MINDING THE GAPS: PROJECTING THE CONSEQUENCES OF ALTERING ASCVD RISK THRESHOLDS ON TYPE 2 DIABETES AND ASCVD

Joseph Engeda

A dissertation submitted to the faculty at the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Department of Epidemiology in the Gillings School of Global Public Health.

Chapel Hill
2019

Approved by:

Christy Avery

Jennifer Lund

Stefan Lhachimi

Thomas Keyserling

Wayne Rosamond

ABSTRACT

Joseph Engeda: Minding the Gaps: Projecting the Consequences of Altering ASCVD Risk Thresholds on Type 2 Diabetes and ASCVD
(Under the direction of Christy L. Avery)

While the cardioprotective effect of statins are undeniable, experimental and observational research has suggested the potential for increased type 2 diabetes (T2D) risk. However, few studies have directly compared statin-associated benefits and harms or examined heterogeneity by population subgroups or assumed treatment effect. Thus, we aimed to project the benefits and harms of statin treatment in primary prevention adult populations newly eligible for statin treatment using four proposed statin treatment recommendations. First, we conducted a meta-analysis of statin-associated T2D risk among randomized controlled trials (RCTSs) and observational studies (OBSs), excluding studies conducted among secondary prevention populations. We identified 23 studies (35% RCTs) of n=4,012,555 participants. There was little evidence for publication bias (P>0.1); however, evidence of heterogeneity was observed overall and among OBSs and RCTs ($P_{Cochran}$=<0.05).

Findings from the meta-analysis provided us with statin-associated T2D risks to be used to project the benefits and harms of statin treatment. A series of simulations were constructed using Markov models and contemporary data from biracial (African American and Caucasian), adult (aged 40-75) national population-based surveys and published meta-analyses. Statin treatment eligibility for each of four recommendations was determined by 10-year atherosclerosis cardiovascular disease (ASCVD) risk and, for one recommendation, age. This simulation framework was used to project statin-associated absolute benefit, quantified as the number needed to treat (NNT) to prevent one ASCVD event, absolute harm, quantified as number needed to harm (NNH) to incur one incident T2D, and relative benefit, quantified as the likelihood to be helped or harmed (LHH, NNH/NNT). Overall, the number of ASCVD events prevented was at least twice as large as the number of incident T2D incurred (LHH range: 2.10-

2.90). However, the relative benefit of statin treatment decreased when higher statin-associated T2D RRs were assumed. Findings highlight the higher relative burden of T2D occurred among female and younger adult populations, with disparities widening as statin-associated T2D RR increased, underscoring the need for more research quantifying statin-associated benefits and harms.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

4S	Scandinavian Simvastatin Survival Study
ACC	American College of Cardiology
AFCAPS/TexCaps	Air Force/Texas Coronary Atherosclerosis Prevention Study
AHA	American Heart Association
ALLHAT-LLT	Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial
ASCVD	Atherosclerotic cardiovascular disease
BAS	Bile acid sequestrant
CAC	Coronary artery calcium
CARE	Cholesterol and Recurrent Events Trial
CIMT	Carotid intima-media thickening
CORONA	Controlled Rosuvastatin Multinational Study in Heart Failure
CTT	Cholesterol Treatment Trialists'Collaboration
CVD	Cardiovascular disease
FDA	Food and Drug Administration
FH	Familial hypercholesterolemia
GISSI	Gruppo Italiano per lo Studio della Sopravvivenza
GLUT 4	Glucose uptake in adipocytes is mediated through glucose transporter 4
HDL-C	High-density lipoprotein cholesterol
HOPE-3	Heart Outcomes Prevention Evaluation
HPS	Heart Protection Study
HR	Hazard ratio
Hs-CRP	High-sensitivity C-reactive protein
IDEAL	Initiating Dialysis Early and Late
JUPITER	Justification for Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin
LDL-C	Low-density lipoprotein cholesterol
LDLR	Low-density lipoprotein receptor
LIPID	Long-Term Intervention with Pravastatin in Ischemic Disease

LRC CPPT	Lipid Research Clinics Coronary Primary Prevention Trial
MEGA	Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese
METISM	Metabolic Syndrome in Men
MI/CHD	Myocardial infarction/coronary heart disease
MRFIT	Multiple Risk Factor Intervention Trial
NCHS	National Center for Health Statistics
NHANES	National Health and Nutrition Examination Survey
NHLBI	National Heart, Lung, and Blood Institute
NIH	National Institutes of Health
OBS	Observational study
OR	Odds ratio
PCSK9	Proprotein convertase subtilisin/kexin type 9
PRINCE	Pravastatin Inflammation/CRP Evaluation
PROSPER	Pravastatin in Elderly Individuals at Risk of Vascular Disease
PROVE-IT-TIMI	Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction
REGARDS	Reasons for Geographic and Racial Differences in Stroke
RR	Relative risk
SNP	Single nucleotide polymorphism
SPARCL	Stroke Prevention by Aggressive Reduction in Cholesterol Levels
STRIP	Special Turku Coronary Risk Factor Intervention Project
T2D	Type 2 Diabetes
TC	Total cholesterol
TNT	Treating to New Targets

USPSTF	US Preventive Services Task Force
WOSCOPS	The West of Scotland Coronary Prevention Study
WHI	Women's Health Initiative

CHAPTER 1. OVERVIEW

Hmg CoA reductase inhibitors, commonly known as statins, are the most widely prescribed class of medication used to prevent atherosclerotic cardiovascular disease (ASCVD).[1, 2] Numerous meta-analyses have demonstrated that statins decrease ASCVD incidence by approximately 20% for every 38 mg/dL reduction in low-density lipoprotein cholesterol (LDL-C), with protective effects that extend to populations at low ASCVD risk.[3, 4] In 2013, American College of Cardiology/American Heart Association (ACC/AHA) cholesterol treatment recommendations changed the threshold to initiate statin treatment for primary prevention from 10% 10-year coronary heart disease (CHD) risk to 7.5% 10-year ASCVD (CHD and stroke) risk. As a result, the number of adults newly eligible for statin treatment for the primary prevention of ASCVD increased by an estimated 10.4 million, with 80% of the increase occurring in populations between the ages of 60-75.[5] Changes in statin eligibility also increased the proportion of females eligible for statins from 21.2% to 53.6%.[6] In 2018, the ACC/AHA continued to recommend the 7.5% 10-year ASCVD risk threshold; however, other recommendations suggest even more aggressive treatment recommendations, for example a 5% 10-year ASCVD risk threshold or initiating statin treatment in populations ≥55 years of age regardless of risk factor profile.[7] In contrast, recommendations calling for more conservative recommendations such as increasing the 10-year ASCVD risk threshold to 10%,[5, 8, 9] also have been proposed.

While the cardioprotective effect of statins are well established[4, 10], experimental and observational research has suggested the potential for adverse drug effects, including type 2 diabetes (T2D).[11-15] Yet, few studies have performed a direct comparison of the number of statin-associated ASCVD events prevented in comparison to the number of statin-associated T2D incurred across proposed statin recommendations. In theory, traditional epidemiologic studies could help address this research gap if such studies (1) were contemporary, (2) spanned ages specified by current recommendations, (3)

included high quality statin adherence measures, and (4) precisely and validly measured ASCVD and T2D incidence within generalizable male and female multi-ethnic populations with adequate follow-up; but very few studies can meet all of these criteria. Additional challenges include estimating valid statin-associated ASCVD and T2D risk in observational settings.[16] As an alternative, simulation tools can help extend the reach of traditional epidemiological studies examining intended and unintended consequences of statin treatment through synthesis of high quality observational, experimental, and meta-analysis data. However, most meta-analyses have restricted analyses to either randomized controlled trials (RCTs) or observational studies (OBSs) and have combined primary and secondary prevention populations to examine statin associated T2D risk. Yet, meta-analyses that incorporate summary data from both study designs may take advantage of the internal validity of RCTs and the external validity of OBSs[17, 18] and the risk of T2D may differ when used for primary vs. secondary prevention.[19] Therefore, this dissertation will first estimate the effect of statins on T2D among populations most affected by changes to statin use recommendations. Second, we will use a simulation framework to combine evidence from meta-analyses, observational studies, and population surveys to estimate statin-associated benefits and harms.[5, 6, 8, 20]

CHAPTER 2. SPECIFIC AIMS

This work will use a simulation framework to combine evidence from meta-analyses of statin-associated ASCVD and T2D risk, observational studies measuring ASCVD and T2D incidence, and population surveys informing ASCVD risk factor distributions and demographics to estimate the number of ASCVD events prevented and incident T2D incurred in primary prevention populations across four proposed 10-year ASCVD risk statin treatment recommendations.[5, 6, 8, 20]

We therefore will:

1. Estimate the effect of statins on T2D incidence among primary prevention populations.
    a. Conduct a meta-analysis of all available published data from large primary prevention RCTs and observational studies.
    b. Investigate publication bias, heterogeneity, and the extent to which both RCTs and observational studies are inherently combinable.
2. Project ASCVD risk reduction and increase in T2D from statin treatment in primary prevention adult populations newly eligible for statin treatment using four proposed statin treatment recommendations.
    a. Build series of Markov models by assembling contemporary and validated data from NHANES (statin eligibility and probability of statin use), REGARDS (T2D and ASCVD incidence and prevalence), published RCT meta-analyses[3, 12](statin associated RRs), and results from aim 1 (statin associated RRs) using decision analyses software TreeAge Pro.
    b. Using Markov models from Aim 2A, estimate the number of ASCVD events prevented and incident T2D incurred across four proposed statin treatment recommendations:
        - 10-year ASCVD risk threshold ≥10%[21]
        - 10-year ASCVD risk threshold ≥7.5%[22]

- 10-year ASCVD risk threshold ≥5%[5]
- 10-year ASCVD risk threshold ≥7.5% and including all populations ≥ 55 years of age[23]

CHAPTER 3. BACKGROUND

A. Low-Density Lipoprotein Cholesterol

Cholesterol is a fat like substance found in cell membranes and was first isolated as a hard, fatty material from gallstones in 1769 by Poulletiere de la Salle.[24, 25] However, it was not until 1910 that a possible association between cholesterol and atherosclerosis, a major risk factor for cardiovascular disease (CVD), was made, when Adolf Windaus reported that aortas with atherosclerosis contained up to 20 times the cholesterol found in normal arterial walls.[26] As more evidence accumulated in support of the association between cholesterol and atherosclerosis, studies revealed a majority of the cholesterol content in the body was transported by low-density lipoproteins.[27] Cholesterol carried by low-density lipoprotein is referred to as low-density lipoprotein cholesterol (LDL-C) and elevated levels of LDL-C have been associated with atherosclerosis and downstream CVD manifestations.[28] To prevent LDL-C-associated CVD, particularly myocardial infarction/coronary heart disease (MI/CHD [refers to MI incidence and CHD mortality, unless otherwise noted]) and ischemic stroke, reducing excessive levels of LDL-C has focused on pharmacological therapy, specifically statins.[6] While existing evidence has demonstrated the reduction of LDL-C levels and risk of MI/CHD from statins, research has suggested that statins may also increase the risk of adverse events, including diabetes mellitus (T2D).[12] Many questions on the association between statins and T2D still remain, particularly, projecting changes in T2D and MI/CHD incidence and prevalence associated with various statin recommendations from cholesterol treatment recommendations.

The purpose of the following sections are to provide an overview of LDL-C and its role in atherosclerosis, starting with a brief description of cholesterol and the underlying biochemistry and pathophysiology of low-density lipoprotein metabolism. Second, I will summarize evidence from the scientific literature for the role of LDL-C in the atherosclerotic process. Third, I will report the

epidemiology of LDL-C and the various treatments that have been recommended to target elevated LDL-C levels. Fourth, I will describe the epidemiology of statins, the primary cholesterol medication used today, and report evidence from the scientific literature for the efficacy of statins in reducing LDL-C levels. Fifth, I will present evidence for potential side effects of statins, with a focus on T2D, including potential mechanisms. Sixth I will summarize the epidemiology of health outcomes associated with elevated LDL-C levels. Seventh, I will describe the development of cholesterol treatment recommendations starting from the first recommendations created until the most recent recommendations released. Finally, I will provide information on the impact of statin therapy on public health.

A.1. Cholesterol

Low-density lipoprotein transports cholesterol to cells throughout the body to enable hormone synthesis, cell membrane formation, and to aid in functions of the central nervous system. Cholesterol serves as a precursor of the bile acids formed in the liver and of steroid hormones.[29] Cholesterol also impacts cell membrane stability, permeability, and fluidity by changing the order of fatty acyl chains and determining the functional properties of membrane-resident proteins like ion channels and transmitter receptors.[30] For example, several studies have demonstrated that an increase in cholesterol content in plasma membranes leads to increased intake of Ca^{2+} in plasma membranes, thereby altering membrane fluidity. In addition, neurons use cholesterol to establish and maintain synaptic connections, essential for the brain to transmit and process information.[31]

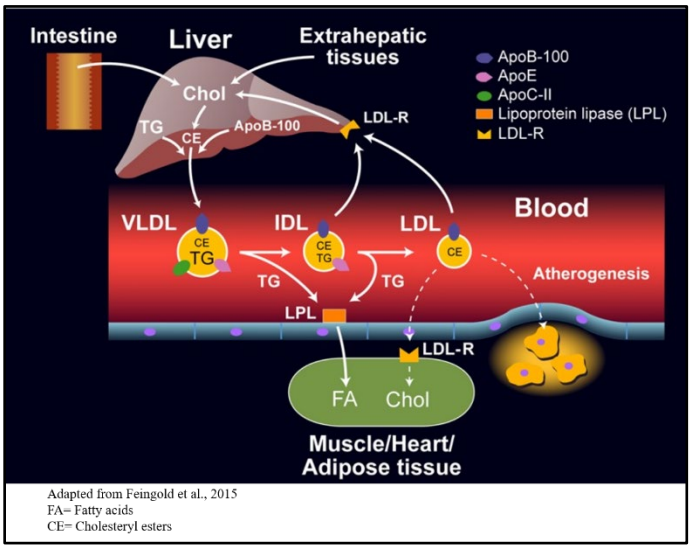
A.2. The Role and Formation of Low-Density Lipoprotein

As mentioned previously, cholesterol plays a major role in all cells for growth and maintenance; however, because of the polarity of cholesterol, it requires plasma lipoproteins to transport it through circulation. Plasma lipoproteins transport hydrophobic cholesterol through the use of hydrophilic phospholipids that surround the cholesterol, preventing it from interacting with an aqueous environments (i.e. blood). A major plasma lipoprotein in the transport of cholesterol is low-density lipoprotein, which carries more than 60% of the total cholesterol (TC) content in blood.[32] Before transport of cholesterol can occur, however, low-density lipoprotein must be produced through the endogenous lipoprotein pathway

(Figure 1). Briefly, in the endogenous lipoprotein pathway, the liver secretes very low-density lipoproteins (VLDL), formed from adipose-derived or de novo synthesis of fatty acids, into circulation (Figure 1).[32, 33]

During the fasting state, when dietary fat is not available, the primary source of fatty acids for VLDL synthesis is the adipocyte.[34] As insulin levels fall, triglycerides (i.e. a type of lipid) attached to adipocytes are hydrolyzed (i.e. broken down with the use of H_20), resulting in the release of fatty acids. The fatty acids are transported to the liver by proteins such as albumin, where they are taken up by hepatocytes for VLDL production. In contrast to the fasting state where the adipocyte is the main source of fatty acids, during the feeding state, VLDLs are synthesized through de novo lipogenesis whereby dietary carbohydrates are converted to fatty acids in the liver.[35] Once fatty acids have been produced or reach the liver, they are esterified (i.e. turned into an ester by replacing the hydrogen with a hydrocarbon group[36]) to form triglycerides. In addition to forming triglycerides, the liver also synthesizes cholesterol from acetyl CoA (see section E.2. Statin Therapy) and loads both triglycerides and cholesterol on an apolipoprotein B-100 ($apoB_{100}$) through the microsomal triglyceride transfer protein complex to form VLDL particles.[32] VLDL particles are then secreted from the liver into circulation, where they are hydrolyzed and release their fatty acids. The loss of fatty acids results in the formation of intermediate-density lipoproteins (IDL) particles containing $apoB_{100}$, cholesterol, and triglycerides (Figure 1). Half of the IDL particles bind to hepatic low-density lipoprotein receptors (LDLR) and are removed from circulation, while the remaining IDL particles are converted to low-density lipoprotein.[32] To form LDL, triglycerides from IDL particles are hydrolyzed and substituted by cholesterol esters and all apolipoproteins except $apoB_{100}$ are removed. This results in LDL particles

Figure 1. Endogenous lipoprotein pathway



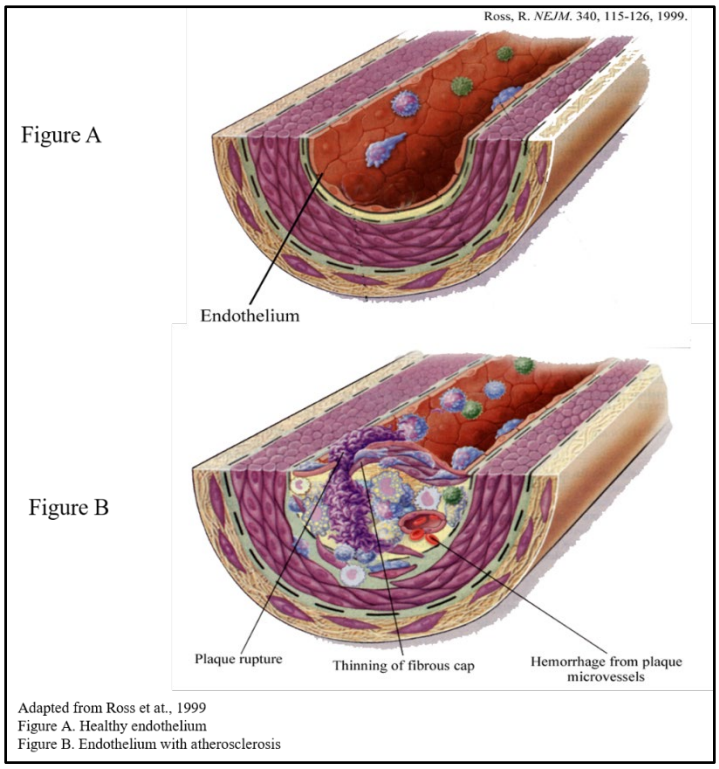
containing mostly apoB$_{100}$ and cholesterol. Low-density lipoprotein particles can then deliver the cholesterol in the form of LDL-C to extrahepatic cells and to the liver by binding to LDLRs.[37]

LDL particles are important for the transport of cholesterol from the liver to cells throughout the body; however, additional plasma lipoproteins play vital roles in helping to maintain body cholesterol homeostasis. For instance, high-density lipoproteins (HDL) deliver free cholesterol and excess cholesterol that cannot be metabolized back to the liver in a process known as reverse cholesterol transport.[38] In depth discussions of HDL and additional plasma lipoproteins, however, are beyond the scope of this dissertation.

A.3. LDL-C and Atherosclerosis

LDL-C is an important mediator between food intake and the narrowing and hardening of the arteries during atherosclerosis. The "lipid hypothesis" states that high levels of LDL-C are a major risk factor and can be a sufficient cause of atherosclerosis and MI/CHD (see section D.1. Myocardial Infarction/Coronary Heart Disease) and stroke (see section D.2. Stroke).[28]

Figure 2. Atherosclerotic thickening of the arterial wall

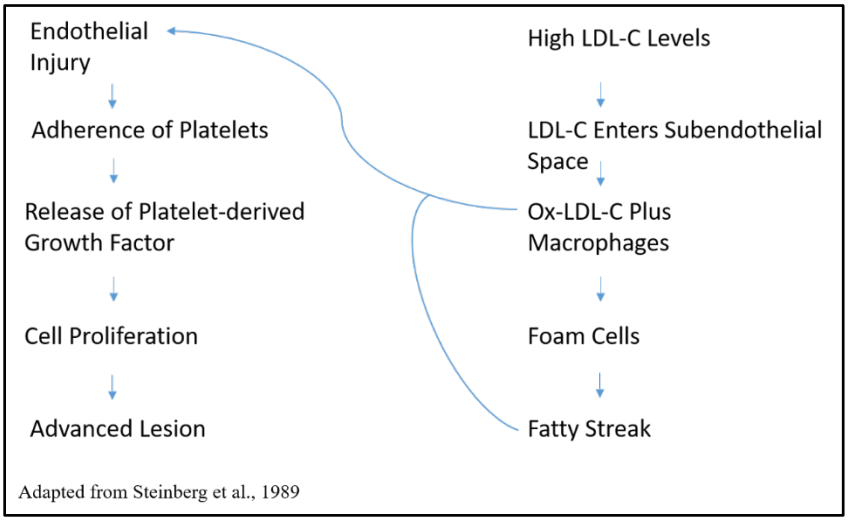


Adapted from Ross et at., 1999
Figure A. Healthy endothelium
Figure B. Endothelium with atherosclerosis

LDL-C is hypothesized to increase the risk of MI/CHD by contributing to the development of atherosclerotic lesions in the artery wall (Figure 2).[28, 39] Briefly, lifestyle (see section C.4.Lifestyle Modification) and genetic risk factors (see section B.2. Genetic Evidence for the Role of LDL-C in Atherosclerosis),[40-42] can result in elevated LDL-C in circulation.[43, 44] Elevated circulating LDL-C can lead to LDL-C retention at atherosclerosis-prone sites in arteries. Factors responsible for focal retention, however, are not clear.[45]

Accumulation of LDL-C particles in the arteries results in fatty streaks and generation of foam cells. Once beneath the endothelium, LDL-C particles undergo oxidation to result in highly toxic and chemoattractant oxidized LDL-C (ox-LDL-C) particles.[46] The formation of ox-LDL-C attracts macrophages and smooth muscle cells, which ingest ox-LDL-C. Macrophages contain receptors for both ox-LDL-C (scavenger receptors) and native LDL-C (LDLR); however downregulation of LDL-C ingestion is only present in LDLR.[47] When downregulation is absent, uptake of ox-LDL-C by scavenger receptors occurs more rapidly than uptake of native LDL-C by LDLR. Accumulation of ox-LDL-C in macrophages and smooth muscle cells generates foam cells underneath the endothelium, with continued buildup resulting in fatty streaks, early indicators of atherosclerosis (Figure 3).[48]

Figure 3. Hypothesized linkage between LDL-C, endothelial injury, and atherosclerosis



The accumulation of macrophages and smooth muscle cells underneath the endothelium can lead to release of toxic ox-LDL-C, resulting in endothelial injury and eventually in the formation of advanced atherosclerotic lesions. Although macrophage ingestion of ox-LDL-C temporarily protects the endothelium from damage by trapping highly toxic ox-LDL-C, once macrophages are heavily loaded, they can become nonfunctional or die, releasing ox-LDL-C and resulting in damage to the endothelium. As this process continues, the sustained damage of the endothelium can lead to an inflammatory response to further damage the walls of the artery and accelerate the development of fatty-streaks (Figure 3).[48, 49] Disruption of the endothelial barrier then can lead to platelets and smooth-muscle cells migrating to the site of the injury and proliferating. This results in the formation of intermediate lesions containing inflammatory response cells and LDL-C, contributing to the

thickening of the artery wall over time.[39] As the process continues, these events can result in the formation of advanced lesions and narrowing of the artery (Figure 3). [50]

B. Evidence for the Role of LDL-C in Atherosclerosis and Clinical Events from Human and Animal Studies

The relationship between LDL-C, and in early studies, TC, with atherosclerosis and downstream clinical events has been examined in numerous observational and experimental studies in both human and animal populations. This section provides a summary of this relationship from the scientific literature that spans findings from the earliest animal studies to results from cholesterol-lowering drug trials.

B.1. Evidence of the Association between TC and Atherosclerosis in Animal Studies

Animal studies have provided evidence of elevated TC levels increasing risk of atherosclerosis since the early 20th century. Anitschkow et al. observed that rabbits fed high levels of cholesterol had elevated TC levels and developed atherosclerosis.[51] Following Anitschkow's work, scientists confirmed his findings in additional rabbit strains and eventually other animals.[52, 53] For instance, Rowsell et al. compared pigs fed egg yolk (mimicking a high cholesterol diet) to those maintaining usual diets and observed increases in both TC levels and the burden of atherosclerosis.[54] Research examining potential long-term effects of high cholesterol diets in rhesus monkeys also found that maintaining elevated levels of TC over 40 months resulted in an increased incidence of MI/CHD.[55, 56] Investigators also examined the impact diets low in cholesterol had on rhesus monkeys with atherosclerosis and found that after a 40-month period, both TC levels and aortic plaque decreased.[57] Together, these and other studies suggested that elevated TC levels increased risk of atherosclerosis and downstream MI/CHD events in animals; however, it was unclear whether these associations generalized to humans.

B.2. Genetic Evidence for the Role of LDL-C in Atherosclerosis

The relationship between LDL-C and MI/CHD has been most clearly shown in studies examining populations with genetic forms of hypercholesterolemia.[58] Familial hypercholesterolemia (FH) is one of five types of familial dyslipidemia and was first identified in 1964.[59] FH is an autosomal dominant disorder that impacts the *LDLR* gene, resulting in reduced function of the LDLR and subsequent elevation

in LDL-C levels.[60] While the prevalence of heterozygous and homozygous FH is low (0.2% and <0.01% respectively), populations with FH have six to ten-fold elevations in LDL-C levels and higher risks of developing MI/CHD compared to populations without the mutation, with homozygous FH patients found to develop MI/CHD by the second decade of life.[59, 61]

In parallel to the discovery of LDLR, Yosio Watanabe studied Watanabe Heritable-Hyperlipidemic (WHHL) rabbits, characterized by abnormally high levels of LDL-C, to better understand mutations in the LDLR and its impact on LDL-C.[62-64] Briefly, Watanabe compared LDL-C levels from normal rabbits and WHHL-rabbits and found accumulation of LDL-C, reduced rate of clearance of LDL-C from blood, and that rabbits subsequently developed atherosclerosis early in life. Watanabe observed a delay in the disappearance of LDL-C from blood and the absence of LDL binding to LDLR in rabbit skin fibroblasts, thereby hypothesizing that mutations in LDLR gave rise to extremely high LDL-C levels. In 1985, Drs. Michael Brown and Joseph Goldstein suggested FH was associated with defects in the LDLR in humans, similar to defects found among WHHL rabbits.

Current genetic evidence on the association of LDL-C and atherosclerosis is contributed by large-scale genetic association studies that identified numerous genetic variants associated with LDL-C, some of which also increased MI/CHD risk. For example, single nucleotide polymorphisms (SNPs) associated with LDL-C and mapping to the *LDL-C*, *APOB* (apolipoprotein B)[65], *PCSK9* (proprotein convertase subtilisin/kexin type 9)[66], and *LDLR*[67] genes also increase MI/CHD incidence.[68] Mendelian Randomization studies, which avoid temporal ambiguity and confounding given "random assignment" of alleles at birth, also support a direct role of LDL-C on MI/CHD.[65-68]

B.3. Observational Evidence of the Association between LDL-C and Atherosclerosis

Results from early observational studies in human populations were consistent with those from animal studies and early family-based studies of Mendelian lipid traits and suggested that elevated TC, the cholesterol metric available at that time, also was associated with atherosclerosis and risk of MI/CHD.[69-72] Observations on the relationship between diet, TC, and atherosclerosis were made as early as 1916, when Dr. Cornelius De Langen compared TC levels of various populations and found that

cholesterol-rich diets and atherosclerosis were associated with elevated levels of TC.[73] For example, after comparing MI/CHD prevalence and incidence among Javanese, Dutch, French, and Germans, De Langen observed that Javanese had the fewest events of both. To understand the differences in MI/CHD disease burden, De Langen observed characteristics of each population, including TC. Comparing average TC levels, De Langen found that Dutch, French, and Germans had similar (high) TC levels, while the Javanese had much lower TC levels; these differences attributed to the low cholesterol and lipid content in the Javanese diet. In addition, he found that Javanese stewards on the Dutch transport liners, who adopted a Dutch diet rich in meat and eggs, had TC levels that were more similar to the Europeans than to other native Javanese, further suggesting a cholesterol-rich diet impacted TC levels.[73]

As work on diet and TC levels continued to be done in the early 20th century[74, 75], the National Heart Institute reported that, by 1948, 44% of deaths in the U.S. could be attributed to MI/CHD, an absolute increase of 20% from 1940.[76] The causes of MI/CHD, however, were poorly understood. In response, the U.S. Public Health Service launched what would become the Framingham Heart Study (FHS), to study prospectively MI/CHD and its risk factors among 5,209 participants with no history of MI/CHD.[77] After 18 years of follow-up, Shurleff et al. reported the incidence rate of MI/CHD was higher among participants with TC levels >220 mg/dl compared to those with TC levels <220 mg/dl (incidence rate difference [IRD] = 8.86 cases/1000 person-years; 95% confidence interval [CI]: 5.57-11.9) among Caucasian men aged 45-64.[72, 78] Consistent with results done in the U.S., studies performed in other countries also suggested direct associations between rising TC levels and incident MI/CHD.[79, 80] For instance, Johnson et al. examined a Japanese population sample of men and women in Hiroshima with mean TC levels (mean TC = 157 mg/dl) lower than those in the US (mean TC=222 mg/dl) between 1958-1964. Using autopsy reports, ECG evidence, and medical history to classify MI/CHD, Johnson et al. found that men with TC values ≥220 mg/dl (95th percentile) had a higher rate of developing incident MI/CHD compared to the rate of those with TC values ≤220 mg/dl (incidence rate difference [IRD] =9.8 events/1000 person-years [95: CI: -02.2-21.7]). No association, however, was found among women (IRD =-0.4/1000 person-years [95% CI: -3.0-2.2]).[80, 81] Johnson et al. also found that as the category of TC

values increased, the rate of incident MI/CHD increased among men; however this relationship was not assessed with TC as a continuous variable.

Until the 1960s, population studies were limited to measuring TC and TGs in blood; however, the introduction of ultracentrifugation made it possible to separate and examine specific components of TC such as LDL-C and VLDL-C. One of the earliest studies to examine multiple cholesterol components was the Honolulu Heart Study in 1970.[82] The Honolulu Heart Study aimed to investigate MI/CHD risk in men of Japanese ancestry born in the years 1990-1919 and living on the island of Oahu in 1967.[83] Using ultra-centrifugation to separate TC components, Rhoads et al. conducted a case-control study and demonstrated that LDL-C was correlated with TC (correlation coefficient =0.78) and that the risk of MI/CHD was higher among populations in the upper (≥ 168 mg/dl) versus lower (≤ 119 mg/dl) quartiles of LDL-C (relative risk [RR] = 1.8).[32] To examine the relationship between LDL-C and MI/CHD prospectively, Medalie et al. studied 10,000 Israeli male government employees over five years and found the risk for incident MI/CHD was associated with increasing LDL-C levels.[84] For instance, the five-year risk of incident MI/CHD among the group with the highest decile (220-460 mg/dl) of LDL-C was 2.5 percentage points higher than the risk of incident MI/CHD among the lowest decile (40-119 mg/dl) (risk difference [RD] = 2.5%). Additional prospective studies found similar associations between LDL-C levels and risk of CHD and MI/CHD; however, studies were largely restricted to employed, Caucasian men.[84-86]

To examine whether the relationship between TC and CHD mortality was continuous, the Multiple Risk Factor Intervention Trial (MRFIT) recruited 356,222 Caucasian men aged 35-57 years and followed participants up to six years.[87] Using International Classification of Diseases (ICD) 9 codes to define CHD mortality, MRFIT

Table 1. Deciles of serum cholesterol and six-year CHD mortality in the MRFIT

Decile	Serum Cholesterol, mg/dL (mmol/L)	Mean Serum Cholesterol, mg/dL (mmol/L)	CHD Mortality		Relative Risk
			No. of Deaths	Rate per 1000	
1	≤167 (≤4.32)	153.2 (3.962)	95	3.16	1.00
2	168-181 (4.34-4.68)	175.0 (4.526)	101	3.32	1.05
3	182-192 (4.71-4.97)	187.1 (4.838)	139	4.15	1.31
4	193-202 (4.99-5.22)	197.6 (5.110)	149	4.21	1.33
5	203-212 (5.25-5.48)	207.5 (5.366)	203	5.43	1.72
6	213-220 (5.51-5.69)	216.1 (5.588)	192	5.81	1.84
7	221-231 (5.72-5.97)	225.9 (5.842)	261	6.94	2.20
8	232-244 (6.00-6.31)	237.7 (6.147)	272	7.35	2.33
9	245-263 (6.34-6.80)	253.4 (6.553)	352	9.10	2.88
10	≥264 (≥6.83)	289.5 (7.486)	494	13.05	4.13

Adapted from Stamler et al., 1986

investigators found that the risk of CHD mortality increased as TC concentration increased, with larger increases in CHD mortality occurring above 180 mg/dl (Table 1). Together, these and other observational studies suggested that the risk of MI/CHD increased as TC or LDL-C levels increased, further motivating studying evaluating the causal relationship between LDL-C and MI/CHD.

B.4. Early Intervention Studies

Observational epidemiologic studies as well as animal experiments and pathologic observations suggested that the higher the LDL-C or TC, the greater the risk of MI/CHD. However, before concluding that TC and LDL-C played a causal role in the pathogenesis of MI/CHD, conclusive evidence from randomized controlled trials (RCTs) was required. To examine the impact of cholesterol-lowering through medication on MI/CHD incidence, the National Heart, Lung, and Blood Institute (NHLBI) commissioned the Lipid Research Clinics Coronary Primary Prevention Trial (LRC CPPT) in 1973.[88] LRC CPPT investigators recruited 3,806 men aged 35-59 years with TC levels ≥265 mg/dl to a trial of either a cholesterol-lowering diet or cholesterol-lowering diet plus cholestyramine resin (bile acid sequestrant [BAS] binds to bile, preventing it from entering the intestine to be used in the formation of plasma lipoproteins as mentioned in section A.2. The Role and Formation of Low-Density Lipoprotein). After seven years, compared to the diet-only group, the diet and medication group had lower LDL-C levels (12.6% lower [$p < 0.01$]) and incidence rate of MI/CHD (19% relative difference [$p < 0.05$]). Thus, the LRC CPPT showed that among Caucasian men with high levels of TC, reductions in LDL-C levels were associated with reductions in incident MI/CHD through medication in a clinical trial setting.

In addition to clinical trials that showed associations between cholesterol-lowering medication and reductions in subsequent MI/CHD events, RCTs also demonstrated benefits of cholesterol-lowering medication on reducing atherosclerotic lesions. The NHLBI Type II Coronary Intervention Study was designed to examine the impact of lowering LDL-C levels through medications and diet on atherosclerotic lesions.[89] The study assigned participants to receive either a low-cholesterol, low-fat diet and cholestyramine treatment or the same diet and placebo. Investigators found after five-years, LDL-C levels were reduced by 5% among the placebo group as compared to 26% among the treated group. Using

coronary angiography to measure changes in lesion size (lesions were identified by analyzing multiple arterial tree segments), results also showed that lesions progressed in 49% of the placebo-treated patients versus 32% of the cholestyramine-treated patients ($p < 0.05$). Thus, the NHLBI Type II Coronary Intervention Study provided further evidence of the impact medications had on coronary angiographic defined atherosclerosis and clinical events; albeit in a limited sample (N =116) of mostly Caucasian men.

Clinical trials providing evidence of LDL-C reduction and its impact on atherosclerosis and clinical events motivated further interventions targeting elevated LDL-C throughout the 1980s. While interventions during this period mostly focused on pharmacotherapy and lifestyle changes, the first statin, the subject of this dissertation and described in detail in section C.3. Statin Therapy, was not approved by the Food and Drug Administration (FDA) until 1987 and, at this time, was decades away from being recommended as the first line cholesterol-lowering medication.

C. Epidemiology and Treatment of LDL-C

C.1. Epidemiology of LDL-C

Since the 1970s when LDL-C levels were first measured in large U.S. population-based surveys, mean levels of LDL-C have decreased among both men and women.[90] Age-adjusted results from national surveys of noninstitutionalized populations found the mean LDL-C levels for adults (≥20 years old) not taking cholesterol-lowering medication declined from 128 mg/dl in 1988-1994 to 124 mg/dl in 1999-2002, and to 119 mg/dl during 2007-2010, with mean LDL-C levels decreasing for both men and women.[90] Similar reductions were found in the prevalence of high LDL-C levels (defined as ≥160mg/dl), decreasing from 59% in 1976-1980 to 42% in 1988-1994, and to 33% in 2001-2004, reaching 27% in 2007-2010 with similar reductions observed among both Caucasian and African American men and women.[90] Changes in diet have been hypothesized as the primary driver in the reduction of LDL-C levels in part due to decreases in consumption of trans-fatty acids.[91]

Decreases in mean LDL-C levels have occurred in parallel to increases in awareness, treatment, and control of elevated levels of LDL-C. For example, among populations with high LDL-C (≥160mg/dl), the percentage of the population aware of their elevated LDL-C increased from 39.2% in 1988-1994 to

63% in 1999-2004.[92] Using the National Health and Nutrition Examination Survey (NHANES), Carroll et al found that from 1988 to 2010, there was an increasing trend in the age-adjusted percentage of adults (≥20 years old) treated for high LDL-C increased from 3.4% in 1988-1994 to 15.5% in 2007-2010, with the largest increases among adults ≥50 year old. To estimate LDL-C control, Hyre et al. examined the percentage of the treated adults ≥20 years old with LDL-C levels lower than goal, as defined by cholesterol treatment recommendations at the time (see section E.3.NCEP-ATP III). Hyre et al. reported that LDL-C control increased from 34.7% in 1988-1994 to 60.7% in 1999-2004. LDL-C control was highest among older adults (ages ≥65 years), women, and Caucasians.[92] As awareness and control of LDL-C levels have increased, however, Kuklina et al. found 51.9% of the NHANES population eligible for medication (based on LDL-C levels or 10-year CHD risk [see section E.3.NCEP-ATP III]) was still untreated[93], consistent with results found in the Multi-Ethnic Study of Atherosclerosis (MESA) where 46% of the medication eligible population was untreated in the middle to late aged cohort (ages 45-80 years old at study baseline in 2000-2002).[94]

LDL-C and TC levels have also been shown to change across the life-course. Cross-sectional and prospective studies suggest that TC increases with age in young and middle-aged adults until peaking around the ages of mid-life, where TC levels then begin to decline with age.[95] Additionally, hormonal changes contribute to LDL-C changes observed among women. For instance, before the ages of menopause, women tend to have lower LDL-C levels than men of the same age; however, afterwards the differences by sex become less apparent and LDL-C levels in women may surpass those of men of the same age due to a decline in estrogen production resulting in changes in lipid metabolism.[96, 97]

C.2. Pharmacologic Treatments

Pharmacologic treatments to lower LDL-C have been available since the 1960s; however, limitations in efficacy and side effects prevented the earliest available treatments from becoming widely used first-line medication for LDL-C reduction. Niacin was the first medication used in the clinical treatment of high LDL-C level, operating by inhibiting triglyceride synthesis and thus decreased secretion of VLDL and LDL particles (see section A.2. The Role and Formation of Low-Density Lipoprotein).

Although niacin reduced TC and LDL-C levels by 12-14% and 15-18%, respectively in randomized trials[98] and has been shown to reduce inflammation and oxidative stress[99], it is often underused in clinical settings due to findings from large secondary prevention RCTs (N>3000), that found niacin had no effect on MI/CHD incidence.[100, 101] In addition, in combination with statins, niacin has also shown an increase in T2D incidence, has been reported to increase hepatic toxicity, peptic ulcers, and deficiencies of clotting factor synthesis,[101] and does not decrease the risk for MI/CHD. Fibrates have been studied since 1962, decreasing LDL-C by stimulating reverse cholesterol transport (see section A.2. Role and Formation of Low-Density Lipoprotein) and increasing LDL-C clearance. Although once viewed as important in LDL-C lowering, RCTs have shown mixed results when using fibrates to reduce MI/CHD incidence.[102] In addition, increased risk of rhabdomyolysis, a syndrome resulting from the breakdown of skeletal muscle with release of muscle cell contents into the blood[103], when combined with statins has been reported, limiting the utility of fibrates as cardioprotective agent.[104] BAS have been proven to reduce LDL-C levels by 15-30% in monotherapy[105] as described in B.4. Early Intervention Studies. In addition to monotherapy, BAS have also have been tested in combination with statins to reduce LDL-C levels by 40-60%[106] and the National Lipid Association has recommended the use of BAS in combination with statins when statin monotherapy is inadequate in lowering LDL-C levels.[107]

Recent clinical trials have evaluated PCSK9 target agents as potential LDL-C lowering therapies. PCSK9 binds to the LDLR and escorts it to the lysosome for degradation; however, blocking the PCSK9-LDLR interaction allows LDLR to continue to clear LDL-C into the liver and reduces LDL-C concentration in the blood.[108, 109] Clinical trials testing PCSK9 inhibitors with statins have shown reduction in LDL-C levels by 61% (95% CI: 59%-63%; P<0.001) for a median absolute reduction of 48 mg/dl.[110] Results have also found MI/CHD incidence to be lower in the PCSK9 inhibitor plus statin group compared to statin-only group (hazard ratio [HR] = 0.47; 95% CI: 0.28-0.78) at one year. Despite associations with reductions in both LDL-C levels and MI/CHD incidence, PCSK9 inhibitors are generally prescribed after treatment with statins plus ezetimibe have failed to reduce LDL-C levels among patients at high risk of ASCVD, due to the high cost compared to statins ($14,000/year vs $50/year) and

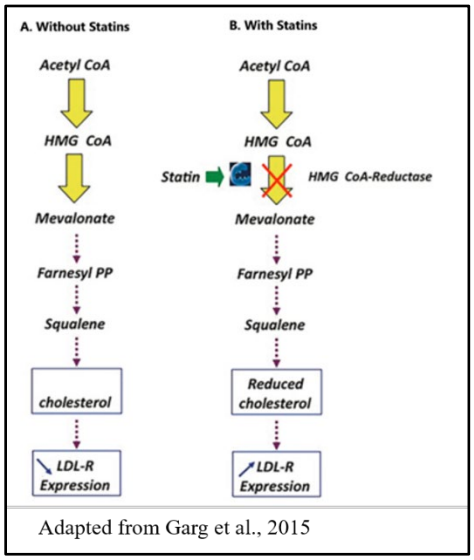
limited data on long-term safety.[111, 112]

C.3. Statin Therapy

Because of their effectiveness at reducing LDL-C and MI/CHD, statins are the most recommended cholesterol-lowering agent.

Mechanism of action. A major factor regulating blood LDL-C levels is the rate LDL-C is cleared into the liver via the LDLR, as approximately 70% of circulating LDL-C in blood is cleared by LDLR activity.[32] Briefly, statins lower the production of LDL-C by targeting the conversion of HMG-CoA to mevalonate, the rate-limiting step in lipogenesis to produce cholesterol from acetyl CoA within the liver (Figure 4).[113] Limiting lipogenesis (see section A.2. The Role and Formation of Low-Density Lipoprotein) results in the reduction of LDL-C content within the liver and induces LDLR expression on the liver cell surface to increase the amount of LDL-C cleared into the liver. This results in an increased removal of LDL-C from the blood and decreased concentrations of circulating LDL-C by approximately 20-63% depending on the dose and specific type of statin.[32]

Figure 4. Cholesterol lipogenesis pathway



Adapted from Garg et al., 2015

Statin Pleiotropic Effects. In addition to LDL-C reduction, statins have pleiotropic effects that extend beyond LDL-C lowering,[114-120]for example reduced inflammation.[121, 122] Previous findings have shown that statin therapy lowers high-sensitivity C-reactive protein (hs-CRP), an inflammatory marker that has been shown to be associated with increased risk of MI/CHD and stroke. For example, the Pravastatin Inflammation/CRP Evaluation trial (PRINCE) evaluated the effect of statins on hs-CRP reduction among a primary prevention cohort of 1,702 men and women from the U.S. The PRINCE investigators found that compared with placebo, participants randomized to statin had median hs-CRP levels that were 16.9% lower ($p < 0.01$) after 24 weeks.[123] As mentioned previously, the process of atherosclerosis can be characterized by the presence of macrophages and smooth muscle cells

damaging the endothelial lining of arteries and resulting in the release of inflammatory cytokines (see section A.2. The Role of Low-Density Lipoprotein); thus, the anti-inflammatory property of statins has been suggested to be one explanation for its beneficial effects on endothelial dysfunction.

Efficacy. From 1993 to 2000, several primary and secondary prevention trials designed to examine the effect of statins on clinical endpoints were conducted (Table 2). Five of the largest multicenter trials (N>4,000) are reviewed below.

