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
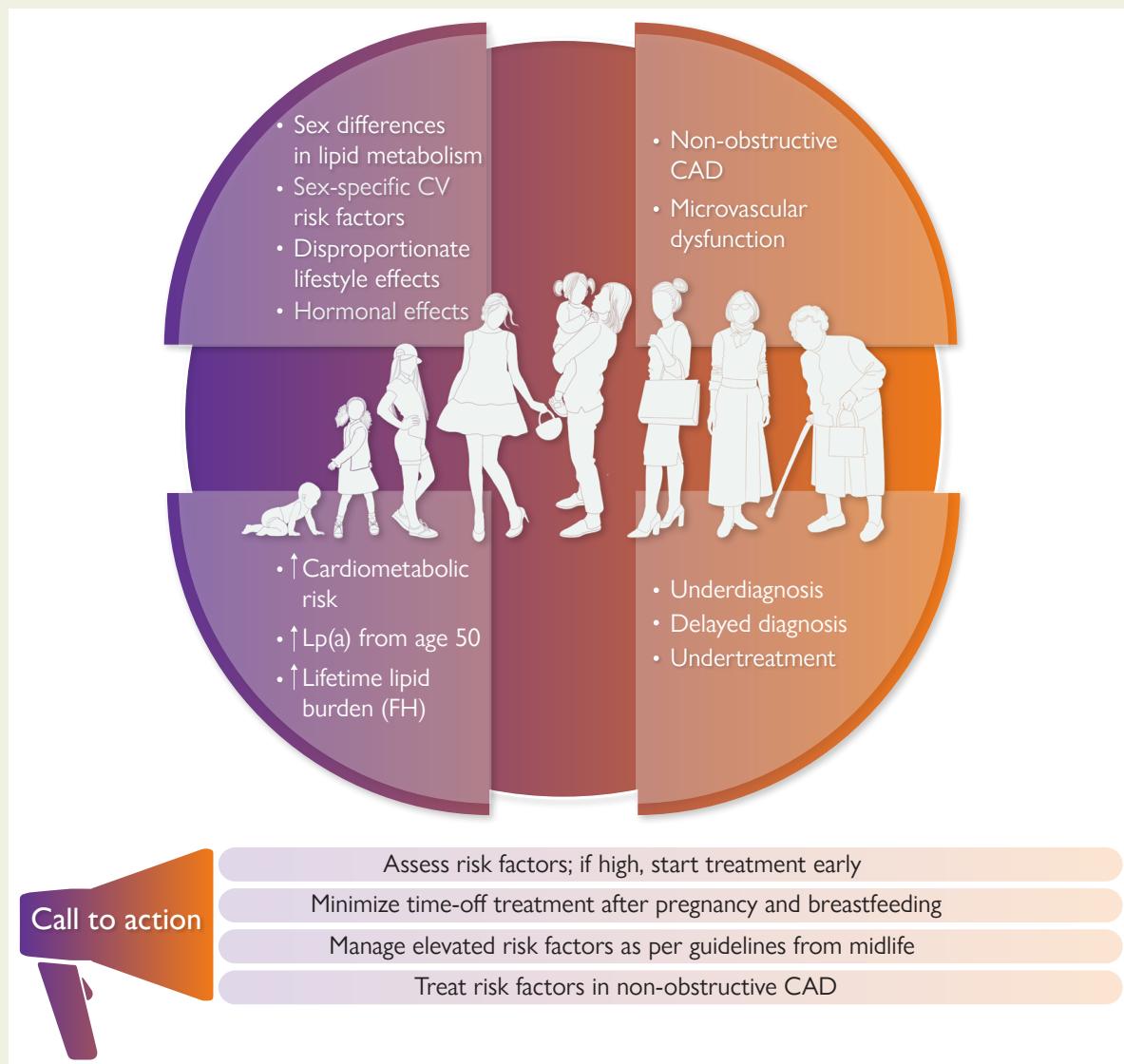
Key messages from this EAS position statement. In addition to sex-specific risk factors, women are disproportionately impacted by some lifestyle factors which increase cardiometabolic risk, and atherosclerotic cardiovascular disease presentation differs from that in men. Action is needed to change the 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.[1–3] 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).[1,2] Thus, a focus on ASCVD risk in women is important.

Missed or delayed diagnosis and undertreatment of ASCVD are key contributors,[4,5] with evidence that women are less likely than men to receive guideline-recommended preventive therapies.[6–10] Familial hypercholesterolaemia (FH) exemplifies this. Global data[11] 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,[12] possibly explaining why the relative impact of FH on cardiovascular risk is higher in women than men.[13,14] The effects of traditional and risk-enhancing factors also differ in women vs. men.[15,16] 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.[17–19] Evaluating women for cardiovascular risk, ideally from midlife,[20] 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.[21] For example, although more prevalent in men,[22] diabetes confers a greater relative (although not necessarily absolute) increase in cardiovascular risk in women vs. men of all ages.[23–27] In part this may relate to greater adiposity and more cardiovascular risk factors in women than men at the time of diagnosis,[27–29] as well as sex-specific risk factors for diabetes (e.g. PCOS and gestational diabetes).[27] Women are also typically less physically active and have a higher body mass index (BMI) than men,[30] which is known to associate with ASCVD risk.[31]

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*),[32] and increases in inflammatory markers and blood pressure, especially systolic blood pressure.[33–37] Whether these changes also associate with increased risk for ASCVD is more contentious. Two longitudinal studies (249 and 890 subjects)[38,39] 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.[37] This latter study did, however, suggest that increasing adiposity and blood glucose with menopausal transition may impact diabetes risk.[37] 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.[18,40,41] Women with PCOS have an increased relative risk of cerebrovascular events but not of ASCVD events.[19]

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.[42] 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.[43] 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*).[44,45] These findings therefore support a similar causal effect of LDL-C on cardiovascular disease in women and men.[46]

Sex-specific factors in women merit consideration.[47,48] 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.[49] 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.[16] Women are also disproportionately at risk of chronic kidney disease, itself a risk factor for ASCVD,[16] which presents earlier than in men.[50] Auto-immune inflammatory diseases,[15] which impact women more than men increasing risk for premature ASCVD[51,52] independent of traditional risk factors,[53–59] are also considered 'risk-enhancing' factors by guidelines (*Table 1*).[16,49,60]

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,[61] who may prioritize family, household, and caregiver responsibilities over their own health.[62] 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.[63–65] This is especially the case for women of non-Caucasian ethnicity,[66] who are less likely to be aware of ASCVD as a cause of death[67] and to seek care.[68]

> ## Key points
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> - 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,[69,70] recent amendments to risk scores in guidelines to include cardiovascular outcomes and fatal and non-fatal events[16,71] 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.[72–76] Even women with a large burden of subclinical atherosclerosis are more likely to be categorized as low risk.[77] 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.[72,78]

Women generally experience ASCVD events at a later age and have lower event rates than men,[79] but given longer life expectancy,[80] have a similar lifetime cardiovascular risk.[69] Evolution of risk factors over the lifetime also differs between the sexes.[81,82] Furthermore, women-
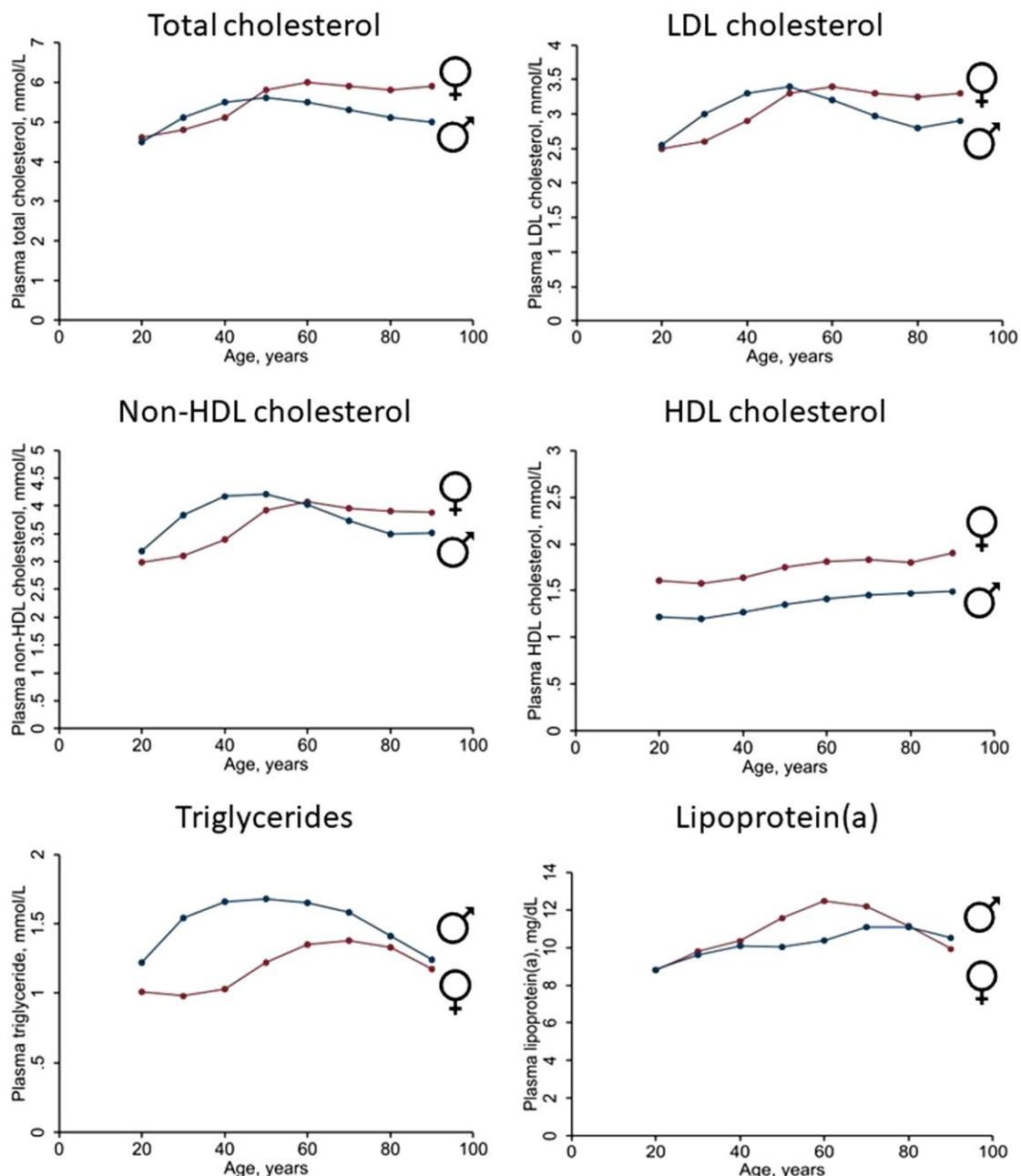
Figure 1 Mean non-fasting plasma levels of total cholesterol, low-density lipoprotein (LDL) cholesterol, non-high-density lipoprotein (HDL) cholesterol, HDL cholesterol, triglycerides (TGs), and lipoprotein(a) [Lp(a)] based on data from 59,278 women and 48,314 men in the Copenhagen General Population 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 ≤4 mmol/L (≤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°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 × Lp(a), mg/dL − 3.83[32]

