



# Sex Differences in Lipid Metabolism: Implications for Systemic Lupus Erythematosus and Cardiovascular Disease Risk

George A. Robinson<sup>1,2\*</sup>, Ines Pineda-Torra<sup>3†</sup>, Coziana Ciurtin<sup>1,2†</sup> and Elizabeth C. Jury<sup>1\*†</sup>

<sup>1</sup> Division of Medicine, Centre for Rheumatology Research, University College London, London, United Kingdom, <sup>2</sup> Division of Medicine, Centre for Adolescent Rheumatology Versus Arthritis, University College London, London, United Kingdom, <sup>3</sup> Division of Medicine, Centre for Cardiometabolic and Vascular Science, University College London, London, United Kingdom

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### \*Correspondence:

Elizabeth C. Jury  
e.jury@ucl.ac.uk  
Coziana Ciurtin  
c.ciurtin@ucl.ac.uk  
Ines Pineda-Torra  
i.torra@ucl.ac.uk  
George A. Robinson  
george.robinson.15@ucl.ac.uk

<sup>†</sup>These authors share senior  
authorship

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It is known that healthy women during childbearing years have a lower risk of cardiovascular disease (CVD) and coronary heart disease compared to age matched men. Various traditional risk factors have been shown to confer differential CVD susceptibilities by sex. Atherosclerosis is a major cause of CVD and mortality and sex differences in CVD risk could be due to reduced atherogenic low and very low-density lipoproteins (LDL and VLDL) and increased atheroprotective high density lipoproteins (HDLs) in women. In contrast, patients with systemic lupus erythematosus (SLE), a chronic inflammatory disease that predominately affects women, have an increased atherosclerotic and CVD risk. This increased CVD risk is largely associated with dyslipidaemia, the imbalance of atherogenic and atheroprotective lipoproteins, a conventional CVD risk factor. In many women with SLE, dyslipidaemia is characterised by elevated LDL and reduced HDL, eradicating the sex-specific CVD protection observed in healthy women compared to men. This review will explore this paradox, reporting what is known regarding sex differences in lipid metabolism and CVD risk in the healthy population and transgender individuals undergoing cross-sex hormone therapy, and provide evidence for how these differences may be compromised in an autoimmune inflammatory disease setting. This could lead to better understanding of mechanistic changes in lipid metabolism driving the increased CVD risk by sex and in autoimmunity and highlight potential therapeutic targets to help reduce this risk.

**Keywords:** sex and gender, lipoproteins, autoimmunity, atherosclerosis, SLE

## INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of mortality worldwide (1, 2). The most common pathogenic process leading to CVD is atherosclerosis, the build-up of lipids and inflammation in the walls of major arteries (atherosclerotic plaque), leading to the narrowing of the interior lumen of the vessel, plaque rupture, thrombosis, and subsequent myocardial infarction or stroke due to the restricted blood flow to the heart or brain, respectively. Importantly, women of a childbearing age

have around half the CVD risk compared to age-matched men, and almost a 10-year delay to first myocardial infarction event (3–5). Whilst sex differences in CVD risk are narrowed in older age groups, the CVD-associated death rate among women never exceeds that of men (6, 7). Traditional risk factors of atherosclerosis that could be modified by sex hormones, such as lipid metabolism, are believed to explain these differential outcomes between men and women (8); however, there is a clear need to investigate these sexually dimorphic mechanisms of CVD to improve outcomes for both men and women.

Alternatively, women represent around 80% of all individuals with autoimmune disease, however, patients with autoimmunity have an increased risk of developing CVD through atherosclerosis (9, 10). With this respect, women between the ages of 35–44 with systemic lupus erythematosus (SLE), a chronic inflammatory disease with a 90% female predominance, have a 50 times increased risk of developing coronary artery disease compared to healthy individuals (11). This shows that the impact of SLE dramatically reduces the female CVD protection seen in healthy individuals. Interplay between traditional risk factors and factors associated with autoimmunity, as well as overlapping factors, such as dyslipidaemia (disrupted lipid metabolism) and inflammation, contribute to accelerated atherosclerosis in SLE patients (12–14).

This review aims to discuss differences in lipid metabolism between men and women, and why this is altered in autoimmunity leading to reduced CVD protection for women. This will aid understanding of the CVD bias by sex and could help to tailor sex specific therapeutic strategies to improve CVD outcomes for both men and women, including those with autoimmunity.