Table 2. Randomized trials of statins and MI/CHD prevention (modified from Grundy 2000)

Trial (Ref)	Prior MI/CHD	Total Population	Follow-Up (years)	Cholesterol Reduction (%)	CHD Mortality (OR)	MI/CHD Incidence (OR)
ACAPS*	No	919	3.0	19.9	0.13	0.56
AFCAPS/TexCAPS*	No	6605	5.2	19.3	0.73	0.60**
CAIUS*	No	305	3.0	12.4	7.54	1.02
CARE	Yes	4159	5.0	20.0	0.80	0.75
KAPS*	No	447	3.0	21.0	1.00	0.62
LIPID	Yes	9014	6.1	17.9	0.75	0.75
MAAS	Yes	381	4.0	23.0	0.97	1.54
PLAC I	Yes	408	3.0	19.0	0.98	0.50
PLAC II	Yes	151	3.0	21.6	0.52	0.40
Post CABG	Yes	1351	4.5	31.6	1.49	0.87
4S	Yes	4444	5.4	25.0	0.57	0.62
WOSCOPS*	No	6595	4.9	20.0	0.67	0.69
All statin trials						
89,123 person-years		34779	4.2	20.0	0.71	0.70

*Primary Prevention Trials. Trt =treatment. Ctrl =control

**Primary endpoint of MI/CHD including unstable angina as well as nonfatal MI and CHD death not shown.

Primary Prevention Trials

The West of Scotland Coronary Prevention Study (WOSCOPS) Study examined the effectiveness of statin medication in men with elevated LDL-C levels and no history of MI.[124] Previous studies like the LRC CPPT did not have the power to detect the reduction in CHD death rate from medication use; however, WOSCOPS purposefully recruited a large sample size and population of middle-aged men to evaluate changes in CHD death rate. Among 6,595 healthy 45-65 year old men with mean follow-up time of 4.9 years, statins lowered LDL-C levels and reduced the risk of CHD death (RR = 0.67 [95% CI: .0.47-.0.97]) and incident MI/CHD (RR= 0.69 [95% CI: 0.57-0.83]) (Table 2) among statin therapy group compared to placebo group. Similarly, the Air Force/Texas Coronary Atherosclerosis Prevention Study

(AFCAPS/TexCaps) examined primary prevention of MI/CHD (defined as fatal or nonfatal MI, unstable angina, or sudden cardiac death) in 5,608 men and 997 women with TC levels between 180-264 mg/dl and LDL-C levels between 130-190 mg/dl.[125] After a mean follow-up of 5.2 years, the risk of MI/CHD was lower among the statin therapy group compared to the control group (RR = 0.63 [95% CI: 0.50-0.79]).

Secondary Prevention Trials

Similar to primary prevention trials, secondary prevention trials also found cardioprotective benefits of statins. The Scandinavian Simvastatin Survival Study (4S) followed 4,444 men and women aged 35 to 70 years with a history of MI from five Nordic countries for a median of 5.4 years.[126] The investigators found a 38% reduction in risk of MI/CHD (RR=0.62 [95% CI: 0.28-0.45]) among statin users compared to the placebo group. Furthermore, the Cholesterol and Recurrent Events Trial (CARE) trial and Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) study reported results consistent with 4S. CARE examined the effect of statins on MI/CHD after recent MI in patients with TC levels (≤240 mg/dl) in the U.S. and Canada. Among 4,159 participants and mean follow up of 5.0 years, the statin therapy group had 28% lower LDL-C levels and lower incidence of MI/CHD than placebo group (RR= 0.75 [95% CI: 0..64-0.91]).[127] Similar to CARE, the LIPID study examined statin therapy for secondary prevention among patients; however, LIPID enrolled patients from Australia and New Zealand with a broad range of TC levels (155 to 271 mg/dl).[128] Among 9,014 patients with a mean follow-up of 6.1 years, the group randomized to statins had a 24% reduction in risk of CHD mortality (RR=0.76 [95% CI: 0.65-0.88]) and 24% reduction in risk in MI/CHD (RR=0.76 [95% CI: 0.68-0.85]) compared to the placebo group. Both primary and secondary prevention trials examining statins demonstrated that the largest absolute change in LDL-C corresponded with the most favorable results for MI/CHD risk, albeit among primarily European populations.

Grundy et al. conducted a meta-analysis including several of the statin RCTs previously discussed and summarized that statins consistently reduced MI/CHD incidence by an estimated 30% (Table 2).[10] When stratified by primary and secondary prevention trials, risk of CHD mortality (RR reduction =0.93

[p-value <0.05]) and MI/CHD incidence (RR reduction =0.93 [p-value <0.05]) were reduced in primary prevention trials, further supporting the use of statins for primary prevention.

Epidemiology. In 2011-2012, more than one-quarter (27.9%) of adults ≥40 years old (ages eligible for treatment under cholesterol recommendations, see section E.3. NCEP-ATP III) had reported taking cholesterol-lowering medication in the past month (measured using medication inventory),with 93% of users classified as using a statin.[2] The proportion of adults ≥40 years of age who have reported taking statins has increased from 16.3% in 2003-2004 to 23.2% in 2011-2012, with similar increases observed among populations taking statins for primary prevention (13.4% in 2004-2005 to 22.2% in 2010-2011).[2, 129]

While statin use has increased overall within the past decade among both men and women, data from the Medical Expenditure Panel Survey found African Americans, Hispanics, and women are less likely to have statin prescriptions (measured using prescriptions filled) compared to Caucasian men.[129] Uninsured populations are also less likely to have statin prescriptions compared to populations with public insurance; findings consistent with research that emphasize equitable access to healthcare to reduce health care disparities.[129, 130] Furthermore, in addition to disparities in obtaining statin prescriptions, observational studies have also suggested adherence to statins to be an obstacle in practice. Ellis et al. examined electronic medical claims databases in the U.S. with approximately 200,000 enrollees.[131] Among 4,802 patients who were ≥18 years of age, non-Medicaid enrollees, and had filled at least two statin prescriptions; Ellis et al. found 50% discontinuation rate of statin use after 3.7 years among primary prevention patients and 50% discontinuation rate after 3.4 years among secondary prevention patients. To examine predictors of non-adherence to statins, Mann et al. conducted a meta-analysis consisting of 22 cohort studies using pharmacy and insurance database refill rates to measure discontinuation and with follow-up times ranging from nine months to 13 years.[132] Mann et al found that women, ethnic minorities, populations <50 years of age, and populations ≥70 years of age were associated with increased non-adherence to statins, while increased testing of LDL-C levels and higher income were associated with increased adherence to statins.

Statin Adverse Events. While numerous studies have emphasized the benefits of statins, evidence has suggested that statins use is associated with side effects as well. For example, meta-analyses have shown statins to be associated with an increased risk of myopathy (i.e. muscle pain or weakness), rhabdomyolysis, and T2D.[133] Rhabdomyolysis is defined as having muscle symptoms with increases in creatine kinase elevations typically greater than 10 times the upper limit of normal. Although rare, with the incidence of rhabdomyolysis per one year of statin therapy approximately 0.0042%, fatal consequences can arise from hyperkalaemia, cardiac arrhythmia, and renal failure.[134] While rhabdomyolysis is rare, statins have been found to be more frequently associated with myopathy.[135] Macedo et al. conducted a meta-analysis among 90 observational studies and reported an increased risk of myopathy (odds ratio [OR] =2.63; 95% CI: 1.50-4.61) among statin users compared to non-statin users, with the number needed to harm (NNH) for an additional case of moderate or severe myopathy over five years of 259 (95% CI: 186-375) for women and 91 (95% CI: 74-112) for men.[136] In practice, clinic-based studies have reported myopathy to be more common than estimated in clinical trials, with one-third of patients on statins reporting myopathy in the Netherlands. Importantly, drug-induced myopathy is reversible if identified at early stages.[137, 138] While evidence on myopathy has been limited, especially among RCTs, the body of evidence from clinical trials has suggested an association between statins and elevated risk for T2D, the focus of this dissertation.

C.3.1. Diabetes Mellitus as a Potential Side Effect of Statins

In addition to the established cardioprotective effects of statins, RCTs have reported a relationship between statins and elevated T2D risk. T2D is characterized by hyperglycemia resulting from defects in insulin secretion, response to insulin action, or both, and can be diagnosed using fasting plasma glucose, oral glucose tolerance, or hemoglobin A1C tests to measure blood glucose levels.[139] The vast majority of cases fall into two types of T2D: type 1 diabetes caused by deficiency of insulin secretion, and type 2 diabetes (more prevalent type) caused when insulin's ability to mediate uptake of glucose is impaired, which results in the body becoming resistant to the effect of insulin.[140] The incidence of T2D has doubled in the past 30 years among adults, with 1.7 million new cases of T2D occurring in 2012.

While burden of T2D is already high –affecting 1 in 10 US adults in 2012 –and continues to rise- the burden disproportionately affects racial/ethnic minorities. National survey data found 7.1% of Caucasians had diabetes compared to 8.4% of Asian Americans, 11.8% of Hispanics, and 12.6% of African Americans.[141]

In addition to the long-term complications of T2D, which include potential loss of vision, nephropathy leading to renal failure, and amputations, T2D also increases the risk of MI/CHD and stroke.[142] For instance, a recent meta-analysis of 102 prospective studies among 264,353 participants (43% women) found participants with T2D had an increased risk of MI/CHD (HR = 2.00 [95% CI: 1.83-2.19]) and stroke (HR =1.56 [95% CI: 1.19-2.05]) compared to participants without T2D.[143] The increased cardiovascular morbidity, mortality, and long-term consequences associated with T2D all contribute to the rising costs of T2D –in 2012, it was estimated as $245 billion–with $176 billion from direct medical costs.[144]

C.3.1.1. Statin Use among Populations with T2D

As mentioned previously, populations with T2D are at an increased risk of MI/CHD and as a result, research has supported the use of statins to reduce the risk of MI/CHD, as well as ASCVD more broadly (classification includes MI/CHD and stroke [all types]) among populations with T2D.[22, 145] The Cholesterol Treatment Trialists' (CTT) Collaboration conducted a meta-analysis of 14 RCTs consisting of 18,686 participants with T2D to evaluate the association between statin use and ASCVD.[146] With mean follow-up time of approximately four years, results showed that ASCVD events were reduced in groups randomized to statins compared to control groups (RR =0.79 [95%CI: 0.72-0.86]). As a result of the benefits of statins among populations with T2D shown from previous studies and recommendations from recommendations, the prevalence of statin use among adults with T2D has increased from 4.2% in 1988-1994 to 28.8% in 1999-2002, and to 44.1% in 2003-2006, reaching 51.4% in 2007-2010.[147]

C.3.1.2. Incidence of T2D among Statin Users

Evidence from RCTs

While evidence has demonstrated the cardioprotective effect of statins on ASCVD risk[4], research has also suggested an increased risk of incident T2D among statin users (Table 3). One of the first major trials to demonstrate a possible association between statins and incident T2D was the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid-Lowering Arm (ASCOT-LLA) trial which examined 10,305 moderately high-risk (hypertensive, elevated TC levels, and ≥3 other MI/CHD risk factors [i.e. smoking, history of MI/CHD, or family history of MI/CHD]) participants.[148]

Table 3. Summary of statins and risk of incident T2D by study design (randomized clinical trial or observational study)

Study Type	Trial Type	Age (years)	Men (%)	Caucasian (%)	Measure of Effect (Statin vs Placebo or control)
RCT					
*WOSCOPS[149]	Primary	55.2	100.0	NA	HR= 0.70[a]
*HPS[150]	Primary[b]	63.9	75.3	NA	OR= 1.1
*LIPID[151]	Secondary	62.0	83.0	NA	OR= 0.91
*ASCOT[148]	Primary	63.1	81.2	94.7	OR= 1.15
*CORONA[152]	Secondary	73.0	76.0	NA	OR= 1.14
*JUPITER[153]	Primary	66.0	61.9	71.2	HR=1.28[a]
*PROSPER[154]	Primary	76.0	48.3	NA	OR= 1.30[a]
***MEGA[155]	Primary	58.3	32.0	0.0	OR= 1.05
*AFCAPSTexCAPS[125]	Primary	58.0	85.0	89.0	OR= 0.97
*4S[126]	Secondary	58.6	82.0	100.0	OR= 1.03
*ALLHAT-LLT[156]	Primary	66.4	51.4	40.8	OR= 1.12
*GISSI HF[157]	Secondary	67.0	76.2	100.0	OR= 1.05
*GISSI PREVENZIONE[158]	Secondary	59.3	86.3	100.0	OR= 0.91
PROVE-IT[159]	Secondary	58.3	78.1	90.7	OR= 1.01
TNT[160]	Secondary	61.0	81.0	94.1	HR= 1.10
IDEAL[161]	Secondary	62.0	80.8	NA	HR= 1.19
SPARCL[162]	Secondary	63.0	60.0	NA	HR= 1.37[a]
HOPE-3[163]	Primary	65.8	53.6	20.0	HR= 1.02
Observational Studies					
WHI[164]	Primary	63.2	0.0	83.7	HR= 1.48[a]
Tricare Prime/Plus[165]	Primary	53.0	61.0	NA	OR= 1.87[a]
METISM[166]	Primary and Secondary	59.4	100.0	100.0	HR= 1.46[a]
Italian Lombardy Region[167]	Primary and Secondary	62.4	48.6	NA	HR = 1.32[a, c]

HR= hazard ratio, OR = Odds ratio

*Included in Sattar et al. 2011. **Japanese Participants.

[a] P-value <0.05

[b] Population with T2D

[c]Consistent statin adherence vs low statin adherence

In contrast to previous RCTs that showed reduction in incident T2D[149], after approximately three years of follow-up, the ASCOT-LLA trial noted 3% of participants randomized to statins developed T2D compared to 2.6% of participants randomized to placebo (p-value =0.25), however it was not statistically significant. Additional evidence was provided by the Justification for Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial, which was designed to determine whether hs-CRP could identify patients with low levels of LDL-C (<130mg/dl) at increased risk for ASCVD. JUPITER recruited men (≥50 years of age) and women (≥60 years of age) with no history of MI/CHD and hs-CRP levels ≥2 mg/l.[153] To investigate the risk of T2D, Ridker et al. conducted a secondary analysis of the JUPITER trial and examined 17,802 participants with various T2D risk factors (i.e. metabolic syndrome, impaired fasting glucose, body mass index ≥30 kg/m^2, or glycosylated hemoglobin (HbA_{1C}) >6%) and found that among participants with at least one T2D risk factor (N =11,508), the risk of incident T2D was greater among participants randomized to statins compared to placebo (HR =1.28 [95% CI: 1.07-1.54]). In addition to the JUPITER trial, several other RCTs collected incident T2D information, providing enough data for meta-analyses. For instance, Sattar et al. performed a meta-analysis of statin-associated T2D in primary and secondary prevention trials and identified 13 RCTs that collected data on incident T2D (11 out of 13 RCTs had information on fasting glucose levels to diagnose T2D; the remaining two studies relied on physician reports), spanned the years 1994-2009, and totaled 91,140 participants with mean follow up time approximately four years (Table 4).[12] Sattar et al. found that statin therapy was associated with a 9% increased risk for incident T2D compared to placebo (OR =1.09 [95% CI: 1.02-1.17]) over a mean of 4 years of follow-up; the association was stronger in older participants at baseline (p-value =0.02). However, baseline BMI and percent change in LDL-C levels were not significant sources of heterogeneity.[13, 168, 169] Mills et al. also conducted a meta-analysis of the RCT statin trial literature to examine associations with T2D among primary and secondary prevention RCTs; differences from Mills and Sattar include the former broadening of the eligibility criteria to include RCTs regardless of study size and length of follow-up time (Table 4). Among 16 RCTs examining incident T2D evaluated by Mills et al., representing three additional studies and 19,863 additional

participants from Sattar et al., Mills et al.reported a similarly increased risk of T2D among participants randomized to statins compared to those randomized to placebo (OR =1.09 [95% CI: 1.02-1.16]) that was slightly more precise.[13]

As described above, several meta-analyses of the association between statins and incident T2D combined primary and secondary prevention trials; however, secondary prevention trials include survivors of MI/CHD whose risk of MI/CHD mortality has been estimated to be five to six times higher than that of people of the same age who did not experience an MI/CHD.[170] Further, the benefits of statins may differ when used for primary vs. secondary prevention.[19] Thus, research was still needed to understand statin-associated T2D among populations free of clinically diagnosed MI/CHD.

Interests in estimating statin-associated T2D risk prompted efforts to quantify the association between statins and incident T2D among primary prevention RCTs. For example, Taylor et al. conducted a meta-analysis among primary prevention trials, excluding studies based on population baseline characteristics and time length (Table 4). Among two RCTs examining the association between statins and T2D, Taylor et al. estimated that 2.8% of participants randomized to statins developed incident T2D (342/12,205) compared to 2.4% of participants randomized to placebo (290/12,202), resulting in an 18% increased risk of T2D among the statin group (RR =1.18 [95% CI: 1.01-1.39]).[14] To inform the development of recommendations on statins for primary prevention of ASCVD in adults ≥40 years of age (see section F.1.Recent Recommendations Recommendations), a recent meta-analysis conducted by the US Preventive Services Task Force (USPSTF) identified six RCTs; differences from Taylor et al. included expanding eligibility criteria based on publication date and availability of previously unpublished work. Chou et al. reported that participants randomized to statins had a higher risk of developing T2D, although not statistically significant, compared to those randomized to placebo (RR =1.05 [95% CI: 0.91-1.20]), however, statistical heterogeneity was present (I^2 =52%, statistical heterogeneity was defined as I^2 >30%; Cochran's Q not reported) .[15] Sensitivity analyses using the profile likelihood method and resulted in similar results (RR =1.06 [95% CI: 0.93-1.18]).

Table 4. Summary of meta-analyses examining statins and incident T2D

Author (date)	Studies included	Rationale	Summary estimate
Sattar (2010)	ASCOT-LLA, HPS, JUPITER, WOSCOPS, LIPID, CORONA, PROSPER, MEGA, AFCAPS TexCAPS, 4S, ALLHAT-LLT, GISSI HF, GISSI PREVENZIONE (13)	Excluded RCTs comparing statins (only included placebo-controlled trials) and RCTs assessing statins among T2D populations, <1,000 participants, and mean follow-up time of ≤ one year. Also only included RCTs published between 1994-2009.	OR =1.09 (95% CI: 1.02-1.17)
Mills (2011)	4S, LIPID, REGRESS, PROSPER, HPS, ASCOT-LLA, WOSCOPS, ATHEROMA, MEGA, AFCAPS TexCAPS, ALLHAT-LLT, GISSI-HF, GISSI Prevenzione, CORONA, JUPITER, Pravastatin Multi (16)	Excluded RCTs evaluating different statins as comparison groups	OR =1.09 (95% CI: 1.02-1.16)
Taylor (2013)	JUPITER, AFCAPS TexCAPS (2)	Included RCTs comparing statins with placebo or usual care for at least 12 months, follow-up time >6 months, RCTs with ≤10% of participants at baseline with a history of MI/CHD, and RCTs published between 1994-2006	RR =1.18 (95% CI: 1.01-1.39)
Chou (2016)	AFCAPS/TexCAPS, ASCOT-LLA, MEGA, WOSCOPS, JUPITER, HOPE-3 (6)	Excluded studies in which ≤10% of the participants had prior MI/CHD events, compared statins to placebo or no statin. Included RCTs published between 1991-2016.	RR =1.05 (95% CI: 0.91-1.20)
Casula* (2017)	Jick (2004), Culver 2012), Danaei (2012), Wang (2012), Chen (2013), Currie (2013), Izzo (2013), Zaharan (2013), Bhattacharya (2014), Cederberg (2014), Macedo (2014), Lichtenstein (2015), Mansi (2015), Radford (2015), van de Woestijne (2015), Calza (2016), Castro (2016), Lin (2016), Olotu (2016), Rha (2016) (20)	Included observational studies examining statin use versus non-use, studies with ≥1,000 participants, and follow-up ≥ one year	RR =1.44 (95% CI: 1.31-1.58)**

*Conducted on observational studies

**Geographic area found to be a source of heterogeneity, P <0.001

Even as meta-analyses of RCT evidence has suggested an increased risk in incident T2D (5-18%) from statins, several characteristics of RCTs may limit the external validity of findings. RCTs can be characterized by exclusive study populations that may only include populations most likely to benefit from the therapy under study.[171] For instance, many of the primary prevention RCTs enrolled populations at increased risk for ASCVD who had LDL-C levels ≥130 mg/dl[124, 125, 155, 172], hypertension[148, 173], or additional ASCVD risk factors (i.e. obesity or current smokers).[163] Some studies specified narrow inclusion criteria. For example, the JUPTER trial assessed the benefit of stains in populations with elevated hs-CRP levels and LDL-C levels ≤130 mg/dl; however, populations with LDL-C levels ≥130 mg/dl, multiple non-LDL-C risk factors, but normal hs-CRP levels were not included.[174] In addition, few RCTs have included diverse populations, missing important segments of the population given the known race/ethnic and sex-specific differences in ASCVD risk, T2D risk, and LDL-C changes across the life course (see sections C.1.Epidemiology of LDL-C, C.3.1.Diabetes Mellitus as a Potential Side Effect of Statins, and D.Health Outcomes Associated with Elevated LDL-C Levels). Thus, although RCTs offer excellent control of confounding, they may have limited external validity, motivating the need to examine associations between statin use and T2D in populations more generalizable to real-world settings.

Evidence from Observational Studies

In addition to RCT evidence, observational studies, generally characterized by larger sample sizes and longer duration of follow-up time compared to RCTs, have also supported an association between T2D and statins. For example, Culver et al. examined the Women's Health Initiative (WHI) study, which recruited postmenopausal women aged 50-79 years at 40 clinical centers across the U.S. and enrolled women into either a clinical trial or prospective observational study.[175] After three years of follow-up among 120,173 women without ASCVD in either the clinical trial or observational study, Culver et al. found statin users (defined using medication inventory data) had a higher risk of incident T2D (defined by questionnaire and self-report of a new physician diagnosis of treated T2D) (HR =1.48 [95% CI: 1.46-1.62]) compared to statin nonusers.[164] Similar results were found among enrollees in the San Antonio Military Area as Tricare Prime/Plus. After six years of follow-up among 25,970 patients aged 30-85 years

without ASCVD, Mansi et al. found the risk of T2D (defined using ICD-9-CM codes) to be higher among statin users (defined as patients who filled a statin for at least 90 days) compared to statin nonusers (OR =1.87 [95% CI: 1.67-2.01]). As more observational studies became available, Casula et al. conducted a meta-analysis and included observational studies examining statin use versus non-use, studies with ≥1,000 participants, and follow-up ≥ one year.[176] Casula et al. identified 20 studies for inclusion in the analysis, with follow-up time ranging from 2-20 years (median 7.2 years) and mean age ranging from 40.0-65.4 years. Compared to statin non-users, statin users experienced a greater risk of incident T2D (RR =1.44 [95% CI: 1.31-1.58]), with geographic area, but not follow-up length of time or propensity score matching, to be a source for heterogeneity (p-value < 0.001). Publication bias was also assessed, and was found for a specific type of statin (atorvastatin [p-value = 0.03], but not for other statins or for use of any statin.

Although meta-analyses of observational studies demonstrated an estimated 30% increased risk of incident T2D compared to previous meta-analyses conducted in RCTs (RR =1.05-1.18 vs RR =1.44), differences may be attributed to characteristics of each study design. RCTs have several limitations that might reduce the strength of the increased risk of incident T2D attributed to statins. Past RCTs, similar to some observational studies, used intention to treat analyses, which compares the groups initially assigned by randomization, despite non-negligible proportions of dropout or non-adherence (12-33%).[12] Non-adherence and dropout result in underestimation of any treatment effect, particularly limiting in trials aimed at uncovering adverse effects of a treatment.[165, 177] In addition, several RCTs, similar to observational studies, relied on physician reports of T2D rather than measuring glucose, potentially underestimating T2D incidence.

While observational studies may be larger and have longer duration of follow-up time, observational studies have limitations of their own. The inability to randomize participants questions exchangeability between comparison groups (i.e. confounding by indication), especially as statin users may be at higher risk of MI/CHD than non-statin users and may be more likely to develop T2D with higher frequency independent of statin use.[178] Several individual observational studies have tried to obtain

comparable groups by adjusting for confounders and propensity score matching, although the number and type of confounders investigated have varied. Multiple observational studies included in the meta-analysis conducted by Casula et al. adjusted for demographic information (i.e. sex and age), however, there was a range with observational studies also including baseline ASCVD risk factors (i.e. BMI and hypertension), medication use, and comorbidities (i.e. prevalence of ASCVD) and one observational study that failed to adjust for any confounders. In addition to the variety of confounders examined, the observational studies, similarly to RCTs, used a variety of methods, ranging in sensitivity, to assess T2D. Several observational studies used multiple criteria to define incident T2D (T2D drugs and/or biochemical measurements), while others relied solely on physician-diagnoses. Furthermore, detection bias may arise in observational studies as participants prescribed statins may be more likely to make and attend appointments with primary care physicians, increasing their chances of being clinically evaluated and obtaining a T2D diagnosis.[179] Currie et al., however, in the first study to the best of my knowledge to use active comparators to evaluate the statin-associated risk of T2D, compared new statin users to new diclofenac users (used to treat pain or symptoms of osteoarthritis or rheumatoid arthritis) and found statin users had a higher risk of T2D (HR =3.31 [2.56-4.30]), even when both groups had similar chances of being evaluated.[180]

Meta-analyses maximizing the internal validity of RCTs and external validity of observational studies and therefore incorporating the totality of the evidence may best quantify the association between statins and incident T2D among populations generalizable to those in the real-world (i.e. with respect to age, sex., and race).[17] Examining both RCTs and observational studies could allow a balance between internal validity of RCTs including the benefits of randomization and external validity of observational studies including generalizability of findings to broader populations. In addition, incorporating additional observational studies would increase power and provide an opportunity to evaluate important sources of heterogeneity between studies as well as sensitivity analyses. For example, past RCT meta analyses did not find baseline BMI as a source of heterogeneity, but observational studies suggested that women with BMI <25 were at greater risk for T2D than those with BMI ≥30, surprising results as BMI is a strong risk

factor for T2D. In addition, Sattar et al. examined percent change in LDL-C as a source of heterogeneity. However, conducting sensitivity analyses examining baseline LDL-C levels may be more informative to better understand the relationship between statins and T2D, as LDL-C levels have been found to have protective effects with incident T2D (see section C.3.1.3.Potential Mechanisms). Furthermore, year of paper publication or year at study baseline have not been examined in a meta-analysis, however, both may reflect possible period effects, as the prevalence of statin use and statin recommendations have changed over time; additionally, early users of statins may have risk factor distributions that differ for populations using statins years (or decades) after their introduction in the late 1980s. Lastly, demographic characteristics such as age are important risk factors when calculating ASCVD risk (see section E.4.ACC/AHA Recommendations); thus conducting further sensitivity analyses may help to determine if T2D risk varies by age. While evidence from RCTs and observational studies examining statins and incident T2D have been evaluated, integrating both study designs may best help quantify the effect of statins on primary prevention populations. Previous published work has shown that combining observational studies and RCTs may increase precision and produce equally or more relevant and valid results compared to results based solely on RCTs.[17, 18, 181] While heterogeneity between study designs may prevent combination, adding to this rich meta-analysis literature will allow us to incorporate large, recently released observational and RCT evidence, examine the effect of additional sources of heterogeneity, and estimate statin effects in primary prevention/population-based settings. This will provide an opportunity to quantify statin-associated T2D risks generalizable to real-world populations, estimates necessary to better understand the side effects of statins and inform our sensitivity analyses.

Subclinical Effects of Statins on Glucose

In addition to meta-analyses examining incident T2D as an outcome, studies have evaluated effects on fasting glucose as well. Sukhija et al. examined the effect of statins on fasting blood sugar (FBS) among 345,417 patients from the Veterans Affairs VISN 16 database (mean age =61 years, 94% men).[182] After two years of follow-up, among patients without T2D (N =324,692), FBS increased by 7 mg/dl in statin users compared to 5 mg/dl in non-statin users, ($p < 0.01$), and for patients with T2D (N =

20,725), FBS increased 39 mg/dl in statin users compared to 32 mg/dl in non-statin users, ($p < 0.01$). Results suggested statin use increased FBS in patients with and without T2D; however, study limitations exist including the lack of information on medications that may have also affected FPG levels (i.e. T2D medications or diuretics).

To study the association between statins and glucose traits, Swerdlow et al. examined the association between a SNP in the *HMG-CoA* reductase gene (targeted by statins) and bodyweight, waist circumference, plasma insulin, and glucose.[183] The investigators found the SNP, which served as a proxy for LDL-C lowering, to be associated with higher plasma insulin concentration (1.62% [95% CI: 0.53-2.72]), plasma glucose concentration (0.23% [95% CI: 0.02-0.44]), bodyweight (0.30 kg [95% CI: 0.18-0.43]), and waist circumference (0.32 cm [95% CI: 0.16-0.47]); further suggesting that lowering LDL-C through statins affects glycemic traits.[183] Additional work, examining the association between glucose traits and statins, however, is suggested as further evidence of the impact of statins on glucose.

The body of evidence linking statins and T2D generated by previous work prompted the FDA in 2012 to decide there was sufficient evidence to add warnings on statin labels, indicating that increases in fasting glucose levels and incident T2D have been reported with statins.[184] However, comparing the trade-offs between the cardioprotective benefits of statins versus the potentially increased risk in T2D becomes necessary as statins continue to be prescribed to larger and larger proportions of the population, particularly in the context of primary prevention.

C.3.1.3. Potential Mechanisms

While the relationship between statins and incident T2D has been examined, the potential mechanisms remain unclear. Below we describe four potential mechanisms currently under investigation.

Pancreatic β-Cells and Insulin Secretion: Pancreatic β-cells secrete insulin in response to elevated glucose to maintain blood glucose homeostasis, [140] which is initiated by an increase in Ca^{2+}controlled by the opening of Ca^{2+} channels.[185] Studies have shown that changes in Ca^{2+} concentration may affect insulin secretion and the ability to maintain glucose homeostasis. Xia et al. showed that chronic depletion of cholesterol impaired insulin secretion and inhibited Ca^{2+} channel currents in mouse

pancreatic β-Cells, suggesting that long-term use of statins to reduce LDL-C may similarly impact insulin secretion.[186] Research examining statin therapy and insulin secretion regulation, however, found that statins increased insulin secretion at low glucose levels, but did not increase insulin secretion when high glucose levels were introduced, suggesting possible loss of insulin secretion regulation.[187] More research on the mechanism underlying the relationship between inhibited lipoprotein synthesis, Ca^{2+} channel function, and insulin secretion is needed.

GLUT 4: Glucose uptake in adipocytes is mediated through glucose transporter 4 (GLUT4) upon activation by insulin.[188] Research has reported a decrease in GLUT4 expression and consequent decreases in glucose uptake in adipocytes after statin use.[189] Chabmerlain et al. examined the impact statins had on the expression of GLUT4 and found statins down-regulated GLUT4 and reduced glucose uptake in cells in response to insulin, suggesting that adipocytes become insulin resistant when GLUT4 expression is decreased.[190]

Modifying LDL-C Levels: While the mechanism between statins and T2D remain unclear, results from multiple Mendelian randomization studies have found that SNPs associated with increasing LDL-C were associated with reduced T2D incidence, suggesting the relationship is related to the change in LDL-C levels.[191-193] For instance, White et al. found a 1-standard deviation genetically instrumented increase in LDL-C levels (equivalent to 38mg/dl increase) was associated with an increase in MI/CHD (OR =1.68 [95% CI: 1.51-1.87]), but showed a decrease in T2D (OR =0.79 [95% CI: 0.71-0.88]). Furthermore, Schmidt et al. found 38.7 mg/dl reductions in LDL-C (identified using *PCSK9* SNP-LDL-C effects) were associated with an increase in bodyweight of 1.03 kg (95% CI: 0.24-1.82) and 3.5 mg/dl (95% CI: 0.8-5.8) higher fasting plasma glucose.[193] Evidence suggests that LDL-C may be protective against T2D and reducing it may increases the risk of T2D; however, more research is still needed to better understand the relationship and the pathogenesis of T2D.[192]

Health behaviors and lifestyle: Research has suggested that statins impact health behaviors and healthy lifestyle choices, although evidence on the relationship is still scarce. Statin-associated muscle symptoms have been previously reported in several RCTs, with myopathy, being reported in 1% to 5% of

patients.[194] As mentioned previously, however, evidence suggests the incidence of myopathy is much larger in real-world practice than when measured in a clinical trial setting and investigators have hypothesized that myopathy could contribute to an inactive lifestyle and T2D. For instance, the Effect of Statins on Skeletal Muscle Performance (STOPM) study, examined the effects of statins on skeletal muscle in a young (mean age of 44 years) population treated with statins for up to six months (N =420). Thompson et al. found 9.4% of patients treated with statins developed myopathy compared to 4.8% of patients in the placebo group; however, the association between statins and T2D with myopathy as a potential mediator has yet to be examined. Research has also suggested statin use is associated with diet. For example, among statin users in NHANES, caloric intake in 2009-2010 was 9.6% greater (95% CI: 1.8-18.1) than that among statin users in 1999-2000, and fat intake was 14.4% greater (95% CI: 3.8-26.1) in 2009-2010 than that among statin users in 1999-2000.[195] The study, however, had several limitations including the use of cross sectional studies preventing temporality to be assessed and comparing inherently different groups (statin users versus statin nonusers) through different time periods (statin users in one wave may be different from statin users in subsequent waves). Investigators have hypothesized myopathy and unhealthy lifestyles to be potential mediators in the statin and T2D association as they can hinder active lifestyles; however, research examining the associations are still needed.

C.4. Lifestyle Modification

Clinical trials have shown the effectiveness of reducing LDL-C levels and MI/CHD risk through medication and diet; however, recent lifestyle interventions have also reduced MI/CHD without affecting LDL-C levels, demonstrating the impact of diet on MI/CHD risk may not be mediated by diet's effect on LDL-C. For example, the Lyon Diet Heart study, a randomized controlled trial, tested the effectiveness of a Mediterranean diet that emphasized fruits, vegetables, breads and cereals, and fish.[196] After 46 months of follow-up, compared to the control group that consisted of less stringent diet requirements, the experimental group had reduced rates of MI/CHD recurrence and MI/CHD mortality; however, there was no effect of the diet on lipoproteins (LDL-C, HDL-C). Consistent results were recently found among the Prevención con Dieta mediterránia (PREDIMED) study conducted in Spain to compare two

Mediterranean diets to a low-fat diet.[197] Compared with the low-fat diet, the Mediterranean diets had lower risks of MI/CHD (HR = 0.70 [95% CI: 0.53-0.91]) after five years; however, there were minimal changes in LDL-C levels.[198]

In contrast to recent literature showing reduction in MI/CHD risk may occur in the absence of reduction in LDL-C levels, previous work has also examined the benefits of maintaining low levels of TC and LDL-C in early life on MI/CHD risk (i.e. primordial prevention). [199-201] For example, the Special Turku Coronary Risk Factor Intervention Project (STRIP) initiated low saturated fat diets to infants and parental counseling from when infants were 7 months old and until the age of 19 years. When children reached 19 years of age, investigators found that LDL-C values were lower in the intervention than control group for boys and girls: -6.96 mg/dl (95% CI: -10.05, -3.87) in boys; and -3.87 mg/dl (95% CI: -7.35,-0.387) in girls. The results are relevant given exposure to even suboptimal LDL-C levels increases MI/CHD risk.[199, 200, 202, 203] Taken together, evidence has shown that various lifestyle modifications, similar to various pharmacologic agents[204] (see section C.2. Pharmacologic Treatments), have demonstrated the ability to reduce MI/CHD without affecting LDL-C or reduce LDL-C levels and subsequent MI/CHD risk; and both have generated evidence that shaped cholesterol treatment recommendations.

D. Health Outcomes Associated with Elevated LDL-C Levels

As mentioned previously, elevated LDL-C levels is an established risk factor for atherosclerosis and downstream MI/CHD. This section reports the epidemiology and public health burden of MI/CHD as well as the composite outcome ASCVD, which includes MI/CHD as well as stroke

D.1. Myocardial Infarction/Coronary Heart Disease

Coronary heart disease (CHD) is the clinical manifestation of the blockage of the epicardial coronary arteries supplying blood to the myocardium. The definition of MI/CHD, typically in observational studies, depends on symptoms, signs, biomarkers (i.e. cardiac troponins, creatine kinase), electrocardiogram (ECG) and/or autopsy findings to classify nonfatal (definite MI/CHD, probable MI/CHD, possible MI/CHD, unrecognized MI/CHD, medical procedure-related event, unstable angina pectoris, and stable angina pectoris) and fatal events (definite fatal MI/CHD, probable fatal MI/CHD, and possible fatal MI/CHD) (Table 5).[205] In several observational studies, MI/CHD ascertainment is reviewed independently by multiple experts, with adjudicator agreement target goals of approximately 80%. Disagreements are resolved by consensus by committee and if individual adjudicator agreements with the final outcome falls below 80%, retraining can be undertaken.[206, 207]

Table 5. Classification of MI/CHD

	Biomarker Findings							
	Cardiac Symptoms or Signs Present				Cardiac Symptoms or Signs Absent			
ECG Findings	Diagnostic	Equivocal	Missing	Normal	Diagnostic	Equivocal	Missing	Normal
Evolving diagnostic	Definite	Definite	Definite	Definite	Definite	Definite	Definite	Definite
Positive	Definite	Probable	Probable	No	Definite	Probable	Possible	No
Nonspecific	Definite	Possible	No	No	Definite*	Possible	No	No
Normal or other ECG findings	Definite	Possible	No	No	Definite*	No	No	No

Definite indicates definite MI/CHD; Probable, probable MI/CHD; Possible, possible MI/CHD; and No, no MI/CHD. Classification of case is at highest level allowed by combinations of 3 characteristics (cardiac signs and symptoms, ECG findings, biomarkers).
*In absence of diagnostic troponin, downgrade to possible.
Adapted from Leupker et al., 2003

MI/CHD imparts a significant public health burden domestically and worldwide. In the U.S. MI/CHD is a leading cause of mortality, accounting for approximately 370,000 deaths annually. In 2013, approximately 660,000 Americans experienced an incident MI.[208] The burden of prevalent CHD is also high—15.4 million in 2013—thereby imparting significant (and rising) health care costs in addition to putting large segments of the population at increased risk for heart failure, cardiac arrhythmias, and sudden death.[40, 142] Even as age-adjusted rates of MI/CHD mortality have continued to decline since the mid-1960s[40], deceleration of the MI/CHD mortality rate has been observed over the past decade, particularly in younger populations.[209] In addition, the estimated medical costs between 2013 and 2030 are projected to double[210], exacerbating already high health care costs: MI ($11.5 billion) and CHD ($10.4

billion) were two of the 10 most expensive hospital principal discharge diagnoses in 2011.[211] Furthermore, MI/CHD disproportionately affects men compared to women and African Americans compared to Caucasians. For instance, the Atherosclerosis Risk in Communities Surveillance Study (ARIC) examined 35-84 year old African American and Caucasian men and women from Washington County, Maryland; Forsyth County, North Carolina; Jackson, Mississippi; and Minneapolis, Minnesota and found that the highest overall MI/CHD attack rates per 1,000 population from 2005-2012 were: African American men, 6.2; African American women, 4.1; Caucasian men, 3.7; and Caucasian women, 2.1.[40, 212, 213]

In addition to major MI/CHD risk factors such as blood pressure, body mass index (BMI), cigarette smoking, and age, the importance of LDL-C as a major risk factor has been well documented, as described above. To estimate the impact LDL-C level reduction can have on the risk of MI/CHD, Law et al. analyzed data from 10 prospective observational cohorts with an average follow-up time of 14.5 years (period of recruitment ranged from 1950-1980).[214]Although the analysis excluded women (studies included did not evaluate women), Law et al. found a 23 mg/dl (approximate mean reduction in LDL-C attained in cohort studies) reduction in LDL-C from medication use was associated with a one-time decrease in incidence of MI/CHD by 54% at age 40 years, 39% at 50, 27% at 60, 20% at 70, and 19% at 80. A recent meta-analysis among 27 RCTs showed LDL-C lowering through statins reduced the risk of MI/CHD by 24% per 38 mg/dl reduction in LDL-C.[3] The strength of evidence regarding the contribution of LDL-C to MI/CHD risk highlights an important opportunity for populations to reduce LDL-C levels for improved MI/CHD prevention efforts and minimization of future health care costs attributed to MI/CHD.[215]

D.2. Stroke

Stroke is a cardiovascular event caused by the acute interruption of blood flow to one or more sections of the brain. There are two main types of stroke: ischemic (87% of stroke cases) caused by the formation of a blood clot and hemorrhagic caused when a weakened blood vessel ruptures; and each type of stroke consists of a number of subtypes.[40, 142] For instance, the two most common subtypes of ischemic

strokes are those due to large-artery atherosclerosis (~30%) and strokes of unknown origin classified as cryptogenic (~30%).[216] Several observational studies, including the Reasons for Geographic and Racial Differences in Stroke (REGARDS), have classified stroke events following similar definitions to the World Health Organization outline (Table 6).[217] Similar to physician adjudicated MI/CHD events conducted in observational studies, physician adjudicators assessing stroke are assessed in an ongoing fashion for agreement >80%.[218]

Table 6. Stroke classification

Stroke classification	Definition
Stroke	Rapidly developing clinical signs of focal, at times global, disturbance of cerebral function, lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin
Clinical stroke	Characterized by symptoms lasting <24 hours, with neuroimaging consistent with acute ischemia or hemorrhage
Probable stroke	Adjudicators agreed that the event was likely a stroke or death related to stroke, but information was incomplete for clinical classification.

An estimated 795,000 adults in the US experience a stroke annually and of those, 185,000 are recurrent strokes.[142] Carandang et al. found the incidence of all stroke was declining over the past 50 years (1950-2000) from 7.6 to 5.3 per 1000 person-years and from 6.2 to 5.1 per 1000 person-years in men and women, respectively in FHS.[219] Fang et al. found stroke incidence decreased as well among a US Medicare population from an age-adjusted rate of 1039 per 100,000 (95% CI: 1032-1045) in 1988 to 639 per 100,000 (95% CI: 634-644) in 2008 with 30-day mortality from stroke also declining from 16.2% in 1988 to 15.2% in 2008 ($p < 0.1$).[220] The burden of prevalent stroke, however, is already high—affecting 6.6 million American adults in 2012 —estimated to increase by 20.5% by 2030, exacerbating already high health care costs (estimated $34 billion currently spent annually).

Evidence has shown the burden of stroke to vary by sex, age, and race/ethnicity

disproportionately placing large segments of the population at risk for lifelong disability and complications including immobility, formation of blood clots, visual impairment, and weakness in limbs.[221, 222] For instance, stroke incidence rates are lower in women than men in younger and middle-age groups (ages 45-75 years); however, in the oldest age groups, the incidence rates are approximately equal or even higher among women (ages ≥75 years).[223, 224] In addition to sex disparities, overall stroke mortality rates among African-Americans are about 50% higher than Caucasians with the largest disparity at younger ages.[218, 225] For instance, Howard et al. used data from the National Longitudinal Mortality Study to examine the burden of stroke mortality among African Americans relative to Caucasians across age. After five years, the risk of stroke mortality for both African American men and women was 4.5 times that of Caucasians at age 45, but decreased with age ($p \leq 0.05$).[225] To examine racial/ethnic disparities in stroke incidence and recent trends, Kleindorfer et al. used medical records from the Greater Cincinnati/Northern Kentucky Stroke Study from 1993 to 2005. The investigators found decreases in stroke incidence from 1993 to 2005 for Caucasian men (178 cases per 100,000 [169-188] to 154 [146-162]), but increases (or no change) among African American men (271 [239-303] to 275 [246-305]).[226-228]

While each stroke type has its own set of distinct risk factors, both ischemic and hemorrhagic stroke also share common risk factors including hypertension, sex, race/ethnicity, and cigarette smoking.[229] In addition, research has found that TC and LDL-C levels can impact stroke. For instance, Iso et al. examined six years of follow-up in the MRFIT, which included >350,000 men, and found that compared to TC levels <160 mg/dl, relative risk of death from ischemic stroke increased for each level of TC (200-239 mg/dl, RR =1.21; 240-279 mg/dl, RR =1.81; >280 mg/dl, RR =2.57; p-value =0.06 [corresponding to a test of homogeneity of adjusted RR estimates]).[230] RCTs have also focused on the reduction of stroke associated with lowering LDL-C levels through statins (see section E.4. ACC/AHA Recommendations).[231, 232] While statins have been shown to reduce MI/CHD events in past RCTs, the CARE study (see section C.3. Statin Therapy) was one of the first major RCTs to show a reduction in incident stroke (all types) among participants randomized to statins compared to those randomized to placebo (RR =0.69 [0.48-0.97]).[127] To further evaluate the impact of statins on incident stroke, Amarenco

et al. conducted a meta-analysis among primary and secondary prevention trials.[233] Among 26 RCTs totaling >90,000 participants and with mean follow-up times ranging from 0.5-6.1 years, Amarenco et al. found the relative odds reduction in incident stroke (all types) among participants randomized to statins compared to those randomized to placebo was 21% (OR: 0.79 [95% CI: 0.73-0.85]). Interests in estimating the impact of statins on stroke among populations free of clinically diagnosed MI/CHD or stroke prompted efforts to quantify the association between statins and incident stroke among primary prevention RCTs. For example, Taylor et al. identified 18 RCTs totaling >56,000 participants (60% men and 86% Caucasian) and found a 38.7 mg/dl reduction in LDL-C levels through statins was associated with a reduction in incident stroke (all types) (RR =0.78 [95% CI: 0.69-0.89]), results similar to those found among meta-analysis evidence of primary and secondary prevention RCTs.[234] Results from the past RCTs and observational studies have strengthened the evidence of the importance of LDL-C on stroke, further highlighting the need to reduce population levels of LDL-C.[234]

D.3. Atherosclerotic Cardiovascular Disease (ASCVD)

As knowledge of the benefits of statins on stroke has accumulated, risk prediction for statin recommendation has begun to emphasize both MI/CHD and stroke (all types). Risk estimators such as the Framingham risk scores determined 10-year MI/CHD risk to help identify populations that would benefit from statins (see section E.3. NCEP-ATP III); however, this method excluded stroke.[235] To better capture the scope of disease impacted by statins, risk prediction has begun focusing on atherosclerotic cardiovascular disease (ASCVD) which includes MI/CHD and fatal or nonfatal stroke (all types) among both Caucasians and African Americans, consistent with past international cholesterol recommendations. For instance, the United Kingdom National Institute for Health and Care Excellence recommends statins to populations ≥40 years with a 10-year ASCVD risk ≥10% (estimated by the QRISK assessment tool[236], a multifactor ASCVD risk prediction algorithm).[237] Similarly, the European Society of Cardiology/European Atherosclerosis Society's latest recommendations for the management of dyslipidemia recommends medication for populations with 10-year fatal ASCVD risk ≥5% (estimated by the Systemic Coronary Risk Estimation).[238] Research has shown that previous risk assessments based on

Framingham data that focused only on MI/CHD events undervalued the risk and potential benefits of statins in women and African Americans.[239] Because stroke accounts for a higher proportion of ASCVD events than MI/CHD in women and 55,000 more women die of stroke than men before the age of 75 years, the inclusion of the stroke end point can identify at-risk women at younger ages that may have been missed by previous risk estimators levels.[240] In addition, the incident risk for MI/CHD and stroke (all types) is higher among African Americans compared to Caucasians, specifically among populations <65 years of age. The inclusion of race-specific coefficients and stroke endpoint helps identify and quantify different risk profiles in African Americans compared to Caucasians, particularly at younger ages.[226, 239]

Consistent with past research demonstrating an association between statins and MI/CHD and stroke, research has shown an association between LDL-C level reduction through statins and reduction in ASCVD mortality (Table 7). For instance, a recent meta-analysis of 27 primary and secondary prevention RCTs found that for each 1 mmol/L (38.7 mg/dl) reduction in LDL-C, statins reduced ASCVD events by about one-fifth.[3] Additionally, comparing participants randomized to statins to participants randomized to placebo, protective effects of statins on ASCVD mortality were found among men (RR =0.87 [95% CI: 0.82-0.92] and women (RR =0.92 [95% CI: 0.82-1.03]), with no evidence of heterogeneity by sex.[3]

Table 7. Review of meta-analyses of TC and LDL-C and ASCVD mortality risk

Author	Year	N of RCTs	RR (95% CI)
CTT Collaborators[241]	2005	14	0.83 (0.79-0.87)
CTT Collaborators[194]	2010	26	0.86 (0.82-0.90)
CTT Collaborators[3]	2015	27	0.88 (0.84-0.91)

RCT: Randomized Controlled Trials
RR: Relative Risk
CI: Confidence Intervals
CTT: Cholesterol Treatment Trialists' Collaborators
ASCVD: MI/CHD and stroke

E. Development of Cholesterol Recommendations

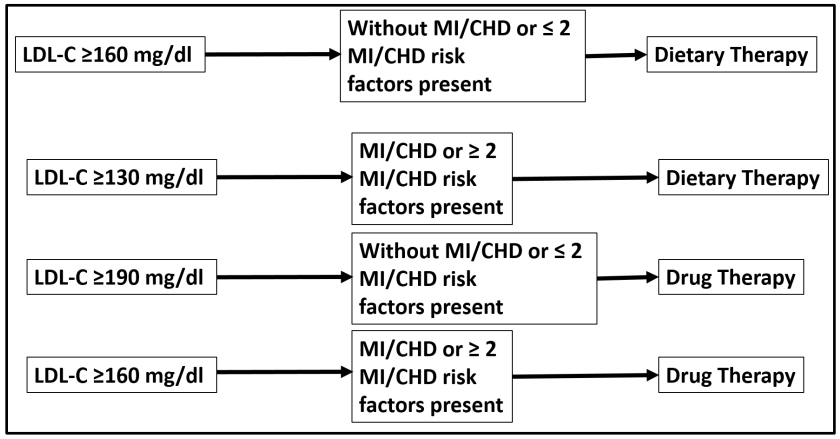
The knowledge based management and therapy of LDL-C is reflected in the evolution of cholesterol recommendations in the past 30 years. The following section describes the development of cholesterol recommendations from the National Cholesterol Education Program's (NCEP) inception to

the most current American College of Cardiology/American Heart Association (ACC/AHA) recommendations.