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

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

|	No. total	No. events		Risk ratio (95% CI)	P value
Myocardial infarction					
Women	56,044	2,084		2.82 (1.29-6.16)	0.009
Men	45,263	3,613		1.53 (0.91-2.59)	0.11
Ischaemic heart disease					
Women	56,044	6,082		1.92 (1.26-2.93)	0.002
Men	45,263	7,854		1.45 (1.05-1.99)	0.023
Cardiovascular death*					
Women	56,044	720		5.31 (3.37-8.37)	<0.001
Men	45,263	940		0.94 (0.54-1.62)	0.82
Death of any cause					
Women	56,044	8,181		4.19 (1.72-10.2)	0.002
Men	45,263	8,776		1.28 (1.02-1.60)	0.036

Risk ratio for a 1 mmol/L higher LDL cholesterol

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.[44,45] 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.[87] Oestrogens decrease atherosclerotic plaque burden

in models of atherosclerosis,[88,89] and oestradiol can increase endothelial nitric oxide production *in vitro*,[90,91] resulting in increased vasodilation and improved endothelial cell function in mouse models,[92] in isolated human arterioles,[93] and in *cis*- and transgender human females treated with oestradiol.[94,95] 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,[96] reduce leucocyte recruitment[97] and interleukin-6 expression[98] in (atherosclerotic) mice, and have been shown to prevent vascular smooth muscle cell (SMC) proliferation and extracellular matrix deposition,[99] 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.[100] 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.[101] The Estrogen in Prevention of Atherosclerosis Trial (EPAT) did, however, suggest an oestrogen-dependent reduction in atherosclerosis progression.[102]

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.[103] 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.[104,105] Female plaque contained more networks associated with SMC phenotypic modulation and endothelial mesenchymal transition, whereas male plaques exhibited pathways associated with immunoreactivity.[105] Consistent with this, carotid endarterectomy specimens from women showed less inflammatory infiltrates, smaller necrotic cores, and enhanced SMC and collagen content.[106] 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.[106] 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.[107,108] 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.[109,110] 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,[111] these differences are small and unlikely to confer a worse clinical prognosis.[112]

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.[113] 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.[113] 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.[114] Another important consideration is bleeding complications, which are more prevalent in women than in men.[111,114,115] 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,[116] and a higher burden of microvascular dysfunction with more ischaemia with non-obstructive coronary arteries (INOCA), especially in the 45–65 year age group.[117–119] As symptoms are more diverse and vague than in men, even with obstructive coronary artery disease,[120–122] MI is often silent or missed.[121,123,124]

Women have similar atheroma burden as men,[125] 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.[126,127] Given the limitations of conventional angiography in women with INOCA,[46] computed tomography angiography is useful to exclude obstructive disease, and to identify plaque burden and low attenuation plaque, a powerful predictor of MI risk.[128,129] 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.[130] A CAC score >100 or ≥75th 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,[131] 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.[130] Irrespective of the pathophysiology, women with acute coronary syndrome tend to have poorer outcomes than men,[132] reflecting increased comorbidities, and delays and underuse of guideline-recommended treatment.[133,134]

Stroke

Stroke is the third leading cause of death and disability in women.[135] Lifetime prevalence is higher and outcome poorer than in men due to older age at onset.[136] As for IHD, women with stroke often present with atypical symptoms, increasing the risk of missed or delayed diagnosis.[137,138] 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.[136] 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).[136] Finally, an adverse lipid profile is one of the most important preventable causes of stroke in women.[139] 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.[6–10,140]

Peripheral artery disease

Although peripheral artery disease (PAD) is at least as prevalent in women as in men,[141,142] 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.[143,144] Even among symptomatic PAD patients, women are more likely to experience atypical limb symptoms rather than intermittent claudication,[145] with greater and faster reduction in functional status. Consequently, women with PAD are more likely to present with advanced, multilevel lower extremity disease[146–149] and are less likely to be treated effectively with antithrombotic medications, and lipid- and blood pressure-lowering therapy than men with PAD.[150–153] While risk for MACE and mortality is similar,[154,155] women with PAD are at higher risk for above knee amputation than men.[156]

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,[157–159] persisting during adolescence.[160,161] Lipids also vary during the menstrual cycle (highest at ovulation),[162] 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*)[163] are important in women with higher pre-pregnancy levels.[13,14,163] Breastfeeding favourably modulates hyperlipidaemia,[164,165] and when continued for >12 months over the lifetime, is associated with lower risk of ASCVD.[166–168] 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.[169,170]

Familial hypercholesterolaemia

Familial hypercholesterolaemia is characterized by elevated LDL-C levels compared with the general population.[171] 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,[172] later diagnosis (on average, by ~2.5 years), and underuse of maximal statin doses or combination LLT.[11] 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; $P = .0007$).[11] These disparities in FH care impact ASCVD risk, with registry data showing the highest excess CHD risk among younger women with FH.[171,173]

Adding to this, discontinuation of LLT before and during pregnancy and breastfeeding[60] 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)[174] was attained earlier by women than men.[12] All FH women had attained this LDL-C threshold by age 33 years, seven years earlier than for FH men.[12] Although updated US Food and Drug Administration (FDA) guidance allows for more flexible options for shared decision making in highest-risk women during pregnancy,[175] 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,[176,177] 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.[178] 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.
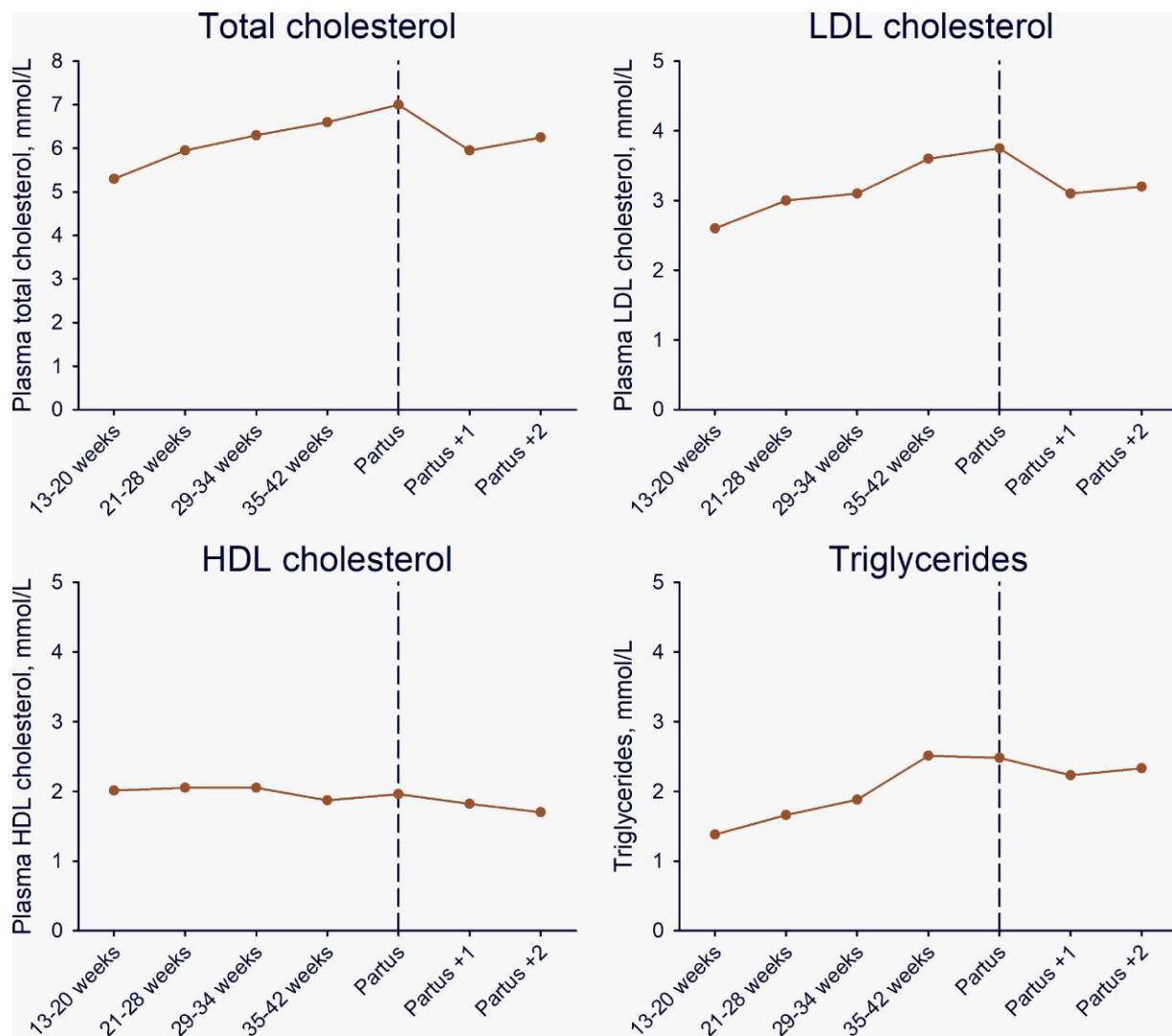

Figure 3 Mean plasma levels of total, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) cholesterol, and triglycerides as a function of pregnancy week, at delivery (partus), and one and two weeks after delivery. Data are medians calculated from the 2.5 and 97.5 percentiles from Klajnbard et al.[163] 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.[179] High plasma TGs also associate with vascular and systemic inflammation.[180,181] Mendelian randomization studies suggested that the observed associations between TGs and remnant cholesterol may be causal[182–187]; however, with the lack of robust evidence that lowering TGs or remnant cholesterol reduces ASCVD,[179,180,188–191] current guidelines do not provide treatment goals.[60]