## SEX DIFFERENCES IN LIPOPROTEIN METABOLISM: IMPLICATIONS FOR CARDIOVASCULAR RISK

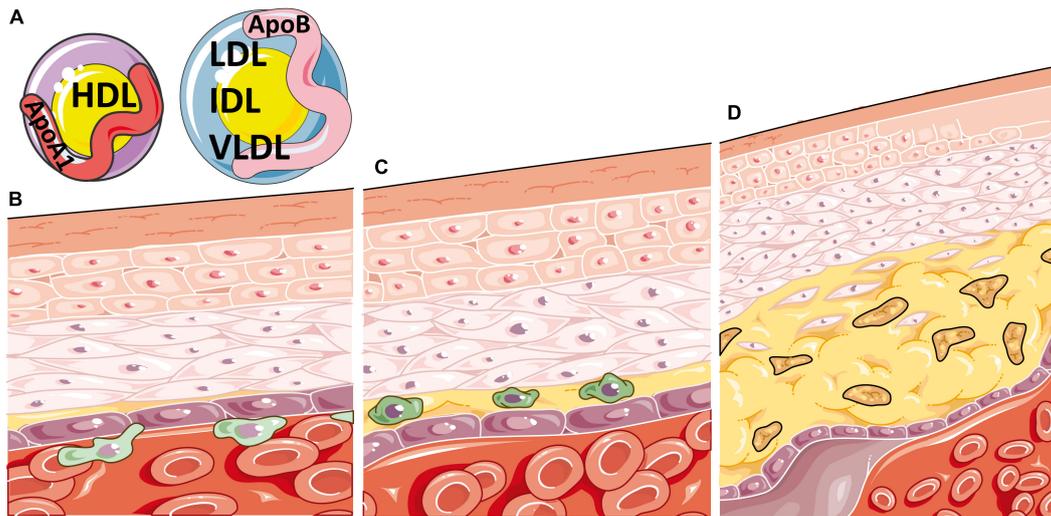
The build-up of lipids in atherosclerotic plaques is largely due to lipoproteins, biochemical assemblies of lipids and apolipoproteins that are structured to enable hydrophobic lipids to transport freely around the blood. Lipoprotein subtypes are defined by their size, density, lipid content and specific apolipoprotein (Apo) expressed on their surface, which together determine their pathogenic contribution to atherosclerosis. Lipoproteins of lower density, including very low, low, and intermediate density lipoproteins (VLDL, LDL, IDL), predominately express ApoB on their surface and promote lipid uptake by inflammatory cells in atherosclerotic plaques following their oxidation. Alternatively, high density lipoproteins (HDLs) express ApoA1 on their surface and play a role in lipid efflux, inferring a role that is typically atheroprotective (15) (**Figure 1**). Emerging research supports that different sizes of lipoprotein sub-classes can infer differential effects on CVD risk (16), highlighting the need for more detailed analytical methods for serum lipid profiling, such as nuclear magnetic resonance (NMR) spectroscopy, to expand the standard lipid fraction routinely measured in clinical practice

(LDL-cholesterol, HDL-cholesterol, total-cholesterol, and total triglycerides, TGs).

It is well established that prior to menopause, the lipoprotein profile of healthy women is more atheroprotective compared to age matched men (17). The Framingham Offspring Study is one of the largest studies to investigate sex differences in CVD risk factors, where subsequent interrogation of this data has identified an increase in smaller and more dense LDL particles in men compared to women (18, 19), a subset that has been previously associated with sex differences in CVD incidence (20–22). Since these observations, NMR spectroscopy analysis of serum from 1574 men and 1692 women (mean age of 52 years) from the Framingham Offspring Study confirmed the lower CVD risk lipid profile in women, where women had a twofold higher concentration of large HDL particles compared to men (23). Large-HDL subsets have been shown to confer higher CVD protection (16). Complimentary to previous studies, the difference in HDL particle size between men and women decreased with age in the Framingham Offspring Study cohort. Furthermore, previously established differences in conventional lipid measures, with men having higher concentrations of TGs, LDL-cholesterol and ApoB, but lower HDL-cholesterol and ApoA1, were also confirmed (23). Importantly, VLDL particles have a high content of TGs relative to other lipoproteins classes, and have also been associated with residual CVD risk independent of circulating TGs (24–26), however, this subset has been less well studied due to the focus of clinical lipid profiles on LDL and HDL-cholesterol measures.

Following menopause, women lose a large amount of their protective lipoprotein fractions which is reflected in increased CVD post-menopause. This is believed to be a result of reduced circulating oestradiol, where lower levels have been shown to infer an increased risk of developing metabolic diseases and CVD (27). A study of post-menopausal women, assessing coronary artery calcification (CAC), a measure of established atherosclerosis using electron beam computed tomography, found that small LDL and all VLDL subclasses were significantly associated with a higher extent of CAC (28). However, large HDL particles, but not small, inversely correlated with the extent of CAC, highlighting the protective role of HDL even in older women with lower oestradiol levels. In support, studies have shown that post-menopause, LDL increases in women to the levels of age-matched men, however, HDL remains higher in women compared to men at all ages despite the decrease post-menopause (29–32).

