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# Women, lipids, and atherosclerotic cardiovascular disease: a call to action from the European Atherosclerosis Society

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## Abstract

Cardiovascular disease is the leading cause of death in women and men globally, with most due to atherosclerotic cardiovascular disease (ASCVD). Despite progress during the last 30 years, ASCVD mortality is now increasing, with the fastest relative increase in middle-aged women. Missed or delayed diagnosis and undertreatment do not fully explain this burden of disease. Sex-specific factors, such as hypertensive disorders of pregnancy, premature menopause (especially primary ovarian insufficiency), and polycystic ovary syndrome are also relevant, with good evidence that these are associated with greater cardiovascular risk. This position statement from the European Atherosclerosis Society focuses on these factors, as well as sex-specific effects on lipids, including lipoprotein(a), over the life course in women which impact ASCVD risk. Women are also disproportionately impacted (in relative terms) by diabetes, chronic kidney disease, and auto-immune inflammatory disease. All these effects are compounded by socio-cultural components related to gender. This panel stresses the need to identify and treat modifiable cardiovascular risk factors earlier in women, especially for those at risk due to sex-specific conditions, to reduce the unacceptably high burden of ASCVD in women.

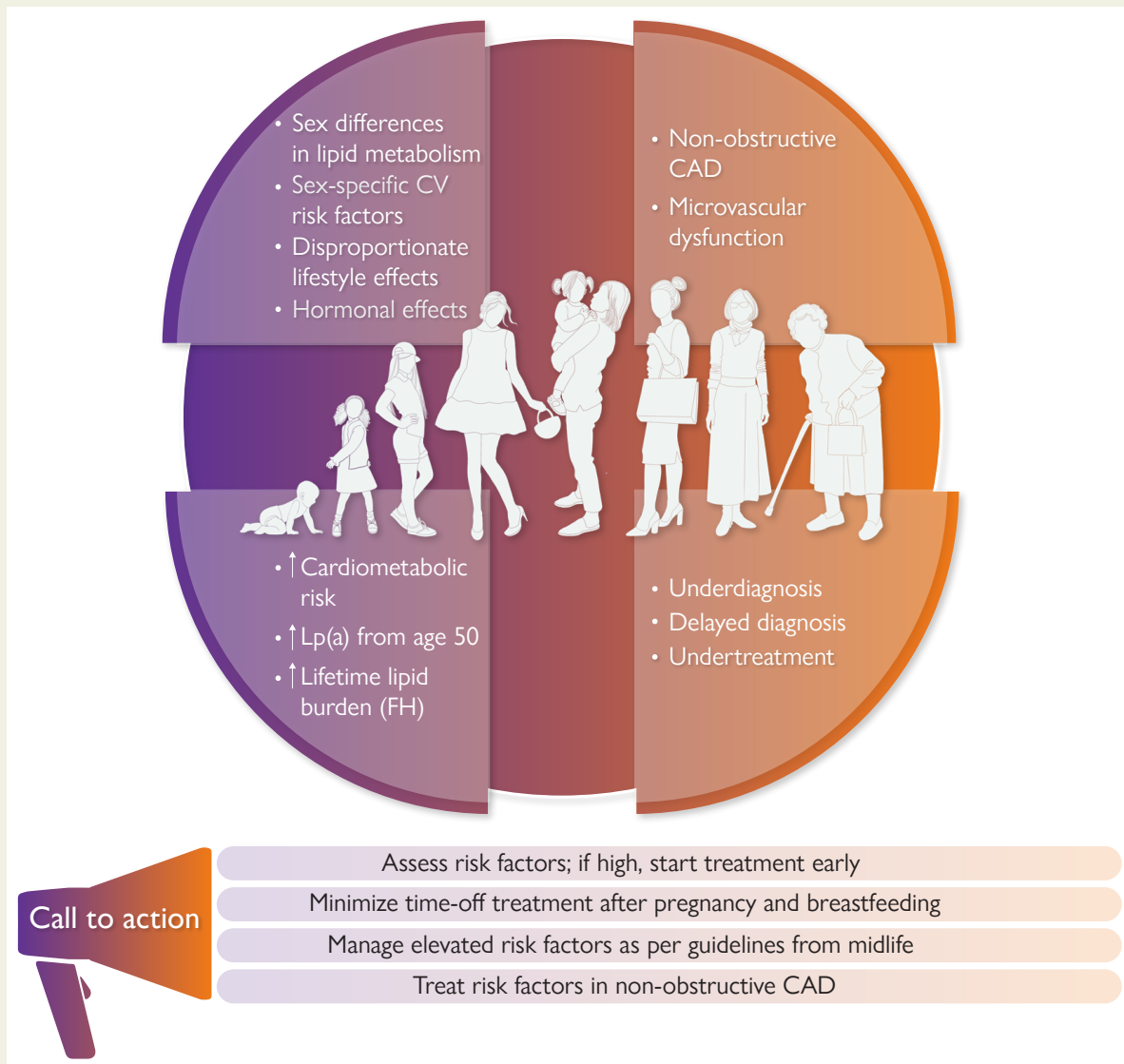
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## Graphical Abstract



Key messages from this EAS position statement. In addition to sex-specific risk factors, women are disproportionately impacted by some lifestyle factors which increase cardiometabolic risk, and atherosclerotic cardiovascular disease presentation differs from that in men. Action is needed to change the perception of risk, assess and treat elevated risk factors early, and address gaps in the management and understanding of cardiovascular risk in women. CAD, coronary artery disease; CV, cardiovascular; FH, familial hypercholesterolaemia; Lp(a), lipoprotein(a).

**Keywords**

Women • Atherosclerotic cardiovascular disease • Sex-specific risk • Lipids • Cholesterol • Triglycerides • Lipoprotein(a)

**Introduction**

Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of death in women and men, and its incidence continues to increase as the pandemics of obesity and cardiometabolic disease escalate.<sup>1–3</sup> Among adults <65 years, men have higher absolute ASCVD event rates than women, but in Europe and the USA, the fastest relative increase in ASCVD mortality is in middle-aged women (45–64 years).<sup>1,2</sup> Thus, a focus on ASCVD risk in women is important.

Missed or delayed diagnosis and undertreatment of ASCVD are key contributors,<sup>4,5</sup> with evidence that women are less likely than men to

receive guideline-recommended preventive therapies.<sup>6–10</sup> Familial hypercholesterolaemia (FH) exemplifies this. Global data<sup>11</sup> show that women are diagnosed later and undertreated, and with time-off lipid-lowering therapy (LLT) during pregnancy and breast feeding, have greater cumulative cholesterol exposure than men with FH,<sup>12</sup> possibly explaining why the relative impact of FH on cardiovascular risk is higher in women than men.<sup>13,14</sup> The effects of traditional and risk-enhancing factors also differ in women vs. men.<sup>15,16</sup> Sex-specific factors such as pregnancy-related complications, polycystic ovary syndrome (PCOS), and premature menopause also adversely influence cardiometabolic risk factors and impact atherosclerosis

progression.<sup>17–19</sup> Evaluating women for cardiovascular risk, ideally from midlife,<sup>20</sup> would improve early identification of those with elevated modifiable risk factors or sex-specific risk factors, and prompt early initiation of guideline-recommended treatment.

This European Atherosclerosis Society (EAS) position statement is a 'call to action' for improving ASCVD prevention strategies in women, with a focus on sex differences in lipids over the life course. The panel acknowledges that while 'female' refers to an individual's biological sex, and 'woman' refers to an individual's gender identity, historically these terms have been used interchangeably in the literature. Therefore, this statement uses the term 'women' for consistency.

