Steroids 185 (2022) 109057

Contents lists available at ScienceDirect

Steroids

journal homepage: www.elsevier.com/locate/steroids

Associations between liver X receptor polymorphisms and blood lipids: A systematic review and meta-analysis

Huifeng Zhang [a,b,1], Priscilia Lianto [a,1], Weiming Li [b], Mengfan Xu [a], J. Bernadette Moore [a], James L. Thorne [a,*]

[a] School of Food Science and Nutrition, University of Leeds, Leeds LS2 9JT, UK
[b] Clinical Nutrition Department, The First Affiliated Hospital of Xi'an Jiaotong University, 277 Yanta West Road, Xi'an 710061, China

ARTICLE INFO

Keywords:
Polymorphisms
Liver X receptors
Blood lipids
Cholesterol
Triglycerides
Atherosclerosis
Meta-analysis

ABSTRACT

Genetic susceptibility to dyslipidaemia remains incompletely understood. The liver X receptors (*LXRs*), members of the nuclear receptor superfamily of ligand dependent transcription factors, are homeostatic regulators of lipid metabolism. Multiple single nucleotide polymorphisms (SNPs) have been identified previously in the coding and regulatory regions of the *LXRs*. The aim of this systematic review and meta-analysis was to summarise associations between SNPs of *LXRs* (α and β isoforms) with blood lipid and lipoprotein traits. Five databases (PubMed, Ovid Embase, Scopus, Web of Science, and the Cochrane Library) were systematically searched for population-based studies that assessed associations between one or more blood lipid/lipoprotein traits and *LXR* SNPs. Of seventeen articles included in the qualitative synthesis, ten were eligible for meta-analysis. Nine *LXRα* SNPs and five *LXRβ* SNPs were identified, and the three most studied *LXRα* SNPs were quantitatively summarised. Carriers of the minor allele A of *LXRα* rs12221497 (−115G>A) had higher triglyceride levels than GG homozygotes (0.13 mmol/L; 95%CI: [0.03, 0.23], $P = 0.01$). Heterozygote carriers of *LXRα* rs2279238 (297C/T) had higher total cholesterol levels (0.12 mmol/L; (95%CI: [0.01, 0.23], $P = 0.04$) than either CC or TT homozygotes. For *LXRα* rs11039155 (−6G>A), no significant differences in blood levels of either triglyceride ($P = 0.39$) or HDL-C ($P = 0.98$) were detected between genotypes in meta-analyses. In addition, there were no strong associations for other SNPs of *LXRα* and *LXRβ*. This study provides the evidence of an association between *LXRα*, but not *LXRβ*, SNPs and blood-lipid traits.

Systematic review registration: PROSPERO No. CRD42021246158.

1. Introduction

Dyslipidaemia, a homeostatic imbalance of blood lipids and lipoproteins, is an important risk factor for obesity, type II diabetes, metabolic syndrome, atherosclerosis and cardiovascular diseases that are leading causes of morbidity and mortality worldwide [1–3]. The aetiology of dyslipidaemia is related to multifactorial causes. Considerable inter-individual variation in lipid traits is observed, with phenotype determined by both genetic factors and environmental variables (e.g., socioeconomic status, physical activity level, smoking, alcohol intake, dietary factors, coffee, etc.) [4,5]. Genome-wide association studies (GWAS) have identified nearly 200 genetic loci related to blood lipid concentrations [6,7]. These GWAS identified genetic loci do not however fully explain the variance of blood lipids thought to be attributable to genetic variability. The identification of additional genetic susceptibility loci associated with blood lipid traits is important to better understand how lipid homeostasis is regulated, and to better predict individuals who are at greatest risk of cardiovascular and other lipid related diseases.

Liver X receptors (LXRs) are ligand-activated transcription factors consisting of two common isoforms, LXRα and LXRβ that share approximately 78% amino acid homology. LXRs are activated by specific lipid molecules (e.g. oxysterols, oxidised derivatives of cholesterol) [8], and function as heterodimers with retinoid X receptors to regulate the expression of downstream target genes (e.g. *ABCA1, ABCG1, APOE, LPL*) [9]. The LXRs maintain cholesterol homeostasis by responding to elevated oxysterol levels and activating downstream target genes involved in cholesterol transport (e.g. ABCA1, ABCG1 [10–12], APOE

* Corresponding author.
E-mail addresses: medjlt@leeds.ac.uk, J.L.Thorne@leeds.ac.uk (J.L. Thorne).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.steroids.2022.109057
Received 8 December 2021; Received in revised form 7 April 2022; Accepted 2 June 2022
Available online 6 June 2022
0039-128X/© 2022 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

[13,14]), efflux (ABCG5 and ABCG8 [15–17]), metabolism (e.g. CH25H [18]), bile acid synthesis (e.g. CYP7A1 [19] in mice), and triglyceride production (SREBP1c [20]).

Expression of the *LXRα* gene (Official Symbol: *NR1H3,* nuclear receptor subfamily 1 group h member 3, located on chromosome 11p11.2), is typically restricted to liver, macrophages, intestine, adipose tissue, and kidneys. The *LXRβ* gene (*NR1H2*), located on chromosome 19q13.3, is ubiquitously expressed [21]. Both isoforms are aberrantly expressed in a range of pathologies including cancer [22–24] and fatty liver disease [25,26]. Changes in LXR target gene expression can be induced by ligand, which are sometimes accompanied by changes in expression of LXR itself. In vitro studies have indicated that LXR synthetic agonists, including GW3965, T0901317, and LXR623, as well as endogenous ligands, increase *LXRα* mRNA expression by 3–6 fold, and LXR target genes such as ABCA1 by>9 fold-increase, for example in macrophages [27–32]. GW3965 also upregulates *LXRα* mRNA expression by 6.6-fold concomitant with an increase in ABCA1 mRNA levels by 125-fold in human preadipocytes [27]. However, GW3965 only upregulated *LXRα* gene expression by 1.5-fold in mature human adipocytes and this was linked to markedly reduced ABCA1 induction [28]. Single nucleotide polymorphisms (SNPs) in *LXRα* are associated with differences in high-density lipoprotein cholesterol (HDL-C) serum concentrations across racially diverse cohorts [33–35]. However, genetic variation in *LXRs* in relation to other blood lipids and lipoproteins, such as triglycerides (TG), total cholesterol (TC), and low-density lipoprotein cholesterol (LDL-C), remains to be confirmed.

This study aimed to systematically summarize the SNPs in both *LXRα* and *LXRβ* genes reported to date that relate to lipid metabolism in population-based studies and evaluate the associations between *LXR* SNPs and blood lipid traits.

2. Methods

This review was performed following the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) statement [18], and is reported in line with the Preferred Reporting Items for Systematic Reviews and meta-analyses (PRISMA) guidelines [17]. The original protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) database (registration number: CRD42021246158) [36].

2.1. Data sources and search strategy

A pilot search was conducted initially on dbSNP database (https://www.ncbi.nlm.nih.gov/snp/) to identify SNPs of *LXRα* and *LXRβ*, and related publications were screened manually to retrieve studies that assessed associations between *LXR* polymorphisms and blood lipids or lipoproteins. A systematic search was then performed on five electronic databases: PubMed, Ovid Embase, Scopus, Web of Science, and the Cochrane Library; from database inception up to December 16th, 2020. The search terms included ("Liver X Receptor*" or "LXR*" or "NR1H3″ or "Nuclear Receptor Subfamily 1 Group H Member 3″ or "NR1H2″ or "Nuclear Receptor Subfamily 1 Group H Member 2″) and ("polymorphism, single nucleotide" or "Single Nucleotide Polymorphism*" or "SNP*" or "gene variant*" or "genetic" or "loci") and ("lipoprotein*" or "lipid*" or "cholesterol*" or "triglyceride*" or "dyslipid*" or "dyslipid?emia" or "hyperlipid*" or "hypercholester*" or "hypertriglyceride*"). The search strategy was reviewed by a librarian (University of Leeds) and full details for each database can be accessed from the PROSPERO record. The search was performed using free text searches in Web of Science and Scopus; and additionally with subject heading searches in PubMed, Ovid Embase, and the Cochrane Library databases.

2.2. Inclusion and exclusion criteria and study selection

Studies were included if they met the following inclusion criteria: (1) original research studies; (2) observational population-based studies, including cross-sectional, case-control, and cohort studies; (3) studies that have explored the association between *LXRs* polymorphisms and blood lipid/lipoprotein traits; (4) all age, gender, and ethnic groups were included and no other restrictions in demographic factors. The exclusion criteria were: (1) animal studies or *in vitro* studies; (2) studies with participants taking lipid-lowering medications; (3) studies not in original research such as reviews, notes, book chapters, editorials, or secondary research such as meta-analysis; (4) articles written in languages other than English; and (5) articles without full texts available.

Three reviewers (H.Z., P.L., M.X.) independently screened first the titles and abstracts, and then the full texts for selection of relevant articles based on the inclusion and exclusion criteria. Screening results were merged in Endnote (version X9, Clarivate Analytics) and disagreements were resolved through discussion.

2.3. Data extraction and quality assessment

Detailed information and data were extracted from each eligible study into a pre-defined summary table including: the first author, publication year, study country, study design, sample size, demographic characteristics of participants, genotyping methods, lipid measurement, *LXR* SNPs, and the main effects. Each *LXR* SNP in relation to lipid or lipoprotein traits was summarized, including: alleles and minor allele frequencies in populations investigated, corresponding effect sizes, and 95% confident interval (CI) and/or standard errors, as well as *P* values. Where crude, minimally-adjusted, or fully-adjusted models were reported for the associations, the highly adjusted estimates were selected.

The study quality assessment tool (SQAT) for observational cohorts and cross-sectional studies was used to assess the quality of included studies [37]. We dropped item 13 that assesses the proportion of loss to follow-up since this review aimed to assess the cross-sectional nature of included studies regardless of the original study design. The tool covered population selection, justification of sample size, exposure and outcome measurement, confounding factors, etc. We assigned 1 score for "Yes" and 0 score for "No" or "Not Reported" with a maximum of 12 scores. Thus, the total quality score ranges from 0 to 12, with 0–4 (poor quality), 5–8 (fair quality), and 9–12 (good quality). The study quality was considered when interpreting data synthesis.

2.4. Statistical analysis

Meta-analysis was performed for quantitative data synthesis where at least three studies reported the same SNP and corresponding blood lipid concentrations by genotypes of that SNP. Specific data for blood lipid concentrations (mmol/L) were sorted out based on the dominant model (e.g., CC versus CT + TT where T is the minor allele) or the over-dominant model (e.g., TT + CC vs. CT where either C or T is the minor allele in different populations). Where blood lipid concentrations were reported by separate genotypes of SNPs, we combined two genotypes into one single group according to the formula from the Cochrane handbook for systematic reviews [38]. Where blood lipid concentrations were reported in the unit of mg/dL, we divided mg/dL by 38.67 for total cholesterol, LDL-C and HDL-C, or by 88.57 for triglycerides to be converted into mmol/L [39]. Where separate estimates were available for subgroups of participants such as male and female, we pooled these in meta-analyses.

Meta-analysis was carried out using random-effects models. The standardised mean difference (SMD) was calculated using the Hedges's g method. The I2 statistic was used to detect heterogeneity between the included studies, and an I2 > 50% was considered substantial. In addition, sensitivity analysis was performed to detect potential sources of heterogeneity by omitting each study sequentially. Funnel plots and Egger's regression tests were used to detect a potential publication bias. All statistical analyses were conducted using Stata 16.1 (StataCorp LP, College Station, TX), and a *P* value of <0.05 was considered statistically

significant.

3. Results

A systematic search resulted in 1983 records, of which 1318 were screened after de-duplication (Fig. 1). After excluding 1268 unrelated records in the title/abstract screening and three records without full texts available, 47 records were assessed in the full-text screening. Based on the inclusion and exclusion criteria, seventeen studies were retrieved as eligible studies, of which ten were included in meta-analyses (Fig. 1).

