POLYMORPHISMS IN REVERSE CHOLESTEROL TRANSPORT PATHWAY-RELATED GENES AND THEIR RELATIONSHIP WITH COMPLEX HEART DISEASES IN HUMAN POPULATIONS

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ABSTRACT

POLYMORPHISMS IN REVERSE CHOLESTEROL TRANSPORT PATHWAY-RELATED GENES AND THEIR RELATIONSHIP WITH COMPLEX HEART DISEASES IN HUMAN POPULATIONS

Cardiovascular diseases have been one of the major causes of mortality worldwide. Genetic factors within the underlying mechanisms are extensively studied but still remain unclear at certain points of views. This master's thesis investigates the genetic factors as single nucleotide polymorphisms and their relationship with complex heart diseases in human populations.

The study employs a comprehensive approach integrating molecular genetics, epidemiology and biostatistics to analyze diverse range of genetic variations within the reverse cholesterol pathway (RCT) playing a role in the cholesterol homeostatis. In a systematic review perspective, by conducting meta-analyses of existing clinical data in literature, the study aims to examine and identify single nucleotide polymorphisms with an increased risk of complex heart disease. Furthermore, the study aims to enrich the set of variants related to coronary heart disease (CHD) and high-density lipoprotein cholesterol (HDL-C) by determination of additional variants in linkage disequilibrium pairs and functional annotation of variants with potential effects.

Publicly available clinical data regarding to the relationships of variants and their effects enabled us to explore the underlying genetic factors of higher CHD risk. The findings have the potential to improve future research directions, clinical practice, and public health initiatives aimed at reducing the global burden of cardiovascular diseases.

ÖZET

TERS KOLESTEROL TAŞINMA YOLLARI İLE İLİŞKİLİ GENLERDEKİ POLİMORFİZMLER VE BUNLARIN İNSAN POPÜLASYONLARINDAKİ KOMPLEKS KALP HASTALIKLARI İLE İLİŞKİSİ

Kardiyovasküler hastalıklar dünya genelinde ölümün önemli nedenlerinden biri olmuştur. Temel mekanizmaları yöneten genetik faktörler yoğun bir şekilde incelenmiş olsa da, bazı bakış açılarından hala belirsizlikler devam etmektedir. Bu yüksek lisans tezi insan genomunda kardiyovasküler hastalıklarla ilişkilendirilme potansiyeline sahip tek nükleotid polimorfizmleri (SNP) ve bunların insan popülasyonlarında etkisini incelemeyi hedeflemiştir.

Çalışma, kolesterol homeostazında rol oynayan ters kolesterol yolundaki genetik varyasyonları analiz etmek için moleküler genetik, epidemiyoloji ve biyoistatistikleri entegre eden kapsamlı bir yaklaşım kullanmaktadır. Sistematik inceleme perspektifinden, literatürde mevcut klinik verilerin meta-analizlerini yaparak, çalışma karmaşık kalp hastalığına artan risk taşıyan tek nükleotid polimorfizmlerini incelemeyi ve tanımayı amaçlamaktadır.

Ayrıca, çalışma koroner kalp hastalığı (KKH) ve yüksek yoğunluklu lipoprotein kolesterolü (HDL-C) ile ilgili varyant grubunu zenginleştirmeyi amaçlayarak, bağlantı dengesizlik çiftlerindeki ek varyantların belirlenmesi ve potansiyel etkileri olan varyantların fonksiyonel bir şekilde anotasyonunu hedeflemektedir.

Varyantların ilişkileri ve etkileri hakkında genelde bulunan klinik veriler, bize daha yüksek KKH riskinin altında yatan genetik faktörleri keşfetme olanağı tanımıştır. Bulgular, gelecekteki araştırma eğilimlerini, klinik uygulamaları ve kardiyovasküler hastalıkların global etkisini azaltmaya yönelik girişimleri bilgilendirecek potansiyele sahiptir.

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LIST OF ABBREVIATIONS

ABCA1 **:** ATP-binding cassette subfamily A member 1

ApoA-I **:** Apolipoprotein A-I

ARH **:** Autosomal-Recessive Hypercholesterolemia

CAD **:** Coronary Artery Disease

CETP **:** Cholesterol Ester Transfer Protein

CHD **:** Coronary Heart Disease

CI **:** Confidence Interval

CM **:** Chylomicron

CVD **:** Cardiovascular Disease

FDB **:** Familial Defective ApoB

FH **:** Familial Hypercholesterolemia

GLCL **:** Global Lipids Genetics Consortium

GWAS **:** Genome-Wide Association Studies

HDL **:** High-Density Lipoprotein

HDL-C **:** High-Density Lipoprotein Cholesterol

IHD **:** Ischemic Heart Disease

LCAT **:** Lecithin-Cholesterol Acyltransferase

LDL **:** Low-Density Lipoprotein

LDL-C **:** Low-Density Lipoprotein

LIPC **:** Hepatic Lipase

LIPG **:** Endothelial Lipase

LPL **:** Lipoprotein Lipase

LRP **:** LDL receptor-related protein

MAF **:** Minor Allele Frequency

MI **:** Myocardial Infarction

OR **:** Odds Ratio

preβ1-HDL **:** pre-beta high-density lipoprotein

PRISMA **:** Preferred Reporting Items for Systematic Reviews and Meta-Analyses

RCT : Reverse Cholesterol Transport Pathway

SMD : Standardized Mean Difference

SNP : Single Nucleotide Polymorphism

SR-BI : Scavenger Receptor Class B Member 1

SREBP : Sterol Regulatory Element Binding Protein

STR : Short Tandem Repeats

TG : Triglyceride

TRL : Triglyceride-rich lipoprotein

VLDL : Very Low-Density Lipoprotein

α-HDL : alpha high-density lipoprotein

CHAPTER 1

INTRODUCTION

1.1. Introduction to Cholesterol Metabolism

Human cholesterol metabolism is complicated process, which can be influenced by both endogenous and exogenous effects through different mechanisms. Considering the vital roles in cell structure including the composition of cell membrane, the synthesis of essential hormones, studies about this subject are of capital importance (Vance et al. 2008). Cholesterol can be produced exogenously by cells or can be acquired from the diet (Caballero et. al. 2003). As might be expected, there are various factors affecting the procedures which increase or decrease the levels of cholesterol in the body (Cabellero et al. 2003). Consequently, this metabolism proves to be a significant and challenging subject of study.

Different organs have responsibility to tightly regulate the levels of cholesterol in the body, especially liver and intestines. Before these mechanisms are handled in these organs, cholesterol must be transported to these units through plasma. Since these biological molecules are insoluble in the plasma, they must be processed by a set of actions (Caballero et al. 2003). Therefore, these hydrophobic lipids are packaged inside a unit which has a polar and charged single layer outer side consisting of lipoproteins and lipid-rich, mostly cholesterol esters and triglycerides, inner side. Thus, the cholesterol molecules can be transported through blood (Vance et al. 2008).

1.2. Overview of Lipid Transport Mechanisms

One of the fundamental processes in lipid metabolism requires the efficient transport of lipids to the responsible organs and tissues (Nghiem-Rao et al. 2014). For this reason, there are different ways to alter the levels of lipids in human body, synthesis of cholesterol endogenously and supplement of lipids from the diet exogenously (Feingold et al. 2000). Depending on the source of lipids, particular types of lipids are processed via specific lipoproteins to reach specific organs, such as the liver and intestines (Nghiem-Rao et al. 2014). As mentioned in the previous context, there are five important classes of lipoproteins based on size, and composition which takes part in the transport of different types of lipids (Feingold et al. 2000). Three main pathways provides the steps to carry the lipids acquired from small intestine and liver. These pathways are exogenous, endogenous, and reverse transport pathways which are performed by chylomicrons, low-density lipoproteins and high-density lipoproteins respectively (Feingold et al. 2000).

1.2.1. Chylomicrons and Exogenous Pathway

Chylomicrons are the lightest and the largest lipoprotein class which carries the emulsified dietary lipids such as triacylglycerol, phospholipids, and cholesteryl esters for the intestinal digestion. Cholesteryl esters are hydrolyzed into unesterified cholesterol and free fatty acids (Feingold et al. 2000). Triacylglycerols are hydrolyzed into 2-monoglycerol and free fatty acids. After these transformations are processed, intestinal epithelial cells absorb the products and package them into chylomicrons to enable products to be soluble for transporting through the aqueous lymph fluid and blood (Dash et al.2015).

As it has been mentioned earlier, depending on the class of specific lipoproteins, there is a particular composition such as apolipoprotein types for each one. Chylomicrons (CM) are mainly triglyceride-rich lipoproteins (TRL) which are formed in enterocytes (Rahmany et al. 2019). Their only and the one non-exchangeable component is the

apolipoprotein B-48 [5, 6]. Besides, they contain other apolipoproteins such as *ApoA-I*, *ApoA-*II, *ApoC-II*, *ApoC-III*, *ApoE* and the others. Each of these components have a distinct assignment in the lipid transport pathways. The main structural protein, apoB-48, is a need for the secretion of the chylomicrons from intestinal cells to lymph fluid where they pass through the systemic circulation (Xiao et al. 2019). Likewise, other apolipoproteins in the composition, act as a cofactor for enzymes such as lipoprotein lipase (*LPL*) or act as a building units for other types of lipoproteins such as high-density lipoprotein (HDL). Also, *ApoA-I* levels of the chylomicrons begin to decrease and other types of apolipoproteins such as ApoE, ApoC-II are brought into the structure because of the interaction with HDL particles (Dashti et al. 2011).

Afterwards, chylomicrons are in the systemic circulation, they interact with the endothelial cells of arterioles. Main enzyme incorporated in this pathway is *LPL* which is expressed at high levels in muscle and adipose tissue. The enzyme is transported to capillaries where they are anchored to capillary endothelial cell surface. Lipoprotein lipases in these endothelial cells are activated with the incorporation of ApoC-II and they hydrolyze the triacylglycerols into free fatty acids and glycerol which are absorbed by muscle cells and adipocytes for energy storage or production (Dashti et al. 2011). In the course of hydrolysis, phospholipids and apolipoproteins such as Apo-A's and Apo-CII are removed from the surface of chylomicrons. The resulting structure is called as "chylomicron remnant" which is smaller in size and later transferred to other lipoproteins such as high-density lipoproteins. After the removal of Apo-CII, activity of *LPL* begin to decrease and the remnants are removed by the liver. Remaining apolipoproteins such as Apo-E on the surface of the chylomicron remnants are bound to low-density lipoprotein receptors or other hepatic receptors [5-7]. Also, the remaining chylomicron remnant contains less triacylglycerols and more esterified cholesterol which will be removed fast after the interaction with LDL receptor-related protein (LRP) on the surface of hepatic cells (Xiao et al. 2019).

1.2.2. Low-Density Lipoproteins and Endogenous Pathway

Endogenous pathway of lipid transport contains three classes of lipoproteins which are very low-density lipoproteins (VLDL), intermediate density lipoproteins (IDL) and low-density lipoproteins (LDL) (Feingold et al. 2000). During the processing of this pathway, conversion of the excess fatty acids and cholesterol into triacylglycerols and cholesteryl esters is conducted in the liver. After the conversion of these lipids, they are packaged into VLDL particles which are lipoproteins responsible for the movement of endogenously produced lipids from the liver to other tissues for energy production or storage (Nghiem-Rao et al. 2014).

VLDL molecules is mainly composed of ApoB-100 and other apolipoproteins such as ApoC-I, ApoC-II, ApoC-III, and ApoE (Venugopal et al. 2019). Some of these components are found in the newly secreted particles like ApoB-100 and ApoC-I but some of them are transferred from HDL particles such as ApoC-II and ApoE (Beisiegel et al. 1989). VLDL is transported to the targeted tissues such as adipose, and muscles similar way to how chylomicrons are transported. After VLDL is transported to the tissues, *LPL* found on the surface of cells in these tissues interacts with ApoC-II and breaks down the triglycerides in the composition of VLDL with the same way it does with chylomicrons (Francke et al. 1984). Also, released fatty acids are taken up by the tissues. Remaining VLDL particles are called as "VLDL remnants" which later form the IDL particles with hydrolysis of core triacylglycerol molecule (Hevonoja et al. 2000).

IDL particles are smaller in size and denser than the VLDL particles. Also, their triglyceride composition is less than VLDL particles. The IDL particles can be cleared from the systemic circulation by the liver like chylomicron remnants upon the interaction of ApoE with LDL and LRP receptors. Remaining IDL particles are transformed into cholesteryl ester-rich LDL particles upon the interaction with hepatic lipase (HL) (Segrest et al. 2001).

LDL particles are the last product of VLDL metabolism (Yang et al. 2018). These lipid-carrying molecules contain mostly cholesteryl esters, triglycerides which is less than the VLDL carries and free cholesterol which is unesterified. Its protein structure is mainly composed of ApoB-100 which is one of the non-exchangeable apolipoproteins. Basic task of the LDL particles is to accompany the free cholesterol to muscle, gonads and adipose

tissue. The interaction between the tissues and LDL is provided by the recognition of ApoB-100 by the LDL receptors on these tissues (Yang et al. 2001). Cells in the tissues are able to internalize the LDL particles after the interaction between the ligand and the receptor. After the endocytosis of LDL particles, degradation of them is done by the lysosomes (Hevonoja et al. 2000). Cholesteryl esters found in the core of LDL are transformed into unesterified free cholesterol and free fatty acids. Free cholesterol in the cells regulates the rate-limiting step of cholesterol biosynthesis that is conducted by HMG-CoA reductase. Also, cholesteryl ester levels against the free cholesterol levels is controlled by acyl cholesterol acyl transferase (ACAT).

The LDL which is not processed through endocytosis by the tissues, return to the liver and recognized by LDL receptors on the liver cells and the cholesterol carried by LDL is transformed to bile-acids or esterified and stored. The procedure which determines the levels of plasma LDL is the rate of LDL production and LDL clearance. The rate of production and clearance are conducted in the hepatic cells which are able to regulate the levels of LDL receptors after the notification of increases and decreases in the hepatic cholesterol levels

Low cholesterol levels in the cells requires other elements such as transcription factors for activation of lipid metabolism-related gene transcription (Venugopal et al. 2019). Sterol regulatory element binding proteins (SREBPs) found in endoplasmic reticulum are transported to Golgi to be activated and increases the expression of LDL receptors in hepatic cells as a transcription factor in the nucleus (Venugopal et al. 2019). Also, they mediate the transcription of HMG-CoA reductase which increases the rate of cholesterol production. Increases in the transcription of LDL receptors, hepatic cells are able to interact with the remaining LDL particles and hydrolyze the lipid core to increase the internal cholesterol levels leading to LDL clearance in the plasma. When the cholesterol levels are high in the cells, SREBPs are not transported to the nucleus. Eventually in a converse way, LDL receptor expression slows down and cells are less able to recognize the LDL particles leading plasma LDL levels to increase (Venugopal et al. 2019).

1.2.3. High-Density Lipoproteins and Reverse Cholesterol Transport Pathway

High-density lipoprotein (HDL) plays a pivotal role in the reverse cholesterol transport (RCT) pathways which involves the removal of cholesterol from peripheral cells and its subsequent transportation back to the liver for disposal (Brunham et al. 2015).

HDL metabolism synthesizes the needed amount of HDL to carry the cholesterol to the liver. HDL is primarily composed of Apolipoprotein A1 (*ApoA-I*) which is dominantly secreted by the liver and intestines. Later, *ApoA-I* known as pre-beta HDL which is the backbone of HDL particles interacts with cholesterol and phospholipids from hepatocytes and enterocytes which are also found in the liver and intestines respectively (Zhou et al. 2015). The interaction between the newly synthesized apolipoprotein which is also called as pre-beta HDL (preβ1-HDL) and the other components is facilitated by a transporter protein called as ATP-binding cassette subfamily A member 1 (*ABCA1*) (Duong et al. 2008). The tissues involved in this metabolism which are composed of muscle cells, adipocytes and other cells are able to express *ABCA1* are able to transport the phospholipids and cholesterol to the lipid-poor preβ1-HDL. In addition to the incorporation of lipids from these cells, the lipid-poor HDL is also able to obtain these lipids from chylomicrons and VLDL during interaction with *LPL* (Brunham et al. 2015).

Even if the *ABCA1* has an important role to transfer the lipids to HDL particle, it is not sufficient for the formation of mature HDL particles. As HDL particles is composed of different molecules such as cholesteryl ester and triglycerides in the core and a shell containing phospholipids, free cholesterol and proteins, there are enzymes and transfer proteins affecting the size of HDL particles. After the transfer of lipids to preβ1-HDL, small HDL particles are produced. The cholesterol transferred from the cells via *ABCA1*, is free cholesterol which is localized to the shell of the HDL particles. In order to form a more mature HDL particle which has a core composed of cholesteryl esters and triglycerides, free cholesterol on the surface of HDL must be esterified with a process that is catalyzed by lecithin-cholesterol acyltransferase (*LCAT*). A fatty acid from phospholipids on the shell is transferred to the free cholesterol for the formation of cholesterol ester by the esterification process of *LCAT* (Zhou et al. 2015). With the action of *LCAT*, newly-synthesized cholesterol esters are able to move from the outer side of the

particle to the core of the particle. *LCAT* can be found as a free enzyme or associated with the lipoproteins such as LDL and HDL. Also the movement of free cholesterol from the surface to the core after the esterification process enables more transportation of cholesterol from the muscle cells, adipocytes and others. Eventually, this process produces a larger particle of HDL which is also called as "α-HDL" (Brunham et al. 2015).

With the activity of *LCAT*, HDL particles with a core composed of cholesterol esters are able to be processed in two ways which are named as indirect or direct reverse cholesterol transport. Both of the pathways include the same processing of HDL particles for maturation, but for the transport of cholesterol back to the liver, indirect pathway uses a longer procedure (Brunham et al. 2015).

Indirect RCT pathway is composed of elements such as VLDL, LDL, *CETP*, LDL-R, and *LPL*. After the maturation of HDL particles, cholesterol ester transfer protein (*CETP*) takes role in the exchange of cholesterol esters in HDL particles with the triglycerides from the ApoB-containing lipoproteins such as VLDL, LDL resulting in triglyceride-rich HDL particles (Brunham et al. 2015). This step forms cholesterol-containing VLDL and LDL particles which can be transferred back to the liver and taken by LDL receptor. Also, triglyceride-rich HDL particles can be hydrolyzed by hepatic lipase which is encoded by *LIPC* gene to small HDL particles. There are two more lipases which are endothelial lipase and lipoprotein lipase which are encoded by *LIPG* and *LPL* genes respectively. Endothelial lipase is responsible for the hydrolysis of phospholipids carried by HDL particles and lipoprotein lipase takes action on triglyceride-rich LDL and VLDL particles. These lipase classes are secreted into the plasma after they are predominantly synthesized by muscle cells, and adipocytes (Brunham et al. 2015).

In the direct RCT pathway, resulting smaller and cholesterol-rich α-HDL particles is transported back to the liver where they interact with scavenger receptor class B member 1 (SR-BI) (Duong et al. 2008). This receptor class has a high affinity for the cholesterol enriched HDL particles (Brunham et al. 2015). After, the interaction between these elements, cholesterol carried by HDL is selectively taken up by the liver. The pathway does not internalize the HDL particles. The resulting HDL is a cholesterol depleted and a smaller version of HDL. The HDL particles are later released back into the circulation (Zhao et al. 2015).

1.3. Cholesterol Metabolism and Cardiovascular Diseases

Cardiovascular diseases are one of the most important worldwide issues when considering its extensity and mortality. Since it has become the leading cause of death globally, research areas about cardiology related issues is a need to understand the details and causes of the heart-related diseases and find a solution (Vos et al. 2016).

There are various diseases related to circulatory system in the human body such as congenital heart disease, arrhythmia, coronary heart disease, myocardial infarction and others [20]. In my subject, I will focus on a type of cardiovascular disease, coronary artery disease (CAD) which is also named as ischemic heart disease (IHD) or coronary heart disease (CHD). This specific type of heart disease caused 46% and 38% of total deaths related to heart diseases in men and women respectively (Wenger et al. 2010).

Ischemia is the term to define the circulation which is not enough for a location or an organ in the body that is due to blockage of circulation in the blood vessels. Narrowing of the arteries that carry blood to the heart can also be named as "atherosclerosis". Atherosclerosis is due to the deposition of fatty material and cholesterol on the lumen of arteries causing the clots which result in the irregular circulation of blood to the heart over many years. The development of atherosclerosis in the arteries feeding the heart muscles is the ischemic heart disease. The blockage of blood circulation through heart muscles can cause the depletion in the oxygen levels in the muscle cells. Eventually, with the presence of coronary artery disease, the body is at the higher risks of resulting in a myocardial infarction which is the scientific term for the heart attack (Wenger et al. 2010)

There are two types of risk factors causing the coronary heart disease which are behavioral and genetic factors. Behavioral factors include the smoking, unhealthy nutrition, alcohol use and physical inactivity. Genetic factors are mainly related to metabolism such as blood pressure, blood sugar and lipids and obesity which are also the causes of other issues such as cholesterol, diabetes. As the behavioral factors can be intervened with the help of specialists in these areas, genetic factors must be studied to dig deep into the mechanisms involved in the complex pathology of the coronary heart disease (Strong et al. 2010).

1.3.1. Genetic Risk Factors of Coronary Artery Disease

Genetic risk is a term used to define the contribution of our genes related to certain systems in possession of specific diseases. The genes that play a role in this process are not the only deciding factor whether or not a human will possess the disease, since the progression of diseases have complex genetic mechanisms. As most of the diseases are candidates for genetic studies to be enlightened by the technological advances in areas such as bioinformatics, genome-wide association studies, coronary artery disease is one of the leading diseases in human populations. With the knowledge that is being collected over many years, coronary artery disease is known to have a complex pathophysiology.

1.3.1.1 Monogenic Disorders in Cholesterol Metabolism

Since the coronary heart disease is based on atherosclerotic events caused by lipid accumulation, the first theory coming into the minds is the lipid metabolism and its products circulating through the arteries and its relationship with the atherosclerosis. The lipid metabolism is known to be one of the most pivotal causes of the heart diseases over sixty years. With the first advances in biology, monogenic disorders related to the decreases and increases in the serum LDL and HDL levels are discovered and thought to be the main cause of the heart diseases. This type of disorders are generally caused by distinct mechanisms, hence they are easily diagnosed by the observation of phenotypes (Freeman et al. 2006).

Three monogenic LDL disorders have been observed in the patients with altering levels of LDL (Strong et al. 2010). These are familial hypercholesterolemia (FH), autosomal-recessive hypercholesterolemia (ARH) and familial defective ApoB (FDB) (Wenger et al. 2010). These disorders are generally caused by the mutations in one allele resulting in the disrupted structure of an element in the metabolism.

Individuals with FH carry a mutation in an allele of a gene encoding for LDL receptor which has an important role in the clearance of LDL by the liver (Dron et al. 2016). With the disruption of LDL receptor, this metabolism is not fully completed and results in the increases of LDL levels in the serum. Besides the effects in the LDL levels,

the disorder is inherited autosomal-codominantly and have increasing effects depending on being heterozygous or homozygous (Freeman et al. 2006). As well as FH patients, ARH patients shows similar clinical symptoms, but the important differentiating factor between two disorders is that ARH is inherited autosomal-recessively which results in a higher but not enough LDL receptor activity.

FDB patients have a disorder caused by mutations close to the carboxy terminus of Apo B which is commonly resulting in a non-synonymous change in the amino acid composition (Freeman et al. 2006). The disorder is inherited autosomal-codomoninantly and most of the patients carry the mutation heterozygously. Since the LDL particles have a backbone primarily composed of Apo B, heterozygous have only one molecule of Apo B in one LDL particle leading to abnormal interaction with LDL receptor. Therefore, the clearance of LDL particles are processed more slowly.

Three monogenic HDL disorders are studied and they have distinctly discovered mechanisms which lead the noticeably decreased levels of HDL. These disorders are generally caused by mutations in the HDL metabolism-related genes in a similar way to monogenic LDL disorders. They are Tangier disease, lecithin cholesterol acyltransferase deficiency (*LCAT* deficiency) and *ApoA-I* mutations (Freeman et al. 2006).

Tangier disease is inherited in a fashion which is autosomal-recessive. It is known to affect the gene encoding for the *ABCA1* which is activated by the basic element of HDL particles and regulates the efflux of cholesterol from cholesterol-rich cells. With the disrupted transporter, the patients has a higher risk of coronary artery diseases (Dron et al. 2016).

The *LCAT* deficiency in individuals result in two clinical syndromes which are fish eye disease and familial *LCAT* deficiency. Considering the role of *LCAT* in the LDL and HDL metabolism, it is needed for the esterification of free cholesterol carried by the lipoproteins and important for the proper transport of cholesterol. Fish eye disease patients has a partial deficient version of *LCAT* that comes with a very low HDL cholesterol levels. Familial *LCAT* deficiency is a more severe type with the observation of symptoms such as renal failure and corneal opacities. Characterization of this disorder is checked by the increases in triglyceride levels and decreases in LDL and HDL levels in the blood (Freeman et al. 2006).

Considering the importance of *ApoA-I* protein's role in the functioning of HDL particles, *ApoA-I* mutations give rise to irregular levels of HDL. Patients with altered structures of this apolipoprotein have almost no circulating HDL and they are at a high

risk of developing early coronary heart disease even if the particular variation in this gene is rare. Most of the patients are homozygous for the mutation. Heterozygous patients carrying a normal allele of *ApoA-I* would eventually have one disrupted allele which is used as a unit for most HDL particles (Freeman et al. 2006)

In summary the explained disorders are molecular genetic defections that are responsible for the abnormal lipid levels in the plasma. The defects contain mutations that cause irregular structures of elements in lipid metabolism such as LDL receptor, *ABCA1*, *LCAT* and ApoB. Apart from these disorders, most of other disorders are due to the mutations affecting the regular operation of lipid metabolism resulting in the markedly decreasing and increasing of serum lipid levels in the blood. It is mainly proven that most of the monogenic disorders that are contributing to the coronary heart disease risk. Since the first discovery of an inverse correlation between HDL and LDL serum lipid levels in the progression of atherosclerosis causing the coronary heart disease, elevated levels of LDL and decreased levels of HDL are thought to be the one of the causative factors in the possession of CHD.

1.3.1.2 Genome-Wide Association Studies and Insights into the Cardiovascular Diseases

Emerging technologies and methods over the past 20 years made a way for various path-breaking projects performed such as 1000Genome Project, HapMap project and others (International HapMap Consortium, 2003). These projects have provided more insights into the genetics of lipid metabolism and disorders related to a range of genes that are affected with the common and rare genetic variants. These advances in molecular biology, opened a new door into the complex mechanism of the pathophysiology of heart diseases. Until the new findings about the cholesterol metabolism and its relationship with the complex heart diseases, phenotypically more observable disorders which are mentioned above are more known to have more causative agents with the emergence of variant mining through genome-wide association studies.

Publications related to genome-wide association studies (GWAS) have evaluated the genetic determinants of these disorders or variants that are effective in the alterations

of serum lipid levels through different mechanism (Teslovich et al. 2010). The studies conducted by Global Lipids Genetics Consortium (GLGC) revealed common and rare genetic variants contributing the changes in lipids and lipoproteins depending on the different populations. One of the landmark studies of GLGC, explained the 10-20% of variation in total, HDL-C, LDL-C and TG and other genetic factors contributing to the variation in the serum lipid levels (Willer et al. 2013). Besides, the polygenic determinants have been evaluated with these studies and the determinants are composed of leading single nucleotide polymorphism (SNP) genotypes in the specific lipid metabolism-related genes (Teslovich et al. 2010). In other words, although the studies containing information about Mendelian disorders caused by common and rare mutations explained the main proteins and mechanisms that have contributed to the possession of heart diseases, this knowledge is not fairly enough to evaluate the majority of genetic variation contributing to the alterations in plasma lipid levels. GWAS have been used to describe the more detailed knowledge about the LDL and HDL metabolisms and their genetic variation through different type of procedures (Jeff et al. 2016).

Genome-wide association studies revealed various loci related to lipid metabolisms through the genotyping of thousands of SNPs in individuals. These studies identified common variants contributing to the Mendelian HDL and LDL disorders and non-studied genes affecting the operation of lipid mechanism (Willer et al. 2013).

In the meantime, discovery of common and rare variants as causative agents for the disorders mentioned above, description of these variants were studied using Mendelian randomization approach in which genetic variants are used as variable instruments to examine the modifiable causal effects on a disease with an analytical point of view (Erdmann et al. 2018). Major basics of Mendelian randomization depend on the consideration of causative roles for variants affecting the exposure variable (Genest et al. 1992). Also, it uses the combination of genetic and observational data as a powerful method to avoid reverse causation and evaluate the genetic variants associating with the exposure variable of interest. Even if this type of analytical approach may result in wrong conclusions because of the factors such as linkage disequilibrium, genetic heterogeneity, pleiotropy, it is still a powerful tool to be used as an approval approach for causative roles of the genetic variations (Strong et al. 2010). Mendelian randomization experiments on the common or rare frequency variations in causative genes proved or disproved roles of the related genes of lipoprotein and lipid metabolisms in the coronary heart disease risk [21]. In terms of rare variants, it is generally preferred to examine the loss-of-function

variants or variants that inactivate the elements in lipid metabolism, because of the easy observation of phenotypes.

Since the beginning of the era for the studies of atherosclerotic cardiovascular diseases, elevated levels of low-density lipoprotein cholesterol (LDL-C) is one of the strong factors in the progression of CHD risk [21-23]. One of the first GWAS projects for lipid metabolism in the human genome, identified SNPs near ApoE and ApoB encoding genes which are the important elements responsible for the alterations in LDL-C levels and SNPs near *CETP*, *LPL* and *LIPC* genes which are the significant determinants of HDL-C levels (Yusuf et al. 2004) The upcoming GWAS, has added more and new loci associated with the LDL-C traits. Eventually, with the largest GWAS that genotyped over 100.000 individuals examined 95 loci in total for LDL-C and HDL-C traits (Rader et al. 2009). After a set of GWAS, 163 loci was found to be associated as risk alleles for CHD. Even if these studies contained only European decent individuals, it is later shown to be related to populations such as Asian and African-American (Erdmann et al. 2018). GWAS proved that there is not only phenotypically observable variations associated with CHD but there are common variants associated to CHD with small effects. At first, smaller sample sizes resulted in mostly common variant discovery, with the increasing sample sizes, it has been possible to evaluate the rare variants associated with CAD risk. The common variants discovered by the GWAS, are known to be located in the non-coding regions or regulatory elements with the annotation by ENCODE project which identified the functional elements of human genome (Rader et al. 2008).

1.4. Reverse Cholesterol Transport and Coronary Heart Disease

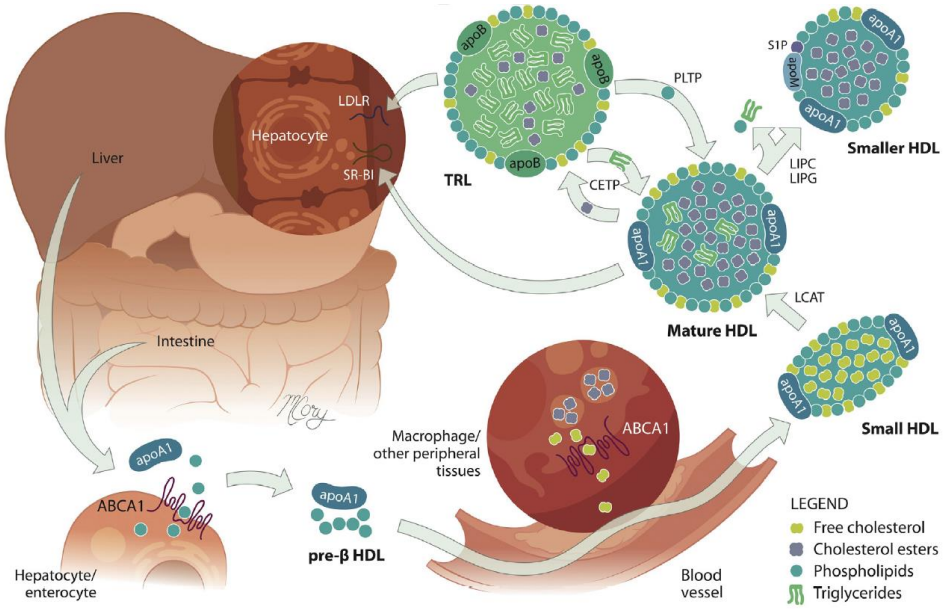


Figure 1. 1. Model of reverse cholesterol transport pathway including different elements of the pathway such as enzymes, transfer proteins and others and their work in the related tissues and cell types (Brunham, et. al., 2015).

Levels of high-density lipoprotein cholesterol in the plasma are related to the atherosclerotic events resulting in the cardiovascular disease risks [31]. High levels of HDL-C in blood are inversely related to the presence of cardiovascular diseases and a stronger predictor of CVD risk compared to the levels of low-density lipoprotein cholesterol [31, 32]. Considering the effect of plasma HDL-C levels, reverse cholesterol transport pathway have been an interest in search for the relationship to cardiovascular disaese risk and a potential therapeutical target. Overall, each element of lipoprotein metabolism plays central roles in lipid accumulation and atherosclerotic plaque formation which eventually increases the coronary heart disease (CHD) risk by narrowing the arterial walls and limit the blood flow (Rader et al. 2009). In literature, low-denisty lipoprotein cholesterol (LDL-C) and triglyceride (TG)-rich lipoproteins are taken by macrophages and initiate and progress the atherosclerotic plaques (Rader et al. 2008). Considering the high-density lipoproteins role in the cholesterol metabolism, HDL

conducts the efflux of cholesterol from macrophages to liver for excretion resulting in an inverse association with CHD, thus lowering or protecting against the atherosclerotic plaque formation (Rader et al. 2009).

The background for the thesis project was based on an idea of statistical investigation of a pre-determined pathway in association with a certain disease which in this case is coronary heart disease. Depending on this idea, a literature review was found in order to provide an extensive way for a whole-pathway based approach (Brunham et al., 2015). The review summarized reverse cholesterol transport pathway and its relationship to monogenic and variant related cholesterol metabolism disorders and complex heart disease. The main motivation behind the study is that reverse cholesterol transport pathway has a role influencing the HDL-C levels and eventually cardiovascular disease risk and genetic variations through the genes of RCT could potentially enhance the CVD risk.

RCT pathway is a complex and multi-step process in which several elements such as transporters, receptors and enzymes take role to provide the transport of excess cholesterol from peripheral tissues back to the liver for excretion. The biochemical theory behind transport mechanism is the key to anti-atherosclerotic events related to the levels of HDL-C (Yusuf et al. 2004). Considering the complex and multi-step nature of the RCT pathway, two specific and related perspectives are needed for a detailed understanding of the processes behind atherosclerotic events. As mentioned in the earlier context, there are genetic causes which can be inherited by common and rare variants with various biochemical consequences. The perspective should include different genetic causes as in a multigene approach and their relationships and correlations with biochemical causations. In this way, a multi-genic approach could be generated and a whole background scene for relationship between RCT pathway and CVD risk can be related to the elements of the pathway (Yusuf et al. 2004).

As mentioned in the earlier context, although monogenic disorders are a precious way to approach and investigate extremely rare phenotypes, studies showing the causes do not account for most of the inter-individual and population level differences in HDL-C and CVD risk. The common and rare variants, comprehensively can alter the CVD risk in a positive or a negative way depending on its effect for the individual (Kathiresan et al. 2012). With the advances in the sequencing technology and genomics, different loci have been identified as associated with the lipid traits. To explore and establish connections between these polymorphisms and CVD risk, a range of studies including

case-control, Mendelian randomization and genome-wide association studies have been conducted (Kathiresan et al. 2012). These approaches investigate different perspectives of relationships in terms of causality and association. While Mendelian randomizations studies are providing the causality between changes in exposure and the changes in outcome, GWAS and case-control studies investigated the possible associations (Davey et al. 2003). Collected data should be examined with different statistical tools to blend the theoretical information for investigation of common polymorphisms in RCT pathway and their effect on CVD risk (McCarthy et al. 2008).

Investigation of genetic variants in terms of their effects on the HDL-C levels in plasma provided data to build the background of a relationship between a pathway and CVD risk. Depending on their pivotal effects in the processing of the RCT pathway, each gene related to the overall activity of mechanism should be investigated individually (Rader et al. 2012). As the literature showed that three Mendelian causes of low levels of HDL-C by mutations in *APOA1* and loss-of-function mutations in *ABCA1* and *LCAT* do not exhibit a clear association with an increased risk of CHD (Keenan et al. 2013). In contrast, Mendelian causes of high levels of HDL-C by mutations in both alleles of *CETP* has not demonstrated a certain association with protection against CHD. Hence, Mendelian disorders have not shown a clear causal relationship between HDL and CVD risk. In these terms, low-frequency and common variants in the HDL metabolism elements are of critical importance for investigation of potential causality between HDL and CHD (Frikke-Schmidt et al. 2010).

1.4.1 ATP-Binding Cassette Transporter A1 (*ABCA1*)

ABCA1 is a crucial gene which is responsible for the transportation of cholesterol from peripheral cells to lipid poor pre-β1-HDL composed of apoA-I to form high-density lipoprotein cholesterol (Barter et al. 2019). Considering the starting point for the transport pathway is the pivotal role by *ABCA1*, common and rare variants on this gene are of critical importance. Tangier disease, in which cholesterol efflux to apoA-I fails and leads to the immature formation of HDL-C resulting in the decreased levels of HDL-C. Although there are specific variants causing the extreme and observable phenotypes,

common variants are a question marked subject in terms of their effects on HDL metabolism. Relationship of common variants with HDL-C were subject to various studies despite showing some non-replicated association and causality to plasma lipid levels or coronary heart disease (Barter et al. 2019).

ABCA1 gene has been identified for various mutations including missense, nonsense, and insertion or deletion mostly resulting in decreased levels of HDL-C and eventually associated with early onset of atherosclerosis (Frikke-Schmidt et al. 2020). GWAS identified multiple functional SNPs located in the region of *ABCA1* gene. The rs2422497 (-565C>T) polymorphism found in the gene promoter region has been linked to changes in *ABCA1* expression (Kyriakou et al. 2005). Furthermore, four different variants, rs2230806 (G-395C), rs4149274 (C-290T) and rs2230808 (C-7T) have exhibited negative associations with HDL levels (Tan et al. 2003). Despite this negative effect, rs4149273 (-14>T) has shown a positive correlation with HDL levels. Variants including rs2230801 (C69T), rs2230802 (C-17G), rs34746515 (InsG319) and rs1800977 (G-191C) in the non-coding regions of the *ABCA1* gene have been linked to alterations in serum lipid levels of CHD patients (Zwarts et al. 2002). Variants in the coding regions of the *ABCA1* gene such as rs2230806 (R219K), rs2066718 (V771M), and rs4149313(M8831I) polymorphisms have been linked to a atheroprotective role in patients with GG, AA and GG genotypes, respectively(Wang et al. 2019). Despite possessing an atheroprotective effect, there is a polymorphism rs9282541 (R230C) shown to be associated with increased risk of CHD progression in the presence of T allele (Andrikovics et al. 2005). Literature have inconsistent findings for investigation of associations between SNPs and effects. G allele of rs4149313 (M8831I) has been associated with HDL-C levels in some studies (Hodoğlugil et al. 2005) while other studies showing no effect (Wang et al. 2000).

Additionally, studies showed that stratification analysis of data sets by ethinicty provides an investigation of causality between populations. Stratified analysis performed by *Jiang et. al.* showed that rs2230806 is associated with CHD in East Asian population but not with Caucasians (Jiang et al. 2011). Also, it has been shown that R219K polymorphism with GG genotype increases the CHD risk in Iranians (Doosti et al. 2010).

1.4.2. Apolipoprotein A1 (*APOA1*)

Apolipoprotein A1 (*APOA1*) is the main building unit of HDL-C. This lipoprotein is able to absorb phospholipids and free cholesterol eventually forming the nascent HDL-C particles (Tall et al. 2001). The synthesis of the *APOA1* in the intestine and the liver results in a lipid-poor form of *APOA1* which is ready to interact with *LCAT* (Rader et al. 2006). After the formation of nascent HDL-C, *APOA1* interacts with *LCAT* and activates it (Rader et al. 2006). Considering the activity of *APOA1* in HDL-C metabolism, it is a crucial element able to activate the other elements of RCT pathway and act as a building unit for the transfer of excess cholesterol to the liver.

According to the studies which investigated the relationship of variants in *APOA1* gene and coronary heart disease, a clear observation and causality were not seen since the studies have shown inconsistent results with other studies (Bandarian et al. 2013). rs670 (*APOA1*-75G/A) is one of the most studied polymorphisms in *APOA1*. The literature have shown no association between rs670 which is an intronic variant and HDL-C levels (Chien et al. 2008). A meta-analysis by *Xu et. al.* showed that there is a protective effect against CHD by minor allele of rs670 (Qi et al. 2007). There are studies showing non-repeatable results for rs5069, a variant in the promoter region of *APOA1*. For example; there are investigations of one study resulting in an association with HDL-C levels (Brown et al. 2006) and the other one proving there is no association with HDL-C levels (Larson et al. 2002).

Additionally there are studies including *APOA1* with APOC3 and APOA4 in cluster in the examination of relationship between this cluster and coronary heart disease or HDL-C levels. Since these elements are found in the similar genomic region, they may have linkage disequilibrium by inheriting the haplotype of polymorphisms from different genes as a group of SNPs. Examination of one gene may not provide the combined effect of the SNP group in this cluster.

1.4.3. Cholesteryl Ester Transfer Protein (*CETP*)

Cholesteryl ester transfer protein (*CETP*) is a hydrophobic protein involved in the reverse cholesterol transport pathway, mainly expressed in the liver adipose tissue small intestine and other tissues and organs. The protein is responsible for transfer of cholesterol esters from HDLs to LDLs, TRLs, and VLDLs. *CETP* also transfers the triacylglycerols from TRLs to LDLs and HDLs (Qureischie et. al., 2008). Studies in the literature showed that increases in the *CETP* gene activity results in lower concentration of HDL-C and eventually causing atherosclerotic events with an increase in coronary heart disease risk (Freeman et. al. 1990). According to the studies related to the polymorphisms found on the gene, proteins activity could be influenced by the polymorphisms. Based on the knowledge, studies focused on the association between the polymorphisms of *CETP* gene and risk of CAD. Most of the studies focused on mainly three polymorphisms; rs708272 (TaqIB), rs5882 (I450V) and rs1800775 (Zhang et. al. 2023).

According to the studies in the literature for the polymorphisms, rs708272 was found to be associated with decreased risk for coronary heart disease with "A" allele carriers of the polymorphism against the "GG" genotype (Boekholdt et. al. 2005). Also Boekholdt et. al. showed that this relationship is significant with HDL-C levels and coronary heart disease risk in Caucasian subjects. In contrary, Li et. al. showed no significant association of the polymorphisms in Chinese population. Depending on the results shown by Wang et. al. and Cao et. al. showed that *CETP* TaqIB-B2 allele is associated with protection against the development of myocardial infarction (MI). In summary for the polymorphism, it was found that there is an association with the HDL-C levels and eventually with coronary heart disease, but unfortunately, the association between populations remained controversial.

