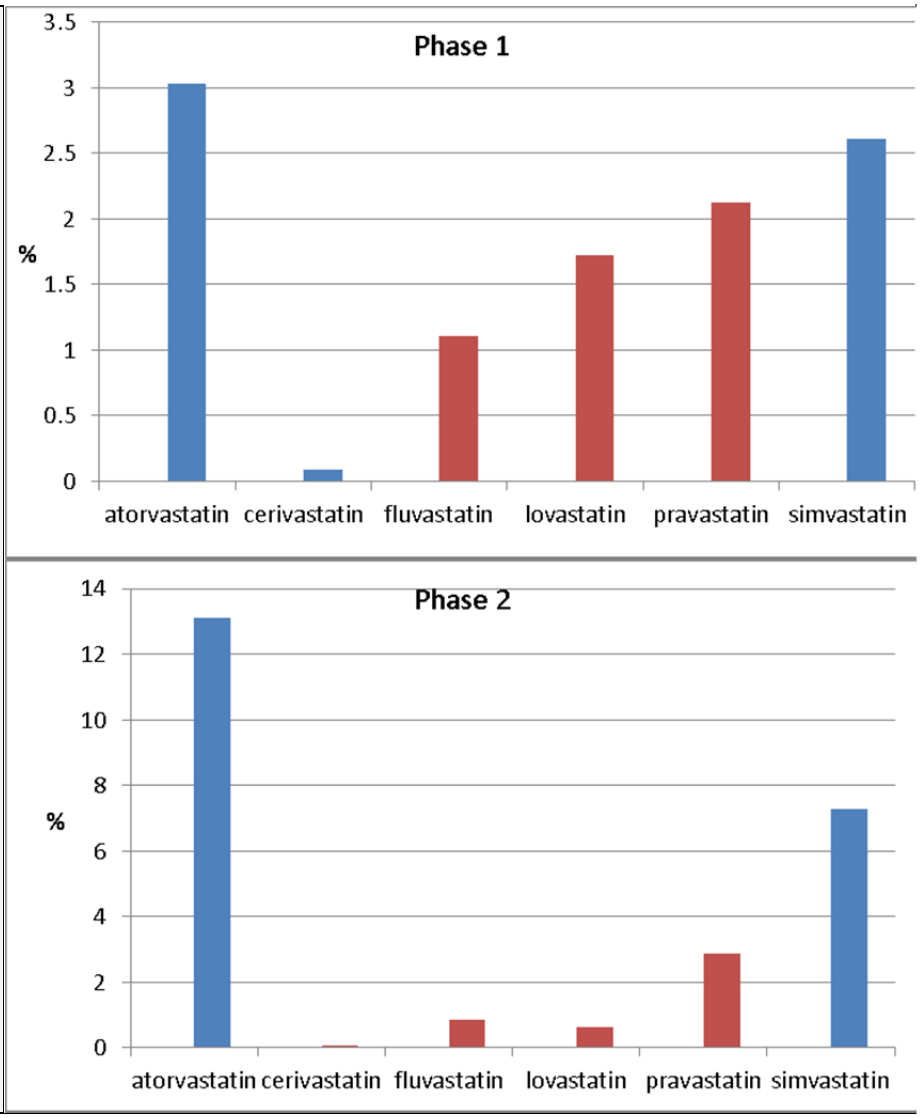
should be mentioned that, although the longitudinal analyses did not achieve significance, trends of increased odds of T2DM and statin use were observed and could suggest a temporal relationship in the African American and Non-Hispanic White populations.

*Statin Pharmacology and Theoretical Impact on Risk for Elevated Blood Glucose Levels or T2DM*

Experimental evidence would suggest a differential potency for the individual statin medications and HMG-CoA reductase inhibition. This has led to the possible link of a differential effect for the individual statins and impact on the T2DM pathway. Although the pharmacodynamic effects of these medications are similar, atorvastatin, simvastatin and cerivastatin exhibit greater inhibitory effects on HMG-CoA reductase whereas lovastatin, pravastatin and fluvastatin exhibit lower potency [Koh *et al*., 2011]. Examination of pravastatin in humans has shown enhanced insulin sensitivity and other studies have demonstrated increased risk of incident T2DM associated with atorvastatin, rosuvastatin and simvastatin [Koh *et al*., 2010; Collins *et al.*, 2003; Sever *et al.*, 2003; Coleman *et al*, 2008; Ridker *et al.*, 2008]. The different inhibitory effects of the individual statin medications upon HMG-CoA reductase need to be further explored with respect to the proposed mechanistic links of statin induced impaired glucose or T2DM such as influence upon isoprenoid synthesis, $Ca^{2+}$ release, insulin secretion, and/or insulin resistance to gain further insight into the potential effects of the distinct statin medications.

In this study, significant risk of T2DM was observed but results were not consistently significant. The primary exposure variable in this study was a composite of the individual statin medications and the evaluation was based upon a pharmacological class effect [Figure 26]. Therefore, it is uncertain if statins with lower potency could be 'masking' the effects of statins with higher potency.

**Figure 26: Percentage of Individual Statin Use in Phase 1 and 2 Across All Populations**




*Social and Environment Factors and Impact on Risk for Changes in Fasting Blood Glucose*

Social and environmental factors are on the causal pathway for changes in blood glucose levels and T2DM. For example, the analyses in this study did account for educational status (> 12 years vs ≤ 12 years) as a stable proxy for SES; however, the concept of residual confounding cannot be excluded. For example, stress as a manifestation of physical factors (i.e. injuries) or psychosocial factors (i.e., unresolved work issues, bereavement) is a known risk factor for T2DM however, these factors were not collected in this study. Access and usage of medical services within the environment

of each center was also not measured. Thus, the concept of residual confounding is particularly important in the examination of statin use across ethnicities, given the different environmental conditions surrounding each center. As such, it should be stressed that all social or environmental factors associated with the surroundings of each center were not measured but could influence the results and explain the any differences across the ethnicities included in the examination of this study.

## 3.6 Strengths and Limitations

This study had several major strengths. One is the large, multiethnic source population that provides a population base to investigate the association of statin medication use and changes in T2DM in different ethnicities within real world clinical practice settings. Although this program included cross sectional analyses giving rise to challenges in assessing temporal associations, this program also included longitudinal analyses to overcome these challenges and allowed for the examination of temporal association between the planned exposure and outcome variables. Longitudinal analyses of the exposure variable were based upon data collected at the time of participant enrollment; however, exact duration of statin medication use was not collected during the participant interview. Therefore, characterization of the onset for statin use and T2DM is not possible in this research program.

## 3.7 Conclusions

Currently, the use of statins is widespread further increased use is anticipated due to the recent ACC/AHA recommendations which now encourage use of these medications earlier in the disease process and in high risk individuals with or without evidence of atherosclerotic cardiovascular disease [Stone *et al*., 2013]. The results of this study consistently demonstrated significant changes in the odds of T2DM with the main effect of statin use across all populations, before and after adjustment, in the cross-sectional analyses. The results in the study are consistent with the results published from randomized and observational research. However, this research in the GENOA study

offers an expanded view of the potential association of statin use and T2DM across diverse ethnic populations in the context of respective regions.

Thus, the results in this study contribute to the body of evidence generated primarily in randomized clinical trials and stress the importance of research in a naturalistic setting. Although this study examined the overall pharmacological class effect of statin use and T2DM, the different inhibitory effects upon HMG-CoA reductase also need to be further explored in order to understand the relative risk of the outcome with respect to individual statin medications.

Overall, the results in the study give rise to the need for further research in order to enhance our depth of knowledge regarding the relative risk of individual statin medication use and T2DM across different ethnicities and regions as complimentary evidence to allow fully informed decisions by healthcare professionals and appropriate treatment of statin use in patients.

# Chapter 4 AIM 3: Investigation of Single Nucleotide Polymorphisms on GENOA Fasting Blood Glucose Levels and Risk of T2DM Before and After Considering Interactions with Statin Medication Use

## 4.1 Introduction

Type 2 diabetes mellitus is a chronic and progressive disease characterized by the process of β-cell dysfunction and/or worsening of peripheral insulin resistance which commonly manifests as deterioration of HbA1C, fasting blood glucose, and/or fasting insulin levels. Proposed underlying mechanisms leading to β-cell dysfunction include glucotoxicity, lipotoxicity, and/or amyloid formation, while inflammatory processes, mitochondrial dysfunction, and increases in non-esterified fatty acids are involved with pathways associated with insulin resistance [Stumvoll *et al.*, 2005]. Clinical factors such as elevated BMI, dyslipidemia, decreased HDL or medications (i.e., thiazides, β-blockers) have been identified as influencers of overall pathophysiology and are known to be accelerators of disease onset [Ferrannini *et al.*, 2004; Fonseca, 2009; Kautzky-Willer *et al.*, 2012; Sandström, 1993; Sarafidis *et al.*, 2007; Schenk *et al*., 2008].

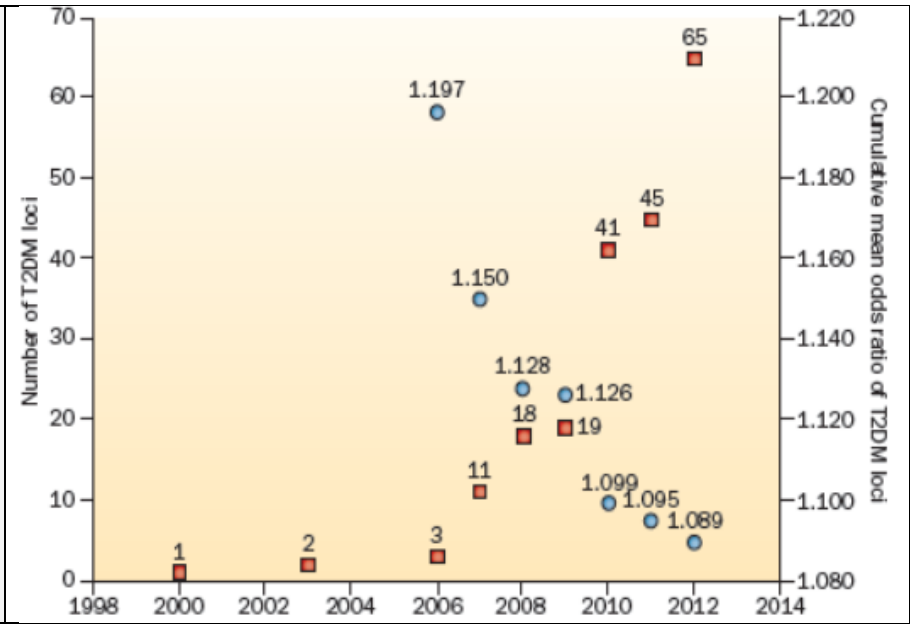
Type 2 diabetes mellitus has a strong genetic component and the initial discovery of susceptibility loci originally occurred through candidate gene studies [McCarthy & Zeggini, 2009]. Advancements in technology and research design now enable the conduct of large genome-wide association studies. Through widespread conduct of these studies, the rapid identification of multiple new T2DM loci has occurred [Hivert et al., 2014]. Of recent, 65 distinct genetic loci associated with T2DM have been confirmed Metabochip genotyping efforts as reported by the DIAbetes Genetics Replication and Meta-Analysis (DIAGRAM) consortium [Morris et al., 2012]. The T2DM component of Metabochip is comprised of 21,774 variants, including 5,057 that were "replication" SNPs capturing the strongest, independent (CEU r2< 0.2) autosomal

association signals from the GWAS meta-analysis that were conducted by the DIAGRAM Consortium. The DIAGRAM genome-wide meta-analysis includes data from 56,862 controls and 12,171 cases of European descent imputed up to 2.5 million autosomal SNPs.

With regard to physiologic indices, a link to β-cell function has been characterized for some of the T2DM loci and, for a small number of other loci, a role in the insulin resistance pathways has been established; however, in most cases, the functional role of these newly identified genetic loci have not been elucidated [Hivert *et al.*, 2014; Morris *et al.*, 2012]. Thus, the need for further genetic research is obviated to help to understand the pathophysiology and multiple pathways of this complex disease.

Although advancements in genetic research have enabled the identification of increasing number of susceptible loci over time, it should be mentioned that the effect size for the individual locus (per allele) has decreased over time [Hivert *et al.*, 2014]. This trend suggests that, the common variants with the most prominent effect size were discovered through earlier studies leading some researchers to believe that a plateau for identification of T2DM has been reached [Hivert *et al.*, 2014] [Figure 27].

**Figure 27: Cumulative Number of T2DM Loci Discovered and T2DM Risk per Risk Allele, by Year, since 2000**




Cumulative number of T2DM loci discovered and T2DM risk per risk allele, by year, since 2000. The left axis (red squares) indicates the number of replicated, genome-wide significant loci associated with T2DM identified during the period 2000-2012 in populations of European, South Asian, and East Asian ancestry. No such loci were discovered before 2000. The right axis (blue circles) indicates the cumulative mean effect size, expressed as the OR, for the index variants at loci discovered from 2006 to 2012. As the number of T2DM loci identified has increased over time, the mean OR has fallen from 1.197 for the three variants known in 2006 to 1.089 for the 65 variants known in 2012. These values equate to a fall from 19.7% increased mean OR per additional risk allele in 2006 to 8.9% in 2012.
OR: odds ratio; T2DM: type 2 diabetes mellitus.
Source: [Hivert *et al.*, 2014].

As more T2DM genetic variants became known, researchers examined the aggregation of genetic information into a genetic risk score (GRS) and the ability to prospectively predict incident cases of disease. In genomic association studies, an additive model is typical, such that a total genetic risk score is typically calculated as a sum of the number of risk alleles carried by an individual. The value for each risk allele may be weighted; however, in the case of T2DM, weighted versus non-weighted analyses has demonstrated no significant influence upon results [Hivert *et al.*, 2014]. Additive unweighted genetic models have become the mainstay when applying GRS in studies for prediction of intermediate mechanisms, such as blood glucose levels or insulin resistance, as well as T2DM [Dimas *et al.*, 2014; Morris *et al.*, 2012].

An initial prediction study, the Framingham Heart Study, examined a GRS comprised of 18 known T2DM susceptibility loci and incident disease over a 28-year follow up period.

Results from the study revealed a significant association in the number of risk alleles for T2DM compared to no T2DM (17.7 ± 2.7 risk alleles versus 17.1 ± 2.6 risk alleles; $p \leq 0.001$; possible range: 0 to 36) [Meigs *et al.*, 2008]. Similar findings were observed in two prospective studies that examined a GRS comprised of 11 susceptibility loci over a 23-year follow-up period [Lyssenko *et al.*, 2008]. An additional observation from this latter study was the enhanced performance of the prediction model during the shorter follow up period. The researchers attributed these positive results to the static nature of the genotype, which is in contrast to dynamic nature of other lifestyle factors or modulators of T2DM such as BMI, dyslipidemia, or use of medications. By increasing the number of genetic loci in a GRS, the predictability of T2DM was improved in the Framingham Offspring Population although these researchers also mentioned that the plateau for the predication model may have been reached with a GRS comprised of 65 SNPs, particularly given the relatively lower effect size contributed by the more recently identified T2DM susceptibility loci [Vassy *et al.*, 2014; Hivert *et al.*, 2014].

Replication studies have revealed that the known T2DM susceptibility loci are similar in the European and non-European populations, despite the increased genetic variability among certain populations such as African Americans. The prediction of incident T2DM using a GRS in adolescents and young adults enrolled in the CARDIA and Bogalusa studies was similar across the Non-Hispanic White and African American populations [Hivert *et al.*, 2014; Vassy *et al.*, 2012a; Vassy *et al.*, 2012b]. In addition, GRS prediction of T2DM in a European case-control study was significantly associated with T2DM in a middle-aged African American population [Cooke *et al.*, 2012].

In addition to advances in genetic research and characterization of disease, genetic factors may also contribute to the underlying susceptibility of drug induced adverse reactions. Moreover, the identification of susceptible genetic factors associated with adverse drug reactions could, in principle, enable safer use of medications on an individual basis. Thus, the fields of pharmacogenomics has emerged with emphasis upon genetic differences and impact upon complex molecular networks and biological

processes that underlie a disease and also focuses on research to understand the potential impact of a drug on these pathways in order to expand our knowledge in areas of individual clinical efficacy, assessment of dosing adjustments as well as risk for adverse reactions. Further, the reverse is also true whereby, if we can elucidate the mechanism of a drug and interaction with a genetic variant, then this could enable further insight into the mechanisms of a disease. Ultimately, the comprehension of genetic variation upon disease pathways is valuable as it helps to determine the potential interaction of a drug or, at times, creates the potential for drug candidates and therapeutic intervention to enhance efficacy or mitigate risks.

With regards to adverse drug reactions, the predominance of evidence for genetic variation has been focused in the area of pharmacokinetics whereby susceptibility loci associated with decreased drug metabolism have been identified [Phillips *et al.*, 2001]. Beyond the area of pharmacokinetics, other predisposing genetic factors have also been identified to be associated with mechanisms underlying drug-induced hypersensitivity [Hetherington *et al.*, 2002], severe cutaneous adverse reactions [Chung *et al.,* 2004], liver injury, myotoxicity and torsade de pointe [Wilke *et al.*, 2007]. Continued advancements in the field of pharmacogenomics would further enhance our ability to undertake a personalized medicine approach and optimize individual care for patients taking medications.

In 2012, FDA warned of the potential increases in blood glucose and risk of T2DM with the use of statin therapy [FDA News Release, 2012]. The primary basis for the concern stemmed from data that emerged from interventional and observational research [FDA News Release, 2012; FDA Drug Safety Communication, 2012; Ridker *et al.*, 2008].

No published studies regarding the influence of statin medication use and risk of T2DM based upon susceptibility loci have been identified. Given the widespread use of statin medications in the US, identification of genetically susceptible individuals who may be at higher risk of developing T2DM when prescribed statin medications is of public health importance. The main goal of this study is to investigate the influence of previously

identified SNPs (in T2DM genes) on GENOA fasting blood glucose levels and risk of T2DM before and after considering interactions with statin medication use. Furthermore, by aggregating previously identified risk alleles, the influences of a GRS on fasting blood glucose levels and risk of T2DM will be examined. The research will be conducted in the Non-Hispanic White as well as African American participants enrolled in the GENOA study.

## 4.2 Methods

### 4.2.1 Study Design

The FBPP, supported by the NHLBI, is a collaboration that serves to identify genetic determinants with possible influence on blood pressure, hypertension and associated target-organ damage. The FBPP offers a robust scientific resource comprised of four multicenter networks. Each network is a family based study, originally intended to well characterize genetic associations and hypertension [FBPP Investigators, 2002]. Since FBPP was established, further research has been conducted to evaluate disease states beyond the initial focus of hypertension.

To address the main goals, this study was conducted in GENOA, one of the individual networks of the FBPP. GENOA is a sibship-based study, originally designed to investigate the genetic linkage of hypertension and T2DM in sibships with at least two hypertensives diagnosed prior to age 60 years old. The GENOA study consisted of two phases: the initial phase (Phase 1) and the second follow-up phase (Phase 2).

In this study, analyses were conducted using a cross-sectional study design of participants enrolled in the Rochester and Jackson field centers during Phase 1 (1996 – 2000). The study protocol was approved by the Human Studies Review Boards of the Mayo Clinic and University of Mississippi. The study protocol was also approved by the University of Michigan Investigational Review Board.

### 4.2.2 Study Eligibility

#### 4.2.2.1 Inclusion Criteria

In the Rochester, MN field center, the Mayo Clinic diagnostic index and medical record linkage system of the Rochester Epidemiology Project were used to identify Non-Hispanic White Olmsted County residents who had the diagnosis of essential hypertension prior to age < 60 years and received care in the county during the previous 3 years [Daniels *et al.*, 2004]. In Jackson, African American sibships were recruited through hypertensive probands who had participated in the ARIC study [ARIC Investigators, 1989]. The ARIC cohort in Jackson was a probability sample of 45- to 64-year-old African American residents of that community.

In both field centers, eligible probands were asked whether they had any siblings living in the area and if so, the siblings were contacted. If at least one additional sibling reported the previous diagnosis of hypertension prior to age 60 years old, all available members of the sibship were invited to the study center. Additional criteria included the requirement for all sibships to express willingness to participate in the study through provision of informed consent.

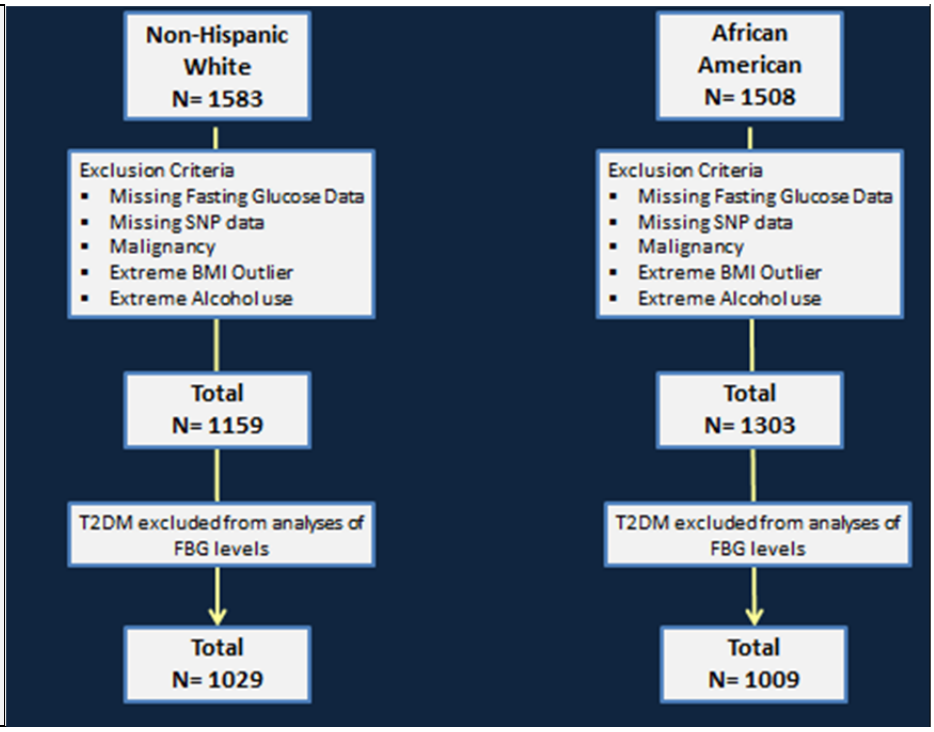
#### 4.2.2.2 Exclusion Criteria

Participants with a diagnosis of secondary hypertension, serum creatinine levels >2.5 mg/dL, alcoholism, drug abuse, pregnancy, Type 1 insulin-dependent diabetes mellitus were excluded from the GENOA study. African American participants were excluded from the Rochester field center study. One participant underwent surgical reassignment and was excluded from the GENOA study.

Additional exclusion criteria were applied for this study which included missing SNP data, missing fasting blood glucose levels, active malignancy, extreme BMI values (values > mean gender specific BMI + [4 x SD]) and extreme alcohol use (values > mean center

specific number drinks/week + [4 x SD]) [Figure 28]. Specific exclusion of T2DM was applied for the analyses for outcome of fasting blood glucose only.

**Figure 28: Study Eligibility Criteria for Phase 1 Non-Hispanic Whites and African Americans**




BMI: body mass index; SNP: single nucleotide polymorphisms.

### 4.2.3 Data Collection

Study visits were conducted in the morning after an overnight fast of at least 8 hours. Participant interview, physical exam and laboratory blood sampling were the primary methods of data collection. Participants were queried for demographic information which included gender and date of birth. Medical history was obtained through participant report of prior diagnosis by a physician, date of diagnosis and treatment of diagnosis. Height and weight were collected during physical exam. Prescription information for medications used in the past $\geq$1 month was collected from pharmacy sources provided by the participant (i.e., label on prescription vial).

### 4.2.4 Exposure Classification and Outcome Measures

EXPOSURE CLASSIFICATION

*Statin Case Definition*

The Medispan Generic Product Identifier drug dictionary was utilized to codify the first six digits that correspond to individual medications. The first six digits identified medications within the same pharmacological class. The primary exposure of interest, STATIN, represents a composite variable of individual medications within the statin pharmacological class (code 394000).

Case definition for STATIN was the participant-reported use of at least one of the following medications at the time of Phase 1 exam:

- Atorvastatin
- Lovastatin
- Pravastatin
- Cerivastatin
- Fluvastatin
- Simvastatin

*Single Nucleotide Polymorphism*

Previously identified SNPs associated with T2DM (listed in [Appendix 1]) were examined in this study [Morris *et al.*, 2012]. The variables included in the analyses were based upon individual SNPs as well as aggregated individual SNPs into a GRS that were identified in the GENOA Non-Hispanic White and African American populations (details in Section 4.3.2).

OUTCOME MEASURES

Fasting plasma glucose levels (collected in the morning) were evaluated as a continuous variable. Samples were assayed in duplicate and fasting blood glucose was measured using Elan Glucose reagent. The sensitivity range was 2–450 mg/dL, with the observed detection limit of 1.02 mg/dL and fasting is defined as ≥ 8 hours of no oral food or fluid intake.

T2DM was evaluated as a binary outcome variable using the following criteria for "DEFINITE DIABETES" as defined in the GENOA study:

a) Fasting blood glucose > 126 mg/dL and/or
b) Current use of antidiabetic medication (i.e., insulin or oral hypoglycemic agents).

## 4.3 Statistical Analysis Plan

### 4.3.1 Covariates

Pre-specified covariates selected for this study are based upon precedence of prior genetic studies (detailed rationale for each covariate provided in [Chapter 1]). Covariates were categorized as quantitative or qualitative and were based upon data collected at the time of Phase 1 examination. Covariates considered in this research analysis included BMI ($kg/m^2$) and age (years) that were treated as continuous variables and gender (M/F) that was treated as a categorical variable.

Given the sibships in the GENOA study, principal components (PCs) were used to control for population stratification. For the Non-Hispanic White population, SNPs were removed that had moderate to poor imputation quality as measured by the estimated $R^2$ between imputed and true genotypes ($R^2 < 0.8$) from Markov Chain Haplotyper (MaCH) output. Then, an unrelated sample of individuals (N=570) was obtained by randomly selecting one individual from each GENOA sibship. The first ten PCs were then calculated on the set of SNPs that were common in both Affymetrix and Illumina platforms and were also available in HapMap (N=226,619 SNPs). An additive model was assumed for the SNPs with standardization of mean equals 0 and variance equals 1. Individuals with outlier values more than 6 standard deviations on any of the 10 PCs (N=45) were removed from the analysis sample to ensure that the PCs were not capturing variation due to poor quality genotyping or single individuals with a dramatically different admixture profile than the remainder of the sample.

Similar methods were utilized in the African American population. An unrelated sample of individuals (N=644) was obtained and calculation of the first 10 PCs on the set of 207,565 SNPs. The loading matrix was then used for these PCs to calculate the PC values in the full sample. Outliers of more than 6 SDs of any of the 10 PCs were removed. Lastly, another sample of unrelated individuals was randomly selected by (N=638) and the first 10 PCs were recalculated.

This study represents an initial examination of the interaction of SNP and statin use and therefore, all analyses were conducted in Non-Hispanic Whites separately from African Americans.

### 4.3.2 Genotyping and Imputation

In GENOA, a majority of Non-Hispanic whites (N=1386) have been successfully genotyped using the protocol outlined by Affymetrix (Affymetrix, 2007) at the Mayo Clinic in Rochester, MN. There were 123 subjects whose genotypes were not successfully measured on the Affymetrix 6.0 platform, so they were re-genotyped using the Illumina Human 1M-DUO BeadChip.

Genotyping was carried out at the Mayo Clinic in Rochester, Minnesota. Preliminary SNP genotype calls were generated using the Dynamic Model (DM) algorithm [Cutler *et al*, 2001]. The final SNP genotype calls were generated by Birdseed, an algorithm designed especially for the Affymetrix® Genome-Wide Human SNP Array 6.0, and based on the robust linear model with Mahalanobis distance classifier algorithm (RLMM) [Rabbee & Speed, 2006]. To obtain the final dataset, the following quality control (QC) thresholds were applied: sample call rates >95% and SNP call rates >95%.

Similar methods were utilized to genotype African American participants (N=1263). A portion of stored blood samples for African Americans contained DNA of poor quality, and therefore, it was not possible to genotype these samples using the Affymetrix 6.0 platform. However, high quality genotyping was feasible using the Illumina® Human1M-Duo BeadChip [Illumina, 2010] for an additional 269 African Americans. An additional

92 African American participants that were identified via the ARIC study were also genotyped at the Broad Institute on the Affymetrix 6.0 platform.

Because only a portion of SNPs of interest have been genotyped, imputation methods were used to infer missing or untyped SNP genotypes based on known haplotype information from HapMap [Li *et al*, 2009]. Imputation was performed for the Non-Hispanic Whites using the single-step approach implemented in Markov Chain Haplotyper (MaCH) 1.0.16 which implements a Markov Chain based algorithm to infer possible pairs of haplotypes for each individual's genotypes up to ~2.5 million SNPs [Li *et al*, 2006]. Reference panels for the imputation in Non-Hispanic Whites was composed of the HapMap phased haplotypes (release 22) from 60 unrelated CEU samples (Utah residents with Northern and Western European ancestry) [The International HapMap Consortium, 2003]. Imputation was performed on three sub-samples of African Americans using the methods by MaCH 1.0.16 [Li *et al*, 2006]. The reference panel for African Americans was composed of the HapMap phased haplotypes (release 22) from 60 unrelated CEU and 60 unrelated YRI samples (Yoruba from Ibadan, Nigeria).

Imputation results are summarized as an "allele dosage" defined as the expected number of copies of the alphabetically higher allele at the SNP (a fractional value between 0.0 and 2.0) for each genotype. The imputation accuracy rates of MaCH have been shown to be similar to IMPUTE and higher than several other imputation methods (e.g., fast PHASE, Beagle, and PLINK) [Marchini *et al*, 2007; Pei *et al*, 2008]. Quality control thresholds were applied as follows: SNPs with imputation quality score $R^2 > 0.3$, and Hardy-Weiberg equilibrium p-value $>10^{-3}$ (tested in the GENOA unrelated sample).

*General Statistical Approach*

Demographic characteristics and intrinsic/extrinsic factors were summarized using descriptive statistics. Sample mean, median and interquartile range were examined for continuous variables of interest and, to meet model assumptions, continuous variables

were also evaluated for normality through examination of histograms and determination of skewness.

Statistical analyses were conducted independently in the Non-Hispanic White from Rochester, MN and African American from Jackson, MS populations in order to examine the interaction of susceptibility loci and statin use upon fasting blood glucose and risk of T2DM in these ethnicities.