3.1. Characteristics of included studies and quality assessment

The seventeen articles included in this study consisted of eight cross-sectional, seven case-control, and two cohort studies (Table 1). These studies were conducted in Europe (n = 6) [34,35,40–43], Asia (n = 8) [44–51], America (n = 2) [33,52], and mixed continents (n = 1) [53]. The sample sizes of the studies ranged from 129 to 5407. Most investigated predominantly middle-aged or older adults. Five studies specified that participants were free of taking lipid-lowering medications [33,43,44,51,52]. Twelve studies reported that blood samples were taken after an overnight fast for lipid measurement [33–35,40,42,44,46–48,50–52]. Although two studies did not report lipid measurement method [45,49], fifteen studies reported use of enzymatic methods to measure blood lipid concentrations. Six of these fifteen studies had specifically indicated their preferences to use the enzymatic method with Friedewald's equation rather than using the automated enzymatic method to measure LDL-C directly [33,35,40,42,52,53]. Commercial DNA extraction kits and a sequencing platform for genotyping SNPs were widely used in these studies. For the study quality assessment, four studies were graded as "Poor", and the remaining studies were graded as "Fair" (Supplementary Table 1).

3.2. Associations between SNPs of LXRα and blood lipid traits

A total of nine *LXRα* SNPs that associated with blood lipid traits were identified: rs2167079, rs200557846, rs3758674, rs7120118, rs12221497, rs11039155, rs2279238, as well as two SNPs (*LXRα* −840C>A and *LXRα* −1003G>A) without Reference SNP (rs) numbers available (Table 1). These last two SNPs (reported in [33,45]) appear to be newly identified *LXRα* SNPs that have not yet been recorded and assigned an ID by the dbSNP database. Loci positions of *LXR* SNPs observed in this study are shown in Fig. 2. Five of nine *LXRα* SNPs are located before the exon 2. rs11039155, rs200557846, rs12221497, and two newly identified *LXRα* (−840C>A and −1003G>A) are located 6, 44, 115, 840, 1003 nucleotides (nt) upstream of the exon 2, respectively. The rs3758674 is located 609 nt before the exon 1. rs2167079 is located intronically, 10 nt upstream of the exon −1. Exons encoding alternative promoter usage or alternative transcription start site sequences are marked with "-". The rs7120118 is located within the intron region connecting exon 7 and exon 8 (3174 nt upstream of the exon 8). In contrast to these SNPs that are located in non-coding areas outside exons, rs2279238 is located within the exon 4; 297C>A, and results in a serine to arginine missense variant, while 297C>T is a synonymous variant. As three or more studies were available for rs12221497, rs11039155, and rs2279238. they were subjected to meta-analyses and pooled quantitatively and described below.

The minor allele copies of two *LXRα* SNPs, rs2167079 and rs200557846, were both positively associated with blood HDL-C concentrations [34,53]. The rs2167079 was also found to be associated with a higher TG level in another African-descent population [52]. In 732 Canadians, carriers of the minor allele C for rs3758674 had higher TC

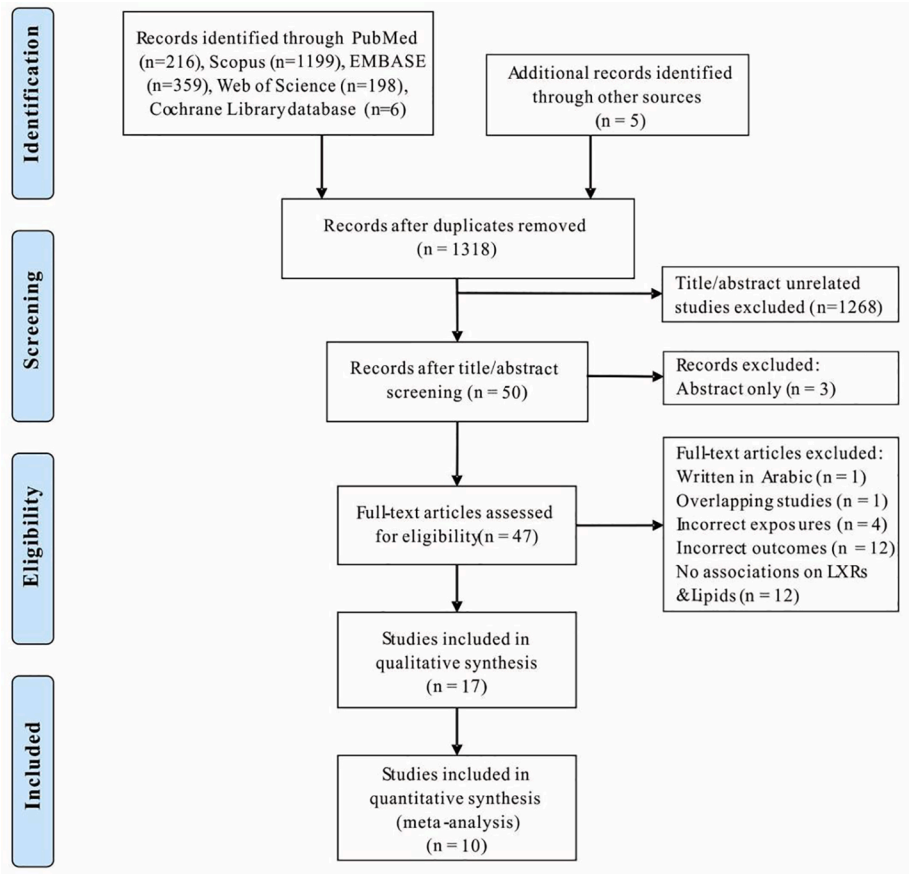

Fig. 1. Flowchart of the literature screening process for associations between liver X receptor polymorphisms and blood lipid profile.

Table 1
Characteristics of included studies and single nucleotide polymorphisms (SNPs) of *LXRs* in relation to blood lipid/lipoprotein traits.

First author, publication year; [Reference]	Study design; Country	Study populations	Sample size; Age (range/ mean ± sd)	DNA preparation; Genotyping measures	Measures of lipid traits	*LXRs* related polymorphism (Minor allele: frequency; rs No. if available)	Findings
Robitaille, J., 2007; [33]	Cross-sectional study; Canada	Subjects free of medication and without type 2 diabetes, type III dysbetalipoproteinaemia, familial hypercholesterolaemia or familial combined hyperlipidaemia	732 (Female/ Male = 118/ 614); 49.2 ± 16.0 years	Qiagen DNA extraction kit; BigDyeTerminator v3.0 cycle sequencing	Blood samples obtained in the morning after a 12 h overnight fast. TG, TC: enzymatic assays; LDL-C: calculated using the Friedewald formula; HDL-C obtained after precipitation of LDL particles in the infranatant with heparin and $MnCl_2$	*LXRα* − 115G>A (A: 14.3%; rs12221497)	Carriers of the − 115A allele had a higher level of TC ($P < 0.05$), TG ($P < 0.05$), than − 115G/G homozygotes adjusting for age, sex, and BMI.
						LXRα − 840C>A (A: 14.2%)	Carriers of the − 840A allele had a higher level of TC ($P < 0.05$), TG ($P < 0.05$), than − 840C/C homozygotes adjusting for age, sex, and BMI.
						LXRα − 1830 T>C (C:11.0%; rs3758674)	Carriers of the − 1830C allele had a higher level of TC ($P < 0.05$), TG ($P < 0.05$), than − 1830 T/T homozygotes adjusting for age, sex, and BMI.
Legry, V., 2008; [40]	Cross-sectional study; France	The urban community of Lille in the North (Lille, n = 1195) and the Haute-Garonne county in the South (Toulouse, n = 1182): the WHO-MONICA population survey.	2290 (Female/ Male = 1090/1200); 35–65 years	DNA extraction kit; Genotyping of SNPs by the restriction fragment length polymorphism method	Blood samples obtained after ≥10 h fast; TG, TC: enzymatic methods; HDL-C: after sodium phosphotungstate/magnesium chloride precipitation; LDL-C: calculated with the Friedewald equation.	*LXRα* − 6G>A (A:11.4%; rs11039155)	Carriers of the − 6A allele had a higher level of HDL-C ($P = 0.02$) but not TG ($P = 0.16$), than − 6G/ G homozygotes adjusting for age, gender, BMI, alcohol consumption, physical activity, smoking habit, and centre.
Sabatti, C., 2009; [34]	Case-control study /GWAS; Northern Finland	Finnish population: the Northern Finnish Birth Cohort of 1966 (NFBC1966).	4518 (Female/ Male = 2377/2141); 31 years	DNA extraction: Illumina Infinium 370cnvDuo array; Genotyping by the Broad Institute Biological Sample Repository (BSP)	Blood samples drawn after overnight fasting in the morning; TG, TC, HDL: enzymatic methods	*LXRα* (MAF: A = 41.7%; rs2167079)	Copies of the minor allele A were associated with blood HDL concentration (β = 0.04, se = 0.007, $P < 5 \times 10^{-7}$) adjusting for sex, pregnancy status, use of oral contraceptive, and BMI.
						LXRα (MAF: G = 41.7%; rs7120118)	Copies of the minor allele G were associated with blood HDL concentration (β = 0.04, se = 0.007, $P < 5 \times 10^{-7}$) adjusting for sex, pregnancy status, use of oral contraceptive, and BMI.
Gupta, R., 2010; [52]	Cross-sectional study; Jamaica	African-descent population free of taking lipid-lowering medications (Caucasian and Jamaican populations)	1466 (Female/ Male = 857/ 609); 25–74 / 45.9 ± 13.7 years	Genotyping was performed with the Sequenom platform, using matrix-assisted laserdesorption ionization time-of-flight mass spectrometry	Serum samples collected after overnight fasting; Serum lipid measurements were performed on an Alcyon 300i autoanalyzer; LDL-C: calculated with the Friedewald equation.	*LXRα* (MAF: A = 40%; rs2167079)	Copies of the minor allele A were associated with serum TG log(10)-transformed concentration (β = 0.07, se = 0.04, $P = 0.05$, N = 1332).
Solaas, K., 2010; [35]	Cross-sectional study; France	Lille Urban Community (Lille, n = 1195) and the Haute-Garonne county (Toulouse, n = 1182): the WHO-MONICA population survey.	2318 (Female/ Male = 1128/1190); 35–65 / 50.7 ± 8.5 years	Genotyping was performed using a PCR-RFLP method	Blood samples obtained after ≥10 h fast; TG, TC: enzymatic methods; HDL-C: after sodium phosphotungstate/magnesium chloride precipitation; LDL-C: calculated with the Friedewald equation.	*LXRβ* − 1339C>G (G:31%; rs17373080)	No differences in blood levels of TG ($P = 0.40$) or HDL-C ($P = 0.36$) between CC and CG + GG genotypes adjusting for age, gender, centre, smoking habit, alcohol consumption, BMI, and physical activity level.
						LXRβ − 1311C>T (T:9%; rs56151148)	No differences in blood levels of TG ($P = 0.27$) or HDL-C ($P = 0.43$) between CC and CT + TT genotypes adjusting for age,

(*continued on next page*)

Table 1 (*continued*)