## Do cardiovascular risk factors differ in women?

While both sexes share many of the traditional cardiovascular risk factors, the impact of these may differ in women vs. men.<sup>21</sup> For example, although more prevalent in men,<sup>22</sup> diabetes confers a greater relative (although not necessarily absolute) increase in cardiovascular risk in women vs. men of all ages.<sup>23–27</sup> In part this may relate to greater adiposity and more cardiovascular risk factors in women than men at the time of diagnosis,<sup>27–29</sup> as well as sex-specific risk factors for diabetes (e.g. PCOS and gestational diabetes).<sup>27</sup> Women are also typically less physically active and have a higher body mass index (BMI) than men,<sup>30</sup> which is known to associate with ASCVD risk.<sup>31</sup>

Disentangling the effects of declining oestradiol levels at menopause from ageing is difficult and much debated. Most of the large longitudinal studies with measurements before, during, and after menopause transition show changes in cardiovascular risk factors including weight gain, visceral adiposity, adverse effects on lipids (Figure 1),<sup>32</sup> and increases in inflammatory markers and blood pressure, especially systolic blood pressure.<sup>33–37</sup> Whether these changes also associate with increased risk for ASCVD is more contentious. Two longitudinal studies (249 and 890 subjects)<sup>38,39</sup> reported progression of carotid intima-media thickness (CIMT) related to the menopause, independent of baseline age, although another study (up to 3892 subjects) showed no association between menopausal transition and CIMT progression.<sup>37</sup> This latter study did, however, suggest that increasing adiposity and blood glucose with menopausal transition may impact diabetes risk.<sup>37</sup> Added to this, premature menopause was shown to be associated with an increased relative risk of incident ASCVD compared with similarly-aged women without premature menopause, especially in those with premature ovarian insufficiency with menopause before the age of 40 years.<sup>18,40,41</sup> Women with PCOS have an increased relative risk of cerebrovascular events but not of ASCVD events.<sup>19</sup>

It has been suggested that low-density lipoprotein cholesterol (LDL-C) is less important as a determinant of ASCVD risk in women vs. men given their lower risk of ASCVD, specifically myocardial infarction (MI), reported in some observational studies.<sup>42</sup> However, in the World Health Organization CVD Risk Chart Working Group report, both sexes had similar risk for fatal and non-fatal MI, coronary heart disease (CHD), and stroke per 1 mmol/L increase in total cholesterol.<sup>43</sup> Data from the Copenhagen City Heart Study and the Copenhagen General Population Study also showed comparable causal genetic effects of LDL-C on risk for MI and ischaemic heart disease (IHD) in both sexes (Figure 2).<sup>44,45</sup> These findings therefore support a similar causal effect of LDL-C on cardiovascular disease in women and men.<sup>46</sup>

Sex-specific factors in women merit consideration.<sup>47,48</sup> In US guidelines, factors such as pre-eclampsia and early menopause are regarded as 'risk-enhancing' with recommendation for statin therapy in women otherwise at borderline or intermediate risk.<sup>49</sup> The 2021 European Society of Cardiology (ESC) Prevention guideline recommends screening for hypertension and diabetes in women with a history of pregnancy-induced hypertension, PCOS, and gestational diabetes.<sup>16</sup> Women are also disproportionately at risk of chronic kidney disease, itself a risk factor for ASCVD,<sup>16</sup> which presents earlier than in men.<sup>50</sup> Auto-immune inflammatory diseases,<sup>15</sup> which impact women more than men increasing risk for premature ASCVD<sup>51,52</sup> independent of traditional risk factors,<sup>53–59</sup> are also considered 'risk-enhancing' factors by guidelines (Table 1).<sup>16,49,60</sup>

## Gender

Sociocultural components of gender additionally impact ASCVD risk. Compared with men, women are less likely to seek healthcare that they need. This is particularly true for those with more traditional roles,<sup>61</sup> who may prioritize family, household, and caregiver responsibilities over their own health.<sup>62</sup> Psychosocial stress is also more evident among women than men, a reflection of higher prevalence of low education attainment, depression, and anxiety contributing to ASCVD risk.<sup>63–65</sup> This is especially the case for women of non-Caucasian ethnicity,<sup>66</sup> who are less likely to be aware of ASCVD as a cause of death<sup>67</sup> and to seek care.<sup>68</sup>