Using SAS 9.3, univariate and multivariable linear and logistic mixed models were utilized to assess the relationship of index SNPs or GRS identified through previous GWAS studies on fasting blood glucose levels and the potential genetic-drug association of statin medication use and these genetic variants, by use of random intercept, accounting for the familial relationships within the study population. If assumptions underlying the Chi-square test were violated (i.e., expected cell counts < 1 or 80% of expected cell counts < 5), re-analyses was conducted by collapsing groups such as combining the 1-allele and 2-alleles groups or combing the no alleles and 1 allele groups.

The allele frequency represents the percentage of an allele at a given loci in a specific population. The Minor Allele Frequency (MAF) refers to the percentage of the occurrence of the least common allele at the particular locus in a given population. Morris *et al.* identified 65 index SNPs associated with T2DM [Morris *et al.*, 2012] and allele frequencies were referred to as “Risk Allele Frequency” (RAF) instead of “MAF” given that the majority of the alleles were not considered the minor allele (RAF > 50%). For these reasons, “RAF” will be the referenced term for this research.

In GENOA, the RAF was calculated separately for the Non-Hispanic White and African American populations, and represents the prevalence of the alleles in the full sample of related individuals (not just unrelated individuals). The initial step was to identify original coded alleles associated with individual SNPs in the GENOA dataset and convert these to the known risk alleles associated with T2DM SNPs [Morris *et al.*, 2012;

Appendix 1]. For allele dosages, the number of copies for a particular allele was also converted using the following scale:

| Dosage Range | Coding |
|---|---|
| [0-0.5] | 0 |
| (0.5-1.5) | 1 |
| (1.5-2) | 2 |

To calculate the RAF for each SNP in the GENOA dataset, the following equation was applied:

$$RAF = [(1 \times n1) + (2 \times n2)] / [2 \times N]$$

Where:

a) n1 = number of participants with 1 copy of the allele (heterozygotes)
b) n2 = number of participants with 2 copies of the allele (homozygotes)
c) N = number of participants

To calculate the GRS for each participant in the GENOA dataset, the following equation was applied:

$$GRS = [(1 \times n1) + (2 \times n2)]$$

Where:

- n1 = number of alleles with 1 copy of the SNP
- n2 = number of alleles with 2 copies of the SNP

*Hypothesis 1: In an analysis of Phase 1 Non-Hispanic White and African American participants, the potential interaction with statin use and index T2DM SNPs and GRS are associated with changes in fasting blood glucose levels*

[Model 3A-1] illustrates the univariate analysis and Model 3A-2 represents the multivariable analyses with adjustments for age, BMI and gender of index SNPs [listed in Appendix 1] and GRS upon fasting plasma glucose level in the Phase 1 population. To adjust for population stratification, the top principal components for the Non-Hispanic White and African American populations were also included in [Model 3A-1 and 3A-2]. The primary coefficient of interest, $\beta(SNP_{ij})$ or $\beta(GRS_{ij})$, is the overall effect of individual

SNP or GRS upon fasting blood glucose; $W_{0j}$ is the random intercept for each sibship and the error term, $\varepsilon_{ij}$, is the residual variation unexplained by the model.

| | |
|---|---|
| Model 3A-1: | ▪ $Y_{ij} = \beta_0 + \beta_1(SNP_{ij}) + \beta_2(PC1_i) + \beta_3(PC2_i) + \beta_4(PC3_i) + \beta_5(PC4_i) + W_{0j} + \varepsilon_{ij}$, for participant *i* in sibship j<br>▪ $Y_{ij} = \beta_0 + \beta_1(GRS_{ij}) + W_{0j} + \varepsilon_{ij}$, for participant *i* in sibship j |
| Model 3A-2: | ▪ $Y_{ij} = \beta_0 + \beta_1(SNP_{ij}) + \beta_2(age_{ij}) + \beta_3(BMI_{ij}) + \beta_4(gender_{ij}) + \beta_5(PC1_i) + \beta_6(PC2_i) + \beta_7(PC3_i) + \beta_8(PC4_i) + W_{0j} + \varepsilon_{ij}$, for participant *i* in sibship j<br>▪ $Y_{ij} = \beta_0 + \beta_1(GRS_{ij}) + \beta_2(age_{ij}) + \beta_3(BMI_{ij}) + \beta_4(gender_{ij}) + W_{0j} + \varepsilon_{ij}$, for participant *i* in sibship j |

[Model 3B] includes an additional covariate, STATIN x SNP or STATIN x GRS, to examine the potential association of the interaction between statin use and pre-established SNPs and fasting blood glucose. In [Model 3B], $variables_{ij}$ are represented by participant i in sibship j and are based upon data collected during Phase 1 for the analyses; $Y_{ij}$ is the value of fasting plasma glucose level and $W_{0j}$ is the random intercept for each sibship. To adjust for population stratification, the top principal components for the Non-Hispanic White and African American populations were also included in [Model 3B-1 and 3B-2]. The error term, $\varepsilon_{ij}$, is the residual variation unexplained by the model. The primary coefficient of interest, $\beta(statin_{ij} \times SNP_{ij})$ or $\beta(statin_{ij} \times GRS_{ij})$ is the overall effect of the interaction of SNP and statin use upon fasting blood glucose.

| | |
|---|---|
| Model 3B: | ▪ $Y_{ij} = \beta_0 + \beta_1(SNP_{ij}) + \beta_2(statin_{ij}) + \beta_3(statin_{ij} \times SNP_{ij}) + \beta_4(PC1_i) + \beta_5(PC2_i) + \beta_6(PC3_i) + \beta_7(PC4_i) + W_{0j} + \varepsilon_{ij}$, for participant *i* in sibship j<br>▪ $Y_{ij} = \beta_0 + \beta_1(GRS_{ij}) + \beta_2(statin_{ij}) + \beta_3(statin_{ij} \times SNP_{ij}) + \beta_4(PC1_i) + \beta_5(PC2_i) + \beta_6(PC3_i) + \beta_7(PC4_i) + W_{0j} + \varepsilon_{ij}$, for participant *i* in sibship j |

[Model 3C] also includes the covariate, STATIN x SNP or STATIN x GRS, to examine the potential interaction of statin use and known T2DM SNPs or GRS upon fasting plasma glucose level, while adjusting for covariates such as age, BMI and gender. To adjust for population stratification, the top principal components for the Non-Hispanic White and African American populations were also included in [Model 3C].

| | |
|---|---|
| Model 3C: | ▪ $Y_{ij} = \beta_0 + \beta_1(SNP_{ij}) + \beta_2(statin_{ij}) + \beta_3(gender_{ij}) + \beta_4(Age_{ij}) + \beta_5(BMI_{ij}) +$<br>▪ $\beta_6(statin_{ij} \times SNP_{ij}) + \beta_7(PC1_i) + \beta_8(PC2_i) + \beta_9(PC3_i) + \beta_{10}(PC4_i) + \ldots. + W_{0j} + \varepsilon_{ij}$, for participant *i* in sibship j<br>▪ $Y_{ij} = \beta_0 + \beta_1(GRS_{ij}) + \beta_2(statin_{ij}) + \beta_3(gender_{ij}) + \beta_4(Age_{ij}) + \beta_5(BMI_{ij}) +$ $\beta_6(statin_{ij} \times SNP_{ij}) + \beta_7(PC1_i) + \beta_8(PC2_i) + \beta_9(PC3_i) + \beta_{10}(PC4_i) + \ldots. + W_{0j} + \varepsilon_{ij}$, for participant *i* in sibship j |

In [Model 3C], variables$_{ij}$ are represented by participant i in sibship j and are based upon data collected during Phase 1 for the analyses; $Y_{ij}$ is the value of fasting plasma glucose level or fasting insulin level and $W_{0j}$ is the random intercept for each sibship. The error term, $\varepsilon_{ij}$, is the residual variation unexplained by the model. The primary coefficient of interest, $\beta(statin_{ij} \times SNP_{ij})$ or $\beta(statin_{ij} \times GRS_{ij})$, is the overall effect of potential interaction of statin use with SNP and fasting blood glucose level, adjusting for the random and fixed effects of the other covariates.

*Hypothesis 2: In an analysis of Phase 1 Non-Hispanic White and African American participants, the potential interaction with statin use and index SNPs and GRS are associated with T2DM*

Univariate and multivariable logistic mixed models will be utilized to assess the relationship of index SNPs or GRS in T2DM genes identified through previous GWAS studies for the odds of T2DM and the potential genetic-drug association of statin medication use and these genetic variants.

[Model 3D-1] illustrates the univariate analysis and Model 3D-2 represents the multivariable analyses with adjustments for age, BMI and gender of index SNPs or GRS [Appendix 1] and T2DM in the Phase 1 population; $W_{0j}$ is the random intercept for each sibship and the error term, $\varepsilon_{ij}$, is the residual variation unexplained by the model. To adjust for population stratification, the top principal components for the Non-Hispanic White and African American populations were also included in [Model 3D-1 and 3D-2].

| | |
|---|---|
| Model 3D-1: | ▪ Logit $DM_{ij} = \beta_0 + \beta_1(SNP_{ij}) + W_{0j} + \varepsilon_{ij}$, for participant *i* in sibship j<br>▪ Logit $DM_{ij} = \beta_0 + \beta_1(GRS_{ij}) + W_{0j} + \varepsilon_{ij}$, for participant *i* in sibship j |

| | |
|---|---|
| Model 3D-2: | ▪ Logit $DM_{ij} = \beta_0 + \beta_1(SNP_{ij}) + \beta_2(age_{ij}) + \beta_3(BMI_{ij}) + \beta_4(gender_{ij}) + \beta_5(PC1_i) + \beta_6(PC2_i) + \beta_7(PC3_i) + \beta_8(PC4_i) + W_{0j} + \varepsilon_{ij}$, for participant *i* in sibship j<br>▪ Logit $DM_{ij} = \beta_0 + \beta_1(GRS_{ij}) + \beta_2(age_{ij}) + \beta_3(BMI_{ij}) + \beta_4(gender_{ij}) + \beta_5(PC1_i) + \beta_6(PC2_i) + \beta_7(PC3_i) + \beta_8(PC4_i) + W_{0j} + \varepsilon_{ij}$, for participant *i* in sibship j |

[Model 3E] includes an additional covariate, STATIN x SNP or STATIN x GRS, to examine the potential interaction of statin use and pre-established SNPs or GRS and influence on the odds of T2DM. In Model 3E, $variables_{ij}$ are represented by participant i in sibship j and are based upon data collected during Phase 1 for the analyses; Logit $DM_{ij}$ is interpreted as the odds of T2DM and $W_{0j}$ is the random intercept for each sibship. The error term, $\varepsilon_{ij}$, is the residual variation unexplained by the model. The primary coefficient of interest, $\beta(statin_{ij} \times SNP_{ij})$ or $\beta(statin_{ij} \times GRS_{ij})$, is the overall estimated effect of the interaction of SNP or GRS and statin use on the odds of T2DM.

| | |
|---|---|
| Model 3E: | ▪ Logit $DM_{ij} = \beta_0 + \beta_1(SNP_{ij}) + \beta_2(statin_{ij}) + \beta_3(statin_{ij} \times SNP_{ij}) + \beta_4(PC1_i) + \beta_5(PC2_i) + \beta_6(PC3_i) + \beta_7(PC4_i) + W_{0j} + \varepsilon_{ij}$, for participant *i* in sibship j<br>▪ Logit $DM_{ij} = \beta_0 + \beta_1(GRS_{ij}) + \beta_2(statin_{ij}) + \beta_3(statin_{ij} \times GRS_{ij}) + \beta_4(PC1_i) + \beta_5(PC2_i) + \beta_6(PC3_i) + \beta_7(PC4_i) + W_{0j} + \varepsilon_{ij}$, for participant *i* in sibship j |

[Model 3F] includes the covariate, STATIN x SNP or STATIN x GRS, to examine the potential interaction of statin use and risk of T2DM, while adjusting for covariates such as age, BMI and gender. To adjust for population stratification, the top principal components were included in [Model 3F].

| | |
|---|---|
| Model 3F: | ▪ Logit $DM_{ij} = \beta_0 + \beta_1(SNP_{ij}) + \beta_2(statin_{ij}) + \beta_3(gender_{ij}) + \beta_4(Age_{ij}) + \beta_5(BMI_{ij}) + \beta_6(statin_{ij} \times SNP_{ij}) + \beta_7(PC1_i) + \beta_8(PC2_i) + \beta_9(PC3_i) + \beta_{10}(PC4_i) + \ldots. + W_{0j} + \varepsilon_{ij}$, for participant *i* in sibship j<br>▪ Logit $DM_{ij} = \beta_0 + \beta_1(GRS_{ij}) + \beta_2(statin_{ij}) + \beta_3(gender_{ij}) + \beta_4(Age_{ij}) + \beta_5(BMI_{ij}) + \beta_6(statin_{ij} \times GRS_{ij}) + \beta_7(PC1_i) + \beta_8(PC2_i) + \beta_9(PC3_i) + \beta_{10}(PC4_i) + \ldots. + W_{0j} + \varepsilon_{ij}$, for participant *i* in sibship j |

In the multivariable mixed logistic models, $variables_{ij}$, are represented by participant i in sibship j and are based upon data collected during Phase 1 for the respective analyses. The outcome, Logit $DM_{ij}$, can be interpreted as the odds of T2DM and $W_{0j}$ is the random effect for each sibship. The primary coefficient of interest, $\beta(statin_{ij} \times SNP_{ij})$ or $\beta(statin_{ij} \times$

$GRS_{ij}$), is the overall estimated effect of the interaction of statin use and SNP on the odds of T2DM, adjusting for the random and fixed effects of the other covariates.

Multiple Hypothesis Testing

The False Discovery Rate (FDR) was used as the method to correct for testing of multiple individual SNPs. These procedures are designed to control the proportion of false positives (incorrect rejection of the null hypothesis). The percentage of false positives is proportional to the number of tests performed and the critical significance level. In this research, FDR was used as the multiple correction method due to the fact that our hypotheses are not independent and other methods (i.e, Bonferroni) may be too conservative. P-values from each test in each hypothesis were calculated and subsequently ranked from smallest to largest, with $p_i$ being the p-value corresponding to the $i^{th}$ hypothesis ($h_i$, i=1…m). Each p-value was then multiplied by the quantity of total number of tests that was divided by the specific test number, $h_i$. An FDR threshold ($\alpha$ = 5%) was used such that one out of every five significant results will be expected to be a false positive.

## 4.4 Results

### 4.4.1 Demographics, Intrinsic and Extrinsic Factors

In the initial phase of the GENOA study (1996-2001), a total of 2462 participants met the inclusion and exclusion criteria for this study of which 1159 were Non-Hispanic White from Rochester, MN and 1303 were African American from Jackson, MS with available genetic data. Of the total number of Phase 1 participants, 54% and 73% were female in the Non-Hispanic White and African American populations, respectively. In Phase 1, the mean age of Non-Hispanic White and African American participants was 56.5 years and 58.9 years, respectively. Of the total number of participants recruited during Phase 1, the highest use of statin medications was reported in the Non-Hispanic White population (16.3%) and lowest in the African American population (5.5%). [Table 17] summarizes demographic, intrinsic and extrinsic factors as well as mean fasting glucose

levels and percent of T2DM for these individual populations in Phase 1 of the study. Mean, median, and interquartile ranges are provided in [Appendix 2 and Appendix 3].

**Table 17: Demographics, Intrinsic and Extrinsic Factors across Centers in Phase 1**

| | | Total N=2462 | |
|---|---|---|---|
| | | **Non-Hispanic White Rochester** | **African American Jackson** |
| **PHASE 1** | | N=1303 | N=1159 |
| Gender | % Female | 54.0 | 73.0 |
| | % Male | 46.0 | 27.0 |
| Age, years | Mean (SD) | 56.47 (10.8) | 58.91 (9.7) |
| BMI | $kg/m^2$ | 30.28 (6.1) | 31.25 (6.7) |
| Statin use | % | 16.29 | 5.53 |
| Glucose, mg/dL | Mean (SD) | 100.20 (28.5) | 111.24 (45.3) |
| T2DM | % | 11.29 | 22.56 |

BMI: body mass index; T2DM: type 2 diabetes mellitus; SD: standard deviation.
Note: Based upon number of participants with genetic data.

When excluding T2DM from the analyses for fasting blood glucose levels (n = 1029 Non-Hispanic Whites; n=1009 African Americans), the demographics were similar. Of the total number of Phase 1 participants, 54% and 72% were female in the Non-Hispanic White and African American populations, respectively. In Phase 1, the mean ages of Non-Hispanic White and African American participants were 55.9 years and 58.4 years, respectively. Of the total number of participants recruited during Phase 1, the highest use of statin medications was reported in the Non-Hispanic White population (15%) and lower in the African American population (4%). The mean BMI was 29.9 and 30.56 in the Non-Hispanic White and African American populations, respectively. Mean fasting glucose levels were lower in both Non-Hispanic White (mean 92.45 mg/dL) and African American (mean 94.89 mg/dL) populations.

Results from the analyses of SNP, SNP and statin medication and GRS, before and after adjustment, for fasting blood glucose and T2DM are described below for the Non-Hispanic White and African American populations.

### 4.4.2 Non-Hispanic Whites

Of the 65 known T2DM SNPs, 64 SNP were included in the analysis. One SNP, rs2075423, was not identified in the GENOA Non-Hispanic White population.

The RAF for remaining 64 SNPs ranged from 0.023 (lowest frequency) to 0.98 (highest frequency) and, for each individual SNP, the frequencies were generally comparable to the known RAF reported by Morris *et al.* [Morris *et al.*, 2012, Appendix 1, Appendix 12].

#### 4.4.2.1 SNP and Fasting Blood Glucose in Non-Hispanic Whites, Before and After Adjustment

Generally, the regression results for testing the association between individual index SNPs and fasting blood glucose, unadjusted and adjusted, were not significant after correction for multiple testing ([Appendix 13 and Appendix 14]; $p \geq 0.05$). [Table 18] provides results for SNPs with p-values < 0.05 before correction for multiple testing; however, after correction for multiple testing, these interactions were considered non-significant ($p \geq 0.05$).

**Table 18: Analyses of SNP and Fasting Blood Glucose in Non-Hispanic Whites**

| SNP | Estimate | Standard Error | Probability | FDR[≠] |
|---|---|---|---|---|
| rs10278336 unadj* | 1.27464 | 0.453078 | 0.005071 | 0.324568 |
| rs8108269 unadj* | 1.257129 | 0.512379 | 0.014442 | 0.462159 |
| rs11717195 unadj* | 1.076712 | 0.519397 | 0.038617 | 0.823821 |
| rs11717195 adj† | 1.352161 | 0.465898 | 0.003848 | 0.2463 |
| rs10278336 adj† | 1.100832 | 0.409075 | 0.007333 | 0.234659 |
| rs10830963 adj† | 1.096046 | 0.429352 | 0.010947 | 0.233529 |
| rs459193 adj† | 1.065871 | 0.454578 | 0.019383 | 0.310132 |
| rs10811661 adj† | 1.137001 | 0.496867 | 0.022484 | 0.287798 |
| rs780094 adj† | 0.848465 | 0.408597 | 0.038293 | 0.408459 |

Adjusted for age, gender, and BMI, and top 4 principal components.
*unadj=unadjusted; †adj=adjusted. BMI: body mass index; FDR: false discovery rate; SNP: single nucleotide polymorphism. [≠]FDR was estimated separately for the adjusted and unadjusted analyses

#### 4.4.2.2 Adjusted SNP and Statin Interaction and Fasting Blood Glucose in Non-Hispanic Whites

Generally, regression results for testing the association between the pairwise interactions for SNP and statin, after adjustment, were not significant ([Appendix 15]; $p \geq 0.05$). [Table 19] provides results for those statin and individual SNP interactions with p-values < 0.05 before correction for multiple testing; however, after correction for multiple testing, these interactions were considered non-significant.

**Table 19: Statin x SNP and Fasting Blood Glucose, After Adjustment in Non-Hispanic Whites**

| Statin x SNP | Estimate | Standard Error | Probability | FDR[≠] |
|---|---|---|---|---|
| statin*rs2261181 | -3.56909 | 1.779987 | 0.045426 | 2.907245 |
| statin*rs8108269 | 2.365109 | 1.22406 | 0.053836 | 1.72274 |

Adjustment for age, gender, BMI, and top 4 principal components.
BMI: body mass index; FDR: false discovery rate; SNP: single nucleotide polymorphism. [≠]FDR was estimated separately for the adjusted and unadjusted analyses

#### 4.4.2.3 Genetic Risk Score, Statin-by-GRS Interaction, and Fasting Blood Glucose in Non-Hispanic Whites, Before and After Adjustment

In the Non-Hispanic White population, the GRS was comprised of 64 SNPs (median 68; maximum 82). The association of increasing GRS and fasting blood glucose achieved statistical significance in the Non-Hispanic White population, before and after adjustment. The interaction of increasing GRS and statin use as compared to non-statin use, before and after adjustment, did not achieve significance ($p \geq 0.05$) [Table 20].

**Table 20: GRS, Interaction of Statin x GRS, and Fasting Blood Glucose, Before and After Adjustment in Non-Hispanic Whites**

| GRS Comprised of 64 SNPs | Estimate | Standard Error | Probability |
|---|---|---|---|
| GRS unadj* | 0.17 | 0.06 | 0.005 |
| GRS adj† | 0.23 | 0.05 | <0.0001 |
| GRS x Statin adj† | 0.05 | 0.16 | 0.7448 |

Adjustment for age, gender, BMI, and top 4 principal components.
*unadj=unadjusted; †adj=adjusted.
BMI: body mass index; GRS: genetic risk score; SNP: single nucleotide polymorphism.

#### 4.4.2.4 SNP and T2DM in Non-Hispanic Whites, Before and After Adjustment

Regression results for testing the association between SNP and T2DM were not significant, before and after adjustment and after correction for multiple testing ([Appendix 16]; $p \geq 0.05$).

#### 4.4.2.5 SNP and Statin Interaction and T2DM in Non-Hispanic Whites

Regression results for testing the association between unadjusted pairwise SNP and statin interaction were not significant after correction for multiple testing ([Appendix 17]; $p \geq 0.05$).

#### 4.4.2.6 Adjusted SNP and Statin Interaction and T2DM in Non-Hispanic Whites

Regression results for testing the association between pairwise interactions of SNP and statin, after adjustment, were not significant after correction for multiple testing ([Appendix 18]; $p \geq 0.05$).

#### 4.4.2.7 Genetic Risk Score, Statin-by-GRS Interaction, and T2DM in Non-Hispanic Whites, Before and After Adjustment

Regression results for testing the association of increasing GRS comprised of 64 SNPs (median 68; maximum 82) and odds of T2DM achieved statistical significance in the Non-Hispanic White population, before and after adjustment (marginal after adjustment). The interaction of increasing GRS and statin use as compared to no statin use also achieved marginal significance before and after adjustment [Table 21].

**Table 21: SNP, Interaction of Statin x SNP and T2DM, Before and After Adjustment in Non-Hispanic Whites**

| GRS Comprised of 64 SNPs | Odds | 95% CI |
|---|---|---|
| GRS unadj* | 1.11 | 1.043, 1.191 |
| GRS adj† | 1.13 | 1.054, 1.208 |
| GRS x Statin | 1.17 | 1.007, 1.346 |
| Adjusted GRS x Statin† | 1.16 | 0.999, 1.345 |

Adjustment for age, gender, BMI, and top 4 principal components.
*unadj=unadjusted; †adj=adjusted.
BMI: body mass index; CI: confidence interval; GRS: genetic risk score; SNP: single nucleotide polymorphism.

### 4.4.3 African Americans

Of the 65 known T2DM SNPs, 57 SNPs were identified in the GENOA African American population.

The RAF for the remaining 57 SNPs ranged from 0.06 (lowest frequency) to 0.96 (highest frequency) and, for each individual SNP, the frequencies were generally comparable to the known RAF reported by Morris *et al.* [Morris *et al.*, 2012; Appendix 1; Appendix 12].

#### 4.4.3.1 SNP and Fasting Blood Glucose in African Americans, Before and After Adjustment

Regression results for testing the association between SNP and fasting blood glucose, unadjusted and adjusted, were generally not significant ([Appendix 19 and Appendix 20]; $p \geq 0.05$); [Table 22] provides estimates for the unadjusted analyses that were considered statistically significant before correction for multiple testing however, after correction for multiple testing, these results were not considered statistically significant for these individual SNPs.

**Table 22: SNP and Fasting Blood Glucose in African Americans**

| SNP | Estimate | Standard Error | Probability | FDR≠ |
|---|---|---|---|---|
| rs7903146 unadj* | 1.442185 | 0.598462 | 0.016331077 | 0.930871 |
| rs10830963 unadj* | 2.474778 | 1.077761 | 0.022087908 | 0.629505 |
| rs10758593 unadj* | -1.09344 | 0.531994 | 0.040377261 | 0.767168 |
| rs12497268 unadj* | -2.00465 | 1.004414 | 0.046509339 | 0.662758 |
| rs7903146 adj† | 1.834206 | 0.571635 | 0.0014239 | 0.081162 |
| rs10830963 adj† | 2.507529 | 1.055683 | 0.017933966 | 0.511118 |
| rs10758593 adj† | -0.99442 | 0.51039 | 0.05196392 | 0.987314 |

Adjustment for age, gender, BMI, and top 10 principal components.
*unadj=unadjusted; †adjusted.
BMI: body mass index; CI: confidence interval; FDR: false discovery rate; SNP: single nucleotide polymorphism.
≠FDR was estimated separately for the adjusted and unadjusted analyses

#### 4.4.3.2 SNP and Statin Interaction and Fasting Blood Glucose, Before and After Adjustment in African Americans

Generally, regression results for testing the association between pairwise interactions for statin and SNP, after adjustment, were not significant ([Appendix 21] $p \geq 0.05$]. [Table 23] provides results for those SNP and statin interactions that achieved significance before correction for multiple testing however, after correction these results were no longer considered statistically significant.

**Table 23: Statin-By-SNP Interactions, and Fasting Blood Glucose After Adjustment and After Correction for Multiple Testing**

| SNP | Estimate | Standard Error | Probability | FDR ≠ |
|---|---|---|---|---|
| rs2334499*statin | 10.80729 | 4.501341 | 0.016741 | 0.95426 |

Adjustment for age, gender, BMI, and top 10 principal components.
*unadj=unadjusted; †adjusted.
BMI: body mass index; CI: confidence interval; FDR: false discovery rate; SNP: single nucleotide polymorphism. ≠FDR was estimated separately for the adjusted and unadjusted analyses

#### 4.4.3.3 Genetic Risk Score and Fasting Blood Glucose in African Americans, Before and After Adjustment

The association of increasing GRS which was comprised of 57 SNPs (median 58; maximum 71) and fasting blood glucose did not achieve statistical significance in the African American population, before and after adjustment. The interaction of increasing

GRS and statin use as compared to non-statin use, before and after adjustment, did not achieve significance ($p \geq 0.05$) [Table 24].

**Table 24: GRS, Interaction of Statin x GRS and Fasting Blood Glucose, Before and After Adjustment in African Americans**

| GRS comprised of 57 SNPs | Estimate | Standard Error | Probability |
|---|---|---|---|
| GRS unadj* | -0.0577 | 0.08613 | 0.5035 |
| GRS adj† | -0.0425 | 0.08227 | 0.6055 |
| GRS x Statin adj† | 0.1159 | 0.424 | 0.7846 |

Adjustment for age, gender, BMI, and top 10 principal components.
*unad=unadjusted; †adj=adjusted.
BMI: body mass index; GRS: genetic risk score; SNP: single nucleotide polymorphism.

#### 4.4.3.4 SNP and T2DM in African Americans, Before and After Adjustment

The regression results for testing the association between SNP and T2DM were not significant, before and after adjustment and after correction for multiple testing ([Appendix 22]; $p \geq 0.05$).

#### 4.4.3.5 SNP and Statin Interaction and T2DM in African Americans

The unadjusted regression results for testing the association between SNP and statin interaction were not considered statistically significant, before or after correction for multiple testing ([Appendix 23]; $p \geq 0.05$).

#### 4.4.3.6 Adjusted SNP and Statin Interaction and T2DM in African Americans

The regression results for testing the association between SNP and statin interaction , after adjustment, were not considered statistically significant, before or after correction for multiple testing ([Appendix 24]; $p \geq 0.05$).

#### 4.4.3.7 Genetic Risk Score, Statin-By-GRS Interaction, and T2DM in African Americans, Before and After Adjustment

The association of increasing GRS which was comprised of 57 SNPs (median 51; maximum 78) and odds of T2DM was marginally significant in the African American

population, before and after adjustment. The interaction of increasing GRS and statin use as compared to non-statin use, before and after adjustment, did not achieve significance [Table 25].

**Table 25: Results of SNP, Interaction of Statin x SNP and Odds of T2DM, Before and After Adjustment in African Americans**

| GRS comprised of 57 SNPs | Odds | 95% CI |
|---|---|---|
| GRS unadj* | 1.04 | 0.98,1.09 |
| GRS adj† | 1.08 | 1.05,1.10 |
| GRS x Statin unadj* | 1.021 | 0.86, 1.22 |
| GRS x Statin adj† | 0.994 | 0.83, 1.19 |

Adjustment for age, gender, BMI, and top 10 principal components.
*unadj=unadjusted †adj=adjusted.
BMI: body mass index; CI: confidence interval; GRS: genetic risk score; SNP: single nucleotide polymorphism; T2DM: type 2 diabetes mellitus.

[Table 26] provides a summary of results from the univariate analyses of SNPs, interactions of statin and SNP and GRS for fasting blood glucose and T2DM in the Non-Hispanic White and African American populations.