First author, publication year; [Reference]	Study design; Country	Study populations	Sample size; Age (range/ mean ± sd)	DNA preparation; Genotyping measures	Measures of lipid traits	*LXRs* related polymorphism (Minor allele: frequency; rs No. if available)	Findings
							gender, centre, smoking habit, alcohol consumption, BMI, and physical activity level.
						LXRβ − 122C>T (T:43%; rs2695121)	No differences in blood levels of TG ($P = 0.51$) or HDL-C ($P = 0.41$) between CC and CT + TT genotypes adjusting for age, gender, centre, smoking habit, alcohol consumption, BMI, and physical activity level.
						LXRβ + 4339A>G (G:8%; rs2303044)	No differences in blood levels of TG ($P = 0.16$) or HDL-C ($P = 0.32$) between CC and CT + TT genotypes adjusting for age, gender, centre, smoking habit, alcohol consumption, BMI, and physical activity level.
						LXRβ + 6225C>T (T:9%; rs3219281)	Carriers of the T allele had a higher level of TG ($P = 0.01$) but not HDL-C ($P = 0.16$), than CC homozygotes adjusting for age, gender, centre, smoking habit, alcohol consumption, BMI, and physical activity level.
	Cross-sectional study; Norway	Non-diabetic subjects, a subset of The Nord-Trøndelag Health Study 2 (HUNT2 Study)	1986 (Female/ Male = 1008/978); 65.6 ± 14.3 years	Genotyping was performed with MASSARRAY platform (Sequenom)	Serum lipid measurements were performed on a Hitachi 911 autoanalyzer;	*LXRβ* − 1339C>G (G:35%; rs17373080)	No differences in blood levels of TG ($P = 0.28$), TC ($P = 0.96$), or HDL-C ($P = 0.31$) between CC and CG + GG genotypes adjusting for age, gender, and BMI.
						LXRβ − 1311C>T (T:8%; rs56151148)	Carriers of the T allele had a higher level of TG ($P = 0.03$) but not TC ($P = 0.57$) or HDL-C ($P = 0.25$), than CC homozygotes adjusting for age, gender, and BMI.
						LXRβ − 122C>T (T:44%; rs2695121)	No differences in blood levels of TG ($P = 0.19$), TC ($P = 0.18$), or HDL-C ($P = 0.12$) between CC and CT + TT genotypes adjusting for age, gender, and BMI.
						LXRβ + 4339A>G (G:7%; rs2303044)	No differences in blood levels of TG ($P = 0.79$), TC ($P = 0.40$, or HDL-C ($P = 0.64$) between CC and CT + TT genotypes adjusting for age, gender, and BMI.
						LXRβ + 6225C>T (T:9%; rs3219281)	No differences in blood levels of TG ($P = 0.63$), TC ($P = 0.07$, or HDL-C ($P = 0.43$) between CC and CT + TT genotypes adjusting for age, gender, and BMI.
	Cross-sectional study;	European adolescents: the Healthy Lifestyle in Europe by Nutrition in	1144 (Female/ Male = 595/	Genotyping was performed with Illumina system using GoldenGate technology	Serum lipid measurements were measured on the Dimension RxL	*LXRβ* − 1339C>G (G:32%; rs17373080)	No differences in blood levels of TG ($P = 0.88$) or HDL-C ($P = 0.28$) between CC and CG + GG

(*continued on next page*)

Table 1 (*continued*)

First author, publication year; [Reference]	Study design; Country	Study populations	Sample size; Age (range/ mean ± sd)	DNA preparation; Genotyping measures	Measures of lipid traits	*LXRs* related polymorphism (Minor allele: frequency; rs No. if available)	Findings
	nine European countries	Adolescence-Cross Sectional Study (HELENA)	549); 14.7 ± 1.4 years		clinical chemistry using enzymatic methods		genotypes adjusting for age, gender, centre, and BMI.
						LXRβ − 1311C>T (T:8%; rs56151148)	No differences in blood levels of TG ($P = 0.93$) or HDL-C ($P = 0.53$) between CC and CT + TT genotypes adjusting for age, gender, centre, and BMI.
						LXRβ − 122C>T (T:40%; rs2695121)	No differences in blood levels of TG ($P = 0.23$) or HDL-C ($P = 0.66$) between CC and CT + TT genotypes adjusting for age, gender, centre, and BMI.
						LXRβ + 4339A>G (G:8%; rs2303044)	No differences in blood levels of TG ($P = 0.29$) or HDL-C ($P = 0.53$) between CC and CT + TT genotypes adjusting for age, gender, centre, and BMI.
						LXRβ + 6225C>T (T:10%; rs3219281)	No differences in blood levels of TG ($P = 0.67$) or HDL-C ($P = 0.31$) between CC and CT + TT genotypes adjusting for age, gender, centre, and BMI.
Legry, V., 2011; [41]	Cross-sectional study; nine European countries	European adolescents: the Healthy Lifestyle in Europe by Nutrition in Adolescence-Cross Sectional Study (HELENA)	1144 (Female/ Male = 595/ 549); 14.7 ± 1.4 years	Genotyping was performed with Illumina system using GoldenGate or VeraCode technologies (rs11039155 typed by restriction length fragment polymorphism)	Serum lipid measurements were measured on the Dimension RxL clinical chemistry using enzymatic methods	*LXRα* − 6G>A (A:14.2%; rs11039155)	SNP rs110391555 was significantly associated with HDL-C concentration (nominal $P = 0.012$) adjusting for age, gender, centre, and BMI.
						LXRα − 115G>A (A: 12.7%; rs12221497)	SNP rs12221497 was significantly associated with HDL-C concentration (nominal $P = 0.046$) adjusting for age, gender, centre, and BMI.
Zhang, Z., 2011; [44]	Case-control study; China	Chinese population including 1360 non-type 2 diabetes controls and 1173 type 2 diabetes patients without using lipid-lowering therapy	2533 (Female/ Male = 1654/879); 61 ± 9 years	QuickGene 610 L Automatic DNA/RNA Extraction System; genotyped by TaqMan technology on an ABI7900 system	Blood samples were collected after an overnight fast; TG, TC, HDL, and LDL were measured enzymatically according to standard methods on the Roche modular P800 autoanalyzer	*LXRα* (MAF: T = 25%; rs7120118)	Copies of the minor allele T were not associated with blood concentrations of log(TG) ($\beta = 0.01$, $P = 0.64$), TC ($\beta = 0$, $P = 0.94$), HDL ($\beta = 0$, $P = 0.76$), or LDL ($\beta = 0.01$, $P = 0.73$) adjusting for age, gender, BMI, and type 2 diabetes status.
Akao, H., 2012; [42]	Cross-sectional study; Scotland, Ireland, Netherlands	Subjects with pre-existing vascular disease (n = 2404) or at least one of three major vascular risk factors (diabetes n = 575, smoking n = 1433, or hypertension n = 3360): the PROSPER study	5407 (Female/ Male = 2790/2617); 70–82 / 75 ± 3 years	Taq Man® SNPs genotyping assays and Applied Biosystems 7900 HT Sequence Detection System	TG, TC, and HDL-C, were assessed after an overnight fast; LDL-C was calculated by the Friedewald formula	*LXRα* − 115G>A (A: 13.9%; rs12221497)	No differences in blood concentrations of TC ($P = 0.936$) and LDL-C ($P = 0.729$) were observed among GG, GA, and AA genotypes adjusted for gender, body mass index, age, alcohol, smoking, diabetes, APOE phenotype, and country.
Knebel, B., 2012; [43]	Case-control study; Germany	Patients with the polycystic ovary syndrome (PCOS) and receiving no medication influencing glucose	129 (Female/ Male = 129/ 0); 14–41 /	Qiagen blood DNA extraction kit; genotyped by direct sequencing methods	Blood and serum samples were collected according to standard protocols; TG, TC, HDL-C, and LDL-C	*LXRα* − 6G>A (A:13.4%; rs11039155)	Carriers of the A allele had a higher level of TG ($P = 0.018$) but not TC ($P = 0.0.480$), LDL-C ($P = 0.844$),

(*continued on next page*)

Table 1 (*continued*)

First author, publication year; [Reference]	Study design; Country	Study populations	Sample size; Age (range/ mean ± sd)	DNA preparation; Genotyping measures	Measures of lipid traits	*LXRs* related polymorphism (Minor allele: frequency; rs No. if available)	Findings
		metabolism or endocrine parameters for at least 3 months	26.68 ± 5.68 years		were measured on Immulite 2000, Nichols Advantage.		or HDL-C ($P = 0.414$), than GG homozygotes.
						LXRα (MAF: A = 13.7%; rs2279238)	No differences in blood levels of TG ($P = 0.151$), TC ($P = 0.310$), LDL-C ($P = 0.263$), or HDL-C ($P = 0.134$) between GG and GA + AA genotypes.
Jeon, J. Y., 2014; [45]	Case-control study; Korea	Korean patients of systemic lupus erythematosus (SLE)	300 (Female/ Male = 267/ 33); 30.6 ± 9.2 years	QuickGene DNA whole blood kit S and direct sequencing for 50 subjects; the SNaPSHOT ddNTP primer extension kit for 250 subjects	n/a	*LXRα* − 115G>A (A: 11.5%; rs12221497)	Carriers of the A allele had a higher level of TG ($P = 0.011$) than GG homozygotes.
						LXRα − 1830 T>C (C: 11%; rs3758674)	No differences in blood levels of TG ($P = 0.108$) between TT and TC + CC genotypes.
						LXRα − 1003G>A (A: 8.8%)	Carriers of the A allele had a higher level of TG ($P = 0.007$) than GG homozygotes.
Rooki, H., 2014; [46]	Cross-sectional study; Iran	Randomly selected using a population-based cluster sampling from Mashhad, the second largest Iranian city	447 (Female/ Male = 295/ 152); 18–60 / 48 ± 7 years	FlexiGene DNA Isolation Kit, Qiagen; TaqMan SNP genotyping assays	Blood samples were taken in the morning after an overnight fast; lipid levels were measured by routine enzymatic methods	*LXRα* − 6G>A (A:18.8%; rs11039155)	Carriers of the A allele had a higher level of TC ($P = 0.031$) but not TG ($P = 0.852$), LDL-C ($P = 0.055$), or HDL-C ($P = 0.965$) than GG homozygotes.
						LXRα (MAF: T = 26.4%; rs2279238)	No differences in blood levels of TG ($P = 0.982$), TC ($P = 0.070$), LDL-C ($P = 0.079$), or HDL-C ($P = 0.545$) between CC, CT, and TT genotypes.
Zhou, Y. F., 2014; [47]	Case-control study; China	240 patients with coronary heart disease and 250 healthy control subjects in Chinese Han population	490 (Female/ Male = 107/ 383); 61.3 ± 11.0 years	DNA-extraction kit; Light Cycler gene amplification detector	12 h-fasting venous blood; lipid measures using a biochemical analyser	*LXRα* − 115G>A (A: 9.4%; rs12221497)	No differences in blood levels of TG ($P = 0.654$), TC ($P = 0.179$), LDL-C ($P = 0.078$), or HDL-C ($P = 0.186$) between GG and GA + AA genotypes.
Yang, J. S., 2015; [48]	Case-control study; China	400 patients with acute hemispheric ischemic stroke and 400 healthy control subjects in Chinese population	800 (Female/ Male = 213/ 587); 58.16 ± 11.01 years	DNA extraction kit; the single fluorescent-labeled probe technique was utilized for genotyping	12-h fasting venous blood; lipid measures using a biochemical analyser	*LXRα* − 115G>A (A: 10.4%; rs12221497)	Carriers of the A allele had a higher level of TC ($P = 0.036$) and LDL-C ($P = 0.031$) but not TG ($P = 0.642$) or HDL-C ($P = 0.186$) than GG homozygotes.
Dai, Y., 2016; [49]	Case-control study; China	413 ischemic stroke patients in Chinese Han population	413 (Female/ Male = 164/ 249); 63.47 ± 11.57 years	DNA extraction kit; genotyping used SNaP shot multiple micro sequencing	n/a	*LXRα* (MAF: C = 30.1%; rs2279238)	No differences in blood levels of TG ($P = 0.564$), TC ($P = 0.112$), LDL-C ($P = 0.326$), or HDL-C ($P = 0.142$) between CC, CT and TT genotypes in patients with ischemic stroke.
		477 healthy control subjects in Chinese Han population	477 (Female/ Male = 198/ 279); 62.68 ± 6.32 years			*LXRα* (MAF: C = 37.2%; rs2279238)	No differences in blood levels of TG ($P = 0.981$), TC ($P = 0.717$), LDL-C ($P = 0.394$), or HDL-C ($P = 0.370$) between CC, CT and TT genotypes in healthy controls.
Helgadottir, A., 2016; [53]	Case-control study /GWAS; Iceland, Netherlands, Iran, and the United States	Cases with coronary artery disease in the Icelandic study and the other three studies from the Netherlands, Iran, and the United States respectively	Varied from study to study	Illumina BeadChip genotyping for Icelandic samples and single-track genotyping and whole-genome sequencing were also used	LDL cholesterol concentration was calculated using the Friedewald equation; non-HDL cholesterol concentration was calculated by	*LXRα* (MAF: A = 0.61%; rs200557846)	The rare allele of rs200557846 in *NR1H3* increased HDL cholesterol levels by 0.12 mmol/L (95%CI: 0.08, 0.16 mmol/L, n = 119,514; $P = 7.2x10^{-10}$) but was not