As heart disease is more common in older age groups and age is an independent risk factor for CVD, studies of CVD are more common in adults (33). However, new studies have explored lipoprotein metabolism in younger age groups, particularly surrounding puberty, where hormones have been shown to become extremely relevant for sexual dimorphisms in CVD risk factors. With this respect, Robinson et al. recently explored sex differences in detailed lipoprotein profiles using NMR metabolomics of serum from young, healthy pre- and post-pubertal individuals (34). This study showed that pre-puberty, no differences in lipoproteins exist, however, following the onset of puberty (assessed clinically using standardised Tanner stages),



**FIGURE 1 |** Atherosclerosis is a disease of inflammation and lipids. **(A)** Atherosclerosis is heavily determined by the circulating balance between atheroprotective high density lipoproteins [HDL, expressing apolipoprotein (Apo)A1 on their surface] or atherogenic very low, low and intermediate density lipoproteins (VLDL, LDL and IDL, expressing ApoB on their surface). **(B)** Atherosclerosis initiates when ApoB containing lipoproteins accumulate, become oxidised, and enter the intima region of the blood vessel. This induces endothelial adhesion molecule expression and inflammatory cell recruitment, which migrate through the vessel wall, beginning the process of atherosclerotic plaque formation. **(C)** Oxidised ApoB containing atherogenic lipoproteins are taken up by macrophages in atherosclerotic plaques through scavenger receptors, increasing their cellular lipid burden and resulting in foam cell formation. **(D)** These lipid laden macrophages enlarge the plaque and produce pro-inflammatory cytokines, resulting in further immune recruitment to the plaque, damage to smooth muscle and endothelial cells, necrotic core formation from the growing mass of extracellular lipids and cell debris, narrowing of the artery and eventual thrombosis. This figure was produced using resources from Servier Medical Art, licenced under a Creative Common Attribution 3.0 Generic License. <http://smart.servier.com/>.

young men develop an atherogenic profile, consisting mostly of increased larger VLDL subsets and VLDL lipid content, whilst young women develop an increase in total, medium and larger HDL particles, HDL lipid content and levels of ApoA1. In addition, this study performed detailed serum lipoprotein profiling of a rare cohort of young transgender individuals, which validated the direct association between oestradiol and increased larger HDL and ApoA1 levels in trans-women (young individuals born phenotypically male, who were treated with puberty blockers followed by oestradiol, as gender reaffirming therapy), as well as between testosterone and increased VLDL levels in trans-men (young individuals born phenotypically female, who were treated with puberty blockers followed by testosterone, as gender reaffirming therapy). As supported by these studies of different age groups, this suggests that VLDL versus LDL could be the dominantly increased atherogenic lipoproteins in younger versus older adult men compared to age matched women. Importantly, increased circulating concentrations of LDL and VLDL in plasma have been shown to induce the development of atherosclerosis, independent of other risk factors (35). Finally, this study showed that HDL was increased by oestradiol in a dose dependent and chromosome independent manner in trans-women, suggesting that HDL may be more sensitive to changing hormones levels than atherogenic lipoproteins at this young age. Sex-specific changes in lipoproteins discussed are summarised in **Table 1**.

Together, these studies highlight that sex differences in atherosclerosis susceptibilities could be inferred from a young age by hormones and supports a role of hormones in driving lipoprotein metabolism at both ends of the age scale, as well as