E.1. NCEP-ATP I

After taking into account the large body of evidence that linked elevated LDL-C levels to MI/CHD, the National Institutes of Health (NIH) created the first Consensus Development Conference on Lowering Blood Cholesterol to Prevent Heart Disease in 1984 to resolve remaining questions regarding the steps that should be taken to diagnose and treat elevated LDL-C levels.[242] The consensus panel provided recommendations for health professionals on which populations to treat, how to treat them, and goals for treatment. The panel also provided recommendations to the public on the importance of maintaining a diet that is low in total fat, saturated fat, and cholesterol to reduce TC and LDL-C levels. To help reduce the prevalence of elevated TC and LDL-C, the panel created the National Cholesterol Education Program (NCEP).[243] Below several NCEP-initiated programs are described.

Figure 5. NCEP-ATP I cholesterol treatment recommendations



To develop recommendations and recommendations, the NCEP created the Adult Treatment Panel (ATP) in 1987 to inform the detection, evaluation, and treatment of high blood TC and LDL-C in adults. In addition to clinical management of high TC and LDL-C levels, the ATP defined TC and LDL-C cut-points and provided recommendations on how to detect and monitor high-risk patients over time. The ATP recommendations defined populations with LDL-C levels ≥160 mg/dl as high-risk and those with LDL-C levels ≥130 mg/dl as borderline-high risk and recommended dietary changes (i.e. reducing saturated fatty acids, cholesterol) as initial treatment (Figure 5). However, because the relationship between LDL-C and MI/CHD was found to be continuous, the ATP cut-points were (recognized as)

somewhat arbitrary, similar to classifications made for other risk factors (i.e. blood pressure).[244] The ATP further recommended drug therapy for populations with LDL-C levels ≥190 mg/dl or ≥160 mg/dl if MI/CHD or two other MI/CHD risk factors (i.e., hypertension, smoking, male sex, family history of MI/CHD or stroke, T2D, and BMI >30) were present (Figure 5). The ATP suggested BAS and nicotinic acid as the primary options for drug therapy, as research demonstrated their ability to lower MI/CHD risk without long-term adverse events (see section C.2. Pharmacologic Treatments).[245]

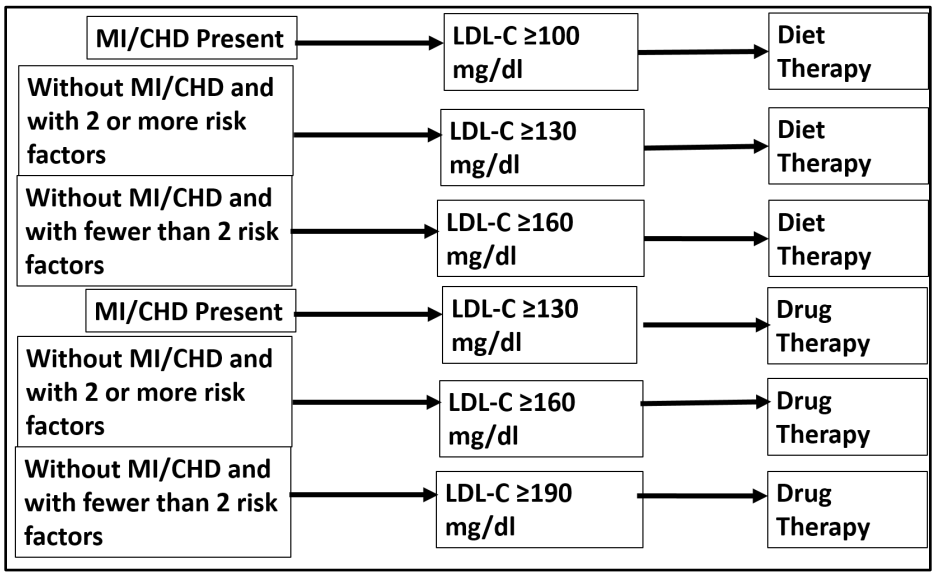
In addition to the ATP recommendations, the NCEP also created panels focused on measuring TC and LDL-C levels and preventing high concentrations of TC and LDL-C at the population level, specifically during childhood. In 1991, the NCEP created the Population Panel to make recommendations focused on the population level to lower TC and LDL-C levels.[246] While the ATP included recommendations suggesting dietary therapy as initial forms of treatment and that drug therapy should be considered only after dietary therapy failed to reduce LDL-C levels, the Population Panel exclusively intended to promote the adoption of healthy eating and lifestyle patterns. The panel envisioned healthy diets would lower TC and LDL-C levels in the majority of the population and concluded that excessive intakes of saturated fatty acids, total fat, and dietary cholesterol, together with excessive body weight, all contributed to elevated levels of TC and LDL-C. The panel emphasized expansion of awareness of TC and LDL-C as a critical risk factor for MI/CHD through mass media and highlighted interventions at the population level to include diet, exercise, and weight control**.** Combined with the ATP recommendations, the NCEP estimated the Population Panel would help prevent large proportions of the population from developing elevated TC and LDL-C levels and result in smaller proportions of the population that would require drug therapy and be at-risk of MI/CHD morbidity and mortality.

E.2. NCEP-ATP II

In 1993, the NCEP updated its ATP recommendations from the first report and released the second report of the Expert Panel in Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP II); however, the NCEP did not update the additional NCEP-initiated panels including the Population Panel.[247] Similar to the ATP I, ATP II emphasized dietary treatment as the initial treatment

with drug therapy reserved for populations at high risk of MI/CHD (Figure 6). Since ATP I was released, however, several topics that were not included in ATP I emerged that deserved mention and considerations in ATP II. For example, in addition to MI/CHD risk factors mentioned in ATP I, ATP II added age as a risk factor, specifically older ages in men (≥45 years) and women (≥55 years). Furthermore, for patients with established MI/CHD, the panel reduced the LDL-C level recommended drug therapy from 160 mg/dl to 130 mg/dl (Figure 6).

Figure 6. NCEP-ATP II cholesterol treatment recommendations



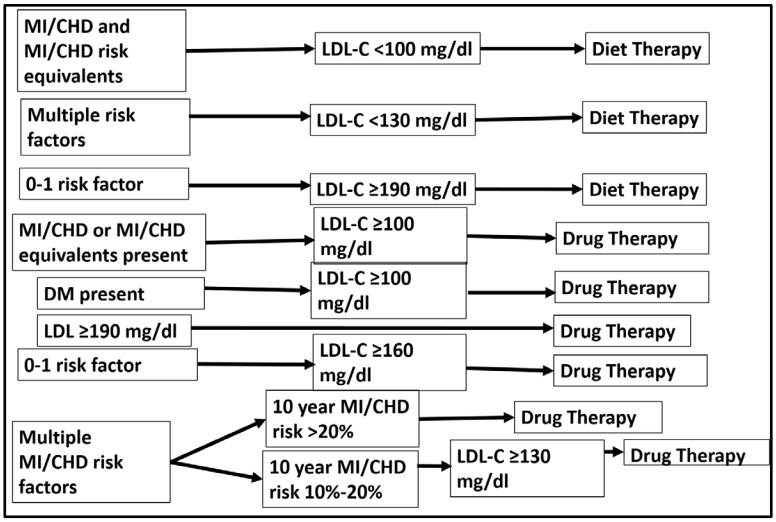
Angiographic studies suggested that net regression of atherosclerosis was proportional to the decrease in LDL-C levels among populations with MI/CHD and prompted recommendations to lower the LDL-C level threshold among populations with MI/CHD from 160 mg/dl to 130 mg/dl.[88, 248] Among a U.S. population of 146 men (≤62 years of age), with family history of MI/CHD, and established atherosclerosis (measured using an arteriogram), Brown et al. used arteriography to examine average percentage change in stenosis (measured as an atherosclerotic lesion occluding the diameter of the artery) after randomizing the population to receive either niacin, statin, or a placebo. After 2.5 years of treatment, stenosis increased by 2.1% among the placebo group, but decreased by 0.7% among the group randomized to statins and 0.9% among the group randomized to niacin (P for trend <0.01). Furthermore, results showed that lipid lowering therapy (both statin and niacin groups compared to placebo) reduced the incidence of MI/CHD by 73% (RR =0.27 [95% CI: 0.10-0.77]), providing further evidence that LDL-C lowering medication helped decrease progression of atherosclerosis, increase regression, and reduce MI/CHD events. As angiographic studies

and clinical trials continued to accumulate data on the benefits of pharmacotherapy, cardioprotective evidence among larger populations spanning multiple years were still needed.

E.3. NCEP-ATP III

In 2001 the NCEP updated its second report and released the third report of the Expert Panel in Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III), modifying cholesterol treatment recommendations. Similar to the ATP I and ATP II recommendations, ATP III emphasized diet and lifestyle changes as initial treatment to lower LDL-C levels and continued to consider high LDL-C levels (≥190 mg/dl) and LDL-C levels ≥160 mg/dl among populations with at least one MI/CHD risk factor as targets for LDL-C lowering drug therapy (Figure 7). However, as mentioned previously (see section C.3. Statin Therapy), from 1993 to 2000, major clinical trials examined statins and MI/CHD risk, finding that statins consistently reduced MI/CHD incidence by an estimated 30% (Table 2).[10] The RCTs provided evidence to modify criteria for the NCEP-ATP II Recommendations and in response, ATP III added new features. ATP III updated treatment recommendation categories to highlight the presence of MI/CHD and MI/CHD risk equivalents (i.e. peripheral arterial disease, carotid artery disease, or abdominal aortic aneurysm), T2D, and multiple MI/CHD risk factors (i.e. cigarette smoking, hypertension, low HDL-C [<40 mg/dl] (Figure 7).

Figure 7. NCEP-ATP III cholesterol treatment recommendations



blood pressure, hypertension medication use, T2D, and cigarette smoking status for estimating risk for MI/CHD in the short term (≤10 years).[212] Previously, ATP II counted risk factors, however, this method did not quantify an estimate of absolute risk, did not account for variability in risk factor level or intensity, and may have underestimated the progressive impact of aging on absolute risk. Instead, ATP III used risk estimation methods, such as the Framingham risk scores, in addition to risk factor counting in order to better quantify absolute risk prediction of hard MI/CHD events (MI and CHD mortality). Additionally, ATP III counted T2D as a MI/CHD risk equivalent rather than part of the list of risk factors that modify LDL-C as evidence showed that patients with T2D had a high risk for developing MI/CHD (see section C.3.1.Diabetes Mellitus as a Potential Side Effect of Statins).

As research continued to examine statins and MI/CHD among populations with various baseline MI/CHD risks, questions remained regarding when to initiate statins, optimal LDL-C target levels, and if the cardioprotective benefits of statin were generalizable to populations excluded from past RCT trials.

E.4. ACC/AHA Recommendations

After the publication of ATP III, major clinical trials assessing statins and clinical endpoints (MI/CHD, with extensions to include stroke) were published to further examine the treatment categories created by ATP III.[249] For example, RCTs examined the effects of reducing LDL-C levels below 100 mg/dl (ATP III recommendation treatment threshold) among high-risk patients to examine if the risk for MI/CHD continued to decrease or if there were no added benefits. The Heart Protection Study (HPS) randomly assigned men and women aged 40-80 years with MI/CHD (N =14,573) or T2D (5,963) from the U.K. to either statins or placebo.[150] After approximately five years of follow-up, results found that participants randomized to statins had a reduced risk of MI/CHD (RR =0.73 [95% CI: 0.67-0.79]) and stroke (RR = 0.75 [95% CI: 0.66-0.85]) compared to participants randomized to placebo, supporting ATP III recommendation recommendations for treating populations deemed at high-risk (≥100 mg/dl with CHD or T2D). Furthermore, HPS investigators reported that the reduction in MI/CHD continued even when LDL-C levels were reduced to 77 mg/dl (levels below LDL-C treatment thresholds for populations with T2D or MI/CHD), suggesting the greatest reduction in absolute LDL-C levels from statins had the

greatest reduction in MI/CHD risk, although albeit in a racially homogenous population with T2D or prevalent MI/CHD.[150]

In addition to examining benefits of treatment at LDL-C levels below NCEP III recommendation-recommended thresholds among high-risk populations, RCTs also examined statin benefits among moderately high-risk (those with ≥2 risk factors and 10%-20% MI/CHD risk) and low-risk (10-year MI/CHD risk <10%) populations. The ASCOT-LLA trial (see section C.3.1.2.Incidence of T2D among Statin Users) examined populations with ≥3 MI/CHD risk factors over approximately three years and found participants randomized to statins not only reduced LDL-C levels by 35% (relative reduction), but had a lower risk of incident MI/CHD (HR =0.64 [95% CI: 0.50-0.83]) compared to those randomized to placebo.[148] Sever et al. also found that benefits of statins were maintained when LDL-C levels were reduced to 88 mg/dl, further suggesting the use of statins to lower LDL-C levels below ATP III treatment thresholds; however, the generalizability of findings was again potentially limited (conducted in a European population of whom 81% were men). Furthermore, interests in estimating the benefits of statins among populations at low risk of MI/CHD prompted efforts to quantify the association between statins and incident MI/CHD among evidence from available RCTs. The Cholesterol Treatment Trialists' (CTT) Collaboration examined the association between statins and incident MI/CHD among populations with 5-year MI/CHD risk <10% and conducted a meta-analysis in 27 RCTs with median follow-up time of approximately five years, mean age of 63, and 23% women. The CTT found that compared to placebo, statins reduced the risk of incident MI/CHD events by 21% per 38 mg/dl reduction in LDL-C level (RR =0.79 [95% CI 0.77-0.81])[4], suggesting the cardioprotective benefits from statins existed among low-risk populations, populations not recommended statins in past ATP recommendations.

In addition to RCT evidence supporting ATP III treatment categories and suggesting more aggressive treatment goals, researchers identified additional recommendations for subsequent recommendations. Researchers argued the Framingham risk scores were too limited in the inputs and were not able to take into account risk factors measured by laboratory testing.[235] For example, the Reynolds Risk Score used hs-CRP, an inflammatory marker used to predict coronary events (see section

C.2.1.Statin Pleiotropic Effects),[250] in addition to Framingham risk score variables when calculating risk. Alternatively, including additional measures such as imaging techniques could better assess risk in intermediate-risk patients through quantifying coronary artery calcium (CAC) and carotid intima-media (CIMT) thickening (precursors to atherosclerosis). Quantifying CAC and CIMT can further capture subclinical indicators of atherosclerosis. Researchers also have criticized the Framingham risk scores for being limited in their outputs (MI/CHD), as evidence had been generated revealing the benefits statins have beyond MI/CHD (see section D.3. Atherosclerotic Cardiovascular Disease). Results suggested future recommendations incorporating stroke as an endpoint along with MI/CHD would more comprehensibly identify populations who would benefit the most from statins.

In reviewing the previous evidence, in 2013 the American College of Cardiology/American Heart Association (ACC/AHA) Recommendations were formed.[22] Instead of focusing on a comprehensive approach to the detection, evaluation, and treatment of high LDL-C in adults, as previous ATP recommendations did, the ACC/AHA Recommendations focused on the development of evidence-based recommendations for the reduction of ASCVD risk. For example, in contrast to previous ATP recommendations, which outlined diet recommendations, the ACC/AHA recommendations acknowledged the importance of lifestyle factors in reducing ASCVD risk by highlighting the 2013 AHA/ACC Recommendations on Lifestyle Management to Reduce Cardiovascular Risk[251]; however, the cholesterol treatment recommendation primarily focused on statins as treatment. In addition to the change in focus, the ACC/AHA recommendations also discontinued using the Framingham risk score due to the derivation in a Caucasian population (although the risk score has been recalibrated for use in other populations)[252] and limited scope in assessing outcomes (MI/CHD). Instead the ACC/AHA developed the Pooled Cohort risk equations to estimate 10-year risk of developing ASCVD using traditional risk factors including age, sex, race/ethnicity, TC, HDL-C, systolic blood pressure, diastolic blood pressure, hypertension medication use, T2D, and smoking status (see Appendix figures 1 and 2). To increase generalizability, the recommendations used data from community-based cohorts of adults from the ARIC Study[253], the Cardiovascular Health Study[254], the Coronary Artery Risk Development in Young Adults (CARDIA)

study[255], and both Framingham Original and Offspring Study[256, 257] to develop the algorithm. Cohorts included African American or Caucasian participants free of clinically diagnosed ASCVD with at least 12 years of follow-up. The focus on ASCVD rather than MI/CHD alone was also consistent with the AHA and American Stroke Association (ASA) call to include stroke events in the outcome of interest for risk assessment, as described previously.[258]

The ACC/AHA aimed to reduce ASCVD by creating four statin benefit groups, which were identified from RCT evidence (Figure 8). Similar to previous recommendations, populations with LDL-C levels ≥190 mg/dl were recommended to statins; however, the ACC/AHA also recommended statins to populations with ASCVD and populations between the ages of 40 and 75 years with 10-year risk of ASCVD ≥ 7.5%. In addition, the ACC/AHA recommendations also lowered the threshold to recommend statins among populations with T2D from 100 mg/dl (ATP III) to 70 mg/dl. Furthermore, instead of treatment goals used to define when LDL-C levels were controlled and if modification of treatment regimen was warranted, the ACC/AHA recommendations assumed long-term treatment (i.e. for life) with statin dose appropriate for risk (low dose vs high dose).

Figure 8. ACC/AHA cholesterol treatment recommendations

Over the past 30 years, efforts to reduce ASCVD morbidity and mortality have evolved from detecting, evaluating, and treating high levels of LDL-C to focusing on the management of ASCVD risk as assessed by the Pooled Cohort risk equation. As definitions for what constitutes as being "at-risk" continue to modify and increase the statin eligible population, research on understanding and weighing the potential consequences of various ASCVD risk reduction thresholds must be conducted.

F. Public Health Significance and Gaps

F.1. Recent Guideline Recommendations

Ideally, public health recommendations would aim to focus on segments of the population that will subsequently develop an incident or recurrent ASCVD event (high sensitivity) while avoiding unnecessary treatment among those in the population who will not develop an ASCVD event (high specificity).[259] Current recommendations prioritize sensitivity but not specificity by recommending statin therapy to populations at lower ASCVD risk.[6] Because the benefits and risks of statin treatment at lower risk thresholds are unknown, the net gain in disease burden is unclear.

Uncertainty in the net benefit of statin treatment for primary prevention prompted changes to treatment recommendations in 2016. In the United States, the USPSTF makes recommendations about the effectiveness of specific preventive care services for patients. In 2016, the USPSTF recommended statins for primary prevention among adults with 10-year ASCVD risk ≥10%, similar to the NCEP-ATP III recommendations. This recommendation contrasts with more recent recommendations for cholesterol treatment issued by the ACC/AHA, which recommended treatment for primary prevention among adults with 10-year ASCVD risk ≥ 7.5%. The USPSTF concluded with moderate certainty that the net benefit is small when initiating statins among populations with 10-year risk of ASCVD 7.5% to 10%. Because the underlying 10-year ASCVD risk is low, a smaller proportion of this population will benefit from treatment because a majority of the population would not develop incident ASCVD.

The proposed recommendations by the USPSTF, although similar to NCEP-ATP III recommendations, still result in substantial proportions of the U.S. population who are newly eligible for statin treatment. If all adults were treated according to USPSTF recommendations, statin therapy initiation would be recommended for an additional 15.8% of adults compared with an additional 24.3% of adults who would be recommended for statin therapy by ACC/AHA recommendations. The result is an excess of 8.9% of adults who would no longer be recommended for statins according to the latest ACC/AHA recommendations compared to the USPSTF recommendations.[21] Projecting estimates to the US population, there could be an estimated 17.1 million versus 26.4 million adults with a new

recommendation for statin initiation, a difference of 9.3 million people. Recent projections have also been estimated comparing the ATP III to ACC/AHA recommendations, which found the change in treatment recommendations would impact 14.4 million adults who would be newly eligible for statins as a result of the ACC/AHA recommendations, with 8.2 million newly eligible for primary prevention.[5]

F.2. Future Cholesterol Treatment Recommendations

Following publication of the ACC/AHA recommendations and despite USPSTF recommendations, researchers have suggested initiating statins at even younger ages.[20, 260, 261] Age is a dominant factor in the pooled cohorts risk calculator, leading to recommended initiation of treatment for the majority of adults in older age. For example, nearly all men exceed the 7.5% risk threshold in their mid to late 60s and nearly all women in their 70s, despite an otherwise optimal risk factor profile.[20] The emphasis of chronological age when calculating ASCVD favors treatment later in life, but treatment may not reverse damage from the accumulation of atherosclerosis throughout life and some RCT evidence has suggested modest to no effect of statin benefits in older populations.[260, 262] Thus, recommended updates to cholesterol recommendations were prompted by the benefits associated with achieving low levels of LDL-C early in life. For example, a series of Mendelian randomization studies estimated the effect of long-term exposure to lower LDL-C levels on the risk of MI/CHD mediated by SNPs.[261] The studies were combined in a meta-analysis and compared to LDL-C level reductions found from statins among adults. Long-term exposure to lower LDL-C was associated with a 55% (95% CI:48.8%-59.5%) reduction in the risk of MI/CHD for each 38.7 mg/dl lower LDL-C compared to LDL-C reductions from statins started later in life, highlighting the potential benefits of maintaining low levels of LDL-C early in life compared to reducing LDL-C levels later in life. [261]

In addition to proponents of initiating statins at younger ages, researchers have argued for statins among populations at low-ASCVD risk. As described above, RCTs have shown that statin therapy reduces ASCVD events in healthy participants at lower risk than recommended by ACC/AHA treatment recommendations.[4, 14] For instance, Boekholdt et al. conducted a meta-analysis among eight RCTs with a mean follow-up of approximately six years and mean LDL-C levels of 132 mg/dl to examine the

association between very low levels of LDL-C (<50 mg/dl) and incident ASCVD. Among 38,153 participants, the risk of incident ASCVD decreased as the level of LDL-C level attained decreased.[263] For example, compared to participants that attained LDL-C levels between 50-75 mg/dl (N =10,395), the risk of incident ASCVD was lower among participants that attained LDL-C levels <50 mg/dl (N =4,375) (RD =0.07 [95% CI: 0.06-0.07]) with the number of participants who would need to be treated to prevent one additional ASCVD event 14.3. Along with the motivation to recommend statins to larger proportions of the population, some researchers have suggested using statins for primary prevention of diseases beyond ASCVD, such as breast cancer, potentially increasing the statin-eligible segment of the population even further.[264]

F.3. Gaps in Statin Associated Outcome Evidence

Our understanding of the relationship between statins and treatment-associated outcome remains incomplete. This section describes gaps in our understanding of these relationships.

F.3.1. Statin-associated Benefits and Harms

Statin-associated benefits and harms remain inadequately quantified. For example, Robinson et al. contrasted statin benefits versus harms by summarizing results from recent RCT meta-analyses and estimated the number needed to treat (NNT) with statins to cause one excess case of T2D. The authors reported that the number needed to harm (NNH) over five-years ranged from 66 to 200 depending on the strength of statin, while the NNT to prevent one ASCVD event over five-years ranged from 40 to 60.[4, 12, 23] However, relying on past meta-analyses to calculate benefits and harms has several limitations. First, the definition of T2D varied by study, potentially underestimating T2D incidence, particularly when studies relied solely on physician self-report.[265] Secondly, non-adherence and withdrawal from RCTs ranged from 11%[155] to 29%[125] among participants randomized to statins, again potentially underestimating T2D incidence. Thirdly, among the primary prevention trials included in the meta-analyses, few were conducted among the elderly and the trials that did include elderly populations selected participants enriched for ASCVD risk factors.[150, 153, 154, 163] These distinctions are important, as according to recent projections, of the 10.4 million adults projected to be eligible for statins for primary

prevention based on the ACC/AHA recommendations compared to the ATP III, 80% are between the ages of 60-75.[5] Past studies of the benefits of statins among older adults with ASCVD risk factors have shown mixed findings, suggesting that there may be insufficient evidence to determine if statin use is beneficial among otherwise healthy older adults.[20] For example, the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT) was a trial conducted among people with hypertension and at least one ASCVD risk factor.[156] Han et al. conducted a post hoc analysis of a subgroup of participants (n =2,867) free of clinically diagnosed ASCVD at baseline and found there was no benefit for ASCVD events among participants aged 65-75 years (HR =0.85 [95% CI:0.62-1.15]) or among participants ≥75 years of age (HR =1.34 [95% CI: 0.98-1.84]) when randomized to statins compared to placebo.[262] Thus, when attempting to quantify the relationship between statins, T2D and ASCVD, it is important to ensure the benefits of statins outweigh potential risks, especially among populations potentially at low risk of ASCVD who are most affected by current recommendations.

Further, to assess adverse outcomes associated with long-term statin use based on 10-year ASCVD risk thresholds, Robinson et al. included 10-year extrapolations conducted by the ACC/AHA cholesterol recommendations. Using meta-analyses results that were used to calculate the five-year NNT and NNH estimates above, 10-year projections of incident T2D and ASCVD were calculated from annual relative risk reductions (NNH =100 [did not specify ASCVD risk threshold] and NNT =67, 44, and 33 for 10-year ASCVD risks of 5%, 7.5%, and 10%).[23] Because of concerns of safety, the ACC/AHA cholesterol recommendations recommended use of statins in participants with characteristics similar to those participating in RCTs; however, few RCTs have conducted follow-up beyond six years or assessed outcomes after the studies have ended to evaluate the long-term efficacy of statins. Ford et al. evaluated the long-term impact of statin therapy on MI/CHD mortality using electronic health records of former participants of the WOSCOPS study and after 20-years of follow-up, MI/CHD mortality was reduced among the participants randomized to statins compared to those randomized to placebo ([HR = 0.79 [95% CI: 0.69-0.90]).[266] Similar results were found among 11.3 years of follow-up (8.6 years of follow-up post-trial) in the PROSPER primary prevention trial (HR =0.81 [95% CI: 0.69-0.95]).[267] In contrast, the

ASCOT-LLA trial found a significant reduction in MI/CHD mortality associated with statins approximately two years post follow-up (HR =0.64 [95% CI: 0.53-0.78]), but not 11 years post follow up (HR =0.89 [95% CI: 0.72-1.11]).[268, 269] The benefits of statins observed in long-term follow up may suggest a legacy benefit of LDL-C lowering by statin use. However, treatment information post-trial was not always known (last 10-years of WOSCOPS and last 8.6 years of PROSPER). These results suggest that three to 10-year treatment periods may be sufficient to produce a benefit while limiting lifetime exposure to statins. However, the association between long-term, persistent use of statins and adverse events such as T2D remains poorly quantified.

F.3.2. Critical Research Barriers to Effective Cholesterol Treatment Recommendations

Despite the vast resources dedicated to developing cholesterol recommendations and criteria, there still remain evidence gaps in the literature informing policymakers' ability to select ASCVD risk reduction thresholds that deliver the most benefit and least harm.[270, 271] Although RCTs have examined the association between statin therapy and T2D[12], these studies were limited by highly selective inclusion criteria that limited generalizability and short duration, which constrained the examination of long-term adverse events. These limitations have left several questions unanswered, including the long-term effects of statin use on T2D incidence among populations with contemporary ASCVD risk factor distributions. Thus, studies to address these gaps are needed. Yet, such studies must (1) be contemporary, (2) span ages specified by current recommendations, (3) include high quality statin measures, and (4) precisely and validly measure ASCVD and T2D incidence (5) within generalizable male and female (6) multi-ethnic populations (7) with adequate follow-up time. Very few individual studies can meet all of these criteria.

F.3.3. The Research-practice Gap: an Opportunity for Simulation Tools

As an alternative, simulation tools can help extend the reach of epidemiological studies and RCTs by synthesizing high quality observational and experimental findings. Pencina et al. used data from the National Health and Nutrition Examination Surveys (NHANES) to estimate the number of people in the U.S. who would become eligible for statins under the ACC/AHA recommendations compared with the ATP III recommendations[5]; however, no study to the best of our knowledge has extended these efforts to

look at intended benefits and side effects of statins. Such a simulation that examines both the intended benefits and adverse effects of statins (1) requires primary data inputs from RCTs and population-based studies, (2) includes adverse event data, and (3) includes health-related outcomes, which as we describe below are available. Therefore the objective of this proposal is to synthesize data from RCT and observational studies using meta-analytic methods and simulation tools to examine the consequences of pre-specified ASCVD risk thresholds on the incidence and prevalence of T2D and ASCVD. Findings from this work can inform how new statin treatment ASCVD risk thresholds may contribute to ASCVD benefits and T2D burdens.

CHAPTER 4. RESEARCH PLAN

A. Overview

This work will be conducted in two parts. In Aim 1, a meta-analysis will be conducted to determine the effects of statins on T2D incidence among populations free of clinically diagnosed ASCVD. We propose conducting this meta-analyses using all available published data from large primary prevention statin RCTs and observational studies. Results from Aim 1 will then be used to inform projections estimated in Aim 2, which will use a Markov model to project changes in T2D and ASCVD incidence and prevalence from changes in ASCVD risk thresholds recommended from various cholesterol treatment recommendations.[6, 21] Aim 2 will be conducted by assembling and integrating contemporary and validated data from NHANES, REGARDS, RCT meta-analyses, and results from Aim 1 into a Markov model using decision analyses software TreeAge Pro.

B. Specific Aim 1

In Aim 1, a meta-analysis will be conducted using both RCT and observational studies. Upon completion, Aim 1 will yield statin-T2D RRs to be used for Aim 2. As described above, previous published work has suggested that combining observational studies and RCTs may increase precision and produce equally or more relevant and valid results compared to results based solely on RCTs.[17, 18, 181] While the importance of using both study designs have been proposed, statistical methods combining RCT and observational studies in a meta-analysis setting are still being developed. In the end, the literature may in fact not be comparable, but obtaining estimates from both study designs would still provide valuable information to inform the sensitivity analyses for Aim 2.

B.1 Data Sources and Search Strategies

B.1.1. Literature Search

Studies will be identified by searching electronic databases and scanning reference lists of articles, particularly published RCT and observational study meta-analyses. This search will be applied to Pubmed (1994-Present) and Embase (1994-Present). We will use the following free text and MeSH terms to search all databases with the following terms consistent with previous systematic reviews and meta-analyses of RCT and observational studies: (Statin OR Statins OR Anticholesteremic Agents OR Anticholesteremic OR Hydroxymethylglutaryl-CoA Reductase Inhibitors) AND (Diabetes OR Diabetes Mellitus II OR Diabetes Mellitus Type II OR Diabetes Mellitus Type 2) AND adverse effects OR adverse events AND cohort study OR case-control study OR trial.

B.1.2. Eligibility Criteria

From the articles resulting from the search terms above, we will examine abstracts (if available) to identify articles that meet all of the following criteria: 1) the study has follow-up >one year; 2) majority of participants are asymptomatic adults without prior ASCVD events (i.e. MI/CHD, stroke) at baseline; 3) the risk estimate is reported as an OR, HR, or RR; and 4) the 95% CI for the risk estimate or information to enable its estimation is included.

B.2. Data Items

B.2.1. Data Extraction

For each study population in each article, we will extract incident T2D estimates and study factors of interest, which include methodological factors and study population characteristics (Table 8). If information on study factors of interest are not available from the articles, we will contact corresponding authors via email with follow-up emails sent two weeks after the initial inquiry as needed.

Table 8. Study factors of interest

Methodological factors
Study design (RCT, Observational study)
Mean length of follow-up time
Study sample size
Year of publication data
Year of study baseline
Method to control confounding (propensity score, adjusted in the model, randomization, did not adjust)
Types of confounders included
Methods to measure and define T2D status (physician diagnosis, medication data, laboratory data)
Type of effect estimate metric (OR, RR, HR)
Baseline study population characteristics
% Female
Mean Age
% Nonwhite
% prescribed statins
Type of statins included
Mean BMI
Mean LDL-C levels
Mean fasting plasma glucose levels
Mean systolic blood pressure levels
% hypertensive
% current smokers
% of population with ASCVD at baseline

B.2.2. Validation of Data Abstraction and Data Entry

Two reviewers will independently scan all potential titles and abstracts. The reviewers will assess full-text versions of potentially relevant articles and abstract all relevant data into tables. The tables will be compared and disagreements will be resolved by consulting with the initial articles.

B.3. Planned Methods of Analysis

B.3.1. Assessment of Risk of Bias

PRISMA criteria will be used to describe the quality of RCTs[272] and assess potential for bias. Specifically, the following dimensions (agree or disagree) will be evaluated: 1) adequate use of measures to conceal allocation (adequate through the use of randomization); 2) application of blinding (whether to the participant, care provider or outcome assessors); 3) proportion of participants lost to follow-up reported; and 4) whether the analysis followed the intention-to-treat principle.[273]

To assess quality of OBSs, articles will be assigned scores using criteria consistent with past meta-analysis of cohort studies[274] (agree or disagree): 1) Was a well-defined sample of participants identified?; 2) Were there clear definitions of statin use and 3) T2D?; 4) Was there information on baseline LDL-C levels and 5) fasting plasma glucose levels by treatment status?; and 6) Were differences in baseline factors accounted for?[275]

B.3.2. Assessment of Publication Bias

Publication bias can result when studies with statistically significant, clinically favorable, or novel results or are more likely to be published than studies with non-significant, unfavorable, or "uninteresting" results.[276] We will assess the possibility of publication bias using both qualitative and quantitative methods overall and by study type (RCT vs observational study). First, we will evaluate a funnel plot displaying each study's effect estimates against each study's precision (i.e. standard error).[277] In the absence of bias, the effect estimates from smaller studies should scatter more widely at the bottom, with the spread narrowing among larger studies.[278] Second, we will calculate a p-value for Begg and Mazumdar's log rank test and Egger's regression test to provide quantitative assessments of the symmetry of the funnel plot.[279, 280] It is important to note that both Begg's and Egger's tests have low statistical

power to detect evidence of asymmetry of funnel plots in the literature; as a result, we will use a high alpha-value, such as 0.1. Third, we will use Duval and Tweedie's trim and fill imputation procedure as an additional analysis to evaluate bias in funnel plots.[281] The trim and fill method imputes effect estimates in three steps: 1) removes estimates that make the funnel asymmetric, forming a trimmed dataset and leaving a symmetric remainder from which the true center of the funnel can be estimated; 2) uses the trimmed dataset to compute a presumptively less biased summary effect and standard error; and 3) the trimmed trials are then replaced and their missing counterparts imputed or filled around the adjusted summary estimate.

B.3.3. Pooled Estimates

Incident T2D RRs and 95% CIs from the available studies will be obtained. Study-specific RRs will be pooled using a random-effects model meta-analysis rather than a fixed-effects model because of the model assumption that the true effect estimate is normally distributed with a different mean and variance in each given study. The random-effects model will account for between-study and between-study type heterogeneity that may have been introduced by the various methods for diagnosing T2D and different study populations included in each study.[282]

B.3.4. Assessment of Overall Heterogeneity and By Study Type

We will assess heterogeneity of effect estimates among published studies to assure observed study-specific estimates are not too inconsistent or heterogeneous to be over-simplified as one summary estimate. Heterogeneity assessment will be implemented by computing a p-value of Cochran's Q statistic in a homogeneity test[283] (alpha value of 0.1 will be applied to assess homogeneity) and using the I^2 statistic, which is derived from Cochran's Q statistic ($I^2 = 100x(Q - df)/Q$) and provides a measure of the proportion of the overall variation attributable to between-study heterogeneity.[284] Negative values of I^2 are set to zero so that I^2 lies between 0% and 100%. A value of 0% indicates no observed heterogeneity and larger values show increasing heterogeneity.

B.3.5. Meta-regression

Meta-regression analyses will be performed in order to explore potential sources of heterogeneous estimates between studies and by study type (RCT vs observational). Meta-regression analyses examines the associations between study-level characteristics and treatment effects, with the outcome as the magnitude of the effect estimate in each study and the independent variables as the study factors of interest (continuous or categorical), providing information regarding the strength of each study factor for explaining potential sources of heterogeneity among studies.[285] A random-effects model will be used to take into account the variability in between-study differences with study weights incorporating both between and within study variance. Meta-regressions will be performed on all methodological factors and baseline study population characteristics (Table 8).

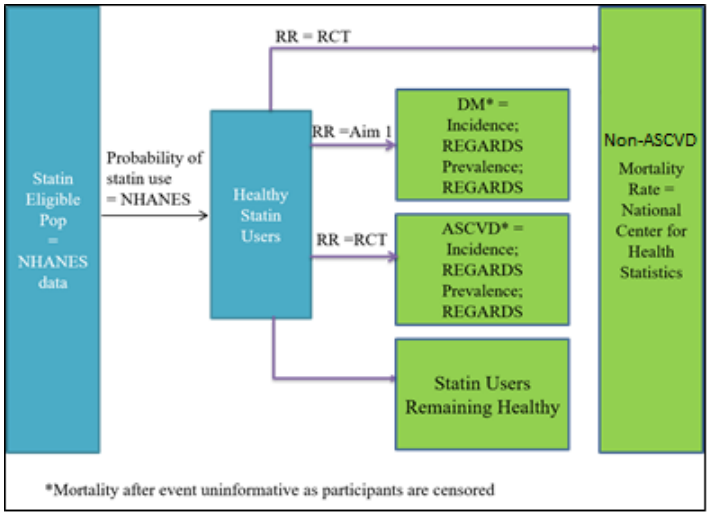
Conclusions

Completion of Aim 1 will yield statin-T2D associated RRs to be used in Markov models for Aim 2.

C. Specific Aim 2

We will leverage multi-ethnic (African American and Caucasian) and sex-specific data from NHANES and REGARDS studies as well as meta-analyses of RCT reported statin associated RRs and results from Aim 1 to assess changes in the number of ASCVD events prevented and cases of T2D incurred associated with changes in cholesterol treatment recommendations (Figure 9).

Figure 9. Conceptual diagram of association of statins and ASCVD and DM



C.1.Data Sources and Inputs

Specific aim 2 will be conducted by assembling and integrating contemporary and validated data from NHANES, REGARDS, past meta-analyses, and results from Aim 1 into a Markov model (Table 9). REGARDS is the only data source that requires a manuscript proposal to obtain data and our REGARDS manuscript proposal (2017-P409) was recently approved (Appendix Figure 1).

Table 9. Characteristics of population-based studies contributing primary data as input to Markov model

Study	~N†	Design	Scope	Race/ethnicity‡	Age	Time
National Health and Nutrition Examination Survey (NHANES)[286]	30,000	Multistage cross-sectional sample	National	AA, EA, MA	0-80+	2005-16‡
Reasons for Geographic and Racial Differences in Stroke (REGARDS)[287]	30,200	Longitudinal cohort	Continental US	AA, EA	45+*	2003-date

*Baseline age. †Restricted to dates for which data will be obtained; ‡Restricted to populations contributing data to Markov model

C.1.1. NHANES

Data from NHANES will be used to construct the initial statin-eligible population (population size and baseline characteristics) and to estimate the prevalence of current statin users required for the statin parameters. NHANES is a series of cross-sectional surveys and physical examinations conducted biennially to assess the health and nutritional status of the U.S. population.[286] NHANES collects demographic, nutritional, and health status information on a nationally representative probability sample of the U.S. civilian population (aged 0-80+ years) instituted by the National Center for Health Statistics (NCHS). Participants are randomly selected through a complex, multistage cluster sampling probability design. Young children, older adults, African Americans, and Mexican Americans are oversampled at each survey to provide sufficient numbers to support analysis in these underrepresented populations. All analyses will use sample weights to produce estimates generalizable to the original sampling frame[288] For this study, we will use data from the three most-recent NHANES population cross-sections, conducted in 2011-2016.

Exclusion criteria

NHANES participants self-reporting congestive heart failure, MI/CHD, angina, stroke (all types), participants classified as having T2D, participants with triglyceride levels >400 mg/dl, participants with LDL-C levels ≥190 mg/dl, and participants with ASCVD risk scores unable to be calculated (i.e. missing data) will be excluded from the study. Additionally, only African American and Caucasian populations between the ages of 40-75 years will be considered in the analysis to overlap with ages eligible for statin treatment under the ACC/AHA treatment recommendations.

C.1.2. REGARDS

Data from REGARDS will be used to estimate ASCVD and T2D incidence and statin discontinuation. REGARDS is a national, population-based, longitudinal study designed to evaluate factors underlying the excess stroke burden in the southeastern US and among African Americans.[218] Potentially eligible REGARDS participants were identified from commercially available nationwide lists of U.S. residents with a recruitment goal of including 30% of participants from the "Stroke Belt" (North Carolina, South Carolina, Georgia, Tennessee, Mississippi, Alabama, Louisiana, and Arkansas). Eligible participants were sent an initial mailing, followed by a telephone call and a subsequent in-home visit. Between January 2003 and October 2007, REGARDS enrolled 30,239 non-institutionalized African-American and Caucasian adults aged ≥45 years. The second in-home visit took place from May 2013 to Dec 2016.

Exclusion criteria

REGARDS participants self-reporting congestive heart failure, MI/CHD, angina, or stroke (all types), participants classified as having T2D, participants with triglycerides >400 mg/dl, or participants with LDL-C ≥190 mg/dl will be excluded from the analyses. Only participants between the ages 45-75 years will be considered in the analysis to overlap with ages eligible for statin treatment under the ACC/AHA treatment recommendations (minimum age for REGARDS is 45 years). Since ASCVD incidence is low in populations <45 years of age, we will assign the ASCVD incidence from the 45-50 year old age-group and assess different specifications via meta-analyses.

C.1.3. Data inputs

C.1.3.1. Data from NHANES

Data from NHANES were used to obtain baseline characteristics of the study population, prevalence and 10-year risk of ASCVD, prevalence of T2D, and prevalence of current use of statins. Questionnaires were used to assess prevalence of ASCVD, demographic information, smoking status, and blood pressure treatment; mean of final two of three blood pressure measurements from the medical examination were used to assess systolic blood pressure; fasting blood samples were used for lipid analyses to measure total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and triglycerides; and low-density lipoprotein cholesterol (LDL-C) levels were calculated using the Friedewald equation.[289] The prevalence of T2D was assessed by participant-report of a doctor or health professional diagnosis of T2D (yes/no) or report of T2D medication use. The prevalence of current use of statins was defined by self-report of ever taking cholesterol medications.