(*continued on next page*)

Table 1 (*continued*)

First author, publication year; [Reference]	Study design; Country	Study populations	Sample size; Age (range/ mean ± sd)	DNA preparation; Genotyping measures	Measures of lipid traits	*LXRs* related polymorphism (Minor allele: frequency; rs No. if available)	Findings
					subtracting HDL cholesterol levels from total cholesterol levels		associated with non-HDL-C level (n = 119,146; P = 0.90) or TG level (n = 80,111; P = 0.0056).
Wu, D. F., 2016; [50]	Case-control study; China	596 healthy controls in Chinese Han population	596 (Female/ Male = 161/ 435); 61.53 ± 10.88 years	Genomic DNA was extracted using the phenol-chloroform method; genotyping by the Snapshot technology platform	Venous blood samples were obtained after at least 12 h of fasting; serum lipids measured by enzymatic methods with commercially available kits	*LXRα* (MAF: T = 23.7%; rs7120118)	No differences in blood levels of TG (P = 0.596), TC (P = 0.396), LDL-C (P = 0.817), or HDL-C (P = 0.306) between CC, CT and TT genotypes in the healthy controls.
Mehrad-Majd, H., 2018; [51]	Cohort study; Iran	Genetically unrelated adult subjects of both genders without taking lipid-lowering medications in Iranian population	453 (Female/ Male = 298/ 155); 18–60 years	Peripheral blood sample with a FlexiGene DNA Kit; allelic discrimination assays using TaqMan probes	Blood samples were taken in the morning after an overnight fast; lipid levels were measured by routine enzymatic methods	*LXRβ* − 122C>T (T:33.8%; rs2695121)	No differences in blood levels of TG (P = 0.918), TC (P = 0.628), LDL-C (P = 0.732), or HDL-C (P = 0.282) between CC, CT and TT genotypes adjusting for age and gender.

Abbrevations: BMI, body mass index; GWAS, genome-wide association study; SNPs, single nucleotide polymorphisms; PROSPER, the PROspective Study of Pravastatin in the Elderly at Risk study; n/a, not available; MAF, minor allele frequency; MONICA, the WHO Multinational MONItoring of Trends and Determinants in CArdiovascular Disease project; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; and LDL-C, low-density lipoprotein cholesterol.

and TG levels than the dominant allele TT homozygotes with adjusting for confounding factors [33]. However, in unadjusted analyses of 300 Koreans no difference in TG levels was observed [45]. The minor allele of *LXRα* rs7120118, was not associated with any blood lipid traits (TG, TC, LDL-C and HDL-C) in two Chinese populations with or without adjusting for covariates [44,50]. However, this SNP was found to be positively associated with HDL-C level in a Finnish population with adjusting for confounding factors [34]. Both newly identified *LXRα* SNPs were also reported to have association with several blood lipid traits. The minor allele A of the *LXRα* −840C>A was associated with higher blood TG and TC levels [33], whereas the minor allele A of the *LXRα* −1003G>A was associated with a higher blood TG level [45].

3.2.1. rs12221497 (LXRα −115G>A) is associated with altered triglycerides

Six studies reported associations with rs12221497 and blood lipid levels. Ranging from 9.4% to 14.3% in different populations, frequencies of the minor allele A were found to be lower in the studies that evaluated Asian populations (9.4%−11.5%) [45,47,48] compared with Europeans (12.7%−13.9%) [41,42] or Canadians (14.3%) [33]. The dominant model was used to compare blood lipid levels between GA + AA and GG genotypes with the dominant homozygotes GG as the reference. As shown in the upper panel of Fig. 2, carriers of the minor allele A had a significantly higher TG level than GG homozygotes by 0.13 mmol/L (95%CI: [0.03, 0.23]; $P = 0.01$). There was no evidence of heterogeneity between studies ($I^2 = 0$, P value of homogeneity test was 0.21) or publication bias (Egger's $P = 0.373$; n = 4) in this pooled analysis, although the number of studies was low. In addition, the funnel plot did not suggest asymmetry (Supplementary Fig. 1a).

In contrast, carriers of the minor allele A did not show significant differences in blood levels of TC, LDL-C, and HDL-C compared with carriers of GG genotype (Fig. 3). There was substantial heterogeneity ($I^2 > 50\%$) between studies and obvious publication bias (asymmetry funnel plots in Supplementary Fig. 1b-c) in the meta-analyses of TC and LDL-C, but not HDL-C. The heterogeneity and publication bias in both meta-analyses came from one study [48].

3.2.2. rs11039155 (LXRα −6G>A) is not associated with blood lipid traits

There were four studies that investigated rs11039155 in relation to blood TG and HDL-C levels. Frequencies of the minor allele A ranged from 11.4% to 18.8% among European and Iranian populations [40,41,43,46], with the highest frequency observed in Iranians (18.8%) [46]. The dominant model was also used in this pooled SNP analyses. No significant differences in TG ($P = 0.39$) or HDL-C ($P = 0.98$) blood levels were detected between GA + AA and GG genotypes in meta-analyses (Fig. 4). Substantial heterogeneity between studies was detected in both TG and HDL-C meta-analyses ($I^2 = 94\%$ and 62%; P values of both homogeneity tests were <0.01 and 0.03, respectively). In addition, the asymmetry funnel plot (Supplementary Fig. 2a) suggested potential publication bias in the meta-analysis of TG. The substantial heterogeneity in the meta-analysis of TG was potentially due to the study design where one study was case-control by Knebel *et al.* [43] and other two studies were cross-sectional by Legry *et al.* [40] and Rooki *et al.* [46] respectively.

3.2.3. rs2279238 (LXRα 297C>T) is associated with altered total cholesterol

Three studies investigated *LXRα* rs2279238 in relation to blood lipid traits. Of them, one study reported A as the minor allele in Germans [43], while two studies reported T/C as the minor allele in Asians [46,49]. More specifically, the T allele was reported as the minor allele in Iranians (frequency: 26.4%) by Rooki *et al.* [46], whereas the C allele was reported as the minor allele in Chinese populations (frequency: 30.1%−37.2%) by Dai *et al.* [49]. Studies that reported same base pairs in rs2279238 were pooled quantitatively, which were those with C and T alleles. An over-dominant model was used to compare blood lipid levels

between CT and CC + TT genotypes with the homozygotes CC + TT as the reference. Since separate estimates were available for subgroups of ischemic stroke patients and healthy controls in one study [49], the two estimates were included in one meta-analysis as Dai *et al.* 2016a and Dai *et al.* 2016b. As shown in Fig. 4, the CT heterozygotes had a significantly higher blood TC level than CC + TT homozygotes by 0.12 mmol/L (95% CI: 0.01, 0.23; $P = 0.04$). However, blood concentrations of TG, LDL-C or HDL-C did not show significant differences between CT heterozygotes and CC + TT homozygotes. No obvious heterogeneity between studies ($I^2 < 50\%$, P values of homogeneity tests were >0.05) and publication bias (Egger's $P = 0.11$; n = 3) were detected in these meta-analyses (Fig. 5). In addition, the funnel plots did not suggest publication bias (Supplementary Fig. 3).

3.3. Associations between SNPs of LXRβ and blood lipid traits

Regarding loci positions of *LXRβ* SNPs, two SNPs, rs17373080 and rs56151148, are located two kb upstream of exon 1, 28 nt apart from each other. rs2695121 is located upstream of the exon 3. The rs2303044 is located 22 nt upstream of the exon 9. The rs3219281 is located within the 3′downstream sequence of *LXRβ*. A total of five SNPs of *LXRβ* that have been investigated in relation to blood lipid traits were identified: rs17373080, rs56151148, rs2695121, rs2303044, and rs3219281 in two studies [35,51] (Table 1). Analyses in European and Iranian populations did not show significant associations between the minor allele of these *LXRβ* SNPs and blood lipid traits (TG, TC, HDL-C, and LDL-C). However, in the French MONICA cross-sectional study, carriers of the minor allele of rs3219281 had a higher TG level than the dominant homozygotes with adjusting for confounding factors [35]. Similarly, in the Norwegian HUNT2 cross-sectional study, carriers of the minor rs56151148 allele had a higher blood TG level adjusting for age, gender, and BMI [35].

4. Discussion

In this systematic review and meta-analysis, we summarized associations between SNPs in *LXRα* and *LXRβ* and blood lipid and lipoprotein levels, including TG, TC, LDL-C, and HDL-C. In total, nine SNPs of *LXRα* and five SNPs of *LXRβ* were identified from seventeen studies. Meta-analyses demonstrated that the minor allele A of rs12221497 (*LXRα* −115G>A) was associated with moderate elevation of blood TG levels; whereas the CT heterozygotes of *LXRα* rs2279238 were associated with higher blood TC levels. There was no evidence of substantial heterogeneity between included studies or potential publication bias for these two meta-analyses. However, for the other *LXRα* SNPs, while some associations with blood lipids were observed, the number of relevant studies was small and pooled quantitative analyses could not be conducted.

Cholesterol and triglyceride, two important plasma lipids in the blood circulation, are generally transported to peripheral tissues and macrophages via lipoproteins such as low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL) respectively [4]. Macrophages laden with LDL-cholesterol are prone to becoming foam cells, which are involved in the initial steps forming atherogenic plaques and atherosclerosis [21]. An increase of total cholesterol from 5.2 to 6.2 mmol/L in men has been found to be associated with 3 times higher risk of death from coronary heart diseases, 2.5 times higher risk of death from cardiovascular diseases, and 1.4 times higher risk of all-cause mortality [54]. In addition, elevated triglycerides or hypertriglyceridemia has been independently associated with high risk of cardiovascular diseases [55,56].

Cholesterol can be generated by endogenous synthesis or derived from food intake. In the context of high circulated cholesterol, HDL serves to remove excess cholesterol from the peripheral tissues (e.g., macrophages) and deliver to the liver. Sterol efflux from peripheral tissues and reverse transport by lipoproteins to the liver are parts of key mechanisms to eliminate the excessive lipids, which are regulated by LXRs [57]. LXRs, acting as lipid sensors, can be activated by increased endogenous ligands and bind to specific DNA sequences to upregulate expression of their target genes, including *ABCA1*, *ABCG1*, and apolipoprotein (*APOE*). The expression of these target genes can generate pre β-HDL, stabilize HDL particles, promote cholesterol efflux, and mediate transport of free cholesterol and phospholipids from triglyceride-rich lipoproteins (TRL) to lipid-poor apolipoproteins and HDL particles [58]. Cholesterol in the liver can be eliminated via bile excretion either in the classical pathway of bile acid synthesis or as free cholesterol, which both can also be regulated by LXRs activation [58,59]. In addition to the reverse transport and bile acid excretion, LXRs activation can also regulate lipid absorption and excretion in the intestine to keep the lipid homeostasis, and thus LXRs have emerged as potential therapy targets for metabolic related diseases [60].