**Table 26: Summary of Results for SNP, Statin x SNP, GRS and GRS x Statin, Before and After Adjustment, in the African American Population**

| | SNP | | Statin x SNP | | GRS | | Statin x GRS | |
|---|---|---|---|---|---|---|---|---|
| | Unadj | Adj | Unadj | Adj | Unadj | Adj | Adj | |
| **FASTING BLOOD GLUCOSE** | | | | | | | | |
| Non-Hispanic White | NS | NS | NS | NS | FBG=0.17 p=0.005 | FBG=0.23 p < 0.001 | NS | |
| African American | NS | NS | NS | NS | NS | NS | NS | |
| **T2DM** | | | | | | | **Unadj** | **Adj** |
| Non-Hispanic White | NS | NS | NS | NS | 1.11 (1.04, 1.19) | 1.13 (1.04, 1.19) | 1.17 (1.05, 1.21) | 1.19 (0.99, 1.35) |
| African American | NS | NS | NS | NS | 1.04 (0.98, 1.09) | 1.08 (1.05, 1.10) | NS | NS |

Adjustment for age, gender, BMI, and top 4 principal components for Non-Hispanic White population and top 10 principal components for African Americans.
Adj: adjusted; FBG: fasting blood glucose; GRS: genetic risk score; NS: not significant; SNP: single nucleotide polymorphism; T2DM: type 2 diabetes mellitus; Unadj: unadjusted.
p-values represent probabilities after correction for multiple testing

## 4.5 Discussion

Morris *et al.* conducted large-scale genotyping to extend the discovery of genetic loci involved in the pathophysiology of T2DM to identification of 65 distinct variants. The RAF reported for these variants reported by Morris *et al.* were generally comparable to the RAF observed in the GENOA Non-Hispanic White population as well as the RAF observed in the GENOA African American population [Morris *et al.*, 2012]. These observations are not unanticipated given that prior studies have replicated these T2DM genetic loci in European and non-European populations, including African Americans [Hivert *et al.*, 2014]. Furthermore, it should be mentioned that, for the majority of T2DM SNPs in GENOA and other published studies, the RAF was >50% and therefore not necessarily considered the "minor" allele. This observation raises the concept of the 'thrifty genotype,' a theory that suggests the continued presence of ancestral genetic traits that were speculated to play a role in processes related to adipose storage. More specifically, these genetic traits were theorized to promote a survival advantage in our ancestors that were subject to periods of nutritional adversity or famine. Years later, or in the present time, as most populations reside in an environment of nutritional abundance, the role of these earlier genetic determinants may have evolved from being advantageous to detrimental as they may now contribute to the emergence of obesity and comorbid conditions such as T2DM [Marshall, 2005; Neel, 1999; Baschetti, 1998; Ong & Dunger, 2000]. If, in fact, these ancestral genes were transmitted through the generations then, the continued presence may explain the relatively high RAF for T2DM susceptibility loci and may also be contributory to the increasing rates of T2DM.

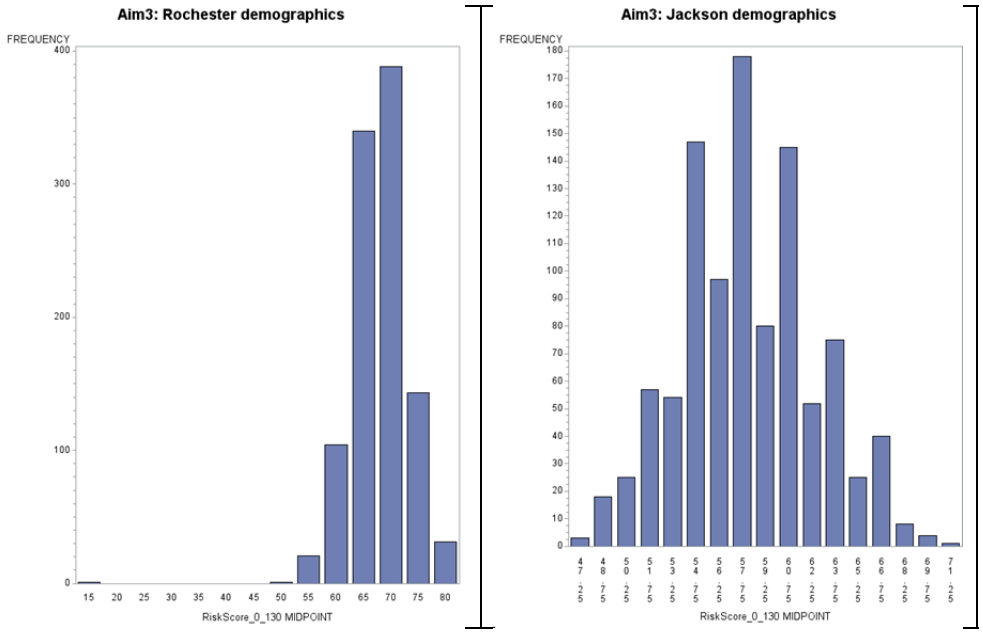
In the Non-Hispanic White population, the unadjusted and adjusted GRS was associated with increased fasting blood glucose and the odds of T2DM. The GRS results in the GENOA Non-Hispanic White population are consistent with prior studies and therefore not unanticipated [Hivert *et al.*, 2014]. Furthermore, the unadjusted and adjusted results for the interaction of statin use and GRS were significant for the odds of T2DM.

In African American participants, the GRS was not associated with changes in fasting blood glucose levels, before or after adjustment; however, the GRS was predictive of T2DM of which is also consistent with prior studies [Hivert *et al.*, 2014]. The interaction of the GRS and statin medication use was not considered significant for changes in fasting blood glucose or the odds of T2DM, before or after adjustment in the African American population.

In the GENOA study, the majority of known T2DM SNPs were identified; however, the number of SNPs in the Non-Hispanic White (64 SNPs) and African American (57 SNPs) was different than the number of SNPs in both populations as reported in published literature (65 SNPs; [Morris et al, 2012]). The discrepancy could be attributed to the difference in sample size of the GENOA population to detect a particular SNP (i.e. with very low RAF) or heterogeneity in populations studied (cases and controls in the DIAGRAM study were of European descent).

The number of SNPs in the aggregated GRS could explain the difference in results observed across these populations. In the Non-Hispanic White population, median GRS was 68 (maximum GRS was 82) whereas in the African American population, the median GRS was 58 (maximum GRS was 71) [Figure 29]. Thus, the relatively lower score and wider distribution of the GRS in the African American population may have influenced these different results.

**Figure 29: Distribution of GRS in the Non-Hispanic White (Rochester) and African American (Jackson) Populations**




GRS: genetic risk score;

Significant GRS for T2DM in the Non-Hispanic White population (unadjusted 1.11; adjusted 1.13) was consistent with the significant results observed with GRS and fasting blood glucose and therefore, not unanticipated. Interestingly, the statin and GRS interaction was also significant which was in contrast to the results of the individual SNP and statin interactions. Given that the GRS is comprised of a variety of SNPs that influence a multitude of T2DM biologic processes, further research is required to elucidate the potential pathways by which statins could influence the risk of T2DM in genetically susceptible Non-Hispanic White individuals. Furthermore, herein lies an example of the potential for gene and drug interactions that could expand our knowledge upon the pathogenesis of complex diseases such as T2DM.

In general, researchers have been able to categorize the function of T2DM SNPs into broad categories of β-cell dysfunction and/or insulin resistance however, details of SNP influence on specific biologic pathways such as those involving glucotoxicity or lipotoxicity that are associated with β-cell dysfunction or increased non-esterified fatty acids, inflammatory mediators or mitochondrial dysfunction associated with insulin resistance are still not clear. For those T2DM SNPs where mechanisms have been elucidated, the majority have been implicated in the pathways associated with β-cell

dysfunction and fewer have been linked to pathways of insulin resistance [Walford *et al.*, 2014].

For example, the role of rs243088 in T2DM, located near BCL11A (on chromosome 2), has not been specifically described however, genetic variation in BCL11A in Europeans and African Americans appears to mediate β-cell function [Simonis-Bik *et al.*, 2010]. More specifically, BCL11A methylation is the suggested pathway for T2DM as demonstrated by Tang *et al.* [Tang *et al.*, 2014]. The role of DNA methylation and factors such as malnutrition, obesity, inflammation or oxidative stress that may influence DNA methylation have emerged as molecular mechanisms underlying β-cell dysfunction and contributors to the increasing rate of T2DM [Gilbert & Liu, 2012]. In addition, Tang *et al.* demonstrated that BCL11A association with T2DM may also be mediated through TG metabolism [Tang *et al.*, 2014]. Thus, given the prior evidence of BCL11A and pathways related to TG metabolism, the effects of statin use and the odds of T2DM could be mediated through the effects upon TG metabolism and statin use. More specifically, if BCL11A variations and elevated TG levels are linked with T2DM, then statin use may interact by influencing fasting blood glucose through the effects of decreasing TG levels. The effect of statin use and decreasing TG levels has been shown to be directly related to the relative potency of statin medications upon reduction of LDL [Bakker-Arkema *et al.*, 1996; Stein *et al*., 1998]. Furthermore, prior studies have demonstrated the inhibitory effect of statin medications upon DNA methyltransferases, the family of enzymes responsible for transfer of methyl groups to DNA and, in the context of cancer research, have been shown to augment the sensitivity of colorectal cancer cells to the effects of chemotherapy. Thus, taken together, it could be postulated that effects upon fasting blood glucose that could be associated with statin use and BCL11A variations may be mediated through TG metabolism and/or epigenetic modification involving DNA methylation.

Rs64402960 is located in the IGF2BP2 gene (on chromosome 3). IGF2BP2 encodes insulin-like growth factor 2 (IGF2), which has been implicated in the biologic pathway

related to β-cell function and evidence would suggest an inverse relationship for IGF2 and blood glucose levels [Zhang *et al*., 2013; Gene Cards, 2014]. Prior results published by Narayanan *et al.* demonstrated that low- and high-dose atorvastatin therapy in participants with T2DM led to decreased effects of IGF2 [Narayanan *et al.*, 2013]. These researchers postulated this mechanism to be the underlying pathway between statin use and T2DM.

Rs16927668 is located in the protein tyrosine phosphatase receptor type D (PTPRD, located on chromosome 9) is widely expressed in various tissues including skeletal muscle, brain and pancreas. The underlying biologic pathway involved in T2DM is still unclear however, it is speculated that PTPRD plays a role in regulation of insulin signaling [Tsai *et al.*, 2010].PTPRD is present upon skeletal muscle and has been implicated in the occurrence of myopathy, a rare but severe side effect associated with statin medication use. The SEARCH Collaborative Group examined multiple genomic regions, including PTPRD, to better understand the association of statin-induced myopathy [The SEARCH Collaborative Group, 2008]. Results of this study did not confirm an association of statin induced myopathy and PTPRD; however, the researchers believed that further research may be required.

Rs6459193 is located near the ANKRD55 gene (on chromosome 5) and previous findings suggest the association of ANKRD55 and T2DM is through pathways of insulin resistance [Morris *et al.*, 2012]. Harder *et al.* demonstrated the association of decreased insulin sensitivity and ANKRD55 which confirmed this prior evidence as the primary physiologic mechanism involved in T2DM [Harder *et al.*, 2013]. Koh *et al.* demonstrated the effects of atorvastatin exposure with significant increases in fasting insulin, which is indicative of insulin resistance in hypercholesterolemic patients [Koh *et al*., 2010].

Other reasons involving biologic causes to explain the differing results in the Non-Hispanic White and African American population are challenging to consider, given that their mechanistic roles in T2DM have not been fully elucidated. Behavioral, SES, and/or environmental factors are also known influencers of T2DM and have been postulated to

underlie the disproportionality of T2DM across different races [Signorello *et al.*, 2007]. Approximately 35% of African American participants achieved $\geq$ 12 years of education (a stable proxy for SES) as compared to 50% of Non-Hispanic White participants ($p \leq 0.001$). Varying levels of education have been associated with differing rates of T2DM and related morbidity [Delamater *et al*., 2001; Williams *et al.*, 2012]. Although, genetic variation and race specific pathogenesis should not be discounted, other risk factors seem to be linked to the different disease rates and therefore, these other influencers may also interact with genetic determinants [Signorello *et al.*, 2007]. Thus, these concepts should be considered when attempting to explain the different results observed from the univariate SNP analyses observed in the GENOA African American and Non-Hispanic White populations.

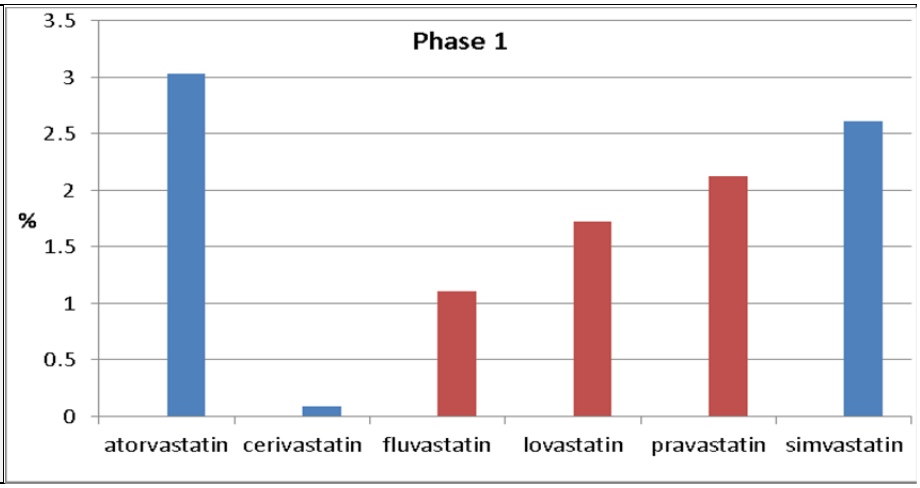
*Statin Pharmacology and Theoretical Impact on Risk for Elevated Blood Glucose Levels or T2DM*

Experimental evidence would suggest a differential potency for the individual statin medications and HMG-CoA reductase inhibition. This has led to the possible link of a differential effect for the individual statins and impact on the diabetic pathway. Although the pharmacodynamic effects of these medications are similar, atorvastatin, simvastatin and cerivastatin exhibit greater inhibitory effects on HMG-CoA reductase whereas lovastatin, pravastatin and fluvastatin exhibit lower potency [Koh *et al*., 2011]. Examination of pravastatin in humans has shown enhanced insulin sensitivity and other studies have demonstrated increased risk of incident T2DM associated with atorvastatin, rosuvastatin and simvastatin [Koh *et al*., 2010; Collins *et al.*, 2003; Sever *et al.*, 2003; Coleman *et al*, 2008; Ridker *et al.*, 2008]. The different inhibitory effects of the individual statin medications upon HMG-CoA reductase need to be further explored with respect to the observed statin and SNP interaction in order to gain further insight into the potential effects of the distinct statin medications.

In this study, the primary exposure variable was a composite of the individual statin medications and the evaluation was based upon a pharmacological class effect

[Figure 30]. Therefore, it is uncertain if statins with lower potency could be 'masking' the effects of statins with higher potency in the analyses of the interaction for statins and individual SNPs or GRS.

**Figure 30: Percentage of Individual Statin Use in Phase 1 and 2 Across All Populations**




*Residual Confounding*

Social and environmental factors are on the causal pathway for T2DM. For example, the analyses included in this study did account for educational status (> 12 years versus ≤ 12 years) as a stable proxy for SES; however, the concept of residual confounding cannot be excluded. Controlling for SES is challenging because it represents a myriad of factors and, in some cases, these factors are prone to a high level of measurement error and in other cases, these factors are often unmeasured. For example, stress as a manifestation of physical factors (i.e., injuries) or psychosocial factors (i.e., unresolved work issues, bereavement) are a known risk factor for T2DM however, these factors were not collected in this study. Additional factors may also include the variation in intensity of clinical monitoring for participants, level of intensity for patient training and other psychosocial reasons such as feelings of coherence and support.

As such, all social or environmental factors were not measured but could influence the results.

## 4.6 Strengths and Limitations

This study had several major strengths. One is the large, multiethnic source population that provides a population base to investigate the association of statin medication use and changes in fasting blood glucose and T2DM in potential genetically susceptible individual and within real world clinical practice settings. Although this program included cross sectional analyses giving rise to challenges in assessing temporal associations, prior studies would suggest that a shorter period of follow up is more predictable of T2DM given the static nature of the genetic variables and greater control over the dynamic nature of the influencing factors such as age and BMI. The population size for this program may not be sufficiently large to detect changes in fasting blood glucose or risk of T2DM based upon statin and SNP interactions, particularly for those SNPs with lower RAFs.

## 4.7 Conclusions

Currently, the use of statins is widespread and usage is anticipated to increase due to the recent ACC/AHA recommendations which now encourage use of these medications earlier in the disease process and in high risk individuals with or without evidence of atherosclerotic cardiovascular disease [Stone *et al.*, 2013]. The results of this study suggest that genetically susceptible Non-Hispanic Whites exposed to statin medications may experience increased risk of T2DM. More so, the Non-Hispanic White population appears to have different susceptibilities as compared to the African American population. Thus, this research in the GENOA study offers an expanded view of the potential association of statin use and T2DM across diverse ethnic populations and regions.

The results in this study contribute to the overall body of evidence generated primarily in randomized clinical trials and stress the importance of research in a naturalistic setting. Although this study examined the overall pharmacological class effect of statin use and T2DM, the different inhibitory effects upon HMG-CoA reductase also need to be

further explored in order to understand the relative risk of the outcome with respect to individual statin medications.

Overall, the results in the study give rise to the need for further research in order to enhance our depth of knowledge regarding the multiple networks and pathways that may underlie T2DM and the potential influence of statin medications upon these pathways. The results of this study offer complimentary evidence to allow fully informed decisions by healthcare professionals and appropriate treatment of statin use in patients.

## Chapter 5 Overall Conclusions

Consistent with findings of prior interventional and observational studies, results of the present research program indicate that statin medication use is associated with increased odds of T2DM in the GENOA population. To complement these findings, this research program was also designed to assess potential changes in the main biologic markers (fasting blood glucose, fasting insulin, HOMA-IR) known to be altered along the T2DM disease pathway as well as to investigate if genetically susceptible individuals may be at higher risk of developing T2DM when prescribed statin medications. Results from the latter provided new discoveries that are not currently described in the published literature.

Type 2 diabetes mellitus is a complex disease influenced by a multitude of biological, genetic, psychological, social and/or environmental factors that may impact the onset or progression of disease [Glasgow, 1994]. There is an abundance of research demonstrating the impact of diabetes related patient awareness, opinion and motivation for self-care upon disease management [Glasgow, 1994]; research in other areas has also proven that the social environment such as community support programs, community resources and/or barriers to health effect management of this disease [Glasgow, 1994]. The complex interplay across these determinants presents challenges during the conduct of T2DM research where the concepts of confounding and/or effect modification are amplified given the various levels for each determinant. This, in turn, raises the importance of collecting a voluminous amount of data, a virtually impossible task whether in the context of randomized or observational studies. In reality, the results generated in T2DM research should be contextualized against the potential for residual confounding due to the lack of ability to measure and/or adjust for every determinant that may influence the disease or outcome.

Phase 1 of the GENOA study was conducted during the time period of 1996-2001 of which 4712 African American, Non-Hispanic White and Hispanic participants were enrolled in the Jackson, Rochester and Starr County field centers, respectively. The odds of T2DM for statin use as compared to no statin use were approximately 1.5-2 fold increased in these populations, after adjustment. In contrast, the magnitude of change for fasting blood glucose, fasting insulin and HOMA-IR across the African American and Non-Hispanic White T2DM populations was minimal and statistically non-significant. Given that these widely used measures are known to be altered along the disease pathway for T2DM and considered standard of care for routine monitoring of T2DM status, one would anticipate that the results for these markers would also be increased. It could be that the cross sectional design of this study may have limited the ability to detect changes in fasting blood glucose as the analyses were carried out at one point in time. In the case of statin medication use and influence upon fasting blood glucose, prior evidence suggests that approximately 24 months of chronic statin medication use was associated with changes in fasting blood glucose [Ridker *et al.*, 2008]. Thus, it is possible that perturbations in fasting blood glucose, fasting insulin and HOMA-IR may have gone undetected given the GENOA study design of one distinct data collection time point in Phase 1. Another explanation for the lack of observed effect could be due to regulatory feedback hormones derived from the pancreas (insulin, amylin and glucagon), intestines (GLP-1, GIP) and/or adrenal glands (cortisol) that may influence glucose levels to maintain homeostasis, particularly at a moment in time (as opposed to the deterioration of regulatory feedback that may occur over time) [Aronoff *et al*., 2004]. Alternatively, it could be speculated that Phase 1 participants who met the definition of T2DM were well controlled with antidiabetic treatment and/or other disease management regimens and therefore, perturbations in fasting blood glucose, fasting insulin and HOMA-IR were not observed.

In the GENOA study, the interaction of statin and field center was not significant, indicating that the prediction of T2DM with statin use was no different in African American and Non-Hispanic White population. However, data related to social,

psychological and/or environmental influencers in the respective regions of Jackson, MS and Rochester, MN were not collected in the GENOA study but could likely be very different with varying impact upon patient disease management. Therefore, it is important to take this into consideration when interpreting these results in the GENOA study.

Over time, GENOA participants were invited to participate in Phase 2 of the study which was conducted during the time period of 2000-2004; approximately 3634 (~76%) of African American, Non-Hispanic White and Hispanic participants voluntarily re-enrolled. The results for the odds of T2DM with use of statin medication as compared to no use were also increased in the Phase 2 population. Although the results in Phase 2 were a replication of the results in Phase 1, the magnitude of effect (i.e., ~1.5-2 fold increased odds of T2DM with statin use compared to no statin use) was similar which was not anticipated given that the prevalence of T2DM was higher in all Phase 2 populations, an expected trend due to the progressive nature of T2DM that is modulated by the loss of glycemic control and/or patient non-compliance with antidiabetic therapy. In this study, the participant-reported use of antidiabetic medication was collected at the time of enrollment in Phase 1 and Phase 2 however, assessments of compliance or adherence to the individual's prescribed regimen was not performed. In addition, the increased use of statin medications over time assumes greater availability, access and/or acceptance by participants and this 'time dimension effect' may influence epidemiologic inferences. More specifically, trends of increased usage could result in greater health awareness and disease monitoring and ultimately lead to decreased risk for the outcome of interest. Lastly, as age increases, the overall disease burden increases, and this 'age effect' may have also led to the expectation of a greater magnitude of effect in Phase 2 as compared to Phase 1. For these reasons, the limitations of the cross-sectional design are apparent when attempting to assess statin use and T2DM over time.

One consideration for the similarity in effect across Phase 1 and Phase2 for statin use and the OR for T2DM is the potential impact of 'loss to follow up'. More specifically, we

could speculate that the majority of participants who did not return to Phase 2 were using a statin medication and developed T2DM (or associated comorbidities) and therefore a negative bias in the estimate may have occurred in Phase 2. It is important to emphasize that the bias in effect due to loss to follow up is pure speculation as the reasons are unknown and therefore, the impact upon the final results is difficult to interpret.

The longitudinal analyses for the relative risk of incident T2DM and statin use were not significant which may have been attributed to the timing for data collection in the GENOA study. More specifically, the data points for T2DM and the other biologic measures were obtained at the time of enrollment in Phase 1 and Phase 2. Therefore, it is quite possible that the onset of T2DM was 'missed' such that it may have occurred after Phase 2 was completed. Although traditional methods to assess an exposure and effect over time are through use of longitudinal analyses, in the case of the GENOA study, the cross sectional analyses in Phase 1 with comparison to Phase 2 may have provided greater insight regarding the association of statin use and T2DM over time.

Similar to Phase 1, results for statin use and fasting blood glucose, fasting insulin and HOMA-IR were non-significant in the Phase 2 Jackson African American and Rochester Non-Hispanic White T2DM population. Prior studies have generated mixed results for statin use and the association with these parameters. Zhou *et al.* conducted a meta-analysis of randomized clinical trials to investigate whether statins deteriorate glycemic control in diabetic patients and found no significant influence on fasting plasma glucose or fasting insulin [Zhou *et al.*, 2013]. In contrast, in the JUPITER study, post-hoc analyses demonstrated that new onset T2DM was associated with statin use in patients with impaired fasting glucose at the time of entry into the study [Rocco *et al.*, 2012].

Thus, given the results in the GENOA Phase 1 and Phase 2 T2DM Jackson African American and Rochester Non-Hispanic White populations, the main effect of statin use does not appear to be predictive of fasting blood glucose, fasting insulin and/or HOMA-IR. The results in all Phase 1 and Phase 2 non-T2DM populations were comparable such

that the assessment of fasting blood glucose, fasting insulin and HOMA-IR with the main effect of statin medication use, after adjustment, was not significant in the GENOA study. These results are similar to other published studies that demonstrated lower fasting blood glucose in non-diabetics human and animal models [Sukhija *et al*., 2009; Kanda *et al.*, 2003]. Furthermore, no changes in blood insulin levels were observed with administration of statins or control in the non-diabetic or diabetic rat model [Kanda *et al.*, 2003].

Therefore, it is reasonable to conclude that statin medications are not predictive of changes of fasting blood glucose, fasting insulin or HOMA-IR in the GENOA T2DM populations or the GENOA non-T2DM Jackson African American and Rochester Non-Hispanic White populations suggesting that these results did not provide complimentary evidence to the significant association observed with statin use and T2DM. As indicated above, the cross-sectional design in this study may have limited the ability to detect changes in these measures.

In contrast to the observed results with the main effect of statin medication use, significant changes in fasting blood glucose, fasting insulin and/or HOMA-IR were observed with statin use and different levels of education, presence of menopause and use of concomitant antihypertensive medications in the African American and Non-Hispanic White populations. These results emphasize the need for further characterization of the implied effects of statin use and T2DM or changes in key parameters in order to identify patient populations at potentially greater risk. For instance, GENOA results for statin use in participants with menopause as compared to no menopause in the individual non-T2DM African American and combined T2DM African American/Non-Hispanic White populations demonstrated decreases in fasting blood glucose, fasting insulin and HOMA-IR. The GENOA decreased effects with statin use in participants with menopause were opposite to the increased effects published by Culver *et al.* [Culver *et al*., 2012]. The difference may be attributed to other region specific factors (i.e. environmental, psychological, social, and/or other community

factors described above) and the decreased effect in the GENOA study was attributed to the possible influence of availability of social support programs in the case of Jackson, MS. The results from the Culver *et al.* study represented the overall observations across multiple US clinical sites; specific site results were not reported and therefore, it is difficult to determine comparability of regions in the Culver study versus the GENOA study. The lack of corroboration between the GENOA and Culver *et al*. results stresses the need for further study in order to understand the effects of statin medication in populations at potential risk while controlling for region specific external factors that may confound or influence the final results.

A similar case can be made for statin use and varying levels of education. In the GENOA study, fasting blood glucose was increased with higher education (> 12 years) as compared to lower education (≤ 12 years) in Phase 1 Hispanic and Phase 2 Non-Hispanic White non-T2DM populations. In this study, education served as proxy for SES and the observed increased effect was attributed to greater access to a 'richer' dietary regimen amongst the more affluent population. Contrary to results in the published literature, these results would suggest that patients with a higher education who are receiving statin medication could be at relatively greater risk and require more intensive monitoring as well as focused interventions. Further study is required for replication of these GENOA results in order to fully comprehend the potential for sub-populations at greater risk.

Thus, the safety communication disseminated by the FDA stating "*…patients being treated with statins may have a small increased risk of increased blood sugar levels and of being diagnosed with type 2 diabetes mellitus. The labels will now warn healthcare professionals and patients of this potential risk*" was a general precaution and did not address particularly higher risk patients. Given the wide use of statin medication and the public health impact of T2DM, it is imperative that the cause and effect of statin use and T2DM is further characterized in particular populations in order to enhance clinician

knowledge and ability to focus treatment and monitoring for patients at particularly greater risk.

The need for additional research is further demonstrated by the results generated in GENOA Hispanics, a population with a relatively higher prevalence of T2DM and/or pre-disposition to T2DM in Starr County. In this population, a significant but unexpected decrease in fasting blood glucose was observed in the Phase 1 and Phase 2 T2DM populations. It is difficult to interpret this observation as it is opposite to the results of prior studies suggesting increased fasting blood glucose with statin medication on the T2DM population and also inconsistent with the GENOA results of increased odds of T2DM with statin use as compared to no statin use in the Starr County Hispanic population. One explanation put forth in this study was the possibility of 'patient awareness' that may be enhanced for participants receiving statin medications during the conduct of the study leading to greater self-management of glycemic control.

It would be ideal if clinicians had the ability to predict disease occurrence or to optimize the safety and efficacy of a medication at the patient level. To date, traditional medical care has focused upon patient presentation of subjective symptoms and/or objective findings of laboratory measures or medical history. There is opportunity to improve upon these traditional methods through use of evidence that has been emerging via human genetic research. By understanding a patient's genetic architecture and influence upon disease, these traditional methods could evolve and possibly become the mainstay for a personalized approach to individual patient care.

For many complex diseases, the pursuit to identify susceptibility genes was initiated decades ago [McCarthy & Zeggini, 2009]. Over the past few years, larger sample sizes have enabled increased power in discovery and replication studies and technological advances have aided the identification of genetic variation (particularly SNPs) across many diseases. In the case of T2DM, few candidate genes were discovered through earlier studies and, as genetic research methods evolved, large consortia had the ability to uncover numerous genetic loci. Morris *et al*. performed large scale genotyping to

identify 65 unique loci that are associated with the influence upon T2DM and identified traits potentially associated with T2DM pathways mapping to fasting glucose, β-cell function, insulin resistance, lipid associations (reduced HDL, elevated triglycerides) as well as common points in the processes underlying risk and protection of T1DM and T2DM. These findings certainly provide initial insight into the disease pathways however, for the most part, the majority of T2DM pathophysiological processes that are mediated by genetic disposition are still unclear [Morris *et al.*, 2012; Hivert *et al.*, 2014].

Examination of these 65 unique loci in the GENOA study revealed that the majority were present in the Rochester Non-Hispanic White (64 of 65 unique loci) and Jackson African Americans (57 of 65 unique loci) populations. Risk allele frequencies in both populations were comparable to the RAFs reported by Morris *et al.* (Non-Hispanic White RAF: 0.02 to 0.98; African American: 0.06 to 0.96) which was not unanticipated given that prior studies were conducted in similar populations composed of African American and European participants [Morris *et al.*, 2012, Hivert *et al.*, 2014]. Translation of the RAFs reported in GENOA African Americans and Non-Hispanic Whites as well as Morris *et al.* to the general population would suggest that, in some cases, risk alleles are the major alleles implying a high prevalence of genetically susceptible individuals that appear to be at potential risk of T2DM.

In the GENOA study, the GRS was predictive of changes in fasting blood glucose, before and after adjustment, in the Non-Hispanic White but not in the African American population. Behavioral, SES, environmental factors, diet, psychodynamic factors (i.e., stress) may alter glycemic control and have been postulated to underlie the disproportionality of new onset or worsening of T2DM across different races [Signorello *et al*., 2007; Dagogo-Jack, 2003; Gary *et al*, 2000]. Although the biologic plausibility for the interaction of these factors and T2DM GRS is possible, these interactions were not analyzed in the GENOA study. Further, the Insulin Resistance Atherosclerosis Study (IRAS) demonstrated different degrees of insulin resistance in African Americans as compared to Non-Hispanic Whites which raises the question of genetically driven

differences in the pathophysiology of T2DM across ethnicities ; Gary *et al*, 2000]. Therefore, influences of regional factors or potential different genetic effects for T2DM SNPs across the populations are concepts to consider.