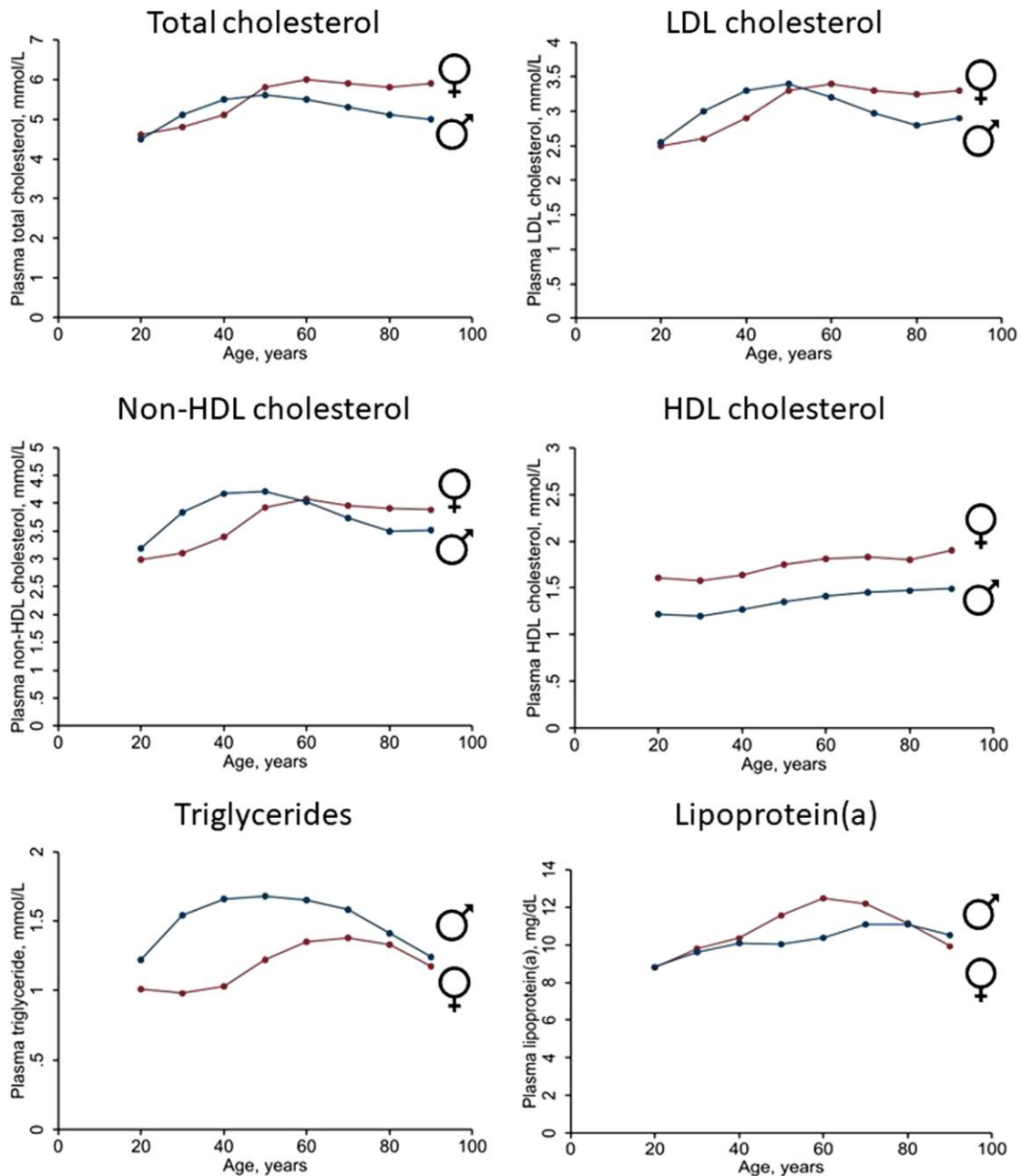
### Key points

- The impact of several lifestyle-related risk factors is disproportionately greater in women than in men. Adverse changes in weight, lipids, blood pressure, and glucose metabolism with menopause transition highlight potential accelerating cardiovascular risk.
- Female-specific risk factors, such as pregnancy-associated disorders, should be considered to promote earlier ASCVD risk factor assessment.
- Gender-related sociocultural contributors also disproportionately influence cardiovascular health in women.

## Does cardiovascular risk prediction differ in women?

As the first manifestation of ASCVD is more likely to be CHD in men but stroke in women,<sup>69,70</sup> recent amendments to risk scores in guidelines to include cardiovascular outcomes and fatal and non-fatal events<sup>16,71</sup> better reflect the total burden of clinical ASCVD in women. Despite this, current cardiovascular risk prediction models based on traditional risk factors relate to 10-year rather than lifetime risk and are biased by underdiagnosis of events in women thereby underestimating risk.<sup>72–76</sup> Even women with a large burden of sub-clinical atherosclerosis are more likely to be categorized as low risk.<sup>77</sup> Given that all prediction models are based on existing data and mostly use retrospective event rates to predict future events, underdiagnosis of events in past studies results in a lower event rate and thus underestimation of risk in models based on these data.<sup>72,78</sup>

Women generally experience ASCVD events at a later age and have lower event rates than men,<sup>79</sup> but given longer life expectancy,<sup>80</sup> have a similar lifetime cardiovascular risk.<sup>69</sup> Evolution of risk factors over the lifetime also differs between the sexes.<sup>81,82</sup> Furthermore, women-

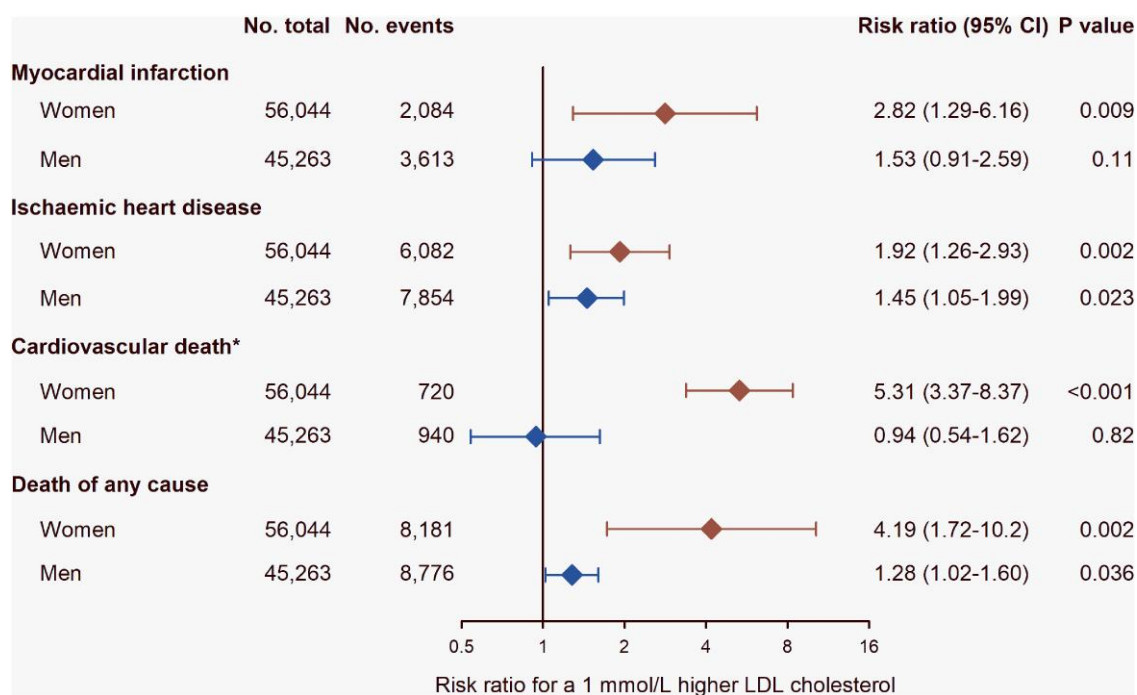


**Figure 1** Mean non-fasting plasma levels of total cholesterol, low-density lipoprotein (LDL) cholesterol, non-high-density lipoprotein (HDL) cholesterol, HDL cholesterol, triglycerides (TGs), and lipoprotein(a) [Lp(a)] based on data from 59,278 women and 48,314 men in the Copenhagen General Population Study. Plasma levels of total cholesterol, HDL cholesterol, and TG were measured using standard hospital assays (Konelab, ThermoFisher Scientific, Waltham, Massachusetts, USA). The LDL cholesterol was calculated using the Friedewald equation if TG was  $\leq 4$  mmol/L ( $\leq 354$  mg/dL) or measured directly. Non-HDL cholesterol was calculated as total cholesterol minus HDL cholesterol. The Lp(a) was analysed with different assays over time, all calibrated corresponding to values using the Denka assay on fresh samples. Samples were either fresh or stored at  $-80^{\circ}\text{C}$  before measurement. Tests for interaction were performed by inclusion of two-factor interaction terms between age and sex in the linear regression model on TG and plasma Lp(a) using a likelihood ratio test between models excluding and including the interaction term. *P*-value for interaction between age and sex on plasma TG =  $3 \times 10^{-207}$ ; on plasma Lp(a) =  $5 \times 10^{-8}$ . To convert cholesterol from mmol/L to mg/dL multiply by 38.7. To convert TG from mmol/L to mg/dL multiply by 88.6. To convert Lp(a) in mg/dL to nmol/L: Lp(a), nmol/L =  $2.18 \times \text{Lp(a), mg/dL} - 3.83^{32}$

specific risk factors are rarely incorporated when developing cardiovascular risk prediction models, given limited supportive evidence.<sup>83,84</sup> Thus, the concepts of lifetime cardiovascular risk and treatment benefit are promising approaches to tailoring ASCVD prevention in women.<sup>16</sup>

Recent findings from the UK Biobank identifying sex differences in genetic loci for CMIT, and correlations with BMI and glucometabolic traits,<sup>85,86</sup> highlight potential for leveraging 'big data' to provide incremental value for ASCVD prediction and prevention in women.