C.1.3.2. Data from REGARDS

Incident and prevalent ASCVD and T2D will be estimated to inform ASCVD and T2D parameters and will be ascertained from the REGARDS study by participant report and adjudicated by physicians.

<u>MI/CHD</u>

Self-reported MI/CHD prevalence will be ascertained using the following questions: (1) “Has a doctor or any other health professional ever told you that you had a myocardial infarction or heart attack?” (2) “Have you ever had a coronary artery bypass surgery, such as a graft, CABG, or a bypass procedure on the arteries of your heart?” and (3) “Have you ever had an angioplasty or stenting of a coronary artery with or without placing a coil in the artery to keep it open?” All questions were scored “yes”, “no”, “don’t know”, and “refused”.[218] MI/CHD was defined as a yes response to any one of those three questions.

Incident MI/CHD events will be ascertained during follow-up. Participants were contacted by telephone every six months to assess hospitalizations, emergency department visits, overnight stays in

nursing homes or rehabilitation centers, or death. If suspected heart event was reported, medical records were pursued. MI/CHD were adjudicated based on the presence of signs or symptoms suggestive of ischemic; diagnostic cardiac enzymes (rising or falling pattern in cardiac troponin or creatinine phosphokinase-MB isoenzyme concentrations over ≥ six hours with a peak concentration greater than twice the upper limit of normal); and ECG changes consistent with ischemia or MI/CHD (see section D.1. Myocardial Infarction/Coronary Heart Disease).[287] In the case where a participant died outside the hospital, interviews with family members or other proxies, proximal hospitalizations, baseline medical history, death certificates, and the National Death Index were used to identify MI/CHD as the underlying cause of death.

Stroke

Prevalent stroke will be defined as a positive response to either "Were you ever told by a physician that you had a stroke?" or "Were you ever told by a physician you had a mini-stroke or TIA, also known as a transient ischemic attack?".[218]

Similar to the ascertainment of incident MI/CHD, incident stroke will be determined during follow-up. Participants were contacted by telephone every six months to assess vital status, identify hospitalizations, emergency department visits, overnight stays in nursing homes or rehabilitation centers, or death during the previous six months. Reasons for medical encounters were asked and medical records were sought for stroke, TIA, death, unknown reason for hospitalization, or if reason was brain aneurysm, brain hemorrhage, sudden weakness, numbness, trouble speaking, sudden loss of vision, headache, other stroke symptoms.[218] Reports of possible incident stroke events were reviewed by a stroke nurse and then reviewed by at least two physician members of a panel of stroke experts in accordance with the World Health Organization definition (see section D.2. Stroke).[226] For proxy reported deaths, interview was conducted with next of kin.

T2D

T2D will be ascertained during the first in-home visit (to ascertain prevalent T2D) and second in-home visit (to ascertain incident T2D) using REGARDS investigator defined outcomes (T2D if fasting glucose ≥126 mg/dl, non-fasting glucose >200 mg/dl or taking T2D medication).[218]

Statin discontinuation

Statin discontinuation will be defined using statin discontinuation estimates obtained from preliminary data provided by an ongoing study conducted in REGARDS and past studies.[132]

C.1.3.3. Additional Data Inputs

Statin associated RRs

Statin-associated RRs will be estimated to inform ASCVD, T2D, and mortality parameters. The statin-T2D RRs will be obtained from our meta analysis from Aim 1. The statin-ASCVD and statin-mortality RRs will be obtained from the Cholesterol Treatment Trialists' meta-analysis comparing the effectiveness of statin therapy for the primary prevention of ASCVD events from 22 trials (statin therapy versus control).[3]

Non-ASCVD Mortality

Non-ASCVD mortality rates were obtained from the National Center for Health Statistics (NCHS) and were calculated based on population estimates for July 1, 2014.[290] Available data were collected by the NCHS from death certificates filed in all 50 states and the District of Columbia and were compiled into a national database. Non-ASCVD deaths/year were defined excluding cardiovascular and cerebrovascular deaths.

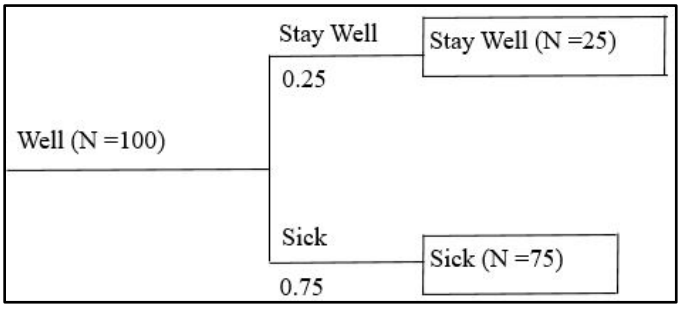
C.2. Markov Models

The simulation tool is constructed as a series of Markov models. Markov models are frequently used to simulate the progression of populations through mutually exclusive health states. Instead of possible outcomes over time being modelled as a large number of possible pathways, Markov models

provide a more complex framework that is reflected as a set of possible transitions (operationalized as user-defined probabilities) between health states over a series of discrete time periods.[291]

The Markov model assumes that a population is always in one of a finite number of states of health ("Markov states") and the population may transition from one state to another. The time horizon of the analysis is divided into equal increments of time, referred to as Markov cycles and can represent any user-defined increment, e.g. days, weeks, years, decades etc. During each cycle, all individuals in the populations can transition from one state to another. Figure 10 shows an example of a Markov model modelling populations transitioning from a healthy state (well) to a sick state. The initial population is healthy ("well") and can transition into one of two states ("stay well" or "sick") after one cycle. The proportion of the populations that "stays well" after a cycle is determined by the user-defined transition probability; here 25% of the participants stay well after one cycle and 75% of the participants transition into "sick". The example in Figure 10 only describes one cycle, however subsequent cycles can be performed. Further, for studies of incidence, the "sick" state can be defined as an "absorbing state", i.e. once populations enter the "sick" state they cannot be reclassified as "well". Therefore, in the above example, defining an "absorbing state" will result in observing the healthy populations after each cycle transitioning to either "sick" or remaining "well" (with transition probabilities remaining constant [i.e. 0.25 and 0.75]); the Markov model could then be repeated until all populations are classified as "sick".

Figure 10. Markov model example



Similar to the example in Figure 10, in Aim 2 we will use a Markov model to simulate the progression of statin-eligible populations to downstream consequences (ASCVD, T2D, mortality) through the use of transition probabilities (Figure 9).

Statin eligibility using ACC/AHA recommendations

To identify statin-eligible populations from NHANES, 10-year ASCVD risk scores will be estimated among a primary prevention population with triglycerides levels ≤400 mg/dl and LDL-C levels <190 mg/dl to focus on participants that will only become statin-eligible through their ASCVD risk scores. The ASCVD risk scores will determine which participants will become statin-eligible based on ASCVD risk thresholds (i.e. 10-year ASCVD risk of 10% vs. 10-year ASCVD risk of 7.5%).

Using NHANES data, the predicted 10-year risk for ASCVD will be calculated using the Pooled Cohort risk equations, developed by the ACC/AHA Task Force on Practice Recommendations.[292] Separate equations were developed for African American and Caucasian men and women, which included the following variables in the equations: age (years), concentration of TC (mg/dl) and HDL-C (mg/dl), treated or untreated systolic blood pressure (mmHg), T2D status (yes/no), and self-reported current smoking status (yes/no).

Calculation of the 10-year ASCVD risk will be done in a series of steps (Appendix 1). First, the natural log of age, TC, HDL-C, and systolic blood pressure will be calculated with systolic blood pressure being either a treated or untreated value. Next, we will multiply these values by the coefficients from the estimated equation parameters of the Pooled Cohort Equations for the specific race-sex group of the population. The sum of the products of the previous calculations are then calculated for the population. Finally, we estimate the 10-year risk of ASCVD event as

$$Predicted\ ASCVD\ Risk = \ 1 - S_0(t)^{e^{Ind\ X'B - Mean\ X'B}}$$

The ASCVD risk will be calculated as 1 minus the survival rate at 10 years (Appendix 1), raised to the power of the exponent of the coefficient*value sum minus the race and sex specific overall mean coefficient*value sum.[293] Each participant is assigned a probability of statin treatment, which is used to determine which participant is statin-eligible according to one of the three 10-year ASCVD risk thresholds we will be testing (10%, 7.5%, and 5%).

Once the statin-eligible population is determined, the Markov model will project the initial population ("healthy") transitioning to one of three states (ASCVD, T2D, or mortality) or remaining in the "healthy" state after one cycle (one cycle = 1 years). The proportion of the population that transitions into one of the three states will be determined by transition probabilities estimated from parameters estimated using data from REGARDS, published statin-ASCVD meta-analyses, and results from Aim 1 (Table 10). For example, to calculate transition probability or ASCVD, we will first estimate the probability of ASCVD for non-statin users, stratifying by age, sex, race/ethnicity, and five-year age groups, according to the formula:

$$Probability\ ASCVD_{non-statin\ users} = Probability\ ASCVD_{incidence\ overall}/((1 - P_{statin\ users}) + P_{statin\ users} * RR_{statin\ users})$$

Where $ASCVD_{incidence\ overall}$ is ASCVD incidence, $P_{statin\ users}$ is the prevalence of current statin users, and $RR_{statin\ users}$ is the RR of ASCVD among statin users compared to non-statin users. Combining estimates of the probability of ASCVD among non-statin users with the previously estimated $RR_{statin\ users}$ allows estimation of the probability to calculate the proportion of the initial population that will transition into the ASCVD state (i.e. transition probability):

$$Probability\ ASCVD_{statin\ users} = Probability\ ASCVD_{non-statin\ users} * RR_{statin\ users}$$

Transition probabilities will be similarly calculated for the proportion of the initial population to transition into the T2D and mortality states.

Table 10. Markov model parameters

Age (5-year) sex-specific parameters	Sources of data	Metric estimated
ASCVD parameters		
ASCVD incidence overall	REGARDS	Annual incidence rate
Statin-ASCVD RR	Cholesterol Treatment Trialists' Collaboration[4]	RR
T2D parameters		
T2D incidence overall	REGARDS	Annual incidence rate
Statin-T2D RR	Past meta-analysis (under review)	RR
Non-ASCVD mortality parameters		
Total non-ASCVD mortality overall	National Center for Health Statistics	Annual mortality rate
Statin-non-ASCVD mortality RR	NA	RR
Statin parameters		
Prevalence of statin discontinuation	REGARDS	Prevalence proportion

**Will vary in sensitivity analyses

C.3. TreeAge Pro Software

The series of Markov models used in these analyses will be implemented through the TreeAge Pro software. TreeAge Pro executes the techniques of decision analysis by organizing and analyzing the decision making process in a use-friendly integrated graphical user interface.[294] Users can create model structures to represent problems being studied, including decision points and all of the events that can occur. Once models are created, TreeAge Pro can automatically generate the algorithms required to evaluate the model and help choose the optimal strategy. One type of model supported by TreeAge Pro, is the healthcare model, which allows users to create decision trees that are evaluated on the basis of cost or effectiveness. Healthcare models generally begin with a decision node including a branch for each treatment option for a specific health condition, with each treatment option branch including any number

of possible outcomes including incidence, prevalence, quality adjusted life years, and cost. If healthcare models need to follow a disease process into the future, a Markov model can be implemented through the decision tree structure supported by TreeAge Pro.[294]

The design of a basic Markov model in TreeAge requires consideration of a number of components (Table 11). Once the Markov model is built, a cohort analysis can be conducted to generate output by cycle and cumulative cycles to identify incident cases (i.e. T2D and ASCVD).

Table 11. Components of Markov models in TreeAge

Component	Definition	Proposal definition/operationalized
States	The set of distinct health states under consideration in the model	(See Figure 9)
Cycle length	The length of time represented by a single cycle in a Markov process	1 years
Initial probabilities	Set of probabilities used only at the outset of the process, describing the initial distribution of the cohort among the states	The entire cohort will start as statin-eligible
Transition probabilities	Probabilities of moving between health states from one cycle to the next	See Table 9
Rewards/tolls	Per-cycle costs or payoffs	NA
Termination condition	A logical test evaluated at the beginning of each new cycle to determine if the process should continue or stop	Projections will run for ten years (10 cycles)

C.3.1. Validation

TreeAge Pro provides users with tools to validate models by checking the most common flaws identified in models. The specific validation checks include missing probabilities, missing states, and unused variables.

C.4. Overview of Interventions

Each scenario will be operationalized by a Markov model stratified by 5-year age groups, sex, and race/ethnicity (African American and Caucasian).

Base-case scenario

ACC/AHA recommendations with the ASCVD risk threshold set to 10% as recommended by the USPSTF. Using the Pooled Cohort risk equations, we will classify populations with 10-year ASCVD risk scores ≥10% as predicted statin users.

Intervention scenarios

We will compare our base case scenario to three different intervention scenarios:

- *ACC/AHA recommendations with the ASCVD risk threshold set to 7.5%.* Using the Pooled Cohort risk equations, we will classify populations with 10-year ASCVD risk scores ≥7.5% as predicted statin users.
- *ACC/AHA recommendations with the ASCVD risk threshold set to 5%.* Using the Pooled Cohort risk equations, we will classify populations with ASCVD risk scores ≥5% as predicted statin users.
- *ACC/AHA recommendations with the ASCVD risk threshold set to 7.5%, but also including all populations ≥55 years of age.* Using the Pooled Cohort risk equations, we will classify populations with ASCVD risk scores ≥7.5% as well as populations ≥55 years of age as predicted statin users.

C.5. Sensitivity Analyses

To evaluate heterogeneity in statin-associated ASCVD and T2D risk[20, 240], we assessed the number of ASCVD events prevented and number of excess T2D events incurred by sex and age. In addition, to examine the influences of our assumptions of statin discontinuation, we

projected the number of ASCVD events prevented and number of excess T2D events incurred under three different statin discontinuation scenarios and assumed annual relative decrease in statin use of 25% and 50%, as well as full adherence across 10 years.[132]

CHAPTER 5. EVIDENCE OF HETEROGENEITY IN STATIN-ASSOCIATED TYPE 2 DIABETES MELLITUS RISK: A META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS AND OBSERVATIONAL STUDIES

A. Introduction

Hmg CoA reductase inhibitors, commonly known as statins, are the most widely prescribed class of medication used to reduce cardiovascular disease CVD risk and to treat elevated low density lipoprotein cholesterol (LDL-C).[2, 295, 296] Changes in cholesterol treatment recommendations from the Third Adult Treatment Panel (ATP III) of the National Cholesterol Education Program recommendations to the American College of Cardiology/American Heart Association (ACC/AHA) 2013 recommendations increased the number of adults newly eligible for statin therapy for primary prevention by an estimated 10.4 million, with 80% of the increase attributable to individuals between the ages of 60-75.[22]

While the cardioprotective effect of statins are undeniable[3, 4], experimental and observational research has also suggested that statins may lead to harm in lower risk individuals by increasing the risk of type 2 diabetes mellitus (T2D).[11-15, 176] Yet, most meta-analyses have combined primary and secondary prevention populations to examine statin associated T2D risk. Secondary prevention populations, however, include survivors of ASCVD whose mortality risk has been estimated to be five to six times higher than that of people of the same age who did not experience an ASCVD.[170] Further, the risk of T2D may differ when used for primary vs. secondary prevention,[19] complicating efforts to quantify statin-associated T2D risk in primary prevention populations. As primary prevention populations are most impacted by the statin-eligibility recommendations, additional research quantifying statin-associated T2D risk is needed.

In addition to combining primary and secondary populations, published meta-analyses of statin-associated T2D risk have also been restricted to either randomized controlled trials (RCTs) or observational studies (OBSs). Yet, meta-analyses that incorporate summary data from both study designs

may take advantage of the internal validity of RCTs and the external validity of OBSs. This approach better reflects the existing evidence base, and may increase statistical power to investigate heterogeneity and expand upon past meta-analyses' limited heterogeneity assessments.[17, 18] Therefore, to estimate the effect of statins on T2D among populations most affected by changes to statin use recommendations and examine potential sources of heterogeneity, we performed a systematic review and meta-analysis of statin-associated T2D risk by synthesizing published data from RCTs and OBSs, excluding secondary prevention populations.

B. Materials and Methods

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations throughout the design, implementation, analysis, and reporting of this meta-analysis.[272]

B.1. Data Sources

In consultations with a reference librarian (MW), studies of statin-associated T2D risk were identified by searching PubMed (1994-present) and EMBASE (1994-present) on 25 January 2018. Reference lists of articles were scanned, which included published RCT and OBS meta-analyses[12-15, 176] and all document types, languages, and publication dates. Consistent with previous systematic reviews and meta-analyses of RCT and OBSs examining statin-associated T2D risk[12-15, 176], the following free text and Medical Subject Headings terms were used: (Statin OR Statins OR Anticholesteremic Agents OR Anticholesteremic OR Hydroxymethylglutaryl-CoA Reductase Inhibitors) AND (Diabetes OR Diabetes Mellitus II OR Diabetes Mellitus Type II OR Diabetes Mellitus Type 2) AND (adverse effects OR adverse events) AND (cohort study OR case-control study OR trial).

B.2. Study Selection

Articles selected for the meta-analysis had to meet all of the following criteria: 1) follow-up >one year; 2) >50% of participants free of clinically diagnosed ASCVD; 3) adult participants ≥30 years old; 4) reported statin-associated T2D effect estimates using the odds ratio (OR), hazard ratio (HR), or risk ratio;

and 5) quantified precision using the 95% confidence interval (CI) or included information to enable estimation.

B.3. Data Extraction and Evaluation

Citations were downloaded to an electronic reference manager (EndNote X7, Thomson Reuters[297]) and duplicates were removed. Two reviewers (JCE and AS) independently reviewed all titles and abstracts and extracted relevant information into tables. The tables were compared and disagreements were resolved by consulting the initial articles. For each study population in each article, the reviewers extracted statin-associated T2D relative risks (RR; primary endpoint), study design, mean length of follow-up time, sample size, year of publication, year of baseline, methods used to address for confounders (in OBSs only), type of effect estimate, methods used to measure and define T2D, residence of participants, proportion of population that is Caucasian, proportion of population taking statins, mean baseline characteristics (age, body mass index [BMI], low-density lipoprotein cholesterol [LDL-C] levels, glucose levels, systolic blood pressure [SBP] levels), baseline characteristics proportions (hypertensive, current smokers, ASCVD) and methodological qualities of each study (Table 14). If information on study and participant characteristics of interest were not available, corresponding authors were contacted via email with one follow-up email sent two weeks after the initial inquiry and a final follow-up email sent two weeks thereafter.

B.4. Quality Assessment

PRISMA criteria were used to describe the quality of RCTs[272] and assess potential for bias. Specifically, the following dimensions (agree or disagree) were evaluated: 1) adequate use of measures to conceal allocation (adequate through the use of randomization); 2) application of blinding (whether to the participant, care provider or outcome assessors); 3) proportion of participants lost to follow-up reported; and 4) whether the analysis followed the intention-to-treat principle.[273]

To assess quality of OBSs, articles were assigned scores using criteria consistent with past meta-analysis of cohort studies[274] (agree or disagree): 1) Was a well-defined sample of participants identified?; 2) Were there clear definitions of statin use and 3) T2D?; 4) Was there information on baseline LDL-C

levels and 5) fasting plasma glucose levels by treatment status?; and 6) Were differences in baseline factors accounted for?[275]

B.5. Data Synthesis

Publication bias was assessed using both qualitative and quantitative methods overall and by study design (OBS; RCT). First, funnel plot asymmetry was evaluated using a plot of each study-specific RR versus its precision.[277] Second, p-values (α=0.1) for Begg and Mazumdar's log rank test and Egger's regression test were calculated to provide quantitative assessments of funnel plot assymetry.[279, 280] Third, Duval and Tweedie's non-parametric trim and fill imputation procedure was conducted to impute hypothetically missing results due to publication bias.[281]

Inter-study heterogeneity was assessed by Cochran's Q test[283] (α=0.1[298]) and the I^2 statistic, which is derived from Cochran's Q test ($I^2 = 100x(Q - df)/Q$).[284] To further assess the extent of heterogeneity between studies, Galbraith plots were constructed displaying each study's effect size divided by each study's standard error (Z score) versus the inverse of each study's standard error.[299]

Variation in the strength and precision of estimated RRs by study design (OBS; RCT) and across levels of the study and participant characteristics was assessed by estimating a summary random-effects RR within each study and participant characteristic using univariable random-effects meta-regression.[282] We considered the following study and participant characteristics for interrogation via meta-regression: mean length of follow-up time, sample size, year of publication, year of baseline, methods used to address for confounders, type of effect estimate, methods used to measure and define T2D, residence of participants, proportion of population that is Caucasian, proportion of population taking statins, mean baseline characteristics (age, BMI, LDL-C, glucose levels, SBP levels), and baseline characteristics proportions (hypertensive, current smokers, ASCVD). All analyses were performed using STATA (College Station, TX).[300]

C. Results

The systematic review identified a total of 459 candidate studies for screening (Figure 11). Of these studies, 23 (5%; eight RCTs and 15 OBSs) met the eligibility criteria for inclusion in the meta-analyses (see Supplement for article references). Eligible studies were conducted between 1998 and 2016, with OBSs on average being published more recently (mean publication date = 2012 vs 2005) and using more recent data (mean baseline study year = 2000 vs 1998) compared to RCTs (Tables 12 and 13). In contrast to RCTs, the mean length of follow-up time was longer (6.9 years vs 4.3 years), participants were more likely to be women (mean proportion of women = 51.5% vs 36%), more likely to be Caucasian (mean proportion Caucasian = 71.2% vs 63.6%), and less likely to be current smokers (mean proportion current smoker = 18% vs 24.5%) among OBSs.

Participant characteristics also differed by study design. Participants in OBSs were on average younger (mean age = 57.4 years vs 63.6 years), had lower mean LDL-C levels at study baseline (124.4 mg/dL vs 145 mg/dL) and mean fasting plasma glucose levels (96.4 mg/dL vs 101.6 mg/dL) compared to participants enrolled in the RCTs (Tables 12,13,15, and 16). In addition, 50% of RCTs used a combination of physician diagnosis, T2D medication, and lab results to define T2D (compared to 13% of OBSs); while 53% of OBSs used physician diagnosis and T2D medication.

Quality assessment of RCTs showed >87% (7/8) of RCTs fulfilled the intention-to-treat, loss to follow-up, and randomization criteria; while two studies (25%) failed to adequately blind participants (Figure 14). The quality evaluation among OBSs found >93% (14/15) of studies accounted for differences in baseline factors and clearly defined the sample, T2D, and statins use. However, >66% (10/15) of studies lacked information on baseline fasting glucose levels and >46% (7/15) of studies lacked information on LDL-C levels at baseline by treatment status (Figure 15).

Among RCTs and OBSs, statin users had higher risk of incident T2D compared to non-statin users, although the magnitude of effect was larger in OBSs (RR = 1.55 [95% CI: 1.39-1.74]) compared with RCTs (RR = 1.11 [95% CI: 1.00-1.22]) (Figure 12). Given the differences in the magnitude of effects, a summary effect is not reported. Funnel plots both overall and by study design suggested little

evidence of publication bias (Figures 16 and 17). This evidence is consistent with results from Begg's and Egger's tests ([RCTs: p-values =0.23 and 0.54] and [OBSs: p-values = 0.91 and 0.32]), but the "trim and fill" method imputed one hypothetically missing RCT (RR = 1.64) and three hypothetically missing OBSs with RRs <1.0. In contrast to RCTs where two studies reported effect estimates below the null (ie. RR < 1.0), all of the OBSs reported effect estimates above the null.

Evidence of heterogeneity varied by study design. Galbraith plots for RCTs indicated that one (Figures 18 and 19) Z score fell outside the 95% confidence bounds, evidence of heterogeneity that was consistent with the Cochran's Q and I^2 tests (I^2= 27% [p-value = 0.21] and $P_{Cochrane}$ = 0.04). Similarly, among OBSs, 47% of Z scores (7/15) fell outside the 95% confidence bounds, providing strong evidence of heterogeneity that was consistent with Cochran's Q and I^2 ($I^2 = 97.6\%$ [p-value <0.01] and $P_{Cochrane}$ <0.01).

Analyses examining sources of heterogeneity overall and by study design demonstrated variations in effect estimates by study and participant characteristics (Figure 13 and Tables 17-19). Overall, the association between statin use and T2D risk was stronger in OBSs compared to RCTs (RR = 1.45 [95% CI: 1.11-1.88]) and in studies published more recently (RR = 1.03 [1.00-1.06]). Comparing participant characteristics across study design, there was a decreased risk for T2D among, participants who were older (RR = 0.79 [95% CI: 0.63-0.98] per 10 year increase); smokers (RR = 0.27 [95% CI: 0.11-0.68] per 1% increase in the proportion of smokers); and had lower LDL-C levels (RR = 0.92 [95% CI: 0.87-0.97] per10mg/dL increase) (Figure 13 and Table 17). Among OBSs, the association between statin use and risk of incident T2D was stronger among study populations from non-European countries and study populations that were younger, had fewer smokers, and lower LDL-C levels (Table 18). No significant variability in effect estimates were found among RCTs (Table 19).

D. Discussion

Results of this meta-analysis, which are consistent with earlier studies synthesizing estimates of statin-associated T2D risk in primary and secondary prevention populations[12, 176], suggest that statins have a moderate effect on T2D risk, increasing risk 11-55%. Yet, strong evidence of heterogeneity was observed, particularly with regard to participant age and baseline LDL-C level. Potential evidence of heterogeneity was not fully examined in earlier meta-analyses and merits further investigation in light of statin recommendations that target growing proportions of primary prevention populations, particularly populations with lower ASCVD risk profiles (e.g. individuals with ASCVD 10-year risk estimates <10%).

The current RCT meta-analysis findings are consistent with results from past meta-analyses conducted among primary and secondary prevention populations that reported T2D risks that were 9%-13% higher in participants randomized to statins compared to placebo.[11, 12, 14, 15] Interestingly, a prior US Preventive Services Task Force (USPSTF) meta-analysis among six primary prevention RCTs suggested an attenuated association (RR = 1.05 [95% CI: 0.91-1.20]). The USPSTF estimated effect is slightly smaller in size and less precise than our estimate of RR=1.11 (95% CI: 1.00-1.22), which included newly available data from the Heart Outcomes Prevention Evaluation (HOPE-3) trial (N= 12,705). Overall, the body of literature examining statin-associated T2D risk in RCTs suggests a modest relative effect that was consistent across primary and secondary populations.

Meta-analyses of OBSs indicated a similarly elevated statin-associated T2D risk, although the magnitude of effect was considerably higher (RR = 1.55 [95% CI: 1.39-1.74]), possibly reflecting differences in source population, outcome measurement error, or confounding. For example, RCTs often exclude participants that demonstrate signs of drug intolerance before randomization, participants who may be more susceptible to developing T2D, and participants with relevant comorbidities.[301, 302] Such exclusions may yield selected populations that are less prone to adverse drug events, including T2D, than community-based populations.[303] Regarding outcome measurement error, in contrast to RCTs, for which a majority included biomarkers (i.e. fasting plasma glucose) when measuring T2D, only four of fifteen

OBS studies included biomarkers to measure T2D. Assessing biomarkers of T2D is important given the large burden of undiagnosed T2D in U.S. populations, as contemporary national estimates suggest that one in three adults with T2D are undiagnosed.[304] Studies also suggest the potential for outcome measurement error to bias results towards the null[305], which, if the case, would suggest that both RCT and OBSs underestimate T2D risk. Yet, use of fasting plasma glucose to define T2D was not a significant predictor of variation in statin-associated T2D risk although the small number of studies that measure fasting plasma glucose may have decreased our ability to detect an association. Finally, the potential for confounding may exist if factors associated with T2D diagnosis also were associated with statin prescription.[306] For example, OBS participants prescribed statins may have been more likely to make and attend appointments with primary care physicians, increasing their chances of being clinically evaluated and obtaining a T2D diagnosis.[179] However, studies using active comparators to evaluate statin-associated T2D risk reported that statin users had an even higher risk of T2D (RR =3.31 [95% CI: 2.56-4.30]) compared to new diclofenac users, even when both groups had similar chances of being evaluated.[180] Overall, the magnitude of statin-associated T2D risk remains difficult to quantify, with the potential that existing studies in aggregate underestimate statin-associated T2D risk.

We also detected evidence of heterogeneity, particularly among OBSs, which may indicate specific subpopulations particularly vulnerable to statin-associated T2D risk. For example, our observation of increased statin-associated T2D risk among studies with lower baseline mean LDL-C levels is consistent with evidence of an inverse association between LDL-C and T2D.[192] Further, a recent meta-analysis among 34 RCTs found more intensive compared with less intensive LDL-C lowering therapy was associated with a greater reduction in risk of ASCVD mortality in populations with baseline LDL-C levels ≥ 100mg/dL, but not among populations with LDL-C levels < 100 mg/dL.[307] Together, these results suggest that populations with the lowest estimated benefits of pharmacologically lowered LDL-C may also have the highest risk of T2D. However, our results remain somewhat tentative as 47% of OBSs included in the present meta-analysis either did not collect or report baseline LDL-C levels. In addition to missing baseline LDL-C levels, the majority of OBSs lacked baseline glucose levels. OBS

populations that did not include fasting plasma glucose levels may have had elevated levels at baseline, potentially biasing the risk estimate for OBS towards a higher risk. However, a major risk factor for elevated fasting plasma glucose levels is BMI, and mean BMI estimates were similar between RCT and OBS (Tables 12 and 13). Meta-regression results examining heterogeneity by fasting plasma glucose levels also were not significant predictors of T2D risk.

The association between statins and T2D also varied by mean participant age. However, we had limited ability to fully interrogate the role of age, as the OBSs on average consisted of younger populations compared to RCTs and evidence of heterogeneity precluded pooling across study designs. Understanding the role age may play in the association between statins and T2D is important because age is a dominant factor when determining ASCVD risk and thus statin initiation. For example, in the U.S. nearly all men exceed the 7.5% ASCVD risk threshold for statin initiation in their mid to late 60s and nearly all women in their 70s, despite an otherwise optimal risk factor profile.[20]

Given the public health and clinical relevance of enumerating statin-associated risks and benefits, future studies specifically designed to accurately estimate statin-associated risk overall and in strata defined by baseline LDL-C and age, and possibly other plausible effect measure modifiers, are needed. Yet, such studies require careful consideration of design features. For example, five of fifteen OBSs were conducted using insurance claims databases, which may not capture participant baseline characteristics, including LDL-C. Contemporary, population-based cohort studies can provide validated baseline measurements on participant characteristics such as LDL-C or information on glucose levels and collect data on T2D incidence and medications. Yet, multi-year gaps between visits complicate the ability to precisely identify statin initiation and T2D diagnosis, although novel approaches that enable linkage with EMRs and claims data may offer opportunities to address some limitations.[308] Other potential avenues include large biobanks linked to EMR (e.g. the UK Biobank), although low response rates may introduce additional sources of bias, the effect of which may be difficult to predict.[309] In sum, these considerations suggest that comprehensively examining statin-associated T2D risk will continue to require multiple study designs, as the optimal design may not be feasible.

Despite many strengths, there are limitations that merit consideration. First, there were several studies that did not respond to repeated requests for additional study or participant characteristics. Obtaining missing estimates may have increased statistical power for heterogeneity investigations and allowed us to further examine potentially important characteristics such as age, LDL-C, fasting plasma glucose levels, or BMI. However, this study provides some of the first evidence of heterogeneity in statin-associated T2D risk, which may motivate future studies that address these limitations. Second, our investigation of heterogeneity leveraged aggregate rather than individual-participant data (IPD). Reliance on aggregate data reflected challenges associated with accessing, understanding, and analyzing separate datasets.[310] Importantly, it has been suggested that an aggregate data meta-analysis is one of the first steps in conducting an IPD meta-analysis and can inform future IPD meta-analyses studies about the potential sources of heterogeneity that warrant examination.[311] Third, our investigation of heterogeneity was limited by study and participant characteristics reported at large enough numbers to enable well-powered investigations. For instance, we were not able to obtain enough information to assess statin dose or type as a source of heterogeneity, although some degree of effect modification by dose on statin-associated T2D has been reported.[282] However, we were able to assess statin use in multiple settings and compare populations under strict observation (i.e. RCT) with populations under conditions more generalizable to broader populations.[171] Fourth, we were unable to investigate the role of statin adherence, although several studies attempted to exclude participants at risk of non-adherence.[312] The effects of statin adherence are difficult to quantify, although failure to address medication non-adherence are long-described.[313] Finally, our meta-analysis was limited to examining T2D, given the unavailability of studies examining statin-associated elevations in prediabetes risk or interval measures of glucose homeostasis. Future studies on these topics are warranted, given the association of fasting plasma glucose with elevated risk of cardiovascular disease.[314]

In conclusion, this meta-analysis adds to a growing body of literature addressing statin-associated T2D risk. Findings highlight potentially increased statin-associated T2D risk in younger populations, and

populations with lower LDL-C concentrations at study baseline. Taken together, these results help to inform risks of statin use across CVD risk profiles and underscore the need for more research on statin-association T2D risk as recommendations continue to evolve.

E. Tables and Figures

Table 12. Selected characteristics of interest among eight randomized controlled trials examining statin-associated type 2 diabetes risk

Studies	Study characteristics				Participant characteristics					
	Mean length of follow-up (years)	Study sample size	Year of baseline data	Method to define T2D	% Women	% Caucasian	Mean age (years)	Mean BMI (kg/m^2)	Mean LDL-C levels (mg/dL)	Mean FPG levels (mg/dL)
Downs (1998)	5.2	6605	1993	T2D diagnosis, T2D medication use, and FPG >126mg/dL	15.1	89	58	26.7	150	R
Freeman (2001)	4.8	6595	1990	T2D medication use, FPG >126mg/dL	0.0	100	55	25.9	193.3	86.5
Furberg (2002)	4.8	10355	1994	FPG >126mg/dL	49	41	66.4	29.9	146	122.1
Shepherd (2002)	3.2	5804	1999	T2D medication use, FPG >126mg/dL	51.7	100	75.3	26.8	146.9	92.5
Sever (2003)	3.3	10341	1999	FPG >126mg/dL	18.8	94	63.2	28.7	131.5	111.7
Nakamura (2006)	5.3	7832	1999	T2D diagnosis, T2D medication use, and FPG >126mg/dL	68.0	0	59	23.9	156	109.1

Ridker (2008)	1.9	17802	2007	T2D diagnosis, T2D medication use, and FPG >126mg/dL	38.2	71.3	66	28.4	108	94
Yusuf (2016)	5.6*	12705	2010	T2D diagnosis, T2D medication use, and FPG >126mg/dL	46.7	20	65.8	27.1	128.6	95.4*
8 studies (1998-2016)	4.3	9754.9	1998		35.9	64.4	63.6	27.2	145.0	101.6

BMI = Body mass index
LDL-C = Low-density lipoprotein
FPG = Fasting plasma glucose
R = Data requested, but not available
*= Median values

Table 13. Selected characteristics of interest among 15 observational studies examining statin-associated type 2 diabetes risk

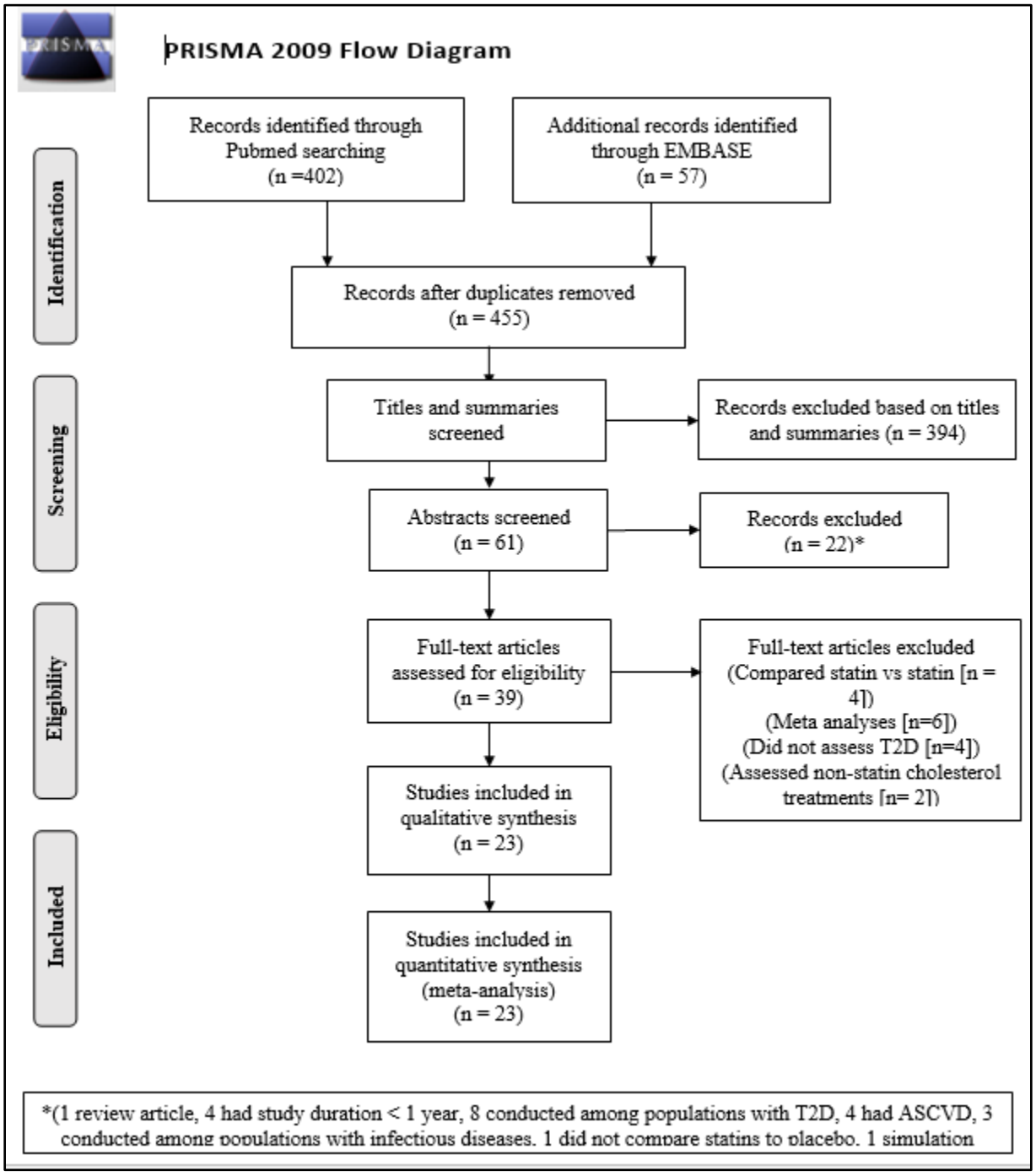
Studies	Study characteristics					Participant characteristics					
	Type of OBS data	Mean length of follow-up (years)	Study sample size	Year of baseline data	Method to define T2D	% Women	% Caucasian	Mean age (years)	Mean BMI (kg/m^2)	Mean LDL-C levels (mg/dL)	Mean FPG levels (mg/dL)
Jick (2004)	Cohort	11	2651	1996	T2D diagnosis, T2D medication use	49.1	100	59.2	27.6	NA	NA
Culver (2012)	Cohort	9	120173	1995	Self-report of physician-diagnosed T2D	100	83.7	63.2	27.8	120.4	94
Wang (2012)	Insurance claims	8	42060	2000	T2D diagnosis, T2D medication use	50	0	63	NA	NA	NA
Danaei (2012)	Insurance claims	9	285864	2000	T2D diagnosis, T2D medication use	55.5	100	63.2	27.7	135.9	NA
Izzo (2013)	Cohort	4.7	4750	1997	T2D diagnosis, T2D medication	42.3	100	58.6	27.7	130.2	95.7

					use, and FPG >126mg/dL						
Chen (2013)	Insurance claims	2	11715	2004	T2D diagnosis	100	0	61.3	NA	NA	NA
Currie (2013)	Cohort	6	32086	2005	T2D diagnosis, T2D medication use	47	69.5	49.9	R	R	R
Zaharan (2013)	Insurance claims	8	1162911	2002	T2D diagnosis, T2D medication use	64	100	R	R	R	R
Macedo (2014)	Cohort	20	2016094	1989	T2D diagnosis	47	100	62.3	NA	NA	NA
Bhattacharya (2014)	Cohort	2	44047	2004	T2D diagnosis	55	73	R	NA	NA	NA
Cederberg (2014)	Cohort	5.9	8749	2010	T2D diagnosis, T2D medication use, and FPG >126 mg/dL	0	100	57.1	26.8	130.2	103
Mansi (2015)	Cohort	10	6702	2004	T2D diagnosis	38.8	NA	53	NA	117	NA
Radford (2015)	Cohort	3	8853	1998	T2D medication	26.4	100	48.2	26	122.8	95.2

					use, FPG >126 mg/dL						
Olotu (2016)	Insurance claims	1.3	106424	2003	T2D diagnosis, T2D medication use	48.9	NA	46.3	NA	NA	NA
Rha (2016)	Insurance claims	3	3398	2004	T2D medication use, FPG >126 mg/dL	48	0	60.3	24.5	114	94
15 studies (2004-2016)		6.9	257098	2000		51.5	71.2	57.4	26.9	124.4	96.4

OBS = Observational study
BMI = Body mass index
LDL-C = Low-density lipoprotein
FPG = Fasting plasma glucose
R = Data requested, but not available

Figure 11. Flow diagram of literature search to identify randomized controlled trials and observational studies for inclusion in meta-analysis examining statin-associated type 2 diabetes risk



T2D = Type 2 diabetes
ASCVD = Atherosclerotic cardiovascular disease

Figure 12. Meta-analysis examining statin-associated type 2 diabetes risk stratified by study design

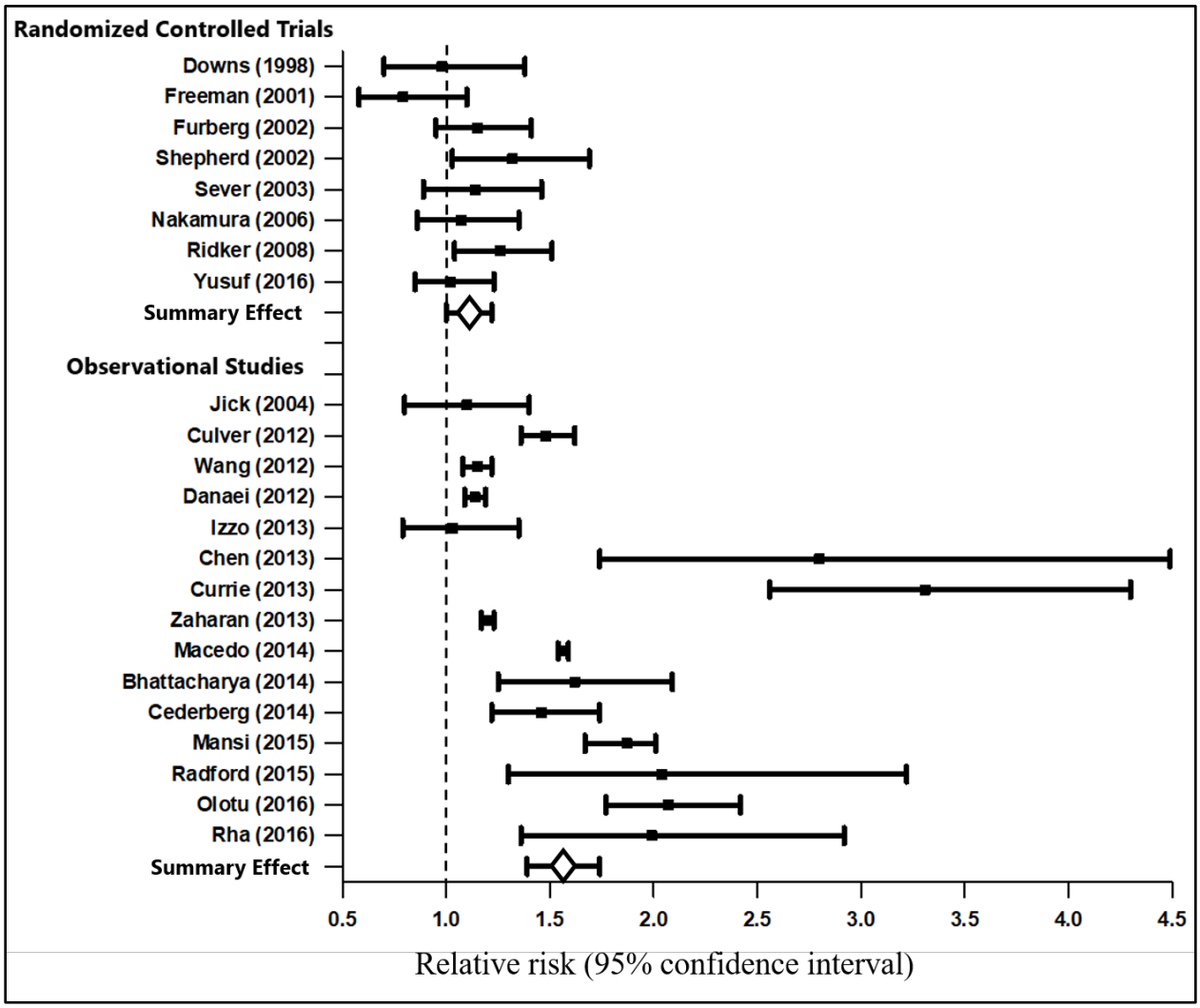
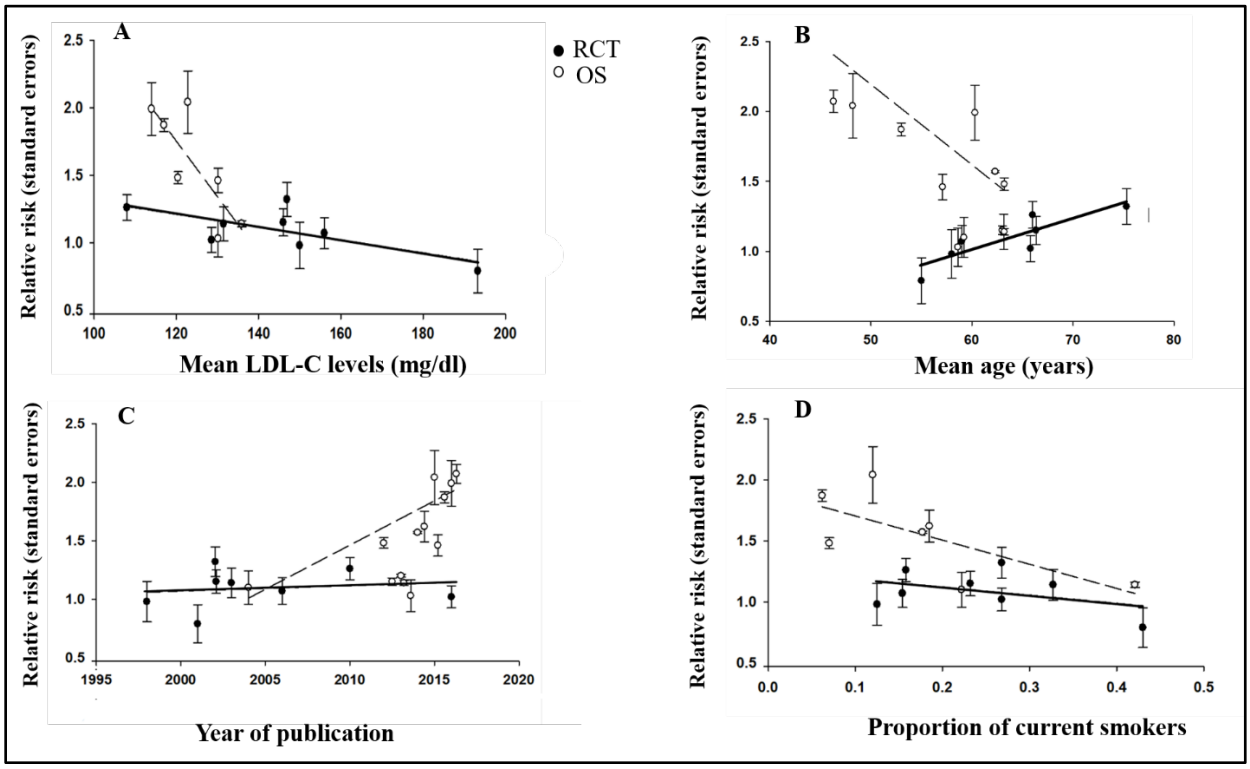