Genotyping for rs5882 (I450V) and rs1800775 in subjects and control showed that there is no clear association between the polymorphism and HDL-C levels or CAD. Zhang et. al. showed no significant association between I450V, rs1800777 and CHD risk. In contrary, there was a clear relationship between "A" allele carriers of the rs5882 and higher risk of developing coronary artery disease (Mirhafez et. al. 2019).

1.4.4. Lecithin-cholesterol Acytltransferase

Lecithin cholesterol acyltransferase (*LCAT*) is responsible for the esterification of free cholesterol on the HDL particles to cholesteryl esters. These cholesteryl esters are later transferred to the core of the HDL which then are exchanged for TG from apoB-containing lipoproteins by *CETP* activity. After the activity of *LCAT*, HDL form was changed to form mature, spherical HDL (Remaley et. al. 2008). Dysfunctionality in the activity of *LCAT* could result in the malformation of the mature HDL form and eventually the transport of cholesterol molecules correctly.

In literature, *LCAT* was studied by seeking the possible associations between the mutations found within and risk of CAD. Clinical-based studies showed that *LCAT* mutations elevate the risk of CAD (Moussa et. al. 2010). Also, Calabresi et. al. showed no clear association between *LCAT* polymorphisms and CAD even there is a clear relationship between decrease in HDL-C levels (Calebresi et. al., 2010). There are no various studies related only to one polymorphism within only one population. According to Vargas-Alcorcon et. al., carriers of *LCAT* rs2292318 – A allele resulted in a lower concentration for circulating HDL-C levels than GG genotype carriers (Vargas-Alcorcon et. al., 2018). Also another polymorphism (S208T) of *LCAT* was not associated with TG levels and Apo-AI levels (Casas et. al., 2006).

1.4.5. Hepatic Lipase (*LIPC*)

Hepatic lipase (*LIPC*) is able to function as a lipolytic enzyme that hydrolyzes phospholipids and triglycerides present in circulating plasma lipoproteins. The enzyme also functions as a ligand that increases the lipoprotein uptake by cell surface elements resulting in modulated lipid delivery. Hepatic lipase is mainly synthesized in the liver and pancreas.

Since the concentration of HDL-C is related to the CAD risk, studies focused on the effect of hepatic lipase on the HDL-C levels. According to the studies in literature, *LIPC* has one of the strongest impact on the HDL-C (Verdier et. al., 2013). In terms of atherogenetic effects of the hepatic lipase, several studies has shown that *LIPC* can modulate atherogenic risk as either a protective or proatherogenic agent. One study showed that low hepatic lipase activity is associated with increased risk of CAD (Klaus et. al. 2001). Also, patients with complex hepatic lipase deficiency has been shown to have increased CAD risk (Connelly et. al. 1998) while other studies showed no significant association between its activity and susceptibility to CAD (Shohet et. al., 1999).

According to the studies relating the polymorphisms of *LIPC* to CAD risk, one study showed a relationship between T allele of (-)514 C/T and increased CAD risk (van Acker et. al., 2008) but one other study has shown no association between (Andersen et. al., 2003). One of the largest meta-analyses studying the variants affecting HDL-C has found an association between rs1800588 with MI (Voight et. al., 2012). Other studies showed varying relationships between various polymorphisms including rs1800588 and -514C/T and CAD risk. Hence, the mechanism and effect of the *LIPC* on the CAD risk remains unclear.

1.4.6. Endothelial Lipase (*LIPG*)

Endothelial lipase which is encoded by *LIPG* is a negative regulator of HDL-C levels in reverse cholesterol transport pathway. EL is mainly synthesized in vascular endothelial cells in humans. This enzyme is able to hydrolyze HDL-phospholipids by cleaving the non-esterified fatty acids from HDL-phospholipids. According to the literature, EL plays an important role in CHD risk by reducing HDL-C in the blood.

According to the studies relating the variants found within *LIPG* genomic region, 584C/T polymorphism was found in an association with HDL-C levels and eventually CAD risk. One study has shown that 584T allele is associated with protection against CAD in Chinese population (Tang et. al., 2008) while another study has found an association of 584T allele is related with acute myocardial infarction (Shimizu et. al., 2007). Jensen et. al. showed no relationship between the variant and the risk of CHD

among Caucasian people (Jensen et. al. 2009). Also another study focusing on the relationship in Chinese population, showed no association between the variant and CHD risk (Cai et. al., 2012). In summary, the associations between the variant and the CAD risk remains unclear for both of the populations and overall.

1.4.7. Lipoprotein Lipase (*LPL*)

Lipoprotein lipase is a crucial enzyme which functions to hydrolyze TG component of plasma lipoproteins. This enzyme is able to break down the plasma triglycerides of TG-rich lipoproteins (TRLs) such as chylomicrons and very low density lipoproteins (VLDL) (Tsutsumi et. al. 2003). Despite the effect of monogenic disorders such as familial *LPL* deficiency are shown to have no effect on atherosclerosis, *LPL* have been studied in terms of its association with coronary heart disease (Tsutsumi et. al. 2003).

According to the studies in literature over 100 mutations have been found in the genomic region of the gene (Jensen et. al. 2009). The studies included variants such as HindIII (rs320), S447X (rs328), PvuII (rs285), N291S (rs268) and D9N (rs1801177). One study showed no significant association between N291S and PvuII (Ma et. al. 2018). The same study also found a relationship between S447X, HindIII and CAD susceptibility in Caucasian populations in a protective manner while D9N showed an increase in CAD risk (Ma et. al. 2018). Another meta-analyses showed an association between the "H^+" allele of HindIII polymorphisms with the risk of CAD and also the "XX" genotype of S447X polymorphisms (Xie et. al. 2017).

1.4.8. Phospholipid Transfer Protein (*PLTP*)

Phospholipid transfer protein (*PLTP*) is able to modulate size and the composition of HDL particles through enhancement of the surface remnant transfer from TRL to HDL during lipolysis resulting in pre-β HDL generation (Eckardstein et. al. 1996). *PLTP* activity is one of the study subjects in the literature. Even the important role of the protein

in lipoprotein metabolism, there is no various studies related to the association of the protein and the HDL-C levels or CAD risk. Despite the small number of studies, *PLTP* activity was investigated whether there is an effect of the protein activity on CAD risk.

According to one study, *PLTP* activity is found to be associated inversely with the HDL-C levels and also Apo-AI levels in Chinese population (Chen et. al. 2009). In another study, it was shown that low *PLTP* activity was shown to have an association with the peripheral artery disease (Schgoer et. al. 2008). In contrary, another study showed that higher *PLTP* activity is related to the higher CAD risk (Schlitt et. al., 2003).

1.4.9. Scavenger Receptor Type Class B Member 1 (*SCARB1*)

Scavenger receptor type class B member 1 (*SCARB1* – SR-BI) is a multiligand membrane receptor which is able to bind HDL, LDL and VLDL resulting in the selective uptake of cholesteryl esters (Acton et. al. 1996). SR-BI plays a critical role in cholesterol efflux and selective cholesterol uptake.

In literature, several human genetic studies showed results in terms of correlation between *SCARB1* polymorphisms and elevated HDL-C, dyslipidemia and CAD (Brunham et. al. 2011). One of the most studied variants is rs5888 of *SCARB1*. In many studies, *SCARB1* rs5888 polymorphism was found in association with CHD through influencing the SR-BI protein expression and serum lipid levels (Rodrigues-Esparragon et. al. 2005). In another study, the variant leads to lower expression and function of *SCARB1* (Constantineau et. al. 2010). Some studies focused on the haplotypes within *SCARB1* genomic region, and was able to show no significant association between rs5888 and serum lipid levels or CHD risk in Chinese population (Zeng et. al. 2017). “T” allele of rs4238001 was found in an association with higher CHD risk in a meta-analysis across race groups (Manichaikul et. al. 2015).

1.5. Objectives of the Study

The main hypothesis of this thesis is that the reverse cholesterol transport pathway is involved in cardiovascular disease risk. Therefore the variants in the genes representing various points in this pathway can significantly influence the cardiovascular disease risk.

Based on this hypothesis, the aims of the thesis are:

1. Identify genes representing various points in reverse cholesterol pathway, that have been shown to influence cardiovascular disease risk in diverse human populations
2. Identify genetic variants in these candidate genes that have been shown to influence cardiovascular disease in diverse human populations
3. Perform genetic meta-analyses with these genes and their variants in order to investigate association between cardiovascular diseases, HDL-C levels, and reverse cholesterol pathway
4. Identify population specific allele frequencies of the cardiovascular disease associated variants and also identify genetic variants that are in strong linkage disequilibrium with these variants
5. Perform functional SNP annotation analysis on the variants that are in strong linkage disequilibrium with cardiovascular disease associated variants in order to identify novel new population specific candidate gene variants

CHAPTER 2

MATERIALS AND METHODS

2.1. Database Search Strategy for Variant Selection and Data Collection

The background for the thesis project was based on an idea of statistical investigation of a pre-determined pathway in relationship with a certain disease which in this case is coronary heart disease. Depending on this idea, a literature review was found in order to provide an extensive way for a whole-pathway based approach (Brunham et al., 2015). The review summarizes a pathway which is responsible for biogenesis of HDL. The pathway consists of nine genes taking specific roles in reverse cholesterol transport pathway (RCT). In the literature there are studies focusing specific relationships between polymorphisms related to the pathway and consequences caused by these SNPs statistically. As this thesis subject aims to dig deep into the relationship between RCT pathway and polymorphisms in the related genes, a search strategy should be determined to most relevant candidates.

Hence, variant selection from different functional classes was conducted using dbSNP: the NCBI database of genetic variation by the pre-specified parameters (Sherry et. al., 2001). Afterwards, depending on the selected polymorphisms, a literature strategy was used to select the studies about these SNPs following the checklist found in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Moher et. Al., 2009).

2.1.1. dbSNP Search Strategy for Variant Selection

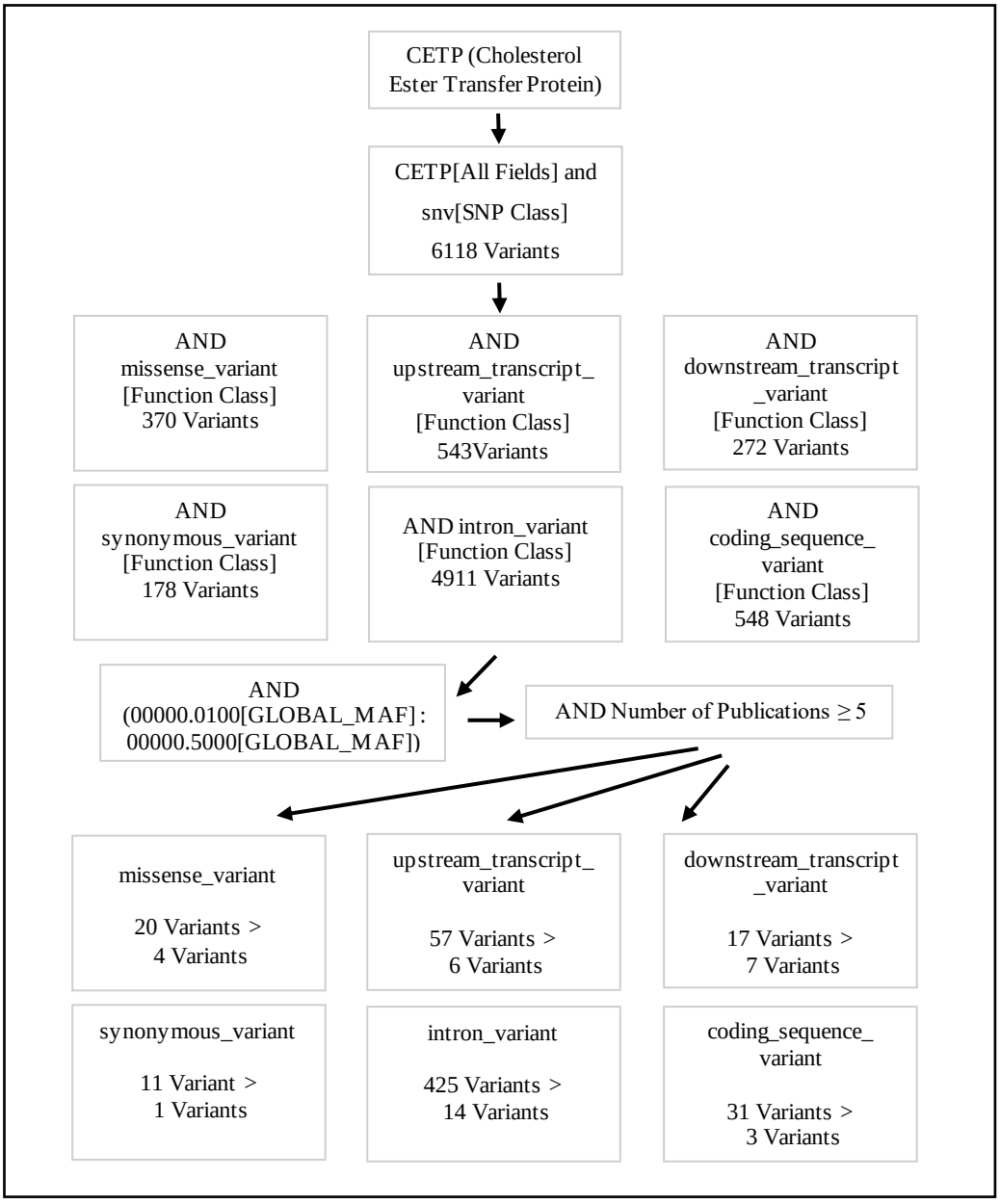
dbSNP is a database of single nucleotide polymorphisms with a broad submissions of simple variants through the human genome (Sherry et. al., 2001). This collection consists of several SNPs with different classes such as single nucleotide variants, multi-base inserts or deletions, short tandem repeats (STRs) and others (Sherry et. al., 2001). In this thesis subject, variants were searched through the dbSNP based on their gene name and other specific parameters such as SNP class, functional class, global minor allele frequency (MAF), and number of publications referenced by the dbSNP (Sherry et. al., 2001).

Nine genes of reverse cholesterol transport pathway, were separately mined through dbSNP in a step-by-step collective approach. At first, genes were browsed depending on their SNP classes. Then, found SNPs were grouped under their functional classes. These results were then limited to the range between 0.010 – 0.500 global MAF. Found variants were separately inspected for their number of publications that were referenced by dbSNP. These parameters were coded into the "Search details" of the dbSNP search engine. An example of the search approach written in dbSNP language can be seen below:

1. GENENAME[All Fields] AND snv[SNP Class]
2. GENENAME[All Fields] AND snv[SNP Class] AND functional_class[Function Class]
3. GENENAME[All Fields] AND snv[SNP Class] AND functional_class[Function Class] AND (00000.0100[GLOBAL_MAF] : 00000.5000[GLOBAL_MAF])
4. Selection of variants with a publication number higher than or equal to five manually.

Since dbSNP does not get any prompts for range input to the search details, each SNP with any of the functional classes were checked for their number of publications manually. An example of the exact and specific parameters used in search details can be found below:

Table 2. 1. An example of a flowchart for searching variants with different functional classes and global MAF for a specific genes. Different prompts were used to search for specific parameters for relevant variants



Different searches for different genes were performed by using the same search approach to find specifically related SNPs through the dbSNP. Below, there is a table (Table 2.1.) consisting of specific searches and the resulting number of variants after each search.

Table 2. 2. Number of variants found through searches in dbSNP for each of the genes responsible in reverse cholesterol transport pathway.

Gene Name	Number of Single Nucleotide Variants (SNV)	Missense Variants	Upstream Transcript Variants	Downstream Transcript Variants	Intron Variants	Synonymous Variants	Coding Sequence Variants	Total Number of SNV (according to publication number)
ABCA1	31752	28	77	16	1314	33	54	15
APOA1	1171	0	23	8	69	0	0	3
CETP	6118	20	57	17	425	11	31	28
LCAT	1896	1	2	6	10	3	3	2
LIPC	38686	11	120	9	1823	24	31	11
LIPG	9212	8	24	13	300	2	9	3
LPL	19358	3	11	9	275	7	14	16
PLTP	3798	3	31	3	113	2	5	3
SCARB1	19548	9	120	17	1104	13	22	4

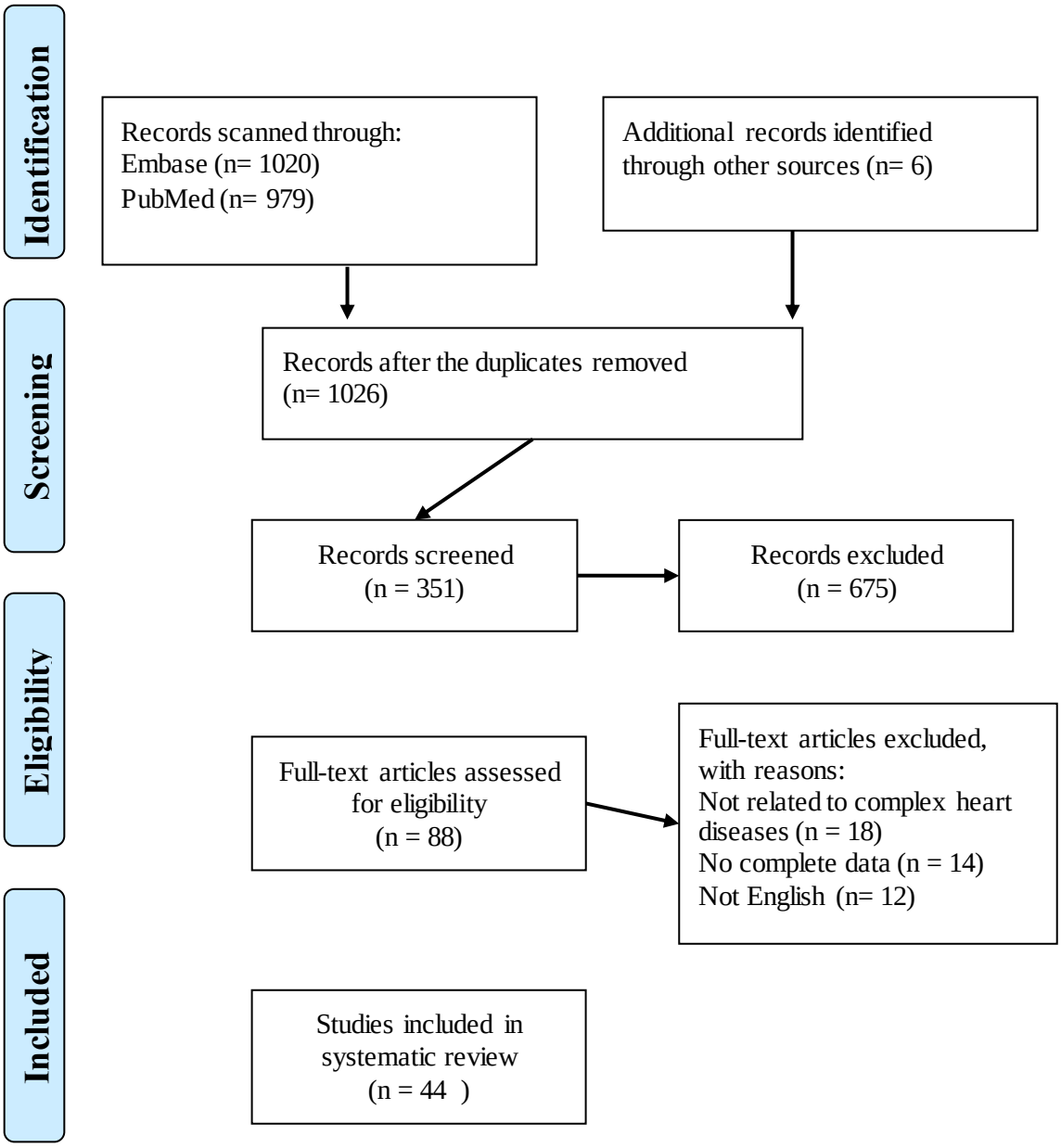
Each gene were searched for specific parameters. For each functional class, variants were grouped and selected depending on the number of publications being larger than or equal to five. Selected variants were recorded on different tables for further searches of the studies found in the literature. These studies were selected by determined parameters which will be explained under the next subtitle.

2.1.2. PRISMA Flow Diagram for Literature Search, Study Selection Criteria and Data Extraction for Meta-Analyses

Performing genetic meta-analyses to detect the relationship between a polymorphism and coronary heart disease requires specific clinical data for an exact and understandable analysis. Hence, every SNP found by the search strategy explained under "2.1.1 dbSNP Search Strategy for Variant Selection" were scanned for specific clinical studies through databases which are PubMed and Embase using different search terms following the PRISMA rules (Moher et. Al., 2009). As an example, an extensive search for *CETP* variants in the literature studies using the search keywords: *CETP* OR (cholesterol ester transfer protein) OR SNP OR (single nucleotide polymorphism) OR variant OR variation OR CHD OR (coronary heart disease) OR CAD OR (coronary artery disease) OR HDL OR (high density lipoprotein) OR rs708272 (SNP code) OR TaqIB. Depending on these terms used in the databases, studies were selected if they are eligible

for meta-analysis of the SNP relationships. Below, there is an example of literature search approach for SNP (rs708272, also named as TaqIB) found on *CETP* gene.

Table 2. 3. An example of a flowchart for searching approach to scan the studies found in the literature. Studies were selected depending on selection criteria



The search terms and selection criteria must be determined specifically for types of the data which will be included in the meta-analyses. As the thesis subject aims to collectively analyze two different aspects of the relationships between the polymorphisms

and their effect on the presence of varying cardiovascular diseases (coronary heart disease (CHD), coronary artery disease (CAD), myocardial infarction (MI), ischemic heart disease (IHD)) and on the circulating high-density lipoprotein cholesterol (HDL-C) levels, two distinct clinical data schemes were required for the performing of meta-analyses.

For the meta-analyses focused on the relationship on the genotype and presence of the disease, clinical data for the specific genotypes of the polymorphisms for the control and subject group were required. The following criteria were used for the selection: (1) if published in peer-reviewed journal and contain original data; (2): if investigated the polymorphism and cardiovascular heart disease; (3): if patients were diagnosed with CHD, CAD, MI or IHD pathologically and angiographically; (4): if sufficient data (genotype frequencies for control and subject groups) for calculation of odds ratio (OR) with a confidence interval is present (CI), p-value and Hardy-Weinberg equilibrium; (5): if contains data for control and subject groups; (6): if language of publication is English.

For meta-analyses focused on the relationship between genotype and HDL-C levels, clinical data for the specific genotypes of the polymorphisms and the circulating HDL-C measurements for the control and subject groups. Hence, study selection and data extraction for these meta-analyses were performed considering a specific selection criteria. The following criteria were used for the selection: (1) if published in peer-reviewed journal and contain original data; (2): if investigated the polymorphism, and circulating HDL-C; (3): if patients were diagnosed with cardiovascular diseases (CHD, CAD, MI or IHD) and other circulating cholesterol related diseases; (4): if contains data for control and subject groups (5): if sufficient data (genotype frequencies of the sub-group and circulating HDL-C level measurements) for calculation of standardized mean difference (SMD), CI and p-value; (6): if language of publication is English.

Selected studies were mined for the clinical data determined to be analyzed by meta-analysis of two different effect measure; (1): odds ratio (OR); (2): standardized mean difference (SMD).

Data extraction for OR calculation from the related studies were performed considering a scheme which is including author's surname, year of publication, country, sample ethnicities, the design of the study, disease, sample sizes, allele and genotype frequencies for genetic model applications, age and gender. According to the data

extraction scheme, clinical data from the selected studies were extracted to various Excel files for each polymorphism.

Data extraction for SMD calculation from the related studies were performed considering a scheme which is including author's surname, year of publication, country, sample ethnicities, the design of the study, disease, sample size, genotype frequencies, mean circulating HDL-C levels and standard deviations for each genotype, age and gender. Mean circulating HDL-C levels and standard deviations were converted for the studies included the levels as mg/mL to mmol/L. According to the data extraction scheme, clinical data from the selected studies were extracted to various Excel files for each polymorphism.

Data table for each polymorphism were saved under specific files for further meta-analyses applications. The data was specifically collected under the columns which were named according to the genetic models to provide easy importing and sub-grouping of the data to the coding environment. Specified parameters for meta-analysis applications are shared in the next subtitle.

2.2. Meta-Analyses of Clinical Data for Relationship between Polymorphisms, Cardiovascular Heart Diseases and Circulating HDL-C Levels

Meta-analyses were conducted to test and analyze the strength of association between the polymorphisms selected and cardiovascular disease risk or circulating HDL-C levels. Data tables for each association were saved in specific files and used as data input files for applications conducted using the R language (R Core Team, 2022) compiled under RStudio environment (RStudio Team, 2022). The data tables were first cleaned and restructured according to the meta-analyses to be applied. Various packages and commands present in the default library of R language (R Core Team, 2022) were used during data cleaning and restructuring. Meta-analyses were carried out using functions of 'meta' package in R (Schwarzer, 2022). Hardy-Weinberg equilibrium (Weinberg, 1908) calculations for present control groups of clinical data were carried out using "HWChisq" function from the 'genetics' package in R (Warnes, 2020).

2.2.1. Relationship between Polymorphisms and Cardiovascular Heart Diseases

Each association between the polymorphism and cardiovascular disease risk was estimated by odds ratios (ORs) with 95% confidence interval (CI). ORs were calculated for both of the control and subject groups' genotype frequencies. Depending on the schemes for genetic models (allelic, additive, dominant and recessive), four different meta-analyses were conducted for each polymorphism if sufficient data was present.'metabin' function of the 'meta' package (Schwarzer, 2022) was used for meta-analysis application. Codes for each statistical analysis of polymorphisms were conducted separately and parameters were kept unvaried for each analysis. Inverse variance method was used for pooling. Two effects model were planned to be used; fixed effects or random effects model. According to the statistical heterogeneity among studies which were analyzed using Q test (Lipsey, 2001) and I^2 statistics (Higgins 2002), one of the models was selected. If p-value for Q test is lower than 0.01 and $I^2 > 50\%$, a random-effects model was selected to estimate the ORs. If p value and I^2 are not in the range, a fixed-effects model was applied. Forest plots for visual presentation were created using 'forest' function from the 'meta' package (Schwarzer, 2022). Potential publication bias was assessed using 'metabias' and 'funnel' function of 'meta' package (Schwarzer, 2022). P-values < 0.05 for asymmetry tests were determined as statistically significant. In total, 57 meta-analyses were carried out for 15 polymorphisms. These meta-analyses were investigated in terms of their significance. If p-value < 0.05, the test was determined as significant. Further visualization of the significant results by forest plots and publication bias by funnel plots were shared under "Chapter 3 – Results and Discussion".

2.2.2. Relationship between Polymorphisms and Circulating HDL-C Levels

Each association between the polymorphism and circulating HDL-C levels was estimated by standardized mean difference (SMD) with 95% confidence interval (CI). SMDs were calculated for genotype frequencies for each genetic model (additive, allelic, dominant and recessive) separately. Estimation of the SMDs was performed using the method of Hedges' g (Hedges, 1981). According to the statistical heterogeneity among studies which were analyzed using Q test (Lipsey, 2001) and I^2 statistics (Higgins 2002), one of the models was selected. If p-value for Q test is lower than 0.01 and $I^2 > 50\%$, a random-effects model was selected to estimate the ORs. If p value and I^2 are not in the range, a fixed-effects model was applied. Forest plots for visual presentation were created using 'forest' function from the 'meta' package (Schwarzer, 2022). Potential publication bias was assessed using 'metabias' and 'funnel' function of 'meta' package (Schwarzer, 2022). P-values < 0.05 for asymmetry tests were determined as statistically significant. In total, 58 meta-analyses were carried out for 14 polymorphisms. These meta-analyses were investigated in terms of their significance. If p-value < 0.05, the test was determined as significant. Further visualization of the results by forest plots and publication bias by funnel plots were shared under "Chapter 3 – Results and Discussion".

2.3. Retrieval of Linkage Disequilibrium Data and Functional Annotation of Variants

Variants with significant meta-analyses were used as an input set for Linkage Disequilibrium (LD) Calculator of Ensembl (Fergal et. al.). Each SNP shared in the Table 3.2 were searched through the possible LD pair relations among the SNPs selected and other SNPs. Each search through the calculator were done according to a specified set of parameters such as calculation type for LD, species, population selection, input data type according to calculation, and threshold for r^2 and D'. Calculation was selected for LD

pairs in a given region which in this term corresponding to the selected gene regions (*ABCA1*, *APOA1*, *CETP*, *LIPC*, *LIPG*, *LPL* and *SCARB1*). Species for the searches was selected as "Human (Homo sapiens)". Populations were selected according to 1000Genomes populations (1000 Genomes Project Consortium) which corresponds to 26 sub-populations from five main populations (AFR, AMR, EAS, EUR and SAS). Gene regions were searched through the Ensemble (Fergal, 2023) for specified genes in Human populations and shared as in Table 2.2. The Ensemble data is retrieved from sequences and annotated genome coded as GRCh38:CM000670.2 (Human Genome version 38). Threshold for r^2 was selected as 0.6 and for D' was left as default setting.

Table 2. 4. Number of variants found through searches in dbSNP for each of the genes responsible in reverse cholesterol transport pathway

Genes	Chromosome Number	Location
ABCA1	Chromosome 9	104,781,006-104,928,155
APOA1	Chromosome 11	116,835,751-116,837,622
CETP	Chromosome 16	56,961,923-56,983,845
LIPC	Chromosome 15	58,410,569-58,569,844
LIPG	Chromosome 18	49,560,699-49,599,185
LPL	Chromosome 8	19,901,717-19,967,259
SCARB1	Chromosome 12	124,776,856-124,882,668

Table 2. 5. Set of variants which were used to sort out the LD pairs found within the locations shared in Table 2.2

Variation ID	Gene Name
rs2066714	*ABCA1*
rs2230806	*ABCA1*
rs5069	*APOA1*
rs708272	*CETP*
rs5882	*CETP*
rs1800588	*LIPC*
rs2000813	*LIPG*
rs320	*LPL*
rs328	*LPL*
rs1801177	*LPL*
rs5888	*SCARB1*

Data created and retrieved from Ensembl with specified parameters were saved for each sub-population and main population separately for further restructuring. The data files for each sub-population consist of information related to the each variant in LD pairs such as variant number, location, consequence and evidence. Since the data tables include all of the LD pairs in specified gene regions (Table 2.2), tables were sorted out for only significant variants (Table 2.1) by meta-analyses. Then, each sub-population were sorted out for unique SNPs which are in linkage disequilibrium with significant SNP group by meta-analyses and for only LD pairs with $r^2 \geq 0.8$. Sub-population specific SNPs for specified parameters were saved under separate files to provide the main population specific variants for further interpretation of the LD relationships through the populations such as AFR, AMR, EUR, EAS, and SAS by 1000Genome Project. Each sub-population data for LD pairs were saved under separate files for further annotation of variants in LD pairs.

SNP Nexus is a web-based database which facilitates the annotation and analysis of SNPs (Barenboim et al. 2013) It was used to retrieve data related to the Variation ID, reference, alternative and minor allele, and frequencies for each population, location, consequence and gene name. These data were saved under separate files for further interpretation.

For each sub-population specific SNP, information from the SNP-Nexus was retrieved and used as an input list for RegulomeDB searches (Boyle, 2012). RegulomeDB is a web-based database and tool designed to annotate and prioritize non-coding functional elements in the human genome. The database contains information regarding the DNA elements involved in the regulation of gene expression, quantitative trait loci, transcription factor binding, motifs, and footprints, chromatin accessibility data. For further interpretation of the LD pair lists specific to the populations, scoring of RegulomeDB and related RegulomeDB probability were retrieved from the database. Interpretation of the SNPs retrieved by the LD pairs is crucial in terms of variants found in the non-coding regions of the genes in RCT pathway. RegulomeDB ranks the variants based on the integration of data from multiple sources such as ENCODE (Encyclopedia of DNA Elements), the Roadmap Epigenomics Project and other functional genomics datasets. There are six levels of ranking by RegulomeDB which are ranging from 1 to 6. Also depending on the data found in database, rankings were given to each with a letter from “a” to “f” such as for first level, they have 1a, 1b, 1c, 1d, 1e, and 1f relating to

number of the data type such as TF motif, caQTL, eQTL and others. Higher the level of ranking, higher the data related to the functional annotation of a variant is found.

After the searches from LD Calculator of Ensembl, SNP Nexus and RegulomeDB databases, the results were stratified according to two different specified parameters. First, results for each LD pair were collected under five different files matching each main population as AFR, AMR, EAS, EUR and SAS. These pairs were sorted out depending on the population specific variants from the LD pairs. Additionally, intersecting variants between the tables were separately saved for further interpretation. Then the lists were sorted out considering the RegulomeDB Probability ≥ 0.9, RegulomeDB Ranking ≥ 3 and RegulomeDB Probability ≥ 0.5, RegulomeDB Ranking ≥ 3 to provide variants with higher and also lower probabilities from RegulomeDB.

CHAPTER 3

RESULTS AND DISCUSSION

3.1. Data Acquisition from dbSNP for Variant Selection

This study focused on 9 genes (*ABCA1*, *APOA1*, *CETP*, *LCAT*, *LIPC*, *LIPG*, *LPL*, *PLTP* and *SCARB1*) which are found in the reverse cholesterol transport mechanism (Brunham et. al., 2015). These 9 genes were set as default gene set for further database and literature searches. Using a dbSNP (Sherry, 2001) search strategy, genes were investigated based on specific parameters. As a result, 90 SNPs were selected after dbSNP (Sherry, 2001) searches.

Further literature searches for these 90 SNPs were conducted using specific keywords to exclusively find the clinical data about relationships of polymorphisms with CHD and circulating HDL-C levels. Literature was evaluated following the PRISMA rules (Moher et. al., 2009). 75 SNPs out of 90 SNPs did not have sufficient and eligible study numbers for further meta-analyses. 15 SNPs from 7 genes were selected for further meta-analyses applications (Table 3.1).

Table 3. 1. Each row of the table represents data for the selected variants from dbSNP according to the search criteria explained in 'Chapter 2 - Materials & Methods'.

rsIDS	AlternativeID	Gene	Consequence	Position	Allele
rs2066714	M883I	ABCA1	Missense Variant	chr9:104824472 (GRCh38.p12)	T/C
rs2230806	R219K	ABCA1	Missense Variant	chr9:104858586 (GRCh38.p12)	T/C
rs5069	G-75A	APOA1	Intron Variant	chr11:116837538 (GRCh38.p12)	G/A
rs708272	TaqIB	CETP	Intron Variant	chr16:56962376 (GRCh38.p12)	G/A
rs1800775	C629-A	CETP	Upstream Transcript Variant	chr16:56961324 (GRCh38.p12)	A/C
rs1800588	514C/T	LIPC	Upstream Transcript Variant	chr15:58431476 (GRCh38.p12)	C/T
rs2000813	584C > T	LIPG	Missense Variant	chr18:49567494 (GRCh38.p12)	C/T
rs268	N291S, N318S	LPL	Missense Variant	chr8:19956018 (GRCh38.p12)	A/G
rs285	PvuII	LPL	Intron Variant	chr8:19957678 (GRCh38.p12)	C/T
rs320	HindIII	LPL	Intron Variant	chr8:19961566 (GRCh38.p12)	G/T
rs328	S447X	LPL	Stop Gained	chr8:19962213 (GRCh38.p12)	C/G
rs1801177	D9N	LPL	Missense Variant	chr8:19948197 (GRCh38.p12)	A/G
rs5888	_1050C/T	SCARB1	Synonymous Variant	chr12:124800202 (GRCh38.p12)	G/A
rs1799837	(-)75G>A	APOA1	Intron Variant	chr11:116837537 (GRCh38.p14)	C>T
rs5882	I405V	CETP	Missense Variant	chr16:56982180 (GRCh38.p14)	G>A

Each variant has information for rsID, alternative SNP name, gene abbreviation, variant type, and the position on the genome, alleles for the specific SNP and frequencies for 1000Genome and GnomAD.

3.2. Data Extraction from Literature

After literature searches were completed and a set of polymorphisms were selected for further statistical analysis, studies found in literature were saved for data extraction. A scheme of data table was shared in 'Chapter 2 – Materials and Methods'. According to that scheme, data tables for cardiovascular disease risk (Table 3.2) and for circulating HDL-C levels (Table 3.3) were constructed and later restructured for meta-analyses.

Table 3. 2. An example of extracted data table of the polymorphism, rs1800775 (*CETP*) for OR (table above) and SMD (table below) calculations for meta-analyses.

Author	Year	Country	Ethnicity	StudyType	Sex	Case Age (Mean)	Control Age (Mean)	Disease	Case Sample Size	Control Sample Size	Case .C.C	Control .C.C	Case .C.A	Control .C.A	Case .A.A	Control .A.A	Case .C	Control .C	Case .A	Control .A
Eiriksdottir	2001	Iceland	Caucasian	Case-Control	Mixed	71	76	MI	378	735	95	165	205	368	78	202	395	698	361	772
Freeman	2003	England	Caucasian	Cohort	Mixed	56,9	56,7	CHD	498	1107	420	955	71	146	7	6	911	2056	85	158
Ghatreh	2009	Iran	Caucasian	Case-Control	Mixed	54,6	52,8	CHD	187	136	23	18	54	57	110	61	100	93	274	179
Lu1	2013	Singapore	Asian	Case-Control	Mixed	42,74	59,34	CHD	442	377	110	94	223	201	109	82	443	389	441	365
Lu2	2013	Singapore	Asian	Case-Control	Mixed	40,66	59,08	CHD	108	151	36	49	53	80	19	22	125	178	91	124
Lu3	2013	Singapore	Asian	Case-Control	Mixed	42,43	60,35	CHD	109	384	19	58	55	187	35	139	93	303	125	465
Meiner	2008	Israel	Caucasian	Case-Control	Male	44	42,2	CHD	312	295	62	70	170	155	80	70	294	295	330	295
Meiner	2008	Israel	Caucasian	Case-Control	Female	50,5	49,5	CHD	244	333	58	63	131	166	55	104	247	292	241	374
Padmaja	2009	India	Caucasian	Case-Control	Male	NA	NA	CHD	458	300	70	43	217	116	171	141	357	202	559	398
Padmaja	2009	India	Caucasian	Case-Control	Female	NA	NA	CHD	46	38	12	5	24	23	10	10	48	33	44	43
Poduri	2009	India	Caucasian	Case-Control	Mixed	47,52	47,01	CHD	262	150	127	105	110	38	25	7	364	248	160	52
Tanrikulu	2009	Turkey	Caucasian	Case-Control	Mixed	NA	NA	CHD	120	120	27	22	56	58	37	40	110	102	130	138
Tobin	2004	England	Caucasian	Case-Control	Mixed	58,6	61,9	MI	547	505	143	121	293	244	69	140	579	486	431	524
Wang	2013	China	Asian	Case-Control	Mixed	66	66	CHD	408	421	100	83	216	222	102	116	416	388	420	454

Author	Year	Country	Ethnicity	StudyType	Sex	Case Age (Mean)	Disease	Case Sample Size	M.Case .C.C	SD.Case .C.C	Case .C.C	M.Case .C.A	SD.Case.C.A	Case .C.A	M.Case .A.A	SD.Case.A.A	Case .A.A
Freeman	2003	Scotland	Caucasian	Case-Control	Mixed	56,9	MI	498	1,00	0,19	139	1,09	0,23	261	1,12	0,22	98
Freeman	2003	Scotland	Caucasian	Case-Control	Mixed	56,7	Control	1108	1,08	0,24	286	1,15	0,25	551	1,19	0,25	270
Lu	2013	China	Asian	Case-Control	Men	-	Control	184	1,15	0,23	50	1,28	0,35	95	1,31	0,32	39
Lu	2013	China	Asian	Case-Control	Women	-	Control	162	1,56	0,37	45	1,53	0,45	81	1,68	0,42	36
Lu	2013	China	Asian	Case-Control	Men	-	Control	138	1,16	0,31	46	1,16	0,24	75	1,23	0,20	17
Lu	2013	China	Asian	Case-Control	Women	-	Control	12	1,45	0,16	5	1,35	0,49	5	1,38	0,18	2
Lu	2013	China	Asian	Case-Control	Men	-	Control	239	1,03	0,29	54	1,03	0,29	133	1,85	1,20	52
Lu	2013	China	Asian	Case-Control	Women	-	Control	142	1,20	0,37	37	1,24	0,34	73	1,41	0,33	32
Poduri	2009	India	Caucasian	Case-Control	Mixed	47,52	CAD	265	0,90	0,23	127	0,90	0,24	110	0,96	0,24	28
Poduri	2009	India	Caucasian	Case-Control	Mixed	47,01	Control	150	1,04	0,23	105	1,13	0,25	38	1,00	0,22	7
Ghatrehsamani	2009	India	Caucasian	Case-Control	Mixed	-	CAD	187	0,90	0,28	110	0,90	0,22	54,0	0,99	0,26	23,0
Ghatrehsamani	2009	India	Caucasian	Case-Control	Mixed	-	Control	136	0,91	0,22	61	0,95	0,27	57	1,08	0,32	18
Tanrikulu	2009	Turkey	Caucasian	Case-Control	Mixed	36	CAD	120	1,01	0,21	27	0,99	0,21	56	0,97	0,25	37
Tanrikulu	2009	Turkey	Caucasian	Case-Control	Mixed	39	Control	120	1,20	0,35	22	1,22	0,37	58	1,28	0,35	40
Wang	2013	China	Asian	Case-Control	Mixed	66	Control	424	1,49	0,72	83	1,45	0,62	222	1,28	0,41	116

3.3. Meta-Analyses of Association between Polymorphisms, Cardiovascular Disease Risk, and Circulating HDL-C Levels

Meta-analyses were conducted depending on the data collected from the literature. These data were sub-grouped or re-structured according to the race, control or subject group, and genetic model applied for each polymorphism. The data were reshaped for meta-analyses with two different effect measures which are ORs and SMDs.

Evaluation of cardiovascular disease risk affected by the polymorphisms was performed using odds ratio as an estimation method for the strength of the association as described in 'Chapter 2 – Materials and Methods'. All of the polymorphisms, except rs1801177 with dominant model only, were analyzed under all genetic models (allelic, additive, dominant and recessive). Depending on the p-values of the relevant meta-analysis and heterogeneity tests, one of the models (fixed or random effects) was selected and checked for its significance (p-value < 0.05). Detailed exhibition of the meta-analyses with significant p-values and odds ratios for two models were shared (Table 3.3). Only these meta-analyses were visualized by forest plots which included data regarding to odds ratios, CI at 95%, I^2 statistics, Chi^2, Tau^2 values, and p-value for heterogeneity tests. Additionally, sample sizes for each experimental and control group, event (genotype frequencies specifically calculated for each genetic model) and total sample sizes, and weight of each study were shared in forest plots.