**Figure 2** Causal effect of a 1 mmol/L (38.7 mg/dL) higher low-density lipoprotein cholesterol (LDL-C) level on risk for myocardial infarction, ischaemic heart disease, cardiovascular death\*, and death from any cause in women and men in the general population, the Copenhagen City Heart Study, and the Copenhagen General Population Study. Data were estimated using Mendelian randomization with a weighted allele score of *LDLR* (rs267607213, rs121908025, and rs138947766), *PCSK9* (rs11591147, rs148195424, rs562556, and rs505151), and *HMGCR* (rs17238484) using instrumental variable analysis.<sup>44,45</sup> The strength of the genetic instrument (i.e. the strength of the association of the genotypes with LDL-C) was similar in women and men (*F*-statistics 70.8 in women and 67.8 in men). \*Cardiovascular death was defined as the primary cause of death. No., number; CI, confidence interval

**Table 1** Cardiovascular risk in women: what to consider?

- Diabetes: greater impact on cardiovascular risk in women vs. men
- Sex-specific risk factors (pregnancy complications including gestational diabetes and hypertensive disorders of pregnancy, polycystic ovary syndrome, and early menopause)
- Risk-enhancing factors (e.g. chronic kidney disease and auto-immune inflammatory disease): more prevalent in women than men
- Impact of the life course on the lipid profile
- Cumulative cholesterol exposure: in familial hypercholesterolaemia, greater cumulative cholesterol exposure in women is exacerbated by discontinuation of treatment during pregnancy and breastfeeding
- Hormonal and chromosomal effects influencing ASCVD progression
- Women with non-obstructive coronary artery disease may have significant atherosclerotic plaque

**Key points**

- Cardiovascular risk prediction based on traditional risk factors over a 10-year span underestimates risk in women.
- Lifetime cardiovascular risk and treatment benefit may be preferable approaches to tailoring cardiovascular disease prevention in women.

**Are there sex-related differences in the pathogenesis of atherosclerosis?**

A key difference between men and women relates to the levels and ratios of the sex hormones 17β oestradiol, progesterone, and testosterone. Although no randomized controlled trials have unequivocally proved an effect of these sex hormones on ASCVD risk, experimental studies have shown that all three affect biological processes relevant to atherosclerosis.<sup>87</sup> Oestrogens decrease atherosclerotic plaque burden

in models of atherosclerosis,<sup>88,89</sup> and oestradiol can increase endothelial nitric oxide production *in vitro*,<sup>90,91</sup> resulting in increased vasodilation and improved endothelial cell function in mouse models,<sup>92</sup> in isolated human arterioles,<sup>93</sup> and in *cis*- and transgender human females treated with oestradiol.<sup>94,95</sup> Oestrogens also affect inflammatory pathways, as they can reduce the up-regulation of cytokine-induced E-selectin, vascular cell and intercellular adhesion molecules in endothelial cells,<sup>96</sup> reduce leucocyte recruitment<sup>97</sup> and interleukin-6 expression<sup>98</sup> in (atherosclerotic) mice, and have been shown to prevent vascular smooth muscle cell (SMC) proliferation and extracellular matrix deposition,<sup>99</sup> all key processes that drive atherogenesis.

Oestradiol is also involved in maintaining lipid homeostasis. With lipid loading, oestrogens can modulate reverse cholesterol transport mechanisms, resulting in lower LDL-C and higher high-density lipoprotein cholesterol (HDL-C) levels, and prevent excessive lipid uptake by macrophages.<sup>100</sup> However, while oestradiol seems to have favourable effects on many pathogenic mechanisms important in atherosclerosis, the cellular and molecular basis of these phenomena, and the crosstalk of these phenomena are largely unknown.

The experimental data fit well with the observation that after menopause, when oestrogen levels decrease, post-menopausal women show a less-favourable lipid profile than in pre-menopausal women, have less efficient vasodilation, and suppress inflammation less efficiently. This suggests that the increase in ASCVD in post-menopausal women may be caused by more complex mechanisms than just oestrogen depletion, or other unspecified effects of oestrogens on ASCVD. The results of clinical trials of post-menopausal hormone replacement therapy (HRT) are inconclusive for the net effect on primary prevention of ASCVD in post-menopausal women, although systematic review of trials and cohort studies did suggest an increase in stroke risk.<sup>101</sup> The Estrogen in Prevention of Atherosclerosis Trial (EPAT) did, however, suggest an oestrogen-dependent reduction in atherosclerosis progression.<sup>102</sup>

The other main difference between female and male sex are the X and Y chromosomes, which contain many (X) vs. few (Y) genes. An experimental mouse model of atherosclerosis showed that the X-chromosome adversely impacted lipid metabolism, promoting increased absorption and availability of dietary fat, leading to increased atherosclerosis.<sup>103</sup> However, human data relating to the impact of the X-chromosome on cardiovascular disease are limited.

Other pathways contribute to differences in ASCVD between women and men. Genome wide association studies identified sex-specific single nucleotide polymorphisms, notably rs16986953 (close to *APOB*) and rs7865618 (*CDKN2B-AS1*), associated with cardiovascular disease solely in men. Integrative systems biology approaches revealed clear differences in gene networks between the sexes.<sup>104,105</sup> Female plaque contained more networks associated with SMC phenotypic modulation and endothelial mesenchymal transition, whereas male plaques exhibited pathways associated with immunoreactivity.<sup>105</sup> Consistent with this, carotid endarterectomy specimens from women showed less inflammatory infiltrates, smaller necrotic cores, and enhanced SMC and collagen content.<sup>106</sup> Imaging studies revealed fewer atherosclerotic plaques with a smaller intima-media thickness and necrotic core, fewer cholesterol crystals, and less calcification, as well as a lower frequency of intraplaque haemorrhage or plaque rupture in women than in men.<sup>106</sup> Thus, despite the paucity of human data, emerging experimental evidence implicates sex as an important player in the pathogenesis of atherosclerosis. Further study is needed to understand mechanisms that drive these differences.

## Does sex impact atherothrombosis risk?

Thrombosis often underlies the transformation of a silent atherosclerotic plaque into an acute ischaemic syndrome.<sup>107,108</sup> Over 30 years ago, studies suggested an impaired platelet response to aspirin in women, although conclusive evidence for effects on the underlying processes in thrombus formation is still lacking.<sup>109,110</sup> While there is support for higher platelet activity, platelet counts and on-treatment platelet reactivity and thus greater propensity for thrombosis in women than in men,<sup>111</sup> these differences are small and unlikely to confer a worse clinical prognosis.<sup>112</sup>

It is plausible that female sex hormones (notably oestrogen) regulate procoagulant protein levels, platelet function, and vessel wall biology and composition, which may translate to sex-based differences in thrombosis.<sup>113</sup> Differences in platelet and coagulation activities may, at least partly, explain observations that women are more likely to be aspirin-resistant, to receive distinct benefit from aspirin therapy in primary prevention, and to present with different patterns of venous thrombosis and stroke.<sup>113</sup> Women also have a higher tendency for a hypercoagulable state, although the underlying mechanism is uncertain. Oestrogen activated platelets and enhanced aggregation and haemostatic activity in a study using platelets showing differential sex-dependent signalling and cellular activation.<sup>114</sup> Another important consideration is bleeding complications, which are more prevalent in women than in men.<sup>111,114,115</sup> Further investigation of sex-based mechanisms regulating thrombosis is merited.

### Key points

- Sex (sex hormones and sex chromosomes) influences the pathogenesis of atherothrombosis, but understanding of the underlying mechanisms is limited.
- Sex-based mechanisms may contribute to differing susceptibility to bleeding complications from antiplatelet and anticoagulant therapy in women and men.