Figure 13. Results from meta-regression analyses examining significant study and baseline participant characteristics among randomized controlled trials and observational studies



A = Mean low-density lipoprotein cholesterol levels by statin associated type 2 diabetes risk
B = Mean age by statin associated type 2 diabetes risk
C = Year of publication by statin associated type 2 diabetes risk
D = Proportion of current smokers by statin associated type 2 diabetes risk

F. Supplemental Material

F.1. Risk of Bias Among Observational Studies

To further assess the risk of bias among observational studies (OBSs), we used the average standardized absolute mean difference (ASAMD) to assess balance between statin-treated and comparison groups, with lower ASAMD indicating better balance.[275] Balance was assessed across covariates selected based on past evidence and theory. ASAMD was calculated by subtracting each of the comparison group means from the corresponding statin-treated group mean, taking the absolute value of each difference, dividing each absolute difference by the pooled standard deviation of the covariate (if continuous), and then computing the mean of the standardized absolute differences.[275]

F.2. Supplemental Figures

Figure 14. Summary of quality assessment for included eight randomized controlled trials examining statin-associated type 2 diabetes risk

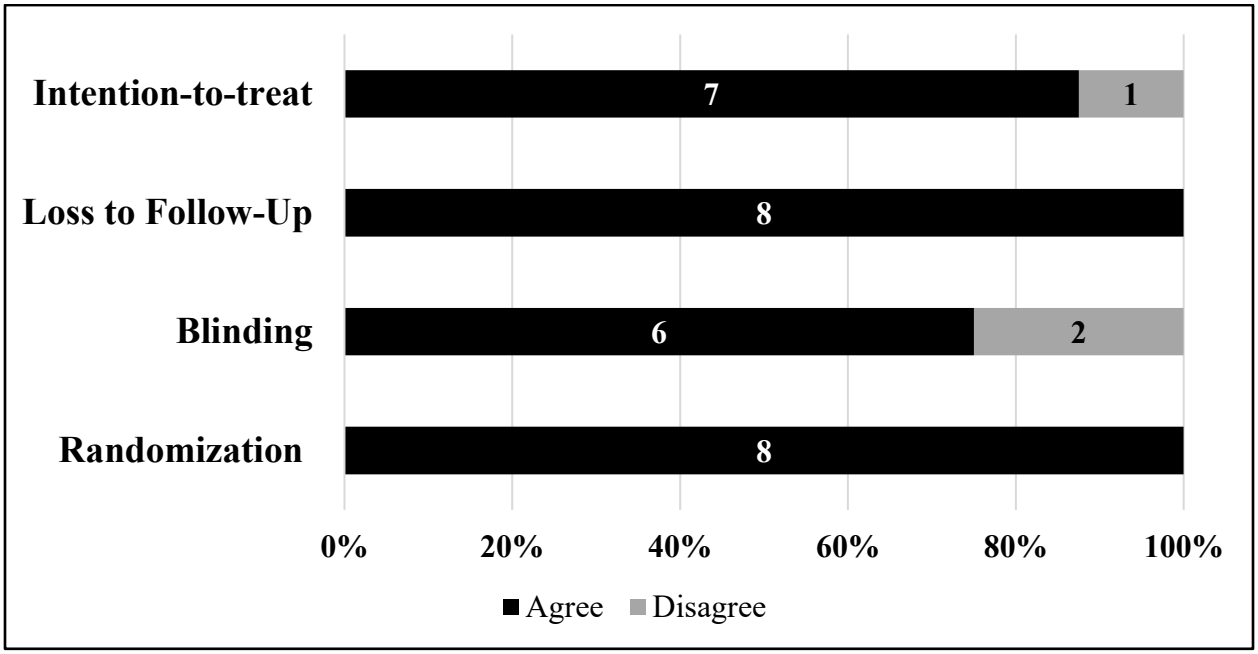
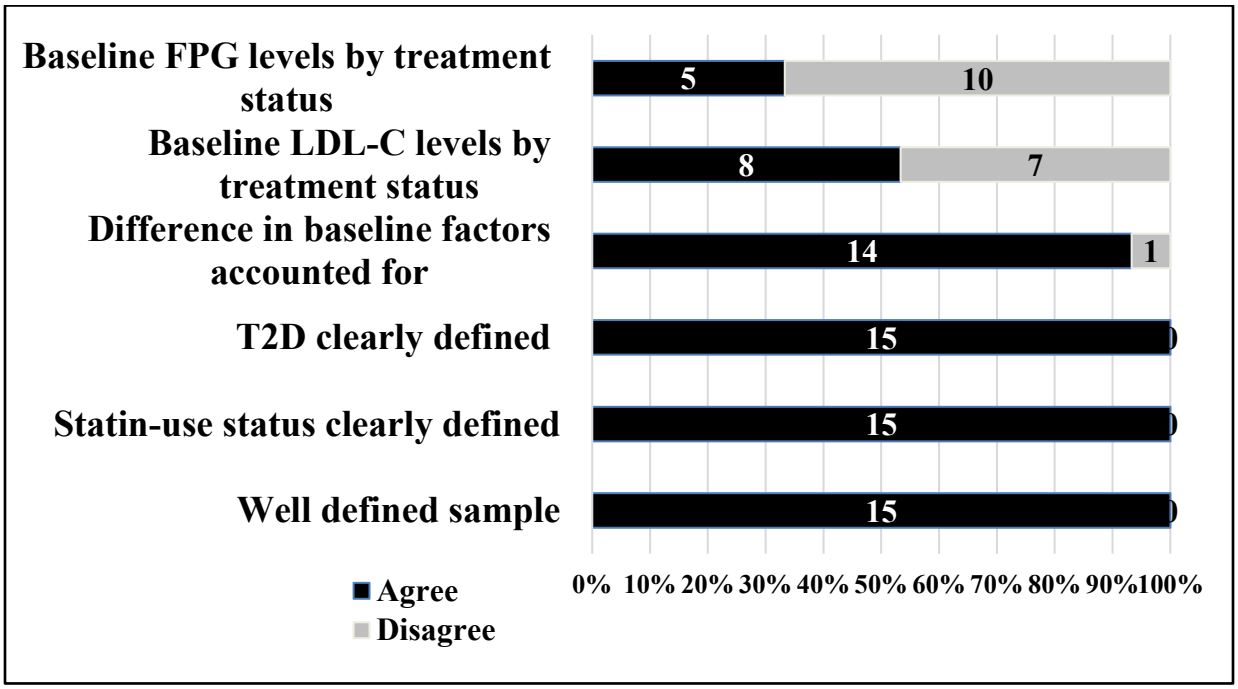


Figure 15. Summary of quality assessment for included 15 observational studies examining statin-associated type 2 diabetes risk



FPG = Fasting plasma glucose
LDL-C = Low-density lipoprotein
T2D = Type 2 diabetes

Figure 16. Funnel plot displaying reported and imputed relative risks examining statin-associated type 2 diabetes risk overall

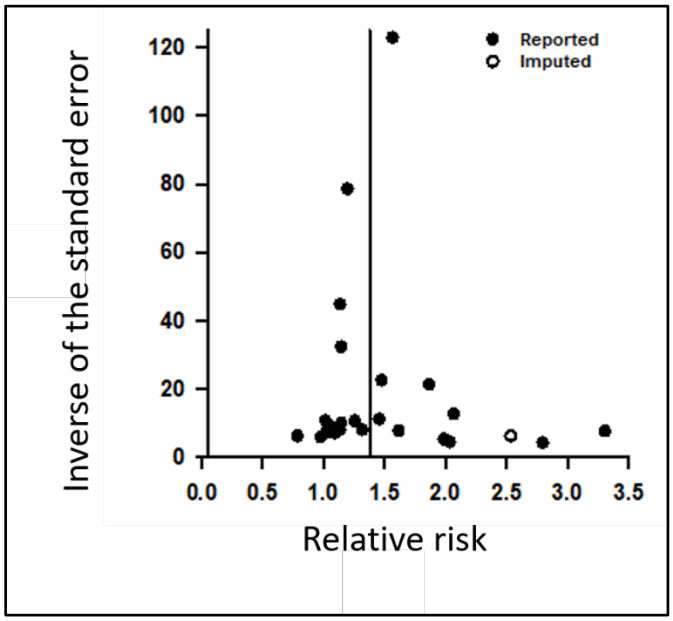


Figure 17. Funnel plots displaying reported and imputed relative risks examining statin-associated type 2 diabetes risk among randomized controlled trials and observational studies

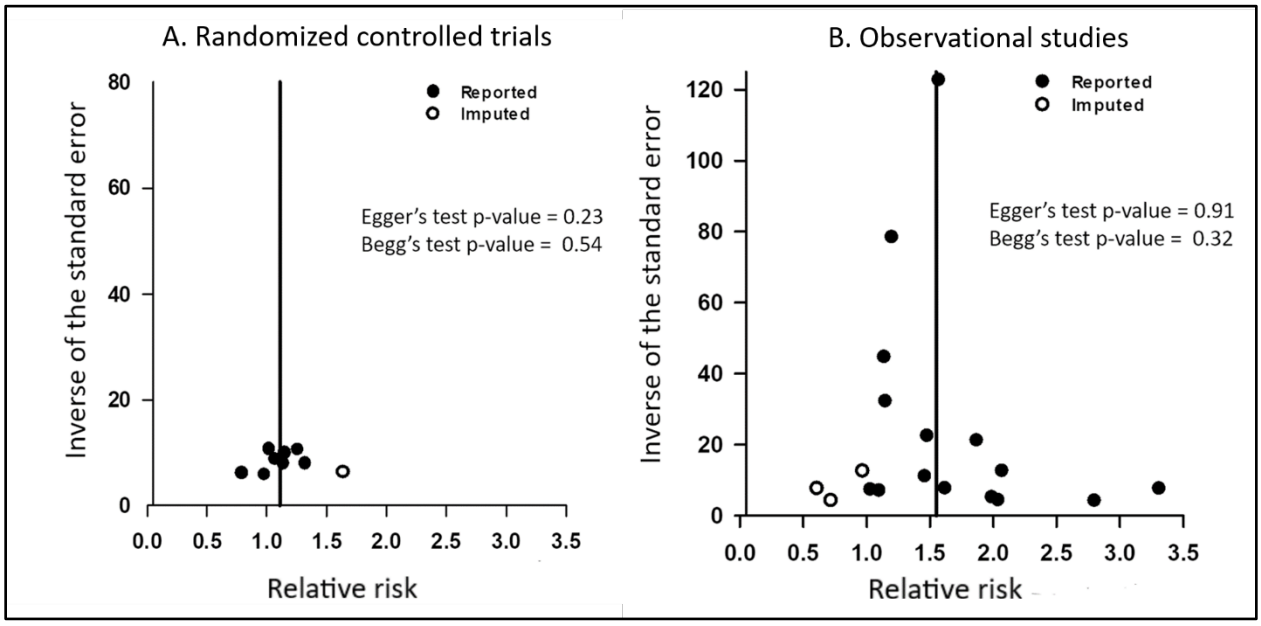


Figure 18. Galbraith plot displaying relative risks examining statin-associated type 2 diabetes risk and 95% confidence intervals overall

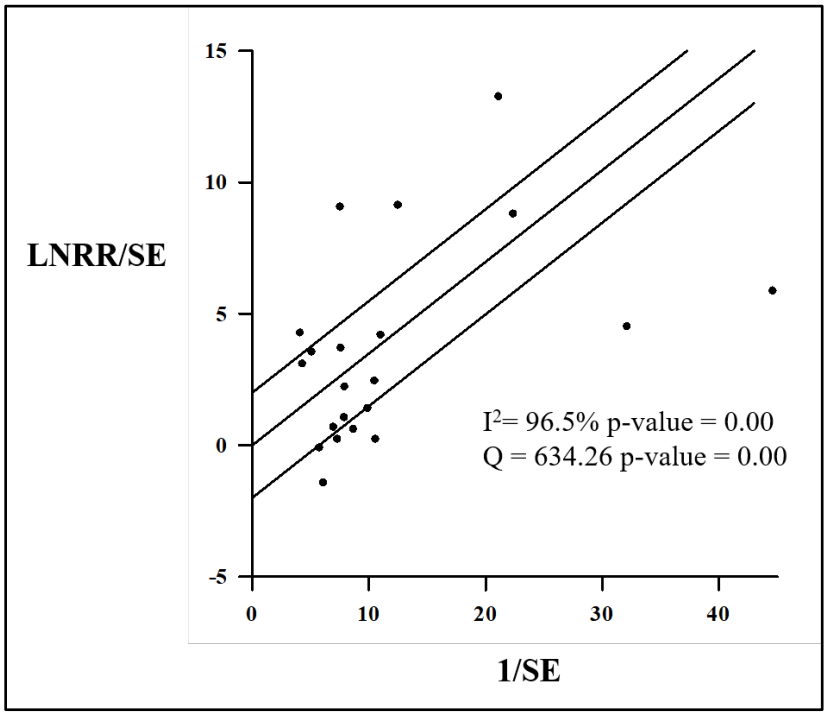
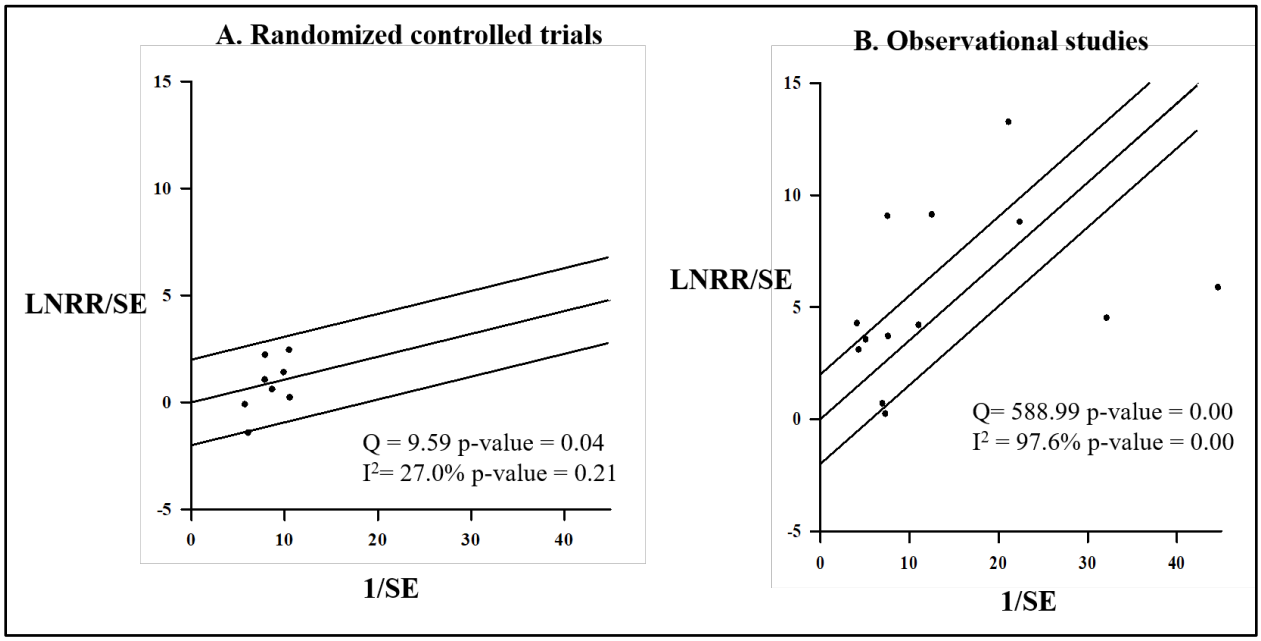


Figure 19. Galbraith plot displaying relative risks examining statin-associated type 2 diabetes risk and 95% confidence intervals among randomized controlled trials and observational studies



F.3. Supplemental Tables

Table 14. Study and baseline participant characteristics abstracted from 23 studies examining statin-associated type 2 diabetes risk

Study characteristics
Study design (randomized controlled trials cohort, case-control, cross sectional)
Mean length of follow-up time
Study sample size
Year of publication data
Year of study baseline
Method to control confounding (propensity score, adjusted in the model, randomization, did not adjust)
Methods to measure and define type 2 diabetes status (physician diagnosis, medication data, laboratory data)
Type of effect estimate metric (odds ratio, relative risk, hazard ratio)
Participant characteristics
% Female
Mean Age (10-year age groups)
% Caucasian
Residence of participant
% prescribed statins
Type of statins included
Mean BMI
Mean LDL-C levels
Mean fasting plasma glucose levels
Mean systolic blood pressure levels
% hypertensive
% current smokers
% of population with ASCVD at baseline

Table 15. Additional characteristics of interest among eight randomized controlled trials examining statin-associated type 2 diabetes risk

	Study characteristics			Participant characteristics				
Studies	Type of effect estimate	Residence of participant	Type of statin	% prescribed statins	Mean systolic blood pressure levels (mmHG)	% Hypertensive	% Current smokers	% of populations with ASCVD at baseline
Downs (1998)[125]	RR	North America	Lovastatin	49.8	138	22	12.5	0
Freeman (2001)[149]	HR	Europe	Pravastatin	50	135	16	43	0
Furberg (2002)[302]	RR	North America	Pravastatin	49.6	145	100	23.2	14
Shepherd (2002)[154]	HR	Europe	Pravastatin	50	154.6	61.9	26.8	44.2
Sever (2003)[148]	HR	Europe	Atorvastatin	50	164.2	100	32.7	11
Nakamura (2006)[155]	HR	Asia	Pravastatin	49.5	132.25	40.9	15.4	0
Ridker (2008)[315]	HR	Multiple	Rosuvastatin	50	134	NA	15.8	0
Yusuf (2016)[163]	HR	Multiple	Rosuvastatin	50	137.9	37.8	26.8	0
8 studies (1998-2016)				50	142.6	54.1	24.5	8.7

ASCVD = Atherosclerotic cardiovascular disease

Table 16. Additional characteristics of interest among 15 observational studies examining statin-associated type 2 diabetes risk

	Study characteristics		Participant characteristics					
Studies	Type of effect estimate	Method to deal with confounding	Residence of participant	% prescribed statins*	Mean systolic blood pressure levels (mmHG)	% Hypertensive	% Current smokers	% of populations with ASCVD at baseline
Jick (2004)[312]	OR	Controlled	Europe	22.0	NA	40.23	22.2	0.0
Culver (2012)[164]	HR	Controlled	North America	7.0	NA	NA	7.0	15.9
Wang (2012)[316]	HR	Unadjusted	Asia	20.0	NA	NA	NA	47.0
Danaei (2012)[317]	HR	Controlled	Europe	4.9	NA	51.3	42.1	0.0
Izzo (2013)[318]	HR	Controlled	Europe	14.0	141.8	NA	NA	0.0
Chen (2013)[319]	OR	Controlled	Asia	3.8	NA	4.0	NA	4.0
Currie (2013)[180]	HR	Controlled	Oceania	39.3	NA	NA	NA	NA
Zaharan (2013)[320]	HR	Controlled	Europe	13.5	NA	NA	NA	5.0
Macedo (2014)[133]	HR	Propensity scores	Europe	21.4	NA	26.2	17.7	36.0
Bhattacharya (2014)[321]	OR	Controlled	North America	50.0	NA	NA	18.5	10.0
Cederberg (2014)[166]	HR	Controlled	Europe	NA	NA	NA	NA	12.0
Mansi (2015)[165]	OR	Propensity scores	North America	50.0	NA	35.4	6.2	0.0
Radford (2015)[322]	OR	Controlled	North America	14.3	NA	12.3	12	0.0

Olotu (2016)[323]	OR	Propensity scores	North America	50.0	NA	17.3	NA	NA
Rha (2016)[324]	OR	Propensity scores	Asia	21.0	NA	53.0	NA	13.0
15 studies (2004-2016)				23.7	141.8	30.0	18.0	11.0

*All OBSs included multiple statins
ASCVD = Atherosclerotic cardiovascular disease

Table 17. Results from meta-regression models among 23 randomized controlled trials and observational studies examining statin-associated type 2 diabetes risk

Characteristics	N	Relative risk (95% CI)	P-value
Study characteristics			
Study design	23		
Randomized controlled trials	8	Ref	
Observational studies	15	1.45 (1.11-1.88)	0.01*
Mean length of follow-up	23	0.99 (0.96-1.03)	0.71
Sample size	23	1 (0.99,1.00)	0.92
Year of publication	23	1.03 (1.00-1.06)	0.01*
Year of baseline	23	1.02(0.99-1.05)	0.10
Methods address confounders	23		
Randomization	8	Ref	
Controlled	10	1.40 (1.05-1.85)	0.03*
Propensity or unadjusted	5	1.53 (1.01-2.15)	0.02*
Type of effect estimate metric	23		
Hazard ratio	16	Ref	
Relative risk or odds ratio	7	1.12 (0.81-1.56)	0.48
Methods to measure and define T2D	23		
Physician report, medication use, lab results	6	Ref	
2 out of 3 methods	9	1.25 (0.88-1.79)	0.20
1 out of 3 methods or self-report	8	1.40 (0.97-2.01)	0.07

Participant characteristics			
Residence of participants	23		
Europe	9	Ref	
North America	7	1.30 (0.93-1.82)	0.12
Other	7	1.30 (0.92-1.83)	0.13
% Women	23	1.49 (0.81-2.76)	0.19
Mean age (10-year increase)	21	0.79 (0.63-0.98)	0.04*
% Caucasian	21	0.88 (0.59-1.32)	0.52
Proportion taking statins	22		
>30%	12	Ref	
<30%	10	1.03 (0.76-1.39)	0.85
Mean BMI (kg/m^2)	15	0.98 (0.90-1.07)	0.69
Mean LDL-C levels (10-mg/dl increase)	15	0.92 (0.87-0.97)	<0.01*
Mean plasma glucose levels (10-mg/dl increase)	12	0.98 (0.83-1.16)	0.80
Mean systolic blood pressure levels (10-mmHG increase)	9	1.00 (0.99-1.02)	0.37
% Hypertensive	15	0.68 (0.34-1.33)	0.23
% Current smokers	15	0.27 (0.11-0.68)	0.01*
% ASCVD	21	1.23 (0.54-2.78)	0.61

*P-value <0.05
FPG = Fasting plasma glucose
BMI = Body mass index
LDL-C = Low-density lipoprotein cholesterol
ASCVD = Atherosclerotic cardiovascular disease

Table 18. Results from meta-regression models among 15 observational studies examining statin-associated type 2 diabetes risk

Characteristics	N	Relative risk (95% CI)	P-value
Study characteristics			
Mean length of follow-up	15	0.98 (0.94, 1.02)	0.24
Sample size	15	0.99 (0.99-1)	0.56
Year of publication	15	1.05 (0.99-1.12)	0.12
Year of baseline	15	1.02 (0.99-1.06)	0.20
Type of effect estimate metric	15		
Hazard ratio	10	Ref	
Odds ratio	5	1.16 (0.76-1.76)	0.47
Methods to measure and define T2D	15		
Used 1 method (physician report, lab results, medication use)	6	Ref	
Used > 1 method	9	0.96 (0.64-1.43)	0.83
Use of FPG to define T2D	15		
Not used	11	Ref	
Used	4	0.95 (0.60-1.51)	0.83
Participant characteristics			
Residence of participants	15		
Europe	6	Ref	
Other	9	1.50 (1.11-2.04)	0.01*
% Women	15	1.12 (0.48-2.59)	0.78

Mean age (10-year increase)	13	0.71 (0.52-0.96)	0.03*
% Caucasian	13	0.75 (0.43-1.28)	0.26
Proportion taking statins	15		
>30%	5	Ref	
<30%	10	0.71 (0.50-1.10)	0.06
Mean BMI (kg/m^2)	7	0.84 (0.70-1.01)	0.06
Mean LDL-C levels (10-mg/dl increase)	7	0.78 (0.67-0.92)	0.01*
Mean glucose levels (10-mg/dl increase)	5	0.89 (0.27-2.95)	0.78
% Hypertensive	8	0.28 (0.07-1.04)	0.06
% Current smokers	7	0.31 (0.11-0.87)	0.03*
% ASCVD	13	0.85 (0.28-2.61)	0.76
Type of statin user			
Prevalent User	12	Ref	
New User	3	1.14 (0.70-1.82)	0.56

*P-value <0.05
BMI = Body mass index
LDL-C = Low-density lipoprotein cholesterol
FPG = Fasting plasma glucose
ASCVD = Atherosclerotic cardiovascular disease

Table 19. Results from meta-regression models among eight randomized controlled trials examining statin-associated type 2 diabetes risk

Characteristics	N	Relative risk (95% CI)	P-value
Study characteristics			
Mean length of follow-up	8	0.94 (0.87-1.00)	0.08
Sample size	8	1(0.99-1.00)	0.41
Year of publication	8	1(0.98-1.03)	0.91
Year of baseline	8	1(0.99-1.03)	0.43
Participant characteristics			
% Women	8	1.39 (0.74-2.61)	0.24
Mean age (10-year increase)	8	1.21 (0.99-1.48)	0.06
% Caucasian	8	1.05 (0.73-1.51)	0.76
Mean BMI (kg/m^2)	8	1.03 (0.96-1.10)	0.34
Mean LDL-C levels (10-mg/dl increase)	8	0.96 (0.92-1.00)	0.10
Mean glucose levels (10-mg/dl increase)	7	1.02 (0.90-1.16)	0.70
Mean systolic blood pressure levels (10-mmHG increase)	8	1.00 (0.99-1.02)	0.39
% Hypertensive	7	1.30 (0.89-1.89)	0.14
% Current smokers	8	0.48 (0.12-2.03)	0.26
% ASCVD	8	1.66 (0.75-3.65)	0.17

BMI = Body mass index
LDL-C = Low-density lipoprotein cholesterol
ASCVD = Atherosclerotic cardiovascular disease

CHAPTER 6. PROJECTIONS OF ATHEROSCLEROTIC CARDIOVASCULAR DISEASE AND TYPE 2 DIABETES ACROSS STATIN TREATMENT RECOMMENDATIONS

A. Introduction

Methyl-glutaryl-Coenzyme A reductase inhibitors, commonly known as statins, are the most widely prescribed class of medication used to prevent atherosclerotic cardiovascular disease (ASCVD).[1, 2] Numerous meta-analyses have demonstrated that statins decrease ASCVD incidence by approximately 20% for every 38 mg/dL reduction low-density lipoprotein cholesterol (LDL-C) and this protective effect extends to populations at low ASCVD risk.[3, 4] In 2013, the American College of Cardiology/American Heart Association (ACC/AHA) cholesterol treatment recommendations were changed from a 10% 10-year coronary heart disease (CHD) risk to a 7.5% 10-year ASCVD (CHD and stroke) risk. As a result, an estimated 10.4 million adults were newly eligible for statin treatment, with females[5] and adults 60-75 years of age[6] experiencing the greatest increases. Other recommendations proposed even more aggressive treatment thresholds, for example a 5% 10-year ASCVD risk threshold or initiating statin treatment in populations ≥55 years of age regardless of risk factor profile,[7] whereas others proposed increasing the 10-year ASCVD risk threshold to 10%.[6, 8, 9]

While the cardioprotective effect of statins are well-established,[4, 10]experimental and observational research has suggested the potential for adverse drug effects, including type 2 diabetes (T2D), a side effect of particular interest because of its associated adverse health outcomes and impact on patient quality of life.[11-15] Accumulating evidence has suggested that statins increase the relative risk (RR) of T2D by 5-55%[12-17], with potentially elevated risks in younger populations compared to older populations and populations with lower LDL-C compared to populations with higher LDL-C. Such findings merit further investigation in light of evolving statin recommendations that target growing proportions of primary prevention populations, for whom the risk-benefit profile of statins remains

incompletely quantified.[18] Specifically, few studies have directly compared the number of statin-associated ASCVD events prevented alongside the number of T2D events incurred across proposed statin recommendations. Therefore, this study projected the number of expected ASCVD events prevented and incident cases of T2D incurred in primary prevention populations across four proposed 10-year ASCVD risk statin treatment recommendations.[5, 6, 8, 19]

B. Methods

B.1. Motivation for Simulation Model

This study employed a simulation model to examine intended and unintended consequences of statin treatment through synthesis of high quality observational and experimental data. A simulation model was needed because few available studies (1) were contemporary, (2) spanned ages specified by current recommendations, (3) included high quality statin adherence measures, and (4) precisely and validly measured ASCVD and T2D incidence within generalizable male and female multi-ethnic populations with adequate follow-up.[20]

B.2. Data Sources and Inputs

The first step in constructing a simulation model is to collect and estimate data inputs. In an attempt to maximize generalizability, we prioritized studies that included multi-ethnic (non-Hispanic African American and non-Hispanic Caucasian; capturing 85% of the U.S. population[21]), male and female statin-eligible adults aged 40-75 years, reflecting the ages specified by primary prevention recommendations.[5]

Demographic characteristics, 10-year ASCVD risk, and population eligibility were estimated using the National Health and Nutrition Examination Survey (NHANES, waves 2007-2014), pooling four waves to ensure sufficient precision of data inputs. NHANES conducts biennial cross-sectional surveys and physical examinations that measures demographic, nutritional, and health status information on nationally representative, independent probability samples of the non-institutionalized US civilian population[22] (see **Supplement**). We defined the primary prevention population as 40-75 year old males and females of self-reported non-Hispanic African American or Caucasian race/ethnicity who did not

report a doctor or health professional diagnosis of ASCVD, T2D, or type 1 diabetes, who reported never taking cholesterol medications (measured by self-report and medication inventory), and who had measured fasting LDL-C levels ≤ 190mg/dl. Race/ethnic-, sex-, -and anti-hypertensive therapy- specific predicted 10-year ASCVD risk for each participant of the primary prevention population were then calculated using the Pooled Cohort Equation (**Supplement**, **Supplemental Table 23**).[23]

ASCVD and T2D incidence rates were estimated using the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study (2003-2015), a national, population-based, longitudinal cohort study designed to evaluate factors underlying the excess stroke burden in the southeastern US and among African Americans versus Caucasians (see **Supplement**).[24] Incident CHD was defined based on medical records, signs and symptoms, diagnostic cardiac enzymes, or ECG changes consistent with ischemia CHD (**Table 20**). Incident stroke was centrally adjudicated by physicians using the World Health Organization definition or by review of final reports from all available neuroimaging studies consistent with acute ischemia.[25, 26] T2D incidence was ascertained at visit 2 and classified using investigator-defined criteria (T2D if fasting glucose ≥126 mg/dl, non-fasting glucose >200 mg/dl or use of T2D medication) (**Table 20**).

Non-ASCVD mortality was obtained data from the National Center for Health Statistics (NCHS),[27] which compiles death certificates filed in all 50 states and the District of Columbia. Non-ASCVD deaths/year were defined excluding cardiovascular (International Statistical classification of Disease, 10th Edition codes [ICD-10]: I00-I09, I11, I13, I20-I51) and cerebrovascular deaths (ICD-10: I60-I69).

Statin-associated ASCVD RRs were obtained from the Cholesterol Treatment Trialists' meta-analysis of 22 trials (statin treatment versus control), from which we abstracted separate RRs for males (0.64) and females (0.84) given statistically significant evidence of heterogeneity by sex.[4] Statin-T2D RRs were obtained from a recent meta-analysis of randomized controlled trials and observational studies: 1.11 (randomized controlled trials [RCTs]), 1.32 (RCT and observational study pooled), and 1.55 (observational studies).[17] Because of evidence of heterogeneity found by study design, we included all

three statin-T2D RRs. In the absence of consistent meta-analysis evidence for the association between statins and non-ASCVD mortality[28], the RR was set to 1.0.

B.3. Model Overview

We contrasted statin-associated ASCVD and T2D incidence associated with four statin treatment recommendations (see below) using state-transition Markov simulation models.[29] For each one-year model cycle, statin-eligible population could either remain alive and non-diseased or transition to having T2D, an ASCVD event, or a non-ASCVD death. The disease and non-ASCVD mortality states were absorbing, i.e. the part of the cohort entering these states was no longer simulated (see example in **Figure 20**).[29] The one-year cycle was repeated 10 times for each age- (one-year) and sex-specific group and for each intervention scenario assessed to project statin-associated 10-year ASCVD and T2D incidence.

Assignment of statin treatment was made at study baseline (i.e. before initiating the first cycle) using predicted 10-year ASCVD risks estimated by the Pooled Cohort Equation. We assigned statin treatment if the predicted 10-year ASCVD risk equaled or exceeded the following four previously proposed treatment recommendations:

- *≥ 10%*[19]
- *≥ 7.5%*[5]
- *≥ 5%*[6]
- *≥ 7.5% or ≥55 years of age*[8]

Statin adherence among statin-eligible adults was informed by past studies.[30] Briefly, full implementation of statin treatment recommendations and 100% statin adherence were assumed at year 0, after which we assumed a 20% absolute annual decrease through year four (**Supplemental Figure 24)**. At year four, we assumed 20% of adults would continue taking statins through year 10.

We then examined a fifth scenario whereby no participants received statin treatment, which served as our reference group (**Supplement**).

Using these scenarios, we calculated the absolute benefit of statin treatment as the number needed to treat (NNT) to prevent one ASCVD event (1/ [statin-associated ASCVD risk difference]), with smaller values indicating a more favorable outcome; hereafter NNT will be referred to as number needed to benefit (NNB). Absolute harm of statin treatment was calculated as the number needed to harm (NNH/ 1/statin-association T2D risk difference) to cause one excess incident case of T2D, with larger values indicating a more favorable outcome.[31] In addition, we estimated the likelihood to be helped or harmed (LHH), defined as the ratio of the NNH to NNB, with larger values indicating a more favorable outcome and values < 1 indicating when the number of incident cases of T2D incurred exceeds the number of ASCVD events prevented.[32] Statistical analyses were performed using STATA (College Station, TX), TreeAge Healthcare Pro Suite 2018 (TreeAge Software, Williamstown, MA), and SAS (Cary, NC).[33]

B.4. Sensitivity Analyses

To evaluate possible sources of heterogeneity, we assessed the expected benefits and harms incurred by sex and age.[19, 34] We also projected the expected number of ASCVD events prevented and expected number of excess incident case of T2D incurred under three annual relative decrease in statin use of 25% and 50%, as well as full adherence (i.e. 0% decrease) across 10 years.[30]

C. Results

When weighted to the 2014 U.S. population, a total of 61,125,042 adults without evidence of prior statin treatment, ASCVD, or T2D composed our primary prevention population. Among the initial population, a majority were female (58.5%) and Caucasian (89.4%) (**Table 21**). The proportion of the population eligible for statin treatment ranged from 21.8% (≥10% ASCVD risk threshold) to 53.2% (≥7.5% ASCVD risk threshold or 55 years of age), representing a difference of 19,218,259 adults (31.4% absolute increase). Adults eligible for statin treatment based on the ≥10% ASCVD risk threshold recommendation had the highest mean age (mean=65.4 years) and lowest levels of total cholesterol (mean=204 mg/dL) when compared to the other three statin treatment recommendations. In contrast, adults with a 10-year ASCVD risk ≥7.5 or who were ≥ 55 years of age were on average younger (mean=62.1 years) and had higher levels of total cholesterol (mean=207 mg/dL); this treatment

recommendation also was the only recommendation for which a majority of the eligible population was female (55%).

Direct associations between the proportion of adults eligible for statin therapy and the number of ASCVD events prevented were observed (**Figure 21**). For example, the ≥10% ASCVD risk threshold recommendation (21.8% of adults eligible for therapy) was projected to prevent the fewest number of ASCVD events (N=103,009) over 10 years (**Figure 21, panel A**). In contrast, the ≥7.5% ASCVD risk threshold or 55 years of age recommendation (53.2% of adults eligible for therapy) was projected to prevent the largest number of ASCVD events over 10 years (N=181,039; N=78,030 additional ASCVD events prevented when compared to the ≥10% ASCVD risk threshold recommendation). These projections corresponded to 10-year NNBs of 155 and 216, respectively (**Figure 25, panel A**) and did not differ by statin-associated T2D risk (**Figure 21, panels A-C**).

The ≥10% ASCVD risk threshold and the ≥7.5% ASCVD risk threshold or 55 years of age recommendations also were associated with the fewest (N=35,990) and greatest (N=86,090) number of incident cases of T2D incurred over 10 years, respectively, when assuming a statin-associated T2D risk of 1.11 (**Figure 21, panel A**). These projections corresponded to 10-year NNHs of 453 (LHH=2.90) and 444 (LHH = 2.10), respectively, indicating that for all statin treatment recommendations, the number of ASCVD events prevented was at least twice as large as the number of incident cases of T2D incurred (**Figure 21, panel D, Supplemental Figure 2, panel A**). However, variability in the assigned statin-associated T2D RR changed this observation. As an example, when the statin-associated T2D RR was increased to 1.32, NNHs strengthened to 199-202 (LLH range: 0.95-1.30) across the four statin treatment recommendations (**Figure 21, panel E**). When the statin-associated T2D RR was increased to 1.55, the number of incident cases of T2D incurred exceeded the number of ASCVD events prevented across all four recommendations (LLH range: 0.66-0.94; **Figure 21, panel F**), indicating that for every 100 ASCVD events prevented, 106-152 incident cases of T2D were incurred. Sensitivity analyses that varied adherence of statin treatment over 10 years from 25% to 100% resulted in proportional decreases in the

number of ASCVD events prevented and incident cases of T2D incurred (**Figure 27**), although the LLH remained relatively unchanged.

We also observed evidence of heterogeneity in the number of ASCVD events prevented and incident cases of T2D incurred for the four statin treatment recommendations by sex. Specifically, when assuming a statin-associated T2D RR of 1.11, females received lower absolute benefits of statin treatment and incurred a higher relative burden of adverse events across the four treatment recommendations (NNB range: 196-281; LHH range: 1.50-2.40) when compared to males (NNB range: 110-131; LHH range: 2.50-3.00) (**Figure 22, panels A and D**). The higher relative burden of adverse events among females became even more pronounced when assuming higher statin-associated T2D RRs. For example, among females, when the statin-associated T2D RR was increased to 1.32, the number of incident cases of T2D incurred exceeded the number of ASCVD events (NNB range: 190-272) prevented for three of the four statin treatment recommendations (LHH range: 0.7-1.11). However, for males, the number of ASCVD events prevented (NNB range: 107-128) always exceeded the number of incident cases of T2D incurred (LHH range: 1.2-1.4) when assuming a statin-associated T2D RR of 1.32 (**Figure 22, panels B and E**).

The absolute and relative benefits of statin treatment also differed age. For instance, when assuming a statin-associated T2D RR of 1.11, adults aged 40-50 received the lowest absolute benefits of statin treatment (NNB range across statin treatment recommendations: 322-378) and incurred the highest relative burden of adverse events. Specifically, for every incident cases of T2D incurred, 1-1.14 ASCVD events were prevented (**Figure 23, panel A**). However, the relative benefit of statin treatment was reversed when higher statin-associated T2D RRs were assumed. For example, when assuming a statin-associated T2D RR of 1.32, every one ASCVD event prevented also incurred 2.04-2.32 incident cases of T2D (**Figure 23, panel E**). In contrast, statin treatment in adults aged 70-75 years was projected to confer absolute benefits (NNB range: 106-107) that were approximately three times as high as the absolute benefits conferred in adults aged 40-50 years. Adults aged 70-75 also incurred the lowest relative burden of adverse events (LHH range: 3.95-3.96) that differed little across statin treatment recommendations (**Figure 23, panel D**). Further, the number of ASCVD events prevented always exceeded the number of

incident cases of T2D incurred among adults aged 70-75 years, regardless of assumed statin associated T2D RR (**Figure 23, panels D, H, L**).

D. Discussion

In this simulation study, we compared the number of ASCVD events prevented and incident cases of T2D incurred across four recently proposed statin treatment recommendations in a contemporary, biracial adult primary prevention population. Overall, we projected that between 13 and 32 million adults would be newly eligible for statin treatment, among whom one ASCVD event would be prevented for every 155-216 adults treated. Projecting the absolute harm of statin treatment was more complex; considerable variability in statin-associated T2D risk was identified, with the highest relative burden of T2D occurring in female and younger adult populations. Further efforts quantifying statin-associated benefits and harms is needed to more precisely characterize populations for whom expansion of statin treatment is warranted, as well as populations for whom statin treatment may introduce a large burden of adverse events.

One major challenge for research comparing harms and benefits of interventions is comparing intended and unintended events that may not be equivalent. We realize the broad clinical spectrum of an ASCVD event (small myocardial infarction diagnosed by biomarker to sudden death) and a new diagnosis of T2D (slightly elevated hemoglobin A1c managed by lifestyle change to diabetes requiring multiple medications, including injectables, and blood frequent blood glucose monitoring) would have different implications for patients. That said, as the goal of statin therapy is to prevent ASCVD events, and T2D is a common, persistent, and clinically important harm associated with statin therapy, this contrast remains a relevant comparison. Particularly of interest are scenarios where the number of incident cases of T2D incurred were greater than, sometimes by five to ten orders of magnitude, the number of ASCVD events prevented.[18] Thus the implications of elevated statin-associated T2D risk remains a critically important, yet unanswered question. One way forward may be to incorporate patient preferences when comparing statin-associated benefits and harms.[35] For example, patients from Ethiopia and Switzerland weighted

ASCVD events as most important outcomes associated with statins;[36] however, quantifying patient preferences, especially among populations that may be at high risk for adverse effects is still warranted as more information on the statin-associated harms become available.

Statin-associated T2D risk was the most influential model input when projecting statin-associated harm as well as the model input with the least consistent evidence base. Inconsistency in the underlying evidence base stems from our decision to include estimates of statin-associated T2D risk from both RCTs and observational studies. Although the majority of published studies examining statin harms and benefits have leveraged statin-associated T2D RRs from RCTs,[18] RCTs may underestimate adverse drug effects through under-reporting of harms and limited follow-up time.[37] Selective RCT inclusion criteria also may make RCT populations less prone to developing adverse drug effects, including T2D, than community-based populations.[38] On the other hand, observational studies may be more prone to confounding.[39] These two sources of data provided a wide-range of statin-associated T2D RRs (1.11-1.55), changing projections of relative benefit by as much as two fold. One way forward may be to prioritize future research in populations for which estimates of statin-associated T2D RR were most influential, e.g. females and younger adult populations.