Considering the significance and the heterogeneity tests, eligible meta-analyses results were shared as forest plots. In total, 57 meta-analyses were conducted with a mixed-race sample groups. 19 of the meta-analyses were evaluated as significant and saved for further observation. Additionally, 40 meta-analyses were conducted with re-structured data based on races; Asian and Caucasian. 19 of the meta-analyses were evaluated as significant and saved for further observation. Related forest plots for significant meta-analyses were shared (Figure 3.1 to Figure 3.19). Meta-analyses for different races with different genetic models were shared (Figure 3.20 to Figure 3.38).

Table 3. 3. Overview of meta-analyses results investigating the relationship between variants and presence of coronary heart disease according to two different models fixed and random effects which were determined by heterogeneity tests. Table is divided into two sections; upper part presents model results and the lower part presents heterogeneity and publication bias test results.

				Fixed Effects Model			Random Effects Model		
Meta-Analysis	**Genetic Model**	**Number of Studies**	**Study Population (Case/Control)**	**Odds Ratio (95% CI)**	**z**	**p-value**	**Odds Ratio (95% CI)**	**z**	**p-value**
rs2066714	Allelic (M vs I)	16	8000/17796	1,25 [1,16; 1,35]	5,75	<0,0001	1,20 [1,07; 1,35]	3,18	0,0015
	Recessive (II + MI vs MM)	16	4000/8898	0,79 [0,71; 0,88]	-5,02	<0,0001	0,79 [0,71; 0,88]	-4,25	<0,0001
rs2230806	Allelic (R vs K)	52	31840/48382	1,16 [1,12; 1,20]	8,54	<0,0001	1,28 [1,19; 1,39]	6,32	<0,0001
	Additive (RR vs KK)	52	9159/14093	1,42 [1,31; 1,53]	8,84	<0,0001	1,64 [1,41; 1,90]	6,41	<0,0001
	Dominant (RR+RK vs KK)	52	15920/24191	1,30 [1,21; 1,39]	7,31	<0,0001	1,46 [1,27; 1,68]	5,4	<0,0001
	Recessive (KK+RK vs RR)	52	15920/24191	0,85 [0,81; 0,90]	-6,49	<0,0001	0,77 [0,71; 0,84]	-6,19	<0,0001
rs708272	Allelic (B1 vs B2)	43	42630/48600	1,12 [1,08; 1,15]	7,32	<0,0001	1,16 [1,10; 1,21]	6,13	<0,0001
	Additive (B1B1 vs B2B2)	43	10688/12299	1,27 [1,19; 1,35]	7,62	<0,0001	1,37 [1,24; 1,52]	6,1	<0,0001
	Dominant (B1B1+B1B2 vs	43	21315/24300	1,23 [1,16; 1,30]	7,39	<0,0001	1,27 [1,17; 1,37]	5,97	<0,0001
	Recessive (B1B1 vs B2B2+	43	21315/24300	0,90 [0,86; 0,94]	-4,79	<0,0001	0,86 [0,80; 0,91]	-4,84	<0,0001
rs1800588	Allelic (C vs T)	16	24886/32110	0,95 [0,91; 1,00]	-2,04	0,0413	0,95 [0,91; 1,00]	-2,04	0,0414
rs2000813	Allelic (C vs T)	7	3224/3062	1,68 [1,49; 1,89]	8,57	<0,0001	2,19 [1,55; 3,09]	4,48	<0,0001
	Additive (CC vs TT)	7	1202/860	1,42 [1,05; 1,91]	2,29	0,0218	2,97 [1,43; 6,15]	2,93	0,0034
	Recessive (TT+CT vs CC)	7	1612/1531	0,46 [0,40; 0,54]	-10,31	<0,0001	0,35 [0,22; 0,56]	-4,41	<0,0001
rs320	Allelic (G vs T)	18	10914/8582	0,87 [0,81; 0,93]	-4,19	<0,0001	0,83 [0,73; 0,94]	-2,84	0,0045
	Additive (GG vs TT)	17	3346/2610	0,71 [0,61; 0,83]	-4,33	<0,0001	0,65 [0,48; 0,87]	-2,84	0,0044
	Dominant (GG+GT vs TT)	18	5457/4291	0,89 [0,82; 0,96]	-2,81	0,0049	0,87 [0,78; 0,97]	-2,49	0,0128
	Recessive (TT+GT vs GG)	17	5457/4291	1,37 [1,18; 1,58]	4,15	<0,0001	1,49 [1,11; 2,00]	2,68	0,0074
rs1801177	Recessive (AA+GA vs GG)	9	3212/3130	1,59 [1,28; 1,99]	4,18	<0,0001	1,59 [1,28; 1,99]	4,18	<0,0001
rs5888	Dominant (GG+GA vs AA)	8	3380/3879	1,52 [1,38; 1,69]	8,1	<0,0001	1,60 [1,18; 2,15]	3,06	0,0022

		Quantifying Heterogeneity			Test of Heterogeneity			Model should be used	Egger's Test			Begg's Test	
Meta-Analysis	**Genetic Model**	I^2 (%)	τ^2	**H**	**Q**	**Degrees of Freedom**	**p-value**		**Coefficient Estimate (b)**	**p-value**	**Confidence Interval (CI)**	**Tau**	**p-value**
rs2066714	Allelic (M vs I)	55	0,0258	1,48	33,04	15	0,0046	Fixed	0.5280	0.0459	0.1818, 0.8742	-0.1667	0.3984
	Recessive (II + MI vs MM)	33	0,0083	1,22	22,34	15	0,0991	Fixed	-0.2371	0.9794	-0.5533, 0.0791	-0.0500	0.8248
rs2230806	Allelic (R vs K)	76	0,0545	2,03	210,85	51	<0,0001	Random	-0.1184	< .0001	-0.3002, 0.0634	0.2398	0.0119
	Additive (RR vs KK)	69	0,1837	1,8	165,54	51	<0,0001	Random	-0.0763	0.0006	-0.4195, 0.2668	0.2293	0.0163
	Dominant (RR+RK vs KK)	69	0,159	1,81	166,73	51	<0,0001	Random	-0.0830	0.0019	-0.3955, 0.2296	0.2775	0.0035
	Recessive (KK+RK vs RR)	62	0,0452	1,62	134,4	51	<0,0001	Random	0.1107	< .0001	-0.0648, 0.2862	-0.1704	0.0757
rs708272	Allelic (B1 vs B2)	47	0,0088	1,37	78,71	42	0,0005	Fixed	0.0139	0.0002	-0.0447, 0.0725	0.1406	0.1885
	Additive (B1B1 vs B2B2)	52	0,0437	1,44	86,66	42	<0,0001	Random	0.0485	0.0002	-0.0685, 0.1655	0.1163	0.2783
	Dominant (B1B1+B1B2 vs B2B2)	46	0,0172	1,36	77,23	42	0,0007	Fixed	0.1182	0.1142	-0.0391, 0.2756	0.0565	0.6029
	Recessive (B1B1 vs B2B2+B1B2)	37	0,0122	1,26	66,69	42	0,009	Fixed	0.0485	< .0001	-0.0379, 0.1349	-0.1805	0.0901
rs1800588	Allelic (C vs T)	41	<0,0001	1,3	25,2	15	0,0473	Fixed	-0.0087	0.2699	-0.0890, 0.0716	-0.0667	0.7566
rs2000813	Allelic (C vs T)	75	0,1493	2	23,98	6	0,0005	Random	0.1607	< .0001	-0.0512, 0.3725	0.6190	0.0690
	Additive (CC vs TT)	70	0,48	1,84	20,21	6	0,0025	Random	-0.2278	0.0026	-0.9817, 0.5260	-0.4286	0.2389
	Recessive (TT+CT vs CC)	73	0,2876	1,92	22,1	6	0,0012	Random	-0.2840	0.0701	-1.1554, 0.5874	-0.7143	0.0302
rs320	Allelic (G vs T)	66	0,0453	1,71	49,75	17	<0,0001	Random	-0.2380	0.7568	-0.6070, 0.1310	-0.1503	0.4101
	Additive (GG vs TT)	67	0,2482	1,75	48,88	16	<0,0001	Random	-0.1846	0.5159	-1.0039, 0.6346	-0.1324	0.4896
	Dominant (GG+GT vs TT)	33	0,0158	1,23	25,56	17	0,0829	Fixed	-0.0911	0.7426	-0.4070, 0.2247	-0.1373	0.4543
	Recessive (TT+GT vs GG)	68	0,2384	1,77	50,22	16	<0,0001	Random	0.2018	0.5903	-0.5832, 0.9868	0.1029	0.5976
rs1801177	Recessive (AA+GA vs GG)	2	0	1,01	8,2	8	0,4142	Fixed	0.7025	0.3027	0.1866, 1.2185	-0.3333	0.2595
rs5888	Dominant (GG+GA vs AA)	85	0,1456	2,57	46,22	7	<0,0001	Random	0.0737	0.1612	-0.5503, 0.6977	0.0714	0.9049

Table 3. 4. Overview of meta-analyses results investigating the relationship between variants and presence of coronary heart disease in two different populations, Asian and Caucasian, according to two different models fixed and random effects which were determined by heterogeneity tests. Table is divided into two sections; upper part presents model results and the lower part presents heterogeneity and publication bias test results.

				Fixed Effects Model			Random Effects Model		
Meta-Analysis	Ethnicity	Genetic Model	Study Population (Case/Control)	Fixed Effects OR (95% CI)	z	p-value	Random Effects OR (95% CI)	z	p-value
rs2066714	Asian	Allelic	5316/4788	1,19 [1,09; 1,31]	3,69	0,0002	1,19 [1,09; 1,31]	3,69	0,0002
		Additive	1710/1492	1,42 [1,12; 1,79]	2,92	0,0035	1,41 [1,11; 1,81]	2,77	0,0057
		Recessive	2658/2394	0,78 [0,70; 0,89]	-3,758	0,0002	0,78 [0,67; 0,91]	-3,2	0,0014
	Caucasian	Recessive	1342/6504	0,78 [0,67; 0,90]	-3,34	0,0009	0,81 [0,67; 0,98]	-2,17	0,0301
rs2230806	Asian	Allelic	11796/10498	1,33 [1,26; 1,40]	10,18	<0,0001	1,37 [1,23; 1,53]	5,73	<0,0001
		Additive	3248/2798	1,77 [1,58; 1,98]	9,96	<0,0001	1,87 [1,53; 2,27]	6,17	<0,0001
		Dominant	5898/5249	1,48 [1,34; 1,63]	7,94	<0,0001	1,63 [1,33; 1,99]	4,75	<0,0001
		Recessive	5898/5249	0,71 [0,65; 0,77]	-8,24	<0,0001	0,71 [0,65; 0,77]	-7,94	<0,0001
	Caucasian	Allelic	18618/36934	1,05 [1,00; 1,10]	1,92	0,0553	1,16 [1,04; 1,30]	2,66	0,0079
		Additive	5509/11030	1,11 [0,99; 1,24]	1,83	0,0674	1,30 [1,04; 1,62]	2,33	0,0198
		Recessive	9309/18467	0,95 [0,89; 1,01]	-1,63	0,1031	0,84 [0,73; 0,96]	-2,49	0,0127
rs708272	Asian	Allelic	5304/4568	1,30 [1,19; 1,41]	6,08	<0,0001	1,28 [1,14; 1,44]	4,09	<0,0001
		Additive	1356/1097	1,67 [1,40; 2,00]	5,63	<0,0001	1,60 [1,24; 2,07]	3,58	<0,0001
		Dominant	2652/2284	1,37 [1,17; 1,59]	3,,98	<0,0001	1,29 [1,04; 1,60]	2,29	<0,0001
		Recessive	2652/2284	0,69 [0,60; 0,78]	-5,77	<0,0001	0,68 [0,59; 0,80]	-4,89	<0,0001
	Caucasian	Allelic	37326/44032	1,09 [1,06; 1,13]	5,53	<0,0001	1,11 [1,06; 1,15]	5,26	<0,0001
		Additive	6332/11202	1,22 [1,15; 1,31]	6,05	<0,0001	1,26 [1,16; 1,36]	5,62	<0,0001
		Dominant	18663/22016	1,21 [1,14; 1,28]	6,4	<0,0001	1,22 [1,14; 1,29]	6,21	<0,0001
		Recessive	18663/22016	0,93 [0,89; 0,98]	-2,98	0,0028	0,92 [0,87; 0,97]	-3,08	0,0021

			Quantifying Heterogeneity			Test of Heterogeneity			Model should be used	Egger's Test			Begg's Test	
Meta-Analysis	Ethnicity	Genetic Model	I^2 (%)	τ^2	H	Q	Degrees of Freedom	p-value		Coefficient Estimate (b)	p-value	Confidence Interval (CI)	Tau	p-value
rs2066714	Asian	Allelic	18	<0,0001	1,11	12,24	10	0,2693	Fixed	0.2266	0.7537	-0.1075, 0.5607	-0.0545	0.8793
		Additive	19	0,0114	1,11	11,17	9	0,2600	Fixed	0.4140	0.8608	-0.3967, 1.2248	0.0667	0.8618
		Recessive	41	0,0161	1,3	16,81	10	0,0800	Fixed	-0.0374	0.3248	-0.4791, 0.4044	-0.2364	0.3587
	Caucasian	Recessive	27	0,0145	1,17	5,51	4	0,2400	Fixed	-0.6586	0.0421	-1.0788, -0.2384	0.400	0.4833
rs2230806	Asian	Allelic	68	0,0604	1,77	91,23	29	<0,0001	Random	-0.0223	0.0333	-0.3484, 0.3038	0.2552	0.0491
		Additive	63	0,1798	1,64	77,54	29	<0,0001	Random	0.0575	0.0272	-0.4771, 0.5920	0.2828	0.0286
		Dominant	72	0,2151	1,9	104,41	29	<0,0001	Random	-0.0942	0.0157	-0.5962, 0.4077	0.3333	0.0093
		Recessive	19	0,0033	1,11	36,02	29	0,1700	Fixed	-0.1931	0.2440	-0.4634, 0.0772	-0.0805	0.5473
	Caucasian	Allelic	75	0,0434	1,99	75,4	19	<0,0001	Random	-0.1935	0.0004	-0.3926, 0.0055	0.3263	0.0468
		Additive	63	0,1398	1,65	51,43	19	<0,0001	Random	-0.2703	0.053	-0.6603, 0.1198	0.2316	0.1650
		Recessive	71	0,0583	1,86	66	19	<0,0001	Random	0.2413	0.0004	0.0030, 0.4795	-0.3263	0.0468
rs708272	Asian	Allelic	45	0,0226	1,35	23,7	13	0,0340	Fixed	0.4513	0.4207	-0.0624, 0.9650	-0.0769	0.7472
		Additive	46	0,1085	1,37	24,28	13	0,0286	Fixed	11.668	0.1902	0.0970, 2.2365	-0.1868	0.3880
		Dominant	44	0,0716	1,34	23,4	13	0,0371	Fixed	0.9883	0.0388	0.2859, 1.6907	-0.2967	0.1572
		Recessive	25	0,0209	1,15	17,23	13	0,1889	Fixed	-0.2791	0.7663	-0.9699, 0.4117	-0.1209	0.5906
	Caucasian	Allelic	32	0,0013	1,21	41,14	28	0,0522	Fixed	0.0146	0.0084	-0.0492, 0.0785	0.1232	0.3613
		Additive	46	0,007	1,36	52,07	28	0,0038	Fixed	0.0236	0.0013	-0.1035, 0.1508	0.1675	0.2109
		Dominant	46	0,001	1,36	51,74	28	0,0041	Fixed	0.0534	0.0053	-0.0592, 0.1659	0.1872	0.1608
		Recessive	7	0,0031	1,04	30,18	28	0,3545	Fixed	0.0152	0.0385	-0.0794, 0.1098	-0.0690	0.6156

Evaluation of circulating HDL-C levels affected by the polymorphisms was performed using standardized mean difference (SMD) as an estimation method for the strength of the association as described in 'Chapter 2 – Materials and Methods'. All of the polymorphisms, except rs328 and rs1801177 with recessive genetic model applied, were analyzed under additive genetic model. Meta-analyses were grouped into 8 different sample types (Table 3.5) Depending on the p-values of the relevant meta-analysis and heterogeneity tests, one of the models (fixed or random effects) was selected and checked for its significance (p-value < 0.05). Detailed exhibition of the meta-analyses with significant p-values and standardized mean differences for two models were shared (Table 3.6). Only shared meta-analyses were visualized by forest plots which includes data regarding to standardized mean differences, CI at 95%, I^2 statistics, Chi^2, Tau^2 values, and p-value for heterogeneity tests. Additionally, sample sizes for each genotype frequencies, mean circulating HDL-C levels (mmol/L), standard deviation (mmol/L) and weight of each study were shared in forest plots.

Considering the significance and the heterogeneity tests, eligible meta-analyses results were shared as forest plots. In total, 58 meta-analyses were conducted with one of the determined sample groups (Table 3.6). 12 of these meta-analyses had only number of studies lower than 5 studies. 17 of the meta-analyses were evaluated as significant for determined effects model and saved for further observation. 4 of the significant studies had number of studies lower than 5 studies. Related forest plots for significant meta-analyses (including the meta.-analyses with lower sample sizes) were shared (Figure 3.39 to Figure 3.50).

Table 3. 5. Sample types determined for the circulating HDL-C levels data from the studies. Depending on the sample type, each meta-analysis were done and interpreted accordingly.

Mixed	All of the sample types were included.
Case	Only case studies were included.
Control	Only control studies were included.
Mixed Sex	Studies w/ mixed subjects in terms of sex were included.
Male	Only studies w/ male subjects were included.
Female	Only studies w/ female subjects were included.
CAD	Studies w/ only CAD subjects.
Caucasian	Studies w/ only Caucasian subjects.

Table 3. 6. Overview of meta-analyses results investigating the relationship between variants and HDL-C levels according to two different models fixed and random effects which were determined by heterogeneity tests. Each row represents meta-analyses with different genetic models or sample types showing significant results depending on p-values.

					Fixed Effects Model			Random Effects Model		
Meta-Analysis	enetic Mod	Sample Type	Number of Studies	Population	Fixed Effects SMD (95% CI)	z	p-value	Random Effects SMD (95% CI)	z	p-value
rs5069	Additive	Case	13	2999/1887	-0,79 [-0,85 ; -0,72]	-23,96	<0,0001	-0,83 [-1,46 ; -0,19]	-2,55	0,0109
	Additive	Control	7	1098/190	0,20 [0,04 ; 0,36]	2,5	0,0125	0,19 [-0,03 ; 0,42]	1,637	0,0956
	Additive	Mixed	20	4097/2077	-0,65 [-0,71 ; -0,59]	-21,26	<0,0001	-0,48 [-0,95 ; -0,01]	-2,01	0,0445
rs708272	Additive	Mixed	20	3245/1842	-0,20 [-0,27 ; -0,14]	-6,26	<0,0001	-0,97 [-1,78 ; -0,15]	-2,33	0,0198
rs1800775	Additive	Control	11	794/629	-0,34 [-0,45 ; -0,23]	-6,05	<0,0001	-0,34 [-0,60 ; -0,08]	-2,6	0,0093
	Additive	Male	3	87/70	-0,41 [-0,73 ; -0,09]	-4,97	<0,0001	-0,41 [-0,73 ; -0,09]	-3,21	0,0013
	Additive	Female	3	150/108	-0,66 [-0,92 ; -0,40]	-2,49	0,0129	-0,62 [-1,01 ; -0,24]	-2,49	0,0129
	Additive	Mixed Sex	9	960/637	-0,29 [-0,40 ; -0,18]	-7,19	<0,0001	-0,22 [-0,47 ; 0,04]	-3,2	0,0014
rs1800588	Additive	Control	3	417/33	-0,50 [-0,90 ; -0,11]	-2,48	0,0132	-0,50 [-0,90 ; -0,11]	-2,48	0,0132
rs2000813	Additive	Mixed	4	2505/389	-0,25 [-0,35 ; -0,14]	-4,47	<0,0001	-0,34 [-0,53 ; -0,14]	-3,29	0,001
	Recessive	Mixed	6	243/179	-0,55 [-0,76 ; -0,34]	-5,14	<0,0001	-0,91 [-1,71 ; -0,11]	-2,24	0,0251
rs328	Recessive	Case	15	4506/941	-0,38 [-0,45 ; -0,31]	-10,41	<0,0001	-0,42 [-0,72 ; -0,12]	-2,71	0,0068
	Recessive	Mixed	21	5668/1187	-0,40 [-0,46 ; -0,33]	-12,04	<0,0001	-0,54 [-0,97 ; -0,11]	-2,47	0,0133
	Recessive	CAD	8	1767/378	-0,61 [-0,72 ; -0,49]	-10,43	<0,0001	-0,52 [-0,98 ; -0,06]	-2,19	0,0283
rs5888	Additive	Asian	15	3997/312	0,38 [0,26 ; 0,50]	6,2	<0,0001	0,41 [0,16 ; 0,65]	3,23	0,0012
	Additive	Caucasian	14	2114/1455	-1,06 [-1,14 ; -0,99]	-27,19	<0,0001	-0,80 [-1,39 ; -0,22]	-2,69	0,0072
rs5882	Additive	Control	6	1282/482	-0,14 [-0,25 ; -0,03]	-2,47	0,0135	-0,14 [-0,25 ; -0,03]	-2,47	0,0135

			Quantifying			Test of Heterogeneity			
Meta-Analysis	Genetic Model	Sample Type	I^2 (%)	τ^2	H	Q	Degrees of Freedom	p-value	Model should be used
rs5069	Additive	Case	99	1,3443	9,07	986,3	12	<0,0001	Random
	Additive	Control	48	0,0445	1,38	11,5	6	0,0741	Fixed
	Additive	Mixed	98	1,1139	7,7	1126,25	19	<0,0001	Random
rs708272	Additive	Mixed	99	3,3941	9,53	1724,35	19	0	Random
rs1800775	Additive	Control	76	0,1202	2,03	41,36	10	<0,0001	Random
	Additive	Male	0	0	1,44	4,15	2	0,1253	Fixed
	Additive	Female	52	0,0587	1	1,61	2	0,4478	Random
	Additive	Mixed Sex	78	0,1009	1,87	48,87	14	<0,0001	Random
rs1800588	Additive	Control	0	0	1	0,2	2	0,9042	Fixed
rs2000813	Additive	Mixed	41	0,0184	1,3	5,08	3	0,1658	Fixed
	Recessive	Mixed	93	0,9059	3,73	69,67	5	<0,0001	Random
rs328	Recessive	Case	93	0,3137	3,81	202,92	14	<0,0001	Random
	Recessive	Mixed	96	0,9506	5,22	544,77	20	<0,0001	Random
	Recessive	CAD	94	0,3903	3,97	110,37	7	<0,0001	Random
rs5888	Additive	Asian	76	0,1536	2,03	49,48	12	<0,0001	Random
	Additive	Caucasian	98	1,217	7,74	779,37	13	<0,0001	Random
rs5882	Additive	Control	0	0	1	1,66	5	0,8938	Fixed

3.3.1. ATP binding cassette subfamily A member 1 (*ABCA1*)

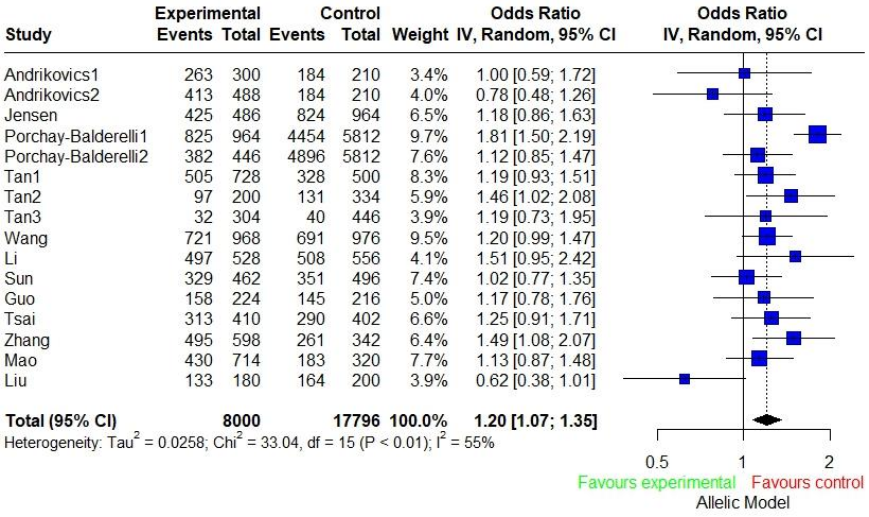


Figure 3. 1. Association between rs2066714 (*ABCA1*) under allelic (M vs. I) genetic model and cardiovascular disease risk estimated by odds ratios

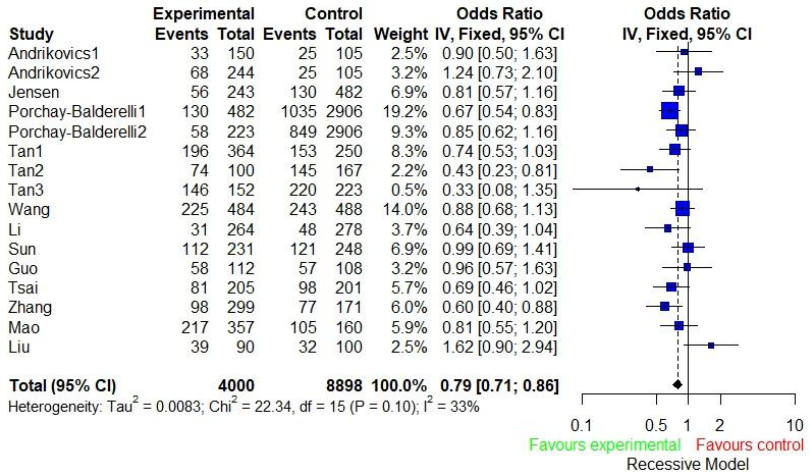


Figure 3. 2. Association between rs2066714 (*ABCA1*) under recessive (II/MI vs. MM) genetic model and cardiovascular disease risk estimated by odds ratios

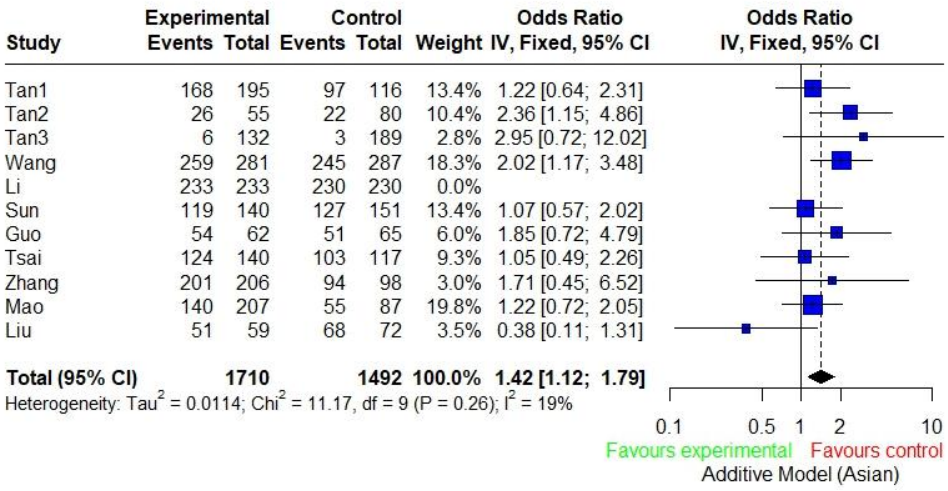


Figure 3. 3. Association between rs2066714 (*ABCA1*) under additive (MM vs. II) genetic model and cardiovascular disease risk estimated by odds ratios for only Asian subjects.

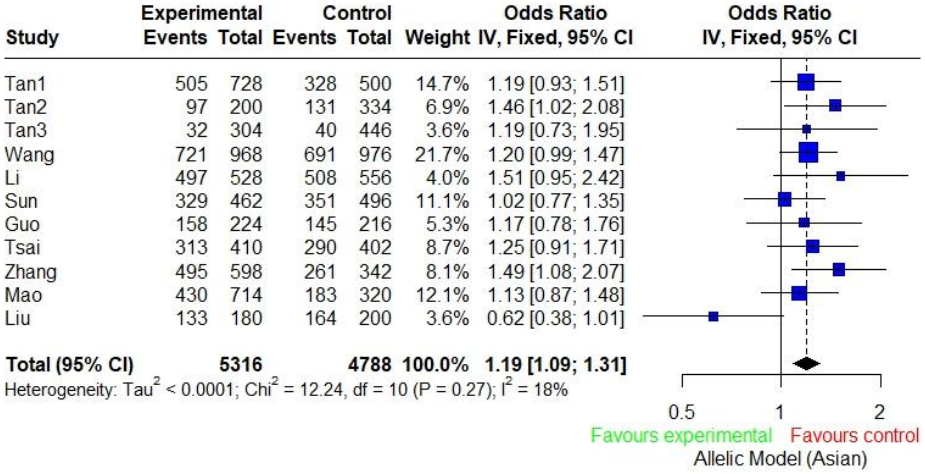


Figure 3. 4. Association between rs2066714 (*ABCA1*) under allelic (M vs. I) genetic model and cardiovascular disease risk estimated by odds ratios for only Asian subjects.

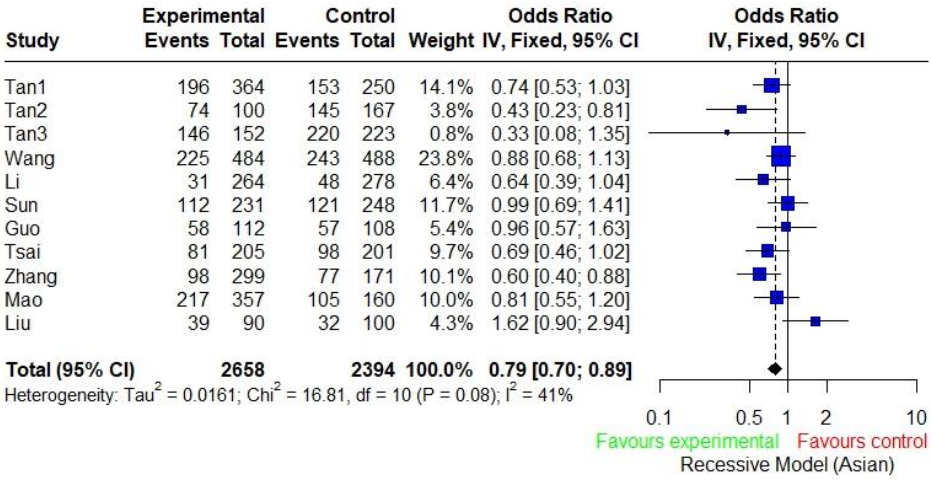


Figure 3. 5. Association between rs2066714 (*ABCA1*) under recessive (II/MI vs. MM) genetic model and cardiovascular disease risk estimated by odds ratios for only Asian subjects.

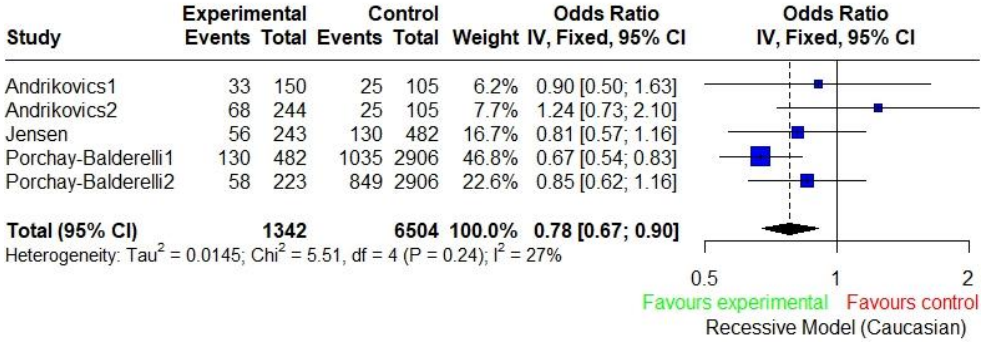


Figure 3. 6. Association between rs2066714 (*ABCA1*) under recessive (II/MI vs. MM) genetic model and cardiovascular disease risk estimated by odds ratios for only Caucasian subjects.

According to the different genetic models applied on the data related to rs2066714 (M883I) variant of *ABCA1* gene, meta-analyses of allelic (Figure 3.1) and recessive (Figure 3.2) genetic models were significant considering the p-values of the analyses. Depending on the heterogeneity test results of each meta-analyses with different genetic models, random effects model was selected for allelic model since the I^2 statistics and Q test showed significant heterogeneity for the data collected and fixed effects model was

selected for recessive model since the heterogeneity tests showed non-significant result with a p value of "0.10". Considering the odds ratio "M" allele of the rs2066714 showed a positive correlation (1.20 [95% CI: 1.07–1.35]) with the presence of coronary heart disease rather than "I" allele in allelic model. In 2014, Yan-Wei Yin et. al. performed a meta-analysis to explore the association between M883I (rs2066714) and atherosclerosis. They found an association between "I" allele and coronary heart disease risk.

Additionally, in terms of recessive model for the meta-analyses, "II/MI" genotypes of this variant showed a lower likelihood (0.79 [95% CI: 0.71 – 0.86]) with the presence of coronary heart disease. Hence, these results showed consistence for the relationship between "M" allele with coronary heart disease in a recessive heritage fashion.

According to the sub-group analyses for Asian subjects only, additive (Figure 3.3), allelic (Figure 3.4) and recessive (Figure 3.5) genetic models for meta-analyses showed significant results. Only recessive model (Figure 3.6) for sub-group analyses for Caucasian subject was found significant. Under additive (1.42 [95% CI: 1.12 – 1.79]) and allelic model (1.19 [95% CI: 1.09 – 1.31]) for Asian subjects, "MM" genotype and "M" allele showed a positive likelihood for the presence of coronary heart disease which is in correlation with the allelic model of the meta-analysis (Figure 3.1). In 2014, Yin et. al. found protective effect of "I" allele carriers in Asian populations. Unfortunately, the results of the same study were not significant for the Caucasian group. Additionally, comparison of the recessive model (0.79 [95% CI: 0.70-0.89]) for Asian subjects showed a lower likelihood of coronary heart disease with genotypes "II/MI" similar to the main analysis (Figure 3.2.). Caucasian subjects under recessive model (0.78 [95% CI: 0.67-0.90]) showed the similar results with Asian subjects which corresponds to the lower likelihood of coronary heart disease in the presence of "II/MM" genotypes. Heterogeneity tests for each of these meta-analyses showed small heterogeneity for I^2 statistics and non-significant Q test results, hence fixed effects model was used.

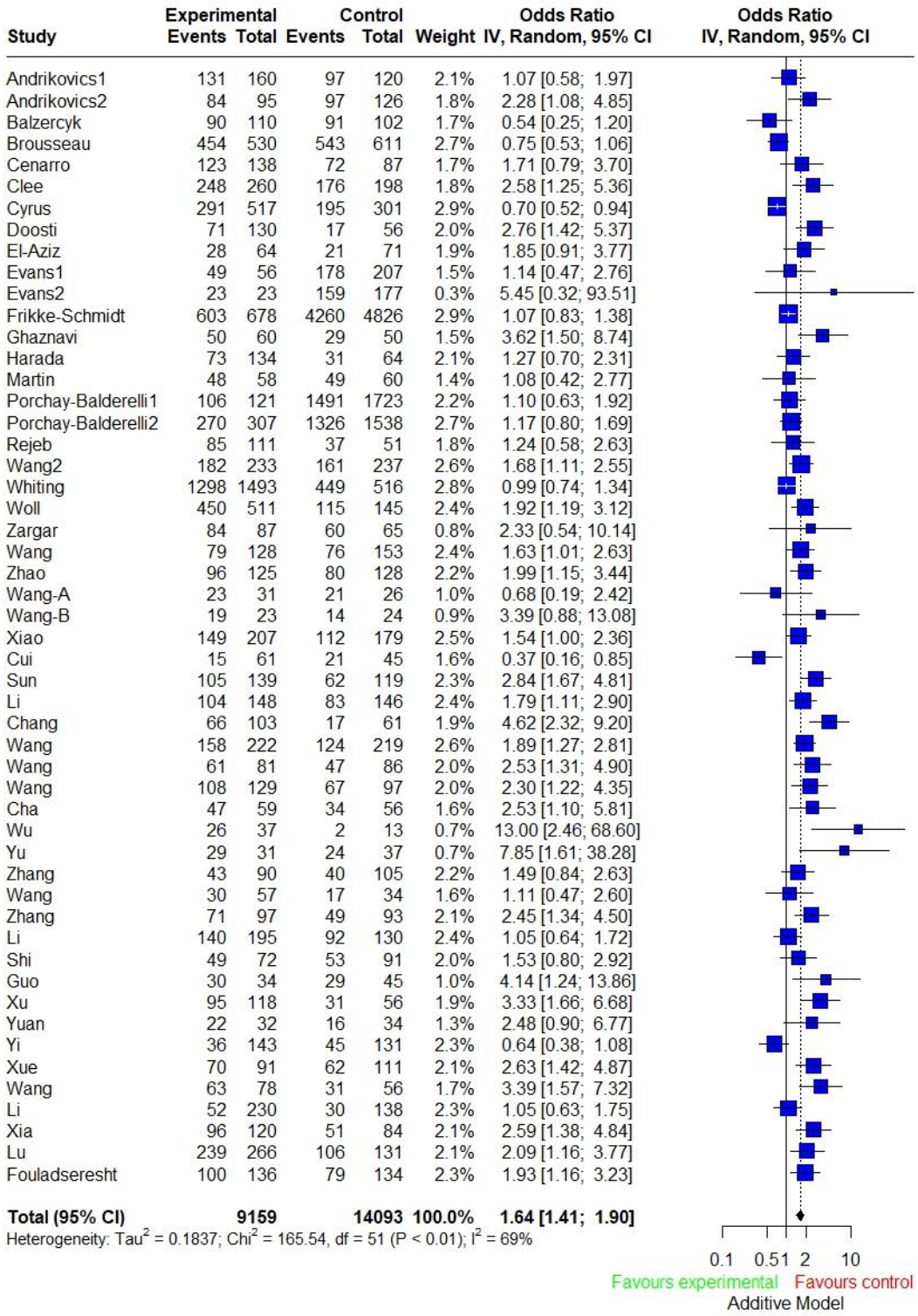


Figure 3. 7. Association between rs2230806 (*ABCA1*) under additive (RR vs. KK) genetic model and cardiovascular disease risk estimated by odds ratios

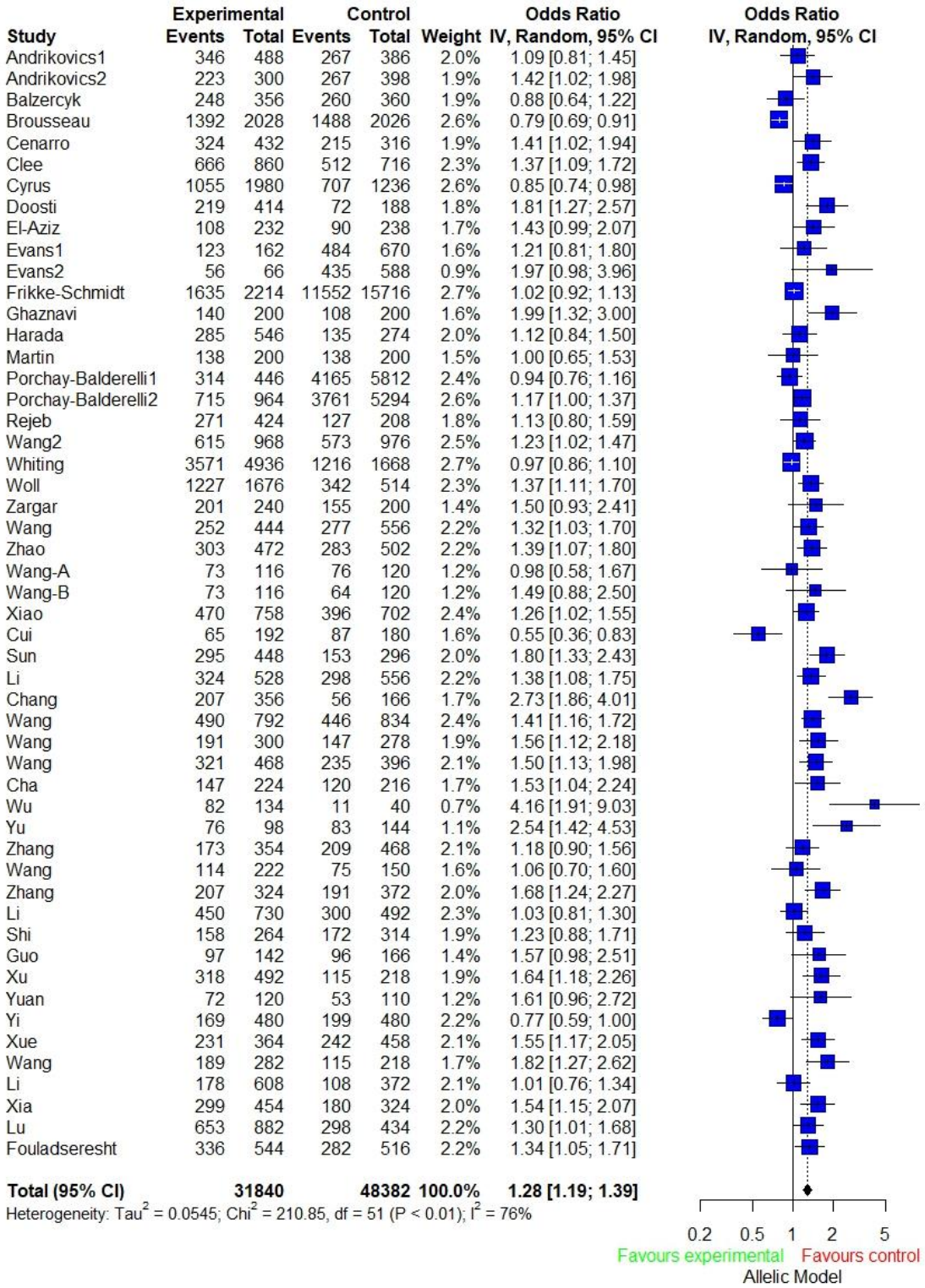


Figure 3. 8. Association between rs2230806 (*ABCA1*) under allelic (R vs. K) genetic model and cardiovascular disease risk estimated by odds ratios