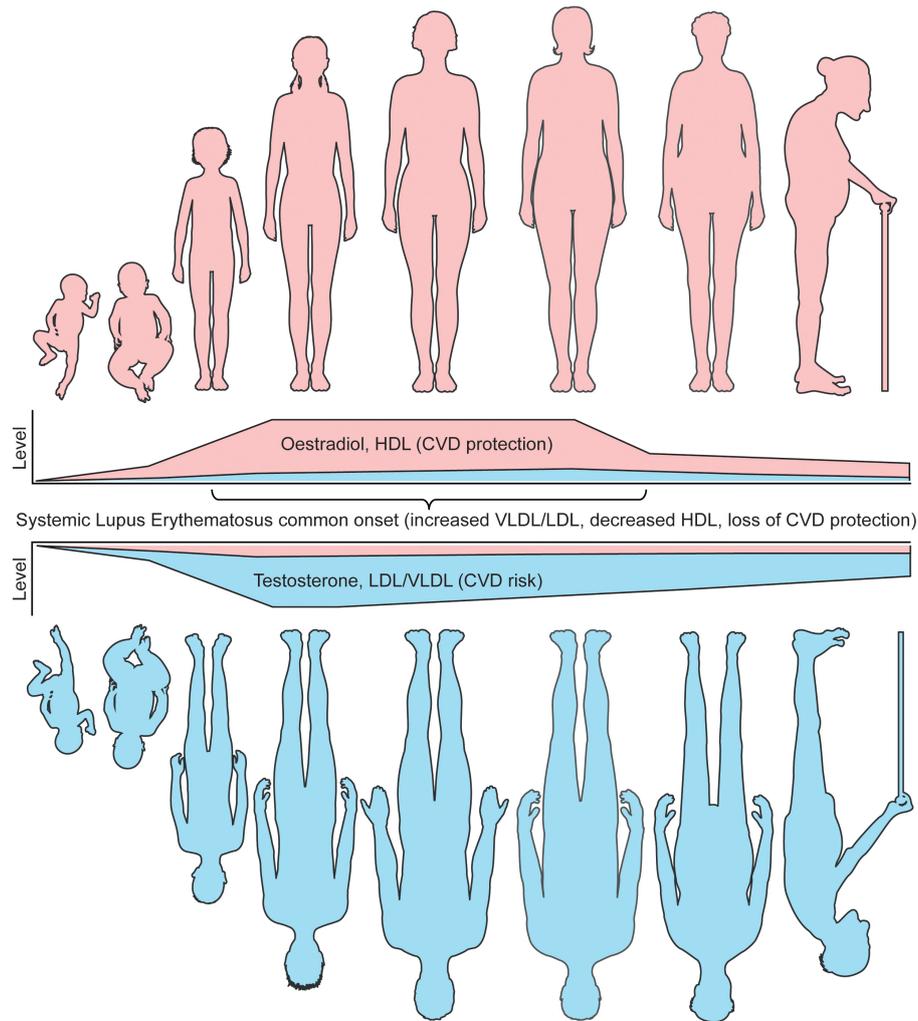
**TABLE 1 |** Sex differences in lipoproteins across pubertal stages.

	Pre-puberty (girls versus boys)	Post-puberty (women versus men)	Post-menopause (women versus age matched men)
ApoB	• No difference (34)	• Increased in men (23)	
VLDL	• No difference (34)	• Increased in men (34)	
LDL	• No difference (34)	• Increased in men (23) • Increased small-LDL in men (18, 19)	• Increased in women (29–31)
ApoA1	• No difference (34)	• Increased in women (23, 34)	
HDL	• No difference (34)	• Increased in women (23, 34) • Twofold higher large-HDL in women (23)	• Lower lipid rich HDL than pre-menopause, but still increased in women (29–32)

the importance of studying lipoproteins and CVD susceptibilities at all ages and genders (**Figure 2**).

## LIPOPROTEIN METABOLISM AND DYSLIPIDAEMIA IN WOMEN WITH SYSTEMIC LUPUS ERYTHEMATOSUS

SLE is a complex and heterogeneous autoimmune disorder characterised by loss of immune cell regulation, chronic inflammation, and multiple organ damage. As well as genetic, environmental, and epigenetic contributions, hormones have



**FIGURE 2 |** Sex differences in lipoproteins and CVD risk coincide with age associated hormone changes. The levels of circulating sex hormones change throughout life. Pre-puberty, research has shown that girls and boys do not have differences in either atherogenic (VLDL/LDL) or atheroprotective (HDL) lipoproteins. Following the onset of puberty, oestradiol increases in young women, which in turn raises the level of circulating HDL, inferring a lower CVD risk compared to young men in healthy individuals. Post-pubertal young men, with increased testosterone and low oestradiol levels, develop a more atherogenic lipoprotein profile, inferring an increased CVD risk compared to young women in healthy individuals. Whilst age is an independent risk factor of CVD risk in both men and women, oestradiol and HDL remain high in women until menopause, where oestradiol dramatically reduces and CVD protection by HDL is less prominent. Despite this, the levels of HDL in women remain higher than men post-menopause. Older men do not experience this dramatic fall in sex hormones, however, the levels of testosterone do slowly reduce with age. A recent study has shown that sex hormone associated lipoprotein changes can be induced by cross sex hormones in young transgender individuals, supporting these CVD risk associated observations. In patients with SLE, a disease with most common onset in women of a childbearing age, where women represent around 90% of all patients, CVD protection in women is dramatically reduced due to dyslipidaemia. This includes increased atherogenic lipoproteins and reduced HDL. It is speculated that this could be due to changes in levels or tissue sensitivity oestradiol, which drives inflammation and altered lipid metabolism. Understanding these fundamental differences in lipoproteins by sex will aid our mechanistic understanding of sexually dimorphic diseases and improve disease prevention and outcomes for CVD and autoimmune patients. This figure was produced using resources from Servier Medical Art, licenced under a Creative Commons Attribution 3.0 Generic License. <http://smart.servier.com/>.