As T2DM genetic variants became known, researchers examined the aggregation of genetic information into a GRS and the ability to prospectively predict incident cases of disease [Morris *et al.*, 2012; Hivert *et al.*, 2014]. In the GENOA study, the GRS was predictive of changes in fasting blood glucose in the Non-Hispanic White population but not in the African American population. One possible explanation was the difference in number of risk alleles within the GRS for the African Americans (57) as compared to the Non-Hispanic Whites (64) as well as the distribution of the GRS in these populations. The GRS was also predictive of T2DM in both populations, before and after adjustment, which corroborates the findings of prior studies [Morris *et al.*, 2012; Hivert *et al.*, 2014].

Leveraging upon the advancements of human genetic research leads us to also reflect upon the progress in the area of pharmacogenomics, an evolving field that focuses upon individual genetic differences in metabolism and probability of clinical response with a particular medication. Furthermore, research in pharmacogenomics has concentrated on susceptible genetic factors associated with adverse drug reactions which, in principle, provides insight to clinicians and enables their ability to mitigate drug-related risk at the individual patient level. The FDA has acknowledged the value of pharmacogenomic data by taking action to describe results related to clinical variability, risk for adverse events and genotype-specific dosing on specific product labels [FDA, 2014].

Extensive pharmacogenetic research with statin medications has successfully identified genetic loci that map to pharmacokinetic and pharmacodynamic pathways associated with statin therapy [Mangravite *et al*., 2006]. For example, genetic variation in statin metabolizing enzymes (CYP enzymes in the liver) aids in determination of appropriate dosage choices, i.e., slow metabolizers would require lower dosages. Further, this information is coupled with the knowledge of the hydrophobic characteristics for the individual statin medications. In other words, genetic variation in CYP enzymes is more

relevant for those statin medications with greater hydrophobicity (i.e., better substrates for CYP metabolism due to ability to passively penetrate into the liver). The application of pharmacogenomics research has also provided valuable insight and the ability to genetically pre-screen individuals to determine susceptibility for statin induced adverse reactions which is particularly important as this relates to severe adverse reactions such as hepatic dysfunction or skeletal myopathies [Mangravite *et al*., 2006].

In the present study, new discoveries of significant statin and T2DM SNP interactions contribute to the existing body of pharmacogenomic evidence for statin medications. The identification of significant interactions for statin medication use and T2DM SNPs in this study may also extend our comprehension of new disease pathways involved with T2DM.

The class of HMG-CoA reductase inhibitors, or statin medications, achieved FDA approval approximately 30 years ago and offered a novel pharmacology leading to clinically significant decreases in total cholesterol, increases in plasma clearance of LDL, decreases in TG and increases in HDL which was considered 'breakthrough' as a therapeutic intervention for CVD. Based upon these clinical effects, statin medications became first line therapy in conjunction with dietary and lifestyle measures for treatment and prevention of CVD. Since the initial approval, methods of active surveillance (post-marketing interventional and/or observational studies) and passive surveillance (FDA MedWatch Adverse Event Reporting System) have enabled the continued generation of safety information, further characterization of the safety profile for statin medications and conduct of ongoing benefit-risk assessments. Of recent, results from the JUPITER study revealed an approximately 27% increase in Investigator reported adverse events of diabetes rosuvastatin compared to placebo (p=0.01) [Ridker *et al.*, 2008]. In this study, clinical efficacy outcomes demonstrated superiority of rosuvastatin compared to placebo for endpoints of myocardial infarction (HR 0.46; 95% CI 0.30 to 0.70), cerebrovascular accident (HR 0.52; 95% CI 0.34 to 0.79), cardiovascular mortality (HR 0.53; 95% CI 0.40 to 0.69) and for all-cause mortality (HR 0.80; 95% CI 0.67

to 0.97). In the PROVE-IT TIMI 22 study, “high-dose statin therapy was associated with worsening glycemic control” [FDA Drug Safety Communication, 2012]. The investigators concluded that intensive lowering of LDL (median mg/dL) as compared to standard approaches for LDL lowering (median 95 mg/dL) reduced the risk of all-cause mortality and cardiovascular events by 16% (p=0.005) in recently hospitalized patients for acute coronary syndrome [Cannon *et al*., 2004]. The CDC reports that a substantial percentage of men (50% in 65-74 years; 45% in 75 years and over) and women (36% in 65-74 years; 39% in 75 years and over) have used statin medications during the period of 2005-2008 with simultaneous declines in hypercholesterolemia and decreasing mortality due to heart disease in the US. Based upon the available evidence, it would appear the benefits of these medications continue to be robust and outweigh the risks for statin medications. However, to further mitigate the risks of statin induced T2DM, it would be important to continue to explore the findings from the GENOA study to identify sub-populations or genetically susceptible individuals who may be at relatively greater risk of statin use and influence upon fasting blood glucose and T2DM.

Future research should be undertaken with studies that are designed to explore the associations of statin medication use across various ethnicities with capability of achieving greater control in psychological, social, environmental and SES factors to minimize bias upon the epidemiological inferences through residual confounding. Longitudinal analyses for a minimum of 24 months would be recommended with serial testing of the critical biomarkers and T2DM in order to detect the onset of any change or disease.

The varying potency of the statin medications upon cholesterol lowering effect raises the question of the relative risk of T2DM across the pharmacological class and therefore, further research should focus upon the risk of individual statin medications. Moreover, the cellular pathways based upon *in vitro* experiments have provided insight into the possible biologic plausibility of statin inhibition of insulin secretion by the β-cell or isoprenoid inhibition of peripheral glucose uptake. These postulations should be carried

forward and examined within a clinical model to further understand the underlying pharmacology of statin induced T2DM in humans.

The discoveries of genetic and statin interactions are an area to further explore in order to continue to build the knowledge in the area of pharmacogenomics and statin medication use. These efforts will also aid in the evolution toward the predictability of efficacy and safety at the individual patient level. Further, to build upon the research in areas of pharmacogenomics, practical use of emerging information is also important and could be achieved through prioritization of educational forums for clinicians and patients within multidisciplinary healthcare systems.

Results from GENOA demonstrated an approximately 1.5-2-fold increase in T2DM with statin use across populations, changes in fasting blood glucose with the main effect of statin medications in the Hispanic T2DM population and changes in fasting blood glucose based upon different levels of education, menopause, use of antihypertensive medications and increasing age in the GENOA non-T2DM and T2DM populations. Furthermore, new discoveries of statin-by-GRS interactions increased odds of T2DM in genetically susceptible individuals. The GENOA results demonstrate the need to understand the safety of statin medications in different populations across different regions and contribute to the ongoing characterization of the safety profile for statin medications. This, in turn, this allows for the continued assessment of the benefit-risk balance with statin medications and, more importantly, informed decision making by clinicians of treatment options and level of monitoring for individual patients.

# Appendices

## Appendix 1: All Genetic Determinants Examined in this Research Program

| CHRM | SNP | Risk Allele/ Other Allele | Locus | CHRM | Locus | Risk Allele/ Other Allele | Locus |
|---|---|---|---|---|---|---|---|
| 1 | rs2075423 | **G**/T | PROX1 or PPP2R5A | 9 | rs2796441 | **G**/A | TLE1 |
| 1 | rs10923931 | **T**/G | NOTCH2 | 9 | rs16927668 | **T**/C | PTPRD |
| 2 | rs10203174 | **C**/T | THADA | 10 | rs11257655 | **T**/C | CDC123/CAMK1D |
| 2 | rs243088 | **T**/A | BCL11A | 10 | rs7903146 | **T**/C | TCF7L2 |
| 2 | rs13389219 | **C**/T | GRB14 | 10 | rs1111875 | **C**/T | HHEX/IDE |
| 2 | rs2943640 | **C**/A | IRS1 | 10 | rs12571751 | **A**/G | ZMIZ1 or PPIF |
| 2 | rs7569522 | **A**/G | RBMS1 | 10 | rs12242953 | **G**/A | VPS26A |
| 2 | rs780094 | **C**/T | GCKR | 11 | rs10830963 | **G**/C | MTNR1B |
| 3 | rs11717195 | **T**/C | ADCY5 | 11 | rs1552224 | **A**/C | ARAP1 (CENTD2) |
| 3 | rs1496653 | **A**/G | UBE2E2 | 11 | rs163184 | **G**/T | KCNQ1 |
| 3 | rs4402960 | **T**/G | IGF2BP2 | 11 | rs5215 | **C**/T | KCNJ11 |
| 3 | rs1801282 | **C**/G | PPARG | 11 | rs2334499 | **T**/C | DUSP8 or HCCA2 (YY1AP1) |
| 3 | rs6795735 | **C**/T | ADAMTS9 | 12 | rs7955901 | **C**/T | TSPAN8/LGR5 |
| 3 | rs12497268 | **G**/C | PSMD6 | 12 | rs11063069 | **G**/A | CCND2 |
| 3 | rs17301514 | **A**/G | ST64GAL1 | 12 | rs12427353 | **G**/C | HNF1A (TCF1) |
| 4 | rs6819243 | **T**/C | MAEA | 12 | rs2261181 | **T**/C | HMGA2 |
| 4 | rs4458523 | **G**/T | WFS1 | 12 | rs10842994 | **C**/T | KLHDC5 or PPFIBP1 |
| 5 | rs6878122 | **G**/A | ZBED3 or PDE8B | 13 | rs1359790 | **G**/A | SPRY2 |
| 5 | rs459193 | **G**/A | ANKRD55 | 15 | rs4502156 | **T**/C | C2CD4A or VPS13C |
| 6 | rs7756992 | **G**/A | CDKAL1 | 15 | rs11634397 | **G**/A | ZFAND6 |
| 6 | rs3734621 | **C**/A | KCNK16 | 15 | rs12899811 | **G**/A | PRC1 |
| 6 | rs4299828 | **A**/G | ZFAND3 | 15 | rs2007084 | **G**/A | AP3S2 |
| 7 | rs17168486 | **T**/C | DGKB | 15 | rs7177055 | **A**/G | HMG20A |
| 7 | rs10278336 | **A**/G | GCK | 16 | rs9936385 | **C**/T | FTO |
| 7 | rs849135 | **G**/A | JAZF1 | 16 | rs7202877 | **T**/G | BCAR1 |
| 7 | rs17867832 | **T**/G | GCC1 or PAX-4 | 17 | rs2447090 | **A**/G | SRR |
| 7 | rs13233731 | **G**/A | KLF14 | 17 | rs4430796 | **G**/A | HNF1B (TCF2) |
| 8 | rs3802177 | G/A | SLC30A8 | 18 | rs12970134 | **A**/G | MC4R |
| 8 | rs7845219 | **T**/C | TP53INP1 | 19 | rs8108269 | **G**/T | GIPR |
| 8 | rs516946 | **C**/T | ANK1 | 19 | rs10401969 | **C**/T | CILP2 |
| 9 | rs10811661 | **T**/C | CDKN2A/B | 19 | rs8182584 | **T**/G | PEPD |
| 9 | rs10758593 | **A**/G | GLIS3 | 20 | rs4812829 | **A**/G | HNF4A |
| 9 | rs17791513 | **A**/G | TLE4 | | | | |

CHRM: chromosome; SNP: single nucleotide polymorphism.

## Appendix 2: Sample Mean, Median and Interquartile Range for Outcomes and Covariates of Interest (Phase 1)

| Center | N Obs | Variable | N | Mean | Standard Deviation | Minimum | Maximum | Median | Lower Quartile | Upper Quartile | Quartile Range |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Jackson** | **1508** | **glucose** | 1508 | 111.0503 | 45.66934 | 41.2 | 463.3 | 95.1 | 87.4 | 110.15 | 22.75 |
| | | **insulin** | 1506 | 11.22221 | 12.34614 | 0.8 | 181 | 8.2 | 5.3 | 13.1 | 7.8 |
| | | **exf_age** | 1508 | 58.41854 | 10.13034 | 20.50103 | 91.16769 | 58.85832 | 52.44216 | 65.36345 | 12.9212868 |
| | | **bmi** | 1508 | 31.10876 | 6.649258 | 14.4039 | 59.90305 | 30.05428 | 26.47072 | 34.65747 | 8.1867498 |
| | | **HOMA-IR** | 1506 | 60.0584 | 85.8621 | 3.04 | 1297.57 | 37.3675 | 22.3751 | 66.9582 | 44.5831 |
| **Rochester** | **1474** | **glucose** | 1474 | 98.96676 | 27.31696 | 59.6 | 362.5 | 92.05 | 85.7 | 100.7 | 15 |
| | | **insulin** | 1440 | 9.572569 | 10.26278 | 1.18 | 222 | 7.27 | 4.7 | 11.165 | 6.465 |
| | | **exf_age** | 1474 | 55.30564 | 10.91758 | 24.89254 | 89.87269 | 55.80424 | 47.1321 | 63.19507 | 16.0629706 |
| | | **bmi** | 1474 | 30.43366 | 6.255935 | 15.79456 | 59.52107 | 29.54344 | 26.08303 | 33.70499 | 7.6219562 |
| | | **HOMA-IR** | 1440 | 46.0744 | 78.5435 | 4.08542 | 2010.83 | 29.9847 | 19.1825 | 50.6578 | 31.4752 |
| **Starr County** | **1730** | **glucose** | 1730 | 153.0579 | 72.1653 | 46.6 | 471.8 | 127.95 | 94.8 | 196.1 | 101.3 |
| | | **insulin** | 1700 | 14.927 | 15.16392 | 1 | 184 | 11 | 6.9 | 17.8 | 10.9 |
| | | **exf_age** | 1728 | 55.54362 | 11.83441 | 18.20945 | 85.9384 | 55.74812 | 47.70021 | 64.16153 | 16.4613279 |
| | | **bmi** | 1730 | 30.84532 | 5.920392 | 13.6337 | 56.10931 | 30.01249 | 26.6782 | 34.24601 | 7.5678129 |
| | | **HOMA-IR** | 1700 | 99.5665 | 116.918 | 4.35067 | 1563.43 | 68.7261 | 39.9689 | 115.039 | 75.0702 |

HOMA IR: homeostasis model assessment of insulin resistance; Obs: observations.

## Appendix 3: Sample Mean, Median and Interquartile Range for Outcomes and Covariates of Interest (Phase 2)

| center | N Obs | Variable | N | Mean | Standard Deviation | Minimum | Maximum | Median | Lower Quartile | Upper Quartile | Quartile Range |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Jackson** | **1260** | **glucose** | 1260 | 111.6718 | 43.87202 | 49.5 | 618 | 98.5 | 90 | 114.5 | 24.5 |
| | | **Ida_insulin** | 1018 | 9.47667 | 12.53486 | 0.22 | 209.1 | 6.465 | 3.84 | 10.92 | 7.08 |
| | | **exf_age** | 1260 | 63.40297 | 9.445448 | 26.40657 | 94.74333 | 63.95619 | 57.89596 | 69.859 | 11.96304 |
| | | **bmi** | 1257 | 31.66382 | 6.630598 | 16.40618 | 60.59062 | 30.78593 | 26.99725 | 35.33176 | 8.334518 |
| | | **HOMA-IR** | 1017 | 48.74464 | 64.44562 | 0.757778 | 998.5333 | 30.12178 | 17.018 | 54.79133 | 37.77333 |
| **Rochester** | **1198** | **glucose** | 1198 | 104.8289 | 24.37537 | 62 | 261 | 98 | 91 | 109 | 18 |
| | | **Ida_insulin** | 1150 | 8.115304 | 7.282192 | 0.32 | 136.7 | 6.305 | 3.97 | 10.31 | 6.34 |
| | | **exf_age** | 1198 | 58.85035 | 10.19769 | 29.62081 | 83.98905 | 59.46886 | 51.32649 | 66.12183 | 14.79535 |
| | | **bmi** | 1198 | 30.80923 | 6.252857 | 17.78283 | 58.99633 | 29.95218 | 26.44687 | 33.98438 | 7.537505 |
| | | **HOMA-IR** | 1149 | 39.83076 | 39.0235 | 1.408 | 360.206 | 28.518 | 16.98133 | 48.65333 | 31.672 |
| **Starr County** | **1176** | **glucose** | 1176 | 152.2611 | 65.632 | 52 | 459 | 130.5 | 101 | 187.5 | 86.5 |
| | | **Ida_insulin** | 673 | 13.35181 | 21.65551 | 1 | 502.26 | 10.06 | 6.94 | 15.27 | 8.33 |
| | | **exf_age** | 1176 | 58.78734 | 11.2121 | 25.82341 | 86.06708 | 59.10609 | 51.30185 | 66.83641 | 15.53457 |
| | | **bmi** | 1166 | 32.07597 | 6.14998 | 17.52943 | 56.68841 | 31.11302 | 27.78614 | 35.52533 | 7.739185 |
| | | **HOMA-IR** | 670 | 76.92293 | 63.27126 | 5.622222 | 570.2727 | 58.80978 | 36.10444 | 99.348 | 63.24356 |

HOMA IR: homeostasis model assessment of insulin resistance; Obs: observations.

## Appendix 4: Summary of Fasting Insulin in the Phase 1 Population

| Phase 1 | No T2DM | | | | T2DM | | | |
|---|---|---|---|---|---|---|---|---|
| | African-American Jackson | Non-Hispanic White Rochester | Hispanic Starr County | African-American/ Non-Hispanic White Jackson/ Rochester | African-American Jackson | Non-Hispanic White Rochester | Hispanic Starr County | African-American/ Non-Hispanic White Jackson/ Rochester |
| | **UNIVARIATE ANALYSES FOR FASTING INSULIN** | | | | **UNIVARIATE ANALYSES FOR FASTING INSULIN** | | | |
| **# Obs Used** | **1173** | **1287** | **653** | **2460** | **333** | **153** | **1058** | **486** |
| Statin | 0.65 | 0.34 | -2.35 | 0.12 | 1.48 | -0.99 | 0.50 | 0.14 |
| | **MIXED MODEL ANALYSES FOR FASTING INSULIN** | | | | **MIXED MODEL ANALYSES FOR FASTING INSULIN** | | | |
| **# Obs Used** | **1173** | **1286** | **641** | **2460** | **333** | **153** | **1058** | **486** |
| Intercept | -0.75 | -8.13*** | -4.13 | -5.39*** | 1.98 | 52.81*** | -5.53* | -0.29 |
| BMI | 0.39*** | 0.49*** | 0.73*** | 0.45*** | 0.46* | --- | 0.67*** | 0.55* |
| Age | -0.05** | 0.03 | -0.08 | 1.05*** | --- | -0.56* | --- | --- |
| HTN med | 1.59** | 0.74* | --- | --- | --- | --- | --- | --- |
| Menopause | --- | -0.30* | --- | --- | --- | --- | --- | --- |
| Family history of diabetes | 0.69 | --- | --- | --- | --- | --- | --- | --- |
| Education | --- | --- | 3.33* | --- | --- | --- | --- | --- |
| Statin | 0.93 | 0.19 | -0.95 | 0.17 | 1.81 | -1.61 | 0.23 | 0.55 |

*0.05 > p > 0.01; **0.01≥ p > 0.001; ***p ≤ 0.001; --- covariate excluded via stepwise selection.

BMI: body mass index; HTN med: anti-hypertensive use; Obs: observations; T2DM: type 2 diabetes mellitus.

## Appendix 5: Summary of HOMA-IR in the Phase 1 Population

| | No T2DM | | | | T2DM | | | |
|---|---|---|---|---|---|---|---|---|
| **Phase 1** | **African-American Jackson** | **Non-Hispanic White Rochester** | **Hispanic Starr County** | **African-American/ Non-Hispanic White Jackson/ Rochester** | **African-American Jackson** | **Non-Hispanic White Rochester** | **Hispanic Starr County** | **African-American/ Non-Hispanic White Jackson/ Rochester** |
| **# Obs Used** | **1173** | **1286** | **641** | **2460** | **333** | **153** | **1058** | **486** |
| Intercept | -12.32 | -43.35*** | -30.37 | -28.07*** | 31.49 | 488.91*** | -40.69 | 28.96 |
| BMI | 1.87*** | 2.24*** | 3.48*** | 2.072*** | 3.00* | --- | 5.29*** | 3.17* |
| Age | -0.18 | 0.20** | -0.28 | | --- | -5.72** | --- | --- |
| HTN med | 7.65*** | 3.94** | --- | 5.62*** | --- | --- | --- | --- |
| Menopause | --- | -1.99** | --- | --- | --- | --- | --- | --- |
| Family history of diabetes | 3.70 | --- | | --- | --- | --- | --- | --- |
| Education | --- | | 13.79 | --- | --- | --- | --- | --- |
| Statin | 3.86 | 0.27 | -4.57 | 0.56 | -24.79 | -28.21 | -7.97 | -24.45 |

*0.05 > p > 0.01; **0.01 ≥ p > 0.001; ***p ≤ 0.001; --- covariate excluded via stepwise selection.
BMI: body mass index; HOMA IR: homeostasis model assessment of insulin resistance; HTN med: antihypertensive use; Obs: observations; T2DM: type 2 diabetes mellitus.

## Appendix 6: Pearson Correlation Coefficients for Continuous Variables included in Aim 1 Analyses (Phase 1)

| | African-American Jackson | | | | | Non-Hispanic White Rochester | | | | | Hispanic Starr County | | | | | African-American/Non-Hispanic White Jackson/Rochester | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Non-Diabetics** | | | | | | | | | | | | | | | | | | | | |
| | exf_age | bmi | glucose | Homa1_IR | insulin | exf_age | bmi | glucose | Homa1_IR | insulin | exf_age | bmi | glucose | Homa1_IR | insulin | exf_age | bmi | glucose | Homa1_IR | insulin |
| exf_age | 1 | | | | | 1 | | | | | 1 | | | | | 1 | | | | |
| | | | | | | | | | | | | | | | | | | | | |
| | 1174 | | | | | 1319 | | | | | 652 | | | | | 2493 | | | | |
| bmi | -0.0968 | 1 | | | | -0.1026 | 1 | | | | -0.1810 | 1 | | | | -0.0941 | 1 | | | |
| | 0.0009 | | | | | 0.0002 | | | | | <.0001 | | | | | <.0001 | | | | |
| | 1174 | 1174 | | | | 1319 | 1319 | | | | 652 | 653 | | | | 2493 | 2493 | | | |
| glucose | 0.1150 | 0.2269 | 1 | | | 0.2594 | 0.2532 | 1 | | | 0.1343 | 0.2121 | 1 | | | 0.1957 | 0.2407 | 1 | | |
| | <.0001 | <.0001 | | | | <.0001 | <.0001 | | | | 0.0006 | <.0001 | | | | <.0001 | <.0001 | | | |
| | 1174 | 1174 | 1174 | | | 1319 | 1319 | 1319 | | | 652 | 653 | 653 | | | 2493 | 2493 | 2493 | | |
| Homa1_IR | -0.0545 | 0.3820 | 0.4852 | 1 | | 0.0493 | 0.4906 | 0.4718 | 1 | | -0.1214 | 0.2992 | 0.3444 | 1 | | 0.0065 | 0.4304 | 0.4823 | 1 | |
| | 0.0621 | <.0001 | <.0001 | | | 0.0769 | <.0001 | <.0001 | | | 0.0021 | <.0001 | <.0001 | | | 0.7463 | <.0001 | <.0001 | | |
| | 1173 | 1173 | 1173 | 1173 | | 1287 | 1287 | 1287 | 1287 | | 641 | 642 | 642 | 642 | | 2460 | 2460 | 2460 | 2460 | |
| insulin | -0.0757 | 0.3820 | 0.3512 | 0.9807 | 1 | 0.0205 | 0.4940 | 0.3542 | 0.9854 | 1 | -0.1425 | 0.2972 | 0.2360 | 0.9843 | 1 | -0.0183 | 0.4331 | 0.3560 | 0.9826 | 1 |
| | 0.0095 | <.0001 | <.0001 | <.0001 | | 0.4631 | <.0001 | <.0001 | <.0001 | | 0.0003 | <.0001 | <.0001 | <.0001 | | 0.3631 | <.0001 | <.0001 | <.0001 | |
| | 1173 | 1173 | 1173 | 1173 | 1173 | 1287 | 1287 | 1287 | 1287 | 1287 | 641 | 642 | 642 | 642 | 642 | 2460 | 2460 | 2460 | 2460 | 2460 |

*Table continued on next page*

## Appendix 6: Pearson Correlation Coefficients for Continuous Variables included in Aim 1 Analyses (Phase 2)

| | African-American Jackson | | | | | Non-Hispanic White Rochester | | | | | Hispanic Starr County | | | | | African-American/Non-Hispanic White Jackson/Rochester | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Diabetics** | | | | | | | | | | | | | | | | | | | | |
| | exf_age | bmi | glucose | Homa1_IR | insulin | exf_age | bmi | glucose | Homa1_IR | insulin | exf_age | bmi | glucose | Homa1_IR | insulin | exf_age | bmi | glucose | Homa1_IR | insulin |
| exf_age | 1 | | | | | 1 | | | | | 1 | | | | | 1 | | | | |
| | | | | | | | | | | | | | | | | | | | | |
| | 334 | | | | | 155 | | | | | 1076 | | | | | 489 | | | | |
| bmi | -0.2421 | 1 | | | | -0.2961 | 1 | | | | -0.2438 | 1 | | | | -0.2600 | 1 | | | |
| | <.0001 | | | | | 0.0002 | | | | | <.0001 | | | | | <.0001 | | | | |
| | 334 | 334 | | | | 155 | 155 | | | | 1076 | 1077 | | | | 489 | 489 | | | |
| glucose | -0.1358 | 0.0240 | 1 | | | -0.1192 | -0.1206 | 1 | | | -0.2292 | -0.0280 | 1 | | | -0.1280 | -0.0155 | 1 | | |
| | 0.0130 | 0.6618 | | | | 0.1397 | 0.1349 | | | | <.0001 | 0.3581 | | | | 0.0046 | 0.7323 | | | |
| | 334 | 334 | 334 | | | 155 | 155 | 155 | | | 1076 | 1077 | 1077 | | | 489 | 489 | 489 | | |
| Homa1_IR | -0.0669 | 0.1228 | 0.2064 | 1 | | -0.2549 | 0.1097 | 0.2209 | 1 | | -0.1401 | 0.2325 | 0.1849 | 1 | | -0.1387 | 0.1168 | 0.2000 | 1 | |
| | 0.2231 | 0.0250 | 0.0001 | | | 0.0015 | 0.1770 | 0.0061 | | | <.0001 | <.0001 | <.0001 | | | 0.0022 | 0.0099 | <.0001 | | |
| | 333 | 333 | 333 | 333 | | 153 | 153 | 153 | 153 | | 1057 | 1058 | 1058 | 1058 | | 486 | 486 | 486 | 486 | |
| insulin | -0.0257 | 0.1334 | -0.0976 | 0.8874 | 1 | -0.2111 | 0.1890 | 0.0162 | 0.9471 | 1 | -0.0881 | 0.2529 | -0.1177 | 0.9066 | 1 | -0.0902 | 0.1532 | -0.0672 | 0.9087 | 1 |
| | 0.6406 | 0.0148 | 0.0753 | <.0001 | | 0.0088 | 0.0193 | 0.8427 | <.0001 | | 0.0041 | <.0001 | 0.0001 | <.0001 | | 0.0468 | 0.0007 | 0.1389 | <.0001 | |
| | 333 | 333 | 333 | 333 | 333 | 153 | 153 | 153 | 153 | 153 | 1057 | 1058 | 1058 | 1058 | 1058 | 486 | 486 | 486 | 486 | 486 |

## Appendix 7: Summary of Fasting Insulin in the Phase 2 Population

| Phase 2 | No T2DM | | | | T2DM | | | |
|---|---|---|---|---|---|---|---|---|
| | African-American Jackson | Non-Hispanic White Rochester | Hispanic Starr County | African-American/ Non-Hispanic White Jackson/ Rochester | African-American Jackson | Non-Hispanic White Rochester | Hispanic Starr County | African-American/ Non-Hispanic White Jackson/ Rochester |
| | **UNIVARIATE ANALYSES FOR FASTING INSULIN** | | | | **UNIVARIATE ANALYSES FOR FASTING INSULIN** | | | |
| **# Obs Used** | **707** | **979** | **307** | **1686** | **311** | **171** | **406** | **482** |
| Statin | 0.96 | 0.65 | 1.86 | 0.72* | -2.79 | 1.84 | -0.86 | -1.12 |
| | **MIXED MODEL ANALYSES FOR FASTING INSULIN** | | | | **MIXED MODEL ANALYSES FOR FASTING INSULIN** | | | |
| **# Obs Used** | **1170** | **1318** | **652** | **2488** | **333** | **155** | **1075** | **488** |
| Intercept | 3.63 | -7.31*** | 2.02 | -4.4*** | 1.61 | 6.15 | -29.95* | 2.29 |
| BMI | 0.29*** | 0.42*** | 0.44*** | 0.37*** | 0.43* | --- | 0.88** | 0.32* |
| Age | -0.09** | 0.26 | -0.03 | --- | --- | --- | 0.29 | --- |
| HTN med | 0.74 | 0.72* | 1.01 | 0.66* | --- | 6.46* | --- | 0.58 |
| Menopause | --- | -0.28* | 0.15 | -0.16 | --- | --- | --- | 1.22 |
| Family history of diabetes | --- | --- | --- | --- | --- | 2.36 | --- | --- |
| Education | --- | --- | 1.86 | --- | --- | --- | --- | --- |
| Statin | 0.52 | -0.02 | 1.76 | 0.26 | -2.61 | 1.54 | 0.44 | -0.83 |

*0.05 > p > 0.01; **0.01≥ p > 0.001; ***p ≤ 0.001; --- covariate excluded via stepwise selection.

BMI: body mass index; HTN med: antihypertensive use; Obs: observations; T2DM: type 2 diabetes mellitus.

## Appendix 8: Summary of HOMA-IR in the Phase 2 Population

| | No T2DM | | | | T2DM | | | |
|---|---|---|---|---|---|---|---|---|
| **Phase 2** | **African-American Jackson** | **Non-Hispanic White Rochester** | **Hispanic Starr County** | **African-American/ Non-Hispanic White Jackson/ Rochester** | **African-American Jackson** | **Non-Hispanic White Rochester** | **Hispanic Starr County** | **African-American/ Non-Hispanic White Jackson/ Rochester** |
| **# Obs Used** | **704** | **978** | **305** | **1682** | **311** | **171** | **364** | **482** |
| Intercept | 9.69 | -41.44*** | -21.21 | -22.87*** | -6.61 | 6.16 | -237.49 | 2.29 |
| BMI | 1.39*** | 2.02*** | 2.25*** | 1.76*** | 3.16* | --- | 6.82** | 0.31* |
| Age | -0.35** | 0.20* | -0.06 | --- | --- | --- | 2.39 | --- |
| HTN med | 3.43 | 3.66* | 4.53 | 3.65** | --- | 6.45* | --- | 0.58 |
| Menopause | --- | -1.82* | 0.61 | -1.15 | --- | --- | --- | 1.22 |
| Family history of diabetes | --- | --- | --- | --- | --- | 2.36 | --- | --- |
| Education | --- | --- | 11.03* | --- | --- | --- | --- | --- |
| Statin | 2.03 | -0.37 | 8.78 | 1.13 | -14.09 | 1.54 | -26.05 | -0.83 |

*0.05 > p > 0.01; **0.01≥ p > 0.001; ***p ≤ 0.001; --- covariate excluded via stepwise selection.
BMI: body mass index; HOMA IR: homeostasis model assessment of insulin resistance; HTN med: antihypertensive use; Obs: observations; T2DM: type 2 diabetes mellitus.