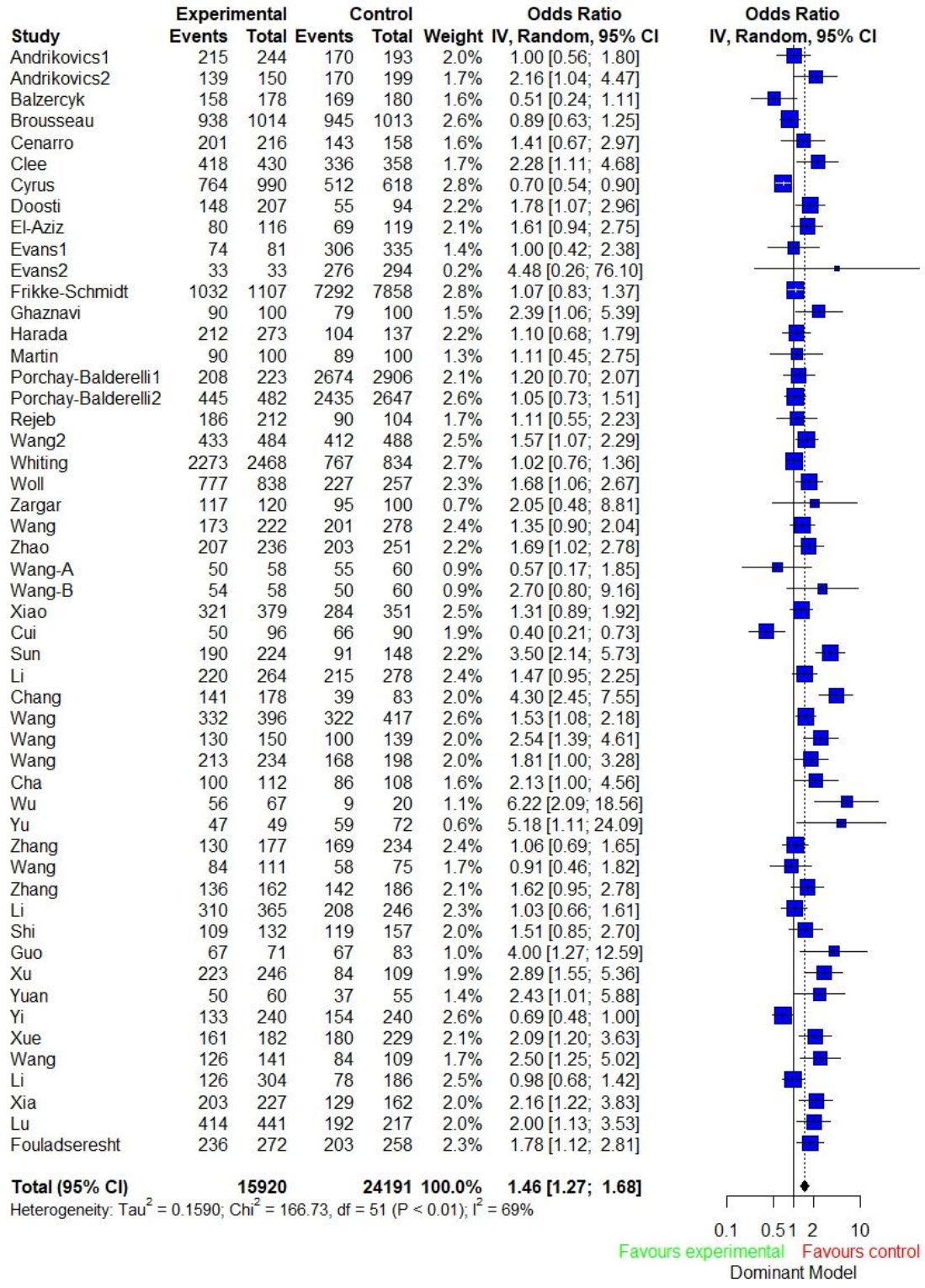


Figure 3. 9. Association between rs2230806 (*ABCA1*) under dominant (RR/RK vs. KK) genetic model and cardiovascular disease risk estimated by odds ratios

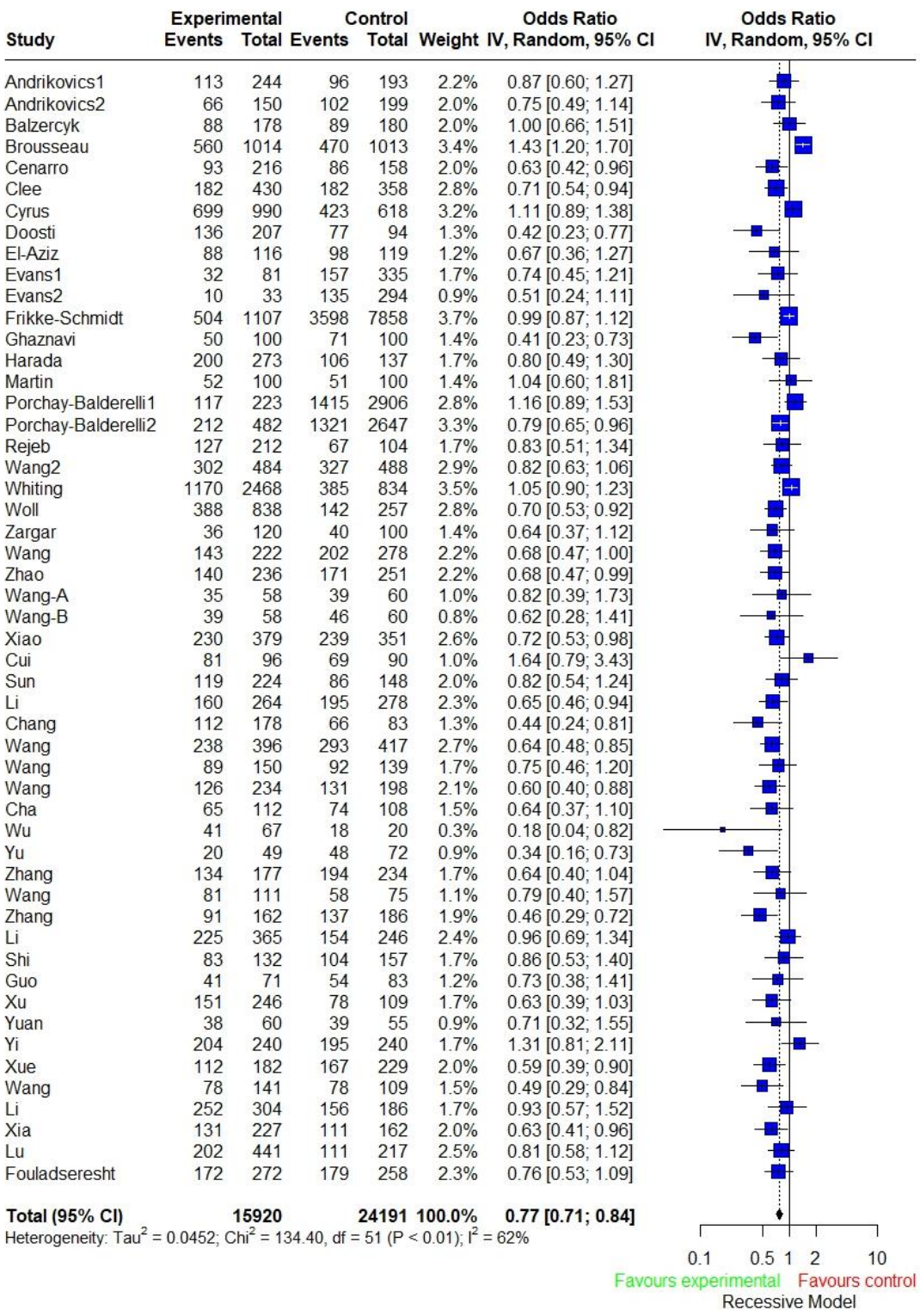


Figure 3. 10. Association between rs2230806 (*ABCA1*) under recessive (RK/KK vs. RR) genetic model and cardiovascular disease risk estimated by odds ratios

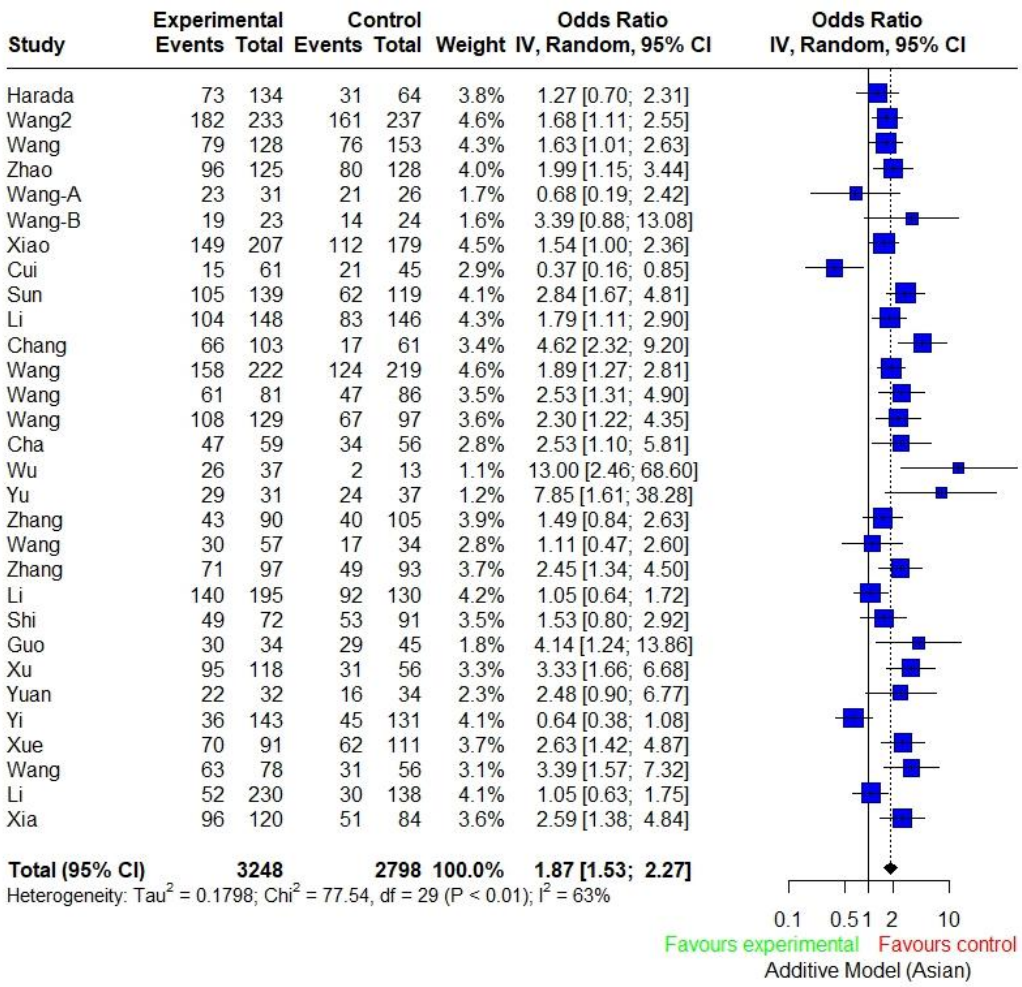


Figure 3. 11. Association between rs2230806 (*ABCA1*) under additive (RR vs. KK) genetic model and cardiovascular disease risk estimated by odds ratios for only Asian subjects.

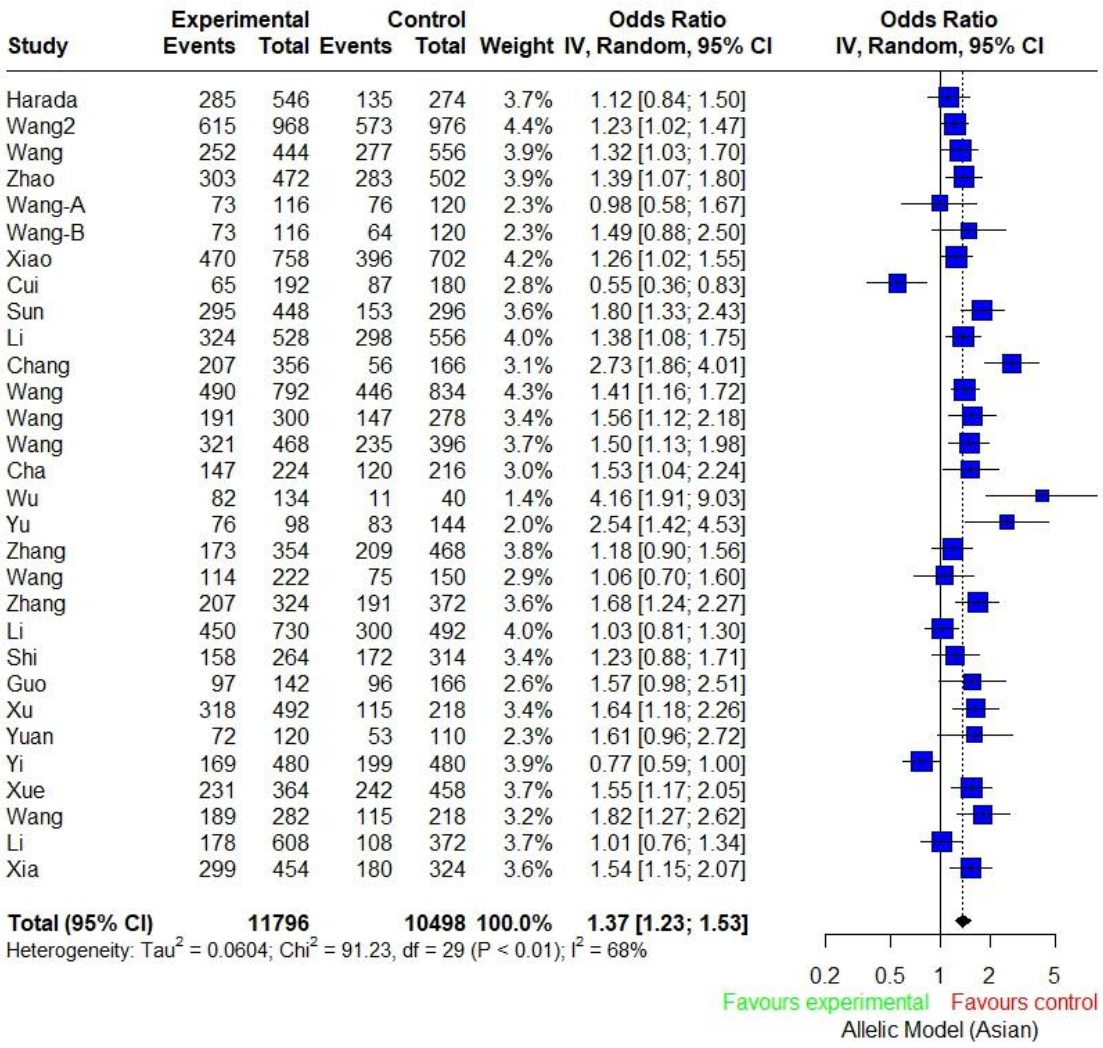


Figure 3. 12. Association between rs2230806 (*ABCA1*) under allelic (R vs. K) genetic model and cardiovascular disease risk estimated by odds ratios for only Asian subjects.

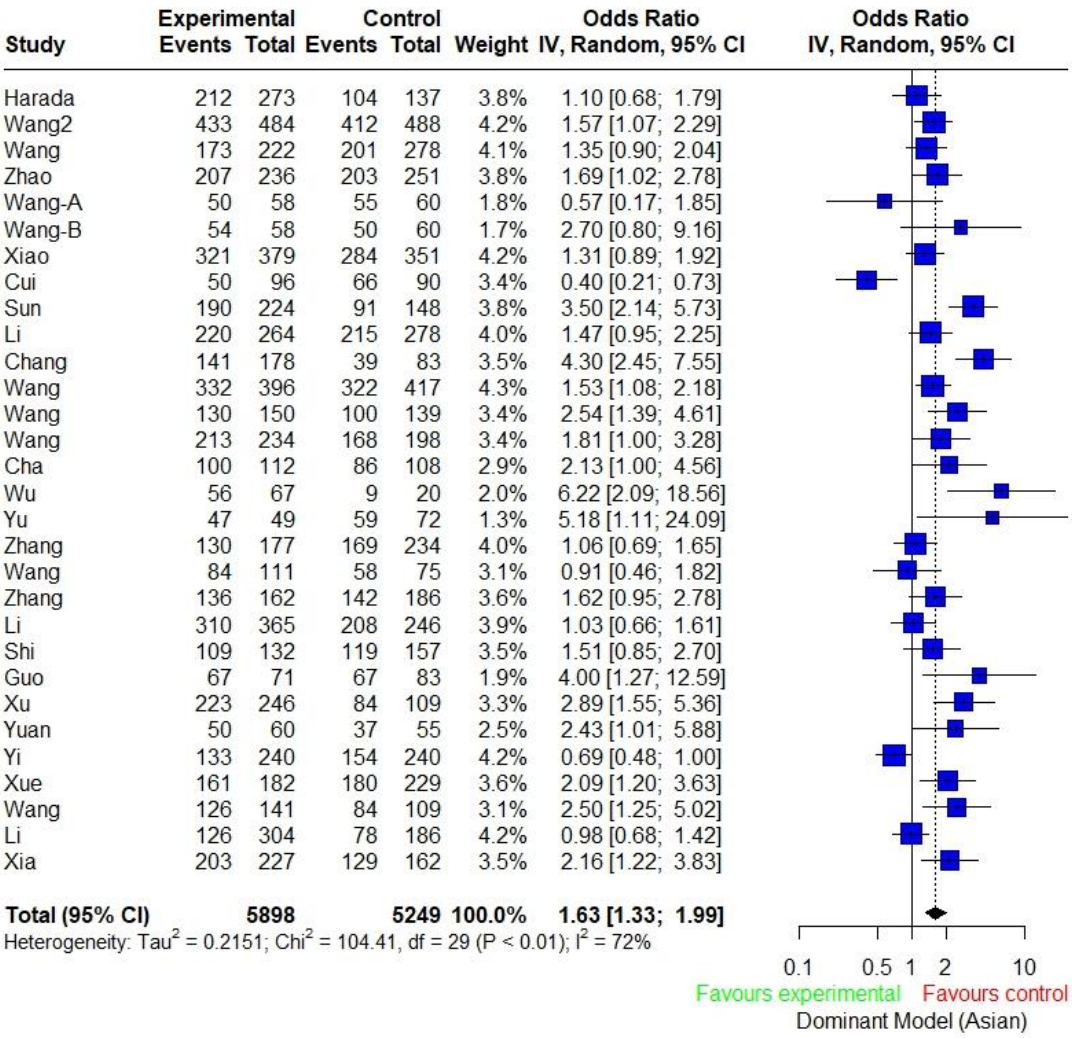


Figure 3. 13. Association between rs2230806 (*ABCA1*) under dominant (RR/RK vs. KK) genetic model and cardiovascular disease risk estimated by odds ratios for only Asian subjects.

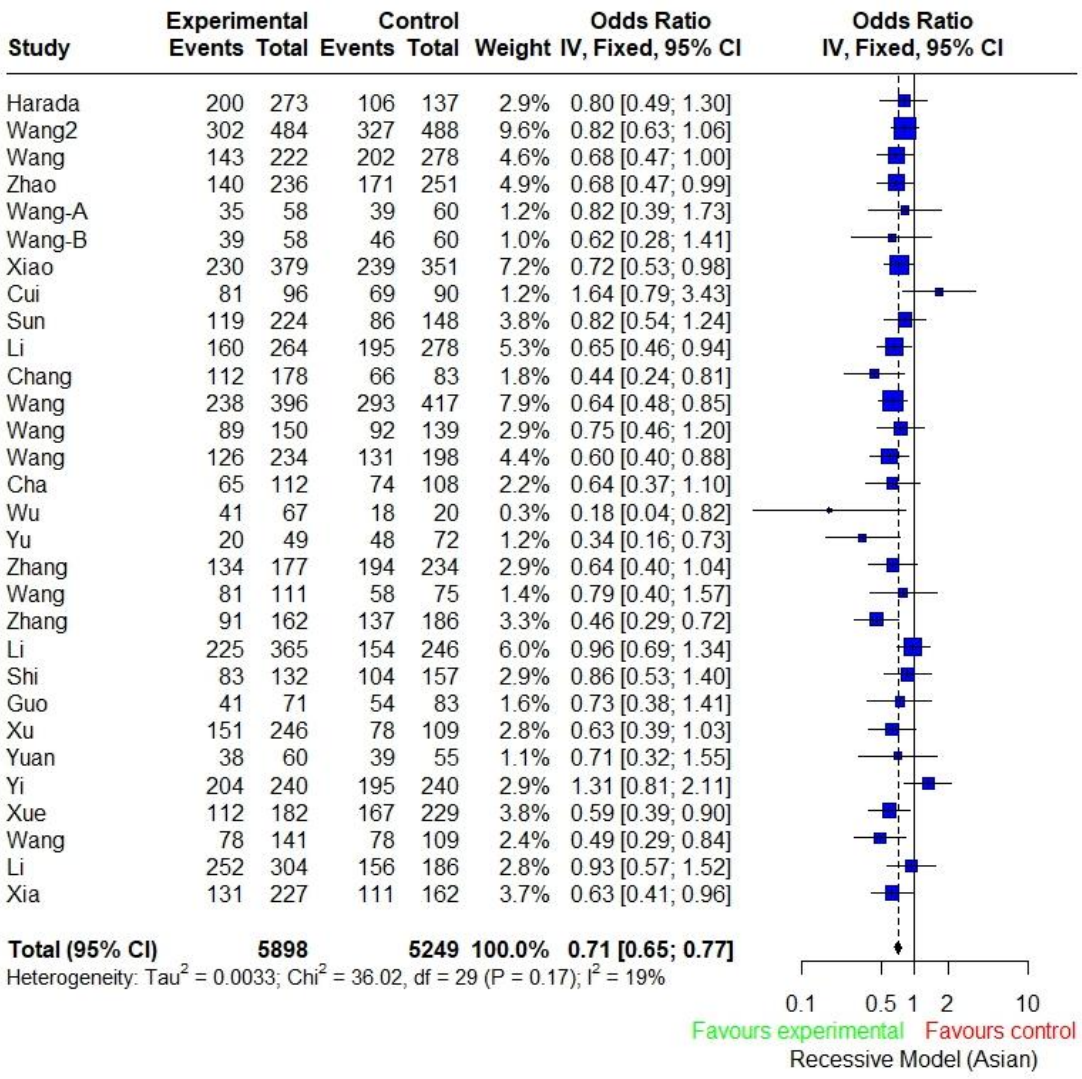


Figure 3. 14. Association between rs2230806 (*ABCA1*) under recessive (KK/RK vs. RR) genetic model and cardiovascular disease risk estimated by odds ratios for only Asian subjects.

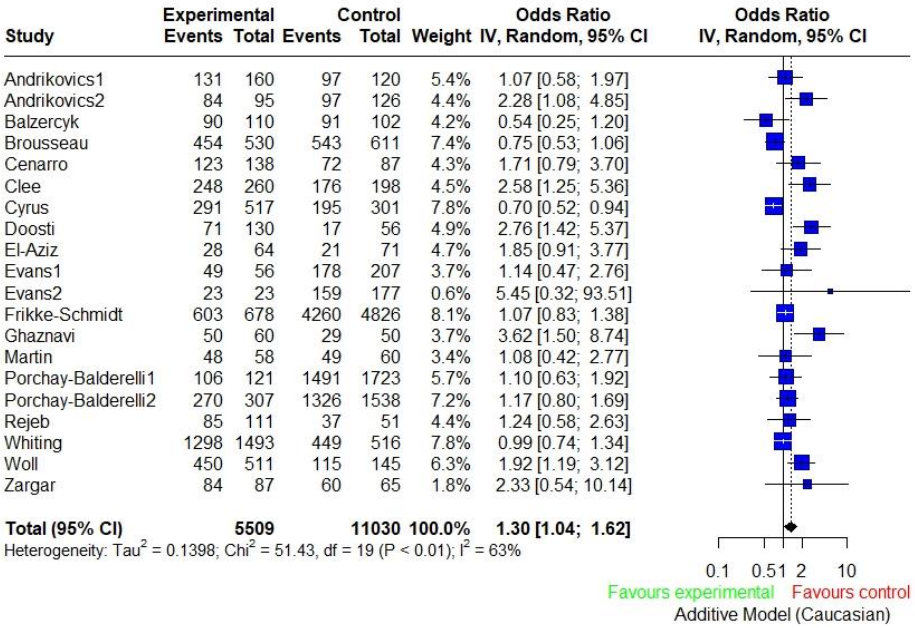


Figure 3. 15. Association between rs2230806 (*ABCA1*) under additive (RR vs. KK) genetic model and cardiovascular disease risk estimated by odds ratios for only Caucasian subjects.

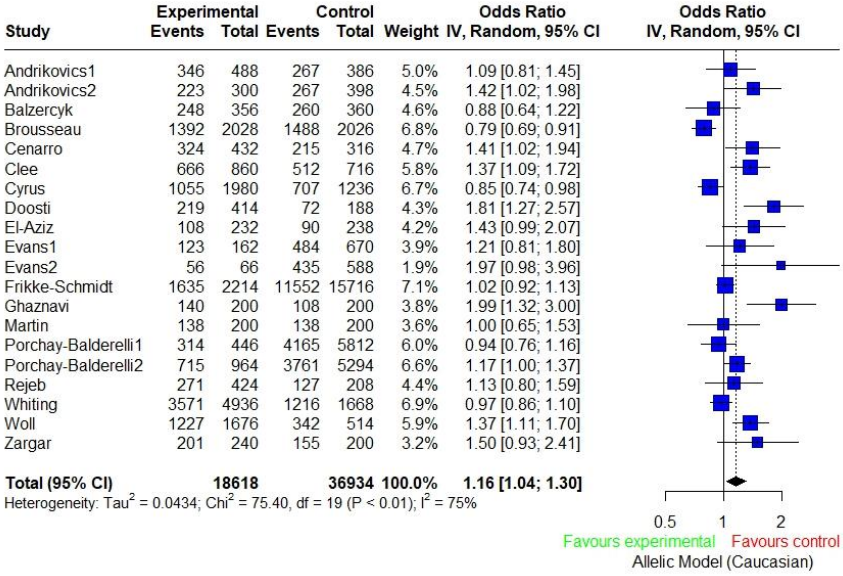


Figure 3. 16. Association between rs2230806 (*ABCA1*) under allelic (R vs. K) genetic model and cardiovascular disease risk estimated by odds ratios for only Caucasian subjects

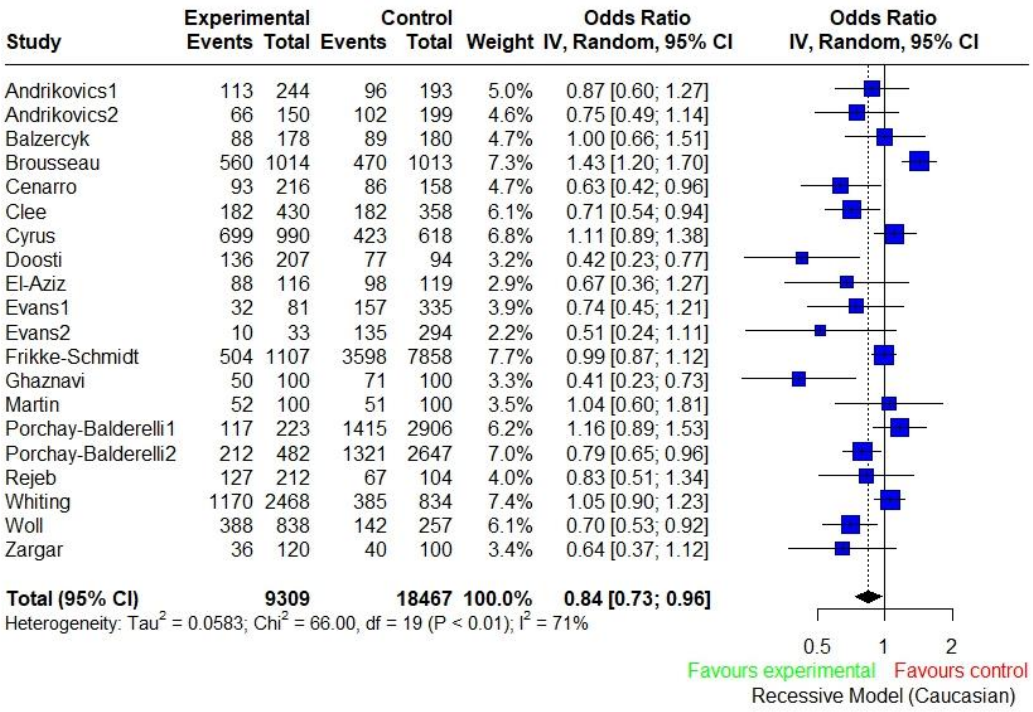


Figure 3. 17. Association between rs2230806 (*ABCA1*) under recessive (KK/RK vs. RR) genetic model and cardiovascular disease risk estimated by odds ratios for only Caucasian subjects

According to the genetic models applied for rs2230806 (*ABCA1*), meta-analyses for each model; additive (Figure 3.7), allelic (Figure 3.8), dominant (Figure 3.9) and recessive (Figure 3.9) had significant results in terms of p-values. Each meta-analysis showed a correlation for the relationship of "R" allele with the higher likelihood of the coronary heart disease. In allelic model (1.28 [95% CI: 1.19-1.39]), R allele showed higher odds of likelihood for the coronary heart disease. Additionally, the results by the dominant (1.46 [95% CI: 1.27-1.68]) and recessive (0.77 [95% CI: 0.71-0.84]) models showed correlated results for the "RR" genotype indicating the higher odds of likelihood for the presence of the disease. In the same manner, additive model (1.67 [95% CI: 1.41-1.90]) indicated that "RR" genotype could result in coronary heart disease in individuals. Depending on the heterogeneity results, all of the studies included in the genetic models, were found heterogeneous resulting in the random effects model application. In 2014, Yan-Wei Yin et. al. found that "KK" genotype carriers had protective effect against developing CHD than those with "RR" genotype. In 2020, Qian Fan et. al. showed that

"K" allele of R219K (rs2230806) is significantly associated with decreased risk of CAD in recessive and additive models. Additionally. "KK" genotype carriers was found to have higher levels of HDL-C than "RR" genotype carriers by Zhan Lu et. al. in 2018. Also, in 2011, Xiang-Yu Ma et. al. provided results showing the "KK" genotype carriers are found to have a lower risk of CAD and had higher levels of HDL-C than those with "RR" genotype.

Sub-group analyses for Asian and Caucasian subjects only, showed significant results for additive (Figure 3.11), allelic (Figure 3.12), dominant (Figure 3.13) and recessive (Figure 3.14) for Asian subjects and additive (Figure 3.15), allelic (Figure 3.16) and recessive (Figure 3.17) for Caucasian subjects. As expected, "RR" genotype for each meta-analyses, showed higher odds for the coronary heart disease. Comparing the results for each race indicated that presence of "RR" genotype in Asian groups (1.87 [95% CI: 1.53-2.27]) is more prone than Caucasian (1.30 [95%CI 1.04-1.62]) groups to results in coronary heart disease according to the odds ratios calculated by additive models. Additionally allelic models for both of the races showed correlated results with the additive models indicating (1.37 [95%CI 1.23-1.53]) for Asian groups and (1.16 [95%CI 1.04-1.30]) for Caucasian groups that "R" allele had higher odds of likelihood for the presence of coronary heart disease. In terms of recessive models for races, (0.71 [95%CI 0.65-0.77]) for Asian groups and (0.84 [95%CI 0.84-0.96]) for Caucasian groups, association for the Asian groups is stronger than the Caucasian groups since odds-ratio for the group is lower than the Caucasian groups. In 2020 and 2014, Qian Fan et. al. and Yan-Yan Li et. al. indicated that "K" allele carriers of R219K was found associated with protective effect in Asian groups. Whereas Qian Fan et. al. was able to show significant results with both of Caucasian and Asian groups, Zhan Lu et. al. was only able to provide significant analysis of Asian groups.

3.3.2. Apolipoprotein 1 (*APOA1*)

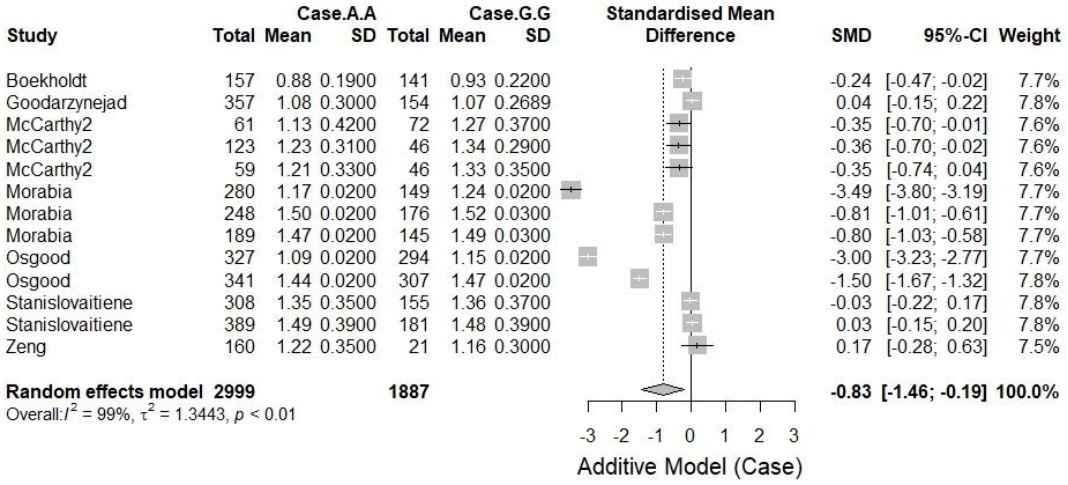


Figure 3. 18. Association between rs5069 (*APOA1*) under additive (AA vs. GG) genetic model estimated by standardized mean differences for only Case groups.

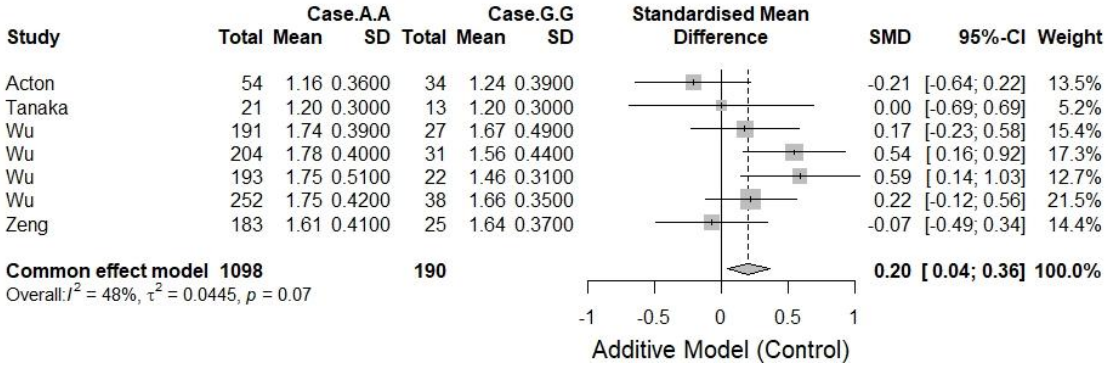


Figure 3. 19. Association between rs5069 (*APOA1*) under additive (AA vs. GG) genetic model estimated by standardized mean differences for only Control groups

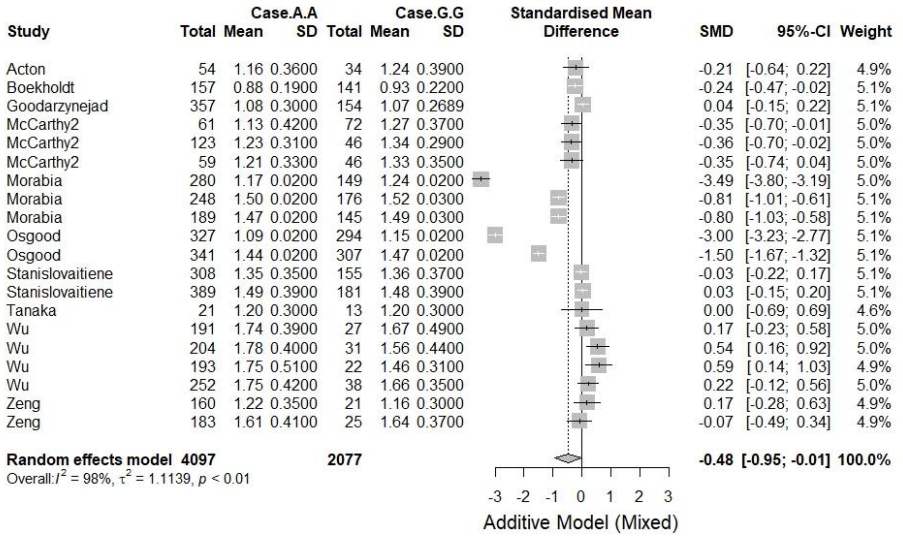


Figure 3. 20. Association between rs5069 (*APOA1*) under additive (AA vs. GG) genetic model estimated by standardized mean differences for both Case and Control groups.

rs5069 variant of *APOA1* gene had significant results in terms of interpretation for association between the variant and HDL-C levels in case and control groups. Three meta-analyses results were shared for additive models with case group (Figure 3.18), control group (Figure 3.19) and mixed (case plus control) (Figure 3.20). According to the case group result (-0.83 [95%CI -1.46: -0.19]), "AA" genotype in cases of coronary heart disease indicated an interval which does not include zero meaning significant result and individuals with the genotype may have a lower mean value for HDL-C levels suggesting a risk for the presence of coronary heart disease. In correlation with the case group results, control group had a standardized mean difference as 0.20 [95%CI 0.04: 0.36]) indicating that "AA" genotype in control groups resulted in slightly higher levels of HDL-C compared to "GG" genotype in individual. Overall, the results for the mixed group, caused by the effect measures in the case group, showed SMD as 0.20 [95%CI -0.95: -0.01]) indicating that "AA" genotype caused a lower HDL-C levels than "GG" genotype. In 2016, Lang-Biao Xu et. al. performed meta-analysis of odds ratios to observe association between *APOA1*, -75G/A (rs5069) variant and coronary heart disease. They found no significant association for additive, allelic, dominant and recessive genetic models.