also been implicated in the aetiology of SLE due to the sexual dimorphism of the disease, where the female to male ratio is 9:1 (36). Deaths attributable to disease activity in SLE have reduced dramatically over the last 50 years due to improved treatments targeting key dysregulated immune pathways, however, deaths associated with atherosclerosis and CVD are still high (37, 38). It has become apparent that the pathogenesis of atherosclerosis shares several autoimmune inflammatory pathways (39). Aside

from inflammation, dyslipidaemia (an imbalance between atherogenic and atheroprotective lipoproteins) is extremely common in SLE and is a conventional CVD-risk factor through atherosclerosis (40). In fact, dyslipidaemia was found in over 70% of premature coronary heart disease cases and hypercholesterolaemia (elevated total and/or LDL/non-HDL-cholesterol) was present in 34–51% of SLE all patients (41). In addition, a Systemic Lupus International Collaborating Clinics'

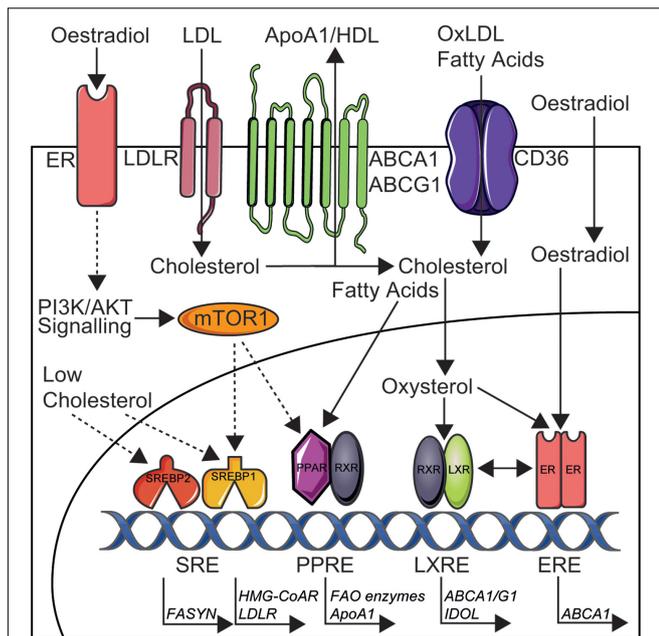
(SLICC) cohort study reported that 36% of newly diagnosed SLE patients had hypercholesterolemia in this large international cohort, which increased to over 60% after 3 years (42, 43). Interplay between traditional CVD risk factors, including dyslipidaemia, and risk factors associated with ongoing chronic inflammation captured in disease activity scores and cumulative steroid treatment (the most used treatment for acute flares in SLE) could contribute to the accelerated development of atherosclerosis in men and women with SLE (12). Whilst healthy women of a childbearing age typically have a more atheroprotective lipoprotein profile compared to men, as the onset of SLE peaks between the ages of 15–55 and the disease has a significant female-bias (44), the atheroprotective lipid profile is replaced by dyslipidaemia which is common in all patients with lupus (**Figure 2** depicts the physiological variation of lipid profile in men versus women; their associations with sex hormones and age, as well as impact of SLE-related chronic inflammation and treatment on driving a dysregulated lipid profile in all patients). Various clinical studies have found that elevated total cholesterol, TGs, circulating LDL-cholesterol and reduced HDL-cholesterol are the most common lipid abnormalities associated with SLE (40), which likely contributes to the higher lipid burden of atherosclerotic plaques, and increased CVD-risk in many patients. However, these standard clinical lipid panels, as well as many established cardio-vascular risk scores, often fail to account for the increased CVD-risk directly associated with SLE disease and treatment, and studies often do not consider how the presence of SLE modifies the impact of sex on CVD-risk (14, 45, 46). Despite this, more detailed investigations into lipoprotein subsets using NMR technology have found that women with SLE have increases in smaller LDL subfractions compared to sex matched healthy controls (HCs) (47). Further to this, a serum NMR metabolomic study by Coelewijn et al., incorporating detailed lipoprotein subclass evaluation, was able to confidently differentiate between adult women with SLE and sex matched HCs by use of machine learning (48). Here, the most influential metabolites in separating SLE from HCs were medium sized HDL measures, which were reduced in SLE, as well as small HDL, VLDL, and IDL particles, which were increased in SLE compared to HCs. This suggests that different HDL sizes are important to consider when studying dyslipidaemia in SLE. In support, another study reported that smaller HDL subsets were reduced in SLE, whilst no difference in the size of VLDL or LDL were reported (49). Dyslipidaemia has also been identified by multiple studies of paediatric patients with juvenile-SLE (50, 51), where onset of SLE occurs before the age of 18 and patients typically have worse disease outcomes and an estimated 100- to 300-fold increased risk of mortality from CVD compared to age-matched healthy individuals (52, 53). Strikingly, dyslipidaemia is present in up to 63% of patients with juvenile-SLE, which is higher in patients with active disease (51). In addition, an NMR metabolomics study of these younger juvenile-SLE patients showed that small HDL subsets were the most significantly reduced lipoproteins in juvenile-SLE patients compared to HCs, validated by machine learning analysis; this reduction was also exacerbated by increased disease activity (54). Importantly, sex was adjusted for in this analysis, despite 81.5% of this cohort