As discussed, TGs increase from childhood until ∼70 years in women and ∼60 years in men (*Figure 1*).[192] From 20–80 years, women consistently have lower TG levels than men, partly explained by higher alcohol intake in men,[182] 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.[182–184,193]

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).[182] 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)].[185] 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
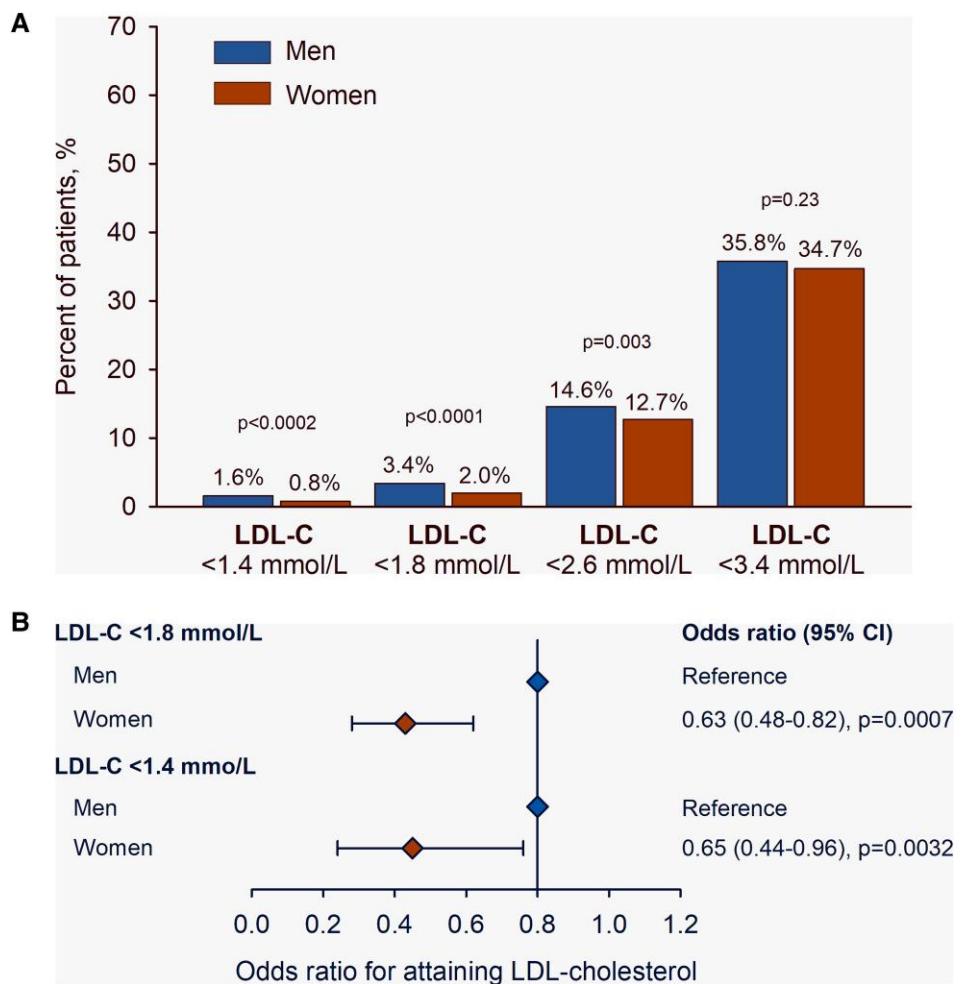
Figure 4 Attainment of low-density lipoprotein cholesterol (LDL-C) targets among men and women with familial hypercholesterolaemia on lipid-lowering therapy (statin, ezetimibe, and/or a PCSK9 inhibitor). Panel A shows the percentage of patients on treatment and below different LDL-C thresholds. Panel 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[11]
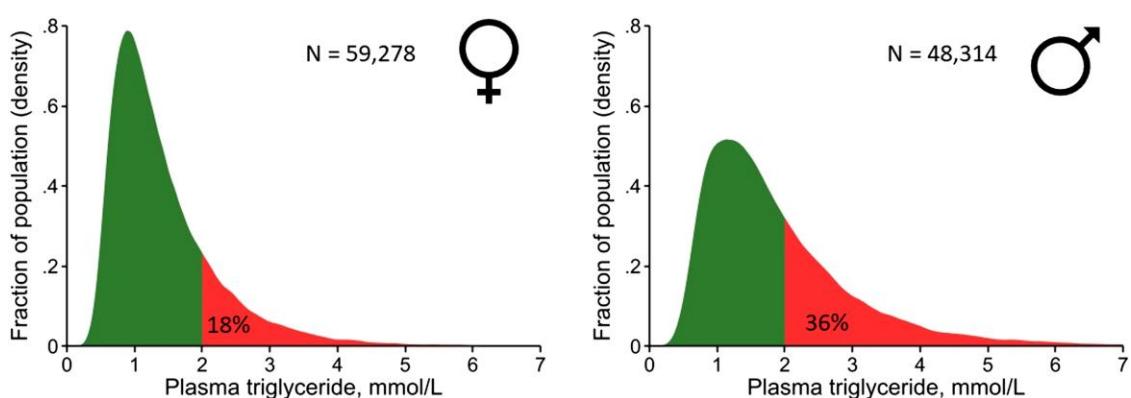
Figure 5 Density distribution of plasma levels of triglycerides in 59,278 women and 48,314 men from the Copenhagen General Population Study. Triglycerides were measured in the non-fasting state and analysed on fresh samples using standard hospital assays. To convert triglycerides from mmol/L to mg/dL 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[194]. In the Women's Health Study in >28,000 subjects,[195] 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.[196–206] Plasma levels of Lp(a) show similar distribution in men and women, varying with ethnicity[207,208] (*Figure 6*). The Lp(a) concentration increases in women around 50 years coinciding with the onset of menopause[209–212] (*Figure 1*), possibly due to hormonal changes and/or ageing. Indeed, Lp(a) concentration is 12%–20% lower in women on HRT vs. controls,[213–215] and approximately doubles in pregnancy.[216,217] 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[218](*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.[60,219]

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,[220] 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,[7] and more likely to refuse or discontinue statin treatment due to perceived side effects.[7,221,222] 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[36] 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.
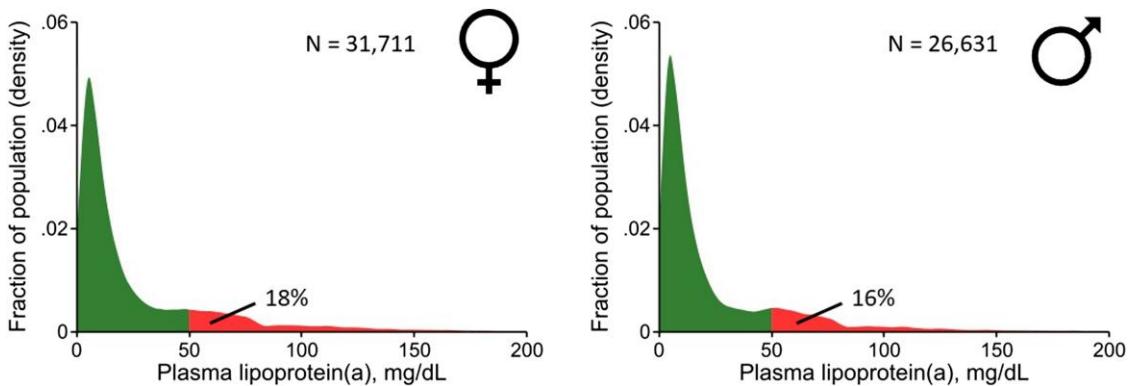
Figure 6 Density distribution of plasma levels of lipoprotein(a) [Lp(a)] in 31,711 women and 26,631 men from the Copenhagen General Population Study. The Lp(a) concentration was measured in the non-fasting state and analysed with different assays over time, but all assays were calibrated corresponding 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°C before measurement. To convert Lp(a) in mg/dL to nmol/L: Lp(a), nmol/L = 2.18 × Lp(a), mg/dL − 3.83[32]

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

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Data Availability

No data were generated or analysed for this manuscript.

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References

1. Timmis A, Vardas P, Townsend N, Torbica A, Katus H, De Smedt D, et al. European Society of Cardiology: cardiovascular disease statistics 2021. Eur Heart J 2022;**43**: 716–99. https://doi.org/10.1093/eurheartj/ehab892
2. Tsao CW, Aday AW, Almarzooq ZI, Alonso A, Beaton AZ, Bittencourt MS, et al. Heart disease and stroke statistics—2022 update: a report from the American Heart Association. Circulation 2022;**145**:e153–639. https://doi.org/10.1161/CIR.0000000000001052
3. Curtin SC. Trends in cancer and heart disease death rates among adults aged 45–64: United States, 1999–2017. Natl Vital Stat Rep 2019;**68**:1–9.
4. Bairey Merz CN, Andersen H, Sprague E, Burns A, Keida M, Walsh MN, et al. Knowledge, attitudes, and beliefs regarding cardiovascular disease in women: the Women's Heart Alliance. J Am Coll Cardiol 2017;**70**:123–32. https://doi.org/10.1016/j.jacc.2017.05.024
5. Cushman M, Shay CM, Howard VJ, Jimenez MC, Lewey J, McSweeney JC, et al. Ten-year differences in women's awareness related to coronary heart disease: results of the 2019 American Heart Association national survey: a special report from the American Heart Association. Circulation 2021;**143**:e239–48. https://doi.org/10.1161/CIR.0000000000000907
6. Redfors B, Angeras O, Ramunddal T, Petursson P, Haraldsson I, Dworeck C, et al. Trends in gender differences in cardiac care and outcome after acute myocardial infarction in Western Sweden: a report from the Swedish web system for enhancement of evidence-based care in heart disease evaluated according to recommended therapies (SWEDEHEART). J Am Heart Assoc 2015;**4**:e001995. https://doi.org/10.1161/JAHA.115.001995
7. Nanna MG, Wang TY, Xiang Q, Goldberg AC, Robinson JG, Roger VL, et al. Sex differences in the use of statins in community practice. Circ Cardiovasc Qual Outcomes 2019;**12**:e005562. https://doi.org/10.1161/CIRCOUTCOMES.118.005562
8. Peters SAE, Colantonio LD, Zhao H, Bittner V, Dai Y, Farkouh ME, et al. Sex differences in high-intensity statin use following myocardial infarction in the United States. J Am Coll Cardiol 2018;**71**:1729–37. https://doi.org/10.1016/j.jacc.2018.02.032
9. Udell JA, Fonarow GC, Maddox TM, Cannon CP, Frank Peacock W, Laskey WK, et al. Sustained sex-based treatment differences in acute coronary syndrome care: insights from the American Heart Association Get With The Guidelines Coronary Artery Disease Registry. Clin Cardiol 2018;**41**:758–68. https://doi.org/10.1002/clc.22938
10. Benson RA, Okoth K, Keerthy D, Gokhale K, Adderley NJ, Nirantharakumar K, et al. Analysis of the relationship between sex and prescriptions for guideline-recommended therapy in peripheral arterial disease, in relation to 1-year all-cause

mortality: a primary care cohort study. *BMJ Open* 2022;**12**:e055952. https://doi.org/10.1136/bmjopen-2021-055952