## Does atherosclerotic cardiovascular disease presentation differ in women?

### Ischaemic heart disease

Compared with men, women have smaller coronary arteries with smaller plaques,<sup>116</sup> and a higher burden of microvascular dysfunction with more ischaemia with non-obstructive coronary arteries (INOCA), especially in the 45–65 year age group.<sup>117–119</sup> As symptoms are more diverse and vague than in men, even with obstructive coronary artery disease,<sup>120–122</sup> MI is often silent or missed.<sup>121,123,124</sup>

Women have similar atheroma burden as men,<sup>125</sup> often with concealed atheroma. Both high-risk plaque and non-obstructive left main disease are stronger predictors of major adverse cardiovascular events (MACE) in women than in men, even after adjustment for the presence of stenosis.<sup>126,127</sup> Given the limitations of conventional angiography in women with INOCA,<sup>46</sup> computed tomography angiography is useful to exclude obstructive disease, and to identify plaque burden and low attenuation plaque, a powerful predictor of MI risk.<sup>128,129</sup> Stress positron emission tomography or stress magnetic resonance imaging can aid diagnosis of coronary microvascular dysfunction. Coronary artery calcium (CAC), although less prevalent in women than men, is associated with a 30% higher risk for cardiovascular death.<sup>130</sup> A CAC score >100 or ≥75<sup>th</sup> age/sex percentile identifies women at elevated risk of MACE; a CAC score >300 was associated with similar event rates as a

stable secondary prevention population,<sup>131</sup> supporting guideline recommendations for treating a CAC score >300 in primary prevention similar to secondary prevention. Greater lesion size and higher plaque density contribute to higher cardiovascular mortality in women than men with extensive calcified disease.<sup>130</sup> Irrespective of the pathophysiology, women with acute coronary syndrome tend to have poorer outcomes than men,<sup>132</sup> reflecting increased comorbidities, and delays and underuse of guideline-recommended treatment.<sup>133,134</sup>

## Stroke

Stroke is the third leading cause of death and disability in women.<sup>135</sup> Lifetime prevalence is higher and outcome poorer than in men due to older age at onset.<sup>136</sup> As for IHD, women with stroke often present with atypical symptoms, increasing the risk of missed or delayed diagnosis.<sup>137,138</sup> Unlike men, stroke is more likely to be cardioembolic due to a higher prevalence of atrial fibrillation and less often due to large vessel disease caused by atherosclerosis.<sup>136</sup> Some traditional risk factors for stroke such as hypertension, metabolic syndrome, and obesity are more prevalent in women. Other risk factors are only present in women (pre-eclampsia, gestational diabetes, and oral contraceptive use) or increase the risk of stroke more in women than in men (migraine with aura and diabetes).<sup>136</sup> Finally, an adverse lipid profile is one of the most important preventable causes of stroke in women.<sup>139</sup> Despite evidence that women gain the same benefit as men from statin treatment, they are less likely to be prescribed treatment or attain desired cholesterol levels.<sup>6–10,140</sup>

## Peripheral artery disease

Although peripheral artery disease (PAD) is at least as prevalent in women as in men,<sup>141,142</sup> women are often asymptomatic and therefore less likely to be diagnosed and treated. In the Women's Health and Aging study, only one in six women with PAD were aware of their condition, and two-thirds of those with PAD did not recognize their symptoms.<sup>143,144</sup> Even among symptomatic PAD patients, women are more likely to experience atypical limb symptoms rather than intermittent claudication,<sup>145</sup> with greater and faster reduction in functional status. Consequently, women with PAD are more likely to present with advanced, multilevel lower extremity disease<sup>146–149</sup> and are less likely to be treated effectively with antithrombotic medications, and lipid- and blood pressure-lowering therapy than men with PAD.<sup>150–153</sup> While risk for MACE and mortality is similar,<sup>154,155</sup> women with PAD are at higher risk for above knee amputation than men.<sup>156</sup>

### Key points

- Symptoms of ASCVD in women are underappreciated and underrecognized.
- Women have a higher burden of microvascular dysfunction than men.
- For all presentations of ASCVD in women, delayed or missed diagnosis is common and contributes to undertreatment.

## Cardiovascular risk factors in women: focus on lipids

There is limited information on how female sex influences major lipids, including LDL-C, triglyceride-rich lipoproteins (TRLs), and lipoprotein(a) [Lp(a)]. Cumulative exposure differs (Figure 1), with higher lipid levels from birth in girls than boys,<sup>157–159</sup> persisting during adolescence.<sup>160,161</sup> Lipids also vary during the menstrual cycle (highest at ovulation),<sup>162</sup> a

possible consideration in lipid testing. Increases during pregnancy in levels of total cholesterol and LDL-C (~30%) and triglycerides (TGs) (~50% at 35–42 weeks) (Figure 3)<sup>163</sup> are important in women with higher pre-pregnancy levels.<sup>13,14,163</sup> Breastfeeding favourably modulates hyperlipidaemia,<sup>164,165</sup> and when continued for >12 months over the lifetime, is associated with lower risk of ASCVD.<sup>166–168</sup> After menopause transition, women experience a worsening in the lipid profile (Figure 1) with increases in total cholesterol, LDL-C, and TG levels potentially contributing to accelerating ASCVD risk.<sup>169,170</sup>

## Familial hypercholesterolaemia

Familial hypercholesterolaemia is characterized by elevated LDL-C levels compared with the general population.<sup>171</sup> Women with FH appear to be at risk of higher cholesterol burden than men with FH for a number of reasons, including higher LDL-C levels from an early age,<sup>172</sup> later diagnosis (on average, by ~2.5 years), and underuse of maximal statin doses or combination LLT.<sup>11</sup> Attainment of LDL-C goal is consequently lower (Figure 4), and ~40% of women do not attain levels <1.8 mmol/L (<70 mg/dL) (odds ratio .63, 95% CI .48–.82; *P* = .0007).<sup>11</sup> These disparities in FH care impact ASCVD risk, with registry data showing the highest excess CHD risk among younger women with FH.<sup>171,173</sup>