being female. In a more sex-specific study of young girls with juvenile-SLE, dyslipidaemia was observed in 39% of the study participants and a significant decrease in HDL-associated ApoA1 in the juvenile-SLE cohort compared to HCs, supporting a more global decrease in HDL in young patients (55).

Based on available literature data, there is compelling evidence that dyslipidaemia associated with SLE could dramatically reduce the lipid protection that healthy women of a childbearing age have from CVD, even in much younger age groups. This was supported recently by Robinson et al., who investigated sex differences in lipoprotein metabolism between young, post-pubertal patients with juvenile-SLE and found that all conventional differences in lipoprotein profiles observed between age-matched healthy men and women were lost in patients with juvenile-SLE (34). A sex-specific sub-analysis showed an increase in VLDL subsets and a decrease in HDL subsets in young women with juvenile-SLE compared to HCs, supporting reduced atheroprotection in disease. This loss of protection could be due to a breakdown in conventional sex hormone signalling, and highlights that sex and age are extremely important when studying the pathogenesis of and associated dyslipidaemia in SLE, where additional factors, such as ongoing inflammation and differential sex hormones are likely to have a significant impact on the overall CVD risk. Sex differences in lipid metabolism and their impact on the CVD-risk of patients with SLE are not commonly studied due to the overwhelming female predominance of the disease; however, this needs to be a priority going forward to enable better understanding of the changes in CVD risk for women with SLE of all ages.

## DISCUSSION

Is it striking that the presence of SLE in women removes the sex-specific cardio-protection through dyslipidaemia and this highlights a possible role for deregulated oestradiol signalling in SLE, in addition to over-activation of proinflammatory pathways and impact of certain SLE medications on lipid metabolism, all ultimately leading to altered lipid profiles in these patients. The association between lipids and sex-hormones is not a new theory, where the combined oral contraceptive pill (oestradiol and progesterone) has been previously shown to increase circulating HDL-cholesterol and TGs, whilst the progesterone only pill has no effect (56). Oestradiol administration has also been shown to increase HDL in post-menopausal women (57, 58), supporting a direct cardioprotective role of sex hormones in lipid metabolism. The study by Robinson et al. outlined above (34), highlighted that trans-men had increased total and LDL-cholesterol and TGs as well as decreased HDL-cholesterol associated to short-term administration of exogenous testosterone as gender-reaffirming treatment (and reduced oestradiol following treatment with puberty blockers), whilst trans-women had decreased total and LDL-cholesterol associated with exposure to short-term therapeutic oestradiol doses (in the context of reduced testosterone following treatment with puberty blockers) (59, 60). Follow up studies will be critical to understand the long-term effects of these sex hormone and



**FIGURE 3 |** Simplified depiction of oestradiol induced signalling pathways that may increase cardioprotection in women through altered lipid metabolism and could be targeted in SLE. Cholesterol is taken up by cells in low density lipoproteins (LDL) via LDL receptors (LDLR) and CD36 [oxidised (ox)LDL] or is synthesised by HMG-CoA reductase (HMG-CoAR). Cholesterol is removed from cells to ApoA1/high density lipoproteins (HDL) via ATP-binding cassette transporter A1 or G1 (ABCA1/G1) or converted to oxysterols intracellularly. Low intracellular cholesterol levels can induce the transcriptional activity of sterol regulatory element-binding proteins 1/2 (SREBP1/2). Fatty acids are taken up by CD36, synthesised by fatty acid synthase (FASN), or metabolised by fatty acid oxidation (FAO). Oestradiol acts via membrane bound oestrogen receptors (ERs) to induce phosphoinositide 3-kinase/protein kinase B (PI3K/AKT) signalling and downstream mTOR1 activation. Activated mTOR1 increases lipogenesis via increased nuclear activity of SREBP1 and peroxisome proliferator-activated receptor (PPAR) transcription factors. Oestradiol can also activate transcription factor ERs in the nucleus and this increased ER nuclear activity can elevate the binding and transcriptional efficiency of liver-x-receptors (LXRs), inducing cardioprotective cholesterol metabolism through upregulated ABCA1/G1 and inducible degrader of the LDLR (IDOL). It is through these metabolic pathways that oestradiol could exert its cardioprotective effects in healthy women and therefore could be disrupted and targeted in SLE to reduce CVD risk for patients. This figure was produced using resources from Servier Medical Art, licenced under a Creative Common Attribution 3.0 Generic License. <http://smart.servier.com/>.