11. EAS Familial Hypercholesterolaemia Studies Collaboration (FHSC). Global perspective of familial hypercholesterolaemia: a cross-sectional study from the EAS Familial Hypercholesterolaemia Studies Collaboration (FHSC). *Lancet* 2021;**398**:1713–25. https://doi.org/10.1016/S0140-6736(21)01122-3

12. Johansen AK, Bogsrud MP, Christensen JJ, Rundblad A, Narverud I, Ulven S, *et al.* Young women with familial hypercholesterolemia have higher LDL-cholesterol burden than men: novel data using repeated measurements during 12-years follow-up. *Atheroscler Plus* 2023;**51**:28–34. https://doi.org/10.1016/j.athplu.2023.01.001

13. Graham DF, Raal FJ. Management of familial hypercholesterolemia in pregnancy. *Curr Opin Lipidol* 2021;**32**:370–7. https://doi.org/10.1097/MOL.0000000000000790

14. Dathan-Stumpf A, Vogel M, Jank A, Thiery J, Kiess W, Stepan H. Reference intervals of serum lipids in the second and third trimesters of pregnancy in a Caucasian cohort: the LIFE Child study. *Arch Gynecol Obstet* 2019;**300**:1531–9. https://doi.org/10.1007/s00404-019-05342-2

15. Fairweather D, Rose NR. Women and autoimmune diseases. *Emerg Infect Dis* 2004;**10**: 2005–11. https://doi.org/10.3201/eid1011.040367

16. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Back M, *et al.* 2021 ESC guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J* 2021;**42**: 3227–337. https://doi.org/10.1093/eurheartj/ehab484

17. Maas A, Rosano G, Cifkova R, Chieffo A, van Dijken D, Hamoda H, *et al.* Cardiovascular health after menopause transition, pregnancy disorders, and other gynaecologic conditions: a consensus document from European cardiologists, gynaecologists, and endocrinologists. *Eur Heart J* 2021;**42**:967–84. https://doi.org/10.1093/eurheartj/ehaa1044

18. Roeters van Lennep JE, Heida KY, Bots ML, Hoek A, collaborators of the Dutch Multidisciplinary Guideline Development Group on Cardiovascular Risk Management after Reproductive Disorders. Cardiovascular disease risk in women with premature ovarian insufficiency: a systematic review and meta-analysis. *Eur J Prev Cardiol* 2016;**23**:178–86. https://doi.org/10.1177/2047487314556600

19. Wekker V, van Dammen L, Koning A, Heida KY, Painter RC, Limpens J, *et al.* Long-term cardiometabolic disease risk in women with PCOS: a systematic review and meta-analysis. *Hum Reprod Update* 2020;**26**:942–60. https://doi.org/10.1093/humupd/dmaa029

20. Shifren JL, Gass ML. The North American Menopause Society recommendations for clinical care of midlife women. *Menopause* 2014;**21**:1038–62. https://doi.org/10.1097/GME.0000000000000319

21. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, *et al.* Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case–control study. *Lancet* 2004;**364**:937–52. https://doi.org/10.1016/S0140-6736(04)17018-9

22. Centers for Disease Control and Prevention. National Diabetes Statistics Report 2020 2021. Available from: https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf (accessed 4 May 2023).

23. Angoulvant D, Ducluzeau PH, Renoult-Pierre P, Fauchier G, Herbert J, Semaan C, *et al.* Impact of gender on relative rates of cardiovascular events in patients with diabetes. *Diabetes Metab* 2021;**47**:101226. https://doi.org/10.1016/j.diabet.2021.101226

24. Ohkuma T, Komorita Y, Peters SAE, Woodward M. Diabetes as a risk factor for heart failure in women and men: a systematic review and meta-analysis of 47 cohorts including 12 million individuals. *Diabetologia* 2019;**62**:1550–60. https://doi.org/10.1007/s00125-019-4926-x

25. Prospective Studies Collaboration and Asia Pacific Cohort Studies Collaboration. Sex-specific relevance of diabetes to occlusive vascular and other mortality: a collaborative meta-analysis of individual data from 980 793 adults from 68 prospective studies. *Lancet Diabetes Endocrinol* 2018;**6**:538–46. https://doi.org/10.1016/S2213-8587(18)30079-2

26. Peters SA, Huxley RR, Woodward M. Diabetes as risk factor for incident coronary heart disease in women compared with men: a systematic review and meta-analysis of 64 cohorts including 858,507 individuals and 28,203 coronary events. *Diabetologia* 2014;**57**:1542–51. https://doi.org/10.1007/s00125-014-3260-6

27. Broni EK, Ndumele CE, Echouffo-Tcheugui JB, Kalyani RR, Bennett WL, Michos ED. The diabetes-cardiovascular connection in women: understanding the known risks, outcomes, and implications for care. *Curr Diab Rep* 2022;**22**:11–25. https://doi.org/10.1007/s11892-021-01444-x

28. Logue J, Walker JJ, Colhoun HM, Leese GP, Lindsay RS, McKnight JA, *et al.* Do men develop type 2 diabetes at lower body mass indices than women? *Diabetologia* 2011;**54**:3003–6. https://doi.org/10.1007/s00125-011-2313-3

29. Wannamethee SG, Papacosta O, Lawlor DA, Whincup PH, Lowe GD, Ebrahim S, *et al.* Do women exhibit greater differences in established and novel risk factors between diabetes and non-diabetes than men? The British Regional Heart Study and British Women's Heart Study. *Diabetologia* 2012;**55**:80–7. https://doi.org/10.1007/s00125-011-2284-4

30. Walli-Attaei M, Joseph P, Rosengren A, Chow CK, Rangarajan S, Lear SA, *et al.* Variations between women and men in risk factors, treatments, cardiovascular disease incidence, and death in 27 high-income, middle-income, and low-income countries

(PURE): a prospective cohort study. *Lancet* 2020;**396**:97–109. https://doi.org/10.1016/S0140-6736(20)30543-2

31. Prospective Studies Collaboration, Whitlock G, Lewington S, Sherliker P, Clarke R, Emberson J, *et al.* Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. *Lancet* 2009;**373**:1083–96. https://doi.org/10.1016/S0140-6736(09)60318-4

32. Langlois MR, Nordestgaard BG, Langsted A, Chapman MJ, Aakre KM, Baum H, *et al.* Quantifying atherogenic lipoproteins for lipid-lowering strategies: consensus-based recommendations from EAS and EFLM. *Clin Chem Lab Med* 2020;**58**:496–517. https://doi.org/10.1515/cclm-2019-1253

33. Matthews KA, Crawford SL, Chae CU, Everson-Rose SA, Sowers MF, Sternfeld B, *et al.* Are changes in cardiovascular disease risk factors in midlife women due to chronological aging or to the menopausal transition? *J Am Coll Cardiol* 2009;**54**:2366–73. https://doi.org/10.1016/j.jacc.2009.10.009

34. Lau ES, Michos ED. Blood pressure trajectories through the menopause transition: different paths, same journey. *Circ Res* 2022;**130**:323–5. https://doi.org/10.1161/CIRCRESAHA.122.320664

35. Samargandy S, Matthews KA, Brooks MM, Barinas-Mitchell E, Magnani JW, Thurston RC, *et al.* Trajectories of blood pressure in midlife women: does menopause matter? *Circ Res* 2022;**130**:312–22. https://doi.org/10.1161/CIRCRESAHA.121.319424

36. Khoudary SRE, Aggarwal B, Beckie TM, Hodis HN, Johnson AE, Langer RD, *et al.* Menopause transition and cardiovascular disease risk: implications for timing of early prevention: a scientific statement from the American Heart Association. *Circulation* 2020;**142**:e506–32. https://doi.org/10.1161/CIR.0000000000000912

37. Clayton GL, Soares AG, Kilpi F, Fraser A, Welsh P, Sattar N, *et al.* Cardiovascular health in the menopause transition: a longitudinal study of up to 3892 women with up to four repeated measures of risk factors. *BMC Med* 2022;**20**:299. https://doi.org/10.1186/s12916-022-02454-6

38. El Khoudary SR, Wildman RP, Matthews K, Thurston RC, Bromberger JT, Sutton-Tyrrell K. Progression rates of carotid intima-media thickness and adventitial diameter during the menopausal transition. *Menopause* 2013;**20**:8–14. https://doi.org/10.1097/gme.0b013e3182611787

39. Matthews KA, Chen X, Barinas-Mitchell E, Brooks MM, Derby CA, Harlow S, *et al.* Age at menopause in relationship to lipid changes and subclinical carotid disease across 20 years: study of women's health across the nation. *J Am Heart Assoc* 2021;**10**:e021362. https://doi.org/10.1161/JAHA.121.021362

40. Honigberg MC, Zekavat SM, Aragam K, Finneran P, Klarin D, Bhatt DL, *et al.* Association of premature natural and surgical menopause with incident cardiovascular disease. *JAMA* 2019;**322**:2411–21. https://doi.org/10.1001/jama.2019.19191

41. Honigberg MC, Zekavat SM, Niroula A, Griffin GK, Bick AG, Pirruccello JP, *et al.* Premature menopause, clonal hematopoiesis, and coronary artery disease in postmenopausal women. *Circulation* 2021;**143**:410–23. https://doi.org/10.1161/CIRCULATIONAHA.120.051775

42. Cupido AJ, Asselbergs FW, Schmidt AF, Hovingh GK. Low-density lipoprotein cholesterol attributable cardiovascular disease risk is sex specific. *J Am Heart Assoc* 2022;**11**: e024248. https://doi.org/10.1161/JAHA.121.024248