Our projections also suggested that females and younger adults incurred lower relative benefits compared to males and older adults. Understanding the risk-benefit profile of statin treatment in younger and female populations is important, given that the majority of the statin-eligible primary prevention population was female and 26% were younger than 50 years of age. Heterogeneity by sex may reflect several factors, including the assigned statin-associated ASCVD RR, which assumes a more protective effect in males (RR=0.64) than females (RR=0.84). The statin-associated RRs, combined with absolute risks of T2D and statin-associated T2D risk that did not differ by sex, contributed to a higher relative burden of T2D in females. Yet, existing evidence suggests that we may be underestimating disparities in statin-associated benefits and harms by sex. For instance, an increased statin-associated T2D risk in females has been found among observational studies and emerging results from past meta-analysis.[17, 40] However, females have been historically underrepresented in RCTs and past studies did not consistently

report results by sex.[4, 41] Quantifying statin-associated T2D RR among meta-analyses including individual-patient data merit further investigation to better characterize statin-associated harms.

In addition, the youngest age groups, who on average had the lowest ASCVD risk[42], did not experience the same statin-associated benefits as the oldest age groups. Examining when statin benefits may outweigh potential harms becomes important, as statin initiation in younger ages may be associated with potentially decades of statin treatment despite mixed evidence of long-term effectiveness. For example, the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm found a significant reduction in ASCVD associated with statins approximately two years post follow-up (HR =0.64 [95% CI: 0.53-0.78]), but not 11 years post follow up (HR =0.89 [95% CI: 0.72-1.11]).[43, 44] In addition, information on post-trial statin use among those initially randomized to statins or placebo was not always known, further suggesting the association between long-term, persistent use of statins and adverse events remains poorly quantified.[43, 45]

Despite many strengths, there are limitations that merit consideration. First, we were unable to examine additional statin associated adverse events, including rhabdomyolysis (breakdown of muscle tissue).[46-48] Although rare, the annual incidence of statin-associated rhabdomyolysis is approximately 0.0042% (potentially impacting 546-1,344 adults who were newly-eligible for treatment in our study),[46] thereby resulting in a very modest underestimate of statin-associated harm. Similarly, we did not consider additional potential benefits of statin treatment, including studies reporting a decreased risk of breast cancer recurrence among females treated with statins. This decision reflected our prioritization of ASCVD for which the evidence base was the strongest, although future simulations may consider breast cancer recurrent and other potential benefits as evidence accumulates.[49-51] Third, our assumptions about statin users may have overestimated the number of statin-associated events. We assumed that adults who would become statin-eligible would initiate statin use; however, current statin recommendations recommend an informed risk-benefit discussion between the patient and physician before the initiation of statin therapy.[5] Fourth, we limited our study to as the age range specified by statin recommendations (~40% of the U.S. population), although the Pooled Cohort Equations has been used among adults >75

years of age to guide statin recommendation; however, that segment of the population is where statin-associated benefits and harms are unclear.[43, 52] Fifth, although we were not able to take into account drop out between REGARDS visits 1 and 2, if we assume that 24% of T2D cases are undiagnosed, then our incident rate would be comparable to our estimated incidence rate.[53] In addition, due to insufficient sample sizes, we were not able to examine further stratification of statin benefits and harms by race/ethnicity.

In conclusion, this simulation study adds to a growing body of literature of projected statin-associated effects. Findings highlight the highest relative burden of T2D occurred among female and younger adult populations, with disparities continuing to widen as statin-associated T2D RR increased. Taken together, these results help to inform the absolute and relative benefits and harms associated with statins treatment recommendations and underscore the need for more research on quantifying statin-associated harms.

E. Tables and Figures

Table 20. Model input parameters stratified by 5-year age groups and sex

Population Parameters	Males (95% CI)	Females (95% CI)
ASCVD		
ASCVD annual incidence rate/10,000 person-years*		
40-45**	50 (30-70)	20 (10-30)
46-50	50 (30-70)	20 (10-30)
51-55	70 (50-90)	30 (20-40)
56-60	60 (50-70)	40 (10-70)
61-65	110 (90-130)	10 (50-80)
66-70	150 (130-170)	100 (70-130)
71-75	200 (160-240)	130 (110-150)
Statin-ASCVD relative risk	0.650	0.740
T2D		
T2D annual incidence rate/ 10,000 person-years*		
40-45**	160 (120-220)	140 (100-180)
46-50	150 (120-190)	180 (120-180)
51-55	170 (140-190)	160 (100-180)
56-60	160 (130-190)	140 (100-180)
61-65	130 (100-150)	150 (120-180)
66-70	140 (110-170)	130 (110-170)
71-75	120 (90-150)	110 (80-140)
Statin-T2D relative risk	1.11-1.55	1.11-1.55
Non-ASCVD mortality		
Non-ASCVD mortality rate/10,000 person-years***		
40-45	20 (16-24)	10 (8-12)
46-50	30 (24-36)	20 (16-24)
51-55	50 (40-60)	30 (24-36)
56-60	60 (50-70)	40 (32-48)
61-65	80 (70-90)	50 (40-60)
66-70	100 (90-110)	70 (60-80)
71-75	160 (140-180)	120 (100-140)
Statin-Non-ASCVD mortality relative risk	1.0	1.0

ASCVD = Atherosclerotic cardiovascular disease
*Estimated from REGARDS[218]
**45-50 year age group IRs were assigned given REGARDS participants ≥45 years in age.
***Estimated from NCHS[290]

Table 21. Comparison of demographic and cardiovascular risk profiles for U.S. Caucasian and African American primary prevention populations aged 40-75 years overall and according to four previously proposed statin treatment recommendations

		Statin treatment recommendation			
Characteristic*	Primary prevention population**	10-year ASCVD risk≥10%	10-year ASCVD risk ≥7.5%	10-year ASCVD risk ≥5.0%	10-year ASCVD risk ≥7.5% or ≥55 years old
N	61,125,042	13,325,617	18,613,696	27,850,426	32,543,876
Female (%)	58.5%	35.0	37.2	41.4	55.0
Caucasian (%)	89.4%	86.2	86.1	87.4	89.7
Age (mean)	54.7	65.4	63.6	61.4	62.1
Mean high-density lipoprotein (mg/dL)	55	51	52	51	55
Mean total cholesterol (mg/dL)	204	204	205	207	207
Mean systolic blood pressure (mmHg)	122	134	133	129	127
On hypertension treatment (%)	34.2	59.8	55.9	50.1	45.3
Current smokers (%)	20.6	29.1	28.6	27.7	20.2

ASCVD = Atherosclerotic cardiovascular disease

*Weighted means and proportions

**After excluding prevalent statin users and adults with self-reported ASCVD and T2D and upweighting to the 2014 U.S. population

Figure 20. Statin treatment recommendation model among females 40 years old through one-year. Rectangles correspond to disease states and arrows represent the allowed transitions. T2D: type 2 diabetes; ASCVD: atherosclerotic cardiovascular disease.

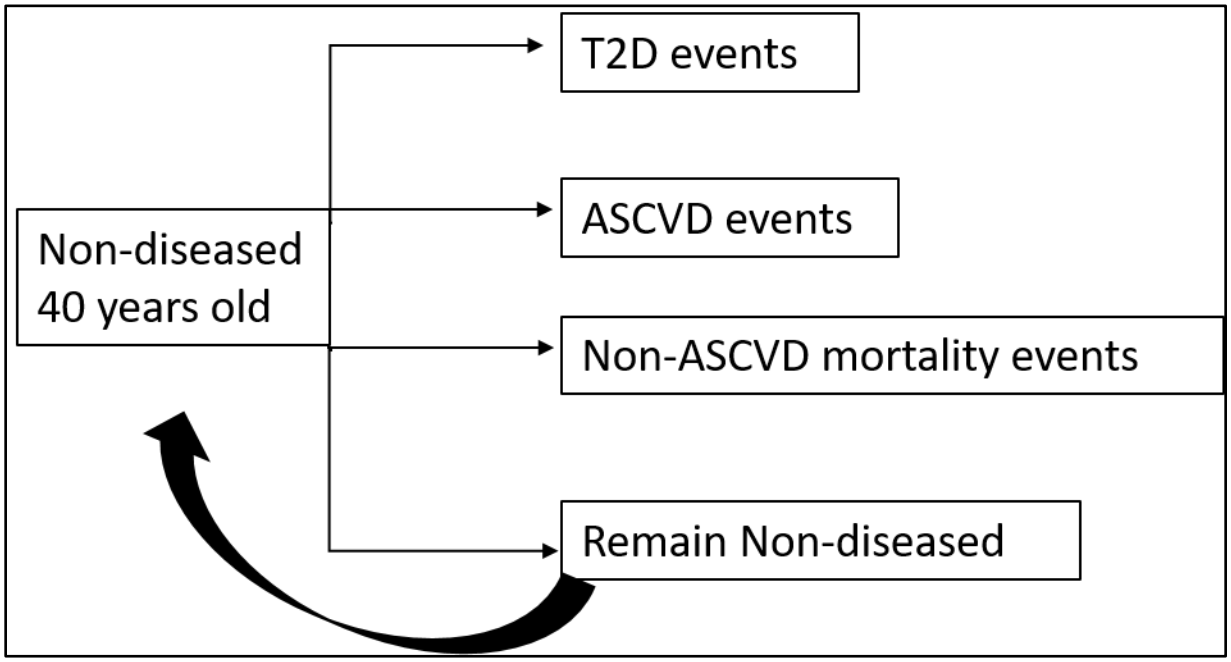


Figure 21. Cumulative number of events of atherosclerotic cardiovascular disease (ASCVD) and type 2 diabetes (T2D) (Panels A-C) and likelihood to be helped or harmed (number needed to harm/number needed to benefit; Panels D-F) associated with four statin treatment.

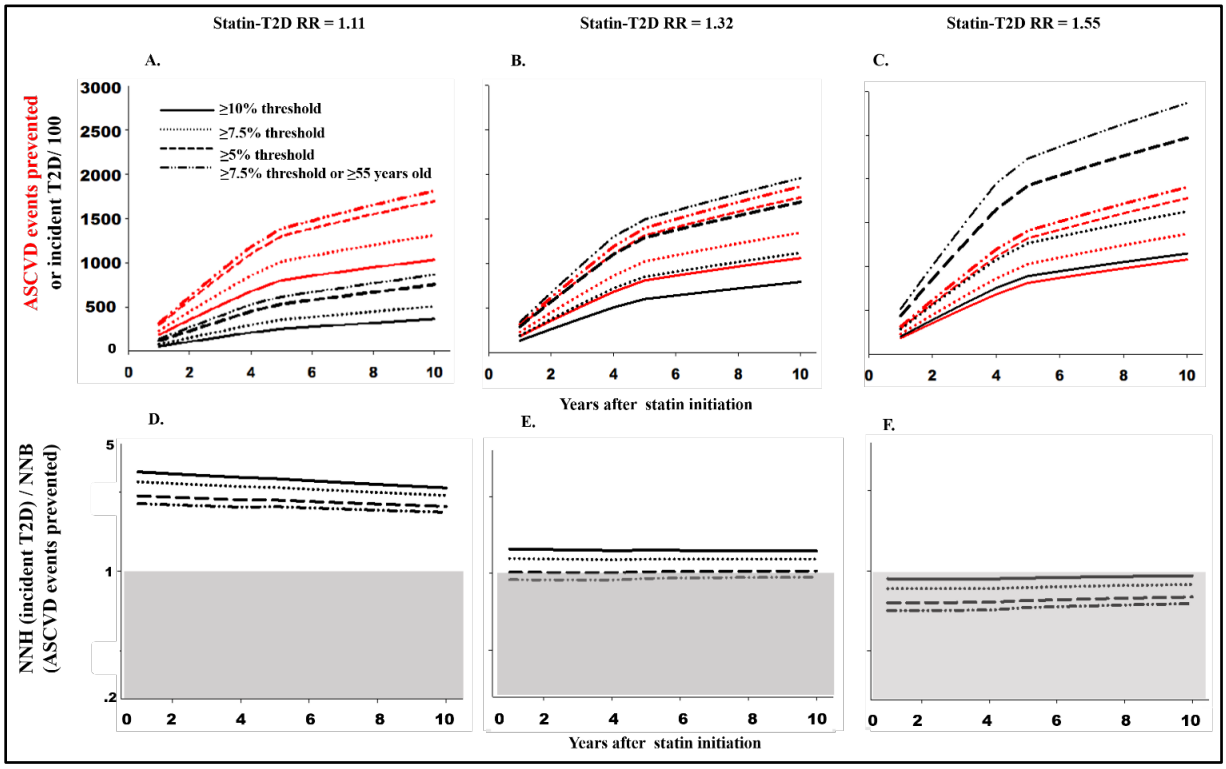


Figure 22. Likelihood to be helped or harmed (number needed to harm/number needed to treat; among females (Panels A-C) and males (Panels D-F) associated with four statin treatment recommendations among eligible African Americans and Caucasians in the US in 2014 from a sample of 61,125,042.

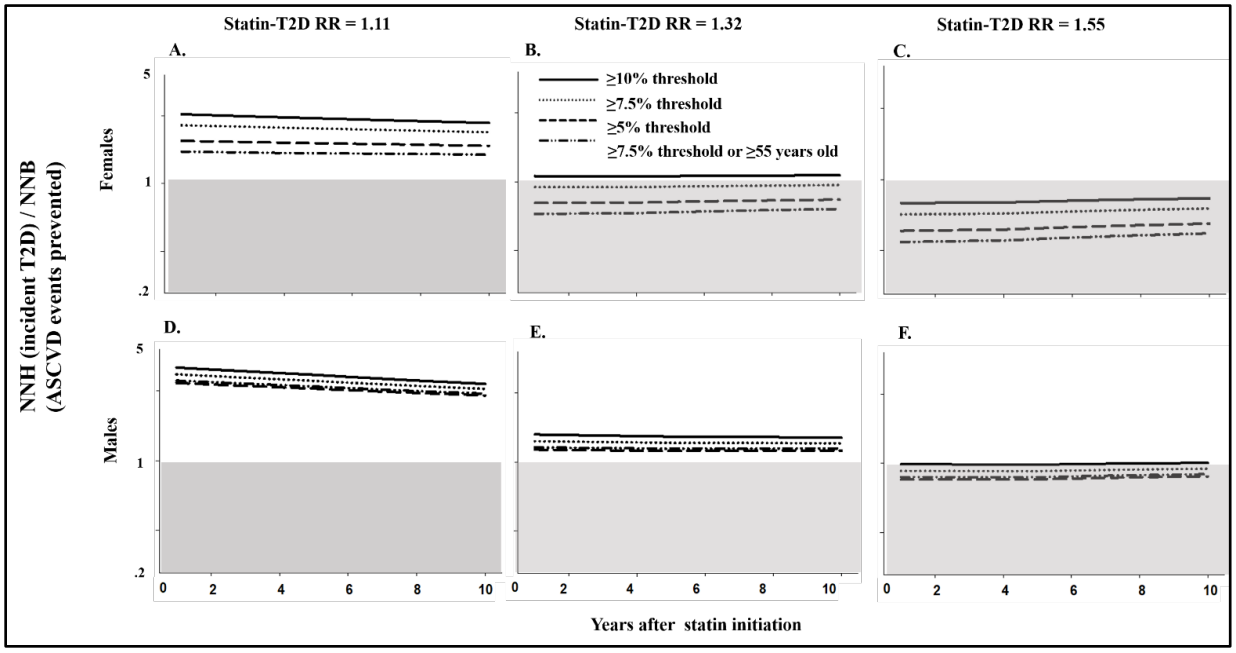
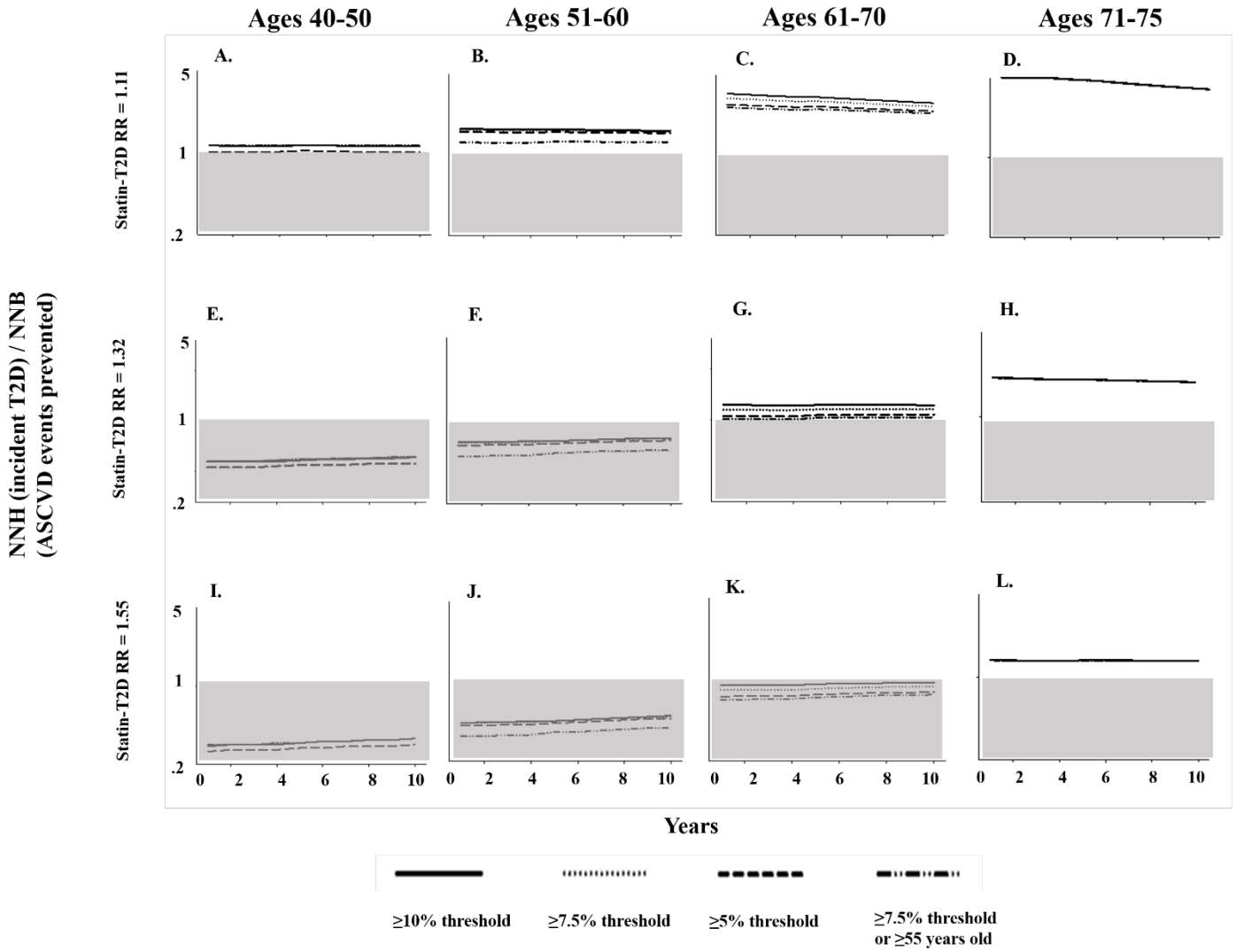


Figure 23. Likelihood to be helped or harmed (number needed to harm/number needed to treat) associated with four statin treatment recommendations among 40-50 (Panels A, E, I) 51-60 (Panels B, F, J) 61-70 (Panels C,G, K) 71-75 (Panels D, H, L) baseline age groups associated with four statin treatment recommendations among eligible African Americans and Caucasians in the US in 2014.



F. Supplemental Material

F.1. Supplemental Methods

We leveraged multi-ethnic (African American and Caucasian) and sex-specific data from the National Health and Nutrition Examination Survey (NHANES) and the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study as well as statin associated relative risks (RRs) from past meta-analyses to assess changes in type 2 diabetes (T2D) and atherosclerotic cardiovascular disease (ASCVD) incidence from changes in 10-year ASCVD risk thresholds.

F.1.1. Data Sources and Inputs

The project was conducted by assembling and integrating contemporary and validated data from NHANES, REGARDS, and past meta-analyses into a Markov model.

F.1.2. NHANES

Data from NHANES were used to construct the initial statin-eligible population (population size and baseline characteristics). NHANES is a series of cross-sectional surveys and physical examinations conducted biennially to assess the health and nutritional status of the U.S. population.[286] NHANES collects demographic, nutritional, and health status information on a nationally representative probability sample of the U.S. civilian population (aged 0-80+ years) instituted by the National Center for Health Statistics (NCHS). Participants are randomly selected through a complex, multistage cluster sampling probability design. Young children, older adults, African Americans, and Mexican Americans are oversampled at each survey to provide sufficient numbers to support analysis in these underrepresented populations. All analyses used sample weights to produce estimates generalizable to the original sampling frame[288] For this study, we used data from three recent NHANES population cross-sections, conducted in 2007-2014.

<u>Exclusion criteria</u>

NHANES participants self-reporting myocardial infarction/coronary heart disease (MI/CHD), angina, stroke (all types), participants classified as having T2D, participants with triglyceride levels >400 mg/dl, participants with LDL-C levels ≥190 mg/dl, and participants with ASCVD risk scores unable to be

calculated (i.e. missing data) were excluded from the study. Additionally, only African American and Caucasian populations between the ages of 40-75 years were considered in the analysis to overlap with ages eligible for statin treatment under the ACC/AHA treatment recommendations.

F.1.3. REGARDS

Data from REGARDS were used to estimate ASCVD and T2D incidence and statin discontinuation. REGARDS is a national, population-based, longitudinal study designed to evaluate factors underlying the excess stroke burden in the southeastern US and among African Americans.[218] Potentially eligible REGARDS participants were identified from commercially available nationwide lists of U.S. residents with a recruitment goal of including 30% of participants from the "Stroke Belt" (North Carolina, South Carolina, Georgia, Tennessee, Mississippi, Alabama, Louisiana, and Arkansas). Eligible participants were sent an initial mailing, followed by a telephone call and a subsequent in-home visit. Between January 2003 and October 2007, REGARDS enrolled 30,239 non-institutionalized African-American and Caucasian adults aged ≥45 years. The second in-home visit took place from May 2013 to Dec 2016.

Exclusion criteria

REGARDS participants self-reporting MI/CHD, angina, or stroke (all types), participants classified as having T2D, participants with triglycerides >400 mg/dl, or participants with LDL-C ≥190 mg/dl were excluded from the analyses. Only participants between the ages 45-75 years were considered in the analysis to overlap with ages eligible for statin treatment under the ACC/AHA treatment recommendations (minimum age for REGARDS is 45 years). Since ASCVD incidence is low in populations <45 years of age, we assigned the ASCVD incidence from the 45-50 year old age-group and assessed different specifications via meta-analyses.

F.1.4. Data Inputs

F.1.4.1. Data from NHANES

Data from NHANES were used to obtain baseline characteristics of the study population, prevalence and 10-year risk of ASCVD, prevalence of T2D, and prevalence of current use of statins.

Questionnaires were used to assess prevalence of ASCVD, demographic information, smoking status, and blood pressure treatment; mean of final two of three blood pressure measurements from the medical examination were used to assess systolic blood pressure; fasting blood samples were used for lipid analyses to measure total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and triglycerides; and low-density lipoprotein cholesterol (LDL-C) levels were calculated using the Friedewald equation.[289] The prevalence of T2D was assessed by participant-report of a doctor or health professional diagnosis of T2D (yes/no) or report of T2D medication use. The prevalence of current use of statins was defined by self-report of ever taking cholesterol medications.

F.1.4.2. Data from REGARDS

Incident and prevalent ASCVD and T2D were estimated to inform ASCVD and T2D parameters and were ascertained from the REGARDS study by participant report and adjudicated by physicians.

MI/CHD

Self-reported MI/CHD prevalence was ascertained using the following questions: (1) "Has a doctor or any other health professional ever told you that you had a myocardial infarction or heart attack?" (2) "Have you ever had a coronary artery bypass surgery, such as a graft, CABG, or a bypass procedure on the arteries of your heart?" and (3) "Have you ever had an angioplasty or stenting of a coronary artery with or without placing a coil in the artery to keep it open?" All questions were scored "yes", "no", "don't know", and "refused".[218] MI/CHD was defined as a yes response to any one of those three questions.

Incident MI/CHD events were ascertained during follow-up. Participants were contacted by telephone every six months to assess hospitalizations, emergency department visits, overnight stays in nursing homes or rehabilitation centers, or death. If suspected heart event was reported, medical records were pursued. MI/CHD were adjudicated based on the presence of signs or symptoms suggestive of ischemic; diagnostic cardiac enzymes (rising or falling pattern in cardiac troponin or creatinine phosphokinase-MB isoenzyme concentrations over ≥ six hours with a peak concentration greater than twice the upper limit of normal); and ECG changes consistent with ischemia or MI/CHD.[287] In the case

where a participant died outside the hospital, interviews with family members or other proxies, proximal hospitalizations, baseline medical history, death certificates, and the National Death Index were used to identify MI/CHD as the underlying cause of death.

Stroke

Prevalent stroke was defined as a positive response to either "Were you ever told by a physician that you had a stroke?" or "Were you ever told by a physician you had a mini-stroke or TIA, also known as a transient ischemic attack?".[218]

Similar to the ascertainment of incident MI/CHD, incident stroke was determined during follow-up. Participants were contacted by telephone every six months to assess vital status, identify hospitalizations, emergency department visits, overnight stays in nursing homes or rehabilitation centers, or death during the previous six months. Reasons for medical encounters were asked and medical records were sought for stroke, TIA, death, unknown reason for hospitalization, or if reason was brain aneruysm, brain hemorrhage, sudden weakness, numbness, trouble speaking, sudden loss of vision, headache, other stroke symptoms.[218] Reports of possible incident stroke events were reviewed by a stroke nurse and then reviewed by at least two physician members of a panel of stroke experts in accordance with the World Health Organization definition.[226] For proxy reported deaths, interview was conducted with next of kin.

T2D

T2D was ascertained during the first in-home visit (to ascertain prevalent T2D) and second in-home visit (to ascertain incident T2D) using REGARDS investigator defined outcomes (T2D if fasting glucose ≥126 mg/dl, non-fasting glucose >200 mg/dl or taking T2D medication).[218]

F.1.5. Statin Eligibility Using Pooled Cohort Risk Equations

To identify statin-eligible populations from NHANES, 10-year ASCVD risk scores were estimated among the primary prevention population to determine statin treatment assignment.

Using NHANES data, the predicted 10-year risk for ASCVD was calculated using the Pooled Cohort risk equations, developed by the ACC/AHA Task Force on Practice Recommendations.[292] Separate equations were developed for African American and Caucasian men and women, which included

the following variables in the equations: age (years), concentration of TC (mg/dl) and HDL-C (mg/dl), treated or untreated systolic blood pressure (mmHg), DM status (yes/no), and self-reported current smoking status (yes/no). First, the natural log of age, TC, HDL-C, and systolic blood pressure were calculated with systolic blood pressure being either a treated or untreated value. Next, we multiplied these values by the coefficients from the estimated equation parameters of the Pooled Cohort Equations for the specific race-sex group of the population. The sum of the products of the previous calculations were then calculated for the population. Finally, we estimated the 10-year risk of ASCVD event as

$$Predicted\ ASCVD\ Risk = \ 1 - S_0(t)^{e^{Ind\ X'B - Mean\ X'B}}$$

The ASCVD risk was then calculated as 1 minus the survival rate at 10 years (Appendix 1), raised to the power of the exponent of the coefficient*value sum minus the race and sex specific overall mean coefficient*value sum.[293] Each participant was assigned a probability of statin treatment, which was used to determine which participant was statin-eligible according to one of the four 10-year ASCVD risk thresholds we evaluated.

F.1.6. Projection of ASCVD and T2D Incidence and Non-ASCVD Mortality

Next, we calculated annual age- and sex-specific ASCVD, T2D, and non-ASCVD mortality transition probabilities by statin treatment. The transition probabilities were then used to project the expected number of incident ASCVD events, incident T2D, and number of non-ASCVD deaths annually in Markov models. As an example, calculation of the one-year transition probability for ASCVD stratified by statin use, sex and five-year age groups, was estimated as:

$$Rate\ of\ ASCVD_{Non\ statin\ users} = \frac{Rate\ ASCVD_{overall}}{((1 - P_{statin\ users}) + P_{statin\ users} * RR_{statin\ users}))}$$

and:

$$Rate\ ASCVD\ _{statin\ users} = Rate\ ASCVD_{Non\ statin\ users} *\ RR_{statin\ users}$$

where $ASCVD_{overall}$ was the one-year incidence rate of ASCVD, $P_{statin\ users}$ was the prevalence of statin users (to accommodate statin discontinuation), and $RR_{statin\ users}$ was the RR of ASCVD among statin users compared to non-statin users.

We then converted the ASCVD rate to the ASCVD transition probability as:

$$Probability\ of\ ASCVD_{statin\ users} = 1 - e^{-Rate\ ASCVD_{statin\ users} * Time}$$

where *Time* corresponded to the number of years each cycle represented (1 cycle = 1 year).

F.1.7. TreeAge Pro Software

The series of Markov models used in these analyses were implemented through the TreeAge Pro software.[294] We used the healthcare model supported by TreeAge Pro to create decision trees for each intervention. Each decision node corresponded to a 5-year age group stratified by sex that included branches for each health state (T2D, ASCVD, mortality).[294] Once the Markov model was built, a cohort analysis was conducted to generate output by one-year cycles to identify incident cases (i.e. T2D and ASCVD). In addition, the TreeAge Pro software allowed us to check missing probabilities, missing states, and unused variables found in our Markov models to validate our models.

F.2. Supplemental Tables

Table 22. Markov model parameters

Age (5-year) sex-specific parameters	Sources of data	Metric estimated
Statin Eligibility	NHANES	10-year ASCVD risk
ASCVD parameters		
ASCVD incidence overall	REGARDS	Annual incidence rate
Statin-ASCVD RR	Cholesterol Treatment Trialists' Collaboration[4]	RR
T2D parameters		
T2D incidence overall	REGARDS	Annual incidence rate
Statin-T2D RR	Past meta-analysis (under review)	RR
Non-ASCVD mortality parameters		
Total non-ASCVD mortality overall	National Center for Health Statistics	Annual mortality rate
Statin-non-ASCVD mortality RR	NA	RR
Statin parameters		
Prevalence of statin discontinuation	REGARDS	Prevalence proportion

Table 23. Estimation of race- and sex-specific ASCVD risk using the ASCVD pooled cohort risk equations

	S0(t) at 5 years	S0(t) at 10 Years	Mean	Individual Score
Participants not taking antihypertensive medications				
Black women	0.98194	0.9533	86.61	= 17.114 × ln(age) + 0.94 × ln(TC) - 18.92 × ln(HDL-C) + 4.475 × ln(age) × ln(HDL-C) + 27.82 × ln(SBP) - 6.087 × ln(age) × ln(SBP) (+ 0.691 if current smoker) (+ 0.874 if diabetes)
White women	0.98898	0.9665	-29.18	= - 29.799 × ln(age) + 4.884 × ln(age)^2 + 13.54 × ln(TC) - 3.114 × ln(age) × ln(TC) -13.578 × ln(HDL-C) + 3.149 × ln(age) × ln(HDL-C) + 1.957 × ln(SBP) (+ 7.574 - 1.665 × ln(age) if current smoker) (+ 0.661 if diabetes)
Black men	0.95726	0.8954	19.54	= 2.469 × ln(age) + 0.302 × ln(TC) - 0.307 × ln(HDL-C) + 1.809 × ln(SBP) (+ 0.549 if current smoker) (+ 0.645 if diabetes)
White men	0.96254	0.9144	61.18	= 12.344 × ln(age) + 11.853 × ln(TC) - 2.664 × ln(age) × ln(TC) - 7.99 × ln(HDL-C) + 1.769 × ln(age) × ln(HDL-C) + 1.764 × ln(SBP) (+ 7.837 - 1.795 × ln(age) if current smoker) (+ 0.658 if diabetes)
Participants taking antihypertensive medications				
Black women	0.98194	0.9533	86.61	= 17.114 × ln(age) + 0.94 × ln(TC) - 18.92 × ln(HDL-C) + 4.475 × ln(age) × ln(HDL-C) + 29.291 × ln(SBP) - 6.432 × ln(age) × ln(SBP) (+ 0.691 if current smoker) (+ 0.874 if diabetes)
White women	0.98898	0.9665	-29.18	= - 29.799 × ln(age) + 4.884 × ln(age)^2 + 13.54 × ln(TC) - 3.114 × ln(age) × ln(TC) -13.578 × ln(HDL-C) + 3.149 × ln(age) × ln(HDL-C) + 2.019 × ln(SBP) (+ 7.574 - 1.665 × ln(age) if current smoker) (+ 0.661 if diabetes)
Black men	0.95726	0.8954	19.54	= 2.469 × ln(age) + 0.302 × ln(TC) - 0.307 × ln(HDL-C) + 1.916 × ln(SBP) (+ 0.549 if current smoker) (+ 0.645 if diabetes)
White men	0.96254	0.9144	61.18	= 12.344 × ln(age) + 11.853 × ln(TC) - 2.664 × ln(age) × ln(TC) - 7.99 × ln(HDL-C) + 1.769 × ln(age) × ln(HDL-C) + 1.797 × ln(SBP) (+ 7.837 - 1.795 × ln(age) if current smoker) (+ 0.658 if diabetes)

TC = total cholesterol
HDL-C = high-density lipoprotein cholesterol
SBP = Systolic blood pressure
Adapted from ACC/AHA Recommendation on the Assessment of Cardiovascular Risk working group et al., 2013

F.3. Supplemental Figures

Figure 24. Proportion of adults adhering to statin treatment recommendations over 10 years among eligible African Americans and Caucasians in the US in 2014 from a sample of 61,125,042.

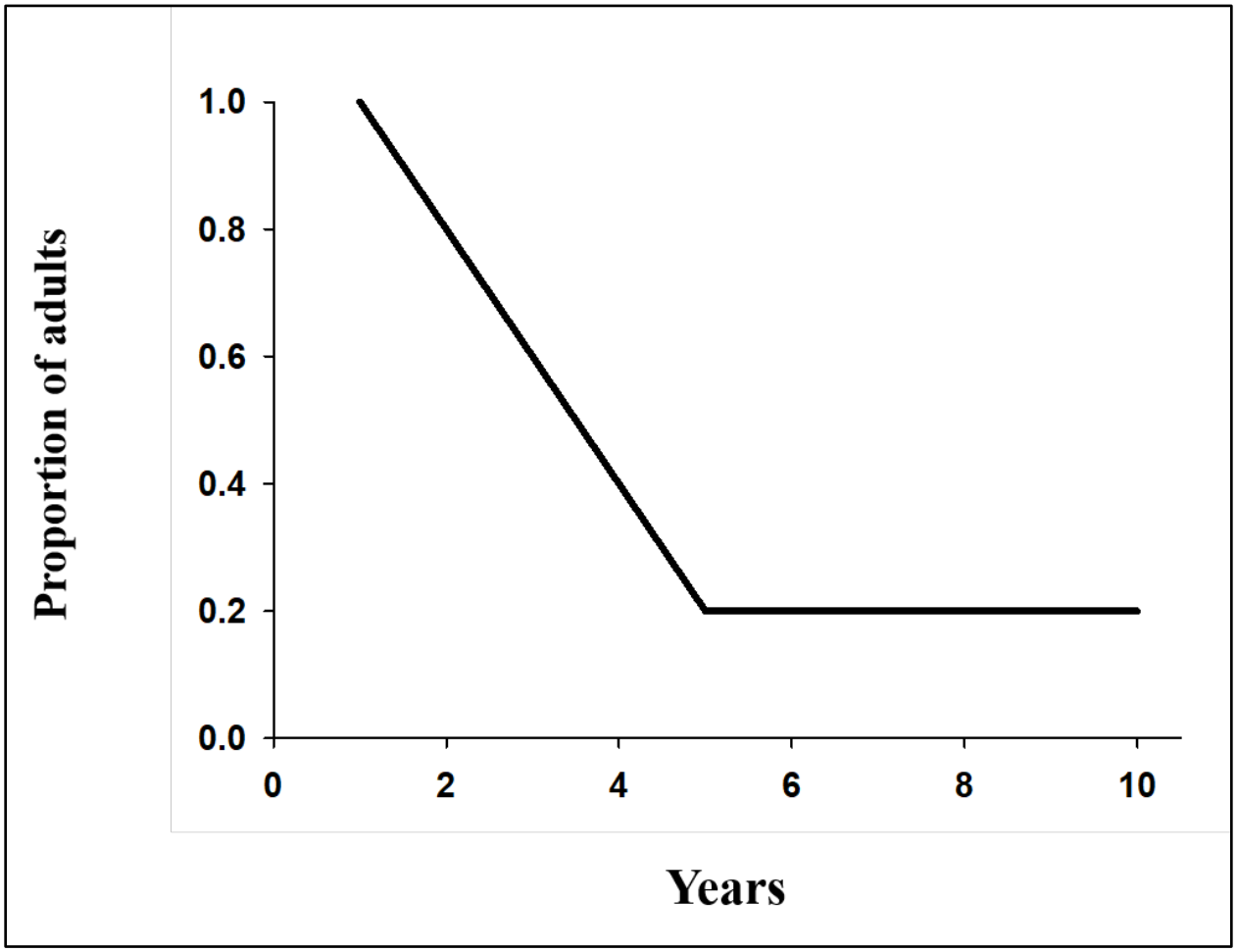


Figure 25. Number needed to treat or harm overall (Panels A-C), among females (Panels D-F), and males (Panels G-I) associated with four statin treatment recommendations among eligible African Americans and Caucasians in the US in 2014 from a sample of 61,125,042.

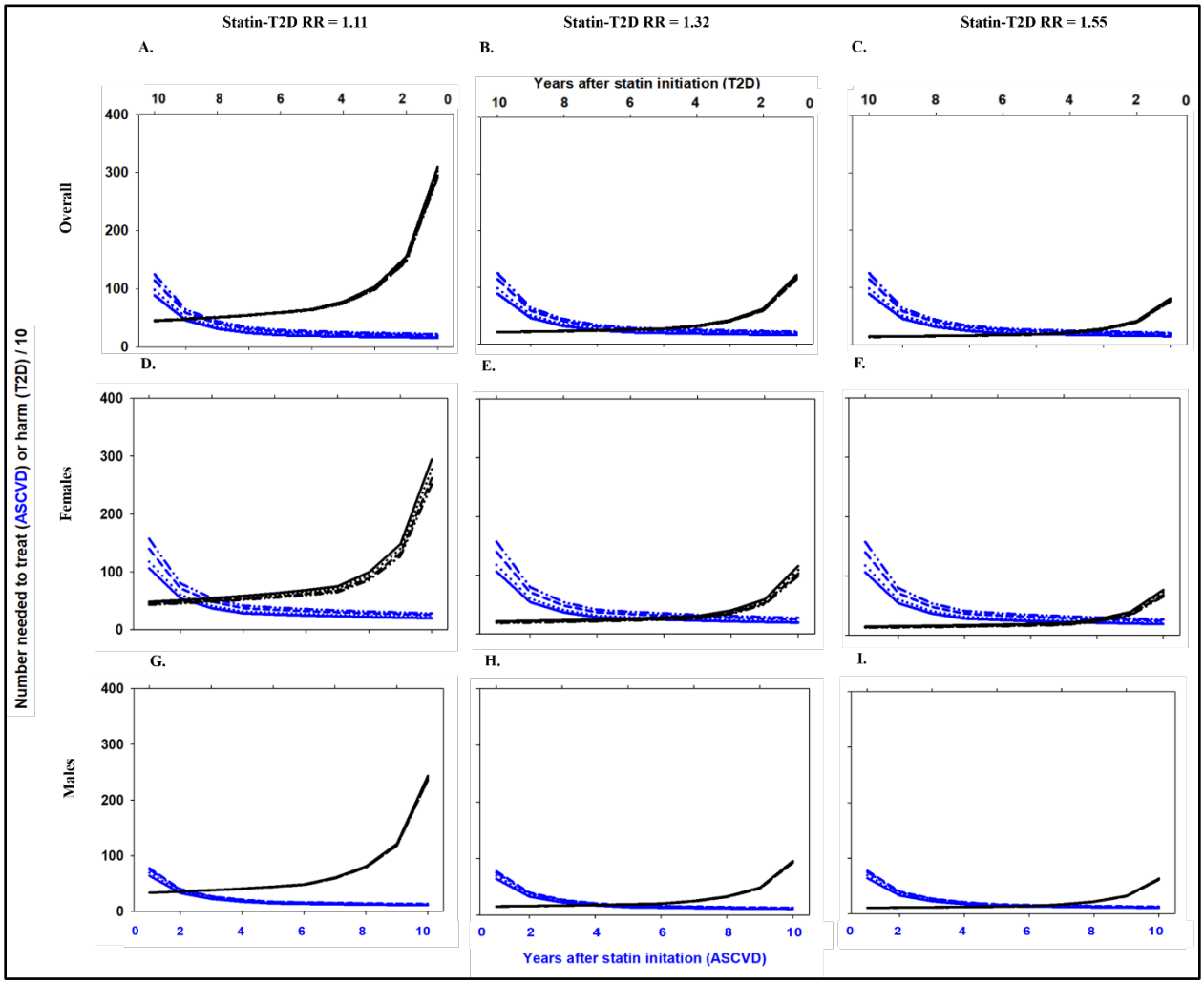


Figure 26. Cumulative number of events of atherosclerotic cardiovascular disease (ASCVD) and type 2 diabetes (T2D) among females (Panels A-C) and males (Panels D-F) associated with four statin treatment recommendations among eligible African Americans and Caucasians in the US in 2014 from a sample of 61,125,042.

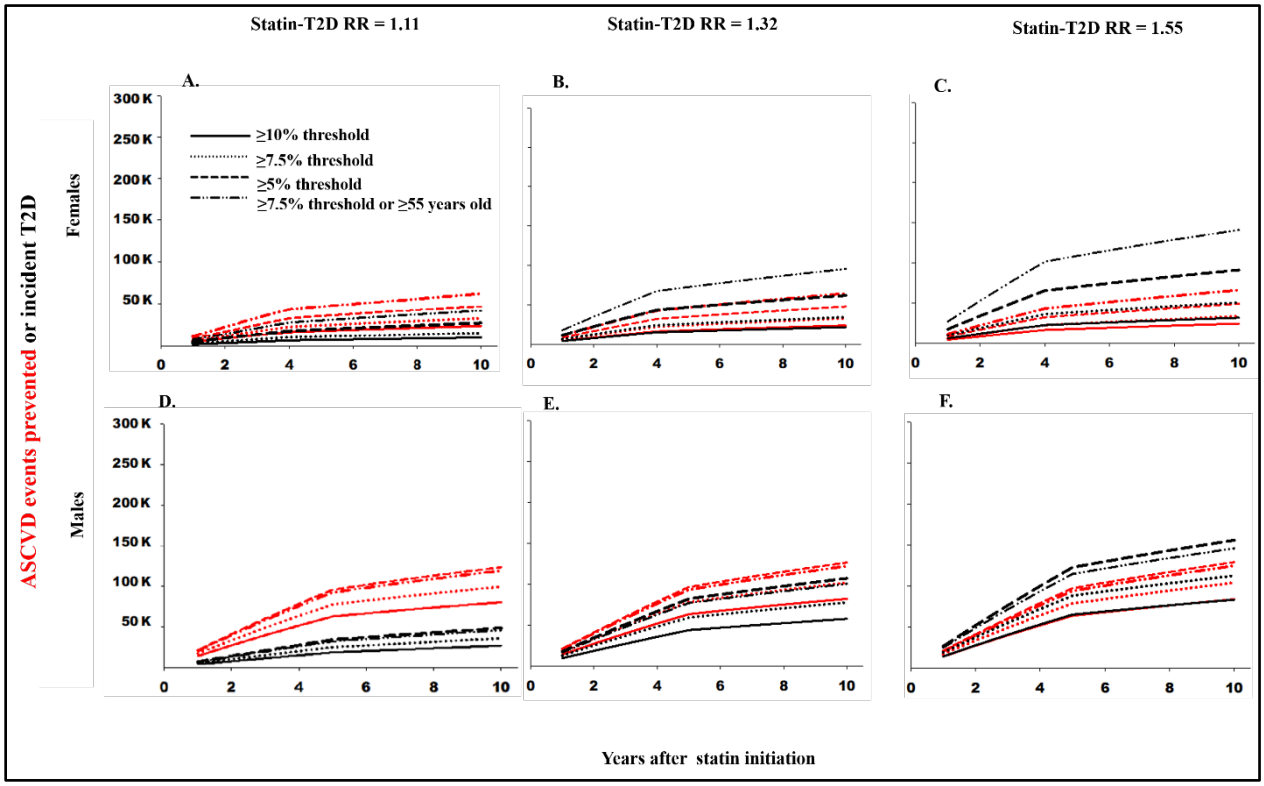
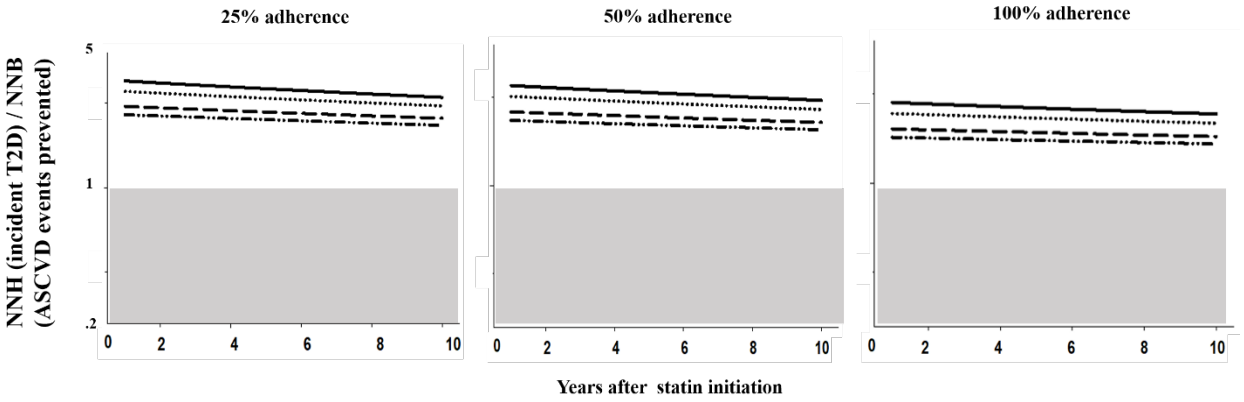


Figure 27. Likelihood to be helped or harmed (number needed to harm/number needed to treat) according to statin adherence assessed for four statin treatment recommendations among eligible African Americans and Caucasians in the US in 2014 from a sample of 61,125,042. Grey line describes threshold when number needed to harm > number needed to treat. Statin-T2D RR = 1.11.