## Appendix 9: Pearson Correlation Coefficients for Covariates included in Aim 1 Analyses (Phase 2)

| | African-American Jackson | | | | | Non-Hispanic White Rochester | | | | | Hispanic Starr County | | | | | African-American/Non-Hispanic White Jackson/Rochester | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Non-Diabetics** | | | | | | | | | | | | | | | | | | | | |
| | exf_age | bmi | glucose | Homa1_IR | insulin | exf_age | bmi | glucose | Homa1_IR | insulin | exf_age | bmi | glucose | Homa1_IR | insulin | exf_age | bmi | glucose | Homa1_IR | insulin |
| exf_age | 1 | | | | | 1 | | | | | 1 | | | | | 1 | | | | |
| | | | | | | | | | | | | | | | | | | | | |
| | 894 | | | | | 1020 | | | | | 404 | | | | | 1914 | | | | |
| bmi | -0.1426 | 1 | | | | -0.1033 | 1 | | | | -0.1892 | 1 | | | | -0.1066 | 1 | | | |
| | <.0001 | | | | | 0.0010 | | | | | 0.0001 | | | | | <.0001 | | | | |
| | 891 | 891 | | | | 1020 | 1020 | | | | 401 | 401 | | | | 1911 | 1911 | | | |
| glucose | 0.2099 | 0.1846 | 1 | | | 0.2661 | 0.2423 | 1 | | | 0.1270 | 0.2007 | 1 | | | 0.2183 | 0.2091 | 1 | | |
| | <.0001 | <.0001 | | | | <.0001 | <.0001 | | | | 0.0106 | <.0001 | | | | <.0001 | <.0001 | | | |
| | 894 | 891 | 894 | | | 1020 | 1020 | 1020 | | | 404 | 401 | 404 | | | 1914 | 1911 | 1914 | | |
| Homa1_IR | -0.1122 | 0.3429 | 0.4600 | 1 | | 0.0716 | 0.4772 | 0.4897 | 1 | | -0.0700 | 0.3604 | 0.4625 | 1 | | <.0001 | 0.4177 | 0.4762 | 1 | |
| | 0.0028 | <.0001 | <.0001 | | | 0.0251 | <.0001 | <.0001 | | | 0.2212 | <.0001 | <.0001 | | | 0.9994 | <.0001 | <.0001 | | |
| | 707 | 704 | 707 | 707 | | 979 | 979 | 979 | 979 | | 307 | 306 | 307 | 307 | | 1686 | 1683 | 1686 | 1686 | |
| insulin | -0.1376 | 0.3482 | 0.3478 | 0.9864 | 1 | 0.0421 | 0.4986 | 0.3843 | 0.9864 | 1 | -0.0982 | 0.3700 | 0.3465 | 0.9881 | 1 | -0.0263 | 0.4307 | 0.3674 | 0.9863 | 1 |
| | 0.0002 | <.0001 | <.0001 | <.0001 | | 0.1881 | <.0001 | <.0001 | <.0001 | | 0.0859 | <.0001 | <.0001 | <.0001 | | 0.2804 | <.0001 | <.0001 | <.0001 | |
| | 707 | 704 | 707 | 707 | 707 | 979 | 979 | 979 | 979 | 979 | 307 | 306 | 307 | 307 | 307 | 1686 | 1683 | 1686 | 1686 | 1686 |

*Table continued on next page*

## Appendix 9: Pearson Correlation Coefficients for Covariates included in Aim 1 Analyses (Phase 2) (Continued)

| | African-American Jackson | | | | | Non-Hispanic White Rochester | | | | | Hispanic Starr County | | | | | African-American/Non-Hispanic White Jackson/Rochester | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Diabetics** | | | | | | | | | | | | | | | | | | | | |
| | exf_age | bmi | glucose | Homa1_IR | insulin | exf_age | bmi | glucose | Homa1_IR | insulin | exf_age | bmi | glucose | Homa1_IR | insulin | exf_age | bmi | glucose | Homa1_IR | insulin |
| exf_age | 1 | | | | | 1 | | | | | 1 | | | | | 1 | | | | |
| | | | | | | | | | | | | | | | | | | | | |
| | 366 | | | | | 178 | | | | | 772 | | | | | 544 | | | | |
| bmi | -0.1984 | 1 | | | | -0.3206 | 1 | | | | -0.2008 | 1 | | | | -0.2456 | 1 | | | |
| | 0.0001 | | | | | <.0001 | | | | | <.0001 | | | | | <.0001 | | | | |
| | 366 | 366 | | | | 178 | 178 | | | | 765 | 765 | | | | 544 | 544 | | | |
| glucose | -0.0867 | -0.0228 | 1 | | | 0.0358 | 0.0626 | 1 | | | -0.2750 | -0.0772 | 1 | | | -0.0544 | -0.0060 | 1 | | |
| | 0.0977 | 0.6642 | | | | 0.6353 | 0.4062 | | | | <.0001 | 0.0329 | | | | 0.2054 | 0.8897 | | | |
| | 366 | 366 | 366 | | | 178 | 178 | 178 | | | 772 | 765 | 772 | | | 544 | 544 | 544 | | |
| Homa1_IR | -0.1109 | 0.1375 | 0.1378 | 1 | | 0.0569 | 0.0983 | 0.2068 | 1 | | 0.0392 | 0.1219 | 0.1547 | 1 | | -0.0542 | 0.1242 | 0.1487 | 1 | |
| | 0.0508 | 0.0153 | 0.015 | | | 0.4597 | 0.2008 | 0.0067 | | | 0.4545 | 0.0200 | 0.0030 | | | 0.2346 | 0.0063 | 0.0011 | | |
| | 311 | 311 | 311 | 311 | | 171 | 171 | 171 | 171 | | 366 | 364 | 366 | 366 | | 482 | 482 | 482 | 482 | |
| insulin | -0.0937 | 0.1372 | -0.0775 | 0.9248 | 1 | 0.0491 | 0.1044 | 0.0043 | 0.9675 | 1 | 0.0482 | 0.1636 | 0.0233 | 0.9785 | 1 | -0.0416 | 0.1242 | -0.0640 | 0.9329 | 1 |
| | 0.0989 | 0.0155 | 0.1724 | <.0001 | | 0.5239 | 0.1742 | 0.9559 | <.0001 | | 0.3583 | 0.0017 | 0.657 | <.0001 | | 0.3624 | 0.0063 | 0.1605 | <.0001 | |
| | 311 | 311 | 311 | 311 | 311 | 171 | 171 | 171 | 171 | 171 | 366 | 364 | 366 | 366 | 366 | 482 | 482 | 482 | 482 | 482 |

## Appendix 10: Statin Use and Changes in Differences in Fasting Blood Glucose (Phase 2 – Phase 1; mg/dL) in the Longitudinal Analyses

| | African-American Jackson | Non-Hispanic White Rochester | Hispanic Starr County | African-American/ Non-Hispanic White Jackson/ Rochester |
|---|---|---|---|---|
| **UNIVARIATE** | | | | |
| **#Obs** | 840 | 1008 | 475 | 1848 |
| **Statin** | -4.43$^{\delta}$ | 1.41$^{\delta}$ | 1.69$^{\delta}$ | 0.65$^{\delta}$ |
| **MULTIVARIABLE** | | | | |
| **# Obs** | N=465 | N=456 | N=475 | N=921 |
| **Statin** | -6.41$^{\delta}$ | 3.61$^{\delta}$ | 12.73$^{\delta}$ | 1.32$^{\delta}$ |

All models adjusted for Phase 1 glucose levels.

$^{\delta}$ $p \geq 0.05$; Obs: observations.

## Appendix 11: Summary of Fasting Insulin in the Longitudinal Analyses

| | African-American Jackson | Non-Hispanic White Rochester | Hispanic Starr County | African-American/ Non-Hispanic White Jackson/ Rochester |
|---|---|---|---|---|
| | **UNIVARIATE ANALYSES FOR FASTING INSULIN** | | | |
| **# Obs Used** | **673** | **967** | **362** | **1640** |
| Statin | -0.18 | 0.37 | -3.21* | 0.25 |
| | **MIXED MODEL ANALYSES FOR FASTING INSULIN** | | | |
| **# Obs Used** | **1170** | **1318** | **652** | **2488** |
| Intercept | 6.92* | -5.81*** | -1.20 | -2.63*** |
| BMI | 0.23*** | 0.38*** | 0.44*** | 0.32*** |
| Age | -0.12*** | 0.03 | --- | --- |
| HTN med | 1.35* | 1.04* | --- | 0.97* |
| Menopause | --- | -0.30 | --- | --- |
| Family history of diabetes | --- | --- | --- | --- |
| Education | --- | --- | --- | --- |
| Statin | 0.05 | -0.15 | 18.09 | 0.16 |

*0.05 > p > 0.01; **0.01≥ p > 0.001; ***p ≤ 0.001; --- covariate excluded via stepwise selection.
BMI: body mass index; HTN med: antihypertensive use; Obs: observations.

## Appendix 12: Risk Allele Frequencies Observed in Rochester and Jackson, Compared to Morris *et al*, 2012

| | Risk Allele Frequency | | |
|---|---|---|---|
| | **Rochester** | **Jackson** | **Morris** |
| **SNP** | N=1159 | N=1303 | |
| rs10203174 | 0.88 | 0.64 | 0.89 |
| rs10278336 | 0.50 | 0.78 | 0.50 |
| rs10401969 | 0.08 | 0.16 | 0.08 |
| rs10758593 | 0.39 | 0.52 | 0.42 |
| rs10811661 | 0.81 | --- | 0.82 |
| rs10830963 | 0.29 | 0.06 | 0.31 |
| rs10842994 | 0.81 | 0.96 | 0.80 |
| rs10923931 | 0.11 | 0.33 | 0.12 |
| rs11063069 | 0.23 | 0.18 | 0.21 |
| rs1111875 | 0.59 | 0.78 | 0.58 |
| rs11257655 | 0.22 | 0.25 | 0.23 |
| rs11634397 | 0.68 | --- | 0.64 |
| rs11717195 | 0.75 | 0.88 | 0.77 |
| rs12242953 | 0.95 | 0.94 | 0.93 |
| rs12427353 | 0.81 | --- | 0.79 |
| rs12497268 | 0.82 | 0.93 | 0.80 |
| rs12571751 | 0.54 | 0.55 | 0.52 |
| rs12899811 | 0.30 | 0.65 | 0.31 |
| rs12970134 | 0.27 | 0.12 | 0.27 |
| rs13233731 | 0.53 | 0.74 | 0.51 |
| rs13389219 | 0.58 | 0.25 | 0.60 |
| rs1359790 | 0.70 | 0.89 | 0.72 |
| rs1496653 | 0.76 | 0.61 | 0.75 |
| rs1552224 | 0.82 | --- | 0.81 |
| rs163184 | 0.49 | 0.19 | 0.50 |
| rs16927668 | 0.21 | 0.76 | 0.24 |
| rs17168486 | 0.18 | 0.11 | 0.19 |
| rs17301514 | 0.13 | 0.05 | 0.13 |
| rs17791513 | 0.93 | 0.96 | 0.91 |
| rs17867832 | 0.91 | 0.85 | 0.91 |
| rs1801282 | 0.85 | --- | 0.86 |
| rs2007084 | 0.93 | --- | 0.92 |
| rs2261181 | 0.10 | 0.22 | 0.10 |
| rs2334499 | 0.42 | 0.11 | 0.43 |
| rs243088 | 0.48 | 0.54 | 0.45 |
| rs2447090 | 0.60 | 0.36 | 0.62 |
| rs2796441 | 0.57 | 0.83 | 0.57 |
| rs2943640 | 0.64 | --- | 0.63 |
| rs3734621 | 0.02 | 0.40 | 0.03 |

*Table continued on next page*

**Appendix 12: Risk Allele Frequencies Observed in Rochester and Jackson, Compared to Morris *et al*, 2012 (Continued)**

| | Risk Allele Frequency | | |
|---|---|---|---|
| | **Rochester** | **Jackson** | **Morris** |
| **SNP** | N=1159 | N=1303 | |
| rs3802177 | 0.67 | 0.92 | 0.66 |
| rs4299828 | 0.79 | 0.73 | 0.79 |
| rs4402960 | 0.30 | 0.54 | 0.33 |
| rs4430796 | 0.50 | 0.59 | - |
| rs4458523 | 0.57 | 0.57 | 0.57 |
| rs4502156 | 0.57 | 0.25 | 0.52 |
| rs459193 | 0.76 | 0.59 | 0.70 |
| rs4812829 | 0.18 | 0.11 | 0.19 |
| rs516946 | 0.76 | 0.78 | 0.76 |
| rs5215 | 0.41 | 0.09 | 0.41 |
| rs6795735 | 0.59 | 0.19 | 0.59 |
| rs6819243 | 0.98 | 0.66 | 0.96 |
| rs6878122 | 0.24 | 0.13 | 0.28 |
| rs7177055 | 0.72 | 0.35 | 0.68 |
| rs7202877 | 0.90 | 0.82 | 0.89 |
| rs7569522 | 0.45 | 0.49 | 0.44 |
| rs7756992 | 0.27 | 0.59 | 0.29 |
| rs780094 | 0.65 | 0.83 | 0.61 |
| rs7845219 | 0.52 | 0.66 | 0.52 |
| rs7903146 | 0.30 | 0.30 | 0.27 |
| rs7955901 | 0.44 | 0.23 | 0.45 |
| rs8108269 | 0.27 | 0.37 | 0.31 |
| rs8182584 | 0.39 | 0.39 | 0.38 |
| rs849135 | 0.52 | 0.75 | 0.52 |
| rs9936385 | 0.42 | 0.47 | 0.41 |

SNP: single nucleotide polymorphism.
*Source: [Morris *et al.*, 2012].

## Appendix 13: Univariate Analyses of SNP and Predicted Fasting Blood Glucose in Non-Hispanic Whites

| SNP | Estimate | Standard Error | Probability | False Discovery Rate |
|---|---|---|---|---|
| rs10278336 | 1.27464 | 0.453078 | 0.005071 | 0.324568 |
| rs8108269 | 1.257129 | 0.512379 | 0.014442 | 0.462159 |
| rs11717195 | 1.076712 | 0.519397 | 0.038617 | 0.823821 |
| rs11063069 | 0.939013 | 0.511632 | 0.066973 | 1.071575 |
| rs3802177 | 0.850528 | 0.470239 | 0.071017 | 0.909022 |
| rs7756992 | -0.84524 | 0.49012 | 0.085144 | 0.908206 |
| rs2007084 | -1.50344 | 0.877849 | 0.087319 | 0.798342 |
| rs10811661 | 0.915763 | 0.554374 | 0.099104 | 0.79283 |
| rs17867832 | 1.149537 | 0.736078 | 0.118907 | 0.845564 |
| rs9936385 | 0.675433 | 0.440874 | 0.126064 | 0.806813 |
| rs1111875 | 0.68491 | 0.451541 | 0.129859 | 0.755545 |
| rs459193 | 0.74898 | 0.503106 | 0.137111 | 0.731261 |
| rs10830963 | 0.692147 | 0.477894 | 0.148071 | 0.728963 |
| rs4299828 | 0.773941 | 0.537548 | 0.150479 | 0.687906 |
| rs780094 | 0.652399 | 0.453572 | 0.150876 | 0.643736 |
| rs2447090 | -0.64266 | 0.459962 | 0.16289 | 0.651559 |
| rs6878122 | 0.655954 | 0.531622 | 0.217754 | 0.81978 |
| rs12899811 | -0.5845 | 0.491087 | 0.234449 | 0.833596 |
| rs1496653 | 0.599723 | 0.51818 | 0.247603 | 0.834032 |
| rs10842994 | 0.648385 | 0.561223 | 0.248445 | 0.795024 |
| rs3734621 | 1.614244 | 1.436017 | 0.261435 | 0.796753 |
| rs4812829 | -0.63294 | 0.566577 | 0.264402 | 0.76917 |
| rs4502156 | 0.458897 | 0.43676 | 0.293845 | 0.817655 |
| rs8182584 | -0.46008 | 0.442122 | 0.298489 | 0.795971 |
| rs7569522 | 0.41454 | 0.43194 | 0.337601 | 0.864258 |
| rs2334499 | -0.41546 | 0.434003 | 0.338832 | 0.834047 |
| rs2796441 | 0.387405 | 0.451532 | 0.391261 | 0.927433 |

*Table continued on next page*

**Appendix 13: Univariate Analyses of SNP and Predicted Fasting Blood Glucose in Non-Hispanic Whites (Continued)**

| SNP | Estimate | Standard Error | Probability | False Discovery Rate |
|---|---|---|---|---|
| rs12497268 | -0.48073 | 0.583574 | 0.41041 | 0.93808 |
| rs10401969 | 0.631899 | 0.77685 | 0.416319 | 0.918773 |
| rs4458523 | 0.315363 | 0.437815 | 0.471627 | 1.006137 |
| rs17168486 | 0.417162 | 0.5807 | 0.472817 | 0.976137 |
| rs6795735 | -0.30357 | 0.429871 | 0.48036 | 0.960719 |
| rs1359790 | -0.34603 | 0.490738 | 0.481018 | 0.932883 |
| rs1801282 | 0.429611 | 0.611173 | 0.482384 | 0.908017 |
| rs12970134 | -0.35143 | 0.509679 | 0.490781 | 0.897428 |
| rs2261181 | 0.530443 | 0.770254 | 0.491315 | 0.87345 |
| rs849135 | 0.312865 | 0.4558 | 0.492732 | 0.852292 |
| rs163184 | 0.296519 | 0.439094 | 0.499758 | 0.841698 |
| rs516946 | 0.341101 | 0.515188 | 0.508178 | 0.833933 |
| rs1552224 | 0.379541 | 0.582426 | 0.514883 | 0.823813 |
| rs10758593 | 0.293122 | 0.455456 | 0.520105 | 0.811872 |
| rs7903146 | -0.29663 | 0.476408 | 0.533764 | 0.813354 |
| rs12427353 | 0.295558 | 0.547664 | 0.589633 | 0.877594 |
| rs11634397 | -0.24039 | 0.463423 | 0.604156 | 0.878773 |
| rs2943640 | 0.22605 | 0.462441 | 0.625157 | 0.889112 |
| rs243088 | 0.20381 | 0.437144 | 0.641228 | 0.892143 |
| rs12242953 | -0.45567 | 0.978721 | 0.641692 | 0.873793 |
| rs13233731 | 0.189368 | 0.449482 | 0.673691 | 0.898255 |
| rs7955901 | -0.1784 | 0.44109 | 0.686032 | 0.896042 |
| rs10923931 | -0.27349 | 0.690983 | 0.692403 | 0.886276 |
| rs4430796 | -0.2037 | 0.53147 | 0.701658 | 0.880512 |
| rs12571751 | 0.16017 | 0.440327 | 0.716176 | 0.881447 |
| rs7177055 | 0.174052 | 0.488875 | 0.721952 | 0.871791 |
| rs16927668 | 0.158778 | 0.544812 | 0.770823 | 0.913568 |

*Table continued on next page*

**Appendix 13: Univariate Analyses of SNP and Predicted Fasting Blood Glucose in Non-Hispanic Whites (Continued)**

| SNP | Estimate | Standard Error | Probability | False Discovery Rate |
|---|---|---|---|---|
| rs7202877 | 0.199757 | 0.712901 | 0.779422 | 0.906964 |
| rs17791513 | 0.190004 | 0.868855 | 0.826975 | 0.945114 |
| rs13389219 | -0.09422 | 0.449971 | 0.834211 | 0.936658 |
| rs4402960 | -0.09418 | 0.463522 | 0.839064 | 0.925864 |
| rs10203174 | 0.093623 | 0.655486 | 0.886474 | 0.961599 |
| rs17301514 | 0.091449 | 0.670425 | 0.891549 | 0.950985 |
| rs6819243 | 0.177359 | 1.469832 | 0.903998 | 0.948457 |
| rs7845219 | 0.047674 | 0.445362 | 0.91479 | 0.944299 |
| rs5215 | 0.006382 | 0.447337 | 0.988621 | 1.004314 |
| rs11257655 | -0.00238 | 0.528467 | 0.996409 | 0.996409 |

SNP: single nucleotide polymorphism.

## Appendix 14: Multivariable Analyses of SNP and Predicted Fasting Blood Glucose in Non-Hispanic Whites

| SNP | Estimate | Standard Error | Probability | False Discovery Rate |
|---|---|---|---|---|
| rs11717195 | 1.352161 | 0.465898 | 0.003848 | 0.2463 |
| rs10278336 | 1.100832 | 0.409075 | 0.007333 | 0.234659 |
| rs10830963 | 1.096046 | 0.429352 | 0.010947 | 0.233529 |
| rs459193 | 1.065871 | 0.454578 | 0.019383 | 0.310132 |
| rs10811661 | 1.137001 | 0.496867 | 0.022484 | 0.287798 |
| rs780094 | 0.848465 | 0.408597 | 0.038293 | 0.408459 |
| rs8182584 | -0.74937 | 0.398076 | 0.060283 | 0.551154 |
| rs1111875 | 0.728919 | 0.405618 | 0.072858 | 0.582861 |
| rs7756992 | -0.75407 | 0.442301 | 0.088765 | 0.631216 |
| rs8108269 | 0.759309 | 0.46458 | 0.102729 | 0.657468 |
| rs3734621 | 2.093115 | 1.288076 | 0.104719 | 0.609273 |
| rs1496653 | 0.721347 | 0.466528 | 0.122612 | 0.653931 |
| rs6878122 | 0.700626 | 0.479823 | 0.144795 | 0.712837 |
| rs13233731 | 0.581165 | 0.406352 | 0.153209 | 0.700384 |
| rs10842994 | 0.707454 | 0.50697 | 0.163424 | 0.697274 |
| rs2007084 | -1.10488 | 0.792354 | 0.163736 | 0.654943 |
| rs7569522 | 0.523177 | 0.389455 | 0.179692 | 0.676488 |
| rs7202877 | 0.852732 | 0.642409 | 0.18491 | 0.657459 |
| rs7845219 | 0.533365 | 0.402336 | 0.185482 | 0.624782 |
| rs10758593 | 0.50656 | 0.410899 | 0.218157 | 0.698103 |
| rs2261181 | 0.853503 | 0.692564 | 0.218317 | 0.665346 |
| rs17867832 | 0.759834 | 0.664657 | 0.253438 | 0.737275 |
| rs4502156 | 0.441374 | 0.393439 | 0.262406 | 0.730173 |
| rs2796441 | 0.452909 | 0.405363 | 0.264342 | 0.704911 |
| rs4299828 | 0.538027 | 0.483128 | 0.265908 | 0.680724 |
| rs3802177 | 0.468946 | 0.424973 | 0.270289 | 0.665326 |
| rs12571751 | 0.378926 | 0.394717 | 0.337467 | 0.799921 |

*Table continued on next page*

**Appendix 14: Multivariable Analyses of SNP and Predicted Fasting Blood Glucose in Non-Hispanic Whites (Continued)**

| SNP | Estimate | Standard Error | Probability | False Discovery Rate |
|---|---|---|---|---|
| rs516946 | 0.426485 | 0.465223 | 0.359673 | 0.82211 |
| rs12899811 | -0.40279 | 0.441954 | 0.362479 | 0.799953 |
| rs11063069 | 0.416135 | 0.46405 | 0.370234 | 0.789832 |
| rs10401969 | 0.616721 | 0.699008 | 0.377999 | 0.780385 |
| rs4812829 | -0.42372 | 0.510628 | 0.406998 | 0.813997 |
| rs10923931 | -0.51225 | 0.620109 | 0.409116 | 0.793437 |
| rs163184 | 0.304482 | 0.395886 | 0.442144 | 0.832272 |
| rs4458523 | 0.299895 | 0.394288 | 0.447212 | 0.817758 |
| rs9936385 | 0.294003 | 0.39854 | 0.461001 | 0.819558 |
| rs12497268 | -0.36241 | 0.524121 | 0.48956 | 0.846806 |
| rs849135 | 0.281304 | 0.411044 | 0.494023 | 0.832039 |
| rs1359790 | -0.29944 | 0.44187 | 0.498259 | 0.817655 |
| rs17168486 | 0.313973 | 0.5215 | 0.547376 | 0.875802 |
| rs11257655 | -0.2788 | 0.475278 | 0.557708 | 0.870569 |
| rs1801282 | 0.313368 | 0.551655 | 0.570224 | 0.868913 |
| rs5215 | -0.18408 | 0.402813 | 0.647859 | 0.964255 |
| rs12427353 | 0.218711 | 0.492822 | 0.657362 | 0.956162 |
| rs13389219 | 0.179898 | 0.405583 | 0.657533 | 0.935159 |
| rs4402960 | -0.17005 | 0.416524 | 0.683234 | 0.950586 |
| rs2334499 | -0.15785 | 0.392892 | 0.688001 | 0.936853 |
| rs12242953 | -0.35289 | 0.894785 | 0.693442 | 0.924589 |
| rs2943640 | 0.151593 | 0.416524 | 0.716031 | 0.935224 |
| rs243088 | -0.14093 | 0.393664 | 0.720474 | 0.922207 |
| rs7903146 | 0.131056 | 0.429532 | 0.760392 | 0.954217 |
| rs1552224 | 0.159664 | 0.524491 | 0.760921 | 0.936519 |
| rs2447090 | -0.11709 | 0.416992 | 0.778975 | 0.940649 |
| rs12970134 | 0.12908 | 0.460756 | 0.779467 | 0.923812 |

*Table continued on next page*

**Appendix 14: Multivariable Analyses of SNP and Predicted Fasting Blood Glucose in Non-Hispanic Whites (Continued)**

| SNP | Estimate | Standard Error | Probability | False Discovery Rate |
|---|---|---|---|---|
| rs17791513 | -0.19563 | 0.781685 | 0.802475 | 0.933789 |
| rs4430796 | 0.114173 | 0.480958 | 0.812443 | 0.928506 |
| rs6819243 | -0.29301 | 1.320243 | 0.824446 | 0.925694 |
| rs6795735 | 0.079935 | 0.388802 | 0.837183 | 0.923788 |
| rs17301514 | -0.11502 | 0.603781 | 0.848985 | 0.920933 |
| rs11634397 | 0.068775 | 0.416836 | 0.869007 | 0.926941 |
| rs7955901 | 0.049763 | 0.396656 | 0.900208 | 0.94448 |
| rs7177055 | 0.039639 | 0.443478 | 0.92881 | 0.958772 |
| rs10203174 | -0.05211 | 0.590153 | 0.929677 | 0.944433 |
| rs16927668 | 0.037698 | 0.489473 | 0.938637 | 0.938637 |

SNP: single nucleotide polymorphism.

## Appendix 15: Interaction of Statin and Individual SNPs and Predicted Fasting Blood Glucose in Non-Hispanic Whites, After Adjusting for Age, Gender, BMI and Top Principal Components

| Statin x SNP | Estimate | Standard Error | Probability | False Discovery Rate |
|---|---|---|---|---|
| rs2261181 | -3.56909 | 1.779987 | 0.045426 | 2.907245 |
| rs8108269 | 2.365109 | 1.22406 | 0.053836 | 1.72274 |
| rs516946 | 2.18197 | 1.239792 | 0.078957 | 1.684409 |
| rs10758593 | 1.680935 | 1.060548 | 0.113532 | 1.816516 |
| rs7569522 | -1.54014 | 1.013482 | 0.129155 | 1.653188 |
| rs7202877 | -2.42297 | 1.60382 | 0.131411 | 1.401718 |
| rs11063069 | 1.582831 | 1.114785 | 0.156201 | 1.428125 |
| rs10203174 | -2.07689 | 1.517918 | 0.171775 | 1.374202 |
| rs6819243 | -4.74507 | 3.643534 | 0.193334 | 1.374822 |
| rs2796441 | -1.29248 | 1.002665 | 0.197909 | 1.266616 |
| rs459193 | -1.47772 | 1.187335 | 0.213806 | 1.243959 |
| rs7845219 | 1.233155 | 1.010838 | 0.222998 | 1.189324 |
| rs10401969 | -2.45386 | 2.052927 | 0.232471 | 1.14447 |
| rs12970134 | 1.458638 | 1.235394 | 0.238215 | 1.088983 |
| rs2447090 | -1.3209 | 1.125122 | 0.240885 | 1.027777 |
| rs3734621 | -4.16997 | 3.63695 | 0.252049 | 1.008195 |
| rs12899811 | -1.33988 | 1.172846 | 0.253764 | 0.955346 |
| rs8182584 | 1.200448 | 1.06639 | 0.260764 | 0.927162 |
| rs10923931 | -1.76839 | 1.650196 | 0.284345 | 0.957795 |
| rs7177055 | 1.138176 | 1.165395 | 0.329163 | 1.053321 |
| rs13389219 | -1.03753 | 1.072946 | 0.333962 | 1.017789 |
| rs17867832 | -1.79999 | 1.879564 | 0.338642 | 0.985141 |
| rs11634397 | 1.11262 | 1.169791 | 0.341946 | 0.951502 |
| rs2943640 | 0.99175 | 1.061223 | 0.350426 | 0.934469 |
| rs9936385 | -0.96229 | 1.068751 | 0.368299 | 0.942846 |
| rs11717195 | -0.89641 | 1.126694 | 0.426591 | 1.05007 |

*Table continued on next page*

**Appendix 15: Interaction of Statin and Individual SNPs and Predicted Fasting Blood Glucose in Non-Hispanic Whites, After Adjusting for Age, Gender, BMI and Top Principal Components (Continued)**

| Statin x SNP | Estimate | Standard Error | Probability | False Discovery Rate |
|---|---|---|---|---|
| rs243088 | 0.733317 | 0.971858 | 0.450832 | 1.068638 |
| rs4299828 | -0.94385 | 1.309535 | 0.471358 | 1.07739 |
| rs7903146 | -0.84181 | 1.168637 | 0.471614 | 1.040803 |
| rs5215 | 0.776794 | 1.082701 | 0.473387 | 1.009892 |
| rs1552224 | -0.96261 | 1.395993 | 0.490758 | 1.013178 |
| rs4430796 | 0.896457 | 1.303281 | 0.491832 | 0.983663 |
| rs1496653 | 0.828724 | 1.208221 | 0.493054 | 0.956226 |
| rs3802177 | -0.74235 | 1.100519 | 0.50024 | 0.941628 |
| rs16927668 | -0.86246 | 1.308044 | 0.509941 | 0.932463 |
| rs12427353 | -0.8532 | 1.308089 | 0.514505 | 0.914675 |
| rs4402960 | 0.641435 | 1.076201 | 0.551402 | 0.953776 |
| rs2334499 | 0.589652 | 1.09628 | 0.590881 | 0.995168 |
| rs11257655 | 0.513526 | 1.267496 | 0.68552 | 1.124956 |
| rs10830963 | 0.40759 | 1.096565 | 0.710257 | 1.136412 |
| rs1359790 | -0.35458 | 1.14219 | 0.756344 | 1.180635 |
| rs17168486 | 0.385172 | 1.377241 | 0.779834 | 1.188318 |
| rs13233731 | -0.25146 | 0.988472 | 0.799284 | 1.189632 |
| rs1801282 | -0.38875 | 1.552182 | 0.802327 | 1.16702 |
| rs163184 | 0.265007 | 1.071722 | 0.804788 | 1.144587 |
| rs4812829 | -0.29919 | 1.337029 | 0.823013 | 1.145061 |
| rs12497268 | 0.283374 | 1.325319 | 0.830768 | 1.131258 |
| rs2007084 | -0.45185 | 2.255587 | 0.841298 | 1.12173 |
| rs7756992 | 0.234603 | 1.17806 | 0.842222 | 1.100045 |
| rs1111875 | -0.18557 | 1.108535 | 0.867116 | 1.109908 |
| rs7955901 | 0.16969 | 1.028033 | 0.868954 | 1.090452 |
| rs17791513 | -0.30524 | 1.945801 | 0.875402 | 1.077418 |

*Table continued on next page*

**Appendix 15: Interaction of Statin and Individual SNPs and Predicted Fasting Blood Glucose in Non-Hispanic Whites, After Adjusting for Age, Gender, BMI and Top Principal Components (Continued)**

| Statin x SNP | Estimate | Standard Error | Probability | False Discovery Rate |
|---|---|---|---|---|
| rs10278336 | 0.159861 | 1.102127 | 0.884725 | 1.068347 |
| rs10842994 | -0.19372 | 1.358349 | 0.886647 | 1.050841 |
| rs12571751 | 0.132005 | 1.040809 | 0.89912 | 1.046249 |
| rs4502156 | 0.1253 | 1.003964 | 0.900722 | 1.029397 |
| rs10811661 | 0.142338 | 1.222556 | 0.907355 | 1.018785 |
| rs780094 | 0.106329 | 0.976902 | 0.913365 | 1.007851 |
| rs6878122 | -0.11215 | 1.331743 | 0.932915 | 1.011975 |
| rs6795735 | -0.07819 | 1.008822 | 0.93825 | 1.0008 |
| rs12242953 | 0.135572 | 2.046982 | 0.947218 | 0.993803 |
| rs849135 | -0.01639 | 1.107316 | 0.988195 | 1.020072 |
| rs17301514 | -0.01455 | 1.622633 | 0.992847 | 1.008606 |
| rs4458523 | -0.00202 | 1.082084 | 0.998511 | 0.998511 |

Adjustment for age, gender, BMI, and top 4 principal components.
BMI: body mass index; SNP: single nucleotide polymorphism.