43. WHO CVD Risk Chart Working Group. World Health Organization cardiovascular disease risk charts: revised models to estimate risk in 21 global regions. *Lancet Glob Health* 2019;**7**:e1332–45. doi:10.1016/S2214-109X(19)30318-3

44. Benn M, Nordestgaard BG, Frikke-Schmidt R, Tybjaerg-Hansen A. Low LDL cholesterol, PCSK9 and HMGCR genetic variation, and risk of Alzheimer's disease and Parkinson's disease: Mendelian randomisation study. *BMJ* 2017;**357**:j1648. https://doi.org/10.1136/bmj.j1648

45. Benn M, Tybjaerg-Hansen A, Nordestgaard BG. Low LDL cholesterol by PCSK9 variation reduces cardiovascular mortality. *J Am Coll Cardiol* 2019;**73**:3102–14. https://doi.org/10.1016/j.jacc.2019.03.517

46. Vogel B, Acevedo M, Appelman Y, Bairey Merz CN, Chieffo A, Figtree GA, *et al.* The Lancet women and cardiovascular disease commission: reducing the global burden by 2030. *Lancet* 2021;**397**:2385–438. https://doi.org/10.1016/S0140-6736(21)00684-X

47. Elder P, Sharma G, Gulati M, Michos ED. Identification of female-specific risk enhancers throughout the lifespan of women to improve cardiovascular disease prevention. *Am J Prev Cardiol* 2020;**2**:100028. https://doi.org/10.1016/j.ajpc.2020.100028

48. Agarwala A, Michos ED, Samad Z, Ballantyne CM, Virani SS. The use of sex-specific factors in the assessment of women's cardiovascular risk. *Circulation* 2020;**141**: 592–9. https://doi.org/10.1161/CIRCULATIONAHA.119.043429

49. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, *et al.* 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *Circulation* 2019;**140**:e596–646. https://doi.org/10.1161/CIR.0000000000000678

50. Ahmed SB, Dumanski SM. Do sex and gender matter in kidney and cardiovascular disease? *Am J Kidney Dis* 2021;**78**:177–9. https://doi.org/10.1053/j.ajkd.2021.05.002

51. Asanuma Y, Oeser A, Shintani AK, Turner E, Olsen N, Fazio S, *et al.* Premature coronary-artery atherosclerosis in systemic lupus erythematosus. *N Engl J Med* 2003;**349**:2407–15. https://doi.org/10.1056/NEJMoa035611

52. Chung CP, Oeser A, Raggi P, Gebretsadik T, Shintani AK, Sokka T, et al. Increased coronary-artery atherosclerosis in rheumatoid arthritis: relationship to disease duration and cardiovascular risk factors. Arthritis Rheum 2005;**52**:3045–53. https://doi.org/10.1002/art.21288

53. del Rincon ID, Williams K, Stern MP, Freeman GL, Escalante A. High incidence of cardiovascular events in a rheumatoid arthritis cohort not explained by traditional cardiac risk factors. Arthritis Rheum 2001;**44**:2737–45. < 2737::AID-ART460>3.0.CO;2-#. https://doi.org/10.1002/1529-0131(200112)44:12<2737::AID-ART460>3.0.CO;2-%23

54. Avina-Zubieta JA, Choi HK, Sadatsafavi M, Etminan M, Esdaile JM, Lacaille D. Risk of cardiovascular mortality in patients with rheumatoid arthritis: a meta-analysis of observational studies. Arthritis Rheum 2008;**59**:1690–7. https://doi.org/10.1002/art.24092

55. Aviña-Zubieta JA, To F, Vostretsova K, De Vera M, Sayre EC, Esdaile JM. Risk of myocardial infarction and stroke in newly diagnosed systemic lupus erythematosus: a general population-based study. Arthritis Care Res (Hoboken). 2017;**69**:849–856. https://doi.org/10.1002/acr.23018

56. Hansildaar R, Vedder D, Baniaamam M, Tausche AK, Gerritsen M, Nurmohamed MT. Cardiovascular risk in inflammatory arthritis: rheumatoid arthritis and gout. Lancet Rheumatol 2021;**3**:e58–70. https://doi.org/10.1016/S2665-9913(20)30221-6

57. Giannelou M, Mavragani CP. Cardiovascular disease in systemic lupus erythematosus: a comprehensive update. J Autoimmun 2017;**82**:1–12. https://doi.org/10.1016/j.jaut.2017.05.008

58. Agca R, Heslinga SC, Rollefstad S, Heslinga M, McInnes IB, Peters MJ, et al. EULAR Recommendations for cardiovascular disease risk management in patients with rheumatoid arthritis and other forms of inflammatory joint disorders: 2015/2016 update. Ann Rheum Dis 2017;**76**:17–28. https://doi.org/10.1136/annrheumdis-2016-209775

59. Conrad N, Verbeke G, Molenberghs G, Goetschalckx L, Callender T, Cambridge G, et al. Autoimmune diseases and cardiovascular risk: a population-based study on 19 autoimmune diseases and 12 cardiovascular diseases in 22 million individuals in the UK. Lancet 2022;**400**:733–43. https://doi.org/10.1016/S0140-6736(22)01349-6

60. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, et al. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J 2020;**41**:111–88. https://doi.org/10.1093/eurheartj/ehz455

61. Pelletier R, Khan NA, Cox J, Daskalopoulou SS, Eisenberg MJ, Bacon SL, et al. Sex versus gender-related characteristics: which predicts outcome after acute coronary syndrome in the young? J Am Coll Cardiol 2016;**67**:127–35. https://doi.org/10.1016/j.jacc.2015.10.067

62. Colella TJF, Hardy M, Hart D, Price JAD, Sarfi H, Mullen KA, et al. The Canadian Women's Heart Health Alliance atlas on the epidemiology, diagnosis, and management of cardiovascular disease in women—chapter 3: patient perspectives. CJC Open 2021;**3**:229–35. https://doi.org/10.1016/j.cjco.2020.11.020

63. Connelly PJ, Azizi Z, Alipour P, Delles C, Pilote L, Raparelli V. The importance of gender to understand sex differences in cardiovascular disease. Can J Cardiol 2021;**37**:699–710. https://doi.org/10.1016/j.cjca.2021.02.005

64. Fabreau GE, Leung AA, Southern DA, Knudtson ML, McWilliams JM, Ayanian JZ, et al. Sex, socioeconomic status, access to cardiac catheterization, and outcomes for acute coronary syndromes in the context of universal healthcare coverage. Circ Cardiovasc Qual Outcomes 2014;**7**:540–9. https://doi.org/10.1161/CIRCOUTCOMES.114.001021

65. Backholer K, Peters SAE, Bots SH, Peeters A, Huxley RR, Woodward M. Sex differences in the relationship between socioeconomic status and cardiovascular disease: a systematic review and meta-analysis. J Epidemiol Community Health 2017;**71**:550–7. https://doi.org/10.1136/jech-2016-207890

66. Norris CM, Yip CYY, Nerenberg KA, Clavel MA, Pacheco C, Foulds HJA, et al. State of the science in women's cardiovascular disease: a Canadian perspective on the influence of sex and gender. J Am Heart Assoc 2020;**9**:e015634. https://doi.org/10.1161/JAHA.119.015634

67. Daponte-Codina A, Knox EC, Mateo-Rodriguez I, Seims A, Regitz-Zagrosek V, Maas A, et al. Gender and social inequalities in awareness of coronary artery disease in European countries. Int J Environ Res Public Health 2022;**19**:1388. https://doi.org/10.3390/ijerph19031388

68. Samulowitz A, Gremyr I, Eriksson E, Hensing G. "Brave Men" and "Emotional Women": a theory-guided literature review on gender bias in health care and gendered norms towards patients with chronic pain. Pain Res Manag 2018;**2018**:6358624. https://doi.org/10.1155/2018/6358624

69. Leening MJ, Ferket BS, Steyerberg EW, Kavousi M, Deckers JW, Nieboer D, et al. Sex differences in lifetime risk and first manifestation of cardiovascular disease: prospective population based cohort study. BMJ 2014;**349**:g5992. https://doi.org/10.1136/bmj.g5992

70. Rexrode KM, Madsen TE, Yu AYX, Carcel C, Lichtman JH, Miller EC. The impact of sex and gender on stroke. Circ Res 2022;**130**:512–28. https://doi.org/10.1161/CIRCRESAHA.121.319915

71. SCORE2 working group and ESC Cardiovascular risk collaboration. SCORE2 risk prediction algorithms: new models to estimate 10-year risk of cardiovascular disease in Europe. Eur Heart J 2021;**42**:2439–54. https://doi.org/10.1093/eurheartj/ehab309

72. Wenzl FA, Kraler S, Ambler G, Weston C, Herzog SA, Raber L, et al. Sex-specific evaluation and redevelopment of the GRACE score in non-ST-segment elevation acute coronary syndromes in populations from the UK and Switzerland: a multinational analysis with external cohort validation. Lancet 2022;**400**:744–56. https://doi.org/10.1016/S0140-6736(22)01483-0

73. Shah AS, Griffiths M, Lee KK, McAllister DA, Hunter AL, Ferry AV, et al. High sensitivity cardiac troponin and the under-diagnosis of myocardial infarction in women: prospective cohort study. BMJ 2015;**350**:g7873. https://doi.org/10.1136/bmj.g7873

74. Cook NR, Paynter NP, Eaton CB, Manson JE, Martin LW, Robinson JG, et al. Comparison of the Framingham and Reynolds risk scores for global cardiovascular risk prediction in the multiethnic women's health initiative. Circulation 2012;**125**:1748–56. S1–11. https://doi.org/10.1161/CIRCULATIONAHA.111.075929

75. Lakoski SG, Greenland P, Wong ND, Schreiner PJ, Herrington DM, Kronmal RA, et al. Coronary artery calcium scores and risk for cardiovascular events in women classified as "low risk" based on Framingham risk score: the multi-ethnic study of atherosclerosis (MESA). Arch Intern Med 2007;**167**:2437–42. https://doi.org/10.1001/archinte.167.22.2437

76. Ridker PM, Buring JE, Rifai N, Cook NR. Development and validation of improved algorithms for the assessment of global cardiovascular risk in women: the Reynolds risk score. JAMA 2007;**297**:611–9. https://doi.org/10.1001/jama.297.6.611

77. Kavousi M, Desai CS, Ayers C, Blumenthal RS, Budoff MJ, Mahabadi AA, et al. Prevalence and prognostic implications of coronary artery calcification in low-risk women: a meta-analysis. JAMA 2016;**316**:2126–34. https://doi.org/10.1001/jama.2016.17020