Identifying genetic determinants of blood lipids and lipoprotein profile has been the focus of extensive research, and several important genetic determinants of lipoprotein levels have been identified including the *LXRs* [21]. However, the underlying mechanisms of three SNPs (rs12221497, rs11039155, rs12221497), which were subjected to meta-analysis in this study, still remain unclear. rs12221497 is located in non-coding sequences of *LXRα*, it is located in a potential branch point for exon 2 of *LXRα*. Branch point nucleotides, located between 18 and 200 nt upstream of the 3′ end of introns, are essential for mRNA splicing [61] and changes in these sequences may alter splicing pattern and ultimately, protein function [61,62]. Given the proximity to the intron–exon junction, it is possible that rs12221497 may alter the splicing pattern of *LXRα* potentially resulting in changes of the protein function. rs11039155 which is just 6 nt away from exon 2, the change of the G to A will cause loss of the binding of the splicing factor srp30c. According to the exon skipped database (ExonSkipDB), the presence of the rs11039155 (−6G>A) is associated with loss of exon 2 [63]. Alterations in coding sequences may change protein expression and subsequently influence protein function; for example, rs2279238 (297C>A) resulted in S(Ser)>R(Arg) which is a missense variant. However, the rs2279238 (297C>T) described in this study is a synonymous variant. the rs2279238 is located within the DNA binding domain (DBD) coding the exon 4 of *LXRα*. Multiple studies have documented synonymous SNPs may modulate the secondary structure of mRNA, leading to alterations of protein translation, folding and conformational changes [64–67]. Multiple transcripts and protein variants of LXRα and LXRβ are produced through genetic splicing [22]. ExonSkipDB indicates that rs2279238 can contribute to the loss of exon 4 of *LXRα* [63]. Noteworthy, a recent GWAS study discovered splice junction quantitative trait loci (sQTL) in the *LXRα* gene that leads to loss of exon 4 in adipose tissue. *LXRα* gene with an sQTL for the skipped exon 4 alters the function of LXR at an HDL-C locus, resulting in the failure of LXR mediated cholesterol efflux activity in adipose tissue [68].

Although some case-control or cohort studies, and GWAS have hinted some *LXR* gene variants influence lipid levels, the contributions were relatively small and some of the small-effect gene variants were not replicated in other studies [4]. For instance, the minor allele T carriers of rs3219281 (*LXRβ* + 6225C>T) had a high TG level compared with CC homozygotes in the French MONICA study. Yet, this higher TG pattern was not found in either the Norwegian HUNT2 study or the HELENA study with participants from nine European countries, even though all studies were under sufficient adjustment [35]. A similar picture was seen in rs56151148 (*LXRβ* −1311C>T), where this *LXRβ* SNP was only associated with a higher TG level in the HUNT2 study [35].

Currently, the isoform-specific physiological roles of *LXRα* and *LXRβ* in regulating lipid metabolism remain unclear. Some studies using *LXR* gene deficient ($LXR^{-/-}$) mice suggested that the conversion of cholesterol to bile acids could be mainly regulated by *LXRα* [19,69]. High-cholesterol diets and oxysterols failed to induce the expression of *CYP7A1* (an enzyme to convert cholesterol into bile acids) and other LXR target genes involved in cholesterol metabolism in $LXR\alpha^{-/-}$ mice [19,69]. Cholesterol also preferentially accumulated in the liver of

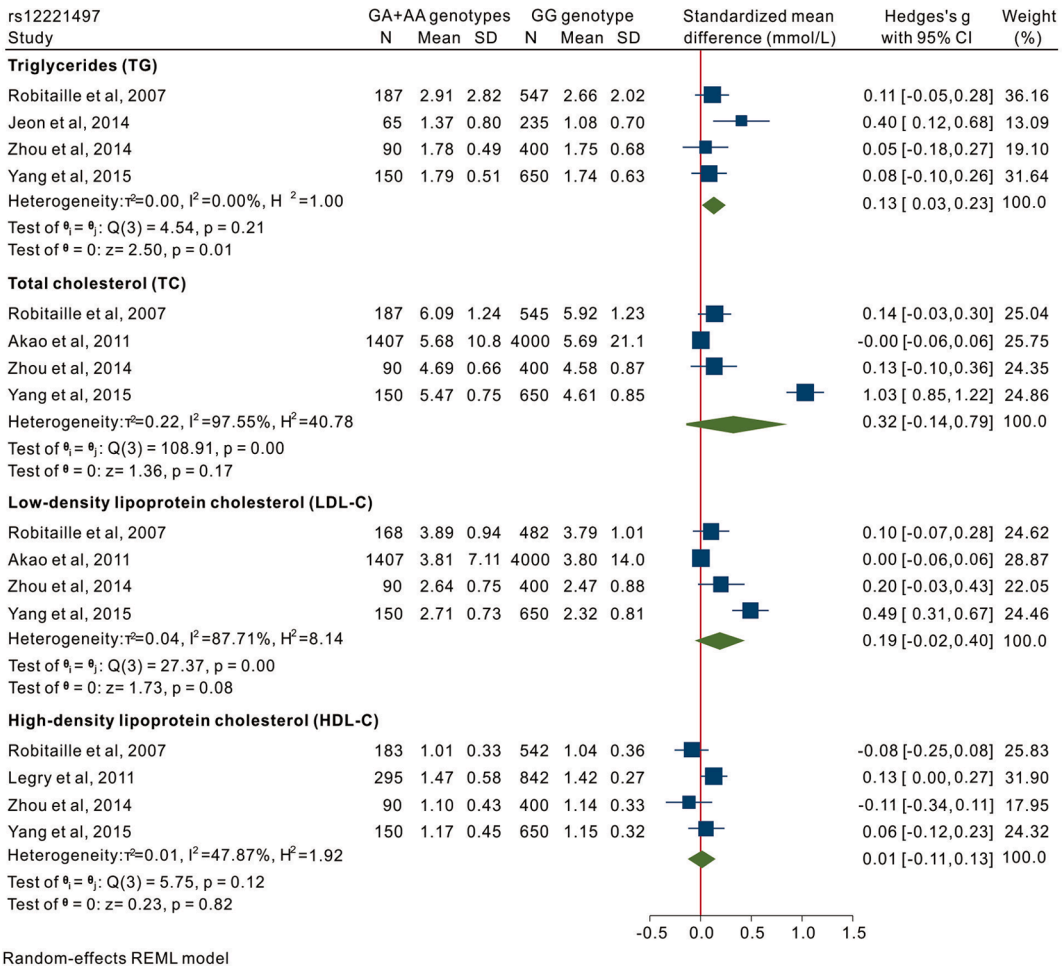

Fig. 2. Forest plot of studies examining the rs12221497 (*LXRα* −115G>A) polymorphism in relation to blood lipid and lipoprotein traits.

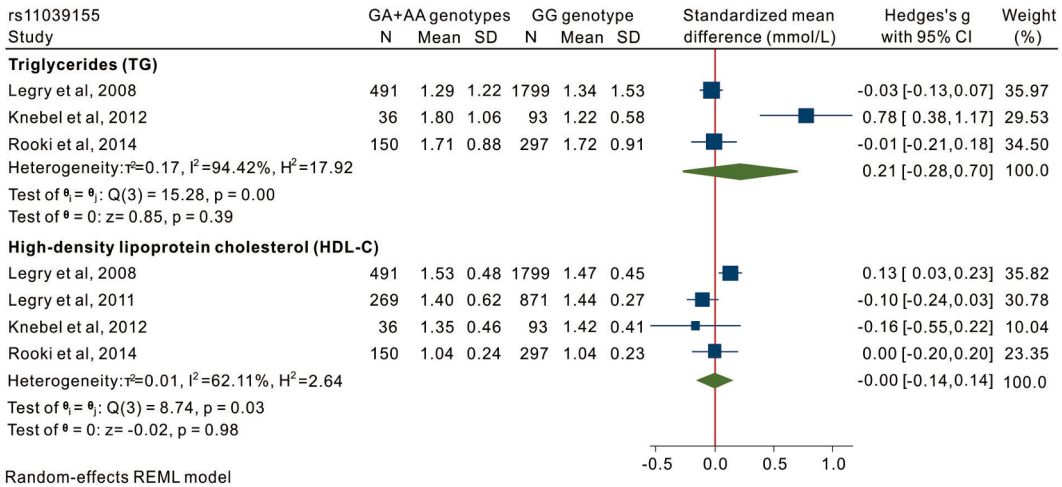

Fig. 3. Forest plot of studies examining rs11039155 (*LXRα* −6G>A) polymorphism in relation to blood lipid and lipoprotein traits.

LXRα$^{-/-}$ over wild-type or *LXRβ*$^{-/-}$ mice [70]. This finding indicated that the absence of *LXRα* could impede the cholesterol elimination and the presence of *LXRβ* could not offset the loss of function in *LXRα*$^{-/-}$ mice. Meanwhile, *LXRα* and *LXRβ* could also demonstrate similar protective roles in preventing the atherosclerosis progression. Combined deficiency in *LXRα/β*$^{-/-}$ mice compared to *LXRα*$^{-/-}$ or *LXRβ*$^{-/-}$ mice alone was associated with impaired TG metabolism, increased LDL-C, and reduced HDL-C levels as well as accumulated foam cells in the arterial wall [71]. Those studies suggested that the physiological roles of *LXRα* and *LXRβ* may be overlapping and not distinct. Thus, investigation on polymorphisms of both LXR isoforms and perhaps interactions between polymorphisms may enhance understanding of the susceptibility to the blood lipid profile.

The strengths of this review include that we used a quantitative

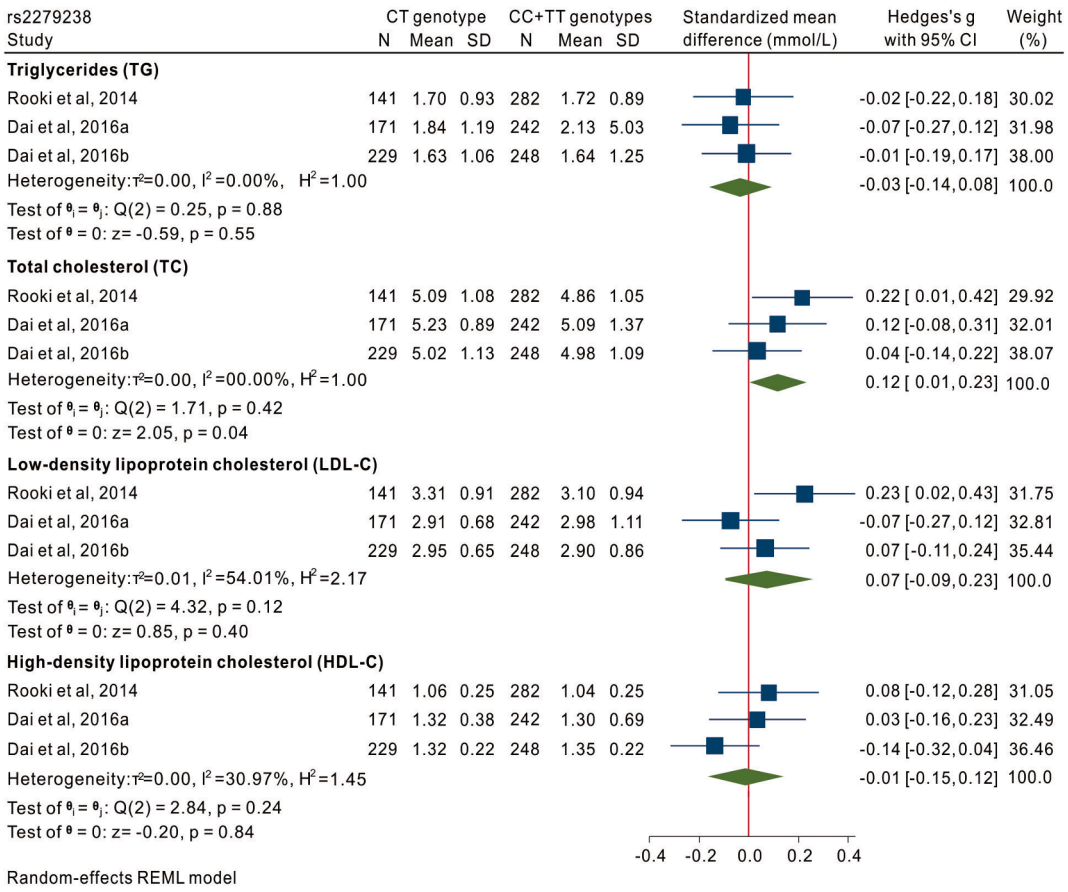

Fig. 4. Forest plot of studies examining rs2279238 (*LXRα* 297C>T) polymorphism in relation to blood lipid and lipoprotein traits.

method to summarize results of the available studies on the three most studied SNPs (rs11039155, rs12221497 and rs2279238) of *LXRα*. To the best of our knowledge, this systematic review and meta-analysis is the first study summarizing associations between LXR polymorphisms and blood lipid/lipoprotein traits comprehensively. These results could shed lights on the susceptibility of *LXRs* to contribute to lipid-related diseases such as atherosclerosis, cardiovascular disorders, and may provide evidence for potential therapeutic targets against disturbed lipid metabolism.