## Appendix 16: Univariate and Multivariable Analyses for Individual SNPs and T2DM in Non-Hispanic Whites

| SNP | 1 Risk Allele | | | | 2 Risk Alleles | | | |
|---|---|---|---|---|---|---|---|---|
| | Estimate | Standard Error | Probability | False Discovery Rate | Estimate | Standard Error | Probability | False Discovery Rate |
| | UNIVARIATE | | | | | | | |
| rs10278336 | -0.14193 | 0.250836 | 0.571707 | 1.045407 | 0.214353 | 0.288436 | 0.45764 | 0.91528 |
| rs10758593 | 0.151806 | 0.219475 | 0.489372 | 0.978743 | 0.013924 | 0.319232 | 0.965222 | 1.187966 |
| rs10811661 | 1.716959 | 1.041468 | 0.099685 | 1.275963 | 1.642954 | 1.035391 | 0.113016 | 1.205501 |
| rs10830963 | 0.015289 | 0.211763 | 0.942465 | 1.159957 | 0.189181 | 0.350716 | 0.589776 | 0.920625 |
| rs10842994 | -0.07067 | 0.582561 | 0.903487 | 1.133787 | 0.021695 | 0.570923 | 0.969699 | 1.170957 |
| rs10923931 | 0.219914 | 0.245063 | 0.36983 | 1.183457 | 0.265643 | 0.684181 | 0.697939 | 1.015185 |
| rs11063069 | 0.038831 | 0.214677 | 0.856512 | 1.11871 | 0.386584 | 0.385975 | 0.316898 | 0.965784 |
| rs1111875 | 0.269965 | 0.299242 | 0.367285 | 1.237171 | 0.223655 | 0.316638 | 0.480212 | 0.931321 |
| rs11257655 | 0.43387 | 0.203956 | 0.03375 | 1.080004 | 0.012142 | 0.514085 | 0.981164 | 1.162861 |
| rs11634397 | 0.493186 | 0.389566 | 0.205944 | 1.464488 | 0.415422 | 0.39156 | 0.289088 | 1.027867 |
| rs11717195 | 0.565566 | 0.559706 | 0.312623 | 1.250494 | 0.516043 | 0.55579 | 0.35348 | 0.942613 |
| rs12242953 | -0.69989 | 1.233732 | 0.570698 | 1.074254 | -0.92692 | 1.209516 | 0.443724 | 0.916075 |
| rs12427353 | 0.623634 | 0.64442 | 0.33351 | 1.255567 | 0.550358 | 0.634879 | 0.386313 | 0.950926 |
| rs12497268 | 0.261279 | 0.673061 | 0.697991 | 1.038871 | 0.312166 | 0.660973 | 0.636875 | 0.970475 |
| rs12571751 | 0.287375 | 0.26722 | 0.28256 | 1.391066 | 0.183203 | 0.297214 | 0.537833 | 0.983466 |
| rs12899811 | 0.348438 | 0.20989 | 0.097348 | 1.557568 | 0.314387 | 0.372357 | 0.398784 | 0.945267 |
| rs12970134 | 0.15008 | 0.211084 | 0.477325 | 1.053407 | 0.975515 | 0.346326 | 0.004989 | 0.319326 |
| rs13233731 | 0.375334 | 0.280762 | 0.181713 | 1.453703 | 0.603288 | 0.306395 | 0.049353 | 1.052874 |
| rs13389219 | -0.36998 | 0.273454 | 0.176497 | 1.61369 | 0.079883 | 0.282311 | 0.777291 | 1.036389 |
| rs1359790 | -0.35143 | 0.367159 | 0.338825 | 1.204711 | 0.093878 | 0.359364 | 0.793991 | 1.037049 |
| rs1496653 | -0.30335 | 0.406112 | 0.455337 | 1.165663 | -0.43366 | 0.398678 | 0.277089 | 1.108356 |
| rs1552224 | -1.10406 | 0.482335 | 0.022381 | 1.43237 | -0.89204 | 0.461806 | 0.053814 | 0.861017 |
| rs163184 | 0.068801 | 0.242519 | 0.776731 | 1.057676 | 0.085603 | 0.284464 | 0.763561 | 1.062345 |

*Table continued on next page*

**Appendix 16: Univariate and Multivariable Analyses for Individual SNPs and T2DM in Non-Hispanic Whites (Continued)**

| | 1 Risk Allele | | | | 2 Risk Alleles | | | |
|---|---|---|---|---|---|---|---|---|
| SNP | Estimate | Standard Error | Probability | False Discovery Rate | Estimate | Standard Error | Probability | False Discovery Rate |
| rs16927668 | -0.03697 | 0.213334 | 0.862485 | 1.10398 | -0.59019 | 0.630924 | 0.349889 | 0.973604 |
| rs17168486 | -0.10201 | 0.228622 | 0.655584 | 0.998985 | 0.562301 | 0.473452 | 0.235374 | 1.158766 |
| rs1801282 | -0.62443 | 0.698191 | 0.371439 | 1.132006 | -0.14747 | 0.671716 | 0.826295 | 1.03692 |
| rs2334499 | 0.010508 | 0.223796 | 0.962565 | 1.140818 | 0.073273 | 0.283971 | 0.79646 | 1.019469 |
| rs243088 | -0.0504 | 0.230605 | 0.827069 | 1.102759 | -0.23443 | 0.287458 | 0.415058 | 0.948704 |
| rs2447090 | 0.015899 | 0.306533 | 0.958649 | 1.157614 | 0.197001 | 0.319658 | 0.537908 | 0.956281 |
| rs2796441 | 0.209547 | 0.294311 | 0.47671 | 1.089622 | 0.441716 | 0.311733 | 0.156943 | 1.434904 |
| rs2943640 | 0.296791 | 0.348183 | 0.394287 | 1.097146 | 0.379484 | 0.355634 | 0.286315 | 1.077893 |
| rs3802177 | 0.259006 | 0.356085 | 0.467245 | 1.107544 | 0.106736 | 0.363845 | 0.769337 | 1.047608 |
| rs4299828 | 0.479878 | 0.645419 | 0.457423 | 1.125964 | 0.841452 | 0.633083 | 0.184242 | 1.179149 |
| rs4402960 | -0.09607 | 0.207951 | 0.644247 | 1.030795 | -0.38792 | 0.378139 | 0.305307 | 0.976983 |
| rs4430796 | 0.257049 | 0.294109 | 0.382426 | 1.112512 | 0.277507 | 0.361389 | 0.442815 | 0.944673 |
| rs4458523 | 0.35658 | 0.288632 | 0.217095 | 1.389409 | 0.169321 | 0.313129 | 0.588862 | 0.942179 |
| rs4502156 | -0.13193 | 0.263374 | 0.616573 | 1.038438 | -0.26528 | 0.287451 | 0.356404 | 0.912394 |
| rs459193 | 0.145722 | 0.436375 | 0.738528 | 1.050352 | 0.193044 | 0.426781 | 0.651177 | 0.969193 |
| rs4812829 | 0.222668 | 0.213606 | 0.297578 | 1.360357 | -0.58759 | 0.761622 | 0.440675 | 0.972525 |
| rs516946 | 0.544073 | 0.529364 | 0.30441 | 1.298816 | 0.690759 | 0.520104 | 0.184577 | 1.073904 |
| rs5215 | 0.378762 | 0.230685 | 0.101065 | 1.078026 | 0.350031 | 0.30547 | 0.252243 | 1.076235 |
| rs6795735 | -0.1224 | 0.259167 | 0.636881 | 1.045138 | -0.39486 | 0.282034 | 0.161945 | 1.295556 |
| rs6878122 | 0.110723 | 0.207317 | 0.593459 | 1.055038 | 0.547916 | 0.422761 | 0.195393 | 1.042097 |
| rs7177055 | 0.351057 | 0.469199 | 0.454591 | 1.212242 | 0.62717 | 0.463038 | 0.17603 | 1.251766 |
| rs7569522 | 0.089332 | 0.235193 | 0.704193 | 1.024281 | 0.195093 | 0.281715 | 0.488844 | 0.920176 |
| rs7756992 | 0.117924 | 0.206103 | 0.567399 | 1.10041 | -0.14864 | 0.439219 | 0.735143 | 1.045536 |
| rs780094 | 0.092099 | 0.324558 | 0.776672 | 1.080587 | 0.199348 | 0.327628 | 0.543083 | 0.939387 |

*Table continued on next page*

**Appendix 16: Univariate and Multivariable Analyses for Individual SNPs and T2DM in Non-Hispanic Whites (Continued)**

| | 1 Risk Allele | | | | 2 Risk Alleles | | | |
|---|---|---|---|---|---|---|---|---|
| SNP | Estimate | Standard Error | Probability | False Discovery Rate | Estimate | Standard Error | Probability | False Discovery Rate |
| rs7845219 | -0.44095 | 0.2436 | 0.070711 | 1.508502 | -0.15777 | 0.273508 | 0.564225 | 0.925907 |
| rs7903146 | 0.237321 | 0.215943 | 0.272152 | 1.451476 | 0.819333 | 0.30422 | 0.007248 | 0.231929 |
| rs7955901 | -0.15683 | 0.224279 | 0.484616 | 1.000497 | -0.28234 | 0.292734 | 0.335128 | 0.974917 |
| rs8108269 | 0.105026 | 0.203101 | 0.605243 | 1.046906 | -0.58344 | 0.553967 | 0.292612 | 0.985642 |
| rs8182584 | -0.09796 | 0.212051 | 0.644256 | 1.005668 | -0.37941 | 0.32654 | 0.245667 | 1.123051 |
| rs849135 | 0.342077 | 0.277392 | 0.217925 | 1.267925 | 0.584427 | 0.304842 | 0.055631 | 0.712071 |
| rs9936385 | 0.159037 | 0.226782 | 0.483366 | 1.031181 | 0.169842 | 0.291182 | 0.55989 | 0.942973 |
| | MULTIVARIABLE | | | | | | | |
| rs10278336 | -0.16621 | 0.258828 | 0.520987 | 1.234931 | 0.152297 | 0.298408 | 0.60996 | 0.887214 |
| rs10758593 | 0.109891 | 0.225615 | 0.626361 | 1.083436 | 0.078146 | 0.327933 | 0.81172 | 1.018629 |
| rs10811661 | 1.785593 | 1.050434 | 0.089608 | 0.955819 | 1.766488 | 1.043893 | 0.091058 | 0.971282 |
| rs10830963 | 0.095279 | 0.217958 | 0.662144 | 0.985516 | 0.216568 | 0.368164 | 0.556566 | 0.913339 |
| rs10842994 | -0.17844 | 0.592782 | 0.763485 | 1.01798 | -0.14628 | 0.580614 | 0.80116 | 1.025484 |
| rs10923931 | 0.154675 | 0.252489 | 0.540342 | 1.192478 | 0.096713 | 0.70928 | 0.891581 | 1.056688 |
| rs11063069 | -0.05327 | 0.22166 | 0.810162 | 1.016674 | 0.227482 | 0.396313 | 0.566157 | 0.905852 |
| rs1111875 | 0.340886 | 0.307622 | 0.268191 | 1.00966 | 0.232144 | 0.325523 | 0.476 | 0.896 |
| rs11257655 | 0.375313 | 0.209856 | 0.074145 | 2.372635 | -0.09792 | 0.524495 | 0.851952 | 1.028773 |
| rs11634397 | 0.451534 | 0.39893 | 0.258087 | 1.032347 | 0.443787 | 0.399906 | 0.267503 | 0.951121 |
| rs11717195 | 0.556147 | 0.57263 | 0.331783 | 1.061704 | 0.519334 | 0.568766 | 0.361515 | 0.925478 |
| rs12242953 | -0.66062 | 1.2633 | 0.601192 | 1.165947 | -0.78537 | 1.234619 | 0.524905 | 0.907943 |
| rs12427353 | 0.836019 | 0.658528 | 0.204682 | 1.007664 | 0.744735 | 0.647697 | 0.250617 | 0.9435 |
| rs12497268 | 0.335063 | 0.688238 | 0.626525 | 1.0552 | 0.353292 | 0.67505 | 0.600894 | 0.894355 |
| rs12571751 | 0.358589 | 0.275263 | 0.193109 | 1.123541 | 0.278913 | 0.30631 | 0.362846 | 0.89316 |
| rs12899811 | 0.375391 | 0.215804 | 0.082393 | 1.054633 | 0.325482 | 0.381204 | 0.393498 | 0.899425 |
| rs12970134 | 0.272097 | 0.217582 | 0.211523 | 0.966964 | 1.058529 | 0.359113 | 0.003311 | 0.105939 |

*Table continued on next page*

**Appendix 16: Univariate and Multivariable Analyses for Individual SNPs and T2DM in Non-Hispanic Whites (Continued)**

| | 1 Risk Allele | | | | 2 Risk Alleles | | | |
|---|---|---|---|---|---|---|---|---|
| SNP | Estimate | Standard Error | Probability | False Discovery Rate | Estimate | Standard Error | Probability | False Discovery Rate |
| rs13233731 | 0.51167 | 0.287934 | 0.076003 | 1.621394 | 0.766742 | 0.314397 | 0.014989 | 0.319762 |
| rs13389219 | -0.37165 | 0.282438 | 0.188653 | 1.207382 | 0.155361 | 0.292603 | 0.595617 | 0.907607 |
| rs1359790 | -0.28874 | 0.37608 | 0.442892 | 1.181045 | 0.132976 | 0.367636 | 0.717683 | 0.97727 |
| rs1496653 | -0.36522 | 0.417589 | 0.382101 | 1.111567 | -0.51324 | 0.40979 | 0.210827 | 0.963783 |
| rs1552224 | -1.07156 | 0.503686 | 0.033739 | 2.159265 | -0.92824 | 0.481488 | 0.054285 | 0.694843 |
| rs163184 | 0.055692 | 0.248741 | 0.822903 | 1.012804 | 0.102482 | 0.29179 | 0.725532 | 0.947633 |
| rs16927668 | -0.01059 | 0.219102 | 0.961458 | 1.139506 | -0.61115 | 0.646028 | 0.344475 | 0.958538 |
| rs17168486 | -0.16127 | 0.235381 | 0.493481 | 1.214723 | 0.631888 | 0.487866 | 0.195682 | 1.138514 |
| rs1801282 | -0.62684 | 0.724802 | 0.387429 | 1.078064 | -0.14602 | 0.697854 | 0.834326 | 1.026862 |
| rs2334499 | 0.10635 | 0.232198 | 0.647085 | 1.010085 | 0.20227 | 0.293167 | 0.49046 | 0.896842 |
| rs243088 | -0.12858 | 0.238717 | 0.590314 | 1.180628 | -0.37772 | 0.297 | 0.203874 | 1.087329 |
| rs2447090 | 0.112695 | 0.315279 | 0.720867 | 1.025233 | 0.358209 | 0.328893 | 0.276474 | 0.931281 |
| rs2796441 | 0.182491 | 0.301862 | 0.545676 | 1.164109 | 0.483668 | 0.319634 | 0.13069 | 1.194879 |
| rs2943640 | 0.323314 | 0.357685 | 0.36636 | 1.116527 | 0.387792 | 0.364961 | 0.288355 | 0.922736 |
| rs3802177 | 0.018354 | 0.368009 | 0.960238 | 1.159533 | -0.15221 | 0.374043 | 0.684176 | 0.97305 |
| rs4299828 | 0.733021 | 0.671178 | 0.275153 | 0.978323 | 0.979619 | 0.657783 | 0.136873 | 0.97332 |
| rs4402960 | -0.07103 | 0.213886 | 0.739914 | 1.007542 | -0.45477 | 0.387944 | 0.241503 | 0.96601 |
| rs4430796 | 0.158 | 0.303021 | 0.602245 | 1.133637 | 0.367829 | 0.372559 | 0.32384 | 0.942081 |
| rs4458523 | 0.379585 | 0.29641 | 0.200763 | 1.070733 | 0.171856 | 0.320914 | 0.592462 | 0.924818 |
| rs4502156 | -0.16623 | 0.271111 | 0.539989 | 1.234262 | -0.24563 | 0.295056 | 0.405417 | 0.894713 |
| rs459193 | 0.200017 | 0.445867 | 0.653859 | 0.996357 | 0.353625 | 0.436246 | 0.41787 | 0.835741 |
| rs4812829 | 0.222394 | 0.220606 | 0.313756 | 1.056863 | -0.54024 | 0.785977 | 0.492097 | 0.87484 |
| rs516946 | 0.6415 | 0.54249 | 0.237411 | 1.012954 | 0.805877 | 0.533801 | 0.131579 | 1.052635 |
| rs5215 | 0.419629 | 0.237538 | 0.077741 | 1.243862 | 0.292943 | 0.315739 | 0.353836 | 0.943563 |
| rs6795735 | -0.07005 | 0.267649 | 0.79362 | 1.015833 | -0.23908 | 0.291309 | 0.412105 | 0.879157 |

*Table continued on next page*

**Appendix 16: Univariate and Multivariable Analyses for Individual SNPs and T2DM in Non-Hispanic Whites (Continued)**

| | 1 Risk Allele | | | | 2 Risk Alleles | | | |
|---|---|---|---|---|---|---|---|---|
| SNP | Estimate | Standard Error | Probability | False Discovery Rate | Estimate | Standard Error | Probability | False Discovery Rate |
| rs6878122 | 0.105029 | 0.21378 | 0.623375 | 1.108223 | 0.536043 | 0.437575 | 0.220982 | 0.942855 |
| rs7177055 | 0.226753 | 0.474269 | 0.632723 | 1.038314 | 0.480454 | 0.467992 | 0.304955 | 0.929388 |
| rs7569522 | 0.140774 | 0.243915 | 0.564032 | 1.164453 | 0.259575 | 0.290658 | 0.372136 | 0.882101 |
| rs7756992 | 0.100633 | 0.211736 | 0.634741 | 1.015586 | -0.16484 | 0.457503 | 0.718732 | 0.958309 |
| rs780094 | 0.117815 | 0.333309 | 0.723844 | 1.007087 | 0.264539 | 0.335953 | 0.431301 | 0.836462 |
| rs7845219 | -0.34543 | 0.250461 | 0.168284 | 1.346276 | -0.10712 | 0.28184 | 0.704001 | 0.97948 |
| rs7903146 | 0.375972 | 0.224154 | 0.093938 | 0.858864 | 1.059675 | 0.315819 | 0.000836 | 0.053517 |
| rs7955901 | -0.17444 | 0.231171 | 0.450746 | 1.153909 | -0.24505 | 0.301795 | 0.417093 | 0.861095 |
| rs8108269 | 0.062102 | 0.20857 | 0.765983 | 1.000468 | -0.75858 | 0.569669 | 0.183428 | 1.173938 |
| rs8182584 | -0.09532 | 0.218922 | 0.663397 | 0.964941 | -0.42244 | 0.335397 | 0.208273 | 1.025342 |
| rs849135 | 0.380738 | 0.285635 | 0.182988 | 1.301247 | 0.622488 | 0.313626 | 0.047562 | 0.760989 |
| rs9936385 | 0.121534 | 0.23485 | 0.604977 | 1.106243 | 0.177129 | 0.29947 | 0.554396 | 0.93372 |

SNP: single nucleotide polymorphism; T2DM: type 2 diabetes mellitus.

## Appendix 17: Interaction of Statin and Individual SNPs and T2DM in Non-Hispanic Whites

| | 1 Risk Allele | | | | 2 Risk Alleles | | | |
|---|---|---|---|---|---|---|---|---|
| Statin x SNP | Estimate | Standard Error | Probability | False Discovery Rate | Estimate | Standard Error | Probability | False Discovery Rate |
| statin*rs10278336 | 0.319238 | 0.593705 | 0.590954 | 1.454656 | 0.847332 | 0.662491 | 0.201325 | 1.431643 |
| statin*rs10758593 | 0.343258 | 0.502641 | 0.494894 | 1.50825 | 0.235397 | 0.724476 | 0.745341 | 1.834685 |
| statin*rs10830963 | 0.24653 | 0.494848 | 0.618507 | 1.364981 | 0.745385 | 0.739993 | 0.314151 | 1.827787 |
| statin*rs11063069 | -0.70761 | 0.492644 | 0.151358 | 2.421729 | -2.44395 | 1.154676 | 0.034655 | 1.108947 |
| statin*rs1111875 | -0.09528 | 0.686995 | 0.889731 | 1.581745 | -1.24328 | 0.768917 | 0.106352 | 1.701636 |
| statin*rs11257655 | -0.3049 | 0.469094 | 0.515929 | 1.435629 | 0.759466 | 1.101287 | 0.490668 | 1.84722 |
| statin*rs11634397 | -0.99111 | 0.849716 | 0.243856 | 1.734088 | -2.27388 | 0.884975 | 0.010396 | 0.665328 |
| statin*rs12427353 | -0.95103 | 1.425615 | 0.504929 | 1.468884 | -0.3351 | 1.381283 | 0.808385 | 1.567776 |
| statin*rs12497268 | 0.176809 | 1.43801 | 0.902179 | 1.51946 | -0.06536 | 1.41006 | 0.963045 | 1.433369 |
| statin*rs12571751 | -0.5138 | 0.616765 | 0.405103 | 1.364558 | -0.36416 | 0.6606 | 0.58164 | 1.861249 |
| statin*rs12899811 | 0.577022 | 0.491255 | 0.240566 | 1.924527 | 0.22452 | 0.875704 | 0.797727 | 1.595455 |
| statin*rs12970134 | 0.52508 | 0.485473 | 0.279816 | 1.628021 | 0.515188 | 0.802106 | 0.520896 | 1.754597 |
| statin*rs13233731 | -0.15253 | 0.623119 | 0.806691 | 1.564492 | -0.04945 | 0.652979 | 0.939659 | 1.466785 |
| statin*rs13389219 | -0.63527 | 0.635813 | 0.318076 | 1.454061 | -0.1297 | 0.623696 | 0.835327 | 1.485026 |
| statin*rs1359790 | 0.412798 | 0.850508 | 0.627579 | 1.338836 | 0.059998 | 0.833679 | 0.942649 | 1.436417 |
| statin*rs1496653 | -0.87161 | 0.893588 | 0.329704 | 1.406736 | -0.4587 | 0.851883 | 0.590439 | 1.799433 |
| statin*rs1552224 | 0.165921 | 1.163074 | 0.886603 | 1.621216 | 0.239958 | 1.103929 | 0.827986 | 1.514032 |
| statin*rs163184 | -0.36547 | 0.562975 | 0.516444 | 1.377183 | -0.11329 | 0.64188 | 0.85996 | 1.487498 |
| statin*rs16927668 | 0.003516 | 0.488511 | 0.994259 | 1.414057 | 0.509298 | 1.396226 | 0.715397 | 1.907725 |
| statin*rs17168486 | -0.03859 | 0.522974 | 0.941202 | 1.469194 | 0.318199 | 1.105788 | 0.773618 | 1.707296 |
| statin*rs2334499 | 0.568903 | 0.526575 | 0.28035 | 1.495198 | 0.582967 | 0.698675 | 0.404351 | 1.848461 |
| statin*rs243088 | -0.27471 | 0.524424 | 0.60056 | 1.372709 | -0.1665 | 0.621296 | 0.788792 | 1.682756 |
| statin*rs2447090 | -0.61196 | 0.680809 | 0.369037 | 1.47615 | -0.66182 | 0.709548 | 0.351283 | 1.873509 |
| statin*rs2796441 | 0.969411 | 0.691151 | 0.161185 | 2.063171 | 0.665735 | 0.731056 | 0.362799 | 1.786087 |

*Table continued on next page*

**Appendix 17: Interaction of Statin and Individual SNPs and T2DM in Non-Hispanic Whites (Continued)**

| | 1 Risk Allele | | | | 2 Risk Alleles | | | |
|---|---|---|---|---|---|---|---|---|
| Statin x SNP | Estimate | Standard Error | Probability | False Discovery Rate | Estimate | Standard Error | Probability | False Discovery Rate |
| statin*rs2943640 | -0.06251 | 0.767666 | 0.935123 | 1.496197 | 0.059272 | 0.772767 | 0.938884 | 1.502214 |
| statin*rs3802177 | -0.01138 | 0.820643 | 0.988944 | 1.471917 | 0.064863 | 0.82896 | 0.937655 | 1.538716 |
| statin*rs4402960 | -0.01296 | 0.480802 | 0.978498 | 1.491044 | -0.62139 | 0.924601 | 0.50177 | 1.78407 |
| statin*rs4430796 | -0.56329 | 0.626724 | 0.369082 | 1.389484 | 0.00701 | 0.785485 | 0.992882 | 1.381401 |
| statin*rs4458523 | -0.64446 | 0.635576 | 0.310949 | 1.530828 | -1.17044 | 0.71552 | 0.10234 | 2.183256 |
| statin*rs4502156 | 0.337442 | 0.637535 | 0.596774 | 1.414575 | 0.458946 | 0.658239 | 0.485892 | 1.943568 |
| statin*rs459193 | -1.61797 | 0.942534 | 0.086499 | 1.845312 | -1.16606 | 0.901719 | 0.196391 | 1.795574 |
| statin*rs516946 | -1.98292 | 1.135697 | 0.081258 | 2.600254 | -1.70957 | 1.100589 | 0.120806 | 1.546317 |
| statin*rs5215 | -0.59791 | 0.525189 | 0.255324 | 1.634074 | -0.33274 | 0.679111 | 0.624313 | 1.737218 |
| statin*rs6795735 | 0.362478 | 0.611256 | 0.553372 | 1.416631 | 0.21515 | 0.651813 | 0.74144 | 1.898085 |
| statin*rs6878122 | 0.352468 | 0.478103 | 0.461239 | 1.475964 | 0.276051 | 1.038862 | 0.790531 | 1.632064 |
| statin*rs7177055 | -0.31675 | 1.023359 | 0.757022 | 1.514044 | 0.018955 | 1.002928 | 0.984927 | 1.400785 |
| statin*rs7569522 | 0.068084 | 0.526762 | 0.897198 | 1.551909 | -0.19385 | 0.647773 | 0.764838 | 1.748202 |
| statin*rs7756992 | -0.00244 | 0.471595 | 0.995875 | 1.385565 | 0.714506 | 0.933285 | 0.444187 | 1.895199 |
| statin*rs780094 | 0.936865 | 0.72809 | 0.198615 | 2.118565 | 0.373719 | 0.735478 | 0.611524 | 1.778978 |
| statin*rs7845219 | -0.04928 | 0.575685 | 0.931809 | 1.529123 | 0.764675 | 0.592248 | 0.197088 | 1.576702 |
| statin*rs7903146 | 0.413552 | 0.489692 | 0.398675 | 1.417513 | 0.172506 | 0.740209 | 0.815791 | 1.535607 |
| statin*rs7955901 | -0.00508 | 0.532542 | 0.992395 | 1.443484 | 0.953649 | 0.639484 | 0.136346 | 1.454355 |
| statin*rs8108269 | -0.19432 | 0.463384 | 0.67509 | 1.393735 | -0.13074 | 1.294162 | 0.919564 | 1.548739 |
| statin*rs8182584 | 1.250271 | 0.502286 | 0.013039 | 0.834522 | -0.02816 | 0.911854 | 0.975372 | 1.418723 |
| statin*rs849135 | -0.73646 | 0.622267 | 0.237013 | 2.16698 | -0.20602 | 0.667796 | 0.757791 | 1.796246 |
| statin*rs9936385 | -0.08292 | 0.530543 | 0.875843 | 1.648646 | 0.769013 | 0.645431 | 0.233879 | 1.496824 |

SNP: single nucleotide polymorphism; T2DM: type 2 diabetes mellitus.