CHAPTER 7. DISCUSSION AND CONCLUSION

While the cardioprotective effect of statins are undeniable[3, 4], experimental and observational research has also suggested that statins may lead to harm in lower risk individuals by increasing the risk of type 2 diabetes (T2D).[11-15, 176] Few studies have been able to perform a direct comparison of the number of statin-associated ASCVD events prevented alongside the number of statin-associated T2D events incurred across various proposed statin recommendations; however, simulation tools can help extend the reach of traditional epidemiological studies examining intended and unintended consequences of statin treatment through synthesis of high quality observational and experimental data.

Therefore, to obtain the required data inputs to project harms of statin treatment, we performed a systematic review and meta-analysis of statin-associated T2D risk to estimate the effect of statin on T2D by synthesizing published data from RCTs and OBSs, excluding secondary prevention populations. Results of this meta-analysis, which are consistent with earlier studies synthesizing estimates of statin-associated T2D risk in primary and secondary prevention populations[12, 176], suggest that statins have a moderate effect on T2D risk, increasing risk 11-55%. Yet, strong evidence of heterogeneity was observed, particularly with regard to participant age and baseline LDL-C level. Potential evidence of heterogeneity was not fully examined in earlier meta-analyses and merits further investigation in light of statin recommendations that target growing proportions of primary prevention populations, particularly populations with lower ASCVD risk profiles (e.g. individuals with ASCVD 10-year risk estimates <10%).

Meta-analyses of OBSs indicated an elevated statin-associated T2D risk, although the magnitude of effect was considerably higher compared to RCT meta-analysis findings, possibly reflecting differences in source population, outcome measurement error, or confounding. For example, RCTs often exclude participants that demonstrate signs of drug intolerance before randomization, participants who

may be more susceptible to developing T2D, and participants with relevant comorbidities.[301, 302] Such exclusions may yield selected populations that are less prone to adverse drug events, including T2D, than community-based populations.[303] Regarding outcome measurement error, in contrast to RCTs, for which a majority included biomarkers (i.e. fasting plasma glucose) when measuring T2D, only four of fifteen OBS studies included biomarkers to measure T2D. Assessing biomarkers of T2D is important given the large burden of undiagnosed T2D in U.S. populations, as contemporary national estimates suggest that one in three adults with T2D are undiagnosed.[304] Studies also suggest the potential for outcome measurement error to bias results towards the null[305], which, if the case, would suggest that both RCT and OBSs underestimate T2D risk. Yet, use of fasting plasma glucose to define T2D was not a significant predictor of variation in statin-associated T2D risk although the small number of studies that measure fasting plasma glucose may have decreased our ability to detect an association. Finally, the potential for confounding may exist if factors associated with T2D diagnosis also were associated with statin prescription.[306] For example, OBS participants prescribed statins may have been more likely to make and attend appointments with primary care physicians, increasing their chances of being clinically evaluated and obtaining a T2D diagnosis.[179] However, studies using active comparators to evaluate statin-associated T2D risk reported that statin users had an even higher risk of T2D (RR =3.31 [95% CI: 2.56-4.30]) compared to new diclofenac users, even when both groups had similar chances of being evaluated.[180] Overall, the magnitude of statin-associated T2D risk remains difficult to quantify, with the potential that existing studies in aggregate underestimate statin-associated T2D risk.

We also detected evidence of heterogeneity, particularly among OBSs, which may indicate specific subpopulations particularly vulnerable to statin-associated T2D risk. For example, our observation of increased statin-associated T2D risk among studies with lower baseline mean LDL-C levels is consistent with evidence of an inverse association between LDL-C and T2D.[192] Further, a recent meta-analysis among 34 RCTs found more intensive compared with less intensive LDL-C lowering therapy was associated with a greater reduction in risk of ASCVD mortality in populations with baseline LDL-C levels ≥ 100mg/dL, but not among populations with LDL-C levels < 100 mg/dL.[307] Together,

these results suggest that populations with the lowest estimated benefits of pharmacologically lowered LDL-C may also have the highest risk of T2D. However, our results remain somewhat tentative as 47% of OBSs included in the present meta-analysis either did not collect or report baseline LDL-C levels. In addition to missing baseline LDL-C levels, the majority of OBSs lacked baseline glucose levels. OBS populations that did not include fasting plasma glucose levels may have had elevated levels at baseline, potentially biasing the risk estimate for OBS towards a higher risk. However, a major risk factor for elevated fasting plasma glucose levels is BMI, and mean BMI estimates were similar between RCT and OBS (Tables 12 and 13). Meta-regression results examining heterogeneity by fasting plasma glucose levels also were not significant predictors of T2D risk.

Our meta-analysis adds to a growing body of literature on statin-associated T2D risk. As a result, the statin-associated T2D RRs obtained from our meta-analysis allowed us to project statin-associated harms. We used a simulation framework to combine evidence from meta-analyses, observational studies measuring ASCVD and T2D incidence, and population surveys informing ASCVD risk factor distributions and demographics to estimate the number of ASCVD events prevented and number of T2D events incurred in primary prevention populations across four proposed 10-year ASCVD risk statin treatment recommendations.[5, 6, 8, 20]

In our simulation study, we compared the number of ASCVD events prevented and T2D events incurred among four recently proposed statin treatment recommendations in a contemporary, biracial adult primary prevention population. We projected that between 13 and 32 million adults would be newly eligible for statin treatment, among whom one ASCVD event would be prevented for every 155-216 adults treated. Projecting the absolute harm of statin treatment was more complex; considerable variability in statin-associated T2D risk was identified, with the highest relative burden of T2D occurring in female and younger adult populations. Further efforts quantifying statin-associated benefits and harms is needed to more precisely characterize populations for whom expansion of statin treatment is warranted, as well as populations for whom for statin treatment may introduce a large burden of adverse events.

Statin-associated T2D risk was the model input that had the largest effect on projections of absolute and relative harm; statin-associated T2D risk also was the parameter for which the evidence base is most heterogeneous. To take into account the internal validity of RCTs and external validity of observational studies, we assessed a range of statin-associated T2D RRs from a recent meta-analysis[325], with the lowest estimated from RCTs (RR=1.11) and highest estimated from observational studies (1.55), with potential underestimation in RCTs possibly reflecting differences in source populations. For example, RCTs often exclude participants that demonstrate signs of drug intolerance before randomization, participants who may be more susceptible to developing T2D, and participants with relevant comorbidities.[149, 301-303] Such exclusions may yield selected populations that may be less prone to adverse drug events, including T2D, than community-based populations.[303] Overall, the magnitude of statin-associated T2D risk remains difficult to quantify, warranting additional efforts to estimate the risk, as well as detect and characterize any sources of heterogeneity.

We also observed evidence of heterogeneity in the projected effects of the four statin treatment recommendations, with females and younger adults incurring lower relative benefits compared to males and older adults. Understanding the risk/benefit profile of statin treatment in younger and female populations is warranted, given that the majority of the statin-eligible primary prevention population was female and 26% were younger than 50 years of age. Heterogeneity by sex may reflect several factors, including the assigned statin-associated ASCVD RR, which assumes a more protective effect in males (RR=0.65) than females (RR=0.74). These estimates, combined with absolute risks of T2D and statin-associated T2D risk that did not differ by sex, contributed to a higher relative burden of T2D in females. Yet, existing evidence suggests that we may be underestimating disparities in statin-associated benefits and harms by sex. For instance, among postmenopausal females in the Women's Health Initiative, the statin-associated T2D RR was found to be higher (RR = 1.48 [95% CI: 1.38-1.59]) than the pooled statin-associated T2D risk (RR=1.11) estimated by RCTs. An increased statin-associated T2D risk in females also is consistent with emerging results from past meta-analysis.[164, 325] However, females have been historically underrepresented in RCTs and past studies did not consistently report results by sex.[4, 333]

Quantifying statin-associated T2D RR among meta-analyses including individual-patient data merit further investigation to better characterize statin-associated harms.

In addition, the youngest age groups, who on average had the lowest ASCVD risk[334], did not experience the same statin-associated benefits as the oldest age groups. Examining when statin benefits may outweigh potential harms becomes important, as statin initiation in younger ages may be associated with potentially decades of statin treatment. Evidence of long-term effectiveness of statins is mixed. For example, follow-up among the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm found a significant reduction in ASCVD associated with statins approximately two years post follow-up (HR =0.64 [95% CI: 0.53-0.78]), but not 11 years post follow up (HR =0.89 [95% CI: 0.72-1.11]).[268, 269] In addition, information on post-trial statin use among those initially randomized to statins or placebo was not always known, further suggesting the association between long-term, persistent use of statins and adverse events remains poorly quantified.[267, 268]

One challenge to research comparing harms and benefits of treatments or interventions is comparing intended and unintended events that may not be equivalent. In the U.S., ASCVD is the leading cause of mortality, which may be increasing[335], accounting for approximately 837,000 deaths annually.[142] Between 2011 and 2014, 36.6% of adults (~92 million) had been diagnosed with prevalent ASCVD, with direct and indirect costs for ASCVD estimated to be $329.7 billion from 2013-2014.[337] T2D, on the other hand, was estimated to impact 31 million adults (diagnosed and undiagnosed T2D) between 2011-2014, with medical costs estimated at $245 billion.[142] Past work has emphasized the increase in T2D risk associated with statin treatment is outweighed by the benefits in ASCVD reduction. However, we identified several plausible scenarios where the number of T2D event incurred were greater than, sometimes by several orders of magnitude, the number of ASCVD events prevented.[23] Research also has suggested T2D as an ASCVD risk equivalent[338]; however, a recent meta-analyses found that individuals with T2D had a 43% lower risk of developing ASCVD than those with prior ASCVD, but without T2D.[339] While the topic of T2D as an ASCVD equivalent may still be controversial, questions on the elevated risk of T2D in association with ASCVD remain unanswered.

Although powerful, we found statins alone may not be the most effective option for continued reduction in ASCVD burden due to gains potentially offset by more T2D, and primordial prevention of elevated lipids may still have to be the emphasis. The ACC/AHA recommended that risk reduction should begin as early as possible in order to effectively reduce lifetime risk of ASCVD, with dietary and lifestyle interventions key components of such primordial prevention initiatives.

In conclusion, this dissertation adds to a growing body of literature on projected statin-associated effects. Taken together, these results help to inform the absolute and relative benefits and harms associated with statins treatment recommendations and underscore the need for more research on quantifying statin-associated harms.

APPENDIX 1. REGARDS PROPOSAL APPROVAL

From: Johnson, Cassandra D
Sent: Tuesday, October 3, 2017 12:08 PM
To: Engeda, Joseph Christopher
Cc: Johnson, Cassandra D
Subject: 2017-P409 (ENGEDA): The more aggressive statin treatment the better?: Projecting the consequences of altering ASCVD risk thresholds on diabetes mellitus and ASCVD

This email is being sent on behalf of the REGARDS Executive Committee.

Dear Mr. Engeda,

The Executive Committee has reviewed your REGARDS manuscript proposal and it was **approved.** We assume that the analyses associated with this manuscript will be conducted by a TBN statistician assigned by the UAB. If this is not the case, please let us know as soon as possible. We will work to identify the appropriate statistician who has expertise and availability and let you know as soon as possible. If you have any questions, please contact Virginia Howard (vjhoward@uab.edu).

In order to expedite all communication pertaining to your proposal, please note the assigned number for your proposal (2017-P409), and reference **2017-P409 (ENGEDA)** in the email subject line on all correspondence.

Please follow the Publications and Presentations Policies and Procedures as described in the attached document. The UAB IRB has determined that the de-identified data that is shared with members of research communities outside of UAB for the purposes of manuscript preparation does not constitute data involving human subjects under the definition of the Office for Human Research Protections (OHRP) Guidance on Research Involving Coded Private Information or Biological Specimens, October 16, 2008. The IRB suggests that researchers who receive these data as described above contact their local institutions for guidance regarding institution policies and procedures for review and approval of data.

Thank you.

2017-P409: The more aggressive statin treatment the better?: Projecting the consequences of altering ASCVD risk thresholds on diabetes mellitus and ASCVD
Author: Joseph Engeda
Co-authors: Christy Avery, Stefan Ihachimi

APPENDIX 2. ESTIMATION OF RACE- AND SEX-SPECIFIC ASCVD RISK USING THE ASCVD POOLED COHORT RISK EQUATIONS

	S0(t) at 5 years	S0(t) at 10 Years	Mean	Individual Score
Participants not taking antihypertensive medications				
Black women	0.98194	0.9533	86.61	= 17.114 × ln(age) + 0.94 × ln(TC) - 18.92 × ln(HDL-C) + 4.475 × ln(age) × ln(HDL-C) + 27.82 × ln(SBP) - 6.087 × ln(age) × ln(SBP) (+ 0.691 if current smoker) (+ 0.874 if diabetes)
White women	0.98898	0.9665	-29.18	= - 29.799 × ln(age) + 4.884 × ln(age)^2 + 13.54 × ln(TC) - 3.114 × ln(age) × ln(TC) -13.578 × ln(HDL-C) + 3.149 × ln(age) × ln(HDL-C) + 1.957 × ln(SBP) (+ 7.574 - 1.665 × ln(age) if current smoker) (+ 0.661 if diabetes)
Black men	0.95726	0.8954	19.54	= 2.469 × ln(age) + 0.302 × ln(TC) - 0.307 × ln(HDL-C) + 1.809 × ln(SBP) (+ 0.549 if current smoker) (+ 0.645 if diabetes)
White men	0.96254	0.9144	61.18	= 12.344 × ln(age) + 11.853 × ln(TC) - 2.664 × ln(age) × ln(TC) - 7.99 × ln(HDL-C) + 1.769 × ln(age) × ln(HDL-C) + 1.764 × ln(SBP) (+ 7.837 - 1.795 × ln(age) if current smoker) (+ 0.658 if diabetes)
Participants taking antihypertensive medications				
Black women	0.98194	0.9533	86.61	= 17.114 × ln(age) + 0.94 × ln(TC) - 18.92 × ln(HDL-C) + 4.475 × ln(age) × ln(HDL-C) + 29.291 × ln(SBP) - 6.432 × ln(age) × ln(SBP) (+ 0.691 if current smoker) (+ 0.874 if diabetes)
White women	0.98898	0.9665	-29.18	= - 29.799 × ln(age) + 4.884 × ln(age)^2 + 13.54 × ln(TC) - 3.114 × ln(age) × ln(TC) -13.578 × ln(HDL-C) + 3.149 × ln(age) × ln(HDL-C) + 2.019 × ln(SBP) (+ 7.574 - 1.665 × ln(age) if current smoker) (+ 0.661 if diabetes)
Black men	0.95726	0.8954	19.54	= 2.469 × ln(age) + 0.302 × ln(TC) - 0.307 × ln(HDL-C) + 1.916 × ln(SBP) (+ 0.549 if current smoker) (+ 0.645 if diabetes)
White men	0.96254	0.9144	61.18	= 12.344 × ln(age) + 11.853 × ln(TC) - 2.664 × ln(age) × ln(TC) - 7.99 × ln(HDL-C) + 1.769 × ln(age) × ln(HDL-C) + 1.797 × ln(SBP) (+ 7.837 - 1.795 × ln(age) if current smoker) (+ 0.658 if diabetes)

Adapted from ACC/AHA Recommendation on the Assessment of Cardiovascular Risk working group et al., 2013

REFERENCES

1. Shah RV and Goldfine AB. Statins and risk of new-onset diabetes mellitus. *Circulation*. 2012;126:e282-e284.

2. Gu Q, Paulose-Ram R, Burt V and Kit B. Prescription cholesterol-lowering medication use in adults aged 40 and over: United States, 2003–2012. NCHS data brief, no 177. Hyattsville, MD: National Center for Health Statistics, US Department of Health and Human Services, CDC; 2014. 2015.

3. Trialists CT. Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174 000 participants in 27 randomised trials. *The Lancet*. 2015;385:1397-1405.

4. Trialists CT. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. *The Lancet*. 2012;380:581-590.

5. Pencina MJ, Navar-Boggan AM, D'Agostino Sr RB, Williams K, Neely B, Sniderman AD and Peterson ED. Application of new cholesterol guidelines to a population-based sample. *New England Journal of Medicine*. 2014;370:1422-1431.

6. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, Goldberg AC, Gordon D, Levy D, Lloyd-Jones DM, McBride P, Schwartz JS, Shero ST, Smith SC, Jr., Watson K, Wilson PW and American College of Cardiology/American Heart Association Task Force on Practice G. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Journal of the American College of Cardiology*. 2014;63:2889-934.

7. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, de Ferranti S, Faiella-Tommasino J and Forman DE. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Journal of the American College of Cardiology*. 2018:25709.

8. Wald NJ, Simmonds M and Morris JK. Screening for future cardiovascular disease using age alone compared with multiple risk factors and age. *PloS one*. 2011;6:e18742.

9. Force. USPST. Recommendations for Primary Care Practice.

10. Grundy S. Cholesterol-lowering trials: a historical perspective. *Cholesterol lowering therapy: evaluation of clinical trial evidence New York: Marcel Dekker Inc*. 2000;1329.

11. Rajpathak SN, Kumbhani DJ, Crandall J, Barzilai N, Alderman M and Ridker PM. Statin therapy and risk of developing type 2 diabetes: a meta-analysis. *Diabetes care*. 2009;32:1924-1929.

12. Sattar N, Preiss D, Murray HM, Welsh P, Buckley BM, de Craen AJ, Seshasai SRK, McMurray JJ, Freeman DJ and Jukema JW. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. *The Lancet*. 2010;375:735-742.

13. Mills E, Wu P, Chong G, Ghement I, Singh S, Akl E, Eyawo O, Guyatt G, Berwanger O and Briel M. Efficacy and safety of statin treatment for cardiovascular disease: a network meta-analysis of 170 255 patients from 76 randomized trials. *QJM: An International Journal of Medicine*. 2011;104:109-124.

14. Taylor F, Huffman MD, Macedo AF, Moore TH, Burke M, Davey Smith G, Ward K and Ebrahim S. Statins for the primary prevention of cardiovascular disease. *The Cochrane Library*. 2013.

15. Chou R, Tracy Dana M, Blazina I, Daeges M and Jeanne TL. Statins for Prevention of Cardiovascular Disease in Adults Evidence Report and Systematic Review for the US Preventive Services Task Force. *JAMA : the journal of the American Medical Association*. 2016;316:2008-2024.

16. Walker AM. Confounding by indication. *Epidemiology*. 1996;7:335-336.

17. Shrier I, Boivin J-F, Steele RJ, Platt RW, Furlan A, Kakuma R, Brophy J and Rossignol M. Should meta-analyses of interventions include observational studies in addition to randomized controlled trials? A critical examination of underlying principles. *American journal of epidemiology*. 2007;166:1203-1209.

18. Faraoni D and Schaefer ST. Randomized controlled trials vs. observational studies: why not just live together? *BMC anesthesiology*. 2016;16:102.

19. Lloyd-Jones DM, Leip EP, Larson MG, d'Agostino RB, Beiser A, Wilson PW, Wolf PA and Levy D. Prediction of lifetime risk for cardiovascular disease by risk factor burden at 50 years of age. *Circulation*. 2006;113:791-798.

20. Bibbins-Domingo K, Grossman DC, Curry SJ, Davidson KW, Epling JW, García FA, Gillman MW, Kemper AR, Krist AH and Kurth AE. Statin use for the primary prevention of cardiovascular disease in adults: US Preventive Services Task Force recommendation statement. *JAMA : the journal of the American Medical Association*. 2016;316:1997-2007.

21. Pagidipati NJ, Navar AM, Mulder H, Sniderman AD, Peterson ED and Pencina MJ. Comparison of Recommended Eligibility for Primary Prevention Statin Therapy Based on the US Preventive Services Task Force Recommendations vs the ACC/AHA Guidelines. *JAMA : the journal of the American Medical Association*. 2017;317:1563-1567.

22. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, Goldberg AC, Gordon D, Levy D, Lloyd-Jones DM, McBride P, Schwartz JS, Shero ST, Smith SC, Jr., Watson K, Wilson PW, Eddleman KM, Jarrett NM, LaBresh K, Nevo L, Wnek J, Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Curtis LH, DeMets D, Hochman JS, Kovacs RJ, Ohman EM, Pressler SJ, Sellke FW, Shen WK, Smith SC, Jr., Tomaselli GF and American College of Cardiology/American Heart Association Task Force on Practice G. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;129:S1-45.

23. Robinson JG. Starting primary prevention earlier with statins. *The American journal of cardiology*. 2014;114:1437-1442.

24. McFarlane AS. The ultracentrifugal protein sedimentation diagram of normal human, cow and horse serum. *Biochemical Journal*. 1935;29:660.

25. Dam H. Historical introduction to cholesterol. *Chemistry, Biochemistry and Pathology (RP Cook, ed) pp*. 1958:1-14.

26. Windaus At. Über den Gehalt normaler und atheromatöser Aorten an Cholesterin und Cholesterinestern. *Hoppe-Seyler´s Zeitschrift für physiologische Chemie*. 1910;67:174-176.

27. Truswell AS. *Cholesterol and Beyond: The Research on Diet and Coronary Heart Disease 1900-2000*: Springer Science & Business Media; 2010.

28. Steinberg D. Lipoproteins and atherosclerosis. A look back and a look ahead. *Arteriosclerosis, thrombosis, and vascular biology*. 1983;3:283-301.

29. Myant N. *Cholesterol metabolism, LDL, and the LDL receptor*: Elsevier; 2012.

30. Bastiaanse EL, Höld KM and Van der Laarse A. The effect of membrane cholesterol content on ion transport processes in plasma membranes. *Cardiovascular research*. 1997;33:272-283.

31. Pfrieger F. Cholesterol homeostasis and function in neurons of the central nervous system. *Cellular and Molecular Life Sciences*. 2003;60:1158-1171.

32. Garg A. *Dyslipidemias: Pathophysiology, Evaluation and Management*: Springer; 2015.

33. Sundaram M and Yao Z. Recent progress in understanding protein and lipid factors affecting hepatic VLDL assembly and secretion. *Nutrition & metabolism*. 2010;7:1.

34. Young SG and Zechner R. Biochemistry and pathophysiology of intravascular and intracellular lipolysis. *Genes & development*. 2013;27:459-484.

35. Ameer F, Scandiuzzi L, Hasnain S, Kalbacher H and Zaidi N. De novo lipogenesis in health and disease. *Metabolism: clinical and experimental*. 2014;63:895-902.

36. Furniss BS. *Vogel's textbook of practical organic chemistry*: Pearson Education India; 1989.

37. Brown MS, Kovanen PT and Goldstein JL. Regulation of plasma cholesterol by lipoprotein receptors. *Science*. 1981;212:628-635.

38. Ohashi R, Mu H, Wang X, Yao Q and Chen C. Reverse cholesterol transport and cholesterol efflux in atherosclerosis. *Qjm*. 2005;98:845-856.

39. Ross R. Atherosclerosis—an inflammatory disease. *New England journal of medicine*. 1999;340:115-126.

40. Marmot MG and Elliott P. *Coronary heart disease epidemiology: from aetiology to public health*: Oxford University Press, USA; 2005.

41. Brown MS and Goldstein JL. A receptor-mediated pathway for cholesterol homeostasis. *Science*. 1986;232:34-47.

42. Hobbs HH, Brown MS and Goldstein JL. Molecular genetics of the LDL receptor gene in familial hypercholesterolemia. *Human mutation*. 1992;1:445-466.

43. Schwenke DC and Carew TE. Initiation of atherosclerotic lesions in cholesterol-fed rabbits. II. Selective retention of LDL vs. selective increases in LDL permeability in susceptible sites of arteries. *Arteriosclerosis, thrombosis, and vascular biology*. 1989;9:908-918.

44. Williams KJ and Tabas I. The response-to-retention hypothesis of early atherogenesis. *Arteriosclerosis, thrombosis, and vascular biology*. 1995;15:551-561.

45. Williams KJ and Tabas I. Lipoprotein retention—and clues for atheroma regression. 2005.

46. Witztum JL and Steinberg D. Role of oxidized low density lipoprotein in atherogenesis. *Journal of Clinical Investigation*. 1991;88:1785.

47. Steinbrecher U, Parthasarathy S, Leake DS, Witztum JL and Steinberg D. Modification of low density lipoprotein by endothelial cells involves lipid peroxidation and degradation of low density lipoprotein phospholipids. *Proceedings of the National Academy of Sciences*. 1984;81:3883-3887.

48. Ross R and Glomset JA. The pathogenesis of atherosclerosis. *New England Journal of Medicine*. 1976;295:369-377.

49. Steinberg D, Parthasarathy S, Carew TE, Khoo JC and Witztum JL. Beyond Cholesterol. *New England Journal of Medicine*. 1989;320:915-924.

50. Davies MJ and Thomas A. Thrombosis and acute coronary-artery lesions in sudden cardiac ischemic death. *New England Journal of Medicine*. 1984;310:1137-1140.

51. Anitschkow N. Experimental arteriosclerosis in animals. *Arteriosclerosis*. 1933:271-322.

52. Wolkoff K. Über die experimentelle Atherosklerose der Coronararterien bei Kaninchen. *Beitr path Anat*. 1930;85:386.

53. Leary T. Experimental atherosclerosis in the rabbit compared with human (coronary) atherosclerosis. *Arch Pathol*. 1934;17:453-492.

54. Rowsell H, Downie H and Mustard J. Comparison of the effect of egg yolk or butter on the development of atherosclerosis in swine. *Canadian Medical Association Journal*. 1960;83:1175.

55. Taylor C, Patton D and Cox G. Atherosclerosis in rhesus monkeys. 6. Fatal myocardial infarction in a monkey fed fat and cholesterol. *Arch Pathol*. 1963;76:404-412.

56. Bullock B, Lehner N, Clarkson T, Feldner M, Wagner W and Lofland H. Comparative primate atherosclerosis: I. Tissue cholesterol concentration and pathologic anatomy. *Experimental and molecular pathology*. 1975;22:151-175.

57. Wissler RW and Vesselinovitch D. Studies of regression of advanced atherosclerosis in experimental animals and man. *Annals of the New York Academy of Sciences*. 1976;275:363-378.

58. Goldstein L and Brown S. The low-density lipoprotein pathway and its relation to atherosclerosis. *Annual review of biochemistry*. 1977;46:897-930.

59. Khachadurian AK. The inheritance of essential familial hypercholesterolemia. *The American journal of medicine*. 1964;37:402-407.

60. Soutar AK and Naoumova RP. Mechanisms of disease: genetic causes of familial hypercholesterolemia. *Nature clinical practice Cardiovascular medicine*. 2007;4:214-225.

61. Frederickson DS, Stanbury JB and Wyngaarden JB. *The metabolic basis of inherited disease*: McGraw-Hill Book Company; 1960.

62. Watanabe Y, Ito T and Kondo T. Breeding of a rabbit strain of hyperlipidemia and characteristic of this strain (author's transl). *Jikken dobutsu Experimental animals*. 1977;26:35-42.

63. Tanzawa K, Shimada Y, Kuroda M, Tsujita Y, Arai M and Watanabe H. WHHL-Rabbit: a low density lipoprotein receptor-deficient animal model for familial hypercholesterolemia. *FEBS letters*. 1980;118:81-84.

64. Watanabe Y. Serial inbreeding of rabbits with hereditary hyperlipidemia (WHHL-rabbit): incidence and development of atherosclerosis and xanthoma. *Atherosclerosis*. 1980;36:261-268.

65. Benn M, Nordestgaard BG, Jensen JS, Grande P, Sillesen H and Tybjærg-Hansen A. Polymorphism in APOB associated with increased low-density lipoprotein levels in both genders in the general population. *The Journal of Clinical Endocrinology & Metabolism*. 2005;90:5797-5803.

66. Kotowski IK, Pertsemlidis A, Luke A, Cooper RS, Vega GL, Cohen JC and Hobbs HH. A spectrum of PCSK9 alleles contributes to plasma levels of low-density lipoprotein cholesterol. *The American Journal of Human Genetics*. 2006;78:410-422.

67. Boright AP, Connelly PW, Brunt JH, Morgan K and Hegele RA. Association and linkage of LDLR gene variation with variation in plasma low density lipoprotein cholesterol. *Journal of human genetics*. 1998;43:153-159.

68. Kathiresan S, Melander O, Anevski D, Guiducci C, Burtt NP, Roos C, Hirschhorn JN, Berglund G, Hedblad B and Groop L. Polymorphisms associated with cholesterol and risk of cardiovascular events. *New England Journal of Medicine*. 2008;358:1240-1249.

69. Guzman M, McMahan C, McGill Jr H, Strong J, Tejada C, Restrepo C, Eggen D, Robertson W and Solberg L. Selected methodologic aspects of the International Atherosclerosis Project. *Laboratory investigation; a journal of technical methods and pathology*. 1968;18:479-497.

70. Kagan A, Harris BR, Winkelstein W, Johnson KG, Kato H, Syme SL, Rhoads GG, Gay ML, Nichaman MZ and Hamilton HB. Epidemiologic studies of coronary heart disease and stroke in Japanese men living in Japan, Hawaii and California: demographic, physical, dietary and biochemical characteristics. *Journal of chronic diseases*. 1974;27:345-364.

71. Toor M, Katchalsky A, Agmon J and Allalouf D. Atherosclerosis and related factors in immigrants to Israel. *Circulation*. 1960;22:265-279.

72. Kannel WB, Castelli WP, Gordon T and McNamara PM. Serum cholesterol, lipoproteins, and the risk of coronary heart disease: the Framingham Study. *Annals of internal medicine*. 1971;74:1-12.

73. DeLangen C. Cholesterol metabolism and racial pathology. *Geneesk Tijdschr Nederl Indië*. 1916;56:1-34.

74. Blackburn H. 20th-Century "medical Marco Polos" in the origins of preventive cardiology and cardiovascular disease epidemiology. *The American journal of cardiology*. 2012;109:756-767.

75. Snapper I. Diet and atherosclerosis: truth and fiction. *The American journal of cardiology*. 1963;11:283-289.

76. Moore F. Minutes, October 14–15, 1949. *Records of the National Institutes of Health, National Advisory Heart Council, Box*. 21.

77. Chen G and Levy D. Contributions of the Framingham Heart Study to the epidemiology of coronary heart disease. *JAMA cardiology*. 2016;1:825-830.

78. Shurleff D. *Some characteristics related to the incidence of cardiovascular disease and death: Framingham Study, 18-year follow-up*: US Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health; 1974.

79. Goldbourt U, Holtzman E and Neufeld H. Total and high density lipoprotein cholesterol in the serum and risk of mortality: evidence of a threshold effect. *Br Med J (Clin Res Ed)*. 1985;290:1239-1243.

80. Johnson KG, Yano K and Kato H. Coronary heart disease in Hiroshima, Japan: a report of a six-year period of surveillance, 1958-1964. *American Journal of Public Health and the Nations Health*. 1968;58:1355-1367.

81. Yano K and Ueda S. Coronary heart disease in Hiroshima, Japan: analysis of the data at the initial examination, 1958-1960. *The Yale journal of biology and medicine*. 1963;35:504.

82. Rhoads GG, Gulbrandsen CL and Kagan A. Serum lipoproteins and coronary heart disease in a population study of Hawaii Japanese men. *New England Journal of Medicine*. 1976;294:293-298.

83. Syme S, Marmot M, Kagan A, Kato H and Rhoads G. Epidemiologic studies of coronary heart disease and stroke in Japanese men living in Japan, Hawaii and California: introduction. *American journal of epidemiology*. 1975;102:477-480.

84. Medalie JH, Kahn HA, Neufeld HN, Riss E and Goldbourt U. Five-year myocardial infarction incidence—II. Association of single variables to age and birthplace. *Journal of chronic diseases*. 1973;26:329-349.

85. Rosenman RH, Brand RJ, Jenkins CD, Friedman M, Straus R and Wurm M. Coronary heart disease in the Western Collaborative Group Study: Final follow-up experience of 8 1/2 years. *JAMA : the journal of the American Medical Association*. 1975;233:872-877.

86. Gofman JW, Hanig M, Jones HB, Lauffer MA, Lawry EY, Lewis LA, Mann GV, Moore FE, Olmsted F and Yeager JF. Evaluation of serum lipoprotein and cholesterol measurements as predictors of clinical complications of atherosclerosis. *Circulation*. 1956;14:689-741.

87. Stamler J, Wentworth D and Neaton JD. Is relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded?: Findings in 356 222

primary screenees of the Multiple Risk Factor Intervention Trial (MRFIT). *JAMA : the journal of the American Medical Association*. 1986;256:2823-2828.

88. Rifkind B. The Lipid Research Clinics Coronary Primary Prevention Trial Results. 2. The Relationship of Reduction in Incidence of Coronary Heart-Disease to Cholesterol Lowering. *Jama-Journal of the American Medical Association*. 1984;251:365-374.

89. Brensike JF, Levy RI, Kelsey SF, Passamani ER, Richardson JM, Loh IK, Stone NJ, Aldrich RF, Battaglini JW and Moriarty DJ. Effects of therapy with cholestyramine on progression of coronary arteriosclerosis: results of the NHLBI Type II Coronary Intervention Study. *Circulation*. 1984;69:313-324.

90. Carroll MD, Kit BK, Lacher DA, Shero ST and Mussolino ME. Trends in lipids and lipoproteins in US adults, 1988-2010. *JAMA : the journal of the American Medical Association*. 2012;308:1545-54.

91. Vesper HW, Kuiper HC, Mirel LB, Johnson CL and Pirkle JL. Levels of plasma trans-fatty acids in non-Hispanic white adults in the United States in 2000 and 2009. *JAMA : the journal of the American Medical Association*. 2012;307:562-563.

92. Hyre AD, Muntner P, Menke A, Raggi P and He J. Trends in ATP-III-defined high blood cholesterol prevalence, awareness, treatment and control among US adults. *Annals of epidemiology*. 2007;17:548-555.

93. Control CfD and Prevention. Vital signs: prevalence, treatment, and control of high levels of low-density lipoprotein cholesterol--United States, 1999-2002 and 2005-200. *MMWR Morbidity and mortality weekly report*. 2011;60:109.

94. Goff DC, Bertoni AG, Kramer H, Bonds D, Blumenthal RS, Tsai MY and Psaty BM. Dyslipidemia prevalence, treatment, and control in the multi-ethnic study of atherosclerosis (MESA). *Circulation*. 2006;113:647-656.

95. Bakx JC, van den Hoogen HJ, Deurenberg P, van Doremalen J and van den Bosch WJ. Changes in serum total cholesterol levels over 18 years in a cohort of men and women: The Nijmegen Cohort Study. *Preventive medicine*. 2000;30:138-45.

96. Demirovic J, Sprafka JM, Folsom AR, Laitinen D and Blackburn H. Menopause and serum cholesterol: differences between blacks and whites. The Minnesota Heart Survey. *American journal of epidemiology*. 1992;136:155-64.

97. Jensen J, Nilas L and Christiansen C. Influence of menopause on serum lipids and lipoproteins. *Maturitas*. 1990;12:321-331.

98. Carlson LA. Nicotinic acid: the broad-spectrum lipid drug. A 50th anniversary review. *Journal of internal medicine*. 2005;258:94-114.

99. Gouni-Berthold I and K Berthold H. The role of niacin in lipid-lowering treatment: are we aiming too high? *Current pharmaceutical design*. 2013;19:3094-3106.

100. Investigators A-H. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. *New England Journal of Medicine*. 2011;365:2255-2267.

101. Group H-TC. Effects of extended-release niacin with laropiprant in high-risk patients. *The New England journal of medicine*. 2014;2014:203-212.

102. Investigators FS. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. *The Lancet*. 2005;366:1849-1861.

103. Gabow PA, Kaehny WD and Kelleher SP. The spectrum of rhabdomyolysis. *Medicine*. 1982;61:141-152.

104. Amend KL, Landon J, Thyagarajan V, Niemcryk S and McAfee A. Incidence of hospitalized rhabdomyolysis with statin and fibrate use in an insured US population. *Annals of Pharmacotherapy*. 2011;45:1230-1239.

105. Insull Jr W. Clinical utility of bile acid sequestrants in the treatment of dyslipidemia: a scientific review. *Southern medical journal*. 2006;99:257-274.

106. Out C, Groen AK and Brufau G. Bile acid sequestrants: more than simple resins. *Current opinion in lipidology*. 2012;23:43-55.

107. Jacobson TA, Ito MK, Maki KC, Orringer CE, Bays HE, Jones PH, McKenney JM, Grundy SM, Gill EA and Wild RA. National Lipid Association recommendations for patient-centered management of dyslipidemia: Part 1–executive summary. *Journal of clinical lipidology*. 2014;8:473-488.

108. Zhang D-W, Garuti R, Tang W-J, Cohen JC and Hobbs HH. Structural requirements for PCSK9-mediated degradation of the low-density lipoprotein receptor. *Proceedings of the National Academy of Sciences*. 2008;105:13045-13050.

109. Stefanutti C, Morozzi C and Di Giacomo S. New clinical perspectives of hypolipidemic drug therapy in severe hypercholesterolemia. *Current medicinal chemistry*. 2012;19:4861-4868.

110. Sabatine MS, Giugliano RP, Wiviott SD, Raal FJ, Blom DJ, Robinson J, Ballantyne CM, Somaratne R, Legg J and Wasserman SM. Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. *New England Journal of Medicine*. 2015;372:1500-1509.

111. Moon JC and Bogle RG. Switching statins: using generic simvastatin as first line could save£ 2bn over five years in England. *BMJ: British Medical Journal*. 2006;332:1344.

112. Tice JA, Kazi DS and Pearson SD. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors for treatment of high cholesterol levels: effectiveness and value. *JAMA internal medicine*. 2016;176:107-108.

113. Rodwell VW, Nordstrom JL and Mitschelen JJ. Regulation of HMG-CoA reductase. *Adv Lipid Res*. 1976;14.

114. Sadowitz B, Maier KG and Gahtan V. Basic science review: Statin therapy-Part I: The pleiotropic effects of statins in cardiovascular disease. *Vascular and endovascular surgery*. 2010;44:241-251.

115. Rikitake Y, Kawashima S, Takeshita S, Yamashita T, Azumi H, Yasuhara M, Nishi H, Inoue N and Yokoyama M. Anti-oxidative properties of fluvastatin, an HMG-CoA reductase inhibitor,

contribute to prevention of atherosclerosis in cholesterol-fed rabbits. *Atherosclerosis*. 2001;154:87-96.

116. Takemoto M and Liao JK. Pleiotropic effects of 3-hydroxy-3-methylglutaryl coenzyme a reductase inhibitors. *Arteriosclerosis, thrombosis, and vascular biology*. 2001;21:1712-1719.

117. Bonetti P, Lerman LO, Napoli C and Lerman A. Statin effects beyond lipid lowering—are they clinically relevant? *European heart journal*. 2003;24:225-248.

118. Zhou Q and Liao JK. Statins and cardiovascular diseases: from cholesterol lowering to pleiotropy. *Current pharmaceutical design*. 2009;15:467-478.

119. Wolfrum S, Jensen KS and Liao JK. Endothelium-dependent effects of statins. *Arteriosclerosis, thrombosis, and vascular biology*. 2003;23:729-736.

120. Davignon J. Beneficial cardiovascular pleiotropic effects of statins. *Circulation*. 2004;109:III-39-III-43.

121. Steinberg D. Atherogenesis in perspective: hypercholesterolemia and inflammation as partners in crime. *Nature medicine*. 2002;8:1211-1217.

122. Wilson SH, Simari RD, Best PJ, Peterson TE, Lerman LO, Aviram M, Nath KA, Holmes DR and Lerman A. Simvastatin preserves coronary endothelial function in hypercholesterolemia in the absence of lipid lowering. *Arteriosclerosis, thrombosis, and vascular biology*. 2001;21:122-128.

123. Albert MA, Danielson E, Rifai N, Ridker PM and Investigators P. Effect of statin therapy on C-reactive protein levels: the pravastatin inflammation/CRP evaluation (PRINCE): a randomized trial and cohort study. *JAMA : the journal of the American Medical Association*. 2001;286:64-70.

124. Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, Macfarlane PW, McKillop JH and Packard CJ. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *New England Journal of Medicine*. 1995;333:1301-1308.

125. Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, Beere PA, Langendorfer A, Stein EA, Kruyer W and Gotto Jr AM. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. *JAMA : the journal of the American Medical Association*. 1998;279:1615-1622.

126. Group SSSS. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *The Lancet*. 1994;344:1383-1389.

127. Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, Brown L, Warnica JW, Arnold JMO and Wun C-C. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *New England Journal of Medicine*. 1996;335:1001-1009.

128. Tonkin A, Alyward P, Colquhoun D, Glasziou P, Harris P, Hunt D, Keech A, MacMahon S, Magnus P and Newel D. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *New England Journal of Medicine*. 1998;339:1349-1357.

129. Salami JA, Warraich H, Valero-Elizondo J, Spatz ES, Desai NR, Rana JS, Virani SS, Blankstein R, Khera A and Blaha MJ. National Trends in Statin Use and Expenditures in the US Adult Population From 2002 to 2013: Insights From the Medical Expenditure Panel Survey. *Jama cardiology*. 2016.

130. Mensah GA. Eliminating disparities in cardiovascular health. *Circulation*. 2005;111:1332-1336.

131. Ellis JJ, Erickson SR, Stevenson JG, Bernstein SJ, Stiles RA and Fendrick AM. Suboptimal statin adherence and discontinuation in primary and secondary prevention populations. *Journal of general internal medicine*. 2004;19:638-645.

132. Mann DM, Woodward M, Muntner P, Falzon L and Kronish I. Predictors of nonadherence to statins: a systematic review and meta-analysis. *Annals of Pharmacotherapy*. 2010;44:1410-1421.

133. Macedo AF, Taylor FC, Casas JP, Adler A, Prieto-Merino D and Ebrahim S. Unintended effects of statins from observational studies in the general population: systematic review and meta-analysis. *BMC medicine*. 2014;12:51.

134. Antons KA, Williams CD, Baker SK and Phillips PS. Clinical perspectives of statin-induced rhabdomyolysis. *The American journal of medicine*. 2006;119:400-409.

135. Thompson PD, Clarkson P and Karas RH. Statin-associated myopathy. *JAMA : the journal of the American Medical Association*. 2003;289:1681-1690.

136. Hippisley-Cox J and Coupland C. Unintended effects of statins in men and women in England and Wales: population based cohort study using the QResearch database. *Bmj*. 2010;340:c2197.

137. Riphagen IJ, van der Veer E, Muskiet FA and DeJongste MJ. Myopathy during statin therapy in the daily practice of an outpatient cardiology clinic: prevalence, predictors and relation with vitamin D. *Current medical research and opinion*. 2012;28:1247-1252.

138. Valiyil R and Christopher-Stine L. Drug-related myopathies of which the clinician should be aware. *Current rheumatology reports*. 2010;12:213-220.

139. Association AD. 2. Classification and diagnosis of diabetes. *Diabetes care*. 2015;38:S8-S16.

140. American Diabetes A. Diagnosis and classification of diabetes mellitus. *Diabetes care*. 2014;37 Suppl 1:S81-90.

141. Control CfD and Prevention. National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United States, 2011. *Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention*. 2011;201.

142. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, de Ferranti S, Despres JP, Fullerton HJ, Howard VJ, Huffman MD, Judd SE, Kissela BM, Lackland DT, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Matchar DB, McGuire DK, Mohler ER, 3rd, Moy CS, Muntner P, Mussolino ME, Nasir K, Neumar RW, Nichol G, Palaniappan L, Pandey DK, Reeves MJ, Rodriguez CJ, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Willey JZ, Woo D, Yeh RW, Turner MB, American Heart Association Statistics C and Stroke Statistics S. Heart disease and stroke statistics--2015 update: a report from the American Heart Association. *Circulation*. 2015;131:e29-322.

143. Collaboration ERF. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *The Lancet*. 2010;375:2215-2222.

144. Association AD. Economic costs of diabetes in the US in 2012. Diabetes Care 2013; 36: 1033–1046. *Diabetes care*. 2013;36:1797.

145. Association AD. Executive summary: standards of medical care in diabetes—2014. 2014.

146. Trialists CT. Efficacy of cholesterol-lowering therapy in 18 686 people with diabetes in 14 randomised trials of statins: a meta-analysis. *The Lancet*. 2008;371:117-125.

147. Casagrande SS, Fradkin JE, Saydah SH, Rust KF and Cowie CC. The prevalence of meeting A1C, blood pressure, and LDL goals among people with diabetes, 1988–2010. *Diabetes care*. 2013;36:2271-2279.

148. Sever PS, Dahlöf B, Poulter NR, Wedel H, Beevers G, Caulfield M, Collins R, Kjeldsen SE, Kristinsson A and McInnes GT. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *The Lancet*. 2003;361:1149-1158.