3.3.3. Cholesteryl Ester Transfer Protein (*CETP*)

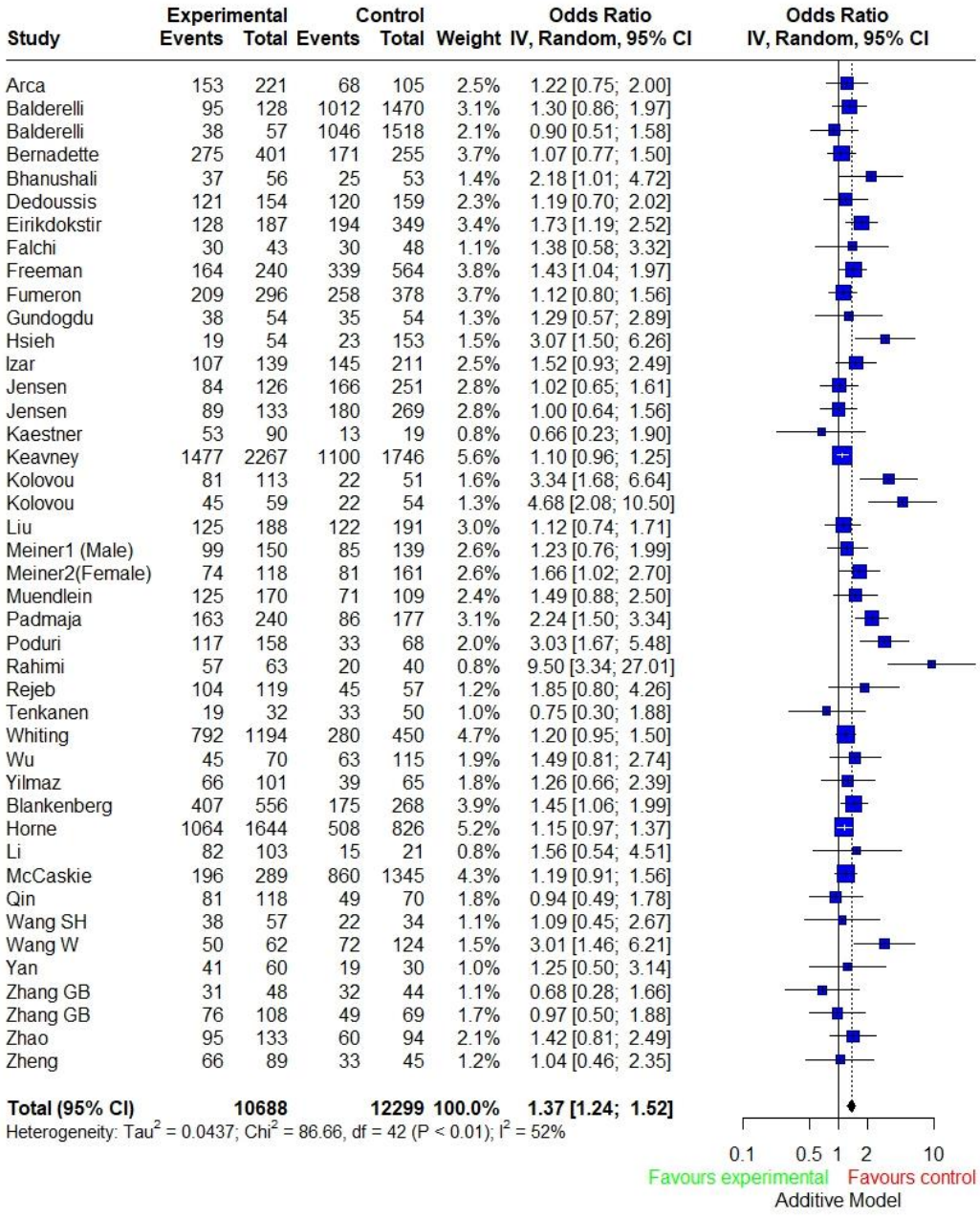


Figure 3. 21. Association between rs708272 (*CETP*) under additive (B1B1 vs. B2B2) genetic model and cardiovascular disease risk estimated by odds ratios

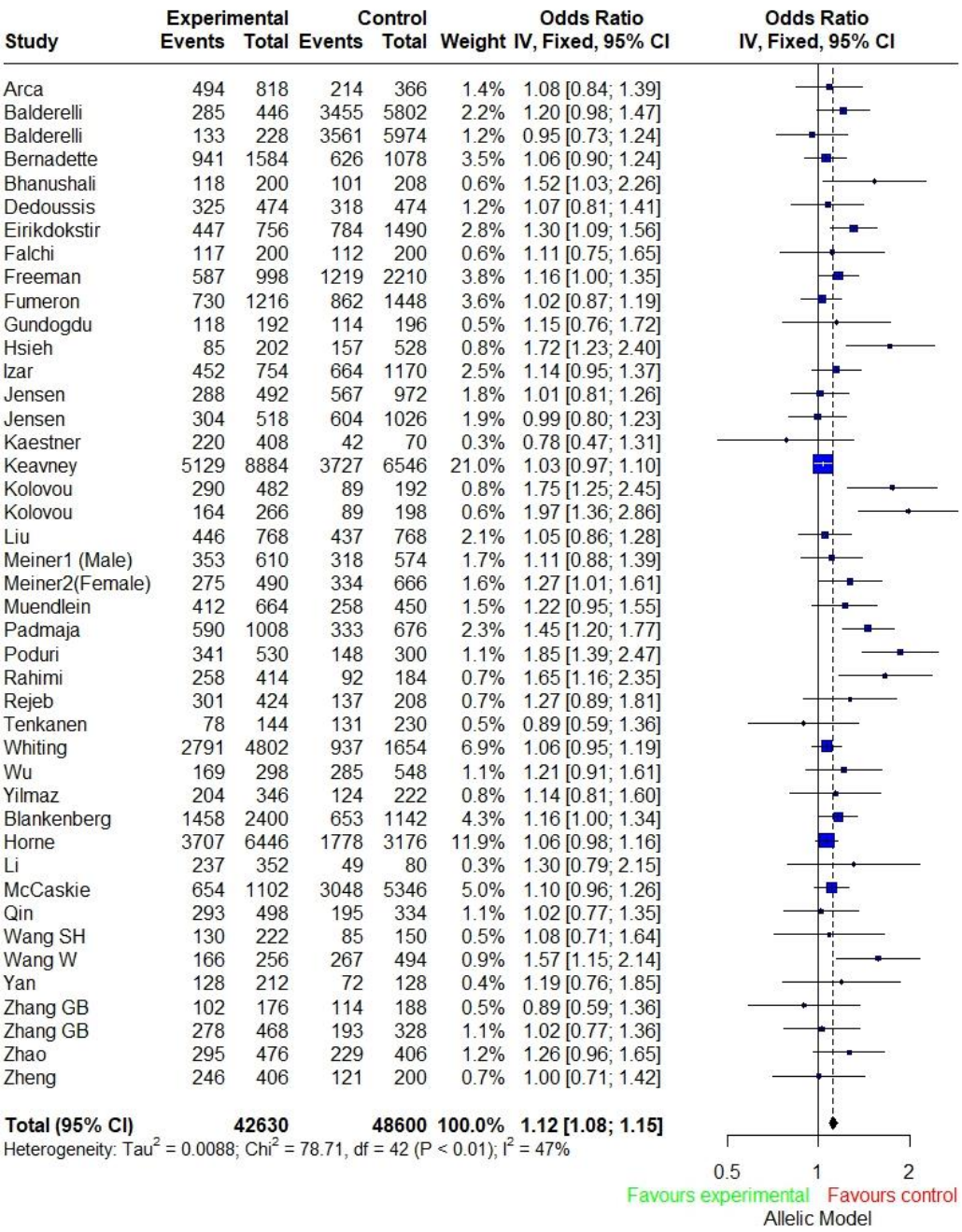


Figure 3. 22. Association between rs708272 (*CETP*) under allelic (B1 vs. B2) genetic model and cardiovascular disease risk estimated by odds ratios

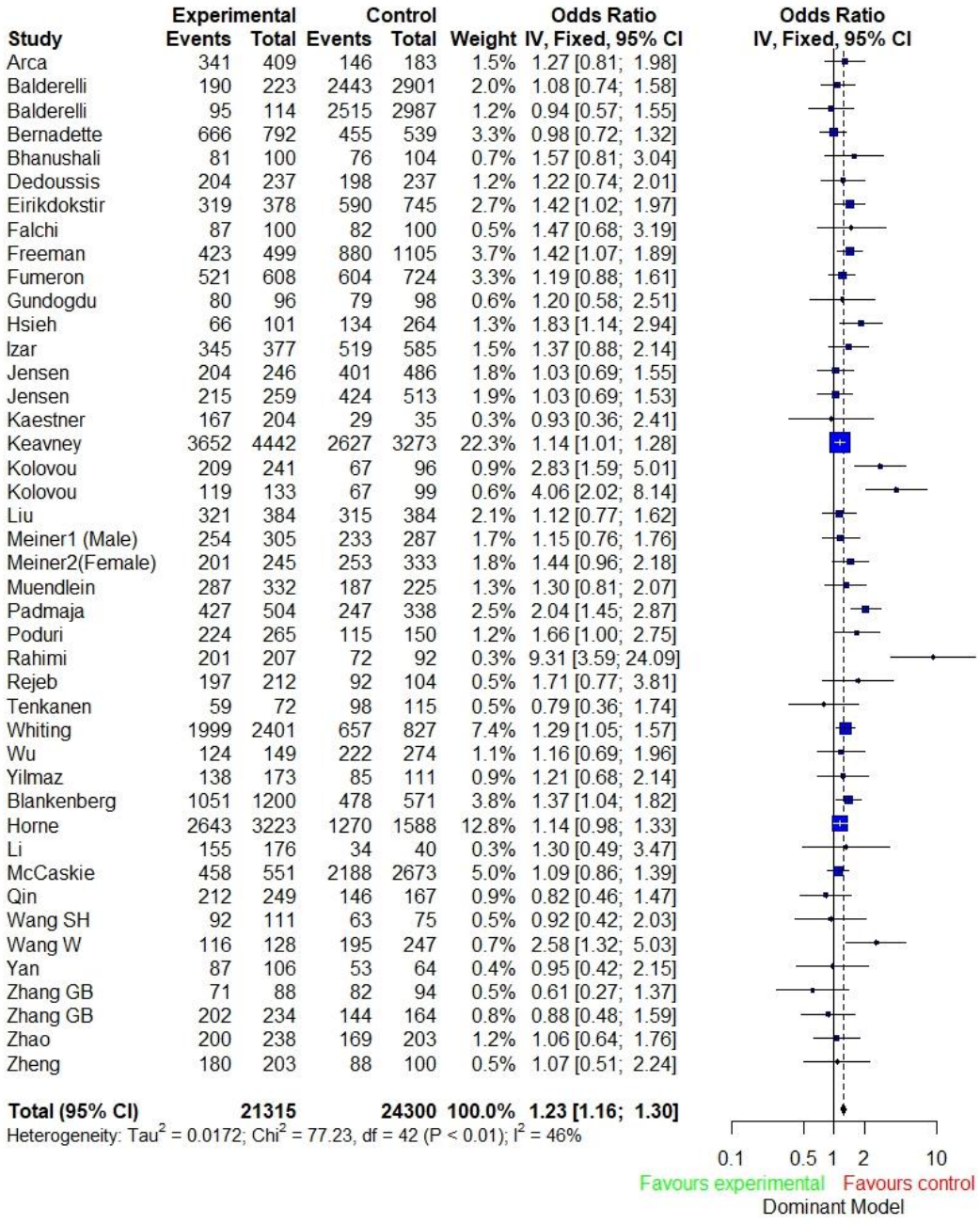


Figure 3. 23. Association between rs708272 (*CETP*) under dominant (B1B1/B1B2 vs. B2B2) genetic model and cardiovascular disease risk estimated by odds ratios

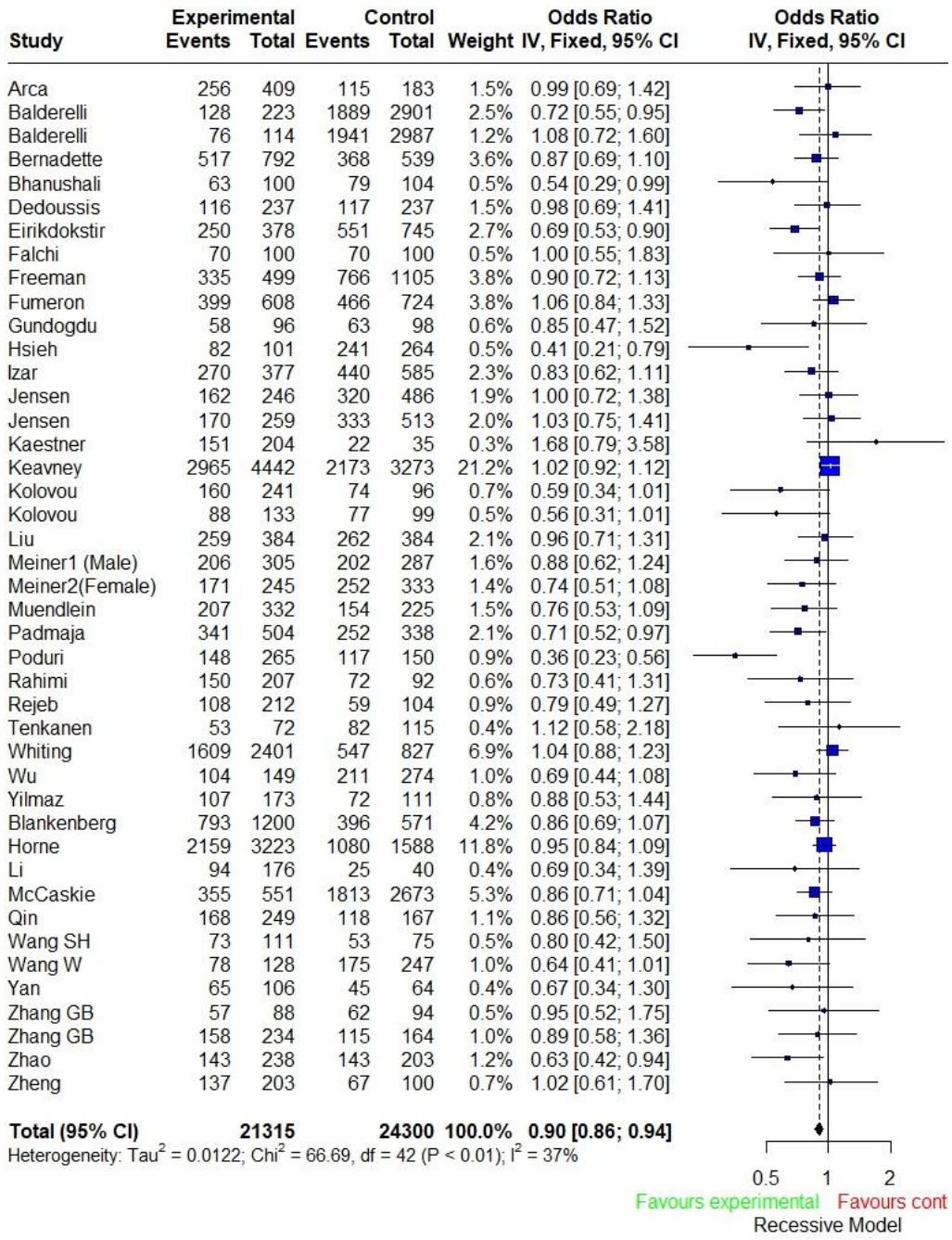


Figure 3. 24. Association between rs708272 (*CETP*) under recessive (B1B1 vs. B2B2/B1B2) genetic model and cardiovascular disease risk estimated by odds ratios.

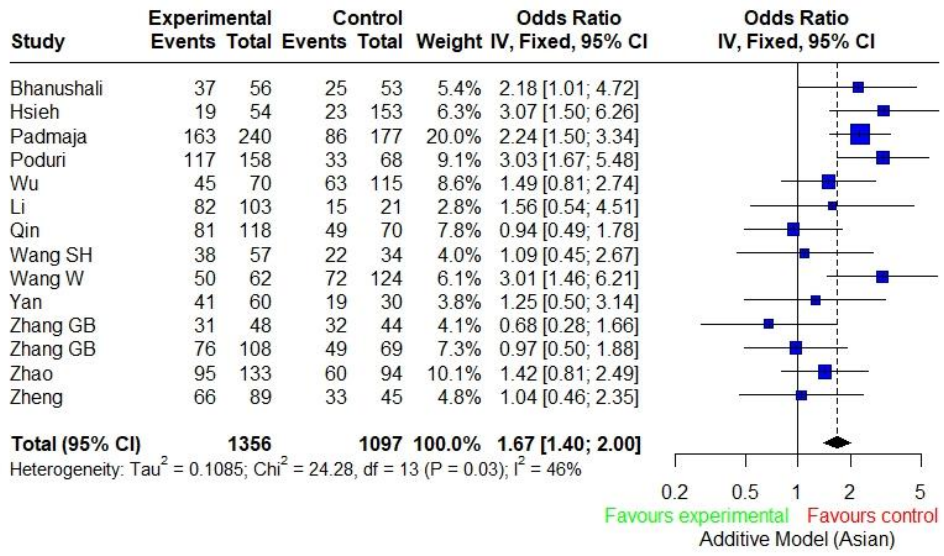


Figure 3. 25. Association between rs708272 (*CETP*) under additive (B1B1 vs. B2B2) genetic model and cardiovascular disease risk estimated by odds ratios for only Asian subjects

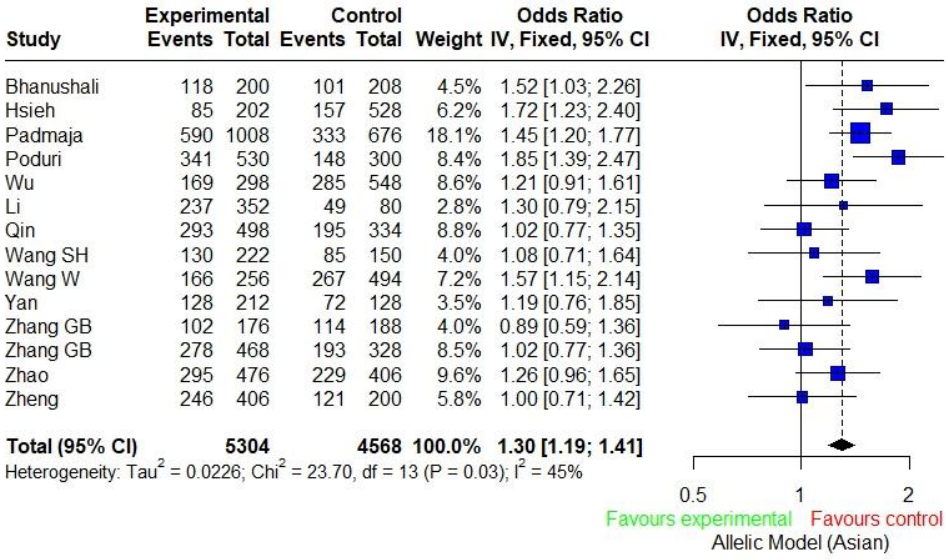


Figure 3. 26. Association between rs708272 under allelic (B1 vs. B2) genetic model and cardiovascular disease risk estimated by odds ratios for only Asian subjects

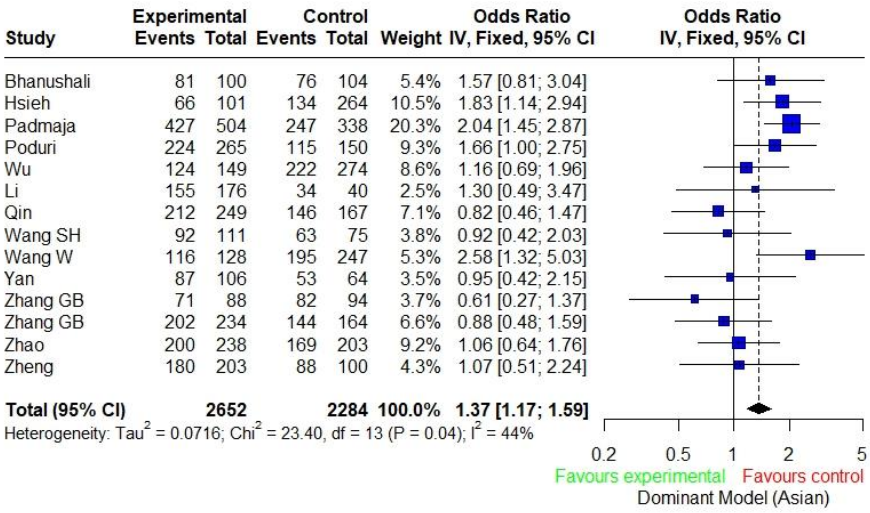


Figure 3. 27. Association between rs708272 (*CETP*) under dominant (B1B1/B1B2 vs. B2B2) genetic model and cardiovascular disease risk estimated by odds ratios for only Asian subjects

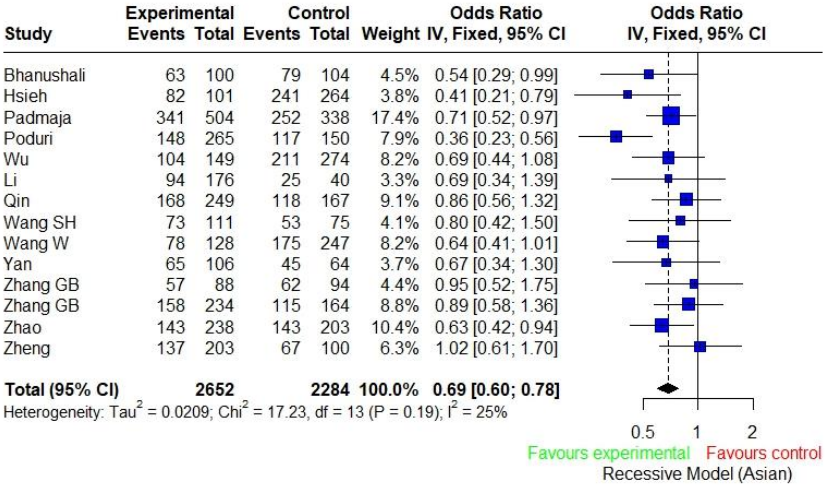


Figure 3. 28. Association between rs708272 (*CETP*) under recessive (B1B1 vs. B2B2/B1B2) genetic model and cardiovascular disease risk estimated by odds ratios for only Asian subjects.

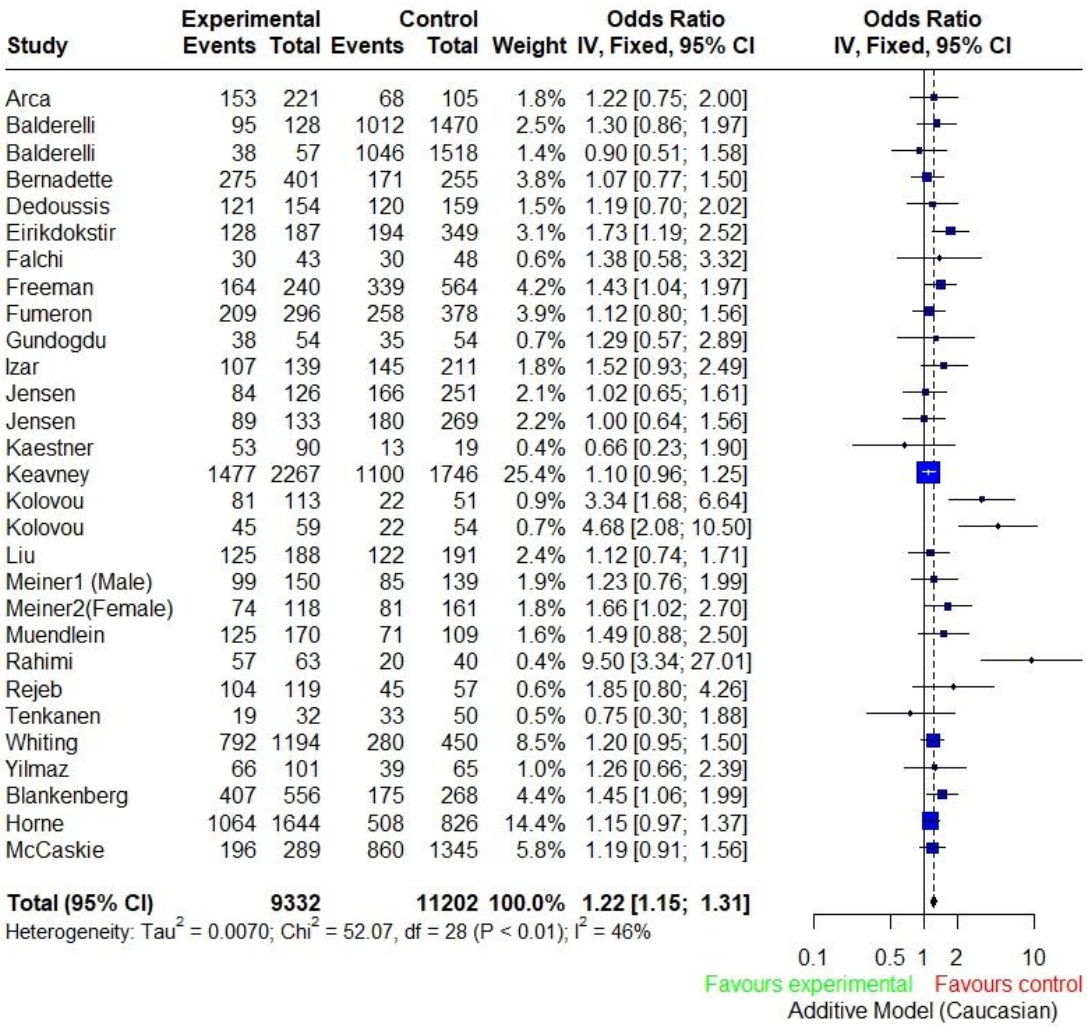


Figure 3. 29. Association between rs708272 (*CETP*) under additive (B1B1 vs. B2B2) genetic model and cardiovascular disease risk estimated by odds ratios for only Caucasian subjects

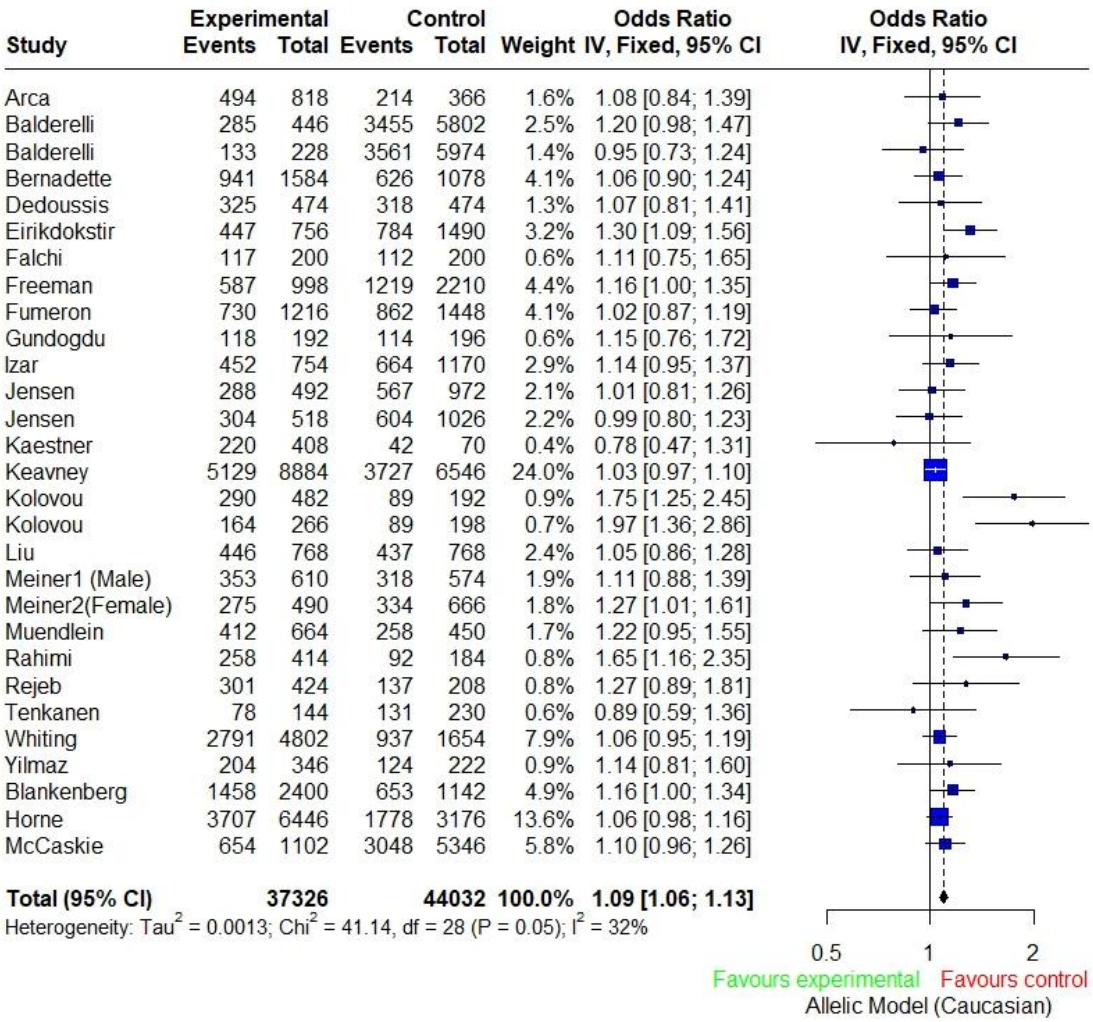


Figure 3. 30. Association between rs708272 (*CETP*) under allelic (B1B1 vs. B2B2) genetic model and cardiovascular disease risk estimated by odds ratios for only Caucasian subjects.

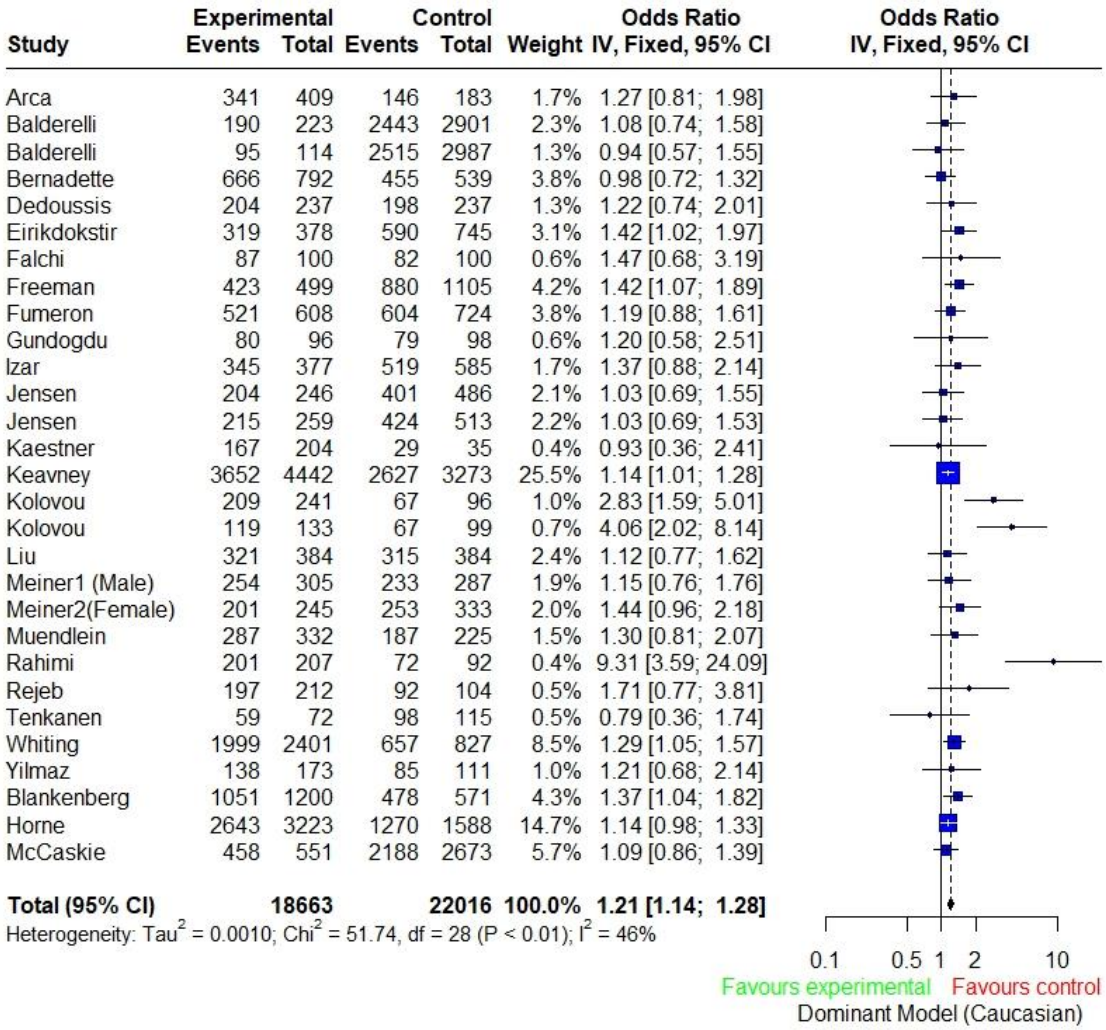


Figure 3. 31. Association between rs708272 (*CETP*) under dominant (B1B1/B1B2 vs. B2B2) genetic model and cardiovascular disease risk estimated by odds ratios for only Caucasian subjects.

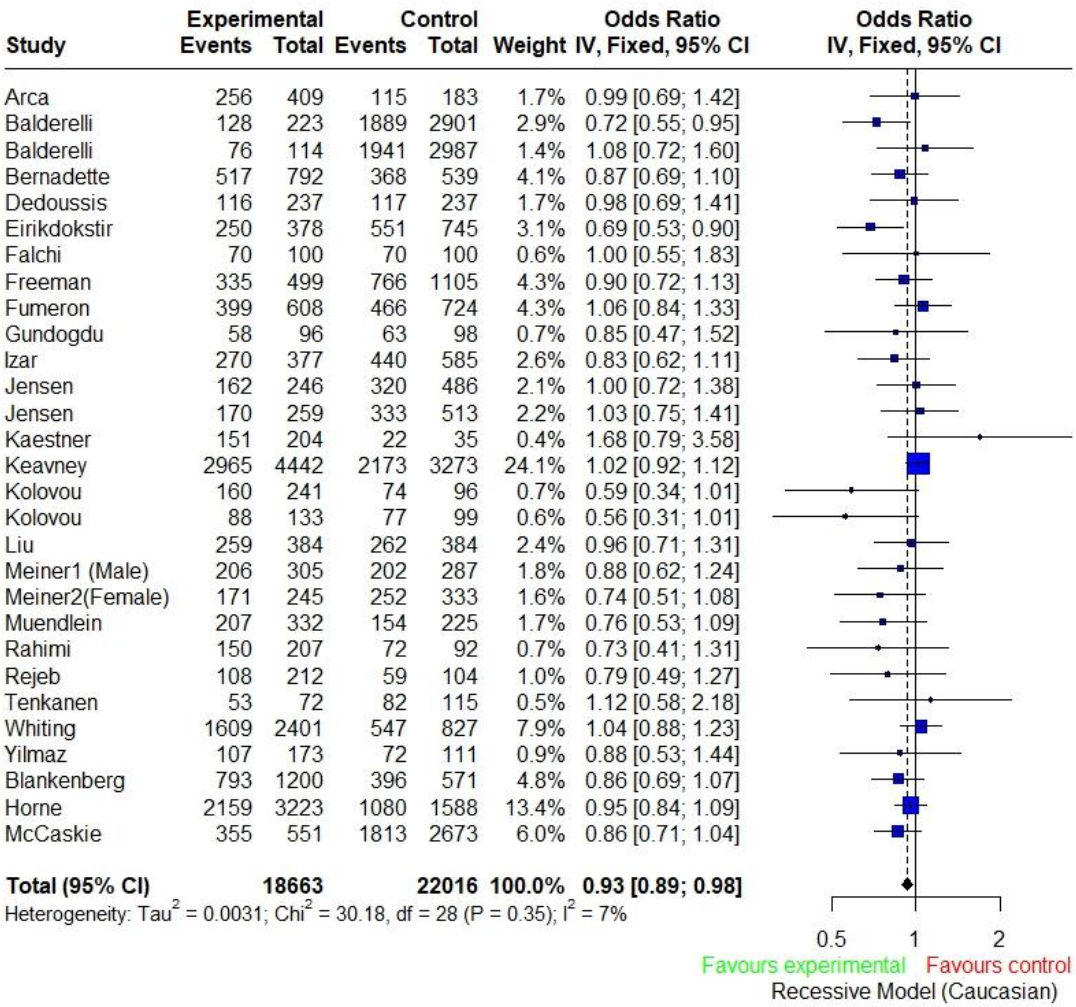


Figure 3. 32. Association between rs708272 (*CETP*) under recessive (B1B1 vs. B2B2/B1B2) genetic model and cardiovascular disease risk estimated by odds ratios for only Caucasian subjects.

According to the genetic models applied to the collected data for rs708272 (*CETP*), meta-analyses for each model; additive (Figure 3.21), allelic (Figure 3.22), dominant (Figure 3.23) and recessive (Figure 3.24) had significant results in terms of p-values. Depending on the heterogeneity results, only data for the additive model was found heterogeneous, thus a random effects model was applied in meta-analysis. Interpretation of the odds ratios for additive (1.37 [95%CI: 1.24-1.52]), allelic (1.12 [95%CI: 1.08-1.15]) and dominant model (1.23 [95%CI: 1.16-1.30]) showed that individuals with B1B1, B1 and at least one B1 allele respectively have higher odds (37%, 12%, and 23% respectively) of likelihood of coronary heart disease. For recessive model (0.90 [95%CI: 0.86-0.94]), analysis indicated having two B1 alleles is necessary to observe %10 decrease in the odds of coronary heart disease. Results depending on these models showed controversial odds ratios in terms of protection against coronary heart disease between additive, allelic, and dominant model and recessive model. In 2016, 2014, and 2012, Shu-Xia Guo et. al., Zhijun Wu et. al., and Qi Yu et. al. respectively showed similar results indicating the "B1" allele carriers to have a higher risk of developing CHD. Only Zhijun Wu et. al. showed this correlated result for Asian groups.

Sub-group analysis for the races, additive (Figure 3.25), allelic (Figure 3.26), dominant (Figure 3.27) and recessive (Figure 3.28) for Asian and additive (Figure 3.29), allelic (Figure 3.30), dominant (Figure 3.31) and recessive (Figure 3.32) for Asian Caucasian were performed with significant p-values with fixed effects model applied. Effect of "B1" allele in the higher odds of coronary heart disease were observed in Asian groups than Caucasian groups. In terms of allelic model, analysis with Asian groups had odds ratio as (1.30 [95%CI: 1.19-1.41]), and with Caucasian groups had odds ratio as (1.09 [95%CI: 1.06-1.13]). In terms of additive model, analysis with Asian groups had odds ratio as (1.67 [95%CI: 1.40-2.00]), and with Caucasian groups had odds ratio as (1.22 [95%CI: 1.15-1.31]). In terms of dominant model, analysis with Asian groups had odds ratio as (1.37 [95%CI: 1.17-1.59]), and with Caucasian groups had odds ratio as (1.22 [95%CI: 1.15-1.31]). In terms of recessive model, analysis with Asian groups had odds ratio as (0.69 [95%CI: 0.60-0.78]), and with Caucasian groups had odds ratio as (0.93 [95%CI: 0.89-0.98]). Overall, sub-group analyses with races indicated the effect of "B1" allele in all genetic models is higher in Asian groups. In terms of correlation between results, even though possession of "B1" allele had higher odds of likelihood for coronary heart disease, recessive model showed a protective effect of "B1" allele against the coronary heart disease but with smaller effect sizes. In 2012, Qi Yu et. al. provided

results showing that Asian sub-group (Han) "B1" allele carriers was found to be associated with CHD.

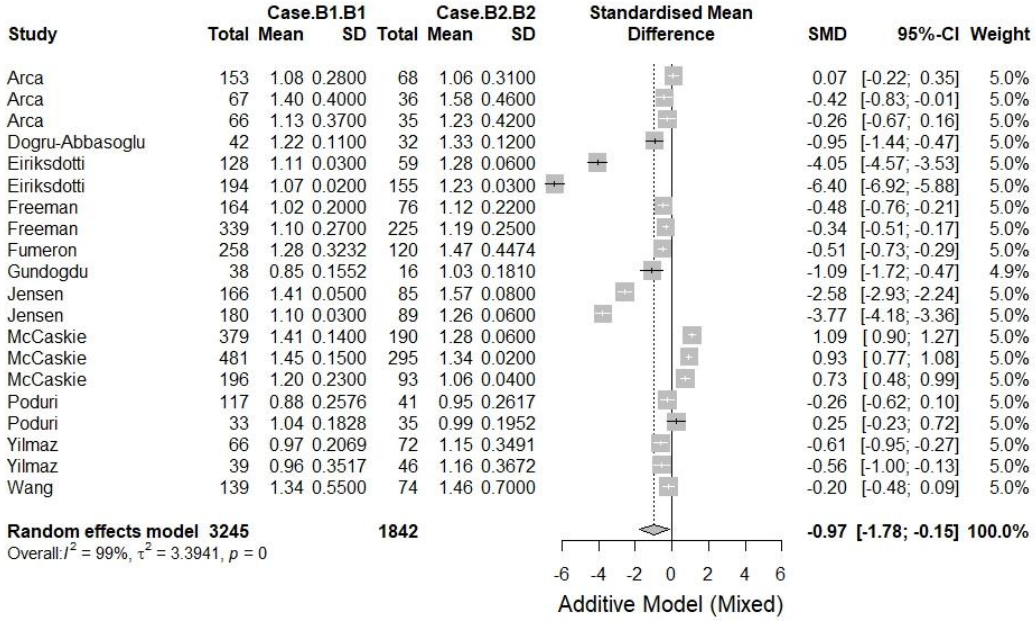


Figure 3. 33. Association between rs708272 (*CETP*) under additive (B1B1 vs. B2B2) genetic model estimated by standardized mean differences for both Case and Control groups.

According to the association between rs708272 (*CETP*) and HDL-C levels in mixed groups with case and control with an additive model (Figure 3.33), subjects with "B1B1" genotype had lower HDL-C levels with SMD showing (-0.97 [95%CI: -1.78:-0.15]) with significant p-values.

In correlation with the findings of this meta-analysis, in 2016 and 2014, Shu-Xia Guo et. al. and Zhijun Wu et. al., respectively showed that "B1B1" homozygotes were found to have lower concentratios of HDL-C than "B2B2" genotype carriers. Shu-Xia Guo et. al. was able to provide this result for Asian and Caucasian populations. Also, Zhijun Wu et. al. showed that "B2" allele carrier Caucasian populations had 0.25 mmol/L increase in HDL-C levels.

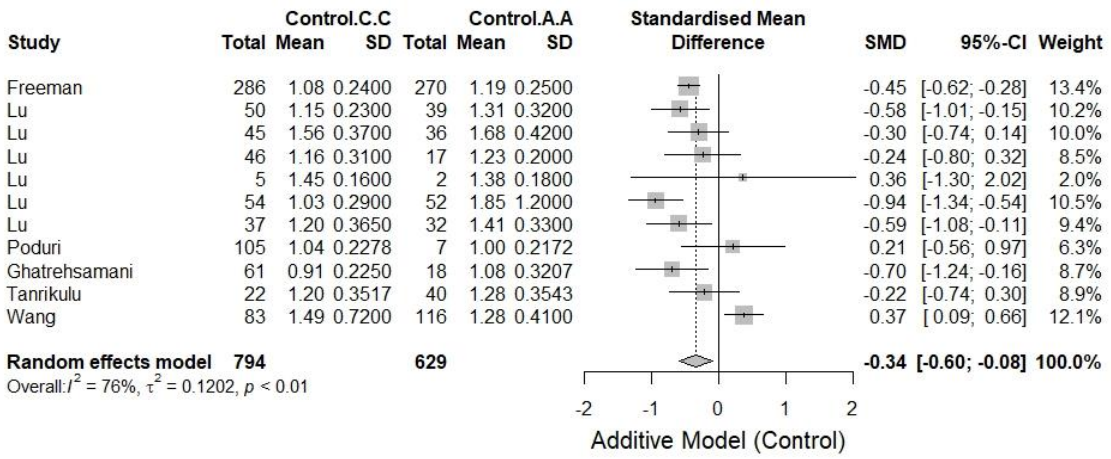


Figure 3. 34. Association between rs1800775 (*CETP*) under additive (CC vs AA) genetic model estimated by standardized mean differences for only Control groups.

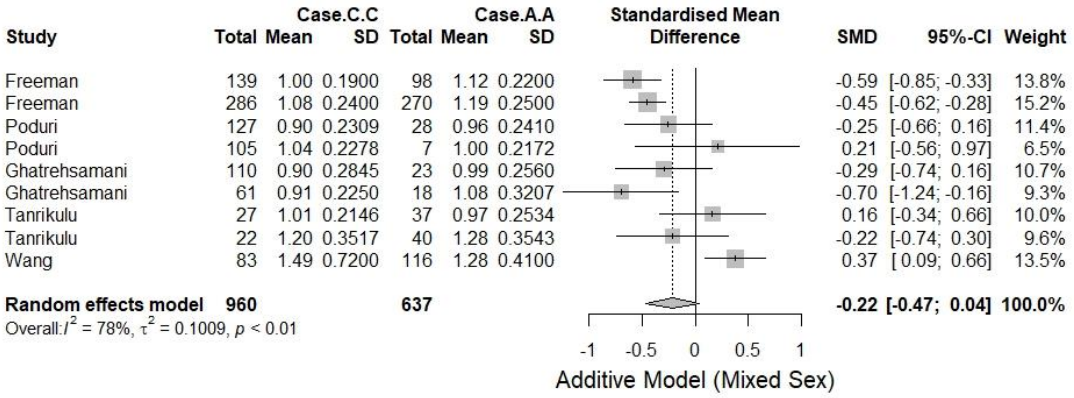


Figure 3. 35. Association between rs1800775 (*CETP*) under additive (CC vs. AA) genetic model estimated by standardized mean differences for groups with Mixed Sex

Additionally, for only control groups, an association between rs1800775 (*CETP*) indicated that "CC" genotype for the variant in the subjects had SMD values as (-0.37 [95%CI: -0.60:-0.08]) showing possible effect of two "C" alleles on the lower levels of HDL-C under additive model. For the same variant, meta-analysis for male and female mixed subject groups (Mixed Sex) showed correlated results for the subjects with "CC" genotype with SMD as (-0.22 [95%CI: -0.47: 0.04]). Despite having a significant p-value for the meta-analysis, confidence interval showed non-significance since zero was

contained in the interval. Shou-Wei Lin et. al. in 2016, showed that "C" allele of rs1800775 (-629C/A) was associated with higher levels of *CETP* but lower levels of HDL-C relative to "AA" genotype carriers.

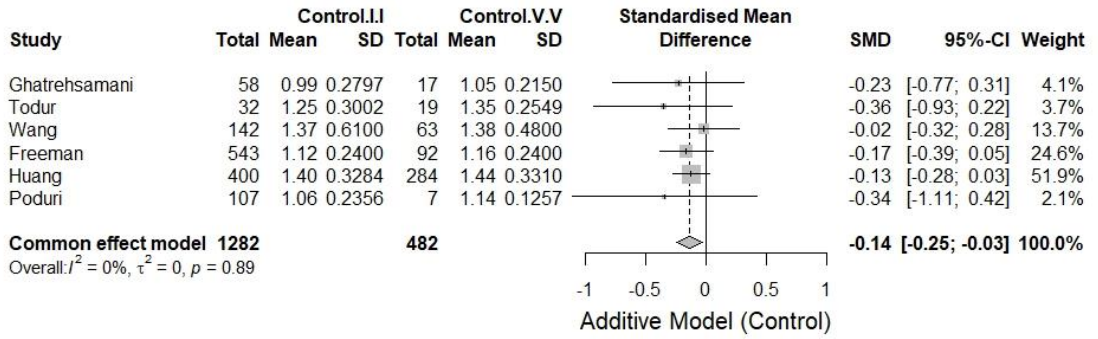


Figure 3. 36. Association between rs5882 (*CETP*) under additive (II vs. VV) genetic model estimated by standardized mean differences for only Control groups

A meta-analysis of SMD for another variant in *CETP*, rs5882, showed a correlation between subjects with "II" genotype showed lower levels of HDL-C than the ones with "VV" genotype with SMD as -0.14 [95%CI: -0.25: -0.03] for control groups. "VV" genotype in control groups had protective effect by having higher HDL-C levels in the subjects indicating the protective effect of possessing two "V" alleles against lower HDL-C levels.