**Appendix 18: Interaction of Statin and Individual SNPs and T2DM in Non-Hispanic Whites, After Adjusting for Age, Gender, BMI and Top Principal Components**

| | 1 Risk Allele | | | | 2 Risk Alleles | | | |
|---|---|---|---|---|---|---|---|---|
| Statin x SNP | Estimate | Standard Error | Probability | False Discovery Rate | Estimate | Standard Error | Probability | False Discovery Rate |
| statin*rs10278336 | 0.269763 | 0.609373 | 0.65813 | 1.560013 | 0.862268 | 0.680575 | 0.205599 | 1.644792 |
| statin*rs10758593 | 0.377868 | 0.517475 | 0.46551 | 1.655147 | 0.215517 | 0.744015 | 0.772159 | 1.764934 |
| statin*rs10830963 | 0.227243 | 0.508666 | 0.655203 | 1.612808 | 0.570861 | 0.775197 | 0.461736 | 1.846942 |
| statin*rs11063069 | -0.84468 | 0.508058 | 0.096858 | 2.066303 | -2.29341 | 1.175862 | 0.051537 | 1.649175 |
| statin*rs1111875 | -0.38948 | 0.701239 | 0.578792 | 1.543446 | -1.53041 | 0.785179 | 0.05169 | 1.102711 |
| statin*rs11257655 | -0.48529 | 0.487495 | 0.319854 | 1.705887 | 0.562676 | 1.117432 | 0.614745 | 1.788348 |
| statin*rs11634397 | -0.97583 | 0.865837 | 0.260125 | 1.849781 | -2.23547 | 0.901075 | 0.013345 | 0.854099 |
| statin*rs12427353 | -0.97026 | 1.447239 | 0.502815 | 1.532388 | -0.37861 | 1.402014 | 0.787203 | 1.625194 |
| statin*rs12497268 | -0.11018 | 1.483878 | 0.940832 | 1.433648 | -0.17405 | 1.453584 | 0.904724 | 1.378627 |
| statin*rs12571751 | -0.62555 | 0.637406 | 0.326746 | 1.493696 | -0.62342 | 0.682909 | 0.361624 | 1.92866 |
| statin*rs12899811 | 0.367509 | 0.505911 | 0.467824 | 1.57583 | 0.242423 | 0.894405 | 0.786439 | 1.677737 |
| statin*rs12970134 | 0.463008 | 0.499319 | 0.35411 | 1.416441 | 0.344023 | 0.817766 | 0.674116 | 1.725737 |
| statin*rs13233731 | -0.19671 | 0.644457 | 0.760286 | 1.474495 | -0.17762 | 0.679314 | 0.793813 | 1.587626 |
| statin*rs13389219 | -0.65099 | 0.662251 | 0.325959 | 1.604721 | -0.15891 | 0.648636 | 0.806536 | 1.518186 |
| statin*rs1359790 | 0.194646 | 0.87466 | 0.823961 | 1.464819 | -0.16939 | 0.858378 | 0.843619 | 1.459233 |
| statin*rs1496653 | -1.09974 | 0.927271 | 0.236035 | 1.888283 | -0.62561 | 0.883069 | 0.478911 | 1.802957 |
| statin*rs1552224 | 0.112222 | 1.195527 | 0.925241 | 1.480386 | 0.255634 | 1.134175 | 0.821742 | 1.460874 |
| statin*rs163184 | -0.18653 | 0.578051 | 0.747025 | 1.494051 | -0.04753 | 0.662163 | 0.942793 | 1.371335 |
| statin*rs16927668 | 0.027995 | 0.5011 | 0.955464 | 1.422086 | 0.75358 | 1.435861 | 0.599873 | 1.828185 |
| statin*rs17168486 | -0.04 | 0.537873 | 0.940734 | 1.468463 | 0.269523 | 1.15177 | 0.815049 | 1.490376 |
| statin*rs2334499 | 0.368164 | 0.543197 | 0.498146 | 1.594067 | 0.584797 | 0.716862 | 0.414915 | 1.896754 |
| statin*rs243088 | -0.14672 | 0.540781 | 0.786233 | 1.479967 | -0.20156 | 0.637707 | 0.752048 | 1.782633 |
| statin*rs2447090 | -0.64468 | 0.694375 | 0.353514 | 1.508327 | -0.67383 | 0.723544 | 0.352032 | 2.253002 |

*Table continued on next page*

**Appendix 18: Interaction of Statin and Individual SNPs and T2DM in Non-Hispanic Whites, After Adjusting for Age, Gender, BMI and Top Principal Components (Continued)**

| | 1 Risk Allele | | | | 2 Risk Alleles | | | |
|---|---|---|---|---|---|---|---|---|
| Statin x SNP | Estimate | Standard Error | Probability | False Discovery Rate | Estimate | Standard Error | Probability | False Discovery Rate |
| statin*rs2796441 | 1.012677 | 0.708805 | 0.153545 | 1.96538 | 0.697521 | 0.749409 | 0.352307 | 2.049784 |
| statin*rs2943640 | -0.0221 | 0.785711 | 0.977571 | 1.421921 | 0.120331 | 0.791497 | 0.879208 | 1.406733 |
| statin*rs3802177 | 0.298396 | 0.84553 | 0.724265 | 1.545099 | 0.342651 | 0.851931 | 0.687659 | 1.6927 |
| statin*rs4402960 | 0.011174 | 0.496991 | 0.982069 | 1.39672 | -0.46081 | 0.943694 | 0.62549 | 1.740493 |
| statin*rs4430796 | -0.39763 | 0.64423 | 0.537294 | 1.49508 | 0.156042 | 0.813308 | 0.847908 | 1.428056 |
| statin*rs4458523 | -0.67345 | 0.648775 | 0.299625 | 1.917598 | -1.11191 | 0.729404 | 0.127871 | 1.363952 |
| statin*rs4502156 | 0.403573 | 0.653182 | 0.536875 | 1.561819 | 0.438617 | 0.676568 | 0.517011 | 1.741512 |
| statin*rs459193 | -1.51656 | 0.970841 | 0.118726 | 1.899616 | -1.00386 | 0.924685 | 0.278031 | 1.977109 |
| statin*rs516946 | -2.35049 | 1.241406 | 0.058726 | 1.87923 | -2.06174 | 1.21159 | 0.089271 | 1.428335 |
| statin*rs5215 | -0.55748 | 0.544162 | 0.305972 | 1.7802 | -0.11284 | 0.703561 | 0.872627 | 1.432003 |
| statin*rs6795735 | 0.270166 | 0.634949 | 0.670612 | 1.532828 | 0.002886 | 0.675089 | 0.996591 | 1.386561 |
| statin*rs6878122 | 0.266458 | 0.491396 | 0.587826 | 1.504835 | 0.576999 | 1.070582 | 0.590092 | 1.888293 |
| statin*rs7177055 | -0.36329 | 1.053118 | 0.730227 | 1.507566 | 0.023527 | 1.030982 | 0.981801 | 1.396339 |
| statin*rs7569522 | 0.057098 | 0.542968 | 0.916281 | 1.503641 | -0.31385 | 0.672074 | 0.640657 | 1.708418 |
| statin*rs7756992 | -0.00934 | 0.485324 | 0.984657 | 1.369957 | 0.803705 | 0.987389 | 0.415946 | 1.774704 |
| statin*rs780094 | 1.047927 | 0.745297 | 0.160163 | 1.708403 | 0.505848 | 0.755083 | 0.503132 | 1.788915 |
| statin*rs7845219 | -0.25129 | 0.595725 | 0.673282 | 1.485863 | 0.523108 | 0.611314 | 0.392458 | 1.932102 |
| statin*rs7903146 | 0.382878 | 0.505789 | 0.449316 | 1.691543 | 0.084572 | 0.765079 | 0.912013 | 1.357415 |
| statin*rs7955901 | -0.05931 | 0.546647 | 0.913634 | 1.538752 | 1.021566 | 0.662097 | 0.123313 | 1.578405 |
| statin*rs8108269 | -0.12481 | 0.477308 | 0.793796 | 1.451513 | -0.3861 | 1.33592 | 0.772659 | 1.705178 |
| statin*rs8182584 | 1.31083 | 0.517906 | 0.011597 | 0.7422 | -0.11673 | 0.926682 | 0.899796 | 1.404559 |
| statin*rs849135 | -0.81209 | 0.639872 | 0.204825 | 1.872687 | -0.17887 | 0.690321 | 0.795633 | 1.543046 |
| statin*rs9936385 | -0.06887 | 0.547556 | 0.899946 | 1.556664 | 0.934153 | 0.661843 | 0.15857 | 1.449785 |

*Table continued on next page*

**Appendix 18: Interaction of Statin and Individual SNPs and T2DM in Non-Hispanic Whites, After Adjusting for Age, Gender, BMI and Top Principal Components (Continued)**

| | 1 Risk Allele | | | | 2 Risk Alleles | | | |
|---|---|---|---|---|---|---|---|---|
| Statin x SNP | Estimate | Standard Error | Probability | False Discovery Rate | Estimate | Standard Error | Probability | False Discovery Rate |

Adjustment for age, gender, BMI, and top 4 principal components.

BMI: body mass index; SNP: single nucleotide polymorphism; T2DM: type 2 diabetes mellitus.

## Appendix 19: Univariate Analyses of SNP and Fasting Blood Glucose in African Americans

| SNP | Estimate | Standard Error | Probability | False Discovery Rate |
|---|---|---|---|---|
| rs7903146 | 1.442185 | 0.598462 | 0.016331077 | 0.930871 |
| rs10830963 | 2.474778 | 1.077761 | 0.022087908 | 0.629505 |
| rs10758593 | -1.09344 | 0.531994 | 0.040377261 | 0.767168 |
| rs12497268 | -2.00465 | 1.004414 | 0.046509339 | 0.662758 |
| rs4299828 | 1.060004 | 0.574956 | 0.065846287 | 0.750648 |
| rs8182584 | -0.96841 | 0.559314 | 0.084012077 | 0.798115 |
| rs1359790 | 1.426893 | 0.834118 | 0.087781935 | 0.714796 |
| rs2261181 | 1.014329 | 0.646812 | 0.11748575 | 0.837086 |
| rs849135 | -0.95109 | 0.615268 | 0.122798873 | 0.777726 |
| rs163184 | -1.05529 | 0.690117 | 0.126879957 | 0.723216 |
| rs10842994 | 1.982439 | 1.37972 | 0.151406568 | 0.784561 |
| rs10923931 | 0.795831 | 0.57284 | 0.165386565 | 0.785586 |
| rs10203174 | 0.762824 | 0.554399 | 0.16947156 | 0.743068 |
| rs516946 | -0.88886 | 0.649595 | 0.171842158 | 0.699643 |
| rs3802177 | 1.311033 | 0.990923 | 0.18644359 | 0.708486 |
| rs17301514 | 1.552617 | 1.175659 | 0.187244446 | 0.667058 |
| rs10278336 | 0.809333 | 0.693701 | 0.243908065 | 0.817809 |
| rs7202877 | 0.822359 | 0.709244 | 0.246826833 | 0.781618 |
| rs10401969 | -0.7801 | 0.706145 | 0.26982562 | 0.809477 |
| rs780094 | 0.766377 | 0.706519 | 0.278582434 | 0.79396 |
| rs6878122 | -0.82671 | 0.789353 | 0.29547142 | 0.801994 |
| rs2334499 | -0.78291 | 0.826724 | 0.344108595 | 0.891554 |
| rs13233731 | -0.56614 | 0.601625 | 0.347161773 | 0.860357 |
| rs12899811 | -0.47365 | 0.546771 | 0.386766881 | 0.918571 |
| rs3734621 | 0.442595 | 0.535259 | 0.408710708 | 0.93186 |
| rs8108269 | -0.49237 | 0.598576 | 0.411155364 | 0.901379 |
| rs243088 | -0.43352 | 0.536752 | 0.419671126 | 0.885972 |

*Table continued on next page*

**Appendix 19: Univariate Analyses of SNP and Fasting Blood Glucose in African Americans (Continued)**

| SNP | Estimate | Standard Error | Probability | False Discovery Rate |
|---|---|---|---|---|
| rs4458523 | -0.40459 | 0.534001 | 0.449021814 | 0.91408 |
| rs16927668 | 0.462624 | 0.617019 | 0.453755108 | 0.891863 |
| rs4430796 | -0.54553 | 0.749935 | 0.467308471 | 0.887886 |
| rs459193 | -0.37764 | 0.545426 | 0.489034403 | 0.899192 |
| rs2796441 | -0.47189 | 0.716003 | 0.510167103 | 0.908735 |
| rs9936385 | -0.28914 | 0.529335 | 0.585151809 | 1.010717 |
| rs7177055 | -0.29667 | 0.550606 | 0.590269516 | 0.989569 |
| rs1496653 | -0.2977 | 0.553618 | 0.591007698 | 0.962498 |
| rs7756992 | -0.27675 | 0.540514 | 0.608879671 | 0.964059 |
| rs11257655 | -0.2835 | 0.617542 | 0.646387942 | 0.995787 |
| rs7845219 | -0.25451 | 0.55495 | 0.646717485 | 0.970076 |
| rs7569522 | -0.23359 | 0.522109 | 0.654793535 | 0.957006 |
| rs6819243 | 0.245129 | 0.548424 | 0.65509594 | 0.933512 |
| rs1111875 | -0.26084 | 0.622655 | 0.675462977 | 0.939058 |
| rs4402960 | -0.22356 | 0.536778 | 0.677234107 | 0.919103 |
| rs12242953 | -0.44889 | 1.104302 | 0.684557198 | 0.907436 |
| rs2447090 | 0.210781 | 0.564828 | 0.709179724 | 0.91871 |
| rs12970134 | 0.303047 | 0.825007 | 0.713535809 | 0.903812 |
| rs4502156 | -0.18519 | 0.61571 | 0.763721061 | 0.94635 |
| rs17867832 | -0.19161 | 0.744173 | 0.796920162 | 0.966478 |
| rs11717195 | 0.184047 | 0.796458 | 0.817348422 | 0.970601 |
| rs12571751 | 0.093269 | 0.528864 | 0.860087113 | 1.000509 |
| rs6795735 | -0.11394 | 0.680776 | 0.867151962 | 0.988553 |
| rs4812829 | -0.09596 | 0.8659 | 0.911801627 | 1.019072 |
| rs17791513 | -0.14312 | 1.378343 | 0.917341955 | 1.005548 |
| rs13389219 | -0.0548 | 0.624521 | 0.930110413 | 1.000307 |
| rs5215 | -0.06782 | 0.958097 | 0.943598544 | 0.996021 |

*Table continued on next page*

**Appendix 19: Univariate Analyses of SNP and Fasting Blood Glucose in African Americans (Continued)**

| SNP | Estimate | Standard Error | Probability | False Discovery Rate |
|---|---|---|---|---|
| rs7955901 | -0.0272 | 0.62205 | 0.965138806 | 1.000235 |
| rs17168486 | -0.02059 | 0.83127 | 0.980246591 | 0.997751 |
| rs11063069 | 0.017043 | 0.695665 | 0.980464174 | 0.980464 |

SNP: single nucleotide polymorphism.

## Appendix 20: Multivariable Analyses of SNP and Fasting Blood Glucose in African Americans

| SNP | Estimate | Standard Error | Probability | False Discovery Rate |
|---|---|---|---|---|
| rs7903146 | 1.834206 | 0.571635 | 0.0014239 | 0.081162 |
| rs10830963 | 2.507529 | 1.055683 | 0.017933966 | 0.511118 |
| rs10758593 | -0.99442 | 0.51039 | 0.05196392 | 0.987314 |
| rs10923931 | 1.064495 | 0.549285 | 0.053222459 | 0.75842 |
| rs12497268 | -1.80449 | 0.963679 | 0.061753442 | 0.703989 |
| rs8182584 | -0.96349 | 0.535903 | 0.072833669 | 0.69192 |
| rs163184 | -1.16996 | 0.659163 | 0.076553376 | 0.623363 |
| rs1359790 | 1.38056 | 0.797699 | 0.084161495 | 0.599651 |
| rs17301514 | 1.894163 | 1.133381 | 0.09533354 | 0.603779 |
| rs516946 | -0.97422 | 0.626807 | 0.120791436 | 0.688511 |
| rs2261181 | 0.955942 | 0.622589 | 0.125346477 | 0.649523 |
| rs3802177 | 1.356321 | 0.953325 | 0.155474653 | 0.738505 |
| rs10842994 | 1.819858 | 1.335216 | 0.173540585 | 0.760909 |
| rs4299828 | 0.718387 | 0.550209 | 0.19230189 | 0.782943 |
| rs2334499 | -1.0018 | 0.797525 | 0.209684686 | 0.796802 |
| rs849135 | -0.72184 | 0.58886 | 0.220873677 | 0.786862 |
| rs10203174 | 0.654119 | 0.534841 | 0.221932455 | 0.744126 |
| rs10401969 | -0.81324 | 0.676474 | 0.229896132 | 0.728004 |
| rs10278336 | 0.669795 | 0.662102 | 0.312237747 | 0.936713 |
| rs9936385 | -0.50177 | 0.506829 | 0.322674465 | 0.919622 |
| rs12899811 | -0.49987 | 0.524882 | 0.341409166 | 0.926682 |
| rs16927668 | 0.523189 | 0.610046 | 0.391535127 | 1.014432 |
| rs4458523 | -0.43683 | 0.511832 | 0.393829841 | 0.976013 |
| rs6878122 | -0.62448 | 0.758483 | 0.410739428 | 0.975506 |
| rs780094 | 0.563233 | 0.685822 | 0.411916081 | 0.939169 |
| rs3734621 | 0.398295 | 0.515532 | 0.440151107 | 0.964947 |
| rs1111875 | -0.43424 | 0.594077 | 0.465168956 | 0.982023 |

*Table continued on next page*

**Appendix 20: Multivariable Analyses of SNP and Fasting Blood Glucose in African Americans (Continued)**

| SNP | Estimate | Standard Error | Probability | False Discovery Rate |
|---|---|---|---|---|
| rs7202877 | 0.488002 | 0.689425 | 0.47939356 | 0.975908 |
| rs13233731 | -0.40583 | 0.576007 | 0.481433844 | 0.946267 |
| rs8108269 | -0.39672 | 0.571215 | 0.487701878 | 0.926634 |
| rs2796441 | -0.46064 | 0.68614 | 0.502326017 | 0.923632 |
| rs4502156 | -0.3747 | 0.596814 | 0.530421347 | 0.944813 |
| rs459193 | -0.31829 | 0.522894 | 0.543005253 | 0.937918 |
| rs1496653 | -0.29477 | 0.531308 | 0.579299108 | 0.971178 |
| rs12242953 | -0.56753 | 1.051879 | 0.589768467 | 0.96048 |
| rs7177055 | -0.27553 | 0.527463 | 0.601658255 | 0.952626 |
| rs17791513 | 0.686971 | 1.320584 | 0.603165942 | 0.929202 |
| rs13389219 | 0.299182 | 0.600332 | 0.61846147 | 0.927692 |
| rs7569522 | -0.24552 | 0.498939 | 0.622891379 | 0.91038 |
| rs7756992 | -0.25621 | 0.522586 | 0.624161031 | 0.889429 |
| rs6819243 | 0.250053 | 0.524604 | 0.633830665 | 0.881179 |
| rs17867832 | -0.24899 | 0.712693 | 0.726969246 | 0.986601 |
| rs243088 | -0.16408 | 0.514194 | 0.749786794 | 0.993903 |
| rs4430796 | -0.21559 | 0.718429 | 0.764244593 | 0.990044 |
| rs4402960 | -0.14777 | 0.516142 | 0.77477767 | 0.981385 |
| rs11717195 | 0.188889 | 0.767723 | 0.80575952 | 0.998441 |
| rs12571751 | 0.11416 | 0.504319 | 0.821016035 | 0.9957 |
| rs5215 | 0.197374 | 0.919849 | 0.830193451 | 0.985855 |
| rs17168486 | -0.16012 | 0.798378 | 0.841135092 | 0.978463 |
| rs11063069 | -0.13229 | 0.669624 | 0.843475685 | 0.961562 |
| rs11257655 | -0.09809 | 0.592388 | 0.868555874 | 0.970739 |
| rs7845219 | -0.07639 | 0.532787 | 0.886048265 | 0.971245 |
| rs12970134 | 0.112605 | 0.787588 | 0.886371581 | 0.953268 |
| rs7955901 | -0.08375 | 0.595529 | 0.888225156 | 0.937571 |

*Table continued on next page*

**Appendix 20: Multivariable Analyses of SNP and Fasting Blood Glucose in African Americans (Continued)**

| SNP | Estimate | Standard Error | Probability | False Discovery Rate |
|---|---|---|---|---|
| rs4812829 | -0.0632 | 0.827206 | 0.939134951 | 0.973285 |
| rs2447090 | 0.034923 | 0.541089 | 0.94856565 | 0.965504 |
| rs6795735 | 0.024174 | 0.66883 | 0.971182758 | 0.971183 |

SNP: single nucleotide polymorphism.

**Appendix 21: Interaction of Statin and Individual SNPs and Fasting Blood Glucose in African Americans, After Adjusting for Age, Gender, BMI and Top Principal Components**

| Statin x SNP | Estimate | Standard Error | Probability | False Discovery Rate |
|---|---|---|---|---|
| rs2334499 | 10.80729 | 4.501341 | 0.016741 | 0.95426 |
| rs4812829 | 6.353231 | 3.881249 | 0.102319 | 2.916078 |
| rs12970134 | 5.859018 | 3.721133 | 0.116038 | 2.204713 |
| rs11717195 | 5.767266 | 3.819817 | 0.131758 | 1.87755 |
| rs4402960 | -3.56464 | 2.410892 | 0.139927 | 1.595167 |
| rs10758593 | 3.784017 | 2.667109 | 0.156627 | 1.487958 |
| rs13389219 | -4.03253 | 3.034388 | 0.18451 | 1.502437 |
| rs10830963 | 7.063939 | 5.703046 | 0.216101 | 1.53972 |
| rs7202877 | -3.23738 | 3.049139 | 0.2889 | 1.829699 |
| rs8182584 | -3.33173 | 3.140363 | 0.289262 | 1.648794 |
| rs10842994 | -6.81208 | 6.67346 | 0.307886 | 1.595412 |
| rs849135 | 2.733765 | 2.814506 | 0.331891 | 1.576484 |
| rs1359790 | 3.933366 | 4.216741 | 0.351402 | 1.540764 |
| rs4430796 | -2.79163 | 3.060153 | 0.362104 | 1.474279 |
| rs6795735 | -3.24287 | 3.764854 | 0.389482 | 1.480031 |
| rs516946 | 2.248641 | 2.684973 | 0.402741 | 1.434766 |
| rs12571751 | -2.07113 | 2.543475 | 0.41589 | 1.394454 |
| rs8108269 | -2.33928 | 2.961088 | 0.429921 | 1.361416 |
| rs243088 | -2.04075 | 2.778872 | 0.463083 | 1.389248 |
| rs13233731 | 2.154636 | 3.008815 | 0.47428 | 1.351697 |
| rs4502156 | -2.03517 | 2.871475 | 0.478828 | 1.299677 |
| rs17301514 | -3.40886 | 4.835988 | 0.481225 | 1.246809 |
| rs7903146 | 1.850853 | 2.643208 | 0.48413 | 1.199799 |
| rs2261181 | 2.101567 | 3.012006 | 0.48569 | 1.153515 |
| rs5215 | 3.772091 | 5.648489 | 0.504585 | 1.150454 |
| rs7845219 | -1.74351 | 2.648396 | 0.51065 | 1.119503 |

*Table continued on next page*

**Appendix 21: Interaction of Statin and Individual SNPs and Fasting Blood Glucose in African Americans, After Adjusting for Age, Gender, BMI and Top Principal Components (Continued)**

| Statin x SNP | Estimate | Standard Error | Probability | False Discovery Rate |
|---|---|---|---|---|
| rs3734621 | -1.68862 | 2.695724 | 0.531352 | 1.121742 |
| rs10923931 | -2.22942 | 3.614695 | 0.537688 | 1.094579 |
| rs780094 | -1.83328 | 3.022961 | 0.544507 | 1.070239 |
| rs2796441 | -1.77178 | 3.057139 | 0.562492 | 1.068735 |
| rs1111875 | 2.103169 | 3.677019 | 0.567611 | 1.043671 |
| rs17867832 | 2.885215 | 5.342918 | 0.589447 | 1.049953 |
| rs7569522 | -1.25753 | 2.432458 | 0.605413 | 1.045713 |
| rs6878122 | 1.819416 | 3.639986 | 0.61742 | 1.035087 |
| rs12497268 | 3.213601 | 6.565454 | 0.624736 | 1.017427 |
| rs12242953 | 2.387092 | 5.415986 | 0.659597 | 1.044361 |
| rs17168486 | 1.276612 | 3.296575 | 0.698743 | 1.076442 |
| rs12899811 | 1.09308 | 2.872572 | 0.703729 | 1.055593 |
| rs163184 | 1.087203 | 3.075655 | 0.723882 | 1.057981 |
| rs2447090 | 0.931222 | 2.711455 | 0.731421 | 1.042275 |
| rs4458523 | 0.767995 | 2.385411 | 0.74763 | 1.039388 |
| rs459193 | 0.728272 | 2.504297 | 0.771325 | 1.046799 |
| rs10401969 | 1.210652 | 4.180295 | 0.772243 | 1.02367 |
| rs17791513 | 1.260408 | 4.895314 | 0.796927 | 1.032382 |
| rs1496653 | -0.54057 | 2.740504 | 0.843715 | 1.068706 |
| rs3802177 | -0.84642 | 4.548872 | 0.852469 | 1.05632 |
| rs7955901 | -0.47083 | 2.661221 | 0.859644 | 1.042547 |
| rs11257655 | -0.56465 | 3.30127 | 0.864265 | 1.026314 |
| rs11063069 | -0.49671 | 3.084941 | 0.872153 | 1.014545 |
| rs10278336 | -0.48732 | 3.029636 | 0.872281 | 0.9944 |
| rs10203174 | 0.367392 | 2.291234 | 0.872677 | 0.975344 |
| rs7177055 | 0.568064 | 3.59768 | 0.874605 | 0.958702 |

*Table continued on next page*

**Appendix 21: Interaction of Statin and Individual SNPs and Fasting Blood Glucose in African Americans, After Adjusting for Age, Gender, BMI and Top Principal Components (Continued)**

| Statin x SNP | Estimate | Standard Error | Probability | False Discovery Rate |
|---|---|---|---|---|
| rs6819243 | -0.22478 | 2.898662 | 0.938223 | 1.009032 |
| rs16927668 | 0.250544 | 3.387877 | 0.941079 | 0.993361 |
| rs9936385 | 0.165742 | 2.600628 | 0.949211 | 0.983728 |
| rs7756992 | 0.089114 | 2.334107 | 0.969561 | 0.986875 |
| rs4299828 | 0.098122 | 3.327057 | 0.976485 | 0.976485 |

Adjustment for age, gender, BMI, and top 10 principal components.
BMI: body mass index; SNP: single nucleotide polymorphism.