78. Mortensen MB, Tybjaerg-Hansen A, Nordestgaard BG. Statin eligibility for primary prevention of cardiovascular disease according to 2021 European prevention guidelines compared with other international guidelines. JAMA Cardiol 2022;**7**:836–43. https://doi.org/10.1001/jamacardio.2022.1876

79. Roth GA, Mensah GA, Fuster V. The global burden of cardiovascular diseases and risks: a compass for global action. J Am Coll Cardiol 2020;**76**:2980–1. https://doi.org/10.1016/j.jacc.2020.11.021

80. Austad SN. Sex differences in health and aging: a dialog between the brain and gonad? Geroscience 2019;**41**:267–73. https://doi.org/10.1007/s11357-019-00081-3

81. Ji H, Kim A, Ebinger JE, Niiranen TJ, Claggett BL, Bairey Merz CN, et al. Sex differences in blood pressure trajectories over the life course. JAMA Cardiol 2020;**5**:19–26. https://doi.org/10.1001/jamacardio.2019.5306

82. Ji H, Niiranen TJ, Rader F, Henglin M, Kim A, Ebinger JE, et al. Sex differences in blood pressure associations with cardiovascular outcomes. Circulation 2021;**143**:761–3. https://doi.org/10.1161/CIRCULATIONAHA.120.049360

83. Baart SJ, Dam V, Scheres LJJ, Damen J, Spijker R, Schuit E, et al. Cardiovascular risk prediction models for women in the general population: a systematic review. PLoS One 2019;**14**:e0210329. https://doi.org/10.1371/journal.pone.0210329

84. Markovitz AR, Stuart JJ, Horn J, Williams PL, Rimm EB, Missmer SA, et al. Does pregnancy complication history improve cardiovascular disease risk prediction? Findings from the HUNT study in Norway. Eur Heart J 2019;**40**:1113–20. https://doi.org/10.1093/eurheartj/ehy863

85. Yeung MW, Wang S, van de Vegte YJ, Borisov O, van Setten J, Snieder H, et al. Twenty-five novel loci for carotid intima-media thickness: a genome-wide association study in >45 000 individuals and meta-analysis of >100 000 individuals. Arterioscler Thromb Vasc Biol 2022;**42**:484–501. https://doi.org/10.1161/ATVBAHA.121.317007

86. Strawbridge RJ, Ward J, Bailey MES, Cullen B, Ferguson A, Graham N, et al. Carotid intima-media thickness: novel loci, sex-specific effects, and genetic correlations with obesity and glucometabolic traits in UK Biobank. Arterioscler Thromb Vasc Biol 2020;**40**:446–61. https://doi.org/10.1161/ATVBAHA.119.313226

87. Vaura F, Palmu J, Aittokallio J, Kauko A, Niiranen T. Genetic, molecular, and cellular determinants of sex-specific cardiovascular traits. Circ Res 2022;**130**:611–31. https://doi.org/10.1161/CIRCRESAHA.121.319891

88. Hodgin JB, Krege JH, Reddick RL, Korach KS, Smithies O, Maeda N. Estrogen receptor alpha is a major mediator of 17beta-estradiol's atheroprotective effects on lesion size in Apoe−/− mice. J Clin Invest 2001;**107**:333–40. https://doi.org/10.1172/JCI11320

89. Bourassa PA, Milos PM, Gaynor BJ, Breslow JL, Aiello RJ. Estrogen reduces atherosclerotic lesion development in apolipoprotein E-deficient mice. Proc Natl Acad Sci U S A 1996;**93**:10022–7. https://doi.org/10.1073/pnas.93.19.10022

90. Schulz E, Anter E, Zou MH, Keaney JF Jr. Estradiol-mediated endothelial nitric oxide synthase association with heat shock protein 90 requires adenosine monophosphate-dependent protein kinase. Circulation 2005;**111**:3473–80. https://doi.org/10.1161/CIRCULATIONAHA.105.546812

91. Vanhoutte PM, Zhao Y, Xu A, Leung SW. Thirty years of saying NO: sources, fate, actions, and misfortunes of the endothelium-derived vasodilator mediator. Circ Res 2016;**119**:375–96. https://doi.org/10.1161/CIRCRESAHA.116.306531

92. Darblade B, Pendaries C, Krust A, Dupont S, Fouque MJ, Rami J, et al. Estradiol alters nitric oxide production in the mouse aorta through the alpha-, but not beta-, estrogen receptor. Circ Res 2002;**90**:413–9. https://doi.org/10.1161/hh0402.105096

93. SenthilKumar G, Katunaric B, Bordas-Murphy H, Young M, Doren EL, Schulz ME, et al. 17beta-estradiol promotes sex-specific dysfunction in isolated human arterioles. Am J

Physiol Heart Circ Physiol 2023;**324**:H330–7. https://doi.org/10.1152/ajpheart.00708.2022

94. Vitale C, Mercuro G, Cerquetani E, Marazzi G, Patrizi R, Pelliccia F, *et al.* Time since menopause influences the acute and chronic effect of estrogens on endothelial function. *Arterioscler Thromb Vasc Biol* 2008;**28**:348–52. https://doi.org/10.1161/ATVBAHA.107.158634

95. New G, Timmins KL, Duffy SJ, Tran BT, O'Brien RC, Harper RW, *et al.* Long-term estrogen therapy improves vascular function in male to female transsexuals. *J Am Coll Cardiol* 1997;**29**:1437–44. https://doi.org/10.1016/S0735-1097(97)00080-6

96. Caulin-Glaser T, Watson CA, Pardi R, Bender JR. Effects of 17beta-estradiol on cytokine-induced endothelial cell adhesion molecule expression. *J Clin Invest* 1996;**98**:36–42. https://doi.org/10.1172/JCI118774

97. Alvarez A, Hermenegildo C, Issekutz AC, Esplugues JV, Sanz MJ. Estrogens inhibit angiotensin II-induced leukocyte-endothelial cell interactions in vivo via rapid endothelial nitric oxide synthase and cyclooxygenase activation. *Circ Res* 2002;**91**:1142–50. https://doi.org/10.1161/01.RES.0000046018.23605.3E

98. Sukovich DA, Kauser K, Shirley FD, DelVecchio V, Halks-Miller M, Rubanyi GM. Expression of interleukin-6 in atherosclerotic lesions of male ApoE-knockout mice: inhibition by 17beta-estradiol. *Arterioscler Thromb Vasc Biol* 1998;**18**:1498–505. https://doi.org/10.1161/01.ATV.18.9.1498

99. Ueda K, Lu Q, Baur W, Aronovitz MJ, Karas RH. Rapid estrogen receptor signaling mediates estrogen-induced inhibition of vascular smooth muscle cell proliferation. *Arterioscler Thromb Vasc Biol* 2013;**33**:1837–43. https://doi.org/10.1161/ATVBAHA.112.300752

100. Fernandez-Suarez ME, Escola-Gil JC, Pastor O, Davalos A, Blanco-Vaca F, Lasuncion MA, *et al.* Clinically used selective estrogen receptor modulators affect different steps of macrophage-specific reverse cholesterol transport. *Sci Rep* 2016;**6**:32105. https://doi.org/10.1038/srep32105

101. Gartlehner G, Patel SV, Reddy S, Rains C, Schwimmer M, Kahwati L. Hormone therapy for the primary prevention of chronic conditions in postmenopausal persons: updated evidence report and systematic review for the US preventive services task force. *JAMA* 2022;**328**:1747–65. https://doi.org/10.1001/jama.2022.18324

102. Hodis HN, Mack WJ, Lobo RA, Shoupe D, Sevanian A, Mahrer PR, *et al.* Estrogen in the prevention of atherosclerosis. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2001;**135**:939–53. https://doi.org/10.7326/0003-4819-135-11-200112040-00005

103. AlSiraj Y, Chen X, Thatcher SE, Temel RE, Cai L, Blalock E, *et al.* XX sex chromosome complement promotes atherosclerosis in mice. *Nat Commun* 2019;**10**:2631. https://doi.org/10.1038/s41467-019-10462-z

104. Pasterkamp G, den Ruijter HM, Giannarelli C. False utopia of one unifying description of the vulnerable atherosclerotic plaque: a call for recalibration that appreciates the diversity of mechanisms leading to atherosclerotic disease. *Arterioscler Thromb Vasc Biol* 2022;**42**:e86–95. https://doi.org/10.1161/ATVBAHA.121.316693

105. Hartman RJG, Owsiany K, Ma L, Koplev S, Hao K, Slenders L, *et al.* Sex-stratified gene regulatory networks reveal female key driver genes of atherosclerosis involved in smooth muscle cell phenotype switching. *Circulation* 2021;**143**:713–26. https://doi.org/10.1161/CIRCULATIONAHA.120.051231

106. Hellings WE, Pasterkamp G, Verhoeven BA, De Kleijn DP, De Vries JP, Seldenrijk KA, *et al.* Gender-associated differences in plaque phenotype of patients undergoing carotid endarterectomy. *J Vasc Surg* 2007;**45**:289–96. discussion 96–7. https://doi.org/10.1016/j.jvs.2006.09.051

107. Badimon L, Padro T, Vilahur G. Atherosclerosis, platelets and thrombosis in acute ischaemic heart disease. *Eur Heart J Acute Cardiovasc Care* 2012;**1**:60–74. https://doi.org/10.1177/2048872612441582

108. Badimon L, Vilahur G. Thrombosis formation on atherosclerotic lesions and plaque rupture. *J Intern Med* 2014;**276**:618–32. https://doi.org/10.1111/joim.12296

109. Libby P, Buring JE, Badimon L, Hansson GK, Deanfield J, Bittencourt MS, *et al.* Atherosclerosis. *Nat Rev Dis Primers* 2019;**5**:56. https://doi.org/10.1038/s41572-019-0106-z

110. Ramaiola I, Padro T, Pena E, Juan-Babot O, Cubedo J, Martin-Yuste V, *et al.* Changes in thrombus composition and profilin-1 release in acute myocardial infarction. *Eur Heart J* 2015;**36**:965–75. https://doi.org/10.1093/eurheartj/ehu356

111. Patti G, De Caterina R, Abbate R, Andreotti F, Biasucci LM, Calabro P, *et al.* Platelet function and long-term antiplatelet therapy in women: is there a gender-specificity? A 'state-of-the-art' paper. *Eur Heart J* 2014;**35**:2213–23. https://doi.org/10.1093/eurheartj/ehu279