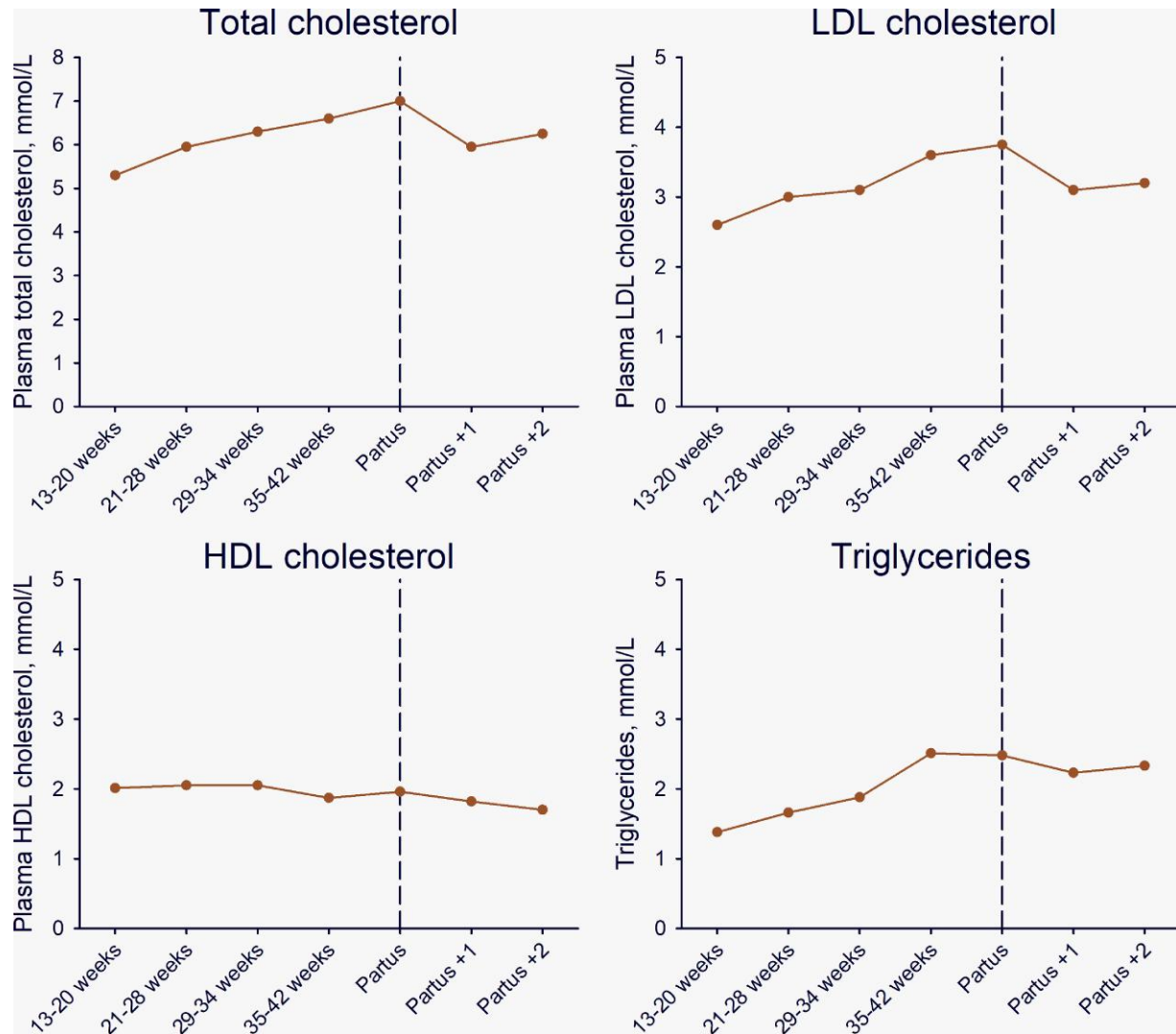
Adding to this, discontinuation of LLT before and during pregnancy and breastfeeding<sup>60</sup> increases LDL-C burden in women with FH. In a recent study of FH subjects with serial lipid measurement over 12 years, a theoretical threshold (area under the curve) for LDL-C burden indicative of higher MI risk (125 mmol/L-years or 5000 mg/dL-years)<sup>174</sup> was attained earlier by women than men.<sup>12</sup> All FH women had attained this LDL-C threshold by age 33 years, seven years earlier than for FH men.<sup>12</sup> Although updated US Food and Drug Administration (FDA) guidance allows for more flexible options for shared decision making in highest-risk women during pregnancy,<sup>175</sup> the FDA also acknowledges the lack of data on the efficacy, risks, and benefits of statin therapy during pregnancy and the need for more research, both into safety for the foetus and adverse effect on high-risk women without effective LLT for this time. While limited evidence suggests no higher risk of preterm delivery, low birth weight, or congenital malformation in infants of FH mothers than in the general population with most pregnancies (85%) successfully carried to full-term,<sup>176,177</sup> further study is needed. The European Medicines Agency has so far not responded to the statement of the FDA. For now, this panel does *not* recommend continuing statin therapy during pregnancy and breastfeeding.

Taken together, childbearing (planning, pregnancy, and breastfeeding) represents a considerable loss of LLT (by ~20% at ~30 years) in women with FH.<sup>178</sup> This panel stresses the need for close monitoring of FH women during pregnancy and breastfeeding, to minimize their time-off statin therapy. Whether LDL-C goals should be lowered in FH women to compensate for lost treatment merits consideration.

### Key points

- Female sex influences lipids during transitions (pregnancy, breastfeeding, and menopause). After menopause, women experience a worsening in the lipid profile, potentially contributing to accelerating ASCVD risk.
- The LDL-C burden associated with FH is higher among women than men due to delayed diagnosis, underuse of maximal statin doses with lower LDL-C goal attainment, and discontinuation of statin therapy before and during pregnancy and breastfeeding.
- This panel recommends action to minimize time-off statin therapy for FH women after pregnancy and breastfeeding.





**Figure 3** Mean plasma levels of total, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) cholesterol, and triglycerides as a function of pregnancy week, at delivery (partus), and one and two weeks after delivery. Data are medians calculated from the 2.5 and 97.5 percentiles from Klajnbard et al.<sup>163</sup> To convert total, LDL, and HDL cholesterol from mmol/L to mg/dL multiply by 38.7. To convert triglycerides from mmol/L to mg/dL multiply by 88.6

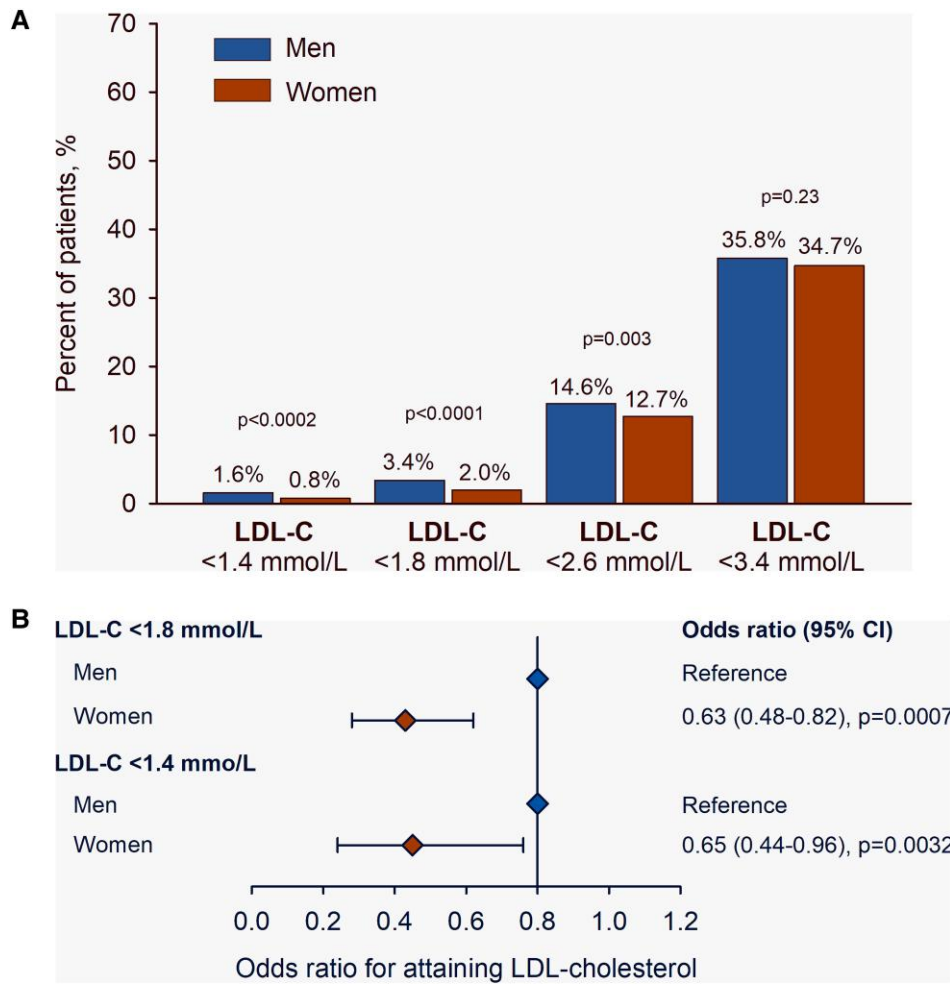
## Triglyceride-rich lipoproteins

High levels of plasma TGs are a marker for high levels of TRLs, and as these are metabolized by cells, the cholesterol component—remnant cholesterol or TRL cholesterol—is more important for atherosclerosis.<sup>179</sup> High plasma TGs also associate with vascular and systemic inflammation.<sup>180,181</sup> Mendelian randomization studies suggested that the observed associations between TGs and remnant cholesterol may be causal<sup>182–187</sup>; however, with the lack of robust evidence that lowering TGs or remnant cholesterol reduces ASCVD,<sup>179,180,188–191</sup> current guidelines do not provide treatment goals.<sup>60</sup>