lipid changes on CVD risk, as well as larger cohort studies to control for confounding factors such as BMI, hypertension and smoking. Studies in mice have also supported a protective role of oestradiol in CVD through lipid metabolism, where different stages of the menstrual cycle determine the size and lipid content of HDL produced by hepatic cells *in vivo*, relative to the levels of circulating oestradiol (61). When oestradiol levels are highest, smaller HDL particles are produced which allow more efficient cholesterol efflux from the liver via ATP-binding cassette transporter A1/G1 (ABCA1/G1), which in turn infers greater CVD protection. This is due to the increased nuclear activity of the oestrogen receptor, which elevates the binding and transcriptional efficiency of liver-x-receptors (ABCA1/G1),

master regulators of cellular cholesterol metabolism (Figure 3). Where smaller HDL particles are more efficient in mice regarding cholesterol efflux, it has been alternatively shown that large- and medium-sized HDL-cholesterol is more protective of myocardial infarction and stroke in humans (16), suggesting complex differences across models. *De novo* clearance of LDL and VLDL is also increased when plasma oestradiol levels are high in mouse models (61, 62), suggesting a dual effect of oestradiol on increasing and decreasing atheroprotective and atherogenic lipoproteins, respectively. Conversely, testosterone has been shown to increase hepatic lipase activity (catalyses the hydrolysis of triglycerides), decrease the levels of HDL and reduce the size of LDL (63). Reports on the specific impact of testosterone on atherosclerosis and CVD is less researched compared to studies of oestradiol (64).

Together, these sex specific lipid changes may explain why women lose their CVD protection following menopause, however, may not explain why women of a childbearing age with SLE develop an increased CVD risk. Although a reduction in oestradiol induced signalling could be a logical explanation for the increase CVD risk in SLE, in fact, many studies have reported that oestradiol and the oestrogenic metabolite, 6  $\alpha$ -hydroxyestrone, are increased in women with SLE (65–68), supporting the predominance of SLE disease onset in women during their reproductive years. Alternatively, it is plausible that oestradiol may promote inflammation in SLE, which increases the impact of non-traditional CVD risk factors including chronic inflammation (36). In support, some reports show that inflammatory flares in SLE are more prominent during pregnancy (69) and that patients with SLE may have exaggerated inflammatory responses to oestradiol (70). Generalised inflammation can reduce HDL levels and increase hepatic VLDL production, whilst reducing the clearance of TG lipoproteins (71). More specifically, inflammation in SLE associated with disease flares and pro-inflammatory cytokines such as IL-6 and TNF- $\alpha$  can increase TG and reduce HDL levels (72, 73). This could be partly due to reduced cell-mediated cholesterol efflux in SLE (74). Larger, TG rich lipoproteins have been associated with a dual effect on inflammation and atherosclerosis, whereas smaller LDL particles can promote atherosclerosis independent of inflammation (75). In addition, VLDL particles may also have difficulty leaving the subendothelial space of blood vessels, promoting local inflammation and atherosclerotic plaque progression (76). Finally, altered liver function, the major regulator of systemic lipid metabolism, is more common in SLE due to inflammation (77–79). This liver inflammation, along with current therapies used to treat SLE, such as steroids, could contribute to the loss of atheroprotection in women through altered lipoprotein metabolism, while treatment with hydroxychloroquine which is currently recommended in all patients with SLE can counterbalance some of the negative effects SLE has on the CVD-risk profile of these patients (80).

Another master regulator of metabolism that also has an impact on lipid synthesis is the mammalian target of rapamycin (mTOR) (81). Specifically, upon stimulation through phosphoinositide 3-kinase/protein kinase B (PI3K/AKT)