Nonetheless, several limitations should be noted. First, the number of studies retrieved for each SNP of *LXRs* was small. These small numbers of related articles limited the ability to do quantitative synthesis (e.g., meta-analysis) for all SNPs. As each meta-analysis conducted for some SNPs in this review only pooled a smaller number of studies, there is a possibility that publication bias may exist, particularly because some non-significant associations are likely not to be reported. Second, the comparability might be attenuated by varying sociodemographic characteristics such as ethnicity and sex across the studies included. Blood lipid levels may vary by age and sex; for example, older age and male sex are more likely associated with a less favourable lipid profile (increased TG, TC, or LDL-C, and decreased HDL-C) [4]. The methodology used in the studies differed from each other; for example, some studies specified their participants were free of taking lipid-lowering medications, while others did not mention this point. These differences may explain the observed substantial heterogeneity in meta-analyses on the rs11039155 (*LXRα* −6G>A) in relation to TG and HDL-C levels, and on the rs12221497 (*LXRα* −115G>A) in relation to TC and LDL-C levels. In addition, the allele frequencies of *LXR* polymorphisms varied across studies with different geographical ancestries; for example, for the *LXRα* SNP rs2279238, the T was the minor allele in Iranians while the C was the minor allele in Chinese, in line with the geographical differences in allele frequencies reported by the dbSNP (https://www.ncbi.nlm.nih.gov/snp/rs2279238). Ethnicity could be a major source of heterogeneity between studies included but we were

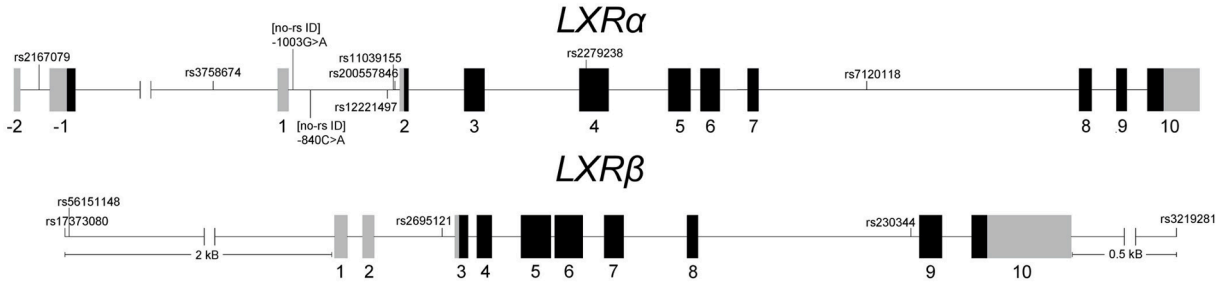

Fig. 5. Loci positions of identified *LXR* SNPs. Black boxes indicate translated (coding) exons; grey boxes indicate untranslated (non-coding) exons; lines connecting exons indicate introns.

unable to investigate stratified associations by these potential confounding factors since there were too few studies available. Therefore, it is recommended to update the review and meta-analyses by subgroups when more studies become available.

5. Conclusion

This study summarized the associations of nine *LXRα* SNPs and five *LXRβ* SNPs with blood lipid and lipoprotein traits. While the evidence body is still incomplete, studies to date show that carriage of the minor allele of two *LXRα* SNPs, rs12221497 and rs2279238, was significantly associated with elevated TG and TC levels, respectively. However, there was no strong evidence for associations between blood lipid and lipoprotein profiles and other SNPs of *LXRα* and *LXRβ*. Additional studies are needed to confirm the mechanisms underpinning the role of *LXR* genetic variants and lipid metabolism.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Acknowledgements

We thank Sally Dalton, MSc (Library Research Support Advisor, University of Leeds) for her help with the development of search strategies. This work was supported a China Scholarship Council (ID: 201806010423) scholarship (HZ), a Leeds International Doctoral Scholarship (PL) and the School of Food Science and Nutrition, University of Leeds (HZ and PL). The sponsors had no role in the design and conduct of the study; screening, data extraction, data analysis and interpretation of the literature synthesis; or preparation, editing, and final approval of this manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.steroids.2022.109057.

References

[1] R.H. Unger, G.O. Clark, P.E. Scherer, L. Orci, Lipid homeostasis, lipotoxicity and the metabolic syndrome, Biochim. Biophys. Acta (BBA) – Mol. Cell Biol. Lipids 1801 (3) (2010) 209–214.

[2] M.L. Buckley, D.P. Ramji, The influence of dysfunctional signaling and lipid homeostasis in mediating the inflammatory responses during atherosclerosis, Biochim. Biophys. Acta (BBA) – Mol. Cell Biol. Lipids 1852 (7) (2015) 1498–1510.

[3] M.S. Rahman, A.J. Murphy, K.J. Woollard, Effects of dyslipidaemia on monocyte production and function in cardiovascular disease, Nat. Rev. Cardiol. 14 (7) (2017) 387.

[4] R.A. Hegele, Plasma lipoproteins: genetic influences and clinical implications, Nat. Rev. Genet. 10 (2) (2009) 109–121.

[5] S.C. Hunt, S.J. Hasstedt, H. Kuida, B.M. Stults, P.N. Hopkins, R.R. Williams, Genetic heritability and common environmental components of resting and stressed blood pressures, lipids, and body mass index in Utah pedigrees and twins, Am. J. Epidemiol. 129 (3) (1989) 625–638.

[6] C.J. Willer, E.M. Schmidt, S. Sengupta, G.M. Peloso, S. Gustafsson, S. Kanoni, A. Ganna, J. Chen, M.L. Buchkovich, S. Mora, J.S. Beckmann, J.L. Bragg-Gresham, H.-Y. Chang, A. Demirkan, H.M. Den Hertog, R. Do, L.A. Donnelly, G.B. Ehret, T. Esko, M.F. Feitosa, T. Ferreira, K. Fischer, P. Fontanillas, R.M. Fraser, D.F. Freitag, D. Gurdasani, K. Heikkilä, E. Hyppönen, A. Isaacs, A.U. Jackson, Å. Johansson, T. Johnson, M. Kaakinen, J. Kettunen, M.E. Kleber, X. Li, J.a. Luan, L.-P. Lyytikäinen, P.K.E. Magnusson, M. Mangino, E. Mihailov, M.E. Montasser, M. Müller-Nurasyid, I.M. Nolte, J.R. O'Connell, C.D. Palmer, M. Perola, A.-K. Petersen, S. Sanna, R. Saxena, S.K. Service, S. Shah, D. Shungin, C. Sidore, C. Song, R.J. Strawbridge, I. Surakka, T. Tanaka, T.M. Teslovich, G. Thorleifsson, E.G. Van den Herik, B.F. Voight, K.A. Volcik, L.L. Waite, A. Wong, Y. Wu, W. Zhang, D. Absher, G. Asiki, I. Barroso, L.F. Been, J.L. Bolton, L.L. Bonnycastle, P. Brambilla, M.S. Burnett, G. Cesana, M. Dimitriou, A.S.F. Doney, A. Döring, P. Elliott, S.E. Epstein, G.I. Eyjolfsson, B. Gigante, M.O. Goodarzi, H. Grallert, M.L. Gravito, C.J. Groves, G. Hallmans, A.-L. Hartikainen, C. Hayward, D. Hernandez, A.A. Hicks, H. Holm, Y.-J. Hung, T. Illig, M.R. Jones, P. Kaleebu, J.J.P. Kastelein, K.-T. Khaw, E. Kim, N. Klopp, P. Komulainen, M. Kumari, C. Langenberg, T. Lehtimäki, S.-Y. Lin, J. Lindström, R.J.F. Loos, F. Mach, W.L. McArdle, C. Meisinger, B.D. Mitchell, G. Müller, R. Nagaraja, N. Narisu, T.V.M. Nieminen, R.N. Nsubuga, I. Olafsson, K.K. Ong, A. Palotie, T. Papamarkou, C. Pomilla, A. Pouta, D.J. Rader, M.P. Reilly, P.M. Ridker, F. Rivadeneira, I. Rudan, A. Ruokonen, N. Samani, H. Scharnagl, J. Seeley, K. Silander, A. Stancáková, K. Stirrups, A.J. Swift, L. Tiret, A.G. Uitterlinden, L.J. van Pelt, S. Vedantam, N. Wainwright, C. Wijmenga, S.H. Wild, G. Willemsen, T. Wilsgaard, J.F. Wilson, E.H. Young, J.H. Zhao, L.S. Adair, D. Arveiler, T.L. Assimes, S. Bandinelli, F. Bennett, M. Bochud, B.O. Boehm, D.I. Boomsma, I.B. Borecki, S.R. Bornstein, P. Bovet, M. Burnier, H. Campbell, A. Chakravarti, J.C. Chambers, Y.-D. I. Chen, F.S. Collins, R.S. Cooper, J. Danesh, G. Dedoussis, U. de Faire, A.B. Feranil, J. Ferrières, L. Ferrucci, N.B. Freimer, C. Gieger, L.C. Groop, V. Gudnason, U. Gyllensten, A. Hamsten, T.B. Harris, A. Hingorani, J.N. Hirschhorn, A. Hofman, G. K. Hovingh, C.A. Hsiung, S.E. Humphries, S.C. Hunt, K. Hveem, C. Iribarren, M.-R. Järvelin, A. Jula, M. Kähönen, J. Kaprio, A. Kesäniemi, M. Kivimaki, J.S. Kooner, P. J. Koudstaal, R.M. Krauss, D. Kuh, J. Kuusisto, K.O. Kyvik, M. Laakso, T.A. Lakka, L. Lind, C.M. Lindgren, N.G. Martin, W. März, M.I. McCarthy, C.A. McKenzie, P. Meneton, A. Metspalu, L. Moilanen, A.D. Morris, P.B. Munroe, I. Njølstad, N.L. Pedersen, C. Power, P.P. Pramstaller, J.F. Price, B.M. Psaty, T. Quertermous, R. Rauramaa, D. Saleheen, V. Salomaa, D.K. Sanghera, J. Saramies, P.E.H. Schwarz, W.H.H. Sheu, A.R. Shuldiner, A. Siegbahn, T.D. Spector, K. Stefansson, D.P. Strachan, B.O. Tayo, E. Tremoli, J. Tuomilehto, M. Uusitupa, C.M. van Duijn, P. Vollenweider, L. Wallentin, N.J. Wareham, J.B. Whitfield, B.H.R. Wolffenbuttel, J. M. Ordovas, E. Boerwinkle, C.N.A. Palmer, U. Thorsteinsdottir, D.I. Chasman, J.I. Rotter, P.W. Franks, S. Ripatti, L.A. Cupples, M.S. Sandhu, S.S. Rich, M. Boehnke, P. Deloukas, S. Kathiresan, K.L. Mohlke, E. Ingelsson, G.R. Abecasis, C. Global Lipids Genetics, Discovery and refinement of loci associated with lipid levels, Nat. Genetics 45(11) (2013) 1274–1283.