112. Breet NJ, Sluman MA, van Berkel MA, van Werkum JW, Bouman HJ, Harmsze AM, *et al.* Effect of gender difference on platelet reactivity. *Neth Heart J* 2011;**19**:451–7. https://doi.org/10.1007/s12471-011-0189-y

113. Bailey AL, Scantlebury DC, Smyth SS. Thrombosis and antithrombotic therapy in women. *Arterioscler Thromb Vasc Biol* 2009;**29**:284–8. https://doi.org/10.1161/ATVBAHA.108.179788

114. Coleman JR, Moore EE, Kelher MR, Samuels JM, Cohen MJ, Sauaia A, *et al.* Female platelets have distinct functional activity compared with male platelets: implications in transfusion practice and treatment of trauma-induced coagulopathy. *J Trauma Acute Care Surg* 2019;**87**:1052–60. https://doi.org/10.1097/TA.0000000000002398

115. Chichareon P, Modolo R, Kerkmeijer L, Tomaniak M, Kogame N, Takahashi K, *et al.* Association of sex with outcomes in patients undergoing percutaneous coronary intervention: a subgroup analysis of the GLOBAL LEADERS randomized clinical trial. *JAMA Cardiol* 2020;**5**:212–9. https://doi.org/10.1001/jamacardio.2019.4296

116. Wentzel JJ, Papafaklis MI, Antoniadis AP, Takahashi S, Cefalo NV, Cormier M, *et al.* Sex-related differences in plaque characteristics and endothelial shear stress related plaque-progression in human coronary arteries. *Atherosclerosis* 2022;**342**:9–18. https://doi.org/10.1016/j.atherosclerosis.2021.12.013

117. Reynolds HR, Shaw LJ, Min JK, Spertus JA, Chaitman BR, Berman DS, *et al.* Association of sex with severity of coronary artery disease, ischemia, and symptom burden in patients with moderate or severe ischemia: secondary analysis of the ISCHEMIA randomized clinical trial. *JAMA Cardiol* 2020;**5**:773–86. https://doi.org/10.1001/jamacardio.2020.0822

118. Shaw LJ, Merz CN, Pepine CJ, Reis SE, Bittner V, Kip KE, *et al.* The economic burden of angina in women with suspected ischemic heart disease: results from the National Institutes of Health–National Heart, Lung, and Blood Institute–sponsored women's ischemia syndrome evaluation. *Circulation* 2006;**114**:894–904. https://doi.org/10.1161/CIRCULATIONAHA.105.609990

119. Shaw LJ, Shaw RE, Merz CN, Brindis RG, Klein LW, Nallamothu B, *et al.* Impact of ethnicity and gender differences on angiographic coronary artery disease prevalence and in-hospital mortality in the American College of Cardiology-National Cardiovascular Data Registry. *Circulation* 2008;**117**:1787–801. https://doi.org/10.1161/CIRCULATIONAHA.107.726562

120. Ferry AV, Anand A, Strachan FE, Mooney L, Stewart SD, Marshall L, *et al.* Presenting symptoms in men and women diagnosed with myocardial infarction using sex-specific criteria. *J Am Heart Assoc* 2019;**8**:e012307. https://doi.org/10.1161/JAHA.119.012307

121. Lichtman JH, Leifheit EC, Safdar B, Bao H, Krumholz HM, Lorenze NP, *et al.* Sex differences in the presentation and perception of symptoms among young patients with myocardial infarction: evidence from the VIRGO study (variation in recovery: role of gender on outcomes of young AMI patients). *Circulation* 2018;**137**:781–90. https://doi.org/10.1161/CIRCULATIONAHA.117.031650

122. Bogsrud MP, Graesdal A, Retterstol K, Holven KB. A physically fit woman in her thirties with exertional dyspnoea. *Tidsskr Nor Laegeforen* 2017;**137**:456–8. https://doi.org/10.4045/tidsskr.16.0538

123. de Torbal A, Boersma E, Kors JA, van Herpen G, Deckers JW, van der Kuip DA, *et al.* Incidence of recognized and unrecognized myocardial infarction in men and women aged 55 and older: the Rotterdam study. *Eur Heart J* 2006;**27**:729–36. https://doi.org/10.1093/eurheartj/ehi707

124. van der Ende MY, Juarez-Orozco LE, Waardenburg I, Lipsic E, Schurer RAJ, van der Werf HW, *et al.* Sex-based differences in unrecognized myocardial infarction. *J Am Heart Assoc* 2020;**9**:e015519. https://doi.org/10.1161/JAHA.119.015519

125. Khuddus MA, Pepine CJ, Handberg EM, Bairey Merz CN, Sopko G, Bavry AA, *et al.* An intravascular ultrasound analysis in women experiencing chest pain in the absence of obstructive coronary artery disease: a substudy from the National Heart, Lung, and Blood Institute-sponsored Women's Ischemia Syndrome Evaluation (WISE). *J Interv Cardiol* 2010;**23**:511–9. https://doi.org/10.1111/j.1540-8183.2010.00598.x

126. Ferencik M, Mayrhofer T, Bittner DO, Emami H, Puchner SB, Lu MT, *et al.* Use of high-risk coronary atherosclerotic plaque detection for risk stratification of patients with stable chest pain: a secondary analysis of the PROMISE randomized clinical trial. *JAMA Cardiol* 2018;**3**:144–52. https://doi.org/10.1001/jamacardio.2017.4973

127. Xie JX, Eshtehardi P, Varghese T, Goyal A, Mehta PK, Kang W, *et al.* Prognostic significance of nonobstructive left main coronary artery disease in women versus men: long-term outcomes from the CONFIRM (coronary CT angiography evaluation for clinical outcomes: an international multicenter) registry. *Circ Cardiovasc Imaging* 2017;**10**:e006246. https://doi.org/10.1161/CIRCIMAGING.117.006246

128. Pagidipati NJ, Hemal K, Coles A, Mark DB, Dolor RJ, Pellikka PA, *et al.* Sex differences in functional and CT angiography testing in patients with suspected coronary artery disease. *J Am Coll Cardiol* 2016;**67**:2607–16. https://doi.org/10.1016/j.jacc.2016.03.523

129. Mansour M, Radaideh Q, Alaiwah MN, Alnimer Y, Devabhaktuni SR, Dhar G, *et al.* Major adverse cardiac events in symptomatic women with non-obstructive CAD on coronary CTA: pooled analysis from PROMISE and SCOT-HEART. *Int J Cardiovasc Imaging* 2022;**38**:683–93. https://doi.org/10.1007/s10554-021-02429-3

130. Shaw LJ, Min JK, Nasir K, Xie JX, Berman DS, Miedema MD, *et al.* Sex differences in calcified plaque and long-term cardiovascular mortality: observations from the CAC consortium. *Eur Heart J* 2018;**39**:3727–35. https://doi.org/10.1093/eurheartj/ehy534

131. Kalra DK, Heo R, Valenti V, Nakazato R, Min JK. Role of computed tomography for diagnosis and risk stratification of patients with suspected or known coronary artery disease. *Arterioscler Thromb Vasc Biol* 2014;**34**:1144–54. https://doi.org/10.1161/ATVBAHA.113.302074

132. Kilickap M, Erol MK, Kayikcioglu M, Kocayigit I, Gitmez M, Can V, *et al.* Short and mid-term outcomes in patients with acute myocardial infarction: results of the nationwide TURKMI registry. *Angiology* 2021;**72**:339–47. https://doi.org/10.1177/0003319720975302

133. Trutter L, Bigeh A, Pecci C, Muzaffar M, Gulati M. Diagnostic and management dilemmas in women presenting with acute coronary syndromes. *Curr Cardiol Rep* 2020;**22**:163. https://doi.org/10.1007/s11886-020-01410-1

134. Bachelet BC, Hyun K, D'Souza M, Chow CK, Redfern J, Brieger DB. Sex differences in the management and outcomes of non-ST-elevation acute coronary syndromes. *Med J Aust* 2022;**216**:153–5. https://doi.org/10.5694/mja2.51220

135. Pan American Health Organization. Leading causes of death, and disability 2019/ Available from: https://www.paho.org/en/enlace/leading-causes-death-and-disability (accessed 4 May 2023).

136. Bushnell C, McCullough LD, Awad IA, Chireau MV, Fedder WN, Furie KL, et al. Guidelines for the prevention of stroke in women: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2014;**45**:1545–88. https://doi.org/10.1161/01.str.0000442009.06663.48

137. Ali M, van Os HJA, van der Weerd N, Schoones JW, Heymans MW, Kruyt ND, et al. Sex differences in presentation of stroke: a systematic review and meta-analysis. *Stroke* 2022;**53**:345–54. https://doi.org/10.1161/STROKEAHA.120.034040

138. Yu AYX, Penn AM, Lesperance ML, Croteau NS, Balshaw RF, Votova K, et al. Sex differences in presentation and outcome after an acute transient or minor neurologic event. *JAMA Neurol* 2019;**76**:962–8. https://doi.org/10.1001/jamaneurol.2019.1305

139. O'Donnell MJ, Chin SL, Rangarajan S, Xavier D, Liu L, Zhang H, et al. Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): a case–control study. *Lancet* 2016;**388**:761–75. https://doi.org/10.1016/S0140-6736(16)30506-2

140. Goldstein LB, Amarenco P, Lamonte M, Gilbert S, Messig M, Callahan A, et al. Relative effects of statin therapy on stroke and cardiovascular events in men and women: secondary analysis of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study. *Stroke* 2008;**39**:2444–8. https://doi.org/10.1161/STROKEAHA.107.513747

141. Higgins JP, Higgins JA. Epidemiology of peripheral arterial disease in women. *J Epidemiol* 2003;**13**:1–14. https://doi.org/10.2188/jea.13.1

142. Srivaratharajah K, Abramson BL. Women and peripheral arterial disease: a review of sex differences in epidemiology, clinical manifestations, and outcomes. *Can J Cardiol* 2018;**34**:356–61. https://doi.org/10.1016/j.cjca.2018.01.009

143. McDermott MM, Fried L, Simonsick E, Ling S, Guralnik JM. Asymptomatic peripheral arterial disease is independently associated with impaired lower extremity functioning: the women's health and aging study. *Circulation* 2000;**101**:1007–12. https://doi.org/10.1161/01.CIR.101.9.1007

144. McDermott MM, Ferrucci L, Simonsick EM, Balfour J, Fried L, Ling S, et al. The ankle brachial index and change in lower extremity functioning over time: the women's health and aging study. *J Am Geriatr Soc* 2002;**50**:238–46. https://doi.org/10.1046/j.1532-5415.2002.50054.x