3.3.4. Lipase C, Hepatic Type (*LIPC*)

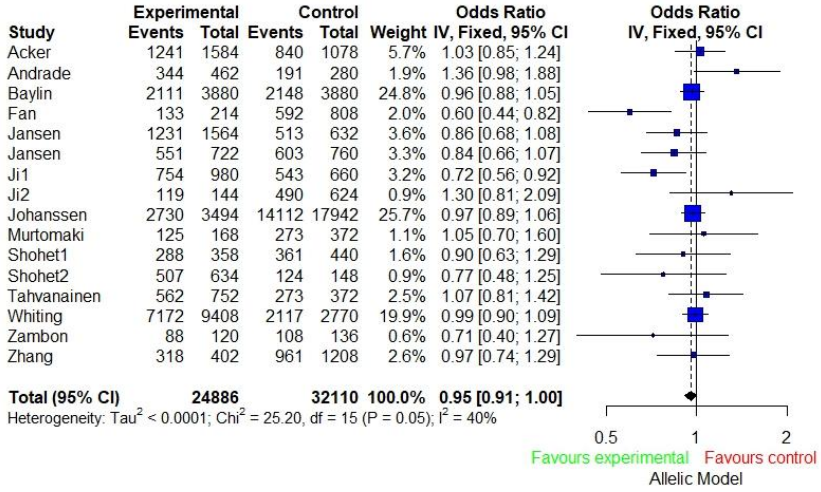


Figure 3. 37. Association between rs1800588 (*LIPC*) under allelic (C vs. T) genetic model and cardiovascular disease risk estimated by odds ratios

Variant, rs1800588 (*LIPC*) was the only polymorphism to have a significant meta-analysis in terms of p-value with allelic model applied. Heterogeneity test for the data showed no heterogeneity resulting in fixed-effects model application. Depending on the odds ratio by the analysis (-0.95 [95%CI: 0.91 – 1.00]), "C" allele of the variant was related to the lower odds of coronary heart disease between groups. Unfortunately, the confidence interval for the odds ratio had 1.00 as a value, result was determined as non-significant even if the p-value for the analysis showed as significant.

In 2010, Hairong Wang et. al. showed no significant association between rs1800588 (-514C/T) in homozygous and heterozygous models of the meta-analysis. In 2004, Aaron Isaacs et. al. observed a significant decrease in Hepatic Lipase activity for "T" allele carriers and significant increase in HDL-C levels "TT" genotype versus "CC" genotype.

3.3.5. Lipase G, Endothelial Type (*LIPG*)

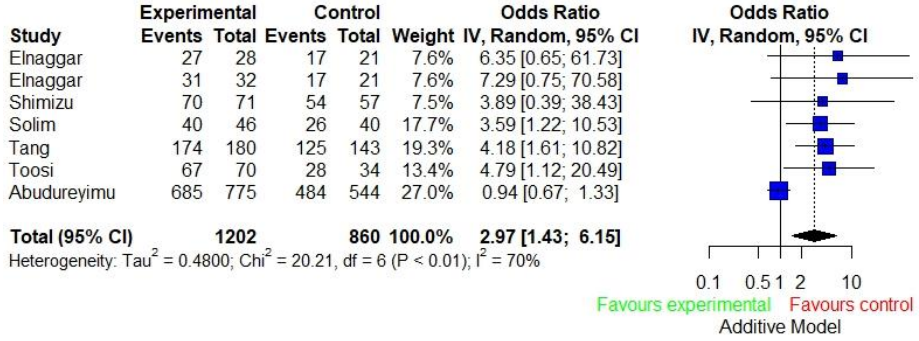


Figure 3. 38. Association between rs2000813 (*LIPG*) under additive (CC vs. TT) genetic model and cardiovascular disease risk estimated by odds ratios

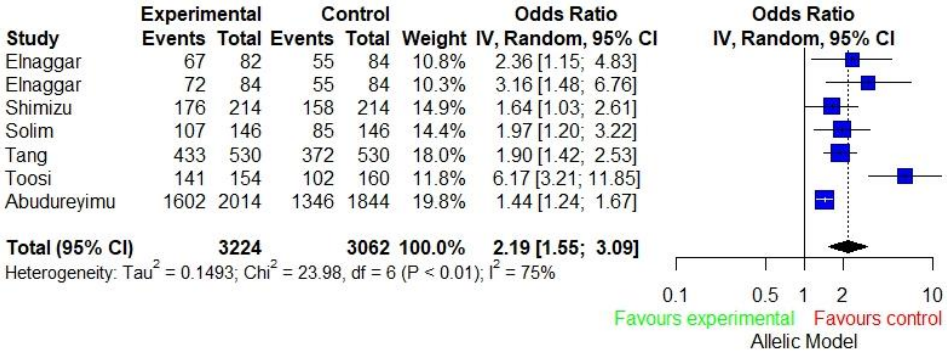


Figure 3. 39. Association between rs2000813 (*LIPG*) under allelic (C vs. T) genetic model and cardiovascular disease risk estimated by odds ratios

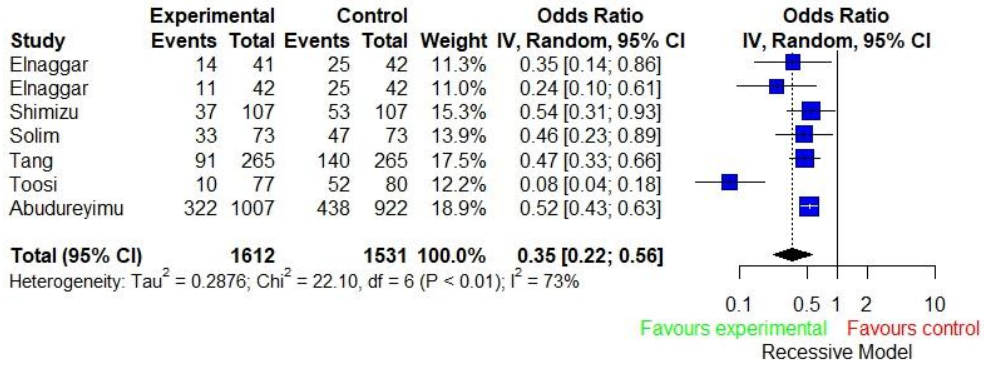


Figure 3. 40. Association between rs2000813 (*LIPG*) under recessive (CT/TT vs.CC) genetic model and cardiovascular disease risk estimated by odds ratios

According to the meta-analyses significantly performed for the rs2000813 (*LIPG*), allelic and additive model showed significant results in terms of p-values. According to heterogeneity tests, data selected for the meta-analyses were showed to be heterogeneous resulting in the application of random-effects model. Additive model (Figure 3.38) showed odds ratio as 2.97 [95%CI: 1.43 – 6.15] indicating that "C" allele in individuals had higher odds of coronary heart disease. Allelic model (Figure3.39) had odds ratio 2.19 [95%CI: 1.55 – 3.09] showing "CC" genotype carriers had higher odds than "TT" genotype carriers in terms of coronary heart disease possibility. According to the results of recessive model, carriers of two "C" alleles had higher odds of coronary heart disease risk with odds ratio as 0.35 [95%CI 0.22 – 0.56]. In other words, recessive model showed carrying one "T" allele had higher protective effect against the cardiovascular heart disease risk. In 2014, Gaojun Cai was able to show no significant association of rs2000183 with CHD.

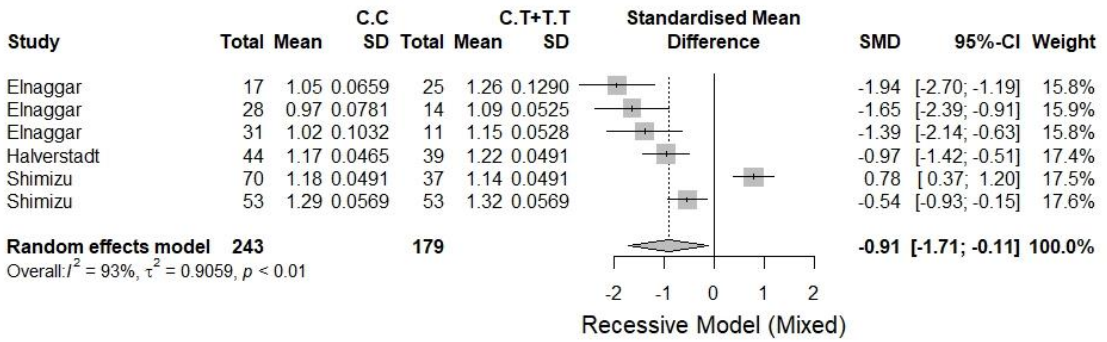


Figure 3. 41. Association between rs2000813 (*LIPG*) under recessive (CC vs. CT/TT) genetic model estimated by standardized mean differences for only Mixed group.

Additionally, association between rs2000813 and HDL-C levels was interpreted according to a meta-analysis of SMD for only mixed group of subjects under recessive model. Depending on the results, "T" allele carriers had higher HDL-C levels compared to "CC" genotype carriers. In 2014, Gaojun Cai indicated an association between the carriers of "T" allele had higher HDL-C levels than non-carriers which is consistent with the findings of this meta-analysis.

3.3.6. Lipoprotein Lipase (*LPL*)

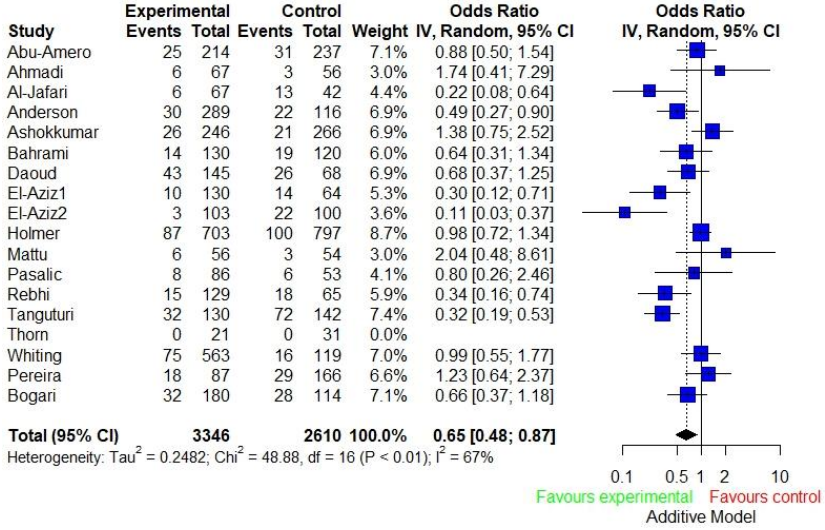


Figure 3. 42. Association between rs320 (*LPL*) under additive (GG vs.TT) genetic model and cardiovascular disease risk estimated by odds ratios

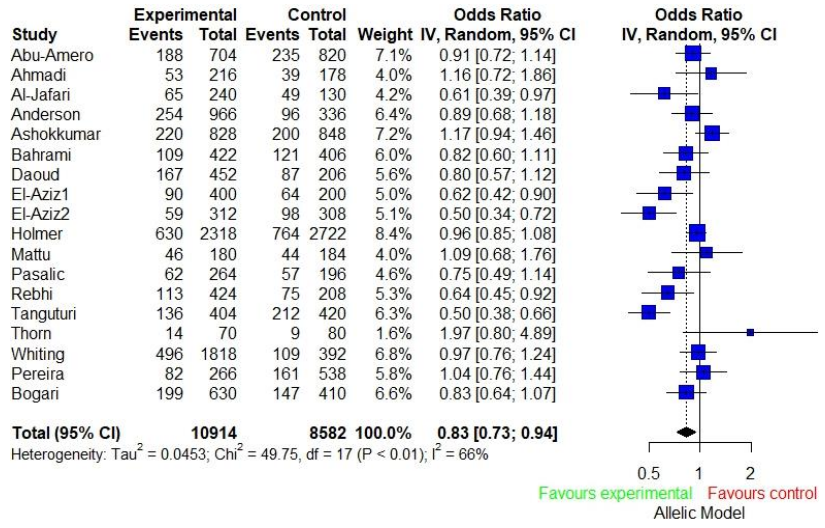


Figure 3. 43. Association between rs320 (*LPL*) under allelic (G vs. T) genetic model and cardiovascular disease risk estimated by odds ratios

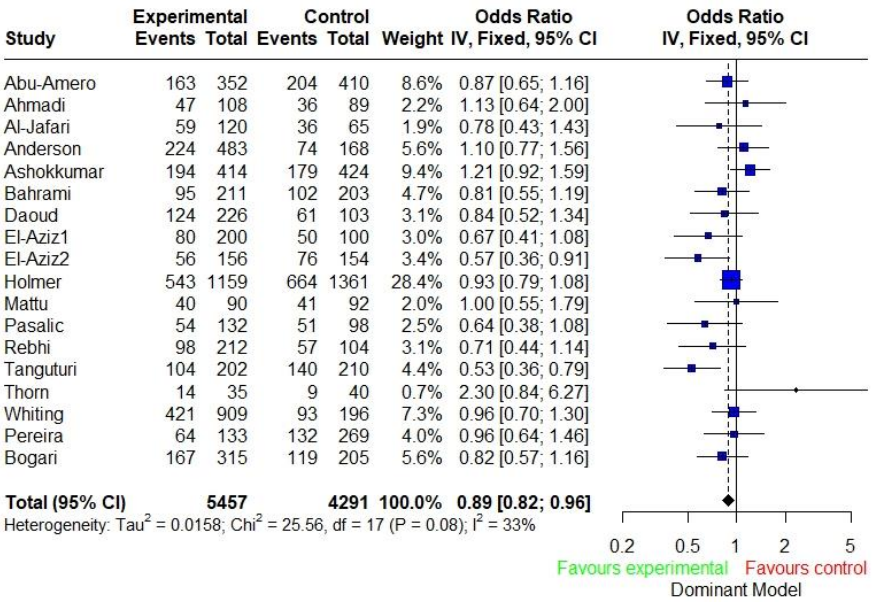


Figure 3. 44. Association between rs320 (*LPL*) under dominant (GG/GT vs. TT) genetic model and cardiovascular disease risk estimated by odds ratios

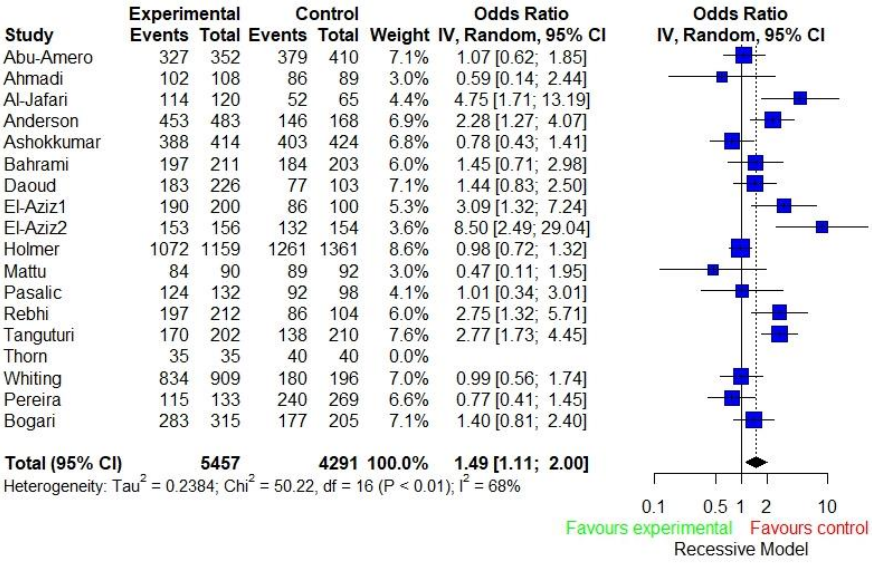


Figure 3. 45. Association between rs320 (*LPL*) under recessive (GT/TT vs. GG) genetic model and cardiovascular disease risk estimated by odds ratios

Meta-analyses for rs320 (*LPL*) were performed under allelic (Figure 3.42), additive (Figure 3.43), dominant (Figure 3.44) and recessive (Figure 3.45) with significant p-values. According to the heterogeneity tests performed, only dominant

model was no heterogeneous, hence fixed-effects model was applied for the dominant data. Depending on the analyses by additive model with odds ratio as 0.65 [95%CI: 0.48 – 0.87] and allelic model with odds ratio as 0.83 [95%CI: 0.73 – 0.94], "GG" genotype and "G" allele carriers respectively had lower odds for cardiovascular disease risk. Additionally for dominant model, odds ratio 0.89 [95%CI: 0.82 – 0.96] showed higher odds of coronary heart disease risk for carriers of "TT" genotype while recessive model with odds ratio as 1.11 [95%CI: 1.49 – 2.00] showed "GG" carriers had lower odds of cardiovascular heart disease risk. As in 2018, Wen-Qi Ma and Lime Cao et. al. and in 2017, Li Xie et. al. indicated that rs320 (HindIII) "GG (H^-H^-)" genotype carriers had a reduced risk of CHD susceptibility compared to "TT (H^+H^+)" or "GT" genotype carriers. The findings of these studies are consistent with the findings from the meta-analysis.

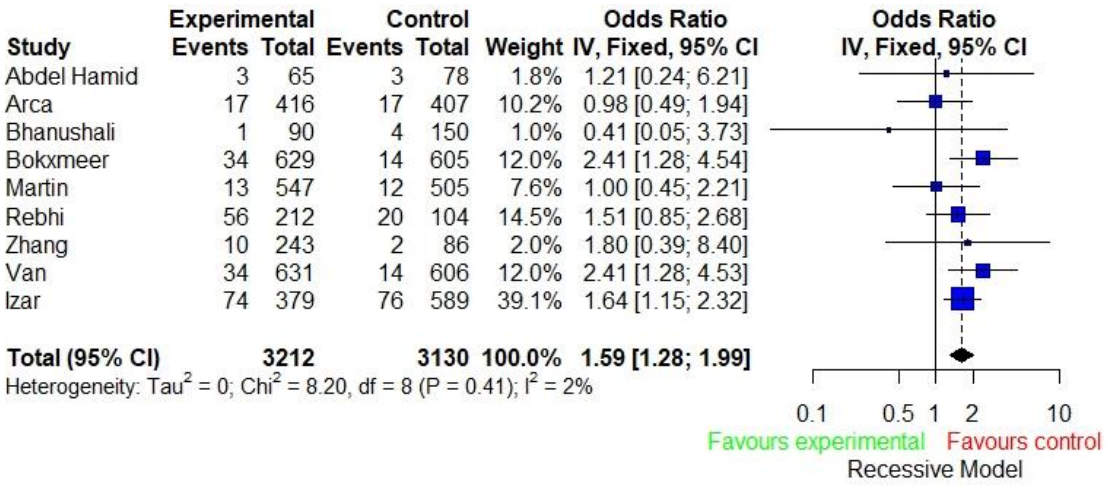


Figure 3. 46. Association between rs1801177 (*LPL*) under recessive (GA/AA vs. GG) genetic model and cardiovascular disease risk estimated by odds ratios

Additionally, for rs1801177, meta-analysis under recessive model showed an odds ratio as 1.59 [95%CI: 1.28 – 1.99] indicating that carriers of "GA/AA" genotypes against "GG" genotype carriers had higher odds of cardiovascular disease risk. In 2018, Wen-Qi Ma et. al. indicated an association between "A" allele carriers and higher cardiovascular disease risk.

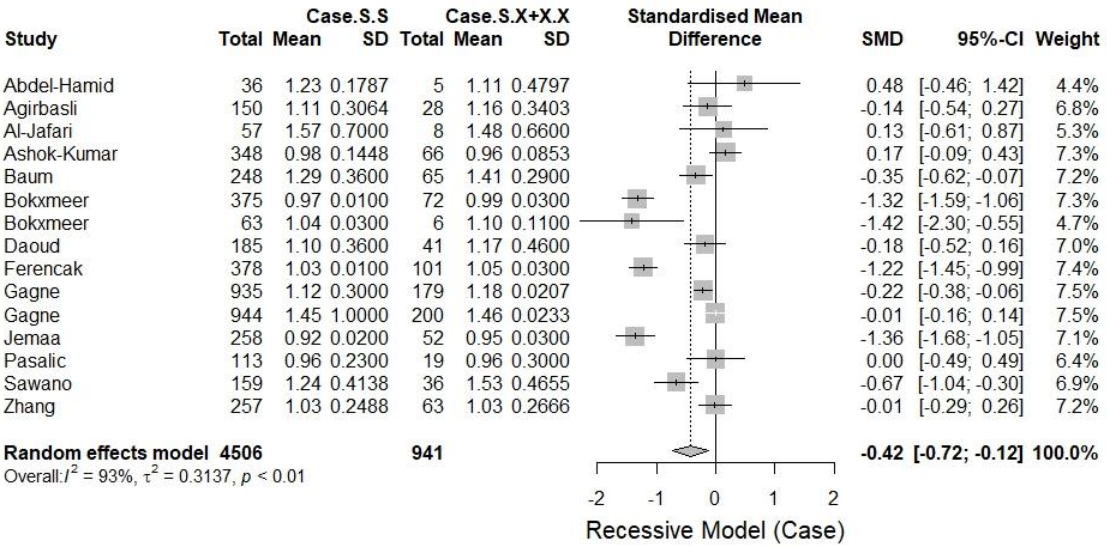


Figure 3. 47. Association between rs328 (*LPL*) under recessive (SS vs. SX/XX) genetic model estimated by standardized mean differences for only Case groups.

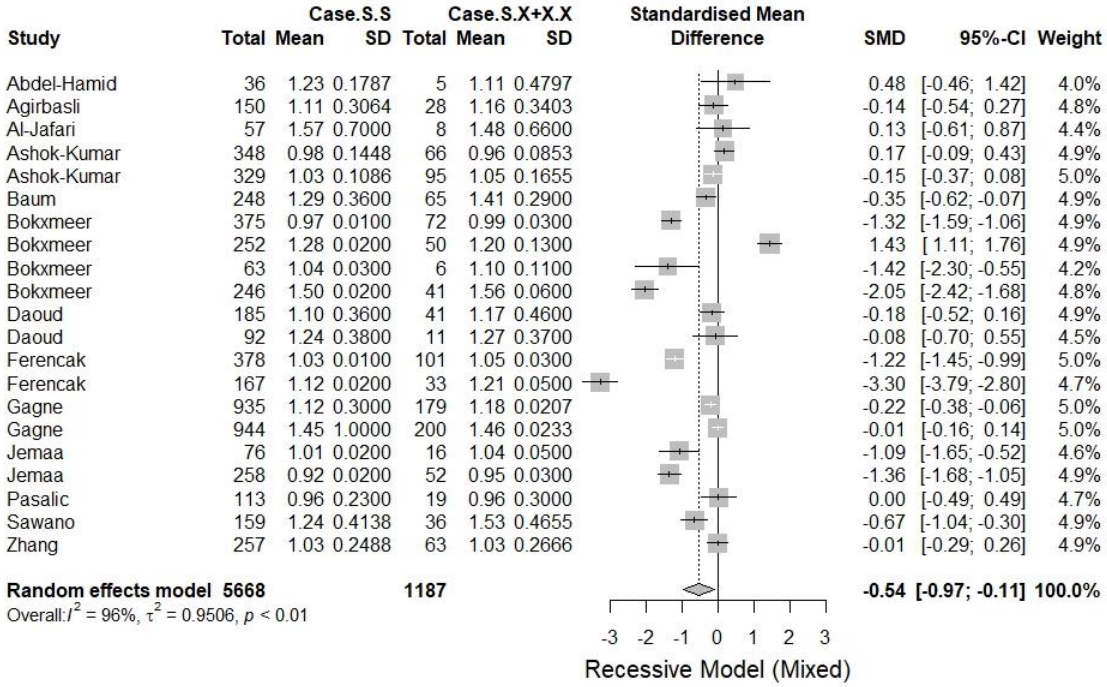


Figure 3. 48. Association between rs328 (*LPL*) under recessive (SS vs. SX/XX) genetic model estimated by standardized mean differences for both Case and Control groups

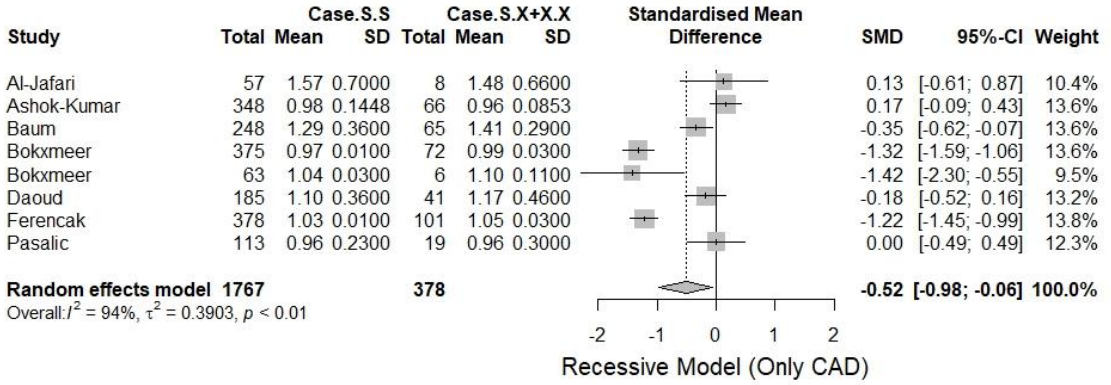


Figure 3. 49. Association between rs328 (*LPL*) under recessive (SS vs. SX/XX) genetic model estimated by standardized mean differences for only Coronary Heart Disease group

Association between rs328 (*LPL*) and HDL-C levels were determined significantly for only case (Figure 3.47), mixed (Figure 3.48) and coronary heart disease groups (Figure 3.49) under recessive model. According to the SMD calculated case group meta-analysis (-0.42 [95%CI: -0.72: -0.12]), carriers of two "S" alleles showed lower levels of HDL-C which is correlated by the mixed group meta-analysis (-0.54 [95%CI: -0.97: -0.11]) with a higher effect size. Also, for only CHD group with SMD as -0.52 [95%CI: -0.98: -0.06], indicated that "SS" genotype carriers had lower levels of HDL-C. No significant meta-analyses of odds-ratios for this variant were found in this study. In 2018, Li Xie et. al. provided results showing "XX" genotype carriers had higher odds of coronary heart disease risk.

3.3.7. Scavenger Receptor Class B Member 1 (*SCARB1*)

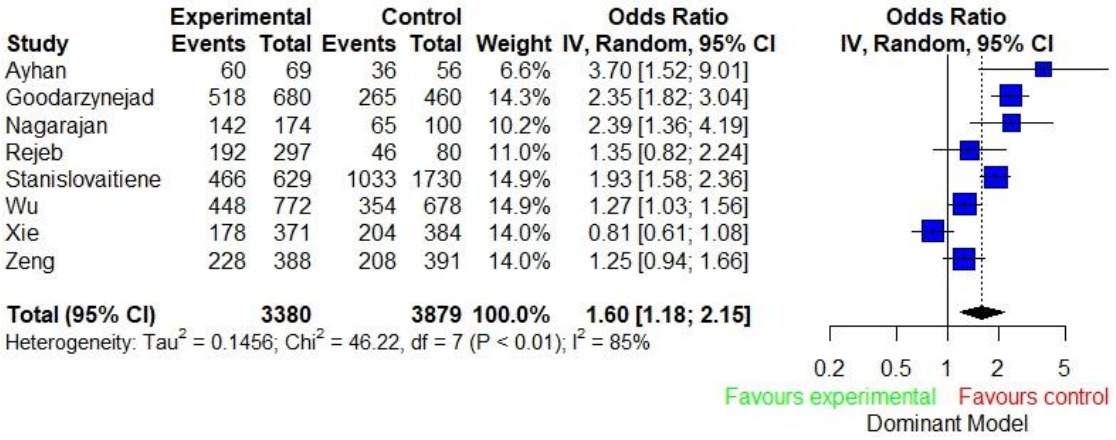


Figure 3. 50. Association between rs5888 (*SCARB1*) under dominant (CC/CT vs. TT) genetic model and cardiovascular disease risk estimated by odds ratios

Meta-analysis for rs5888 (*SCARB1*) was only performed for dominant model (Figure 3.50) significantly. According to heterogeneity tests, data was found to be heterogeneous resulting in the random-effects model application. Odds ratio as 1.60 [95%CI: 1.18 – 2.15] indicated that the carriers of one "C" allele carriers had higher odds of cardiovascular heart disease risk. In consistence with the findings of this study, in 2018, Rucha Ma et. al. investigated an association between "T" allele carriers of rs5888 and lower risk of coronary heart disease in allelic model. Also, they showed an association of "TC/TT" carriers of the variant had lower risk of CHD in males with allelic model.

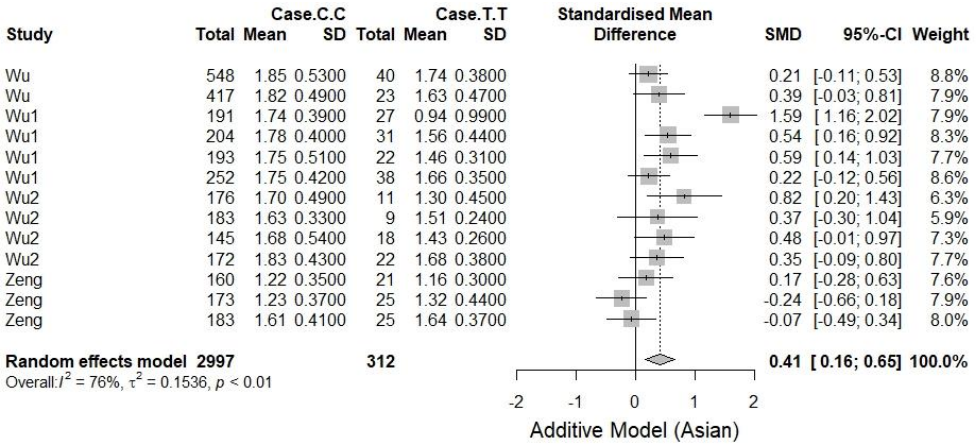


Figure 3. 51. Association between rs5888 (*SCARB1*) under additive (CC vs.TT) genetic model estimated by standardized mean differences for only Asian groups

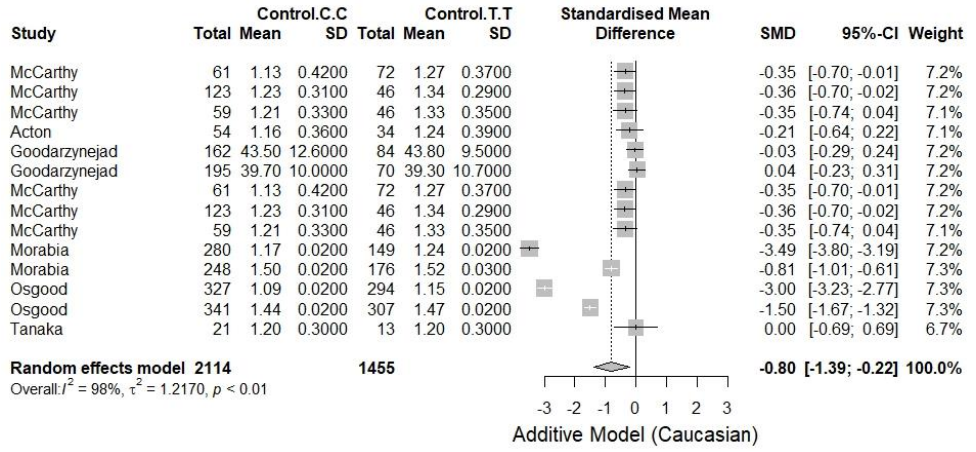


Figure 3. 52. Association between rs5888 (*SCARB1*) under additive (CC vs.TT) genetic model estimated by standardized mean differences for only Caucasian groups

Additionally, two meta-analyses for the association of rs5888 and HDL-C levels were performed significantly under additive models for only Asian and Caucasian groups. SMD calculated for those meta-analyses 0.41 [95%CI: 0.16 – 0.66] and 0.83 [95%CI:-1.39: -0.22] for Asian and Caucasian groups respectively showed that, Asian groups with "CC" genotype had higher HDL-C levels than Caucasian groups with "CC" genotype carriers.. In 2021, Sahebi et. al. showed that carriers of "T" allele had decreased serum HDL-C levels. The findings of this study correlated with Sahebi et. al.

3.3. Linkage Disequilibrium Pairs of Significant Variants and Functional Annotation

Retrieval of the data regarding to LD pairs were performed and the data was saved for further restructuring in R environment. LD pairs from each table belonging to twenty-six sub-population of five main populations (AFR, AMR, EAS, EUR and SAS) were sorted out from the data extracted from Linkage Calculator of Ensembl as Excel tables. These tables were sorted out for unique SNPs to each population by determination of the intersected variants through sub-populations for each main population. Hence, a table of potential population specific variants were retrieved. This table was enriched by information regarding to variants such as location, frequencies for main populations, reference, alternative and minor alleles, and RegulomeDB rankings and probabilities of rankings.

According to the data sorted out from the LD pairs with p-value ≥ 0.8, intersecting variants between main populations and population specific variants were observed. The variants belonged to different types of consequences such as non-coding intronic, 3' upstream transcript variant, 3' downstream variant and others. Each main population had different numbers of variants which are 83, 126, 103, 270 and 125 observations for AFR, AMR, EAS, EUR and SAS respectively. Depending on the variant number Europe population had the most number of variants which are in LD pairs with the significant variants by meta-analyses (Table 3.5). Most of the variants were found on the *ABCA1* gene since two of the significantly related variants were found within this gene. 68 intersecting variants between main populations were observed meaning that 68 more variants were found to be related with all of the variants included in the meta-analyses for all 1000Genomes populations and may increase the potential cardiovascular disease risk. 33 of these variants were found to have a RegulomeDB Ranking ≥ 3, and six of them (Table 3.8) had a RegulomeDB probability ≥ 0.9 for possible significant functional annotation by RegulomeDB.

Table 4. 1. Intersected variants between main populations found to be in LD pair ≥ 0.8 and have RegulomeDB Ranking ≥ 3, RegulomeDB Probability ≥ 0.9. and RegulomeDB Probability ≥ 0.5 together. Table was ordered according to the RegulomeDB probabilities

Variation ID	Gene	Consequence	Ref. Allele	Alt. Allele	Min. Allele	Regulome DB Probability	Regulome DB Ranking	GWAS Hits
rs5069	*APOA1*	intronic,5utr	G	A	A	1,00	1b	-
rs2694826	*SCARB1*	intronic,non-coding intronic	A	G	G	1,00	2b	-
rs12679834	*LPL*	intronic	T	C	C	0,99	1b	15
rs2070895	*LIPC*	intronic,5upstream,non-coding intronic	G	A	A	0,97	1d	196
rs1077834	*LIPC*	intronic,5upstream,non-coding intronic	T	C	C	0,94	1a	86
rs291	*LPL*	intronic	T	C	C	0,90	1d	1
rs2472439	*ABCA1*	3downstream,intronic	A	G	G	0,81	2b	-
rs2472444	*ABCA1*	intronic	A	G	G	0,80	2b	-
rs5888	*SCARB1*	coding syn|syn,non-coding	A	G	G	0,73	2b	2
rs2472438	*ABCA1*	3downstream,intronic	A	C	C	0,67	1f	-
rs297	*LPL*	intronic	T	C	C	0,67	1f	-
rs3780543	*ABCA1*	intronic,non-coding intronic	A	G	G	0,55	1f	1
rs2472384	*ABCA1*	intronic	T	C	C	0,55	1f	-
rs2472437	*ABCA1*	3downstream,intronic	C	T	T	0,55	1f	-
rs5076	*APOA1*	intronic	G	A	A	0,55	1f	-
rs708272	*CETP*	intronic,non-coding intronic	G	A	A	0,55	1f	4
rs711752	*CETP*	intronic,non-coding intronic	G	A	A	0,55	1f	7
rs1077835	*LIPC*	5upstream,intronic,non-coding intronic	A	G	G	0,55	1f	148
rs1800588	*LIPC*	intronic,5upstream,non-coding intronic	C	T	T	0,55	1f	129
rs331	*LPL*	intronic	G	A	A	0,55	1f	16
rs289	*LPL*	intronic	T	C	C	0,55	1f	
rs287	*LPL*	intronic	A	G	G	0,55	1f	53

Searches in GWAS catalog for any hits of intersected variants (Table 3.8) showed that two variants (rs2070895 of *LIPC*, rs1077834 of *LIPC*) were associated with a trait and with a RegulomeDB probability > 0.90. Nine and six of associations related to HDL-C levels were found for the variants respectively. In total over thirty associations of these variants were found to be related to any cholesterol related traits. According to

RegulomeDB rankings, these variants were classified as "1d" and "1a" with p-values as 0.97 and 0.94 respectively. With the functional annotation of RegulomeDB, these variants could be seen as a potential effective variant in terms of coronary heart disease or altering HDL-C levels. Unfortunately, the meta-analysis performed for rs1800588 which is in LD pairs with both of the *LIPC* variants, did not provide any significant relationship.

According to the table re-arranged for annotations with RegulomeDB Probability ≥ 0.5, 23 more variants were searched for any associations with a cholesterol related trait. Variants, such as rs1077835 of *LIPC* and rs1800588 of *LIPC* were found to be associated with traits for 148 and 129 times respectively. These traits included HDL-C levels for 9 and 10 times for the variants. Since these annotations had p-values as 0.55, more searches through databases and comprehensive studies should be carried out for confirmation of any functional annotation. Additionally, all of the variants with GWAS hits were all ranked as "1f" or higher than as RegulomeDB ranking meaning that information about TF binding and motifs, eQTL(expression quantitative trait loci), caQTL (chromatin accessibility quantitative trait loci) related to effects on the gene expression are found within the annotation.

Moreover, 25, 58, 35, 202 and 57 variants were found specific for main populations which are for AFR, AMR, EAS, EUR and SAS respectively. These variants were sorted out depending on the parameters; RegulomeDB Ranking ≥ 3, RegulomeDB Probability ≥ 0.9. According to the sorted tables no functional annotation were found among, the variants specific to AFR, AMR, and EAS populations, ranking of RegulomeDB with a probability ≥ 0.9. Fortunately, six and one variants were found for EUR and SAS populations respectively. The variants for EUR population were shared in Table 3.9 and for SAS, only rs12720926 of *CETP* gene was found.

According to EUR population table (Table 3.9), two variants (rs7011846 of *LPL* and rs12720926 of *CETP*) had GWAS hits as nine and six times. rs7011846 was found to be associated with traits related to myocardial infarction. The SNP was also found in LD pair with rs1801177 which was related to higher cardiovascular disease risk in "A" allele carriers. Since rs1801177 is a missense variant, the effect of the rs7011846 as an intronic region variant will be less than. Also rs12720926 was found to be associated with HDL-C levels shown by GWAS catalog. The variant is also in LD pairs with rs708272 which was found to be related to the cardiovascular disease risk. In functional annotation of rs1720926 by RegulomeDB, it was indicated that the ranking is "1b" which is almost the highest ranking in terms of functionality. Regarding to the quantitative trait loci (QTL)

data found in RegulomeDB, rs12720926 was found as caQTL in smooth muscle cells of coronary artery.

According to the tables stratified with RegulomeDB probability ≥ 0.5, more variants were found to be related to HDL-C and coronary artery disease considering the hits by GWAS. There was no association with any of these traits for AFR populations even if the RegulomeDB probability was higher than 0.5.

In AMR populations, 14 variants were detected and 5 of these variants were found to be associated with either HDL-C levels or coronary heart disease with at least 10 hits by GWAS. rs6997330 and rs295of *LPL* was found to be associated with coronary heart disease with one GWAS hit which are in LD pair with rs1801177 and rs320 respectively. Moreover, rs35980001 of *LIPC* and rs261334 of *LIPC* were found to associated with HDL-C with 1 and 10 hits respectively. According to the RegulomeDB rankings, these variants had levels as "1f" meaning that variants had information about eQTL/ caQTL, TF binding and chromatin accessibility peak. rs35980001 of *LIPC* had data related to the ChIP-seq and the data has shown effects of the variant on TF factors in organs such as bodily fluid and blood. Also, rs261334 had the similar effects on TF factors in the same organs but with less ChIP-seq data.

For EAS populations, 7 more variants were found and rs295 of *LPL* of these had GWAS hits for 34 times. As found by the GWAS associations, the same variant was also detected in AFR population which is related to coronary artery disease. RegulomeDB rankin showed "1f" for the variant but the data provided by the RegulomeDB is not enough to prove the association. Also rs2482445 of *ABCA1* and rs12970066 of *LIPG* had GWAS hits as 2 times for both of the variants. These hits have shown associations of the variants with HDL-C levels.

For EUR populations (Table 3.9), as expected more variants were found to be related to HDL-C levels and coronary heart disease. Same variants (rs295 and rs6997330) from the AMR populations were also detected in this group with RegulomeDB probability higher than 0.5. 7 more variants (rs8034802, rs261342, rs35980001, rs261334 of *LIPC*, rs6999612, rs28645722 of *LPL* and rs1532624, rs7205804 of *CETP* were found to be associated with HDL-C levels by GWAS hits over than total 10 hits. Especially rs6999612 was found associated with any trait with 77 GWAS hits and 22 of them are related to HDL-C levels but no effective information related to RegulomeDB ranking as "1f" was found through the database. Also, rs8034802 had the highest rank by RegulomeDB as "1a" meaning that the variant was found as functionally effective but

had only 2 GWAS hits related to HDL-C levels. rs7205804 of *CETP*, rs261342, rs261334 of *LIPC* had GWAS hits about HDL-C levels as 4, 4 and 10 times respectively. Even the GWAS hits indicated a relationship between HDL-C and the variants, RegulomeDB showed only 2 eQTLs activities found for liver and pancreas.

Table 4. 2. Variants found to be in LD pair ≥ 0.8 and have RegulomeDB Ranking ≥ 3, RegulomeDB Probability ≥ 0.5. Tables were ordered according to RegulomeDB Ranking for EUR population. Table was ordered according to RegulomeDB probability.