[7] T.M. Teslovich, K. Musunuru, A.V. Smith, A.C. Edmondson, I.M. Stylianou, M. Koseki, J.P. Pirruccello, S. Ripatti, D.I. Chasman, C.J. Willer, C.T. Johansen, S.W. Fouchier, A. Isaacs, G.M. Peloso, M. Barbalic, S.L. Ricketts, J.C. Bis, Y.S. Aulchenko, G. Thorleifsson, M.F. Feitosa, J. Chambers, M. Orho-Melander, O. Melander, T. Johnson, X. Li, X. Guo, M. Li, Y. Shin Cho, M. Jin Go, Y. Jin Kim, J.-Y. Lee, T. Park, K. Kim, X. Sim, R. Twee-Hee Ong, D.C. Croteau-Chonka, L.A. Lange, J. D. Smith, K. Song, J. Hua Zhao, X. Yuan, J.a. Luan, C. Lamina, A. Ziegler, W. Zhang, R.Y.L. Zee, A.F. Wright, J.C.M. Witteman, J.F. Wilson, G. Willemsen, H.E. Wichmann, J.B. Whitfield, D.M. Waterworth, N.J. Wareham, G. Waeber, P. Vollenweider, B.F. Voight, V. Vitart, A.G. Uitterlinden, M. Uda, J. Tuomilehto, J.R. Thompson, T. Tanaka, I. Surakka, H.M. Stringham, T.D. Spector, N. Soranzo, J.H. Smit, J. Sinisalo, K. Silander, E.J.G. Sijbrands, A. Scuteri, J. Scott, D. Schlessinger, S. Sanna, V. Salomaa, J. Saharinen, C. Sabatti, A. Ruokonen, I. Rudan, L.M. Rose, R. Roberts, M. Rieder, B.M. Psaty, P.P. Pramstaller, I. Pichler, M. Perola, B.W.J.H. Penninx, N.L. Pedersen, C. Pattaro, A.N. Parker, G. Pare, B.A. Oostra, C.J. O'Donnell, M.S. Nieminen, D.A. Nickerson, G.W. Montgomery, T. Meitinger, R. McPherson, M.I. McCarthy, W. McArdle, D. Masson, N.G. Martin, F. Marroni, M. Mangino, P.K.E. Magnusson, G. Lucas, R. Luben, R.J.F. Loos, M.-L. Lokki, G. Lettre, C. Langenberg, L.J. Launer, E.G. Lakatta, R. Laaksonen, K.O. Kyvik, F. Kronenberg, I.R. König, K.-T. Khaw, J. Kaprio, L.M. Kaplan, Å. Johansson, M.-R. Jarvelin, A. Cecile J. W. Janssens, E. Ingelsson, W. Igl, G. Kees Hovingh, J.-J. Hottenga, A. Hofman, A.A. Hicks, C. Hengstenberg, I.M. Heid, C. Hayward, A.S. Havulinna, N.D. Hastie, T.B. Harris, T. Haritunians, A.S. Hall, U. Gyllensten, C. Guiducci, L.C. Groop, E. Gonzalez, C. Gieger, N.B. Freimer, L. Ferrucci, J. Erdmann, P. Elliott, K.G. Ejebe, A. Döring, A.F. Dominiczak, S. Demissie, P. Deloukas, E.J.C. de Geus, U. de Faire, G. Crawford, F.S. Collins, Y.-d.I. Chen, M.J. Caulfield, H. Campbell, N.P. Burtt, L.L. Bonnycastle, D.I. Boomsma, S.M. Boekholdt, R.N. Bergman, I. Barroso, S. Bandinelli, C.M. Ballantyne, T.L. Assimes, T. Quertermous, D. Altshuler, M. Seielstad, T.Y. Wong, E.S. Tai, A.B. Feranil, C.W. Kuzawa, L.S. Adair, H.A. Taylor Jr, I.B. Borecki, S.B. Gabriel, J.G. Wilson, H. Holm, U. Thorsteinsdottir, V. Gudnason, R.M. Krauss, K.L. Mohlke, J.M. Ordovas, P.B. Munroe, J.S. Kooner, A.R. Tall, R.A. Hegele, J.J.P. Kastelein, E.E. Schadt, J.I. Rotter, E. Boerwinkle, D.P. Strachan, V. Mooser, K. Stefansson, M.P. Reilly, N.J. Samani, H. Schunkert, L.A. Cupples, M.S. Sandhu, P.M. Ridker, D.J. Rader, C.M. van Duijn, L. Peltonen, G.R. Abecasis, M. Boehnke, S. Kathiresan, Biological, clinical and population relevance of 95 loci for blood lipids, Nature 466(7307) (2010) 707–713.

[8] B.A. Janowski, M.J. Grogan, S.A. Jones, G.B. Wisely, S.A. Kliewer, E.J. Corey, D. J. Mangelsdorf, Structural requirements of ligands for the oxysterol liver X receptors LXRalpha and LXRbeta, Proc. Natl. Acad. Sci. U.S.A. 96 (1) (1999) 266–271.

[9] P. Tontonoz, D.J. Mangelsdorf, Liver X receptor signaling pathways in cardiovascular disease, Mol. Endocrinol. 17 (6) (2003) 985–993.

[10] R.R. Singaraja, M. Van Eck, N. Bissada, F. Zimetti, H.L. Collins, R.B. Hildebrand, A. Hayden, L.R. Brunham, M.H. Kang, J.-C. Fruchart, Both hepatic and extrahepatic ABCA1 have discrete and essential functions in the maintenance of plasma high-density lipoprotein cholesterol levels in vivo, Circulation 114 (12) (2006) 1301–1309.

[11] X. Wang, H.L. Collins, M. Ranalletta, I.V. Fuki, J.T. Billheimer, G.H. Rothblat, A. R. Tall, D.J. Rader, Macrophage ABCA1 and ABCG1, but not SR-BI, promote macrophage reverse cholesterol transport in vivo, J. Clin. Investig. 117 (8) (2007) 2216–2224.

[12] L. Yvan-Charvet, M. Ranalletta, N. Wang, S. Han, N. Terasaka, R. Li, C. Welch, A. R. Tall, Combined deficiency of ABCA1 and ABCG1 promotes foam cell