## Appendix 22: Univariate and Multivariate Analyses for Individual SNPs and T2DM in African Americans

| SNP | 1 Risk Allele | | | | 2 Risk Alleles | | | |
|---|---|---|---|---|---|---|---|---|
| | Estimate | Standard Error | Probability | False Discovery Rate | Estimate | Standard Error | Probability | False Discovery Rate |
| | UNIVARIATE | | | | | | | |
| rs10203174 | 0.166375 | 0.23626 | 0.481543 | 0.604728 | 0.295295 | 0.242563 | 0.22387 | 0.257212 |
| rs10278336 | 0.288493 | 0.543248 | 0.595554 | 0.61846 | 0.189125 | 0.542474 | 0.72747 | 1.061713 |
| rs10401969 | -0.26901 | 0.170882 | 0.11589 | 0.894012 | 0.113635 | 0.402604 | 0.777837 | 1.312601 |
| rs10758593 | -0.25191 | 0.176199 | 0.153255 | 1.034468 | -0.25964 | 0.201596 | 0.198201 | 0.972986 |
| rs10830963 | -0.01191 | 0.224677 | 0.957755 | 2.248642 | -0.49177 | 1.178466 | 0.676589 | 7.307164 |
| rs10923931 | 0.088177 | 0.153339 | 0.565451 | 0.848177 | 0.410238 | 0.233864 | 0.079845 | 0.087993 |
| rs11063069 | 0.083045 | 0.156594 | 0.596059 | 0.919633 | -0.10822 | 0.434345 | 0.803318 | 2.168959 |
| rs1111875 | 0.242127 | 0.357103 | 0.49798 | 0.537818 | 0.434692 | 0.34877 | 0.213056 | 0.2301 |
| rs11257655 | 0.160644 | 0.150211 | 0.285241 | 0.366738 | 0.212127 | 0.303835 | 0.48531 | 0.655168 |
| rs11717195 | -0.8348 | 0.498028 | 0.094151 | 2.542083 | -0.44584 | 0.477462 | 0.350752 | 3.156772 |
| rs12242953 | -1.12993 | 1.078564 | 0.29518 | 15.9397 | -1.21338 | 1.065534 | 0.255204 | 13.78099 |
| rs12497268 | 0.028077 | 0.872349 | 0.974333 | 1.948666 | 0.031262 | 0.854108 | 0.970813 | 1.941626 |
| rs12571751 | 0.122668 | 0.188673 | 0.515803 | 0.732983 | 0.040288 | 0.207146 | 0.845847 | 1.631277 |
| rs12899811 | 0.251735 | 0.235909 | 0.286308 | 0.30315 | 0.213943 | 0.241196 | 0.375383 | 0.494407 |
| rs12970134 | -0.01631 | 0.17508 | 0.925816 | 2.272459 | 0.834763 | 0.508062 | 0.100832 | 0.098999 |
| rs13233731 | 0.168909 | 0.304493 | 0.579264 | 0.710915 | 0.101826 | 0.30079 | 0.735069 | 1.280442 |
| rs13389219 | 0.239967 | 0.151288 | 0.11316 | 0.124707 | 0.629234 | 0.283627 | 0.026844 | 0.026844 |
| rs1359790 | -0.03817 | 0.633565 | 0.951977 | 3.023928 | 0.048527 | 0.619132 | 0.937549 | 1.745781 |
| rs1496653 | -0.19357 | 0.210378 | 0.357839 | 1.756664 | -0.06575 | 0.219661 | 0.764785 | 1.720766 |
| rs163184 | 0.141526 | 0.155372 | 0.362675 | 0.502165 | 0.200477 | 0.391338 | 0.608614 | 0.864873 |
| rs16927668 | -0.40551 | 0.298611 | 0.174916 | 3.148483 | -0.22907 | 0.290708 | 0.43098 | 1.93941 |
| rs17168486 | 0.160058 | 0.179971 | 0.374123 | 0.492748 | -0.43412 | 0.666812 | 0.515235 | 3.974672 |
| rs17301514 | -0.07518 | 0.239393 | 0.753573 | 2.712862 | 0.589179 | 1.312738 | 0.653705 | 0.666039 |

*Table continued on next page*

**Appendix 22: Univariate and Multivariate Analyses for Individual SNPs and T2DM in African Americans (Continued)**

| | 1 Risk Allele | | | | 2 Risk Alleles | | | |
|---|---|---|---|---|---|---|---|---|
| SNP | Estimate | Standard Error | Probability | False Discovery Rate | Estimate | Standard Error | Probability | False Discovery Rate |
| rs17791513 | -0.00678 | 1.273714 | 0.995757 | 2.240453 | 0.004204 | 1.253158 | 0.997325 | 2.154221 |
| rs17867832 | 0.063111 | 0.456062 | 0.889978 | 1.501838 | -0.18825 | 0.446243 | 0.673262 | 2.272259 |
| rs2261181 | 0.068524 | 0.150337 | 0.648675 | 1.061469 | -0.13188 | 0.387324 | 0.733601 | 2.200803 |
| rs2334499 | -0.23575 | 0.183352 | 0.198949 | 1.193691 | -0.52404 | 0.801628 | 0.513514 | 6.932438 |
| rs243088 | 0.172609 | 0.189332 | 0.362261 | 0.434713 | 0.166752 | 0.211466 | 0.430643 | 0.66442 |
| rs2447090 | 0.367146 | 0.155271 | 0.018328 | 0.018674 | 0.203576 | 0.248772 | 0.413455 | 0.572476 |
| rs2796441 | -0.04605 | 0.457129 | 0.919796 | 3.104311 | -0.074 | 0.446552 | 0.868437 | 2.03894 |
| rs3734621 | -0.01937 | 0.156548 | 0.901577 | 2.318342 | -0.22281 | 0.220278 | 0.312128 | 1.296534 |
| rs4299828 | 0.047675 | 0.277211 | 0.863502 | 1.554304 | 0.137201 | 0.271197 | 0.613083 | 1.003227 |
| rs4402960 | -0.03118 | 0.182765 | 0.864591 | 2.593774 | -0.27783 | 0.210924 | 0.188208 | 1.016321 |
| rs4430796 | -0.3261 | 0.318978 | 0.306979 | 3.315372 | -0.67872 | 0.351526 | 0.053919 | 1.455802 |
| rs4458523 | 0.069919 | 0.19362 | 0.718125 | 1.140551 | -0.22197 | 0.214169 | 0.300379 | 1.158603 |
| rs4502156 | -0.03118 | 0.150179 | 0.835608 | 2.374887 | 0.270819 | 0.291902 | 0.353849 | 0.424619 |
| rs459193 | -0.00558 | 0.20002 | 0.977735 | 2.111907 | -0.12631 | 0.216001 | 0.558892 | 1.588429 |
| rs4812829 | 0.198183 | 0.176706 | 0.262448 | 0.301536 | 0.218455 | 0.705069 | 0.75678 | 0.973002 |
| rs516946 | 0.41459 | 0.388935 | 0.286814 | 0.286814 | 0.167835 | 0.385178 | 0.663166 | 0.99475 |
| rs5215 | 0.037485 | 0.193879 | 0.846747 | 1.576702 | 0.477303 | 0.769254 | 0.53515 | 0.566629 |
| rs6795735 | -0.13024 | 0.157437 | 0.408385 | 1.69637 | -0.17276 | 0.433334 | 0.69025 | 2.19256 |
| rs6819243 | 0.175984 | 0.245586 | 0.473871 | 0.556283 | 0.260895 | 0.247029 | 0.291279 | 0.357478 |
| rs6878122 | -0.22636 | 0.177101 | 0.201628 | 1.088794 | 0.480138 | 0.511188 | 0.347927 | 0.361309 |
| rs7177055 | 0.094887 | 0.152772 | 0.534737 | 0.780426 | 0.007239 | 0.235712 | 0.975509 | 2.026058 |
| rs7202877 | -0.17626 | 0.38983 | 0.651297 | 2.930837 | -0.56912 | 0.383689 | 0.138457 | 2.492225 |
| rs7569522 | 0.057982 | 0.168868 | 0.731433 | 1.274109 | -0.21489 | 0.208559 | 0.303208 | 1.091549 |
| rs7756992 | 0.22376 | 0.211713 | 0.290927 | 0.327292 | 0.288143 | 0.223577 | 0.197905 | 0.232323 |

*Table continued on next page*

**Appendix 22: Univariate and Multivariate Analyses for Individual SNPs and T2DM in African Americans (Continued)**

| | 1 Risk Allele | | | | 2 Risk Alleles | | | |
|---|---|---|---|---|---|---|---|---|
| SNP | Estimate | Standard Error | Probability | False Discovery Rate | Estimate | Standard Error | Probability | False Discovery Rate |
| rs780094 | -0.27597 | 0.399429 | 0.489859 | 4.40873 | -0.28371 | 0.388285 | 0.46523 | 2.79138 |
| rs7845219 | 0.031846 | 0.232869 | 0.891264 | 1.718867 | 0.06898 | 0.234127 | 0.768368 | 1.383063 |
| rs7903146 | 0.460665 | 0.149757 | 0.00218 | 0.002141 | 0.252321 | 0.29119 | 0.386508 | 0.485382 |
| rs7955901 | 0.012964 | 0.152426 | 0.932248 | 1.936207 | -0.31947 | 0.350451 | 0.362297 | 2.445503 |
| rs8108269 | -0.33035 | 0.152588 | 0.030731 | 0.414871 | 0.138296 | 0.240489 | 0.565438 | 0.898048 |
| rs8182584 | -0.02432 | 0.155341 | 0.875651 | 2.364258 | -0.09071 | 0.231819 | 0.695714 | 1.788979 |
| rs849135 | -0.10959 | 0.306621 | 0.720895 | 2.780594 | -0.08254 | 0.301058 | 0.784029 | 1.924434 |
| rs9936385 | 0.142639 | 0.171709 | 0.406428 | 0.548678 | 0.315303 | 0.202901 | 0.12065 | 0.135731 |
| | MULTIVARIABLE | | | | | | | |
| rs10203174 | 0.216671 | 0.241502 | 0.369937 | 1.109812 | 0.301509 | 0.247544 | 1.217999 | 0.223643 |
| rs10278336 | 0.353455 | 0.559371 | 0.527676 | 1.156829 | 0.238307 | 0.558617 | 0.426602 | 0.669803 |
| rs10401969 | -0.29606 | 0.174732 | 0.090647 | 1.03337 | 0.169772 | 0.412303 | 0.411764 | 0.680641 |
| rs10758593 | -0.17746 | 0.180855 | 0.326829 | 1.164328 | -0.22792 | 0.206249 | -1.10509 | 0.269509 |
| rs10830963 | 0.071369 | 0.229121 | 0.755521 | 1.02535 | -0.69351 | 1.264978 | -0.54824 | 0.583708 |
| rs10923931 | 0.143231 | 0.1571 | 0.362239 | 1.147089 | 0.441084 | 0.238884 | 1.846437 | 0.065259 |
| rs11063069 | 0.100713 | 0.159561 | 0.52813 | 1.11494 | -0.19296 | 0.44283 | -0.43573 | 0.663167 |
| rs1111875 | 0.221628 | 0.363151 | 0.541871 | 1.103095 | 0.370377 | 0.353985 | 1.046307 | 0.295788 |
| rs11257655 | 0.163322 | 0.153949 | 0.289117 | 1.177117 | 0.165211 | 0.311205 | 0.530877 | 0.595676 |
| rs11717195 | -0.72188 | 0.50883 | 0.15644 | 1.273871 | -0.35124 | 0.487789 | -0.72007 | 0.471727 |
| rs12242953 | -1.43174 | 1.089762 | 0.18935 | 1.34912 | -1.50937 | 1.07568 | -1.40318 | 0.161016 |
| rs12497268 | 0.240579 | 0.889382 | 0.786856 | 1.019336 | 0.208885 | 0.869965 | 0.240107 | 0.810319 |
| rs12571751 | 0.049482 | 0.192728 | 0.797454 | 1.010108 | 0.031709 | 0.210747 | 0.15046 | 0.880446 |
| rs12899811 | 0.209018 | 0.241632 | 0.387327 | 1.103882 | 0.14627 | 0.246959 | 0.592285 | 0.553855 |
| rs12970134 | -0.07443 | 0.179515 | 0.67856 | 1.105084 | 0.752285 | 0.523026 | 1.438332 | 0.150796 |
| rs13233731 | 0.175635 | 0.312151 | 0.573851 | 1.090317 | 0.152497 | 0.307722 | 0.495568 | 0.620358 |

*Table continued on next page*

**Appendix 22: Univariate and Multivariate Analyses for Individual SNPs and T2DM in African Americans (Continued)**

| | 1 Risk Allele | | | | 2 Risk Alleles | | | |
|---|---|---|---|---|---|---|---|---|
| SNP | Estimate | Standard Error | Probability | False Discovery Rate | Estimate | Standard Error | Probability | False Discovery Rate |
| rs13389219 | 0.293738 | 0.154886 | 0.058318 | 0.831026 | 0.759157 | 0.290705 | 2.611431 | 0.009214 |
| rs1359790 | 0.020937 | 0.6456 | 0.974138 | 1.028257 | 0.111958 | 0.630599 | 0.177542 | 0.859135 |
| rs1496653 | -0.16412 | 0.215681 | 0.446959 | 1.107681 | -0.03951 | 0.224283 | -0.17614 | 0.860233 |
| rs163184 | 0.131878 | 0.158725 | 0.406344 | 1.102934 | 0.10497 | 0.408327 | 0.257073 | 0.797199 |
| rs16927668 | -0.39009 | 0.306372 | 0.203354 | 1.28791 | -0.2723 | 0.29851 | -0.9122 | 0.361986 |
| rs17168486 | 0.208564 | 0.184128 | 0.257732 | 1.224228 | -0.69825 | 0.700225 | -0.99719 | 0.319026 |
| rs17301514 | 0.053868 | 0.245168 | 0.826156 | 1.023715 | 0.582697 | 1.333459 | 0.436981 | 0.662262 |
| rs17791513 | -0.41613 | 1.297309 | 0.748485 | 1.066592 | -0.37946 | 1.275345 | -0.29753 | 0.766151 |
| rs17867832 | -0.07385 | 0.463488 | 0.873447 | 1.037218 | -0.3348 | 0.453434 | -0.73837 | 0.46054 |
| rs2261181 | 0.057989 | 0.153972 | 0.706571 | 1.059857 | -0.19923 | 0.397345 | -0.50139 | 0.616257 |
| rs2334499 | -0.28423 | 0.187974 | 0.130972 | 1.244234 | -0.5646 | 0.84118 | -0.6712 | 0.502316 |
| rs243088 | 0.220022 | 0.194114 | 0.257415 | 1.333876 | 0.274997 | 0.216762 | 1.268661 | 0.204992 |
| rs2447090 | 0.350998 | 0.158412 | 0.027038 | 0.770571 | 0.215724 | 0.253938 | 0.849518 | 0.39589 |
| rs2796441 | -0.02708 | 0.465767 | 0.953653 | 1.025627 | -0.07194 | 0.454314 | -0.15834 | 0.874234 |
| rs3734621 | -0.02312 | 0.15974 | 0.884969 | 1.008865 | -0.34613 | 0.226602 | -1.52748 | 0.127103 |
| rs4299828 | 0.113672 | 0.283714 | 0.688798 | 1.090597 | 0.127511 | 0.276887 | 0.460519 | 0.64529 |
| rs4402960 | 0.02928 | 0.187565 | 0.875994 | 1.019013 | -0.24501 | 0.215595 | -1.13645 | 0.256164 |
| rs4430796 | -0.1046 | 0.332742 | 0.753335 | 1.047319 | -0.48955 | 0.364761 | -1.34211 | 0.180005 |
| rs4458523 | 0.078479 | 0.198461 | 0.692643 | 1.067044 | -0.21761 | 0.219128 | -0.99305 | 0.321035 |
| rs4502156 | -0.02153 | 0.153331 | 0.888391 | 0.992908 | 0.28138 | 0.299289 | 0.940163 | 0.347465 |
| rs459193 | -0.03356 | 0.20506 | 0.870048 | 1.055164 | -0.12113 | 0.22063 | -0.54904 | 0.583158 |
| rs4812829 | 0.220733 | 0.180724 | 0.22236 | 1.267451 | 0.211725 | 0.706872 | 0.299523 | 0.764631 |
| rs516946 | 0.426221 | 0.399068 | 0.285877 | 1.253462 | 0.218687 | 0.395096 | 0.553505 | 0.580098 |
| rs5215 | 0.098863 | 0.19821 | 0.618095 | 1.067619 | 0.283555 | 0.771859 | 0.367367 | 0.713459 |
| rs6795735 | -0.08643 | 0.160977 | 0.591492 | 1.087582 | -0.12625 | 0.445307 | -0.28351 | 0.776875 |

*Table continued on next page*

**Appendix 22: Univariate and Multivariate Analyses for Individual SNPs and T2DM in African Americans (Continued)**

| | 1 Risk Allele | | | | 2 Risk Alleles | | | |
|---|---|---|---|---|---|---|---|---|
| SNP | Estimate | Standard Error | Probability | False Discovery Rate | Estimate | Standard Error | Probability | False Discovery Rate |
| rs6819243 | 0.18612 | 0.252068 | 0.460543 | 1.093789 | 0.303245 | 0.253158 | 1.197846 | 0.231391 |
| rs6878122 | -0.14774 | 0.181187 | 0.415137 | 1.075581 | 0.471834 | 0.513648 | 0.918594 | 0.358631 |
| rs7177055 | 0.088107 | 0.156284 | 0.573099 | 1.126435 | 0.061421 | 0.240777 | 0.255096 | 0.798725 |
| rs7202877 | -0.18848 | 0.396378 | 0.63458 | 1.063855 | -0.62459 | 0.390134 | -1.60095 | 0.109849 |
| rs7569522 | 0.09048 | 0.172949 | 0.601031 | 1.070586 | -0.17132 | 0.212738 | -0.80533 | 0.420907 |
| rs7756992 | 0.201923 | 0.215974 | 0.350148 | 1.174027 | 0.291409 | 0.227501 | 1.280916 | 0.200656 |
| rs780094 | -0.40646 | 0.41185 | 0.324028 | 1.231305 | -0.36567 | 0.399572 | -0.91516 | 0.360431 |
| rs7845219 | 0.07868 | 0.238174 | 0.741238 | 1.083348 | 0.083254 | 0.239035 | 0.348293 | 0.727727 |
| rs7903146 | 0.507805 | 0.153871 | 0.001016 | 0.057922 | 0.307768 | 0.297516 | 1.034461 | 0.301285 |
| rs7955901 | 0.048395 | 0.155952 | 0.75641 | 1.002683 | -0.35934 | 0.358584 | -1.00211 | 0.316643 |
| rs8108269 | -0.30345 | 0.156382 | 0.052734 | 1.001938 | 0.238518 | 0.2466 | 0.967227 | 0.333771 |
| rs8182584 | 0.011265 | 0.159643 | 0.943765 | 1.034511 | -0.09251 | 0.237426 | -0.38962 | 0.696937 |
| rs849135 | -0.00393 | 0.31331 | 0.989994 | 1.025994 | 0.042135 | 0.307696 | 0.136936 | 0.891122 |
| rs9936385 | 0.119422 | 0.175466 | 0.496353 | 1.131686 | 0.246976 | 0.20731 | 1.19134 | 0.233932 |

SNP: single nucleotide polymorphism; T2DM: type 2 diabetes mellitus.

## Appendix 23: Interaction of Statin and Individual SNPs and T2DM in African Americans

| | 1 Risk Allele | | | | 2 Risk Alleles | | | |
|---|---|---|---|---|---|---|---|---|
| Statin x SNP | Estimate | Standard Error | Probability | False Discovery Rate | Estimate | Standard Error | Probability | False Discovery Rate |
| statin*rs10203174 | 0.803198 | 0.763166 | 0.292961 | 1.438174 | 0.50168 | 0.767335 | 0.513463 | 1.459315 |
| statin*rs10278336 | 0.577505 | 1.486696 | 0.697805 | 1.345766 | 0.371644 | 1.467835 | 0.800196 | 1.167854 |
| statin*rs10758593 | 0.138165 | 0.595506 | 0.816598 | 1.33625 | -0.37062 | 0.857724 | 0.665806 | 1.382827 |
| statin*rs10830963 | 0 | --- | --- | 0 | 0.506277 | 0.805425 | 0.529831 | 1.430543 |
| statin*rs11063069 | 0.355055 | 0.565765 | 0.530498 | 1.364137 | 0.585039 | 1.221314 | 0.632074 | 1.422167 |
| statin*rs11257655 | 0.197866 | 0.540485 | 0.71441 | 1.285938 | -0.06 | 1.678216 | 0.971488 | 1.279521 |
| statin*rs12571751 | -1.25029 | 0.684082 | 0.068031 | 3.673655 | -1.17212 | 0.724432 | 0.106126 | 1.910261 |
| statin*rs12899811 | -1.43999 | 0.919777 | 0.117908 | 2.122336 | -0.61012 | 0.907013 | 0.501384 | 1.592631 |
| statin*rs12970134 | 0.406518 | 0.646034 | 0.529394 | 1.504593 | -0.65888 | 1.63261 | 0.68665 | 1.27859 |
| statin*rs13233731 | -1.40999 | 1.029347 | 0.171201 | 1.540813 | -1.70345 | 0.99437 | 0.087146 | 2.352946 |
| statin*rs13389219 | 0.087706 | 0.556528 | 0.874823 | 1.349726 | 0.050428 | 1.107487 | 0.963695 | 1.300989 |
| statin*rs1496653 | -0.68136 | 0.779544 | 0.382399 | 1.376635 | -0.05184 | 0.787832 | 0.947553 | 1.311996 |
| statin*rs163184 | -0.48097 | 0.622583 | 0.440058 | 1.485196 | 0.191001 | 1.107847 | 0.863168 | 1.226608 |
| statin*rs16927668 | -2.05678 | 1.313613 | 0.11787 | 3.182495 | -1.62297 | 1.233063 | 0.188543 | 2.036267 |
| statin*rs17301514 | 0 | --- | --- | 0 | -1.81783 | 1.168829 | 0.120345 | 1.624661 |
| statin*rs2261181 | 0.120485 | 0.561948 | 0.830294 | 1.318703 | -0.42802 | 1.399973 | 0.759902 | 1.17242 |
| statin*rs2334499 | 0 | --- | --- | 0 | -0.63365 | 0.80193 | 0.429706 | 1.784931 |
| statin*rs243088 | -0.53373 | 0.723727 | 0.461083 | 1.464616 | -0.27217 | 0.808967 | 0.736645 | 1.169966 |
| statin*rs2447090 | 0.562401 | 0.576441 | 0.329585 | 1.369045 | -0.46651 | 1.053499 | 0.658034 | 1.421354 |
| statin*rs2796441 | 0.215605 | 1.488495 | 0.884874 | 1.32731 | 0.737746 | 1.417498 | 0.602913 | 1.415536 |
| statin*rs3734621 | -0.30316 | 0.598678 | 0.612747 | 1.272628 | -0.7006 | 0.852848 | 0.411657 | 2.222948 |
| statin*rs4299828 | -0.87754 | 1.395522 | 0.52967 | 1.43011 | -1.17481 | 1.365888 | 0.390031 | 3.008811 |
| statin*rs4402960 | 0.175566 | 0.67172 | 0.793887 | 1.339685 | -0.56215 | 0.751849 | 0.454904 | 1.535301 |
| statin*rs4430796 | 1.218409 | 1.019666 | 0.232535 | 1.39521 | 0.611611 | 1.152736 | 0.595887 | 1.462631 |

*Table continued on next page*

**Appendix 23: Interaction of Statin and Individual SNPs and T2DM in African Americans (Continued)**

| | 1 Risk Allele | | | | 2 Risk Alleles | | | |
|---|---|---|---|---|---|---|---|---|
| Statin x SNP | Estimate | Standard Error | Probability | False Discovery Rate | Estimate | Standard Error | Probability | False Discovery Rate |
| statin*rs4458523 | -0.61962 | 0.653102 | 0.34309 | 1.323348 | -0.54723 | 0.703929 | 0.437194 | 1.686319 |
| statin*rs4502156 | -0.15578 | 0.55751 | 0.780006 | 1.358719 | -0.27984 | 1.008309 | 0.781456 | 1.172184 |
| statin*rs459193 | -0.27101 | 0.735025 | 0.712455 | 1.326641 | -0.31553 | 0.750745 | 0.674408 | 1.348817 |
| statin*rs4812829 | 0 | --- | --- | 0 | -1.18279 | 0.667682 | 0.076923 | 4.15383 |
| statin*rs516946 | 1.680405 | 1.317302 | 0.202514 | 1.366971 | 1.057633 | 1.282027 | 0.409676 | 2.765311 |
| statin*rs6819243 | -0.9351 | 0.947706 | 0.324141 | 1.458633 | -0.3454 | 0.934951 | 0.711916 | 1.201359 |
| statin*rs6878122 | 0.449302 | 0.671792 | 0.503841 | 1.511524 | 0.580594 | 1.461635 | 0.691327 | 1.244389 |
| statin*rs7569522 | 0.268448 | 0.605231 | 0.65751 | 1.315021 | -0.54816 | 0.816174 | 0.502051 | 1.506154 |
| statin*rs7756992 | 0.389933 | 0.719835 | 0.588203 | 1.270518 | 0.27612 | 0.734855 | 0.707221 | 1.231933 |
| statin*rs780094 | 2.171392 | 1.423145 | 0.127528 | 1.721627 | 1.112381 | 1.348907 | 0.409855 | 2.459129 |
| statin*rs7845219 | 0.527212 | 0.901276 | 0.558766 | 1.311885 | -0.69226 | 0.899255 | 0.441674 | 1.590026 |
| statin*rs7903146 | 0.315174 | 0.56875 | 0.579655 | 1.304224 | -0.56967 | 1.047862 | 0.586858 | 1.509063 |
| statin*rs7955901 | 0.372155 | 0.594523 | 0.531541 | 1.304692 | -1.03601 | 1.267214 | 0.413898 | 2.031863 |
| statin*rs8108269 | 0.781349 | 0.578822 | 0.177495 | 1.369246 | 0.755343 | 0.929986 | 0.416954 | 1.876291 |
| statin*rs8182584 | -0.82296 | 0.563051 | 0.144306 | 1.558507 | 0.425 | 1.030907 | 0.680279 | 1.311967 |
| statin*rs849135 | -1.06878 | 0.921784 | 0.246669 | 1.332013 | -1.13983 | 0.899403 | 0.20547 | 1.849227 |
| statin*rs9936385 | 0.03351 | 0.640041 | 0.95826 | 1.398542 | 0.269452 | 0.758107 | 0.722378 | 1.182074 |

SNP: single nucleotide polymorphism; T2DM: type 2 diabetes mellitus.

**Appendix 24: Interaction of Statin and Individual SNPs and T2DM in African Americans, After Adjusting for Age, Gender, BMI and Top Principal Components**

| | 1 Risk Allele | | | | 2 Risk Alleles | | | |
|---|---|---|---|---|---|---|---|---|
| Statin x SNP | Estimate | Standard Error | Probability | False Discovery Rate | Estimate | Standard Error | Probability | False Discovery Rate |
| statin*rs10203174 | 0.925743 | 0.786707 | 0.239719 | 0.359578 | 0.684562 | 0.785465 | 0.383772 | 0.560099 |
| statin*rs10278336 | 0.177802 | 1.601433 | 0.911628 | 1.924548 | 0.217726 | 1.584164 | 0.890725 | 1.551585 |
| statin*rs10758593 | -0.02962 | 0.613298 | 0.96149 | 3.223819 | -0.64455 | 0.891743 | 0.470056 | 1.692201 |
| statin*rs10830963 | 0 | --- | --- | 0 | 0.355874 | 0.821347 | 0.664949 | 1.122102 |
| statin*rs11063069 | 0.134617 | 0.582797 | 0.817397 | 1.863664 | 0.837301 | 1.255607 | 0.505097 | 0.681881 |
| statin*rs11257655 | 0.188069 | 0.559214 | 0.736743 | 1.499797 | -0.4372 | 1.688532 | 0.795776 | 2.148595 |
| statin*rs12571751 | -1.36481 | 0.712127 | 0.055722 | 0.794033 | -1.2738 | 0.747133 | 0.088672 | 0.95766 |
| statin*rs12899811 | -1.5938 | 0.94521 | 0.092223 | 2.628367 | -0.83032 | 0.93153 | 0.37306 | 2.014526 |
| statin*rs12970134 | 0.479601 | 0.672317 | 0.475873 | 0.797788 | -0.23883 | 1.645419 | 0.884638 | 1.910818 |
| statin*rs13233731 | -1.48649 | 1.087047 | 0.171938 | 3.266815 | -1.88783 | 1.048713 | 0.072286 | 3.903443 |
| statin*rs13389219 | 0.141853 | 0.574126 | 0.804924 | 1.764641 | -0.27371 | 1.127927 | 0.808339 | 1.818763 |
| statin*rs1496653 | -0.51828 | 0.79395 | 0.514116 | 2.664055 | 0.208049 | 0.801445 | 0.795258 | 1.431464 |
| statin*rs163184 | -0.51163 | 0.638689 | 0.423377 | 2.011041 | -0.1154 | 1.121465 | 0.918072 | 1.836143 |
| statin*rs16927668 | -2.19337 | 1.333074 | 0.100364 | 5.720776 | -1.80741 | 1.252256 | 0.149396 | 4.033681 |
| statin*rs17301514 | 0 | --- | --- | 0 | -1.57813 | 1.181626 | 0.182144 | 3.278588 |
| statin*rs2261181 | 0.018748 | 0.581874 | 0.974306 | 2.414585 | -0.42624 | 1.407098 | 0.762042 | 1.959538 |
| statin*rs2334499 | 0 | --- | --- | 0 | -1.02527 | 0.820712 | 0.21201 | 1.635506 |
| statin*rs243088 | -0.53523 | 0.75278 | 0.477329 | 2.720776 | -0.33394 | 0.83899 | 0.690737 | 1.695445 |
| statin*rs2447090 | 0.595699 | 0.593488 | 0.315872 | 0.51442 | -0.48705 | 1.081199 | 0.652515 | 1.957544 |
| statin*rs2796441 | -0.00626 | 1.520908 | 0.996716 | 3.156267 | 0.564124 | 1.44653 | 0.696672 | 1.074865 |
| statin*rs3734621 | -0.4251 | 0.61941 | 0.492766 | 2.160589 | -0.74919 | 0.875564 | 0.39249 | 1.630343 |
| statin*rs4299828 | -1.31724 | 1.446021 | 0.362653 | 3.4452 | -1.44175 | 1.411292 | 0.307345 | 4.149155 |
| statin*rs4402960 | -0.1518 | 0.698262 | 0.82797 | 3.146285 | -0.75317 | 0.786585 | 0.338647 | 1.523911 |

*Table continued on next page*

**Appendix 24: Interaction of Statin and Individual SNPs and T2DM in African Americans, After Adjusting for Age, Gender, BMI and Top Principal Components (Continued)**

| | 1 Risk Allele | | | | 2 Risk Alleles | | | |
|---|---|---|---|---|---|---|---|---|
| Statin x SNP | Estimate | Standard Error | Probability | False Discovery Rate | Estimate | Standard Error | Probability | False Discovery Rate |
| statin*rs4430796 | 0.934917 | 1.065632 | 0.380617 | 0.556287 | 0.618973 | 1.198242 | 0.605628 | 0.908441 |
| statin*rs4458523 | -0.5484 | 0.673377 | 0.415701 | 2.632771 | -0.47287 | 0.723935 | 0.513855 | 1.460429 |
| statin*rs4502156 | -0.13063 | 0.575381 | 0.820474 | 2.922939 | -0.29963 | 1.039478 | 0.773242 | 1.815437 |
| statin*rs459193 | -0.36895 | 0.758847 | 0.626989 | 2.55274 | -0.19968 | 0.777475 | 0.797385 | 1.656108 |
| statin*rs4812829 | 0 | --- | --- | 0 | -1.04435 | 0.684239 | 0.127404 | 1.14664 |
| statin*rs516946 | 1.455142 | 1.338422 | 0.277334 | 0.395202 | 0.689891 | 1.299634 | 0.595708 | 0.846533 |
| statin*rs6819243 | -1.32671 | 0.979251 | 0.17593 | 2.005603 | -0.63234 | 0.962135 | 0.51126 | 1.725501 |
| statin*rs6878122 | 0.749512 | 0.693678 | 0.280311 | 0.443826 | 0.15565 | 1.448566 | 0.914463 | 1.702793 |
| statin*rs7569522 | 0.219292 | 0.626203 | 0.726303 | 1.427561 | -0.60512 | 0.842292 | 0.472747 | 1.501668 |
| statin*rs7756992 | 0.479506 | 0.743209 | 0.519028 | 0.896502 | 0.36228 | 0.764559 | 0.635766 | 1.040345 |
| statin*rs780094 | 2.157135 | 1.463485 | 0.140957 | 0.195965 | 1.111045 | 1.385744 | 0.42297 | 0.557083 |
| statin*rs7845219 | 0.451141 | 0.929608 | 0.62762 | 1.117948 | -0.79095 | 0.929408 | 0.395061 | 1.93939 |
| statin*rs7903146 | 0.297347 | 0.589668 | 0.614243 | 1.129414 | -0.73786 | 1.058365 | 0.485936 | 1.874324 |
| statin*rs7955901 | 0.265157 | 0.611885 | 0.664904 | 1.263318 | -0.94865 | 1.313605 | 0.470437 | 3.17545 |
| statin*rs8108269 | 0.859807 | 0.594589 | 0.148628 | 0.228968 | 0.769777 | 0.962389 | 0.424074 | 0.58718 |
| statin*rs8182584 | -0.83545 | 0.57934 | 0.149749 | 1.219384 | 0.453785 | 1.070971 | 0.67191 | 1.067151 |
| statin*rs849135 | -0.71221 | 0.940767 | 0.449281 | 3.201129 | -0.89917 | 0.915789 | 0.326526 | 1.959157 |
| statin*rs9936385 | 0.066789 | 0.657707 | 0.919145 | 2.18297 | 0.11857 | 0.778666 | 0.879017 | 1.695248 |

Adjustment for age, gender, BMI, and top 10 principal components.

BMI: body mass index; SNP: single nucleotide polymorphism; T2DM: type 2 diabetes mellitus.

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