Variation ID	Gene	Consequence	Ref. Allele	Alt. Allele	Min. Allele	Regulome DB Probability	Regulome DB Ranking	GWAS Hits
rs1800590	*LPL*	intronic,5utr,5upstream	T	G	G	1,00	2a	-
rs7011846	*LPL*	intronic	G	A	A	1,00	2b	9
rs12819677	*SCARB1*	intronic,non-coding intronic	C	T	T	1,00	2b	-
rs12720926	*CETP*	intronic,non-coding intronic	A	G	G	0,99	1b	3
rs10102021	*LPL*	intronic	C	T	T	0,93	1b	-
rs4765610	*SCARB1*	intronic,non-coding intronic	T	C	C	0,92	2a	-
rs6984990	*LPL*	intronic	C	T	T	0,87	2a	-
rs34474737	*LIPG*	intronic,5upstream,5utr	T	G	G	0,81	1b	-
rs141473638	*LPL*	intronic	-	AG	AG	0,76	3a	-
rs304	*LPL*	intronic	T	G	G	0,70	1f	5
rs8034802	*LIPC*	intronic,non-coding intronic,3downstream	T	A	A	0,70	1a	11
rs28575919	*LPL*	non-coding intronic,intronic	C	G	G	0,68	1b	-
rs150730448	*LPL*	intronic,non-coding intronic	-	A	A	0,67	3a	-
rs261342	*LIPC*	non-coding intronic,intronic	G	C	C	0,67	1f	56
rs145772119	*LPL*	intronic	T	C	C	0,61	3a	-
rs3951339	*LPL*	intronic	T	C	C	0,58	2b	-

(cont. on next page)

Table 4.2 cont.

rs7205804	*CETP*	intronic,non-coding intronic	G	A	A	0,55	1f	43
rs6999612	*LPL*	non-coding intronic,intronic	T	C	C	0,55	1f	77
rs60901125	*LPL*	5upstream,intronic	C	T	T	0,55	1f	-
rs59811201	*LPL*	intronic,non-coding intronic	T	C	C	0,55	1f	1
rs4784741	*CETP*	intronic,non-coding intronic	C	T	T	0,55	1f	-
rs3816117	*CETP*	non-coding intronic,5utr,intronic	T	C	C	0,55	1f	6
rs35980001	*LIPC*	non-coding intronic,5upstream,intronic	-	C	C	0,55	1f	35
rs34620476	*CETP*	intronic,non-coding intronic	C	A	A	0,55	1f	1
rs34145065	*CETP*	intronic,non-coding intronic	CC	-	-	0,55	1f	-
rs295	*LPL*	intronic	A	C	C	0,55	1f	34
rs28645722	*LPL*	non-coding intronic,intronic	G	A	A	0,55	1f	-
rs261334	*LIPC*	intronic,non-coding intronic	G	C	C	0,55	1f	74
rs1532625	*CETP*	intronic,non-coding intronic	C	T	T	0,55	1f	-
rs1532624	*CETP*	intronic,non-coding intronic	C	A	A	0,55	1f	17
rs1320700	*LIPG*	3downstream,intronic	G	A	A	0,55	1f	1
rs12970066	*LIPG*	intronic	C	G	G	0,55	1f	2
rs12444012	*CETP*	intronic,non-coding intronic	G	A	A	0,55	1f	-
rs12326944	*LIPG*	intronic	G	C	C	0,55	1f	-
rs11608501	*SCARB1*	intronic,non-coding intronic	T	G	G	0,55	1f	-
rs11508026	*CETP*	intronic,non-coding intronic	C	T	T	0,55	1f	4
rs10102045	*LPL*	intronic	G	C	C	0,55	1f	-
rs6997330	*LPL*	non-coding intronic,intronic	G	C	C	0,55	1f	1

For SAS populations (Table 3.10), 17 more variants were detected by RegulomeDB probability higher than 0.5. rs295, rs261334 and rs35980001 were the intersecting variants between EUR, EAS and SAS. Other than these variants, specific to SAS, there were 1 more variant (rs1532624 of *CETP*) was associated with HDL-C levels with 4 GWAS hits out of 17 hits. Also, rs12720926 of *CETP* was found in relationship with HDL-C with 1 GWAS hits. The variants were annotated as "1f" and "1b" respectively by RegulomeDB ranking. These variants were found to have efficient information related to the effects of them on chromatin states and activities in related organs such as bodily fluid, blood, liver and others. Especially, rs12720926 was found to be associated as caQTL in smooth muscle cell of the coronary artery.

Table 4. 3. Variants found to be in LD pair ≥ 0.8 and have RegulomeDB Ranking ≥ 3, RegulomeDB Probability ≥ 0.5. Tables were ordered according to RegulomeDB Ranking for SAS population. Table was ordered according to RegulomeDB probability.

Variation ID	Gene	Consequence	Ref. Allele	Alt. Allele	Min. Allele	Regulome DB Probability	Regulome DB Ranking	GWAS Hits
rs12720926	*CETP*	intronic,non-coding intronic	A	G	G	0,99173	1b	3
rs34474737	*LIPG*	intronic,5upstream,5utr	T	G	G	0,80717	1b	-
rs304	*LPL*	intronic	T	G	G	0,70294	1f	5
rs34145065	*CETP*	intronic,non-coding intronic	CC	-	-	0,55436	1f	-
rs34620476	*CETP*	intronic,non-coding intronic	C	A	A	0,55436	1f	1
rs11508026	*CETP*	intronic,non-coding intronic	C	T	T	0,55436	1f	4
rs1532624	*CETP*	intronic,non-coding intronic	C	A	A	0,55436	1f	17
rs4784741	*CETP*	intronic,non-coding intronic	C	T	T	0,55436	1f	-
rs1532625	*CETP*	intronic,non-coding intronic	C	T	T	0,55436	1f	-
rs12444012	*CETP*	intronic,non-coding intronic	G	A	A	0,55436	1f	-
rs261334	*LIPC*	intronic,non-coding intronic	G	C	C	0,55436	1f	74
rs1320700	*LIPG*	3downstream,intronic	G	A	A	0,55436	1f	1
rs12970066	*LIPG*	intronic	C	G	G	0,55436	1f	2
rs35980001	*LIPC*	non-coding intronic,5upstream,intronic	-	C	C	0,55436	1f	35
rs295	*LPL*	intronic	A	C	C	0,55436	1f	34
rs12326944	*LIPG*	intronic	G	C	C	0,55436	1f	-

In general, variants with significant meta-analyses results were used as an input LD pair detection and these variants were found within LD pairs with other variant with an r^2 value higher than 0.8. These variant were used as an input for different databases seeking the association between the variant and possible functional attributes. After database searches, 17 more variants which are in LD pairs with significant variants were detected to have relationship either HDL-C levels or coronary artery disease with a RegulomeDB probability higher than 0.5. 3 of these variants were shared between the populations; EAS, EUR and SAS which are the only populations that were included in the meta-analyses as Asian and European populations. Additionally, within the tables arranged for the intersecting variants between all main populations, 2 more variant were detected to be associated with HDL-C levels with a RegulomeDB probability over 0.9.

CHAPTER 4

CONCLUSION

Cardiovascular diseases have been one of the death causes worldwide and are possessing a complex mechanism behind the development of the disease in the individuals. Since the projects related to variation within the human genome, the reasons behind the disease have been extensively studied using different perspectives of the disease. Monogenic disorders found affected by the variants in the specific gene regions provided information about the certain effects of variants through the development of the diseases. Unfortunately, these candidate genes detected by the monogenic disorders are not enough to understand and explain the complex mechanisms behind.

In literature, with the development of different sequencing technologies, various insights were used to detect the comprehensive effective variants. These variants included genome-wide association studies, functionality studies for non-coding variants, clinical studies performed with case and control subjects with variant specific sequencing data, and Mendelian randomization studies. According to the studies in literature, various analysis procedures were also used such as meta-analyses to provide combined analyses of results from multiple scientific studies. Meta-analyses were used to combine multiple studies for a specific variant from different populations and provided various perspectives in understanding of the candidate relationship between variants and underlying mechanisms of the disease. The literature claims that cholesterol metabolism related genes and the traits affected by them are associated with coronary heart disease and there is a relationship between HDL-C levels and cardiovascular heart disease risk inversely.

Considering the different insights, this study aimed to investigate the hypothesis which is that the reverse cholesterol transport pathway is involved in cardiovascular disease risk. Therefore the variants in the genes representing various points in this pathway can significantly influence the cardiovascular disease risk with 5 different aims. Provided results by this study claim that genes in reverse cholesterol transport pathway are found in association with coronary heart disease and HDL-C levels.

Meta-analyses with significant results shows that specific alleles of the shared variants are found in relationship with CHD or HDL-C levels. Variants investigated under four genetic models for any coronary heart disease relationship were rs2066714, rs2230806 of *ABCA1*, rs708272 of *CETP*, rs1800588 of *LIPC*, rs2000813 of *LIPG*, rs320, rs1801177 of *LPL* and rs5888 of *SCARB1*. Other than these variants, meta-analyses showed no significant relationship between the variants (rs5069 of *APOA1*, rs1800775, rs1799837 of *CETP*, rs328, rs268, and rs285 of *LPL*). Even the meta-analyses showed a positive or negative odds ratios for the variants, the results were not significant in terms of p-values for the analyses. It was concluded that the variants with significant results had considerable effects on the development of the cardiovascular diseases.

Variants investigated for any HDL-C levels relationship were rs5069 of *APOA1*, rs708272, rs5882, rs1800775 of *CETP*, rs1800588 of *LIPC*, rs2000813 of *LIPG*, rs328 of *LPL* and rs5888 of *SCARB1*. Other than these variants, there were no significant meta-analyses for the variants (rs220806 of *ABCA1*, rs1799837 of *APOA1*, rs268, rs285, and rs320 of *LPL*, rs1801177 of *LIPG*).

Two different variants of *ABCA1*; rs2066714 (M883I) and rs2230806 (R219K) which are missense variants causing amino acid changes in coding regions of *ABCA1*. "M" allele carriers of rs2066714 were found to have higher risk for cardiovascular disease development in correlation with the studies in the literature. Both of the races carrying "M" allele had a higher tendency for cardiovascular disease. "R" allele carriers of rs2230806 were also found to have higher odds for cardiovascular disease for both of the races. Since missense variants have higher effect on the gene regions, these variants can be stated as possible risk variants.

One variant of *CETP*; rs708272 which is an intron and extensively studied variant was found to be related to coronary heart disease. According to the meta-analyses, "B1" allele of this variant was found to be associated with higher risks for coronary heart disease for all genetic models except recessive model. Recessive model for the meta-analysis of this variant indicated a decrease in the odds ratio for the disease by %10. In literature, "B1" allele was investigated and indicated as a potential risk. Results of this study partly confirmed the correlated results within the literature. The effect by the recessive model was also observed for the races but with a higher effect for the Asian subgroups meaning that overall meta-analysis was affected by the Asian groups. The effects observed by the other genetic models also indicated that effect of the variant was higher in Asian groups in terms of higher odds for cardiovascular disease. Meta-analysis

for HDL-C relationship for this variant indicated correlated results showing that "B1B1" carriers had lower HDL-C levels. The finding fits to the idea of the higher the HDL-C level, the higher the risk of cardiovascular disease. Moreover rs1800775 of *CETP* for "CC" genotype carriers for meta-analysis of control groups under additive genetic model was found to be related with lower HDL-C levels. Additionally, rs5882 (I450V) was found to be related with lower levels of HDL-C for "II" carriers of this variant.

One variant of *LIPC*; rs1800588 was found to be related to lower risk for CHD, unfortunately confidence interval for odds ratios included 1.00 in the range meaning that result is non-significant.

One variant of *LIPG*; rs2000813 was found to be related to higher risks of CHD for "CC" genotype carriers under additive and recessive genetic model. Moreover, "C" allele was also found to be related to higher odds for CHD than "T" allele carrier. The important point of this finding is that meta-analysis in the literature by Gaojun Cai et. al. showed no significant relationship between the variant and CHD. Investigation of the association between the variant and HDL-C levels indicated that "T" allele carriers had higher levels of HDL-C compared to "CC" genotype carriers in recessive model. Gaojun Cai et. al. was able to find a relationship between the carriers of "T" allele and higher HDL-C levels.

One variant of *LPL*, rs320 were investigated for CHD relationship and it was found that "G" allele carriers had lower odds for cardiovascular disease risk under additive and allelic models. Also, under dominant model, "TT" genotype carriers had higher risk for CHD while recessive genetic model showed a relationship between "GG" genotype carriers and lower risks of CHD. Also, "A" allele carriers of rs1801177 were found to have higher odds of CHD risk. Moreover, rs328 (S447X) of *LPL* was found to be associated with lower levels of HDL-C for "SS" genotype carriers in case and mixed groups. "XX" genotype carriers had higher HDL-C levels for case (only CHD) group which is controversial to the protective effect of higher HDL-C levels against CHD.

One variant of *SCARB1* was found to be related to higher odds of cardiovascular disease for "C" allele carriers of rs5888 under dominant model. Unfortunately, meta-analyses for HDL-C level relationship showed an association of the variant with "CC" genotype carriers with lower HDL-C levels in Asian populations and higher HDL-C levels for Caucasian groups.

The study also indicated important relationships between the specific alleles for the significantly related variants for HDL-C and cardiovascular disease risk. The study

also aimed to dig deep into the variant databases for any LD pair relationship to detect other variants which were possible candidate functional variants. Prepared tables showed huge amounts of LD pairs within the gene regions with $r^2 > 0.8$ such as tables with over 1000 LD pairs. After the tables of LD pairs for significant variants were arranged, various variants in non-coding regions were found to be associated with HDL-C levels and coronary heart disease by RegulomeDB and GWAS Catalog respectively. 2 variants (rs2070895, rs1077834) of *LIPC* were found to be related with HDL-C levels according to the data collected with higher probabilities for all of the main populations. Also, 2 of the variants (rs0177835, rs1800588) of *LIPC* with RegulomeDB probability > 0.5 were found in association with HDL-C levels. Moreover, through 3 main populations EAS, EUR, and SAS, rs295 was found to be related to coronary artery disease by GWAS Catalog. The variants may have considerable effect in the development of CHD. 2 more variants (rs261334, rs35980001) were also shared between the 3 main populations. Specific to AMR populations, rs6997330 was also found to have GWAS hit for coronary heart disease. In total 17 more variants which are specific to population or shared between more than one populations were detected and may have potential effect in development of coronary heart disease or in HDL-C levels.

Based on the main hypothesis of this thesis stated that reverse cholesterol could be involved in cardiovascular disease risk and hence genes related to this pathway can significantly influence the cardiovascular disease risk, methodology to test the hypothesis was performed. In conclusion, the findings of this thesis genes representing different elements related to reverse cholesterol transport pathway could be potential agents influencing the HDL-C levels and eventually cardiovascular disease risk. According to the aims of the thesis, genes were determined through a literature search and investigated whether they are influencing the cardiovascular disease risk. Also, these genes were investigated based on the genetic variants influencing the cardiovascular disease risk using meta-analyses of various data associated with disease or non-disease groups. Additionally, these variants were investigated in terms of their effects on the HDL-C levels by meta-analyses. The effective variants were also investigated for any genetic variant in strong linkage disequilibrium. These LD pairs were then functionally annotated by using the necessary tools and interpreted depending on their functional effects. The used methodology accordingly showed that genes and the genetic variants in the genic regions could potentially influence the cardiovascular disease risk directly or indirectly by affecting the HDL-C levels. The effect of the genetic variants are supported by meta-

analyses of the clinical data of genotypes for control and subject groups or ethnic groups. Variants in non-coding regions of the genes were associated with different LD pairs and functionality. In summary, the findings of the study supports the potential cardiovascular agents and their effects on the CVD risk and needs further research for deep understanding of the potential variants behind the cardiovascular disease risk.

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APPENDIX A - dbSNP Search Flowcharts

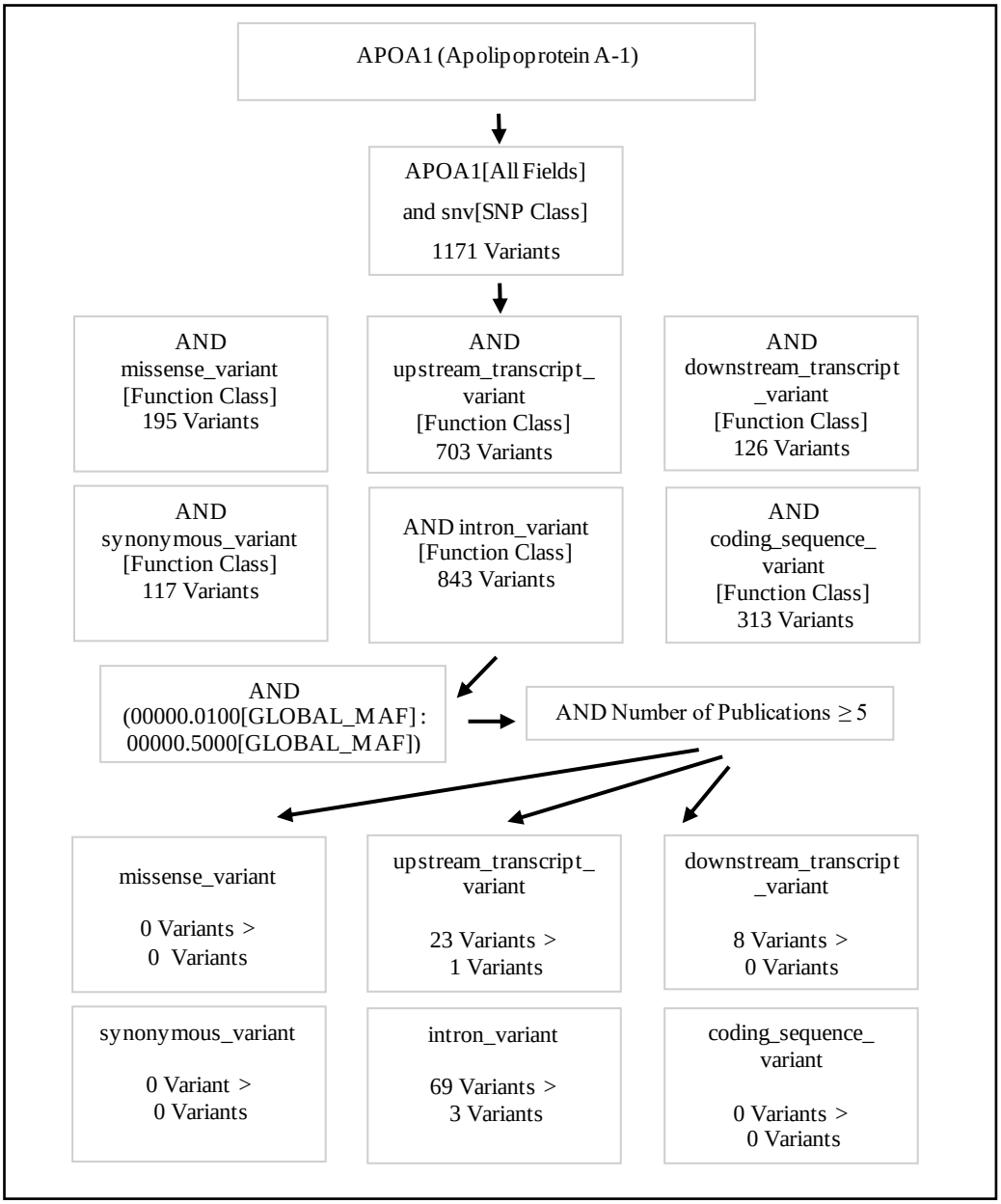

Table A.1. Flowchart for searching variants with different functional classes and global MAF for *APOA1* gene.

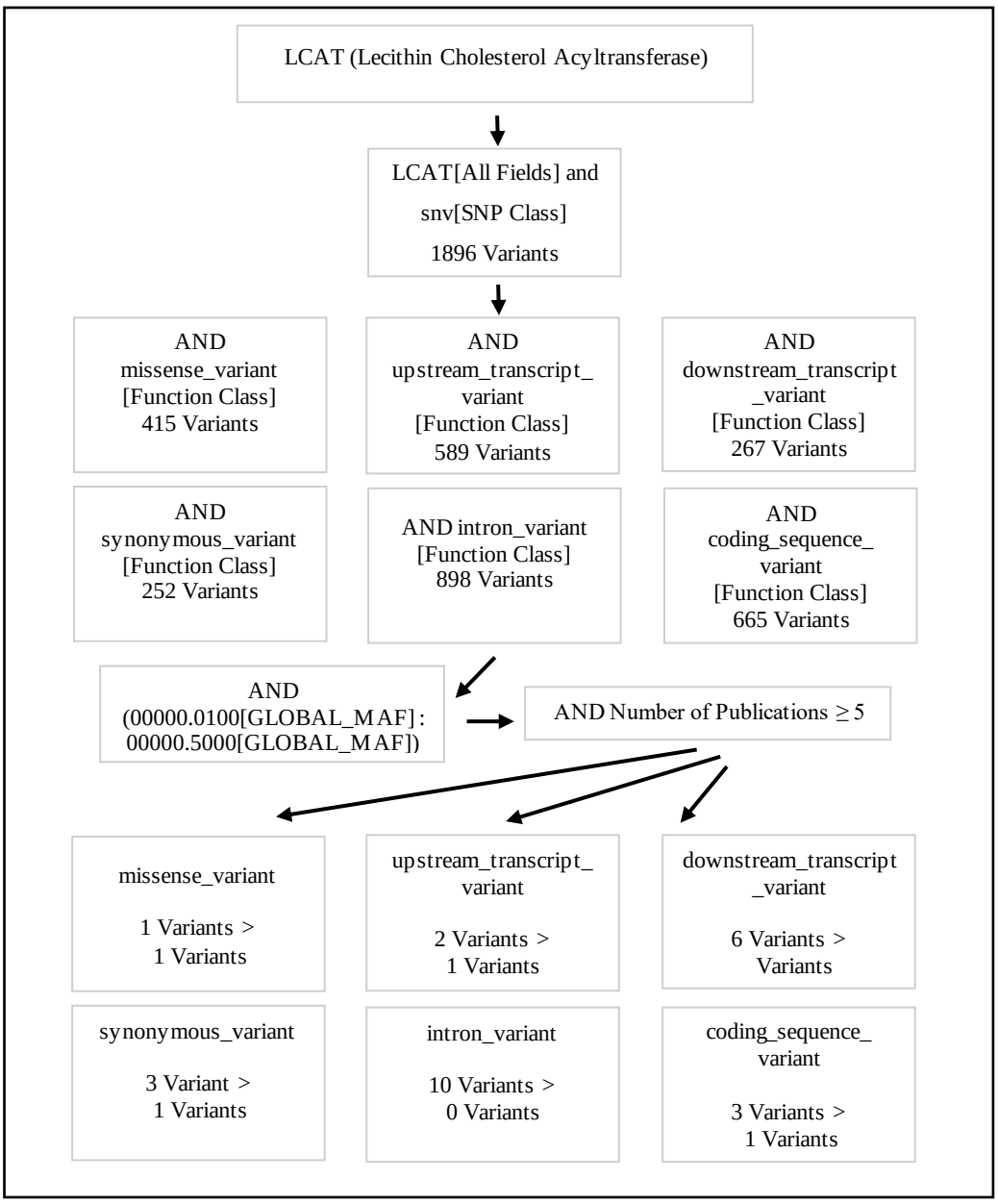

Table A.2. Flowchart for searching variants with different functional classes and global MAF for *LCAT* gene.

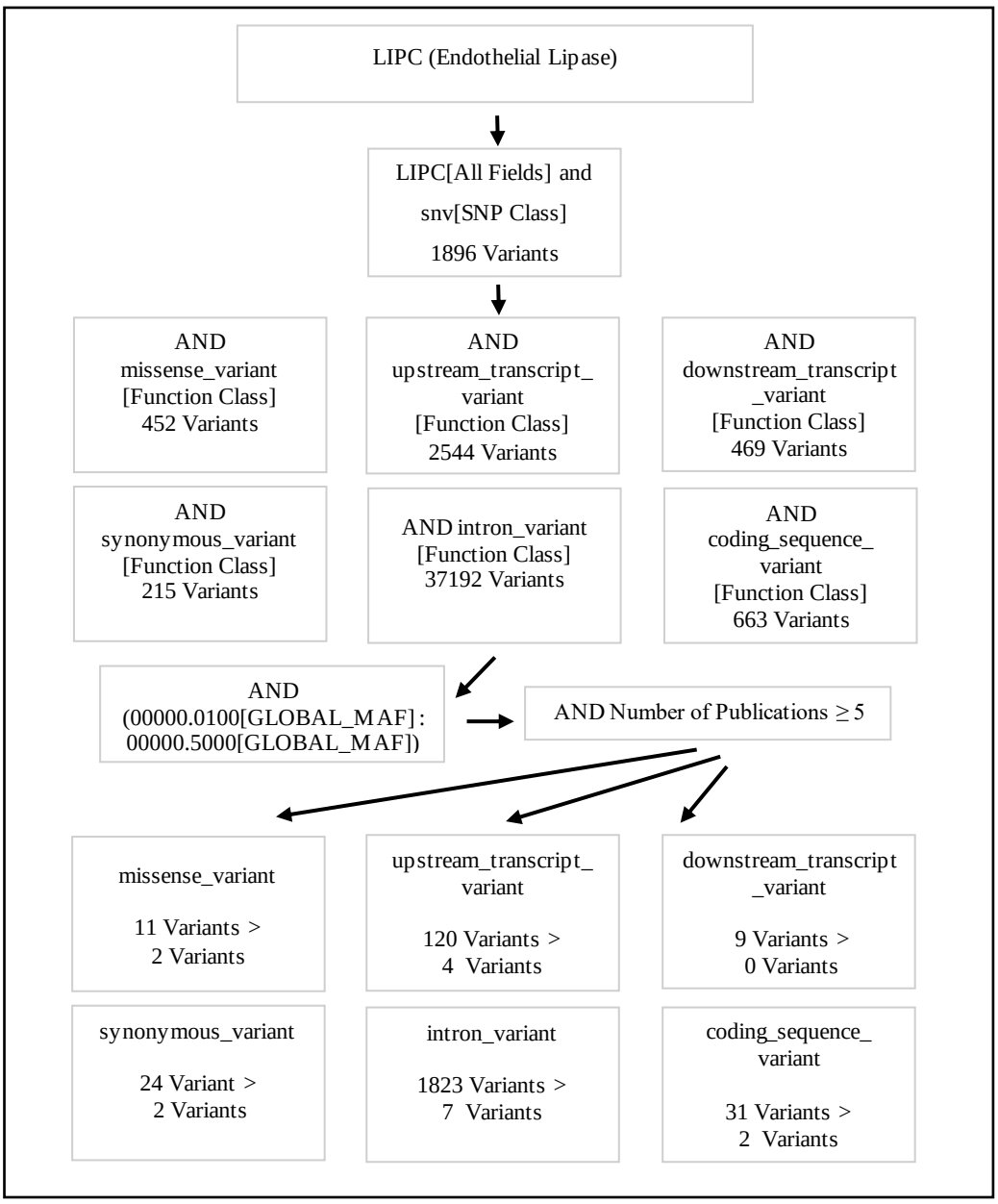

Table A.3. Flowchart for searching variants with different functional classes and global MAF for *LIPC* gene.

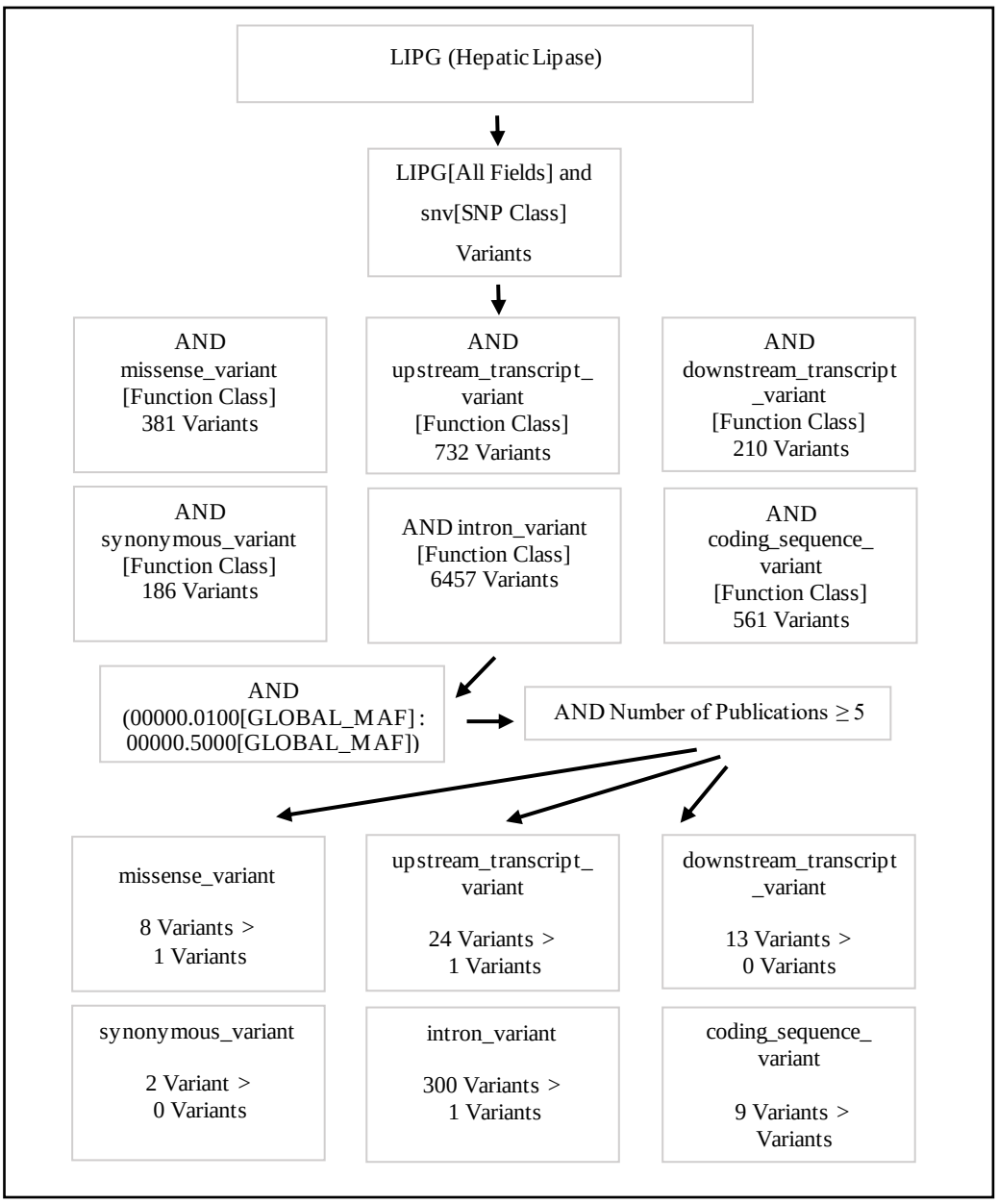

Table A.4. Flowchart for searching variants with different functional classes and global MAF for *LIPG* gene.

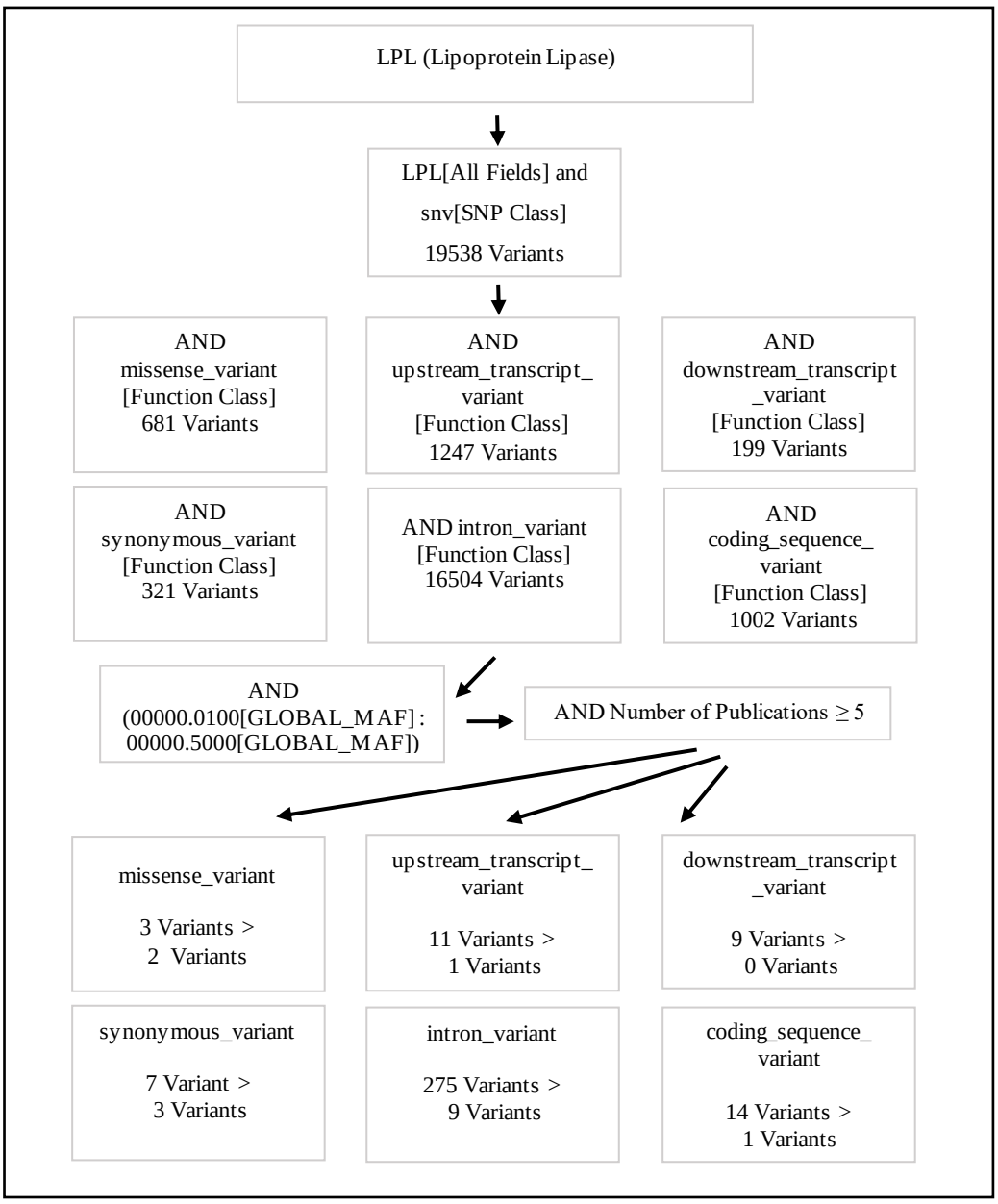

Table A.5. Flowchart for searching variants with different functional classes and global MAF for *LPL* gene.

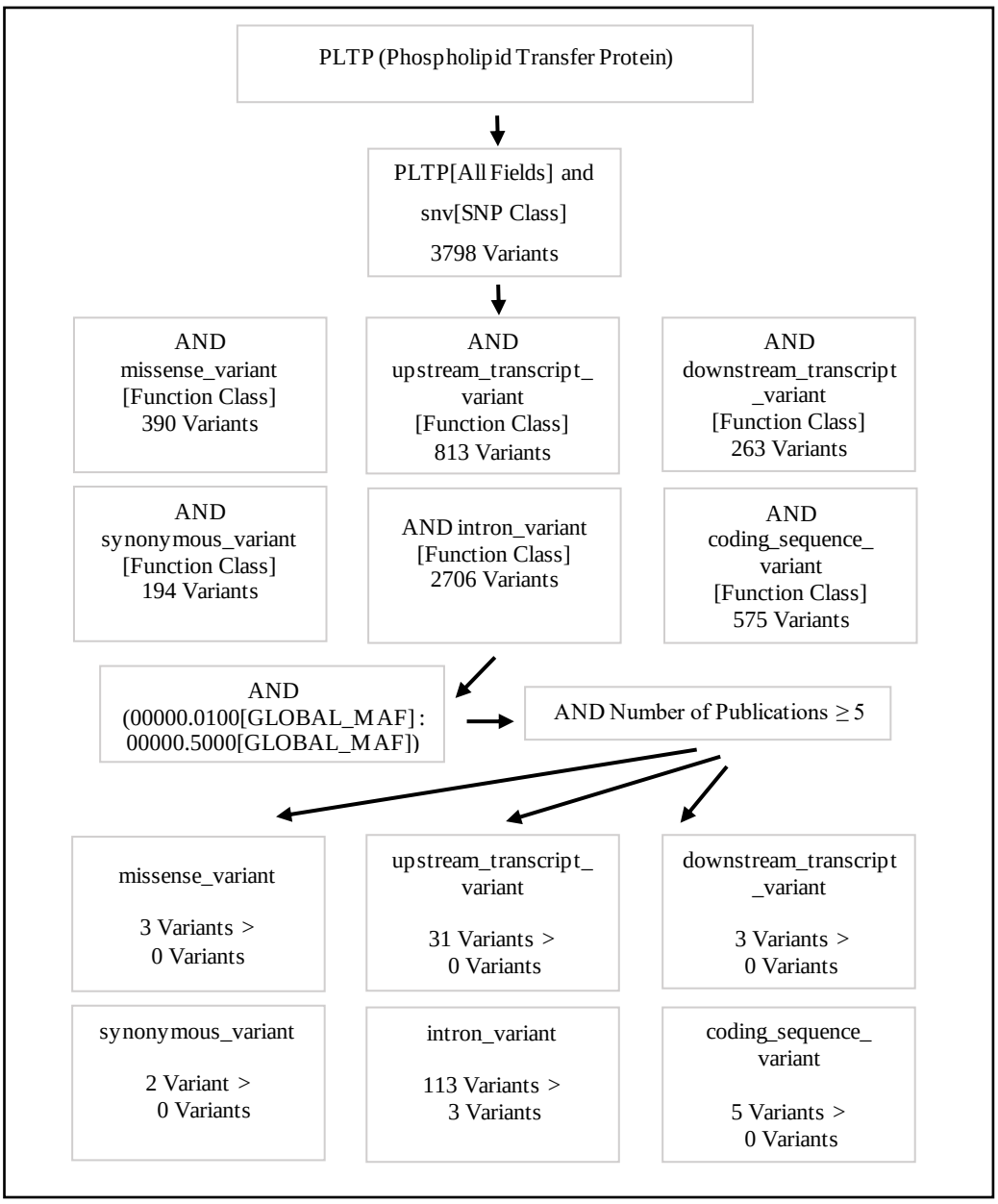

Table A.6. Flowchart for searching variants with different functional classes and global MAF for *PLTP* gene.

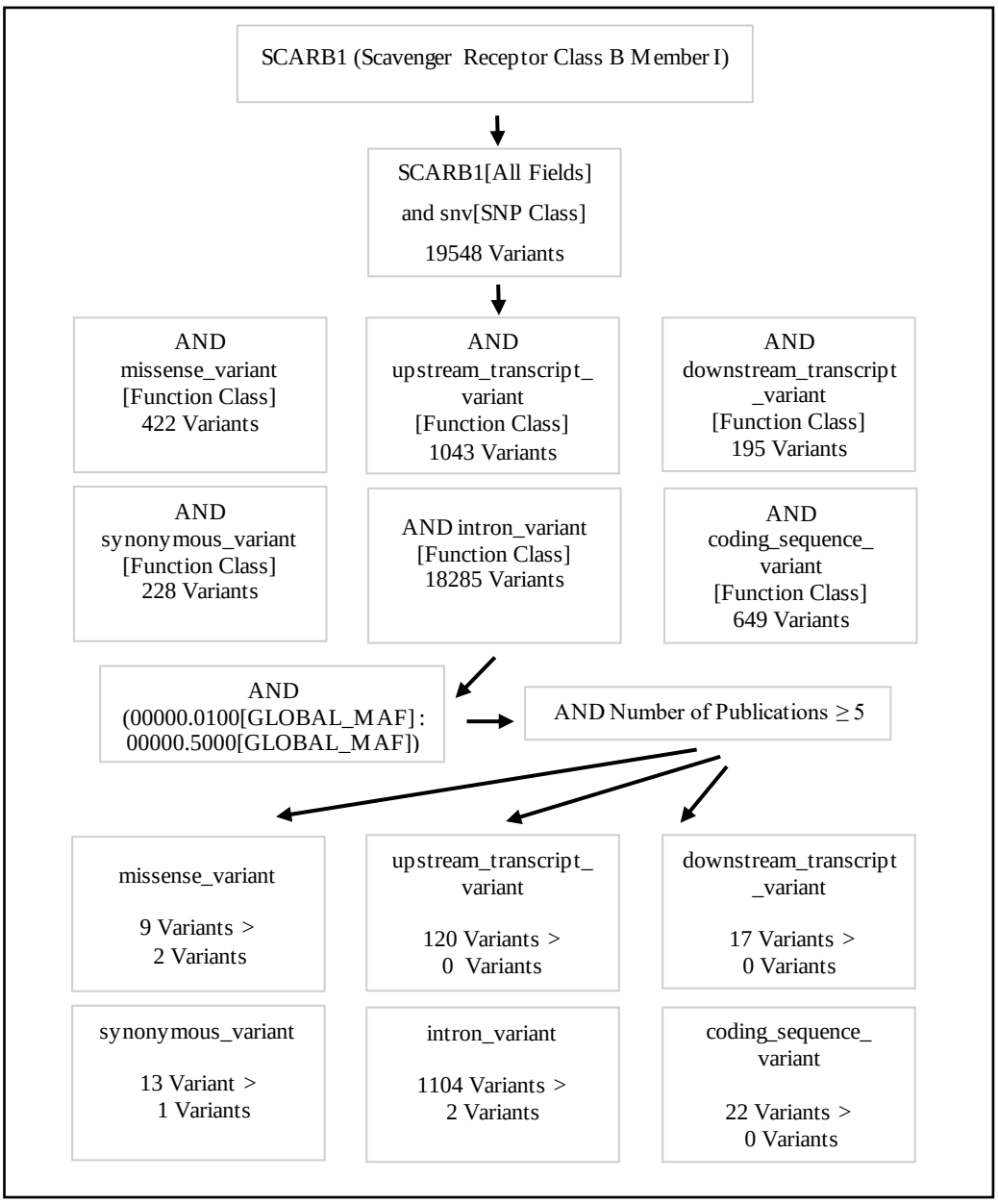

Table A.7. Flowchart for searching variants with different functional classes and global MAF for *SCARB1* gene.

Table B.1. Overview of all meta-analyses results investigating the relationship between variants and presence of coronary heart disease according to two different models fixed and random effects which were determined by heterogeneity tests.