accumulation and accelerates atherosclerosis in mice, J. Clin. Investig. 117 (12) (2007) 3900–3908.
[13] C.-Y. Lin, H. Duan, T. Mazzone, Apolipoprotein E-dependent cholesterol efflux from macrophages: kinetic study and divergent mechanisms for endogenous versus exogenous apolipoprotein E, J. Lipid Res. 40 (9) (1999) 1618–1626.
[14] I. Zanotti, M. Pedrelli, F. Potì, G. Stomeo, M. Gomaraschi, L. Calabresi, F. Bernini, Macrophage, but not systemic, apolipoprotein E is necessary for macrophage reverse cholesterol transport in vivo, Arterioscler. Thromb. Vasc. Biol. 31 (1) (2011) 74–80.
[15] L. Yu, J. York, K. Von Bergmann, D. Lutjohann, J.C. Cohen, H.H. Hobbs, Stimulation of cholesterol excretion by the liver X receptor agonist requires ATP-binding cassette transporters G5 and G8, J. Biol. Chem. 278 (18) (2003) 15565–15570.
[16] X.H. Yu, K. Qian, N. Jiang, X.L. Zheng, F.S. Cayabyab, C.K. Tang, ABCG5/ABCG8 in cholesterol excretion and atherosclerosis, Clin. Chim. Acta 428 (2014) 82–88.
[17] S.S. Back, J. Kim, D. Choi, E.S. Lee, S.Y. Choi, K. Han, Cooperative transcriptional activation of ATP-binding cassette sterol transporters ABCG5 and ABCG8 genes by nuclear receptors including Liver-X-Receptor, BMB Rep 46 (6) (2013) 322–327.
[18] Y. Liu, Z. Wei, X. Ma, X. Yang, Y. Chen, L. Sun, C. Ma, Q.R. Miao, D.P. Hajjar, J. Han, Y. Duan, 25-Hydroxycholesterol activates the expression of cholesterol 25-hydroxylase in an LXR-dependent mechanism, J. Lipid Res. 59 (3) (2018) 439–451.
[19] D.J. Peet, S.D. Turley, W. Ma, B.A. Janowski, J.-M.-A. Lobaccaro, R.E. Hammer, D. J. Mangelsdorf, Cholesterol and bile acid metabolism are impaired in mice lacking the nuclear oxysterol receptor LXRα, Cell 93 (5) (1998) 693–704.
[20] T. Yoshikawa, H. Shimano, M. Amemiya-Kudo, N. Yahagi, A.H. Hasty, T. Matsuzaka, H. Okazaki, Y. Tamura, Y. Iizuka, K. Ohashi, Identification of liver X receptor-retinoid X receptor as an activator of the sterol regulatory element-binding protein 1c gene promoter, Mol. Cell. Biol. 21 (9) (2001) 2991–3000.
[21] J.J. Repa, D.J. Mangelsdorf, The liver X receptor gene team: potential new players in atherosclerosis, Nat. Med. 8 (11) (2002) 1243–1248.
[22] P. Lianto, S.A. Hutchinson, J.B. Moore, T.A. Hughes, J.L. Thorne, Characterization and prognostic value of LXR splice variants in triple-negative breast cancer, iScience 24(10) (2021) 103212.
[23] S.A. Hutchinson, A. Websdale, G. Cioccoloni, H. Roberg-Larsen, P. Lianto, B. Kim, A. Rose, C. Soteriou, A. Pramanik, L.M. Wastall, B.J. Williams, M.A. Henn, J. J. Chen, L. Ma, J.B. Moore, E. Nelson, T.A. Hughes, J.L. Thorne, Liver x receptor alpha drives chemoresistance in response to side-chain hydroxycholesterols in triple negative breast cancer, Oncogene 40 (16) (2021) 2872–2883.
[24] S.A. Hutchinson, P. Lianto, H. Roberg-Larsen, S. Battaglia, T.A. Hughes, J. L. Thorne, ER-negative breast cancer is highly responsive to cholesterol metabolite signalling, Nutrients 11 (11) (2019).
[25] N. Becares, I. Pineda-Torra, Identification of nuclear receptor targets by chromatin immunoprecipitation in fatty liver, Methods Mol. Biol. 2019 (1951) 179–188.
[26] N. Becares, M.C. Gage, M. Voisin, E. Shrestha, L. Martin-Gutierrez, N. Liang, R. Louie, B. Pourcet, O.M. Pello, T.V. Luong, S. Goni, C. Pichardo-Almarza, H. Roberg-Larsen, V. Diaz-Zuccarini, K.R. Steffensen, A. O'Brien, M.J. Garabedian, K. Rombouts, E. Treuter, I. Pineda-Torra, Impaired LXRalpha phosphorylation attenuates progression of fatty liver disease, Cell Rep. 26(4) (2019) 984–995 e6.
[27] B.A. Laffitte, S.B. Joseph, R. Walczak, L. Pei, D.C. Wilpitz, J.L. Collins, P. Tontonoz, Autoregulation of the human liver X receptor α promoter, Mol. Cell. Biol. 21 (22) (2001) 7558–7568.
[28] K.D. Whitney, M.A. Watson, B. Goodwin, C.M. Galardi, J.M. Maglich, J.G. Wilson, T.M. Willson, J.L. Collins, S.A. Kliewer, Liver X receptor (LXR) regulation of the LXRα gene in human macrophages, J. Biol. Chem. 276 (47) (2001) 43509–43515.
[29] Y. Li, C. Bolten, B.G. Bhat, J. Woodring-Dietz, S. Li, S.K. Prayaga, C. Xia, D.S. Lala, Induction of human liver X receptor α gene expression via an autoregulatory loop mechanism, Mol. Endocrinol. 16 (3) (2002) 506–514.
[30] I.D. Ignatova, J. Angdisen, E. Moran, I.G. Schulman, Differential regulation of gene expression by LXRs in response to macrophage cholesterol loading, Mol. Endocrinol. 27 (7) (2013) 1036–1047.
[31] T. Wang, Y. Zhao, Z. You, X. Li, M. Xiong, H. Li, N. Yan, Endoplasmic reticulum stress affects cholesterol homeostasis by inhibiting LXRα expression in hepatocytes and macrophages, Nutrients 12 (10) (2020).
[32] M. Hirakata, R. Tozawa, Y. Imura, Y. Sugiyama, Comparison of the effects of pioglitazone and rosiglitazone on macrophage foam cell formation, Biochem. Biophys. Res. Commun. 323 (3) (2004) 782–788.
[33] J. Robitaille, A. Houde, S. Lemieux, D. Gaudet, L. Pérusse, M.-C. Vohl, The lipoprotein/lipid profile is modulated by a gene–diet interaction effect between polymorphisms in the liver X receptor-α and dietary cholesterol intake in French-Canadians, Br. J. Nutr. 97 (1) (2007) 11–18.
[34] C. Sabatti, S.K. Service, A.-L. Hartikainen, A. Pouta, S. Ripatti, J. Brodsky, C. G. Jones, N.A. Zaitlen, T. Varilo, M. Kaakinen, Genome-wide association analysis of metabolic traits in a birth cohort from a founder population, Nat. Genet. 41 (1) (2009) 35.
[35] K. Solaas, V. Legry, K. Retterstol, P.R. Berg, K.B. Holven, J. Ferrières, P. Amouyel, S. Lien, J. Romeo, J. Valtueña, Suggestive evidence of associations between liver X receptor β polymorphisms with type 2 diabetes mellitus and obesity in three cohort studies: HUNT2 (Norway), MONICA (France) and HELENA (Europe), BMC Med. Genet. 11 (1) (2010) 1–11.
[36] Liver X receptor polymorphisms and serum lipids: a systematic review and meta-analysis, PROSPERO 2021 CRD42021246158. https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021246158.
[37] Quality assessment tool for observational cohort and cross-sectional studies, 2014. https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools. (Accessed May 1 2021).
[38] Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0, 2011. https://handbook-5-1.cochrane.org/chapter_7/7_7_3_8_combining_groups.htm. (Accessed May 1 2021).
[39] Screening and Treatment of Subclinical Hypothyroidism or Hyperthyroidism, 2011. https://www.ncbi.nlm.nih.gov/books/NBK83505/. (Accessed May 1 2021).
[40] V. Legry, D. Cottel, J. Ferrières, G. Chinetti, T. Deroide, B. Staels, P. Amouyel, A. Meirhaeghe, Association between liver X receptor alpha gene polymorphisms and risk of metabolic syndrome in French populations, Int J. Obesity 32 (3) (2005) 421–428.
[41] V. Legry, S. Bokor, L. Beghin, M. Galfo, M. Gonzalez-Gross, D. Molnar, L. A. Moreno, P. Amouyel, J. Dallongeville, A. Meirhaeghe, Associations between common genetic polymorphisms in the liver X receptor alpha and its target genes with the serum HDL-cholesterol concentration in adolescents of the HELENA Study, Atherosclerosis 216 (1) (2011) 166–169.
[42] H. Akao, E. Polisecki, K. Kajinami, S. Trompet, M. Robertson, I. Ford, J.W. Jukema, A.J. de Craen, R.G. Westendorp, J. Shepherd, C. Packard, B.M. Buckley, E. J. Schaefer, Genetic variation at the SLCO1B1 gene locus and low density lipoprotein cholesterol lowering response to pravastatin in the elderly, Atherosclerosis 220 (2) (2012) 413–417.
[43] B. Knebel, O.E. Janssen, S. Hahn, S. Jacob, U. Nitzgen, J. Haas, D. Muller-Wieland, J. Kotzka, Genetic variations in SREBP-1 and LXRα are not directly associated to PCOS but contribute to the physiological specifics of the syndrome, Mol. Biol. Rep. 39 (6) (2012) 6835–6842.
[44] Z. Zhang, L. Tao, Z. Chen, D. Zhou, M. Kan, D. Zhang, C. Li, L. He, Y. Liu, Association of genetic loci with blood lipids in the Chinese population, PLoS ONE 6 (11) (2011), e27305.
[45] J.Y. Jeon, J.Y. Nam, H.A. Kim, Y.B. Park, S.C. Bae, C.H. Suh, Liver X receptors alpha gene (NR1H3) promoter polymorphisms are associated with systemic lupus erythematosus in Koreans, Arthritis Res. Therapy 16 (3) (2014) R112.
[46] H. Rooki, M. Ghayour-Mobarhan, M.A. Pourhosseingholi, M.R. Azarpazhooh, M. Ebrahimi, G. Ferns, M.R. Zali, Association of LXRα polymorphisms with obesity and obesity-related phenotypes in an Iranian population, Ann. Hum. Biol. 41 (3) (2014) 214–219.
[47] Y.F. Zhou, J. Zhang, Z.X. Li, J.L. Miao, Q.X. Yin, J.J. Li, X.Y. Zhang, Y.Y. Li, H. L. Luo, Association of liver X receptor α (LXRα) gene polymorphism and coronary heart disease, serum lipids and glucose levels, Lipids Health Dis. 13 (2014) 34.
[48] J.S. Yang, J.J. Hao, S.S. Wang, Z.F. Zhu, Q. Fang, H. Bao, H.P. Zhang, Association between the LXRα polymorphism and stroke in a Chinese population, Genetics Mol. Res.: GMR 14 (1) (2015) 1757–1762.
[49] Y. Dai, Z. Jiang, D. Guo, S. Lin, W. Guo, L. Zhu, X. Zhang, B. Zhang, Gene polymorphism of LXRα is associated with the pathogenesis of ischemic stroke in Han population in northern China, Int. J. Clin. Exp. Med. 9 (6) (2016) 11958–11965.
[50] D.F. Wu, R.X. Yin, X.L. Cao, F. Huang, J.Z. Wu, W.X. Chen, MADD-FOLH1 polymorphisms and their haplotypes with serum lipid levels and the risk of coronary heart disease and ischemic stroke in a chinese han population, Nutrients 8 (4) (2016) 208.
[51] H. Mehrad-Majd, M. Ghayour-Mobarhan, M.R. Zali, Genetic association of liver X receptor beta rs2695121 polymorphism with obesity-related traits in a northeastern Iranian population, Electronic Phys. 10 (1) (2018) 6249–6254.
[52] R. Gupta, K. Ejebe, J. Butler, G. Lettre, H. Lyon, C. Guiducci, R. Wilks, F. Bennett, T. Forrester, B. Tayo, K. Musunuru, J. Hirschhorn, S. Kathiresan, R.S. Cooper, C. A. McKenzie, Association of common DNA sequence variants at 33 genetic loci with blood lipids in individuals of African ancestry from Jamaica, Hum. Genet. 128 (5) (2010) 557–561.
[53] A. Helgadottir, S. Gretarsdottir, G. Thorleifsson, E. Hjartarson, A. Sigurdsson, A. Magnusdottir, A. Jonasdottir, H. Kristjansson, P. Sulem, A. Oddsson, G. Sveinbjornsson, V. Steinthorsdottir, T. Rafnar, G. Masson, I. Jonsdottir, I. Olafsson, G.I. Eyjolfsson, O. Sigurdardottir, M.S. Daneshpour, D. Khalili, F. Azizi, D.W. Swinkels, L. Kiemeney, A.A. Quyyumi, A.I. Levey, R.S. Patel, S.S. Hayek, I. J. Gudmundsdottir, G. Thorgeirsson, U. Thorsteinsdottir, D.F. Gudbjartsson, H. Holm, K. Stefansson, Variants with large effects on blood lipids and the role of cholesterol and triglycerides in coronary disease, Nat. Genet. 48 (6) (2016) 634–639.
[54] J. Stamler, M.L. Daviglus, D.B. Garside, A.R. Dyer, P. Greenland, J.D. Neaton, Relationship of baseline serum cholesterol levels in 3 large cohorts of younger men to long-term coronary, cardiovascular, and all-cause mortality and to longevity, JAMA 284 (3) (2000) 311–318.
[55] B.G. Nordestgaard, M. Benn, P. Schnohr, A. Tybjærg-Hansen, Nonfasting triglycerides and risk of myocardial infarction, ischemic heart disease, and death in men and women, JAMA 298 (3) (2007) 299–308.
[56] M.A. Austin, B. McKnight, K.L. Edwards, C.M. Bradley, M.J. McNeely, B.M. Psaty, J.D. Brunzell, A.G. Motulsky, Cardiovascular disease mortality in familial forms of hypertriglyceridemia: a 20-year prospective study, Circulation 101 (24) (2000) 2777–2782.
[57] A.D. Attie, J.P. Kastelein, M.R. Hayden, Pivotal role of ABCA1 in reverse cholesterol transport influencing HDL levels and susceptibility to atherosclerosis, J. Lipid Res. 42 (11) (2001) 1717–1726.
[58] C. Zhao, K. Dahlman-Wright, Liver X receptor in cholesterol metabolism, J. Endocrinol. 204 (3) (2010) 233–240.
[59] S.M. Ulven, K.T. Dalen, J.-Å. Gustafsson, H.I. Nebb, LXR is crucial in lipid metabolism, Prostaglandins Leukot. Essent. Fatty Acids 73 (1) (2005) 59–63.
[60] M.H. Oosterveer, A. Grefhorst, A.K. Groen, F. Kuipers, The liver X receptor: control of cellular lipid homeostasis and beyond: Implications for drug design, Prog. Lipid Res. 49 (4) (2010) 343–352.

[61] D. Baralle, M. Baralle, Splicing in action: assessing disease causing sequence changes, J. Med. Genet. 42 (10) (2005) 737–748.
[62] A. Corvelo, M. Hallegger, C.W. Smith, E. Eyras, Genome-wide association between branch point properties and alternative splicing, PLoS Comput. Biol. 6 (11) (2010), e1001016.
[63] P. Kim, M. Yang, K. Yiya, W. Zhao, X. Zhou, ExonSkipDB: functional annotation of exon skipping event in human, Nucleic Acids Res. 48 (D1) (2020) D896–D907.
[64] C. Kimchi-Sarfaty, J.M. Oh, I.-W. Kim, Z.E. Sauna, A.M. Calcagno, S.V. Ambudkar, M.M. Gottesman, A" silent" polymorphism in the MDR1 gene changes substrate specificity, Science 315 (5811) (2007) 525–528.
[65] A. Pawlik, M. Baskiewicz-Masiuk, B. Machalinski, M. Kurzawski, B. Gawronska-Szklarz, Involvement of C3435T and G2677T multidrug resistance gene polymorphisms in release of cytokines from peripheral blood mononuclear cells treated with methotrexate and dexamethasone, Eur. J. Pharmacol. 528 (1–3) (2005) 27–36.
[66] O. Goreva, A.Y. Grishanova, O. Mukhin, N. Domnikova, V. Lyakhovich, Possible prediction of the efficiency of chemotherapy in patients with lymphoproliferative diseases based on MDR1 gene G2677T and C3435T polymorphisms, Bull. Exp. Biol. Med. 136 (2) (2003) 183–185.
[67] D. Zhu, H. Taguchi-Nakamura, M. Goto, T. Odawara, T. Nakamura, H. Yamada, H. Kotaki, W. Sugiura, A. Iwamoto, Y. Kitamura, Influence of single-nucleotide polymorphisms in the multidrug resistance-1 gene on the cellular export of nelfinavir and its clinical implication for highly active antiretroviral therapy, Antivir Ther 9 (6) (2004) 929–935.
[68] S.M. Brotman, C.K. Raulerson, S. Vadlamudi, K.W. Currin, Q. Shen, V.A. Parsons, A.K. Iyengar, T.S. Roman, T.S. Furey, J. Kuusisto, Subcutaneous adipose tissue splice quantitative trait loci reveal differences in isoform usage associated with cardiometabolic traits, Am. J. Hum. Gen. 109 (1) (2022) 66–80.
[69] E.M. Quinet, D.A. Savio, A.R. Halpern, L. Chen, G.U. Schuster, J.A. Gustafsson, M. D. Basso, P. Nambi, Liver X receptor (LXR)-beta regulation in LXRalpha-deficient mice: implications for therapeutic targeting, Mol. Pharmacol. 70 (4) (2006) 1340–1349.
[70] M. Korach-André, P. Parini, L. Larsson, A. Arner, K.R. Steffensen, J.A. Gustafsson, Separate and overlapping metabolic functions of LXRalpha and LXRbeta in C57Bl/6 female mice, Am. J. Physiol. Endocrinol. Metab. 298 (2) (2010) E167–E178.
[71] G.U. Schuster, P. Parini, L. Wang, S. Alberti, K.R. Steffensen, G.K. Hansson, B. Angelin, J.A. Gustafsson, Accumulation of foam cells in liver X receptor-deficient mice, Circulation 106 (9) (2002) 1147–1153.