149. Freeman DJ, Norrie J, Sattar N, Neely RDG, Cobbe SM, Ford I, Isles C, Lorimer AR, Macfarlane PW and McKillop JH. Pravastatin and the development of diabetes mellitus evidence for a protective treatment effect in the West of Scotland Coronary Prevention Study. *Circulation*. 2001;103:357-362.

150. Group HPSC. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *The Lancet*. 2003;361:2005-2016.

151. Keech A, Colquhoun D, Best J, Kirby A, Simes RJ, Hunt D, Hague W, Beller E, Arulchelvam M and Baker J. Secondary Prevention of Cardiovascular Events With Long-Term Pravastatin in Patients With Diabetes or Impaired Fasting Glucose Results from the LIPID trial. *Diabetes care*. 2003;26:2713-2721.

152. Kjekshus J, Apetrei E, Barrios V, Böhm M, Cleland JG, Cornel JH, Dunselman P, Fonseca C, Goudev A and Grande P. Rosuvastatin in older patients with systolic heart failure. *New England Journal of Medicine*. 2007;357:2248-2261.

153. Ridker PM, Pradhan A, MacFadyen JG, Libby P and Glynn RJ. Cardiovascular benefits and diabetes risks of statin therapy in primary prevention: an analysis from the JUPITER trial. *The Lancet*. 2012;380:565-571.

154. Shepherd J, Blauw GJ, Murphy MB, Bollen EL, Buckley BM, Cobbe SM, Ford I, Gaw A, Hyland M and Jukema JW. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *The Lancet*. 2002;360:1623-1630.

155. Nakamura H, Arakawa K, Itakura H, Kitabatake A, Goto Y, Toyota T, Nakaya N, Nishimoto S, Muranaka M and Yamamoto A. Primary prevention of cardiovascular disease with pravastatin in

Japan (MEGA Study): a prospective randomised controlled trial. *The Lancet*. 2006;368:1155-1163.

156. ALLHAT O, The A and Group CftACR. Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). *JAMA : the journal of the American Medical Association*. 2002;288:2998.

157. Tavazzi L, Maggioni AP, Marchioli R, Barlera S, Franzosi MG, Latini R, Lucci D, Nicolosi GL, Porcu M and Tognoni G. Effect of rosuvastatin in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. *Lancet (London, England)*. 2008;372:1231-1239.

158. Investigators GP. Results of the low-dose (20 mg) pravastatin GISSI Prevenzione trial in 4271 patients with recent myocardial infarction: do stopped trials contribute to overall knowledge. *Italian heart journal : official journal of the Italian Federation of Cardiology*. 2000;1:810-820.

159. Cannon C. Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE IT). *Diabetes*. 1911;91:90.4.

160. LaRosa JC, Grundy SM, Waters DD, Shear C, Barter P, Fruchart J-C, Gotto AM, Greten H, Kastelein JJ and Shepherd J. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *New England Journal of Medicine*. 2005;352:1425-1435.

161. Pedersen TR, Faergeman O, Kastelein JJ, Olsson AG, Tikkanen MJ, Holme I, Larsen ML, Bendiksen FS, Lindahl C and Szarek M. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial. *JAMA : the journal of the American Medical Association*. 2005;294:2437-2445.

162. Amarenco P, Goldstein LB, Szarek M, Sillesen H, Rudolph AE, Callahan A, 3rd, Hennerici M, Simunovic L, Zivin JA, Welch KM and Investigators S. Effects of intense low-density lipoprotein cholesterol reduction in patients with stroke or transient ischemic attack: the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial. *Stroke; a journal of cerebral circulation*. 2007;38:3198-204.

163. Yusuf S, Bosch J, Dagenais G, Zhu J, Xavier D, Liu L, Pais P, López-Jaramillo P, Leiter LA and Dans A. Cholesterol lowering in intermediate-risk persons without cardiovascular disease. *New England Journal of Medicine*. 2016;374:2021-2031.

164. Culver AL, Ockene IS, Balasubramanian R, Olendzki BC, Sepavich DM, Wactawski-Wende J, Manson JE, Qiao Y, Liu S and Merriam PA. Statin use and risk of diabetes mellitus in postmenopausal women in the Women's Health Initiative. *Archives of internal medicine*. 2012;172:144-152.

165. Mansi I, Frei CR, Wang C-P and Mortensen EM. Statins and new-onset diabetes mellitus and diabetic complications: a retrospective cohort study of US healthy adults. *Journal of general internal medicine*. 2015;30:1599-1610.

166. Cederberg H, Stančáková A, Yaluri N, Modi S, Kuusisto J and Laakso M. Increased risk of diabetes with statin treatment is associated with impaired insulin sensitivity and insulin secretion: a 6 year follow-up study of the METSIM cohort. *Diabetologia*. 2015;58:1109-1117.

167. Corrao G, Ibrahim B, Nicotra F, Soranna D, Merlino L, Catapano AL, Tragni E, Casula M, Grassi G and Mancia G. Statins and the risk of diabetes: evidence from a large population-based cohort study. *Diabetes care*. 2014;37:2225-2232.

168. Alberton M, Wu P, Druyts E, Briel M and Mills E. Adverse events associated with individual statin treatments for cardiovascular disease: an indirect comparison meta-analysis. *QJM: An International Journal of Medicine*. 2011;105:145-157.

169. Naci H, Brugts J and Ades T. Comparative tolerability and harms of individual statins. *Circulation: Cardiovascular Quality and Outcomes*. 2013:CIRCOUTCOMES. 111.000071.

170. Mendis S, Abegunde D, Yusuf S, Ebrahim S, Shaper G, Ghannem H and Shengelia B. WHO study on Prevention of REcurrences of Myocardial Infarction and StrokE (WHO-PREMISE). *Bulletin of the World Health Organization*. 2005;83:820-829.

171. Rothwell PM. External validity of randomised controlled trials:"to whom do the results of this trial apply?". *The Lancet*. 2005;365:82-93.

172. Muldoon MF, Ryan CM, Sereika SM, Flory JD and Manuck SB. Randomized trial of the effects of simvastatin on cognitive functioning in hypercholesterolemic adults. *The American journal of medicine*. 2004;117:823-829.

173. Anderssen SA, Hjelstuen AK, Hjermann I, Bjerkan K and Holme I. Fluvastatin and lifestyle modification for reduction of carotid intima–media thickness and left ventricular mass progression in drug-treated hypertensives. *Atherosclerosis*. 2005;178:387-397.

174. Lopez-Jimenez F, Simha V, Thomas RJ, Allison TG, Basu A, Fernandes R, Hurst RT, Kopecky SL, Kullo IJ and Mulvagh SL. A summary and critical assessment of the 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular disease risk in adults: filling the gaps. *Mayo Clinic proceedings*. 2014;89:1257-1278.

175. Study TWsHI. Design of the women's health initiative clinical trial and observational study. *Controlled clinical trials*. 1998;19:61-109.

176. Casula M, Mozzanica F, Scotti L, Tragni E, Pirillo A, Corrao G and Catapano AL. Statin use and risk of new-onset diabetes: A meta-analysis of observational studies. *Nutrition, Metabolism and Cardiovascular Diseases*. 2017;27:396-406.

177. Rothman KJ. Six persistent research misconceptions. *Journal of general internal medicine*. 2014;29:1060-1064.

178. Schrom JR, Caraballo PJ, Castro MR and Simon GJ. Quantifying the effect of statin use in pre-diabetic phenotypes discovered through association rule mining. *AMIA Annual Symposium Proceedings*. 2013;2013:1249.

179. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Savović J, Schulz KF, Weeks L and Sterne JA. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *Bmj*. 2011;343:d5928.

180. Currie O, Mangin D, Williman J, McKinnon-Gee B and Bridgford P. The comparative risk of new-onset diabetes after prescription of drugs for cardiovascular risk prevention in primary care: a national cohort study. *BMJ open*. 2013;3:e003475.

181. Shrier I. Stretching before exercise does not reduce the risk of local muscle injury: a critical review of the clinical and basic science literature. *Clinical Journal of Sport Medicine*. 1999;9:221-227.

182. Sukhija R, Prayaga S, Marashdeh M, Bursac Z, Kakar P, Bansal D, Sachdeva R, Kesan SH and Mehta JL. Effect of statins on fasting plasma glucose in diabetic and nondiabetic patients. *Journal of Investigative Medicine*. 2009;57:495-499.

183. Swerdlow DI, Preiss D, Kuchenbaecker KB, Holmes MV, Engmann JE, Shah T, Sofat R, Stender S, Johnson PC and Scott RA. HMG-coenzyme A reductase inhibition, type 2 diabetes, and bodyweight: evidence from genetic analysis and randomised trials. *The Lancet*. 2015;385:351-361.

184. Food U and Administration D. FDA Drug Safety Communication: Important safety label changes to cholesterol-lowering statin drugs. *Rockville, MD: US Food and Drug Administration*. 2012.

185. Rorsman P and Renström E. Insulin granule dynamics in pancreatic beta cells. *Diabetologia*. 2003;46:1029-1045.

186. Xia F, Xie L, Mihic A, Gao X, Chen Y, Gaisano HY and Tsushima RG. Inhibition of cholesterol biosynthesis impairs insulin secretion and voltage-gated calcium channel function in pancreatic β-cells. *Endocrinology*. 2008;149:5136-5145.

187. Ishikawa M, Okajima F, Inoue N, Motomura K, Kato T, Takahashi A, Oikawa S, Yamada N and Shimano H. Distinct effects of pravastatin, atorvastatin, and simvastatin on insulin secretion from a β-cell line, MIN6 cells. *Journal of atherosclerosis and thrombosis*. 2006;13:329-335.

188. Khan A and Pessin J. Insulin regulation of glucose uptake: a complex interplay of intracellular signalling pathways. *Diabetologia*. 2002;45:1475-1483.

189. Nakata M, Nagasaka S, Kusaka I, Matsuoka H, Ishibashi S and Yada T. Effects of statins on the adipocyte maturation and expression of glucose transporter 4 (SLC2A4): implications in glycaemic control. *Diabetologia*. 2006;49:1881-1892.

190. Chamberlain LH. Inhibition of isoprenoid biosynthesis causes insulin resistance in 3T3-L1 adipocytes. *FEBS letters*. 2001;507:357-361.

191. Fall T, Xie W, Poon W, Yaghootkar H, Mägi R, Knowles JW, Lyssenko V, Weedon M, Frayling TM and Ingelsson E. Using genetic variants to assess the relationship between circulating lipids and type 2 diabetes. *Diabetes*. 2015:db141710.

192. Saleheen D, Rader DJ and Voight BF. Disentangling the Causal Association of Plasma Lipid Traits and Type 2 Diabetes Using Human Genetics. *JAMA cardiology*. 2016;1:631-633.

193. Schmidt AF, Swerdlow DI, Holmes MV, Patel RS, Fairhurst-Hunter Z, Lyall DM, Hartwig FP, Horta BL, Hyppönen E and Power C. PCSK9 genetic variants and risk of type 2 diabetes: a mendelian randomisation study. *The lancet Diabetes & endocrinology*. 2017;5:97-105.

194. Trialists CT. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. *The Lancet*. 2010;376:1670-1681.

195. Sugiyama T, Tsugawa Y, Tseng C-H, Kobayashi Y and Shapiro MF. Different time trends of caloric and fat intake between statin users and nonusers among US adults: gluttony in the time of statins? *JAMA internal medicine*. 2014;174:1038-1045.

196. De Lorgeril M, Renaud S, Salen P, Monjaud I, Mamelle N, Martin J, Guidollet J, Touboul P and Delaye J. Mediterranean alpha-linolenic acid-rich diet in secondary prevention of coronary heart disease. *The Lancet*. 1994;343:1454-1459.

197. Estruch R, Martínez-González MA, Corella D, Salas-Salvadó J, Ruiz-Gutiérrez V, Covas MI, Fiol M, Gómez-Gracia E, López-Sabater MC and Vinyoles E. Effects of a Mediterranean-style diet on cardiovascular risk factors: a randomized trial. *Annals of internal medicine*. 2006;145:1-11.

198. Martínez-González MA, Salas-Salvadó J, Estruch R, Corella D, Fitó M and Ros E. Benefits of the Mediterranean diet: insights from the PREDIMED study. *Progress in cardiovascular diseases*. 2015;58:50-60.

199. Gillman MW. Primordial prevention of cardiovascular disease. *Circulation*. 2015:CIRCULATIONAHA. 115.014849.

200. Niinikoski H, Pahkala K, Ala-Korpela M, Viikari J, Rönnemaa T, Lagström H, Jokinen E, Jula A, Savolainen MJ and Simell O. Effect of repeated dietary counseling on serum lipoproteins from infancy to adulthood. *Pediatrics*. 2012:peds. 2011-1503.

201. Ginsberg HN, Kris-Etherton P, Dennis B, Elmer PJ, Ershow A, Lefevre M, Pearson T, Roheim P, Ramakrishnan R and Reed R. Effects of reducing dietary saturated fatty acids on plasma lipids and lipoproteins in healthy subjects The Delta Study, Protocol 1. *Arteriosclerosis, thrombosis, and vascular biology*. 1998;18:441-449.

202. Simell O, Niinikoski H, Rönnemaa T, Raitakari OT, Lagström H, Laurinen M, Aromaa M, Hakala P, Jula A and Jokinen E. Cohort profile: the STRIP Study (Special Turku Coronary Risk Factor Intervention Project), an infancy-onset dietary and life-style intervention trial. *International journal of epidemiology*. 2009;38:650-655.

203. Navar-Boggan AM, Peterson ED, D'agostino RB, Neely B, Sniderman AD and Pencina MJ. Hyperlipidemia in early adulthood increases long-term risk of coronary heart disease. *Circulation*. 2015:CIRCULATIONAHA. 114.012477.

204. McKenney JM, Davidson MH, Shear CL and Revkin JH. Efficacy and safety of torcetrapib, a novel cholesteryl ester transfer protein inhibitor, in individuals with below-average high-density lipoprotein cholesterol levels on a background of atorvastatin. *Journal of the American College of Cardiology*. 2006;48:1782-1790.

205. Luepker RV, Apple FS, Christenson RH, Crow RS, Fortmann SP, Goff D, Goldberg RJ, Hand MM, Jaffe AS and Julian DG. Case definitions for acute coronary heart disease in epidemiology and clinical research studies. *Circulation*. 2003;108:2543-2549.

206. Curb JD, Mctiernan A, Heckbert SR, Kooperberg C, Stanford J, Nevitt M, Johnson KC, Proulx-Burns L, Pastore L and Criqui M. Outcomes ascertainment and adjudication methods in the Women's Health Initiative. *Annals of epidemiology*. 2003;13:S122-S128.

207. Parmar G, Ghuge P, Halanych JH, Funkhouser E and Safford MM. Cardiovascular outcome ascertainment was similar using blinded and unblinded adjudicators in a national prospective study. *Journal of clinical epidemiology*. 2010;63:1159-1163.

208. Statistics NCfH. Mortality multiple cause micro-data files. 2013. *Public use data file and documentation NHLBI tabulations: National Center for Health Statistics*. 2011.

209. Mensah GA, Wei GS, Sorlie PD, Fine LJ, Rosenberg Y, Kaufmann PG, Mussolino ME, Hsu LL, Addou E and Engelgau MM. Decline in Cardiovascular Mortality. *Circulation research*. 2017;120:366-380.

210. Heidenreich PA, Trogdon JG, Khavjou OA, Butler J, Dracup K, Ezekowitz MD, Finkelstein EA, Hong Y, Johnston SC, Khera A, Lloyd-Jones DM, Nelson SA, Nichol G, Orenstein D, Wilson PW, Woo YJ, American Heart Association Advocacy Coordinating C, Stroke C, Council on Cardiovascular R, Intervention, Council on Clinical C, Council on E, Prevention, Council on A, Thrombosis, Vascular B, Council on C, Critical C, Perioperative, Resuscitation, Council on Cardiovascular N, Council on the Kidney in Cardiovascular D, Council on Cardiovascular S, Anesthesia, Interdisciplinary Council on Quality of C and Outcomes R. Forecasting the future of cardiovascular disease in the United States: a policy statement from the American Heart Association. *Circulation*. 2011;123:933-44.

211. Pfuntner A, Wier L and Steiner C. Healthcare cost and utilization project statistical brief# 168: Costs for hospital stays in the United States, 2011. *Agency for Healthcare Research Quality*. 2013.

212. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H and Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation*. 1998;97:1837-1847.

213. Clark LT, Ferdinand KC, Flack JM, Gavin 3rd J, Hall WD, Kumanyika SK, Reed JW, Saunders E, Valantine HA and Watson K. Coronary heart disease in African Americans. *Heart disease (Hagerstown, Md)*. 2000;3:97-108.

214. Law MR, Wald NJ and Thompson SG. By how much and how quickly does reduction in serum cholesterol concentration lower risk of ischaemic heart disease? *Bmj*. 1994;308:367-72.

215. Labarthe DR. *Epidemiology and prevention of cardiovascular diseases: a global challenge*: Jones & Bartlett Publishers; 2010.

216. Adams HP, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL and Marsh Er. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke; a journal of cerebral circulation*. 1993;24:35-41.

217. Stroke W. Recommendations on stroke prevention, diagnosis, and therapy. Report of the WHO Task Force on Stroke and other Cerebrovascular Disorders. *Stroke; a journal of cerebral circulation*. 1989;20:1407-1431.

218. Howard VJ, Cushman M, Pulley L, Gomez CR, Go RC, Prineas RJ, Graham A, Moy CS and Howard G. The reasons for geographic and racial differences in stroke study: objectives and design. *Neuroepidemiology*. 2005;25:135-143.

219. Carandang R, Seshadri S, Beiser A, Kelly-Hayes M, Kase CS, Kannel WB and Wolf PA. Trends in incidence, lifetime risk, severity, and 30-day mortality of stroke over the past 50 years. *JAMA : the journal of the American Medical Association*. 2006;296:2939-2946.

220. Fang MC, Perraillon MC, Ghosh K, Cutler DM and Rosen AB. Trends in stroke rates, risk, and outcomes in the United States, 1988 to 2008. *The American journal of medicine*. 2014;127:608-615.

221. Ali M, Hazelton C, Lyden P, Pollock A and Brady M. Recovery from poststroke visual impairment: evidence from a clinical trials resource. *Neurorehabilitation and neural repair*. 2013;27:133-141.

222. Murray CJ, Abraham J, Ali MK, Alvarado M, Atkinson C, Baddour LM, Bartels DH, Benjamin EJ, Bhalla K and Birbeck G. The state of US health, 1990-2010: burden of diseases, injuries, and risk factors. *JAMA : the journal of the American Medical Association*. 2013;310:591-606.

223. Reeves MJ, Bushnell CD, Howard G, Gargano JW, Duncan PW, Lynch G, Khatiwoda A and Lisabeth L. Sex differences in stroke: epidemiology, clinical presentation, medical care, and outcomes. *The Lancet Neurology*. 2008;7:915-926.

224. Kissela B, Schneider A, Kleindorfer D, Khoury J, Miller R, Alwell K, Woo D, Szaflarski J, Gebel J and Moomaw C. Stroke in a biracial population. *Stroke; a journal of cerebral circulation*. 2004;35:426-431.

225. Howard G, Anderson R, Sorlie P, Andrews V, Backlund E and Burke GL. Ethnic differences in stroke mortality between non-Hispanic whites, Hispanic whites, and blacks. The National Longitudinal Mortality Study. *Stroke; a journal of cerebral circulation*. 1994;25:2120-2125.

226. Howard VJ, Kleindorfer DO, Judd SE, McClure LA, Safford MM, Rhodes JD, Cushman M, Moy CS, Soliman EZ and Kissela BM. Disparities in stroke incidence contributing to disparities in stroke mortality. *Annals of neurology*. 2011;69:619-627.

227. Howard G and Howard V. Ethnic disparities in stroke: the scope of the problem. *Ethnicity & disease*. 2000;11:761-768.

228. Kleindorfer DO, Khoury J, Moomaw CJ, Alwell K, Woo D, Flaherty ML, Khatri P, Adeoye O, Ferioli S, Broderick JP and Kissela BM. Stroke incidence is decreasing in whites but not in blacks: a population-based estimate of temporal trends in stroke incidence from the Greater Cincinnati/Northern Kentucky Stroke Study. *Stroke; a journal of cerebral circulation*. 2010;41:1326-31.

229. Goldstein LB, Bushnell CD, Adams RJ, Appel LJ, Braun LT, Chaturvedi S, Creager MA, Culebras A, Eckel RH and Hart RG. Guidelines for the primary prevention of stroke. A guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke; a journal of cerebral circulation*. 2010.

230. Iso H, Jacobs Jr DR, Wentworth D, Neaton JD and Cohen JD. Serum cholesterol levels and six-year mortality from stroke in 350,977 men screened for the multiple risk factor intervention trial. *New England Journal of Medicine*. 1989;320:904-910.

231. Collaboration PS. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *The Lancet*. 2002;360:1903-1913.

232. Stamler J, Stamler R and Neaton JD. Blood pressure, systolic and diastolic, and cardiovascular risks: US population data. *Archives of internal medicine*. 1993;153:598-615.

233. Amarenco P and Labreuche J. Lipid management in the prevention of stroke: review and updated meta-analysis of statins for stroke prevention. *The Lancet Neurology*. 2009;8:453-463.

234. Taylor FC, Huffman M and Ebrahim S. Statin therapy for primary prevention of cardiovascular disease. *JAMA : the journal of the American Medical Association*. 2013;310:2451-2452.

235. Martin SS, Metkus TS, Horne A, Blaha MJ, Hasan R, Campbell CY, Yousuf O, Joshi P, Kaul S and Miller M. Waiting for the National Cholesterol Education Program Adult Treatment Panel IV Guidelines, and in the meantime, some challenges and recommendations. *The American journal of cardiology*. 2012;110:307-313.

236. Wald NJ and Morris JK. Assessing risk factors as potential screening tests: a simple assessment tool. *Archives of internal medicine*. 2011;171:286-291.

237. Rabar S, Harker M, O'flynn N and Wierzbicki AS. Lipid modification and cardiovascular risk assessment for the primary and secondary prevention of cardiovascular disease: summary of updated NICE guidance. *BMJ: British Medical Journal (Online)*. 2014;349.

238. Catapano AL, Graham I, De Backer G, Wiklund O, Chapman MJ, Drexel H, Hoes AW, Jennings CS, Landmesser U and Pedersen TR. 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias. *European heart journal*. 2016;37:2999-3058.

239. Karmali KN, Goff DC, Ning H and Lloyd-Jones DM. A systematic examination of the 2013 ACC/AHA pooled cohort risk assessment tool for atherosclerotic cardiovascular disease. *Journal of the American College of Cardiology*. 2014;64:959-968.

240. Mosca L, Benjamin EJ, Berra K, Bezanson JL, Dolor RJ, Lloyd-Jones DM, Newby LK, Piña IL, Roger VL and Shaw LJ. Effectiveness-based guidelines for the prevention of cardiovascular disease in women—2011 update. *Circulation*. 2011:CIR. 0b013e31820faaf8.

241. Trialists CT. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90 056 participants in 14 randomised trials of statins. *The Lancet*. 2005;366:1267-1278.

242. National Heart L and Institute B. Consensus Conference: lowering blood cholesterol to prevent heart disease. *JAMA : the journal of the American Medical Association*. 1985;253:2080-2090.

243. Ernst ND and Cleeman J. Reducing high blood cholesterol levels: recommendations from the National Cholesterol Education Program. *Journal of Nutrition Education*. 1988;20:23-29.

244. Chobanian AV, Alderman MH, DeQuattro V, Frohlich ED, Gifford RW, Hill MN, Kaplan NM, Langford HG, Moore MA and Nickey WA. The 1988 report of the Joint National Committee on detection, evaluation, and treatment of high blood pressure. *Archives of internal medicine*. 1988;148:1023-1038.

245. Reduction NCEPEPoPSfBC and Program NCE. *Report of the Expert Panel on Population Strategies for Blood Cholesterol Reduction*: The Program; 1990.

246. Carleton R, Dwyer J, Finberg L, Flora J and Goodman D. Expert Panel on Population Strategies for Blood Cholesterol Reduction. Report of the Expert Panel on Population Strategies for Blood Cholesterol Reduction: A statement from the National Cholesterol Education Program, National Heart, Lung, and Blood Institute, National Institutes of Health. *Circulation*. 1991;83:2154-2232.

247. Grundy SM. National cholesterol education program: second report of the expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel II). *Circulation*. 1994;89:1329-1445.

248. Brown G, Albers JJ, Fisher LD, Schaefer SM, Lin J-T, Kaplan C, Zhao X-Q, Bisson BD, Fitzpatrick VF and Dodge HT. Regression of coronary artery disease as a result of intensive lipid-lowering therapy in men with high levels of apolipoprotein B. *New England Journal of Medicine*. 1990;323:1289-1298.

249. Grundy SM, Cleeman JI, Merz CNB, Brewer HB, Clark LT, Hunninghake DB, Pasternak RC, Smith SC and Stone NJ. Implications of recent clinical trials for the national cholesterol education program adult treatment panel III guidelines. *Journal of the American College of Cardiology*. 2004;44:720-732.

250. Danesh J, Wheeler JG, Hirschfield GM, Eda S, Eiriksdottir G, Rumley A, Lowe GD, Pepys MB and Gudnason V. C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. *New England Journal of Medicine*. 2004;350:1387-1397.

251. Eckel RH, Jakicic JM, Ard JD, de Jesus JM, Houston Miller N, Hubbard VS, Lee IM, Lichtenstein AH, Loria CM, Millen BE, Nonas CA, Sacks FM, Smith SC, Jr., Svetkey LP, Wadden TA, Yanovski SZ, Kendall KA, Morgan LC, Trisolini MG, Velasco G, Wnek J, Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Curtis LH, DeMets D, Hochman JS, Kovacs RJ, Ohman EM, Pressler SJ, Sellke FW, Shen WK, Smith SC, Jr., Tomaselli GF and American College of Cardiology/American Heart Association Task Force on Practice G. 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;129:S76-99.

252. Lakoski SG, Greenland P, Wong ND, Schreiner PJ, Herrington DM, Kronmal RA, Liu K and Blumenthal RS. Coronary artery calcium scores and risk for cardiovascular events in women classified as "low risk" based on Framingham risk score: the multi-ethnic study of atherosclerosis (MESA). *Archives of internal medicine*. 2007;167:2437-2442.

253. The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. The ARIC investigators. *American journal of epidemiology*. 1989;129:687-702.

254. Fried LP, Borhani NO, Enright P, Furberg CD, Gardin JM, Kronmal RA, Kuller LH, Manolio TA, Mittelmark MB and Newman A. The cardiovascular health study: design and rationale. *Annals of epidemiology*. 1991;1:263-276.

255. Friedman GD, Cutter GR, Donahue RP, Hughes GH, Hulley SB, Jacobs DR, Liu K and Savage PJ. CARDIA: study design, recruitment, and some characteristics of the examined subjects. *Journal of clinical epidemiology*. 1988;41:1105-1116.

256. Dawber TR, Meadors GF and Moore Jr FE. Epidemiological approaches to heart disease: the Framingham Study. *American Journal of Public Health and the Nations Health*. 1951;41:279-286.

257. Feinleib M, Kannel WB, Garrison RJ, McNamara PM and Castelli WP. The Framingham offspring study. Design and preliminary data. *Preventive medicine*. 1975;4:518-525.

258. Grundy SM. The Changing Face of Cardiovascular Risk** Editorials published in the Journal of the American College of Cardiology reflect the views of the authors and do not necessarily represent the views of JACC or the American College of Cardiology. *Journal of the American College of Cardiology*. 2005;46:173.

259. Navar-Boggan AM, Peterson ED, D'Agostino RB, Pencina MJ and Sniderman AD. Using age- and sex-specific risk thresholds to guide statin therapy: one size may not fit all. *Journal of the American College of Cardiology*. 2015;65:1633-1639.

260. Raymond C, Cho L, Rocco M and Hazen SL. New guidelines for reduction of blood cholesterol: Was it worth the wait? *Cleveland Clinic journal of medicine*. 2014;81:11.

261. Ference BA, Yoo W, Alesh I, Mahajan N, Mirowska KK, Mewada A, Kahn J, Afonso L, Williams KA and Flack JM. Effect of long-term exposure to lower low-density lipoprotein cholesterol beginning early in life on the risk of coronary heart disease: a Mendelian randomization analysis. *Journal of the American College of Cardiology*. 2012;60:2631-2639.

262. Han BH, Sutin D, Williamson JD, Davis BR, Piller LB, Pervin H, Pressel SL and Blaum CS. Effect of statin treatment vs usual care on primary cardiovascular prevention among older adults: the ALLHAT-LLT randomized clinical trial. *JAMA Internal Medicine*. 2017.

263. Boekholdt SM, Hovingh GK, Mora S, Arsenault BJ, Amarenco P, Pedersen TR, LaRosa JC, Waters DD, DeMicco DA and Simes RJ. Very low levels of atherogenic lipoproteins and the risk for cardiovascular events: a meta-analysis of statin trials. *Journal of the American College of Cardiology*. 2014;64:485-494.

264. Ahern TP, Lash TL, Damkier P, Christiansen PM and Cronin-Fenton DP. Statins and breast cancer prognosis: evidence and opportunities. *The lancet oncology*. 2014;15:e461-e468.

265. Mansi I and Palmer BF. Statin adverse events in primary prevention: between randomized trials and observational studies. *The American journal of the medical sciences*. 2015;350:330-337.

266. Ford I, Murray H, McCowan C and Packard CJ. Long term safety and efficacy of lowering LDL cholesterol with statin therapy: 20-Year Follow-Up of West of Scotland Coronary Prevention study. *Circulation*. 2016:CIRCULATIONAHA. 115.019014.

267. Lloyd SM, Stott DJ, de Craen AJ, Kearney PM, Sattar N, Perry I, Packard CJ, Briggs A, Marchbank L and Comber H. Long-term effects of statin treatment in elderly people: extended follow-up of the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER). *PloS one*. 2013;8:e72642.

268. Sever PS, Chang CL, Gupta AK, Whitehouse A and Poulter NR. The Anglo-Scandinavian Cardiac Outcomes Trial: 11-year mortality follow-up of the lipid-lowering arm in the UK. *European heart journal*. 2011:ehr333.

269. Sever PS, Poulter NR, Dahlof B, Wedel H, Beevers G, Caulfield M, Collins R, Kjeldsen SE, Kristinsson A and McInnes G. The Anglo-Scandinavian Cardiac Outcomes Trial lipid lowering arm: extended observations 2 years after trial closure. *European heart journal*. 2008;29:499-508.

270. Sterman JD. Learning from evidence in a complex world. *American journal of public health*. 2006;96:505-514.

271. Homer JB and Hirsch GB. System dynamics modeling for public health: background and opportunities. *American journal of public health*. 2006;96:452-458.

272. Moher D, Liberati A, Tetzlaff J and Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *International journal of surgery*. 2010;8:336-341.

273. Guyatt G, Rennie D, Meade M and Cook D. *Users' guides to the medical literature*: McGraw-Hill Medical:; 2015.

274. Wilson K, Gibson N, Willan A and Cook D. Effect of smoking cessation on mortality after myocardial infarction: meta-analysis of cohort studies. *Archives of internal medicine*. 2000;160:939-944.

275. Austin PC. The relative ability of different propensity score methods to balance measured covariates between treated and untreated subjects in observational studies. *Medical Decision Making*. 2009;29:661-677.

276. Sterne JA, Egger M and Smith GD. Systematic reviews in health care: Investigating and dealing with publication and other biases in meta-analysis. *BMJ: British Medical Journal*. 2001;323:101.

277. Sterne JA, Sutton AJ, Ioannidis JP, Terrin N, Jones DR, Lau J, Carpenter J, Rücker G, Harbord RM and Schmid CH. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *Bmj*. 2011;343:d4002.

278. Begg CB and Berlin JA. Publication bias: a problem in interpreting medical data. *Journal of the Royal Statistical Society Series A (Statistics in Society)*. 1988:419-463.

279. Egger M, Smith GD, Schneider M and Minder C. Bias in meta-analysis detected by a simple, graphical test. *Bmj*. 1997;315:629-634.

280. Begg CB and Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics*. 1994:1088-1101.

281. Duval S and Tweedie R. Trim and fill: a simple funnel-plot–based method of testing and adjusting for publication bias in meta-analysis. *Biometrics*. 2000;56:455-463.

282. Preiss D, Seshasai SRK, Welsh P, Murphy SA, Ho JE, Waters DD, DeMicco DA, Barter P, Cannon CP and Sabatine MS. Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis. *JAMA : the journal of the American Medical Association*. 2011;305:2556-2564.

283. Cochran WG. The combination of estimates from different experiments. *Biometrics*. 1954;10:101-129.

284. Higgins JP, Thompson SG, Deeks JJ and Altman DG. Measuring inconsistency in meta-analyses. *BMJ: British Medical Journal*. 2003;327:557.

285. Baker W, Michael White C, Cappelleri J, Kluger J and Coleman C. Understanding heterogeneity in meta-analysis: the role of meta-regression. *International journal of clinical practice*. 2009;63:1426-1434.

286. Centers for Disease Control and Prevention. National Health and Nutrition Examination Survey. 2012;2012.

287. Longstreth WT, Jr. The REasons for Geographic And Racial Differences in Stroke (REGARDS) Study and the National Institute of Neurological Disorders and Stroke (NINDS). *Stroke; a journal of cerebral circulation*. 2006;37:1147.

288. Johnson CL, Paulose-Ram R, Ogden CL, Carroll MD, Kruszan-Moran D, Dohrmann SM and Curtin LR. National health and nutrition examination survey. Analytic guidelines, 1999-2010. 2013.

289. Friedewald WT, Levy RI and Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clinical chemistry*. 1972;18:499-502.

290. Statistics NCfH. Mortality in US 2010. 2010.

291. Briggs AH, Claxton K and Sculpher MJ. *Decision modelling for health economic evaluation*: Oxford University Press, USA; 2006.

292. Goff DC, Jr., Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB, Gibbons R, Greenland P, Lackland DT, Levy D, O'Donnell CJ, Robinson JG, Schwartz JS, Shero ST, Smith SC, Jr., Sorlie P, Stone NJ, Wilson PW, Jordan HS, Nevo L, Wnek J, Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Curtis LH, DeMets D, Hochman JS, Kovacs RJ, Ohman EM, Pressler SJ, Sellke FW, Shen WK, Smith SC, Jr., Tomaselli GF and American College of Cardiology/American Heart Association Task Force on Practice G. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;129:S49-73.

293. Muntner P, Colantonio LD, Cushman M, Goff DC, Howard G, Howard VJ, Kissela B, Levitan EB, Lloyd-Jones DM and Safford MM. Validation of the atherosclerotic cardiovascular disease Pooled Cohort risk equations. *JAMA : the journal of the American Medical Association*. 2014;311:1406-1415.

294. Pro T. TreeAge Software. *Inc Williamstown, MA*. 2014.

295. Kantor ED, Rehm CD, Haas JS, Chan AT and Giovannucci EL. Trends in prescription drug use among adults in the United States from 1999-2012. *JAMA : the journal of the American Medical Association*. 2015;314:1818-1830.

296. Goff DC, Jr., Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB, Sr., Gibbons R, Greenland P, Lackland DT, Levy D, O'Donnell CJ, Robinson JG, Schwartz JS, Shero ST, Smith SC, Jr., Sorlie P, Stone NJ, Wilson PW and American College of Cardiology/American Heart Association Task Force on Practice G. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Journal of the American College of Cardiology*. 2014;63:2935-59.

297. Reuters T. EndNote X7. *Philadelphia: Thomson Reuters*. 2013.

298. Furlan AD, Pennick V, Bombardier C and van Tulder M. 2009 updated method guidelines for systematic reviews in the Cochrane Back Review Group. *Spine*. 2009;34:1929-1941.

299. Bax L, Ikeda N, Fukui N, Yaju Y, Tsuruta H and Moons KG. More than numbers: the power of graphs in meta-analysis. *American journal of epidemiology*. 2008;169:249-255.

300. StataCorp. Stata Statistical Software:Release 15. *College Station, TX: StataCorp LLC*. 2017.

301. Yola M and Lucien A. Evidence of the depletion of susceptibles effect in non-experimental pharmacoepidemiologic research. *Journal of clinical epidemiology*. 1994;47:731-737.

302. Furberg CD, Wright JT, Davis BR, Cutler JA, Alderman M, Black H, Cushman W, Grimm R, Haywood LJ and Leenen F. Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). *JAMA-Journal of the American Medical Association*. 2002;288:2998-3007.

303. Wilke R, Xu H, Denny J, Roden D, Krauss R, McCarty C, Davis R, Skaar T, Lamba J and Savova G. The emerging role of electronic medical records in pharmacogenomics. *Clinical Pharmacology & Therapeutics*. 2011;89:379-386.

304. Menke A, Casagrande S, Geiss L and Cowie CC. Prevalence of and trends in diabetes among adults in the United States, 1988-2012. *JAMA : the journal of the American Medical Association*. 2015;314:1021-1029.

305. Magder LS and Hughes JP. Logistic regression when the outcome is measured with uncertainty. *American journal of epidemiology*. 1997;146:195-203.

306. Lévesque LE, Hanley JA, Kezouh A and Suissa S. Problem of immortal time bias in cohort studies: example using statins for preventing progression of diabetes. *Bmj*. 2010;340:b5087.

307. Navarese EP, Robinson JG, Kowalewski M, Kołodziejczak M, Andreotti F, Bliden K, Tantry U, Kubica J, Raggi P and Gurbel PA. Association between baseline LDL-C level and total and cardiovascular mortality after LDL-C lowering: a systematic review and meta-analysis. *JAMA : the journal of the American Medical Association*. 2018;319:1566-1579.

308. Selby JV, Smith DH, Johnson ES, Raebel MA, Friedman GD and McFarland BH. Kaiser Permanente medical care program. *Pharmacoepidemiology, Fourth Edition*. 2005:241-259.

309. Lawlor DA. Commentary: Two-sample Mendelian randomization: opportunities and challenges. *International journal of epidemiology*. 2016;45:908-15.

310. Riley RD, Lambert PC and Abo-Zaid G. Meta-analysis of individual participant data: rationale, conduct, and reporting. *Bmj*. 2010;340:c221.

311. Cooper H and Patall EA. The relative benefits of meta-analysis conducted with individual participant data versus aggregated data. *Psychological methods*. 2009;14:165.

312. Jick SS and Bradbury BD. Statins and newly diagnosed diabetes. *British journal of clinical pharmacology*. 2004;58:303-309.

313. Sheiner LB and Rubin DB. Intention-to-treat analysis and the goals of clinical trials. *Clinical Pharmacology & Therapeutics*. 1995;57:6-15.

314. Coutinho M, Gerstein HC, Wang Y and Yusuf S. The relationship between glucose and incident cardiovascular events. A metaregression analysis of published data from 20 studies of 95,783 individuals followed for 12.4 years. *Diabetes care*. 1999;22:233-240.

315. Ridker PM, Danielson E, Fonseca F, Genest J, Gotto Jr AM, Kastelein J, Koenig W, Libby P, Lorenzatti AJ and MacFadyen JG. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *New England Journal of Medicine*. 2008;359:2195.

316. Wang K-L, Liu C-J, Chao T-F, Huang C-M, Wu C-H, Chen S-J, Chen T-J, Lin S-J and Chiang C-E. Statins, risk of diabetes, and implications on outcomes in the general population. *Journal of the American College of Cardiology*. 2012;60:1231-1238.

317. Danaei G, Rodríguez LAG, Cantero OF and Hernán MA. Statins and risk of diabetes: an analysis of electronic medical records to evaluate possible bias due to differential survival. *Diabetes care*. 2013;36:1236-1240.

318. Izzo R, De Simone G, Trimarco V, Giudice R, De Marco M, Di Renzo G, De Luca N and Trimarco B. Primary prevention with statins and incident diabetes in hypertensive patients at high cardiovascular risk. *Nutrition, Metabolism and Cardiovascular Diseases*. 2013;23:1101-1106.

319. Chen C-W, Chen T-C, Huang K-Y, Chou P, Chen P-F and Lee C-C. Differential impact of statin on new-onset diabetes in different age groups: a population-based case-control study in women from an asian country. *PloS one*. 2013;8:e71817.

320. Zaharan NL, Williams D and Bennett K. Statins and risk of treated incident diabetes in a primary care population. *British journal of clinical pharmacology*. 2013;75:1118-1124.

321. Bhattacharya R, Ajmera M, Bhattacharjee S and Sambamoorthi U. Use of antidepressants and statins and short-term risk of new-onset diabetes among high risk adults. *Diabetes research and clinical practice*. 2014;105:251-260.

322. Radford NB, DeFina LF, Barlow CE, Kerr A, Chakravorty R, Khera A and Levine BD. Effect of fitness on incident diabetes from statin use in primary prevention. *Atherosclerosis*. 2015;239:43-49.

323. Olotu BS, Shepherd MD, Novak S, Lawson KA, Wilson JP, Richards KM and Rasu RS. Use of statins and the risk of incident diabetes: a retrospective cohort study. *American Journal of Cardiovascular Drugs*. 2016;16:377-390.

324. Rha S-W, Choi BG, Seo HS, Park S-H, Park JY, Chen K-Y, Park Y, Choi SY, Shim M-S and Kim JB. Impact of statin use on development of new-onset diabetes mellitus in Asian population. *American Journal of Cardiology*. 2016;117:382-387.

325. Engeda JS, A; White, M; Rosamond, WD; Lhachimi, SK; Lund, JL; Keyserling, TC; Avery, CL. Evidence of heterogeneity in statins-associated type 2 diabetes risk: a meta-analysis of randomized controlled trials and observational studies. *Under Review*. 2018.

326. US Census Bureau Population Estimates. Vintage 2012: Downloadable Data Files.

327. Colantonio LD, Tanner RM, Monda KL, Dent R, Farkouh ME, Taylor B, Rosenson RS, Muntner P and Safford MM. Age, Sex, and Race Differences in Statin Discontinuation and Side Effect Patterns. The REasons for Geographic And Racial Differences in Stroke (REGARDS) Study. 2016.

328. Cheung BM, Lauder IJ, Lau CP and Kumana CR. Meta-analysis of large randomized controlled trials to evaluate the impact of statins on cardiovascular outcomes. *British journal of clinical pharmacology*. 2004;57:640-651.

329. Eckel RH, Jakicic JM, Ard JD, de Jesus JM, Houston Miller N, Hubbard VS, Lee IM, Lichtenstein AH, Loria CM, Millen BE, Nonas CA, Sacks FM, Smith SC, Jr., Svetkey LP, Wadden TA, Yanovski SZ and American College of Cardiology/American Heart Association Task Force on Practice G. 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Journal of the American College of Cardiology*. 2014;63:2960-84.

330. Cook RJ and Sackett DL. The number needed to treat: a clinically useful measure of treatment effect. *BMJ: British Medical Journal*. 1995;310:452.

331. Citrome L and Ketter T. When does a difference make a difference? Interpretation of number needed to treat, number needed to harm, and likelihood to be helped or harmed. *International journal of clinical practice*. 2013;67:407-411.

332. Design and estimation for the National Health Interview Survey, 1995-2004. *Vital Health Stat 2*. 2000:1-31.

333. Sattar N. Gender aspects in type 2 diabetes mellitus and cardiometabolic risk. *Best practice & research Clinical endocrinology & metabolism*. 2013;27:501-507.

334. Yeh RW, Sidney S, Chandra M, Sorel M, Selby JV and Go AS. Population trends in the incidence and outcomes of acute myocardial infarction. *The New England journal of medicine*. 2010;362:2155-65.

335. Sidney S, Quesenberry CP, Jaffe MG, Sorel M, Nguyen-Huynh MN, Kushi LH, Go AS and Rana JS. Recent trends in cardiovascular mortality in the United States and public health goals. *JAMA cardiology*. 2016;1:594-599.

336. Benjamin EJ, Virani SS, Callaway CW, Chamberlain AM, Chang AR, Cheng S, Chiuve SE, Cushman M, Delling FN and Deo R. Heart disease and stroke statistics—2018 update: a report from the American Heart Association. *Circulation*. 2018;137:e67-e492.

337. Nelson S, Whitsel L, Khavjou O, Phelps D and Leib A. Projections of Cardiovascular Disease Prevalence and Costs. 2016.

338. Haffner SM, Lehto S, Rönnemaa T, Pyörälä K and Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *New England journal of medicine*. 1998;339:229-234.

339. Bulugahapitiya U, Siyambalapitiya S, Sithole J and Idris I. Is diabetes a coronary risk equivalent? Systematic review and meta-analysis. *Diabetic Medicine*. 2009;26:142-148.

340. Oesterle A, Laufs U and Liao JK. Pleiotropic effects of statins on the cardiovascular system. *Circulation research*. 2017;120:229-243.

341. McCarey DW, McInnes IB, Madhok R, Hampson R, Scherbakova O, Ford I, Capell HA and Sattar N. Trial of Atorvastatin in Rheumatoid Arthritis (TARA): double-blind, randomised placebo-controlled trial. *The Lancet*. 2004;363:2015-2021.

342. Bjarnadottir O, Romero Q, Bendahl P-O, Jirström K, Rydén L, Loman N, Uhlén M, Johannesson H, Rose C and Grabau D. Targeting HMG-CoA reductase with statins in a window-of-opportunity breast cancer trial. *Breast cancer research and treatment*. 2013;138:499-508.

343. Ramos R, Comas-Cufí M, Martí-Lluch R, Balló E, Ponjoan A, Alves-Cabratosa L, Blanch J, Marrugat J, Elosua R and Grau M. Statins for primary prevention of cardiovascular events and mortality in old and very old adults with and without type 2 diabetes: retrospective cohort study. *Bmj*. 2018;362:k3359.