					Fixed Effects Model			Random Effects Model		
Meta-Analysis		**Genetic Model**	**Number of Studies**	**Study Population (Case/Control)**	**Odds Ratio (95% CI)**	**z**	**p-value**	**Odds Ratio (95% CI)**	**z**	**p-value**
rs2066714	**ABCA1**	Allelic (M vs I)	16	8000/17796	1,25 [1,16; 1,35]	5,75	<0,0001	1,20 [1,07; 1,35]	3,18	0,0015
		Additive (MM vs II)	15	2738/6334	1,54 [1,25; 1,90]	4,08	<0,0001	1,43 [1,00; 2,06]	1,93	0,0531
		Dominant (MM+MI vs II)	15	4000/8898	1,30 [1,08; 1,57]	2,82	0,0048	1,24 [0,89; 1,72]	1,25	0,2113
		Recessive (II + MI vs MM)	16	4000/8898	0,79 [0,71; 0,88]	-5,02	<0,0001	0,79 [0,71; 0,88]	-4,25	<0,0001
rs2230806	**ABCA1**	Allelic (R vs K)	52	31840/48382	1,16 [1,12; 1,20]	8,54	<0,0001	1,28 [1,19; 1,39]	6,32	<0,0001
		Additive (RR vs KK)	52	9159/14093	1,42 [1,31; 1,53]	8,84	<0,0001	1,64 [1,41; 1,90]	6,41	<0,0001
		Dominant (RR+RK vs KK)	52	15920/24191	1,30 [1,21; 1,39]	7,31	<0,0001	1,46 [1,27; 1,68]	5,4	<0,0001
		Recessive (KK+RK vs RR)	52	15920/24191	0,85 [0,81; 0,90]	-6,49	<0,0001	0,77 [0,71; 0,84]	-6,19	<0,0001
rs5069	**APOA1**	Allelic (G vs A)	13	5094/3848	1,05 [0,94; 1,17]	0,8	0,4246	1,08 [0,69; 1,66]	0,33	0,7438
		Additive (GG vs AA)	10	1889/1331	0,83 [0,64; 1,08]	-1,36	0,1729	0,75 [0,32; 1,75]	-0,67	0,5011
		Dominant (GG+GA vs AA)	10	2547/1924	0,76 [0,59; 0,99]	-2,06	0,0398	0,71 [0,33; 1,50]	-0,9	0,3705
		Recessive (AA+GA vs GG)	13	2547/1924	0,84 [0,73; 0,97]	-2,36	0,0185	0,80 [0,49; 1,31]	-0,88	0,3797
rs708272	**CETP**	Allelic (B1 vs B2)	43	42630/48600	1,12 [1,08; 1,15]	7,32	<0,0001	1,16 [1,10; 1,21]	6,13	<0,0001
		Additive (B1B1 vs B2B2)	43	10688/12299	1,27 [1,19; 1,35]	7,62	<0,0001	1,37 [1,24; 1,52]	6,1	<0,0001
		Dominant (B1B1+B1B2 vs B2B2)	43	21315/24300	1,23 [1,16; 1,30]	7,39	<0,0001	1,27 [1,17; 1,37]	5,97	<0,0001
		Recessive (B1B1 vs B2B2+B1B2)	43	21315/24300	0,90 [0,86; 0,94]	-4,79	<0,0001	0,86 [0,80; 0,91]	-4,84	<0,0001
rs1800775	**CETP**	Allelic (C vs A)	14	8174/10104	1,09 [1,02; 1,16]	2,52	0,1119	1,03 [0,89; 1,20]	0,39	0,6935
		Additive (CC vs AA)	14	2209/2991	1,25 [1,09; 1,43]	3,17	0,0017	1,13 [0,87; 1,47]	0,94	0,3485
		Dominant (CC+CA vs AA)	14	4087/5052	1,21 [1,09; 1,35]	3,47	0,0005	1,09 [0,86; 1,38]	0,71	0,4757
		Recessive (AA+CA vs CC)	14	4087/5052	0,97 [0,88; 1,08]	-0,53	0,5978	0,98 [0,82; 1,16]	-0,06	0,791
rs1800588	**LIPC**	Allelic (C vs T)	16	24886/32110	0,95 [0,91; 1,00]	-2,04	0,0413	0,95 [0,91; 1,00]	-2,04	0,0414
		Additive (CC vs TT)	16	7789/10294	0,90 [0,81; 1,00]	-1,78	0,0755	0,90 [0,81; 1,00]	-1,78	0,0755
		Dominant (CC+CT vs TT)	16	12443/16055	0,91 [0,82; 1,01]	-1,76	0,0778	0,91 [0,82; 1,01]	-1,76	0,0778
		Recessive (TT+CT vs CC)	16	12443/16055	1,05 [0,99; 1,11]	1,61	0,1072	1,05 [0,99; 1,11]	1,61	0,1072
rs2000813	**LIPG**	Allelic (C vs T)	7	3224/3062	1,68 [1,49; 1,89]	8,57	<0,0001	2,19 [1,55; 3,09]	4,48	<0,0001
		Additive (CC vs TT)	7	1202/860	1,42 [1,05; 1,91]	2,29	0,0218	2,97 [1,43; 6,15]	2,93	0,0034
		Dominant (CC+CT vs TT)	7	1612/1531	1,03 [0,77; 1,38]	0,22	0,8221	1,97 [0,99; 3,92]	1,94	0,0528
		Recessive (TT+CT vs CC)	7	1612/1531	0,46 [0,40; 0,54]	-10,31	<0,0001	0,35 [0,22; 0,56]	-4,41	<0,0001

(cont. on next page)

Table B.1 (cont.)

rs268	**LPL**	Allelic (G vs A)	10	16928/28620	0,89 [0,77; 1,03]	-1,59	0,1111	0,89 [0,77; 1,03]	-1,59	0,1111
		Additive (GG vs AA)	NO DATA							
		Dominant (GG+GA vs AA)	NO DATA							
		Recessive (AA+GA vs GG)	10	8464/14310	1,13 [0,98; 1,31]	1,7	0,0890	1,13 [0,98; 1,31]	1,7	0,089
rs285	**LPL**	Allelic (C vs T)	15	13528/11166	0.83 [0.79; 0.87]	-7,07	<0,0001	0.95 [0.84; 1.07]	-0,8	0,4262
		Additive (CC vs TT)	15	3311/2957	0.66 [0.59; 0.73]	-7,73	<0,0001	0.87 [0.68; 1.12]	-1,04	0,3006
		Dominant (CC+CT vs TT)	15	6764/5583	0.88 [0.82; 0.96]	-2,9	0,0038	0.99 [0.85; 1.14]	-0,12	0,9054
		Recessive (TT+CT vs CC)	15	6764/5583	1.50 [1.37; 1.64]	8,94	<0,0001	1.15 [0.92; 1.44]	1,25	0,2118
rs320	**LPL**	Allelic (G vs T)	18	10914/8582	0,87 [0,81; 0,93]	-4,19	<0,0001	0,83 [0,73; 0,94]	-2,84	0,0045
		Additive (GG vs TT)	17	3346/2610	0,71 [0,61; 0,83]	-4,33	<0,0001	0,65 [0,48; 0,87]	-2,84	0,0044
		Dominant (GG+GT vs TT)	18	5457/4291	0,89 [0,82; 0,96]	-2,81	0,0049	0,87 [0,78; 0,97]	-2,49	0,0128
		Recessive (TT+GT vs GG)	17	5457/4291	1,37 [1,18; 1,58]	4,15	<0,0001	1,49 [1,11; 2,00]	2,68	0,0074
rs328	**LPL**	Allelic (G vs C)	14	6822/5104	0,79 [0,70; 0,89]	-3,89	0,0001	0,82 [0,64; 1,06]	-1,53	0,1254
		Additive (GG vs CC)	12	2846/1882	1,00 [0,60; 1,66]	-0,01	0,9918	0,98 [0,56; 1,70]	-0,09	0,9301
		Dominant (GG+GC vs CC)	22	4374/3256	0,64 [0,56; 0,73]	-6,78	<0,0001	0,64 [0,40; 1,03]	-1,84	0,0652
		Recessive (CC+GC vs GG)	12	3411/2552	0,63 [0,38; 1,04]	-1,8	0,0720	0,66 [0,28; 1,57]	-0,94	0,3461
rs1801177	**LPL**	Recessive (AA+GA vs GG)	9	3212/3130	1,59 [1,28; 1,99]	4,18	<0,0001	1,59 [1,28; 1,99]	4,18	<0,0001
rs5888	**SCARB1**	Allelic (G vs A)	8	5102/8214	0,98 [0,90; 1,06]	-0,52	0,6002	0,94 [0,75; 1,18]	-0,54	0,5858
		Additive (GG vs AA)	8	1435/2211	0,96 [0,80; 1,16]	-0,39	0,6950	1,12 [0,67; 1,85]	0,43	0,67
		Dominant (GG+GA vs AA)	8	3380/3879	1,52 [1,38; 1,69]	8,1	<0,0001	1,60 [1,18; 2,15]	3,06	0,0022
		Recessive (AA+GA vs GG)	8	2551/4107	0,98 [0,82; 1,16]	-0,28	0,7796	1,09 [0,74; 1,60]	0,42	0,6747
rs1799837	**APOA1**	Allelic	9	3044/2890	0.97 [0.85; 1.10]	-0,44	0.6596	1.1712 [0.7406; 1.8522]	0.68	0.4991
		Additive	8	1042/916	0,76 [0,55; 1,05]	-1,68	0,0939	0,83 [0,33; 2,06]	-0,41	0,6854
		Dominant	8	1522/1445	0,72 [0,53; 0,98]	-2,08	0,0377	0,79 [0,34; 1,84]	-0,55	0,5805
		Recessive	9	1522/1445	0,94 [0,80; 1,10]	-0,75	0,4506	0,74 [0,44; 1,26]	-1,1	0,2697
rs5882	**CETP**	Allelic	6	3996/3998	1,02 [0,93; 1,11]	0,33	0,7422	1,02 [0,93; 1,11]	0,33	0,7422
		Additive	6	1081/1076	0,96 [0,79; 1,17]	-0,37	0,7123	0,96 [0,79; 1,17]	-0,37	0,7123
		Dominant	6	1998/1999	1,01 [0,89; 1,15]	0,13	0,8942	1,01 [0,89; 1,15]	0,13	0,8942
		Recessive	6	1998/1999	0,96 [0,80; 1,15]	-0,46	0,6475	0,96 [0,80; 1,15]	-0,46	0,6475

Table B.2. Overview of all heterogeneity tests for meta-analyses investigating the relationship between variants and presence of coronary heart disease.

					Quantifying Heterogeneity			Test of Heterogeneity		
Meta-Analysis		**Genetic Model**	**Number of Studies**	**Study Population (Case/Control)**	**I^2 (%)**	**τ^2**	**H**	**Q**	**Degrees of Freedom**	**p-value**
rs2066714	**ABCA1**	Allelic (M vs I)	1	8000/17796	55	0,0258	1,48	33,04	15	0,0046
		Additive (MM vs II)	1	2738/6334	61	0,2816	1,6	36,06	14	0,001
		Dominant (MM+MI vs II)	1	4000/8898	61	0,2396	1,61	36,13	14	0,001
		Recessive (II + MI vs MM)	1	4000/8898	33	0,0083	1,22	22,34	15	0,0991
rs2230806	**ABCA1**	Allelic (R vs K)	1	31840/48382	76	0,0545	2,03	210,85	51	<0,0001
		Additive (RR vs KK)	1	9159/14093	69	0,1837	1,8	165,54	51	<0,0001
		Dominant (RR+RK vs KK)	1	15920/24191	69	0,159	1,81	166,73	51	<0,0001
		Recessive (KK+RK vs RR)	1	15920/24191	62	0,0452	1,62	134,4	51	<0,0001
rs5069	**APOA1**	Allelic (G vs A)	1	5094/3848	88	0,5365	2,92	102,5	12	<0,0001
		Additive (GG vs AA)	1	1889/1331	84	1,4229	2,49	56,01	9	<0,0001
		Dominant (GG+GA vs AA)	1	2547/1924	82	1,0661	2,34	49,49	9	<0,0001
		Recessive (AA+GA vs GG)	1	2547/1924	84	0,6534	2,48	73,78	12	<0,0001
rs708272	**CETP**	Allelic (B1 vs B2)	1	42630/48600	47	0,0088	1,37	78,71	42	0,0005
		Additive (B1B1 vs B2B2)	1	10688/12299	52	0,0437	1,44	86,66	42	<0,0001
		Dominant (B1B1+B1B2 vs B2B2)	1	21315/24300	46	0,0172	1,36	77,23	42	0,0007
		Recessive (B1B1 vs B2B2+B1B2)	1	21315/24300	37	0,0122	1,26	66,69	42	0,009
rs1800775	**CETP**	Allelic (C vs A)	1	8174/10104	76	0,0601	2,04	54,19	13	<0,0001
		Additive (CC vs AA)	1	2209/2991	67	0,1512	1,73	39,13	13	0,0002
		Dominant (CC+CA vs AA)	1	4087/5052	75	0,1394	1,99	51,7	13	<0,0001
		Recessive (AA+CA vs CC)	1	4087/5052	57	0,0594	1,53	30,57	13	0,0039
rs1800588	**LIPC**	Allelic (C vs T)	1	24886/32110	41	<0,0001	1,3	25,2	15	0,0473
		Additive (CC vs TT)	1	7789/10294	6	0	1,03	15,9	15	0,3885
		Dominant (CC+CT vs TT)	1	12443/16055	0	0	1	12,59	15	0,6342
		Recessive (TT+CT vs CC)	1	12443/16055	43	<0,0001	1,33	26,43	15	0,0338
rs2000813	**LIPG**	Allelic (C vs T)	1	3224/3062	75	0,1493	2	23,98	6	0,0005
		Additive (CC vs TT)	1	1202/860	70	0,48	1,84	20,21	6	0,0025
		Dominant (CC+CT vs TT)	1	1612/1531	67	0,4072	1,74	18,17	6	0,0058
		Recessive (TT+CT vs CC)	1	1612/1531	73	0,2876	1,92	22,1	6	0,0012
rs268	**LPL**	Allelic (G vs A)	1	16928/28620	0	0	1	8,92	9	0,4447
		Additive (GG vs AA)		NO DATA	NO DATA					
		Dominant (GG+GA vs AA)		NO DATA	NO DATA					
		Recessive (AA+GA vs GG)	1	8464/14310	0	0	1	8,94	9	0,4426
rs285	**LPL**	Allelic (C vs T)	1	13528/11166	70	0,025	1,83	47	14	<0,0001
		Additive (CC vs TT)	1	3311/2957	70	0,1074	1,84	47,18	14	<0,0001
		Dominant (CC+CT vs TT)	1	6764/5583	38,5	0,0238	1,28	22,77	14	0,0641
		Recessive (TT+CT vs CC)	1	6764/5583	73,9	0.1015	1,96	53,73	14	<0,0001
rs320	**LPL**	Allelic (G vs T)	1	10914/8582	66	0,0453	1,71	49,75	17	<0,0001
		Additive (GG vs TT)	1	3346/2610	67	0,2482	1,75	48,88	16	<0,0001
		Dominant (GG+GT vs TT)	1	5457/4291	33	0,0158	1,23	25,56	17	0,0829
		Recessive (TT+GT vs GG)	1	5457/4291	68	0,2384	1,77	50,22	16	<0,0001
rs328	**LPL**	Allelic (G vs C)	1	6822/5104	74	0,1463	1,97	50,29	13	<0,0001
		Additive (GG vs CC)	1	2846/1882	0	0,1087	1	10,68	11	0,4707
		Dominant (GG+GC vs CC)	1	4374/3256	91	1,1059	3,4	242,32	21	<0,0001
		Recessive (CC+GC vs GG)	1	3411/2552	68	1,3564	1,76	33,97	11	0,0004
rs1801177	**LPL**	Recessive (AA+GA vs GG)	1	3212/3130	2	0	1,01	8,2	8	0,4142
rs5888	**SCARB1**	Allelic (G vs A)	1	5102/8214	82	0,088	2,36	39,07	7	<0,0001
		Additive (GG vs AA)	1	1435/2211	76	0,406	2,04	29,01	7	0,0001
		Dominant (GG+GA vs AA)	1	3380/3879	85	0,1456	2,57	46,22	7	<0,0001
		Recessive (AA+GA vs GG)	1	2551/4107	71	0,2137	1,85	23,94	7	0,0012
rs1799837	**APOA1**	Allelic	1	3044/2890	87	0,4317	2,83	63,87	8	<0,0001
		Additive	1	1042/916	84	1,3062	2,48	43,07	7	<0,0001
		Dominant	1	1522/1445	83	1,1074	2,44	41,54	7	<0,0001
		Recessive	1	1522/1445	82	0,5607	2,33	43,33	8	<0,0001
rs5882	**CETP**	Allelic	1	3996/3998	0	0	1	1,2	5	0,9446
		Additive	1	1081/1076	0	0	1	1,34	5	0,9309
		Dominant	1	1998/1999	0	0	1	1,26	5	0,9388
		Recessive	1	1998/1999	0	0	1	1,2	5	0,9451

Table B.3. Overview of meta-analyses results investigating the relationship between variants and presence of coronary heart disease in two different populations, Asian and Caucasian, according to two different models fixed and random effects which were determined by heterogeneity tests.

				Fixed Effects Model			Random Effects Model		
Meta-Analysis	**Ethnicity**	**Genetic Model**	**Study Population (Case/Control)**	**Fixed Effects OR (95% CI)**	**z**	**p-value**	**Random Effects OR (95% CI)**	**z**	**p-value**
rs2066714	**Asian**	Allelic	5316/4788	1,19 [1,09; 1,31]	3,69	0,0002	1,19 [1,09; 1,31]	3,69	0,0002
		Additive	1710/1492	1,42 [1,12; 1,79]	2,92	0,0035	1,41 [1,11; 1,81]	2,77	0,0057
		Dominant	2658/2394	1,19 [0,97; 1,46]	1,69	0,0903	1,19 [0,97; 1,46]	1,69	0,0903
		Recessive	2658/2394	0,78 [0,70; 0,89]	-3,758	0,0002	0,78 [0,67; 0,91]	-3,2	0,0014
	Caucasian	Allelic	2684/13008	1,37 [1,20; 1,56]	4,74	<0,0001	1,19 [0,89; 1,58]	1,18	0,2368
		Additive	1028/4842	2,12 [1,35; 3,34]	3,25	0,0011	1,19 [0,38; 3,70]	0,3	0,7648
		Dominant	1342/6504	2,05 [1,30; 3,22]	3,11	0,0019	1,15 [0,37; 3,58]	0,25	0,8048
		Recessive	1342/6504	0,78 [0,67; 0,90]	-3,34	0,0009	0,81 [0,67; 0,98]	-2,17	0,0301
rs2230806	**Asian**	Allelic	11796/10498	1,33 [1,26; 1,40]	10,18	<0,0001	1,37 [1,23; 1,53]	5,73	<0,0001
		Additive	3248/2798	1,77 [1,58; 1,98]	9,96	<0,0001	1,87 [1,53; 2,27]	6,17	<0,0001
		Dominant	5898/5249	1,48 [1,34; 1,63]	7,94	<0,0001	1,63 [1,33; 1,99]	4,75	<0,0001
		Recessive	5898/5249	0,71 [0,65; 0,77]	-8,24	<0,0001	0,71 [0,65; 0,77]	-7,94	<0,0001
	Caucasian	Allelic	18618/36934	1,05 [1,00; 1,10]	1,92	0,0553	1,16 [1,04; 1,30]	2,66	0,0079
		Additive	5509/11030	1,11 [0,99; 1,24]	1,83	0,0674	1,30 [1,04; 1,62]	2,33	0,0198
		Dominant	9309/18467	1,08 [0,97; 1,20]	1,4	0,1608	1,19 [1,00; 1,41]	1,94	0,0525
		Recessive	9309/18467	0,95 [0,89; 1,01]	-1,63	0,1031	0,84 [0,73; 0,96]	-2,49	0,0127
rs5069	**Asian**	Allelic	3052/2228	1,02 [0,90; 1,16]	0,36	0,7167	0,98 [0,55; 1,74]	-0,06	0,9510
		Additive	1031/651	0,82 [0,62; 1,08]	-1,41	0,1597	0,75 [0,32; 1,74]	-0,67	0,5004
		Dominant	1526/1114	0,76 [0,58; 0,99]	-2,05	0,0406	0,76 [0,34; 1,51]	-0,88	0,3782
		Recessive	1526/1114	0,86 [0,73; 1,01]	-1,81	0,0699	0,85 [0,42; 1,71]	-0,46	0,6483
	Caucasian	Allelic	2042/1620	1,15 [0,89; 1,49]	1,09	0,2773	1,29 [0,63; 2,64]	0,7	0,4862
		Additive	858/680	0,98 [0,36; 2,66]	-0,03	0,9742	0,64 [0,04; 10,28]	-0,31	0,7558
		Dominant	1021/810	0,86 [0,32; 2,31]	-0,3	0,7633	0,56 [0,05; 7,63]	-0,41	0,6843
		Recessive	1021/810	0,79 [0,59; 1,06]	-1,58	0,1139	0,71 [0,36; 1,41]	-0,98	0,3278

(cont. on next page)

Table B.3 (cont.)

rs708272	**Asian**	Allelic	5304/4568	1,30 [1,19; 1,41]	6,08	<0,0001	1,28 [1,14; 1,44]	4,09	<0,0001
		Additive	1356/1097	1,67 [1,40; 2,00]	5,63	<0,0001	1,60 [1,24; 2,07]	3,58	<0,0001
		Dominant	2652/2284	1,37 [1,17; 1,59]	3,,98	<0,0001	1,29 [1,04; 1,60]	2,29	<0,0001
		Recessive	2652/2284	0,69 [0,60; 0,78]	-5,77	<0,0001	0,68 [0,59; 0,80]	-4,89	<0,0001
	Caucasian	Allelic	37326/44032	1,09 [1,06; 1,13]	5,53	<0,0001	1,11 [1,06; 1,15]	5,26	<0,0001
		Additive	6332/11202	1,22 [1,15; 1,31]	6,05	<0,0001	1,26 [1,16; 1,36]	5,62	<0,0001
		Dominant	18663/22016	1,21 [1,14; 1,28]	6,4	<0,0001	1,22 [1,14; 1,29]	6,21	<0,0001
		Recessive	18663/22016	0,93 [0,89; 0,98]	-2,98	0,0028	0,92 [0,87; 0,97]	-3,08	0,0021
rs1800775	**Asian**	Allelic	2154/2666	1,05 [0,93; 1,18]	0,81	0,4169	1,05 [0,92; 1,19]	0,74	0,4608
		Additive	530/643	1,10 [0,86; 1,40]	0,75	0,4530	1,10 [0,83; 1,45]	0,64	0,5208
		Dominant	1077/1333	1,02 [0,84; 1,24]	0,22	0,8288	1,02 [0,82; 1,26]	0,18	0,8578
		Recessive	1077/1333	0,89 [0,73; 1,09]	-1,13	0,2578	0,89 [0,73; 1,09]	-1,13	0,2578
	Caucasian	Allelic	6020/7438	1,10 [1,02; 1,19]	2,48	0,0132	1,02 [0,82; 1,26]	0,17	0,8669
		Additive	1679/2348	1,33 [1,12; 1,57]	3,3	0,0010	1,12 [0,77; 1,65]	0,6	0,5513
		Dominant	3010/3719	1,31 [1,15; 1,49]	4,05	<0,0001	1,10 [0,79; 1,55]	0,57	0,5691
		Recessive	3010/3719	1,01 [0,89; 1,14]	0,09	0,9308	1,01 [0,79; 1,29]	0,08	0,9357

Table B.4. Overview of all heterogeneity tests for meta-analyses investigating the relationship between variants and presence of coronary heart disease in two different populations, Asian and Caucasian.

				Quantifying Heterogeneity			Test of Heterogeneity		
Meta-Analysis	**Ethnicity**	**Genetic Model**	**Study Population (Case/Control)**	**I^2 (%)**	**τ^2**	**H**	**Q**	**Degrees of Freedom**	**p-value**
rs2066714	**Asian**	Allelic	5316/4788	18	<0,0001	1,11	12,24	10	0,2693
		Additive	1710/1492	19	0,0114	1,11	11,17	9	0,2600
		Dominant	2658/2394	0	<0,0001	1	8,75	9	0,4600
		Recessive	2658/2394	41	0,0161	1,3	16,81	10	0,0800
	Caucasian	Allelic	2684/13008	78	0,0744	2,11	17,85	4	0,0013
		Additive	1028/4842	82	1,195	2,37	22,47	4	0,0002
		Dominant	1342/6504	82	1,189	2,39	22,77	4	0,0001
		Recessive	1342/6504	27	0,0145	1,17	5,51	4	0,2400
rs2230806	**Asian**	Allelic	11796/10498	68	0,0604	1,77	91,23	29	<0,0001
		Additive	3248/2798	63	0,1798	1,64	77,54	29	<0,0001
		Dominant	5898/5249	72	0,2151	1,9	104,41	29	<0,0001
		Recessive	5898/5249	19	0,0033	1,11	36,02	29	0,1700
	Caucasian	Allelic	18618/36934	75	0,0434	1,99	75,4	19	<0,0001
		Additive	5509/11030	63	0,1398	1,65	51,43	19	<0,0001
		Dominant	9309/18467	52	0,0676	1,44	39,19	19	0,0042
		Recessive	9309/18467	71	0,0583	1,86	66	19	<0,0001
rs5069	**Asian**	Allelic	3052/2228	91	0,6215	3,33	77,47	7	<0,0001
		Additive	1031/651	86	1,0211	2,64	41,73	6	<0,0001
		Dominant	1526/1114	84	0,779	2,5	37,38	6	<0,0001
		Recessive	1526/1114	88	0,9098	2,83	56,05	7	<0,0001
	Caucasian	Allelic	2042/1620	84	0,4711	2,47	24,35	4	<0,0001
		Additive	858/680	86	4,8634	2,66	14,15	2	0,0008
		Dominant	1021/810	83	4,0263	2,45	12,05	2	0,0024
		Recessive	1021/810	77	0,401	2,09	17,49	4	0,0016
rs708272	**Asian**	Allelic	5304/4568	45	0,0226	1,35	23,7	13	0,0340
		Additive	1356/1097	46	0,1085	1,37	24,28	13	0,0286
		Dominant	2652/2284	44	0,0716	1,34	23,4	13	0,0371
		Recessive	2652/2284	25	0,0209	1,15	17,23	13	0,1889
	Caucasian	Allelic	37326/44032	32	0,0013	1,21	41,14	28	0,0522
		Additive	6332/11202	46	0,007	1,36	52,07	28	0,0038
		Dominant	18663/22016	46	0,001	1,36	51,74	28	0,0041
		Recessive	18663/22016	7	0,0031	1,04	30,18	28	0,3545
rs1800775	**Asian**	Allelic	2154/2666	0	0,0024	1	2,76	3	0,4305
		Additive	530/643	4	0,0157	1,02	3,12	3	0,3739
		Dominant	1077/1333	2	0,007	1,01	3,05	3	0,3841
		Recessive	1077/1333	0	0	1	1,26	3	0,7380
	Caucasian	Allelic	6020/7438	82	0,0965	2,38	50,95	9	<0,0001
		Additive	1679/2348	74	0,2647	1,96	34,42	9	<0,0001
		Dominant	3010/3719	80	0,2188	2,22	44,26	9	<0,0001
		Recessive	3010/3719	68	0,0988	1,77	28,29	9	0,0009

Table B.5. Overview of meta-analyses results investigating the relationship between variants and HDL-C levels according to two different models fixed and random effects which were determined by heterogeneity tests.

					Fixed Effects Model			Random Effects Model		
Meta-Analysis	**Genetic Mode**	**Sample Type**	**Number of Studies**	**Population**	**Fixed Effects OR (95% CI)**	**z**	**p-value**	**Random Effects OR (95% CI)**	**z**	**p-value**
rs2230806	Additive	Case	5	1271/194	-0,18 [-0,34 ; -0,02]	-2,22	0,0262	-0,03 [-0,51 ; 0,46]	-0,11	0,9158
	Additive	Control	2	144/51	-1,30 [-1,66 ; -0,94]	-7,06	<0,0001	-1,14 [-3,02 ; -0,75]	-1,18	0,2382
	Additive	Mixed	7	1415/245	-0,36 [-0,51 ; -0,22]	-4,89	<0,0001	-0,33 [-0,99 ; -0,33]	-0,98	0,3295
rs5069	Additive	Case	13	2999/1887	-0,79 [-0,85 ; -0,72]	-23,96	<0,0001	-0,83 [-1,46 ; -0,19]	-2,55	0,0109
	Additive	Control	7	1098/190	0,20 [0,04 ; 0,36]	2,5	0,0125	0,19 [-0,03 ; 0,42]	1,637	0,0956
	Additive	Mixed	20	4097/2077	-0,65 [-0,71 ; -0,59]	-21,26	<0,0001	-0,48 [-0,95 ; -0,01]	-2,01	0,0445
	Additive	Female	9	1866/1042	-0,59 [-0,67 ; -0,50]	-14,01	<0,0001	-0,39 [-0,79 ; 0,01]	-1,89	0,0591
	Additive	Male	6	1320/660	-1,30 [-1,42 ; -1,18]	-21,24	<0,0001	-0,97 [-2,41 ; -0,47]	-1,32	0,1868
rs708272	Additive	Case	9	1255/694	0,04 [-0,06 ; 0,14]	0,71	0,4775	-0,73 [-1,63 ; 0,16]	-1,61	0,1068
	Additive	Control	11	1990/1148	-0,37 [-0,45 ; -0,29]	-8,75	<0,0001	-1,15 [-2,47 ; 0,16]	-1,72	0,0859
	Additive	Mixed	20	3245/1842	-0,20 [-0,27 ; -0,14]	-6,26	<0,0001	-0,97 [-1,78 ; -0,15]	-2,33	0,0198
rs1800775	Additive	Case	4	403/186	-0,37 [-0,55 ; -0,18]	-3,9	<0,0001	-0,29 [-0,60 ; 0,02]	-1,85	0,0649
	Additive	Control	11	794/629	-0,34 [-0,45 ; -0,23]	-6,05	<0,0001	-0,34 [-0,60 ; -0,08]	-2,6	0,0093
	Additive	Male	3	87/70	-0,41 [-0,73 ; -0,09]	-4,97	<0,0001	-0,41 [-0,73 ; -0,09]	-3,21	0,0013
	Additive	Female	3	150/108	-0,66 [-0,92 ; -0,40]	-2,49	0,0129	-0,62 [-1,01 ; -0,24]	-2,49	0,0129
	Additive	Mixed	15	1197/815	-0,35 [-0,44 ; -0,25]	-5,25	<0,0001	-0,32 [-0,52 ; -0,12]	-1,69	0,0919
	Additive	Mixed Sex	9	960/637	-0,29 [-0,40 ; -0,18]	-7,19	<0,0001	-0,22 [-0,47 ; 0,04]	-3,2	0,0014
rs1800588	Additive	Case	10	4307/335	-0,09 [-0,21 ; 0,02]	-1,63	0,1024	-0,27 [-0,60 ; 0,06]	-1,59	0,1129
	Additive	Control	3	417/33	-0,50 [-0,90 ; -0,11]	-2,48	0,0132	-0,50 [-0,90 ; -0,11]	-2,48	0,0132
	Additive	Male	4	1197/77	-0,21 [-0,42 ; -0,00]	-1,96	0,0497	-0,45 [-0,94 ; 0,03]	-1,82	0,0682
	Additive	Female	6	1562/102	0,22 [-0,01 ; 0,46]	1,9	0,0568	-0,13 [-0,75 ; 0,50]	-0,39	0,693
	Additive	Mixed	13	4724/368	-0,13 [-0,23 ; -0,02]	-2,99	0,0028	-0,30 [-0,56 ; -0,03]	-1,61	0,1072
rs2000813	Additive	Mixed	4	2505/389	-0,25 [-0,35 ; -0,14]	-4,47	<0,0001	-0,34 [-0,53 ; -0,14]	-3,29	0,001
	Recessive	Mixed	6	243/179	-0,55 [-0,76 ; -0,34]	-5,14	<0,0001	-0,91 [-1,71 ; -0,11]	-2,24	0,0251
rs268	Recessive	Case	5	1969/146	0,54 [0,36 ; 0,72]	5,95	<0,0001	0,70 [-0,87 ; 2,27]	0,87	0,3833
	Recessive	Control	3	834/30	4,40 [3,92 ; 4,87]	18,14	<0,0001	5,53 [-0,83 ; 11,89]	1,7	0,0883
	Recessive	Mixed Sex	5	1664/134	0,32 [0,13 ; 0,51]	3,35	0,0008	0,29 [-1,34 ; 1,91]	0,35	0,7282
	Recessive	Mixed	8	2803/176	1,02 [0,86; 1,19]	11,97	<0,0001	2,50 [-0,37; 5,36]	1,71	0,0871

(cont. on next page)

Table B.5 (cont.)

rs285	Additive	Case	4	210/170	0,69 [0,44 ; 0,94]	5,44	<0,0001	0,69 [-1,05 ; 2,42]	0,78	0,4376
	Additive	Control	2	65/27	0,67 [0,44 ; 0,94]	2,63	0,0085	0,96 [-0,96 ; 0,94]	0,98	0,3288
	Additive	Mixed	6	275/197	0,69 [0,47 ; 0,91]	6,06	<0,0001	0,78 [0,43 ; 1,99]	1,26	0,2083
	Additive	Mixed Sex	5	217/105	0,05 [-0,20 ; 0,30]	0,4	0,687	0,23 [-0,54 ; 1,01]	0,59	0,5536
rs320	Additive	Case	6	1146/204	-0,63 [-0,80 ; -0,46]	-7,19	<0,0001	-1,21 [-3,26 ; 0,84]	-1,15	0,2484
	Additive	Control	2	112/98	-0,48 [-0,76 ; 0,54]	-3,36	0,0008	-0,34 [-1,23 ; 0,54]	-0,76	0,4481
	Additive	Mixed	8	1258/302	-0,59 [-0,74 ; -0,44]	-7,89	<0,0001	-0,99 [-2,52 ; 0,55]	-1,26	0,2079
	Additive	Mixed Sex	5	436/178	-0,35 [-0,54 ; -0,16]	-3,66	0,0003	-0,27 [-0,64 ; 0,10]	-1,42	0,1548
rs328	Recessive	Case	15	4506/941	-0,38 [-0,45 ; -0,31]	-10,41	<0,0001	-0,42 [-0,72 ; -0,12]	-2,71	0,0068
	Recessive	Control	6	1162/246	-0,46 [-0,61 ; -0,31]	-6,12	<0,0001	-0,87 [-2,20 ; 0,47]	-1,28	0,2021
	Recessive	Mixed	21	5668/1187	-0,40 [-0,46 ; -0,33]	-12,04	<0,0001	-0,54 [-0,97 ; -0,11]	-2,47	0,0133
	Recessive	Mixed Sex	13	2519/571	-0,42 [-0,51 ; -0,32]	-8,76	<0,0001	-0,42 [-0,94 ; 0,10]	-1,6	0,11
	Recessive	Male	5	1896/369	-0,40 [-0,52 ; -0,29]	-6,85	<0,0001	-0,51 [-1,54 ; 0,53]	-0,96	0,3388
	Recessive	CAD	8	1767/378	-0,61 [-0,72 ; -0,49]	-10,43	<0,0001	-0,52 [-0,98 ; -0,06]	-2,19	0,0283
rs1801177	Recessive	Case	5	1495/78	0,55 [0,28 ; 0,83]	3,98	<0,0001	-1,29 [-7,47 ; 4,89]	-0,41	0,6827
	Recessive	Control	2	591/14	0,47 [-0,07 ; 1,00]	1,72	0,0857	0,60 [-1,30 ; 2,50]	0,62	0,5349
	Recessive	Mixed	7	2086/92	0,54 [0,29 ; 0,78]	4,33	<0,0001	-0,73 [-5,04 ; 3,58]	-0,33	0,7411
rs5888	Additive	Case	23	4658/1625	-0,71 [-0,78 ; -0,64]	-20,41	<0,0001	-0,25 [-0,72 ; 0,22]	-1,05	0,2958
	Additive	Control	4	453/142	-0,04 [-0,23; 0,15]	-0,4	0,6903	-0,04 [-0,23; 0,15]	-0,4	0,6903
	Additive	Mixed	27	5111/1767	-0,64 [-0,70 ; -0,57]	-19,38	<0,0001	-0,22 [-0,62 ; 0,18]	-1,1	0,2726
	Additive	Mixed Sex	7	1838/288	0,06 [-0,7 ; 0,19]	0,88	0,3783	-0,06 [-0,7 ; 0,19]	0,88	0,3783
	Additive	Male	8	1387/568	-1,46 [-1,60 ; -1,32]	-21,07	<0,0001	-0,41 [-1,70 ; 0,87]	-0,63	0,5276
	Additive	Female	12	1886/911	-0,61 [-0,70 ; -0,52]	-13,51	<0,0001	-0,27 [-0,60 ; 0,06]	-1,63	0,1037
	Additive	Asian	15	3997/312	0,38 [0,26 ; 0,50]	6,2	<0,0001	0,41 [0,16 ; 0,65]	3,23	0,0012
	Additive	Caucasian	14	2114/1455	-1,06 [-1,14 ; -0,99]	-27,19	<0,0001	-0,80 [-1,39 ; -0,22]	-2,69	0,0072
rs1799837	Additive	Mixed	6	554/131	-0,22 [-0,44 ; -0,01]	-2,05	0,04	0,98 [-1,18 ; 3,15]	0,89	0,3732
	Recessive	Mixed	5	524/379	-0,06 [-0,20 ; 0,08]	-0,83	0,4068	-0,13 [-0,56 ; 0,30]	-0,59	0,5521
rs5882	Additive	Case	5	527/159	-0,38 [-0,56 ; -0,20]	-4,04	<0,0001	-0,58 [-1,43 ; 0,26]	-1,35	0,1772
	Additive	Control	6	1282/482	-0,14 [-0,25 ; -0,03]	-2,47	0,0135	-0,14 [-0,25 ; -0,03]	-2,47	0,0135
	Additive	Mixed	11	1809/641	-0,20 [-0,30 ; -0,11]	-4,19	<0,0001	-0,36 [-0,72 ; 0,01]	-1,93	0,0534

Table B.6. Overview of all heterogeneity tests for meta-analyses investigating the relationship between variants and HDL-C levels

					Quantifying Heterogeneity			Test of Heterogeneity		
Meta-Analysis	**Genetic Model**	**Sample Type**	**Number of Studies**	**Population**	**I^2 (%)**	**τ^2**	**H**	**Q**	**Degrees of Freedom**	**p-value**
rs2230806	Additive	Case	5	1271/194	91	0,2643	3,25	26,49	1	<0,0001
	Additive	Control	2	144/51	96	1,7834	5,15	42,19	4	<0,0001
	Additive	Mixed	7	1415/245	94	0,7411	4,07	99,61	6	<0,0001
rs5069	Additive	Case	13	2999/1887	99	1,3443	9,07	986,3	12	<0,0001
	Additive	Control	7	1098/190	48	0,0445	1,38	11,5	6	0,0741
	Additive	Mixed	20	4097/2077	98	1,1139	7,7	1126,25	19	<0,0001
	Additive	Female	9	1866/1042	96	0,358	5,24	219,24	8	<0,0001
	Additive	Male	6	1320/660	99	3,1857	11,88	705,62	5	<0,0001
rs708272	Additive	Case	9	1255/694	98	1,8223	7,35	432,13	8	<0,0001
	Additive	Control	11	1990/1148	99	4,9126	11,2	1254,46	10	<0,0001
	Additive	Mixed	20	3245/1842	99	3,3941	9,53	1724,35	19	0
rs1800775	Additive	Case	4	403/186	60	0,0565	1,58	7,46	3	0,0587
	Additive	Control	11	794/629	76	0,1202	2,03	41,36	10	<0,0001
	Additive	Male	3	87/70	0	0	1,44	4,15	2	0,1253
	Additive	Female	3	150/108	52	0,0587	1	1,61	2	0,4478
	Additive	Mixed	15	1197/815	71	0,0939	2,13	36,39	8	<0,0001
	Additive	Mixed Se	9	960/637	78	0,1009	1,87	48,87	14	<0,0001
rs1800588	Additive	Case	10	4307/335	80	0,20	2,25	45,41	9	<0,0001
	Additive	Control	3	417/33	0	0	1	0,2	2	0,9042
	Additive	Male	4	1197/77	65	0,2267	1,7	14,41	5	0,0132
	Additive	Female	6	1562/102	79	0,2613	2,21	14,63	3	0,0022
	Additive	Mixed	13	4724/368	76	0,1489	2,12	8,95	2	0,0114
rs2000813	Additive	Mixed	4	2505/389	41	0,0184	1,3	5,08	3	0,1658
	Recessive	Mixed	6	243/179	93	0,9059	3,73	69,67	5	<0,0001
rs268	Recessive	Case	5	1969/146	98	3,125	7,06	199,29	4	<0,0001
	Recessive	Control	3	834/30	99	31,3816	13,8	380,86	2	<0,0001
	Recessive	Mixed Se	5	1664/134	98	3,3457	6,98	195,12	4	<0,0001
	Recessive	Mixed	8	2803/176	99	16,9123	10,7	801,27	7	<0,0001
rs285	Additive	Case	4	210/170	98	3,058	6,8	138,58	3	<0,0001
	Additive	Control	2	65/27	92	1,7766	3,65	13,32	1	0,0003
	Additive	Mixed	6	275/197	97	2,1867	5,5	151,33	5	<0,0001
	Additive	Mixed Se	5	217/105	82	0,6831	2,36	22,33	4	0,0002
rs320	Additive	Case	6	1146/204	99	6,5119	11,13	619,71	5	<0,0001
	Additive	Control	2	112/98	89	0,3611	2,96	8,79	1	0,003
	Additive	Mixed	8	1258/302	99	4,8549	9,48	629,3	7	<0,0001
	Additive	Mixed Se	5	436/178	72	0,1214	1,88	14,12	4	0,0069
rs328	Recessive	Case	15	4506/941	93	0,3137	3,81	202,92	14	<0,0001
	Recessive	Control	6	1162/246	99	2,7205	8,26	340,87	5	<0,0001
	Recessive	Mixed	21	5668/1187	96	0,9506	5,22	544,77	20	<0,0001
	Recessive	Mixed Se	13	2519/571	95	0,8448	4,31	223,33	12	<0,0001
	Recessive	Male	5	1896/369	98	1,34706	7,33	214,94	4	<0,0001
	Recessive	CAD	8	1767/378	94	0,3903	3,97	110,37	7	<0,0001
rs1801177	Recessive	Case	5	1495/78	100	49,3694	14,72	866,14	4	<0,0001
	Recessive	Control	2	591/14	92	1,7325	3,53	12,44	1	0,0004
	Recessive	Mixed	7	2086/92	99	33,5707	12,1	878,66	6	<0,0001
rs5888	Additive	Case	23	4658/1625	98	1,2624	7,36	1190,4	22	<0,0001
	Additive	Control	4	453/142	0	0	1	0,98	3	0,8053
	Additive	Mixed	27	5111/1767	98	1,0743	6,88	1232,37	26	<0,0001
	Additive	Mixed Se	7	1838/288	2	<0,0001	1,01	6,15	6	0,4064
	Additive	Male	8	1387/568	99	3,3764	10,53	775,73	7	<0,0001
	Additive	Female	12	1886/911	94	0,3	4,25	198,81	11	<0,0001
	Additive	Asian	15	3997/312	76	0,1536	2,03	49,48	12	<0,0001
	Additive	Caucasian	14	2114/1455	98	1,217	7,74	779,37	13	<0,0001
rs1799837	Additive	Mixed	6	554/131	96	7,1352	5,09	129,5	5	<0,0001
	Recessive	Mixed	5	524/379	83	0,195	2,39	22,88	4	0,0001
rs5882	Additive	Case	5	527/159	92	0,8782	3,54	50,09	4	<0,0001
	Additive	Control	6	1282/482	0	0	1	1,66	5	0,8938
	Additive	Mixed	11	1809/641	82	0,3281	2,38	56,62	10	<0,0001