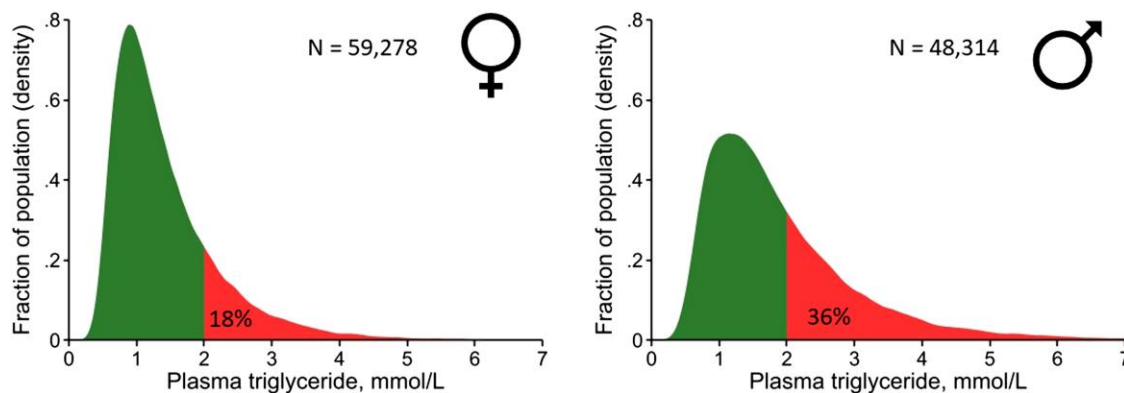
As discussed, TGs increase from childhood until ~70 years in women and ~60 years in men (Figure 1).<sup>192</sup> From 20–80 years, women consistently have lower TG levels than men, partly explained by higher alcohol intake in men,<sup>182</sup> contributing to a lower prevalence with TGs >2 mmol/L (Figure 5).

Risk of ASCVD and mortality increases similarly in women and men as TG and remnant cholesterol levels increase.<sup>182–184,193</sup>

Although there is no solid evidence that TG concentration is a better predictor of ASCVD in women than in men, large prospective studies provide insights. The Copenhagen City Heart Study showed a higher risk of MI (HR 1.20, 95% CI 1.05–1.37) and total mortality (HR 1.18, 95% CI 1.10–1.27) in women vs. men per 1 mmol/L increase in non-fasting TG (after multifactorial adjustment for age, total cholesterol, BMI, hypertension, diabetes, smoking, alcohol consumption, physical inactivity, lipid-lowering treatment, post-menopausal status, and HRT).<sup>182</sup> A similar trend per 1 mmol/L increase in remnant cholesterol was reported for PAD [HR 1.6, 95% CI 1.3–1.9 in women and 1.2, 95% CI 1.1–1.3 in men (*P* for interaction sex per remnant cholesterol on risk of PAD = .01)].<sup>185</sup> The Emerging Risk Factors Collaboration showed interaction between sex and fasting TG on risk of CHD (*P* for interaction = .02) with a slightly higher risk per 1



**Figure 4** Attainment of low-density lipoprotein cholesterol (LDL-C) targets among men and women with familial hypercholesterolaemia on lipid-lowering therapy (statin, ezetimibe, and/or a PCSK9 inhibitor). Panel A shows the percentage of patients on treatment and below different LDL-C thresholds. Panel B shows the likelihood of attaining an LDL-C below different thresholds according to sex, using men as the reference. The odds ratio was adjusted by age, baseline comorbidities (hypertension, diabetes, smoking, and body mass index), high-density lipoprotein cholesterol, logtriglycerides, lipid-lowering therapy, and index case status. CI, confidence interval. Reproduced with permission<sup>11</sup>



**Figure 5** Density distribution of plasma levels of triglycerides in 59,278 women and 48,314 men from the Copenhagen General Population Study. Triglycerides were measured in the non-fasting state and analysed on fresh samples using standard hospital assays. To convert triglycerides from mmol/L to mg/dL multiply by 88.6

standard deviation (SD) increase in TGs in women (HR 1.06, 95% CI .96–1.16) than men (HR .97, 95% CI .91–1.03) but no interactions between sex and HDL-C or non-HDL-C on risk<sup>194</sup>. In the Women's Health Study in >28,000 subjects,<sup>195</sup> a 1 SD increase in LDL-C was associated with 38% higher CHD risk before age 55 years, but 1 SD increase in non-HDL-C, TGs, and remnant cholesterol increased CHD risk by 67%, 114%, and 66%, respectively. Thus, as for men, elevated TRLs are important to ASCVD risk in women, with lifestyle intervention a priority for management.

### Key points

- Triglyceride levels are a marker for TRL; remnant cholesterol contained in TRL is important for atherosclerosis.
- The association of increasing TG levels and ASCVD risk is similar in men and women.
- While there is currently no solid evidence that TG concentration is a better predictor of ASCVD in women than in men, evidence suggests that TRLs are important risk factors for premature CHD in women.

## Lipoprotein(a)

There is clear evidence for the causality of Lp(a) in ASCVD and aortic valve stenosis.<sup>196–206</sup> Plasma levels of Lp(a) show similar distribution in men and women, varying with ethnicity<sup>207,208</sup> (Figure 6). The Lp(a) concentration increases in women around 50 years coinciding with the onset of menopause<sup>209–212</sup> (Figure 1), possibly due to hormonal changes and/or ageing. Indeed, Lp(a) concentration is 12%–20% lower in women on HRT vs. controls,<sup>213–215</sup> and approximately doubles in pregnancy.<sup>216,217</sup> In the Copenhagen General Population Study in >70,000 individuals, Lp(a) levels were generally similar in men and women aged 20–49 years, but on average 17% higher in women from age 50<sup>218</sup> (Figure 1). While both sexes show similar associations between high Lp(a) (>40 mg/dL or >83 nmol/L) and cardiovascular morbidity and mortality after age 50 years, higher levels in women (Figure 1) suggest that Lp(a) at this age is a relatively more common cardiovascular risk factor than in men. These findings therefore challenge current

recommendations that only one Lp(a) measurement is adequate to capture the lifetime concentration of Lp(a) in women.<sup>60,219</sup>