signalling, mTORC1 inhibits lipolysis and induces lipogenesis *via* the activation of peroxisome proliferator-activated receptor  $\gamma$  (PPAR $\gamma$ ) and sterol regulatory element-binding transcription factor 1 (SREBP1) (82, 83). Separately, activated mTORC2 can induce AKT signalling and therefore mTORC1 activation indirectly. With respect to these mechanisms, liver-specific deletion of mTORC1 can induce cardioprotective effects and render mice resistant to western diet induced hypercholesterolaemia (82, 84). mTOR inhibition with rapamycin has also led to a significant reduction of atherosclerotic lesions in LDL-receptor (LDLR) deficient male mice, despite severe hypercholesterolaemia (85). Despite these beneficial effects of mTOR inhibition on cardiovascular health, mTORC1 inhibition can also cause dyslipidaemia, a common risk factor for atherosclerosis, through downregulation of hepatic LDLRs and stimulation of lipophagy, resulting in a respective increase in circulating levels of LDL-cholesterol and droplet-released lipids (86, 87), meaning that the overall contribution of mTOR to atherosclerotic risk is complex (88). To add to this complexity, sex differences in mTOR signalling have been described in mouse models, where oestradiol stimulation of the oestrogen receptor can induce PI3K/AKT signalling and downstream mTOR activation (89, 90). mTOR suppression with rapamycin can increase the lifespan of mice (91), leading to an interest in its sex-specific effects on cardiovascular health. With this respect, increased mTORC1 activity has been observed in the liver and heart tissue of young female mice compared to male mice of the same age (92), and rapamycin treatment in mice also has sex specific effects on mTORC1 and mTORC2 (93). mTOR inhibition has also been shown to improve testosterone-induced myocardial hypertrophy in hypertensive rats (94), together supporting the potential sex-specific effects of mTOR on cardiovascular health. This suggests an alternative metabolic pathway to liver-x-receptors that oestradiol may exert its cardioprotective effects in healthy women and could be disrupted in SLE (Figure 3). It is also reported that patients with SLE have genetic activation of mTORC1 (95), and its blockade exerts potential therapeutic efficacy in SLE through reducing pro-inflammatory T-cell and macrophage differentiation (96). mTOR activation has also been implicated in increased CVD in SLE (97). Various mTOR inhibitors, less or more selective, have been developed for use in cancers and transplant medicine, owing to their important antiproliferative and cellular effects and immunosuppressive effects, although further research is required to address the limitations of dose-related toxicity and lack of tissue selectivity (98). Therefore, the cardiovascular and inflammatory effects of mTOR appear to be model, tissue, disease, and sex specific, adding to the complexity of investigating sex differences in CVD and autoimmune susceptibilities; more human studies are warranted.

## CONCLUSION AND PERSPECTIVES

Whilst CVD is more common in men, and SLE in women, sex and gender needs to be taken into account in all medical research. With this respect, CVD is the leading cause for

mortality in women, representing 35% of all global deaths (99). According to a recent study by The Lancet, 275 million women were diagnosed with CVD and 8.9 million died from CVD in 2019 (100). Despite this, women are hugely under-represented in clinical trials of CVD due to the increased risk in men, which is a major global health research limitation which needs to be addressed. Not only this, but women are often under-researched, underdiagnosed and undertreated as a result of this sex bias in CVD risk. In response, The Lancet have produced The Lancet women and CVD commission, aiming to reducing the global burden of CVD on women by 2030 (101). Here, an all-female led commission outlined new recommendations to tackle inequities in diagnosis, treatment, and prevention to reduce CVD in women. With regard to lipids, a standardised case-control study of acute myocardial infarction across 52 countries, the INTERHEART study, showed that abnormal lipids were the highest population attributable risk factor for CVD with very little contributable difference between sexes (49.5% for men and 47.1% for women) (8), validating the importance of considering both sexes in CVD, particularly when studying lipid metabolism.

It is also important to note that men are underrepresented in studies and clinical trials of SLE (102). Relative to CVD, however, SLE is relatively rare in the general population and men only represent around 10% of all SLE cases. This makes equality in SLE research difficult, particularly regarding sex, where men only represent around 7% of randomised controlled trials of patients with SLE (102). Despite this, it has been shown that men with SLE tend to develop more severe renal manifestations and higher risk of end-stage renal disease, requiring increased monitoring in clinical practice (103). With this respect, men should be considered more in research and clinical trials of SLE to improve disease prognosis. As highlighted in this review, equality in research cohorts and clinical trials not only improves lives of men and women, but also helps us to understand the pathogenic mechanisms of sexually dimorphic diseases.

To conclude, whilst oestradiol conventionally promotes atheroprotective lipoprotein metabolism in healthy individuals, chronic inflammation due to altered oestradiol sensitivity in patients with SLE, as well as other SLE-related treatment factors could alter finely tuned mechanisms of lipid regulation and induce circulating lipoprotein changes toward a more atherogenic profile. It is clear that further mechanistic investigations are warranted, however, uncovering these mechanisms of fundamental sex hormone driven changes in lipid metabolism will aid disease prevention and outcomes for both patients with CVD and autoimmunity, regardless of sex or gender, highlighting the importance of considering sex hormones in medical research.

## AUTHOR CONTRIBUTIONS

GR performed the literature review and wrote the first draft of the manuscript. All authors reviewed the manuscript and approved the final version.

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