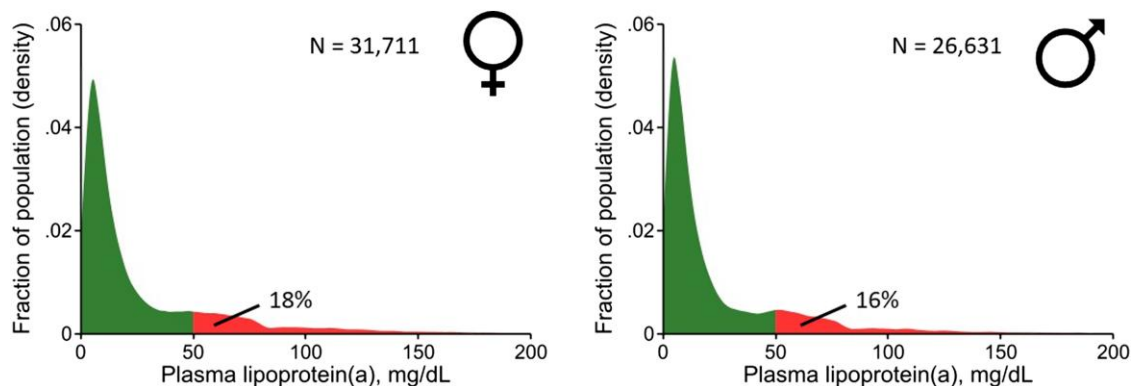
### Key points

- In women, Lp(a) concentration increases during pregnancy, and from the onset of menopause (circa 50 years).
- High Lp(a) levels are more common in women than men after 50 years, which may impact ASCVD risk. This might suggest that guideline recommendations to measure Lp(a) once are inadequate in women.

## Call to action for women and atherosclerotic cardiovascular disease

Although ASCVD is the leading cause of death in women, their cardiovascular health is often neglected. Underappreciation of women's ASCVD risk, missed or delayed diagnosis, and undertreatment are important contributors. Despite clear evidence that statin therapy is similarly efficacious in both sexes,<sup>220</sup> women at high risk for ASCVD are less likely than men to be prescribed any statin therapy or to receive a statin at guideline-recommended intensity,<sup>7</sup> and more likely to refuse or discontinue statin treatment due to perceived side effects.<sup>7,221,222</sup> Clearly, action is needed to overcome these inequities.

As discussed in this EAS statement, there are also other important considerations. Women are disproportionately impacted by some lifestyle factors, and sociocultural components related to gender impact risk. Hormonal and chromosomal effects also influence ASCVD progression, although gaps remain in understanding the underlying mechanisms (Graphical abstract). Lipids influence ASCVD risk in women during life course events (pregnancy, breastfeeding, and menopause). During menopause transition, LDL-C levels increase<sup>36</sup> and elevated Lp(a) is more common than in men. In women with FH, discontinuation of statin therapy with pregnancy and breastfeeding contributes to greater cumulative cholesterol exposure compared with men with FH.



**Figure 6** Density distribution of plasma levels of lipoprotein(a) [Lp(a)] in 31,711 women and 26,631 men from the Copenhagen General Population Study. The Lp(a) concentration was measured in the non-fasting state and analysed with different assays over time, but all assays were calibrated corresponding to values using the Denka assay on fresh samples. The majority of measurements was performed on fresh samples using this assay. Samples stored prior to measurements were kept at  $-80^{\circ}\text{C}$  before measurement. To convert Lp(a) in mg/dL to nmol/L:  $\text{Lp(a), nmol/L} = 2.18 \times \text{Lp(a), mg/dL} - 3.83$ <sup>32</sup>

**Table 2** Key recommendations

- Cardiovascular health should be assessed routinely in women from a young age. This should involve review of traditional cardiovascular risk-enhancing factors, sex-specific cardiovascular risk factors, and gender-related cardiovascular risk factors.
- Elevated lipids (LDL-C, triglycerides, and lipoprotein(a)) should be treated early with guideline-recommended therapy.
- As high lipoprotein(a) levels are more common in women than men after 50 years, repeat measurement may be indicated.
- Women with FH should be closely followed to minimize time-off statin therapy due to pregnancy and breastfeeding. Whether treatment targets should be lowered in FH women to compensate for lost treatment time merits consideration.
- Women with non-obstructive coronary plaque should receive aggressive risk factor management.
- Further study is needed to understand how sex hormones and sex chromosomes influence the pathogenesis of atherosclerosis.

This panel stresses the importance of early assessment of cardiovascular risk and early treatment of dyslipidaemia in women (Table 2 and Graphical abstract). Further studies to understand the effects of female sex hormones on atherosclerosis development and progression are needed. Targeted action to address these gaps is a priority to reduce the unacceptably high burden of ASCVD in women.

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## Declarations

### Disclosure of Interest

Potential conflicts of interest outside the submitted work (participation in trials; receipt of fellowships, or grants for travel, research, or staffing support; and/or personal honoraria for consultancy or lectures/speaker's bureau) are summarized as follows: Ab-Biotics (L.B.), Abbott (L.S.T.), Abdi Ibrahim (M.K.), Amarin-PACE (L.B.), Akcea (A.T.H.), Amgen (C.N.H., K.B.H., A.T.H., L.S.T., and E.D.M.), American College of Surgeons (C.N.H.), Amryt Pharma (M.K. and J.E.R.V.), AstraZeneca (L.B., E.D.M., A.T.H., and L.S.T.), Bayer (C.N.H., E.D.M., and L.S.T.), Boehringer Ingelheim (E.D.M.), Canadian Institutes of Health (S.M.D.), Daiichi Sankyo (L.S.T.), Draupnir Bio (A.T.H.), Edwards (E.D.M.), Esperion (E.D.M.), European Union (Covirna, Transbioline, Cardiateam, and Era-CVD; L.B.), Health Institute Carlos III Spain (L.B.), International Aspirin Foundation (L.B.), International Atherosclerosis Society (L.B.), Ionis (L.B.), Janssen (C.N.H. and L.S.T.), Kidney Foundation (S.M.D.), LIB Therapeutics (M.K.), Medtronic (E.D.M.), Ministry of Research Spain (L.B.), MSD (L.S.T.), Mylan (L.S.T.), NHLBI (M.G.), Novartis (M.K., E.L., E.D.M., J.E.R.V., A.T.H., and L.S.T.), Novo-Nordisk (L.B., M.K., E.L., E.D.M., and L.S.T.), Novonordisk (L.B.), Pfizer (L.B., E.D.M., and L.S.T.), Recordati (L.S.T.), Regeneron (A.T.H.), Sanofi (L.B., K.B.H., J.E.R.V., A.T.H., and L.S.T.), Sanovel (M.K.), Servier (L.S.T.), Silence Therapeutics (A.T.H.), and US Department of Defence (M.G.). J.K.S. reports stock in AstraZeneca and GSK.

L.B. has patents planned, issued, or pending for Gly-ApoJ, Ivestatin, and DJ-1F (unrelated to work), and is a member European Society of Cardiology (ESC)-Nominating Committee. S.M.D. is a member of the Canadian Women's Heart Health Alliance—and the Women's Health Research Cluster. C.N.H. receives royalties as co-author on UpToDate section on Investigational Therapies in Treatment of Peripheral Artery Disease. M.G. is President of the American Society for Preventive Cardiology. K.B.H. and J.E.R.V. are members of the

scientific board of FH Europe. M.K. is chair of FH Turkey. E.L. is Chair of the ESC Working Group on Atherosclerosis and Vascular Biology, and a member of the programme committee for ATVB and AHA. J.E.R.V. is a member advisory board LEEFH, and the executive board of the EAS. L.S.T. is Past President of the EAS and the Past President of the Turkish Society of Cardiology. Membership of a Data Safety Monitoring Board is reported by C.N.H. (LIMIT trial) and M.J.H.W. (Trident trial). M.B., M.K., and E.P. have no disclosures.

## Data Availability

No data were generated or analysed for this manuscript.

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