145. McDermott MM, Mehta S, Greenland P. Exertional leg symptoms other than intermittent claudication are common in peripheral arterial disease. *Arch Intern Med* 1999;**159**:387–92. https://doi.org/10.1001/archinte.159.4.387

146. Vouyouka AG, Egorova NN, Salloum A, Kleinman L, Marin M, Faries PL, et al. Lessons learned from the analysis of gender effect on risk factors and procedural outcomes of lower extremity arterial disease. *J Vasc Surg* 2010;**52**:1196–202. https://doi.org/10.1016/j.jvs.2010.05.106

147. Ramkumar N, Suckow BD, Brown JR, Sedrakyan A, Cronenwett JL, Goodney PP. Sex-based assessment of patient presentation, lesion characteristics, and treatment modalities in patients undergoing peripheral vascular intervention. *Circ Cardiovasc Interv* 2018;**11**:e005749. https://doi.org/10.1161/CIRCINTERVENTIONS.117.005749

148. McCoach CE, Armstrong EJ, Singh S, Javed U, Anderson D, Yeo KK, et al. Gender-related variation in the clinical presentation and outcomes of critical limb ischemia. *Vasc Med* 2013;**18**:19–26. https://doi.org/10.1177/1358863X13475836

149. Jackson EA, Munir K, Schreiber T, Rubin JR, Cuff R, Gallagher KA, et al. Impact of sex on morbidity and mortality rates after lower extremity interventions for peripheral arterial disease: observations from the Blue Cross Blue Shield of Michigan Cardiovascular Consortium. *J Am Coll Cardiol* 2014;**63**:2525–30. https://doi.org/10.1016/j.jacc.2014.03.036

150. Altin SE, Castro-Dominguez YS, Kennedy KF, Orion KC, Lanksy AJ, Abbott JD, et al. Predictors of underutilization of medical therapy in patients undergoing endovascular revascularization for peripheral artery disease. *JACC Cardiovasc Interv* 2020;**13**:2911–8. https://doi.org/10.1016/j.jcin.2020.08.036

151. Sigvant B, Wiberg-Hedman K, Bergqvist D, Rolandsson O, Wahlberg E. Risk factor profiles and use of cardiovascular drug prevention in women and men with peripheral arterial disease. *Eur J Cardiovasc Prev Rehabil* 2009;**16**:39–46. https://doi.org/10.1097/HJR.0b013e32831c1383

152. Hess CN, Cannon CP, Beckman JA, Goodney PP, Patel MR, Hiatt WR, et al. Effectiveness of blood lipid management in patients with peripheral artery disease. *J Am Coll Cardiol* 2021;**77**:3016–27. https://doi.org/10.1016/j.jacc.2021.04.060

153. Cacoub PP, Abola MT, Baumgartner I, Bhatt DL, Creager MA, Liau CS, et al. Cardiovascular risk factor control and outcomes in peripheral artery disease patients in the reduction of atherothrombosis for continued health (REACH) registry. *Atherosclerosis* 2009;**204**:e86–92. https://doi.org/10.1016/j.atherosclerosis.2008.10.023

154. Steg PG, Bhatt DL, Wilson PW, D'Agostino R Sr., Ohman EM, Rother J, et al. One-year cardiovascular event rates in outpatients with atherothrombosis. *JAMA* 2007;**297**:1197–206. https://doi.org/10.1001/jama.297.11.1197

155. Dreyer RP, van Zitteren M, Beltrame JF, Fitridge R, Denollet J, Vriens PW, et al. Gender differences in health status and adverse outcomes among patients with peripheral arterial disease. *J Am Heart Assoc* 2014;**4**:e000863. https://doi.org/10.1161/JAHA.114.000863

156. Lefebvre KM, Chevan J. The persistence of gender and racial disparities in vascular lower extremity amputation: an examination of HCUP-NIS data (2002–2011). *Vasc Med* 2015;**20**:51–9. https://doi.org/10.1177/1358863X14565373

157. Oyri LKL, Bogsrud MP, Christensen JJ, Ulven SM, Brantsaeter AL, Retterstol K, et al. Novel associations between parental and newborn cord blood metabolic profiles in the Norwegian mother, father and child cohort study. *BMC Med* 2021;**19**:91. https://doi.org/10.1186/s12916-021-01959-w

158. Bansal N, Cruickshank JK, McElduff P, Durrington PN. Cord blood lipoproteins and prenatal influences. *Curr Opin Lipidol* 2005;**16**:400–8. https://doi.org/10.1097/01.mol.0000174154.61307.16

159. Morrison KM, Anand SS, Yusuf S, Atkinson SA, Schulze KM, Rao-Melacini P, et al. Maternal and pregnancy related predictors of cardiometabolic traits in newborns. *PLoS One* 2013;**8**:e55815. https://doi.org/10.1371/journal.pone.0055815

160. Balder JW, Lansberg PJ, Hof MH, Wiegman A, Hutten BA, Kuivenhoven JA. Pediatric lipid reference values in the general population: the Dutch lifelines cohort study. *J Clin Lipidol* 2018;**12**:1208–16. https://doi.org/10.1016/j.jacl.2018.05.011

161. Dathan-Stumpf A, Vogel M, Hiemisch A, Thiery J, Burkhardt R, Kratzsch J, et al. Pediatric reference data of serum lipids and prevalence of dyslipidemia: results from a population-based cohort in Germany. *Clin Biochem* 2016;**49**:740–9. https://doi.org/10.1016/j.clinbiochem.2016.02.010

162. Mumford SL, Dasharathy S, Pollack AZ, Schisterman EF. Variations in lipid levels according to menstrual cycle phase: clinical implications. *Clin Lipidol* 2011;**6**:225–34. https://doi.org/10.2217/clp.11.9

163. Klajnbard A, Szecsi PB, Colov NP, Andersen MR, Jorgensen M, Bjorngaard B, et al. Laboratory reference intervals during pregnancy, delivery and the early postpartum period. *Clin Chem Lab Med* 2010;**48**:237–48. https://doi.org/10.1515/CCLM.2010.033

164. Zhang Z, Lai M, Piro AL, Alexeeff SE, Allalou A, Rost HL, et al. Intensive lactation among women with recent gestational diabetes significantly alters the early postpartum circulating lipid profile: the SWIFT study. *BMC Med* 2021;**19**:241. https://doi.org/10.1186/s12916-021-02095-1

165. Knopp RH, Walden CE, Wahl PW, Bergelin R, Chapman M, Irvine S, et al. Effect of postpartum lactation on lipoprotein lipids and apoproteins. *J Clin Endocrinol Metab* 1985;**60**:542–7. https://doi.org/10.1210/jcem-60-3-542

166. Stuebe AM, Michels KB, Willett WC, Manson JE, Rexrode K, Rich-Edwards JW. Duration of lactation and incidence of myocardial infarction in middle to late adulthood. *Am J Obstet Gynecol* 2009;**200**:138.e1–8. https://doi.org/10.1016/j.ajog.2008.10.001

167. Schwarz EB, Ray RM, Stuebe AM, Allison MA, Ness RB, Freiberg MS, et al. Duration of lactation and risk factors for maternal cardiovascular disease. *Obstet Gynecol* 2009;**113**:974–82. https://doi.org/10.1097/01.AOG.0000346884.67796.ca

168. Peters SAE, Yang L, Guo Y, Chen Y, Bian Z, Du J, et al. Breastfeeding and the risk of maternal cardiovascular disease: a prospective study of 300 000 Chinese women. *J Am Heart Assoc* 2017;**6**:e006081. https://doi.org/10.1161/JAHA.117.006081

169. Ambikairajah A, Walsh E, Cherbuin N. Lipid profile differences during menopause: a review with meta-analysis. *Menopause* 2019;**26**:1327–33. https://doi.org/10.1097/GME.0000000000001440

170. Raguindin PF, Cardona I, Muka T, Lambrinoudaki I, Gebhard C, Franco OH, et al. Does reproductive stage impact cardiovascular disease risk factors? Results from a population-based cohort in Lausanne (CoLaus study). *Clin Endocrinol (Oxf)* 2022;**97**:568–80. https://doi.org/10.1111/cen.14730

171. Iyen B, Qureshi N, Weng S, Roderick P, Kai J, Capps N, et al. Sex differences in cardiovascular morbidity associated with familial hypercholesterolaemia: a retrospective cohort study of the UK Simon Broome register linked to national hospital records. *Atherosclerosis* 2020;**315**:131–7. https://doi.org/10.1016/j.atherosclerosis.2020.10.895

172. Holven KB, Narverud I, van Lennep JR, Versmissen J, Oyri LKL, Galema-Boers A, et al. Sex differences in cholesterol levels from birth to 19 years of age may lead to increased cholesterol burden in females with FH. *J Clin Lipidol* 2018;**12**:748–755.e2. https://doi.org/10.1016/j.jacl.2018.02.021

173. Mundal L, Sarancic M, Ose L, Iversen PO, Borgan JK, Veierod MB, et al. Mortality among patients with familial hypercholesterolemia: a registry-based study in Norway, 1992–2010. *J Am Heart Assoc* 2014;**3**:e001236. https://doi.org/10.1161/JAHA.114.001236

174. Ference BA, Graham I, Tokgozoglu L, Catapano AL. Impact of lipids on cardiovascular health: JACC health promotion series. *J Am Coll Cardiol* 2018;**72**:1141–56. https://doi.org/10.1016/j.jacc.2018.06.046

175. US Food and Drug Administration. Statins: Drug Safety Communication - FDA Requests Removal of Strongest Warning Against Using Cholesterol-lowering Statins During Pregnancy 2021. Available from: https://www.fda.gov/safety/medical-product-safety-information/statins-drug-safety-communication-fda-requests-removal-strongest-warning-against-using-cholesterol (accessed 4 May 2023).

176. Toleikyte I, Retterstol K, Leren TP, Iversen PO. Pregnancy outcomes in familial hypercholesterolemia: a registry-based study. *Circulation* 2011;**124**:1606–14. https://doi.org/10.1161/CIRCULATIONAHA.110.990929

177. Botha TC, Pilcher GJ, Wolmarans K, Blom DJ, Raal FJ. Statins and other lipid-lowering therapy and pregnancy outcomes in homozygous familial hypercholesterolaemia: a retrospective review of 39 pregnancies. *Atherosclerosis* 2018;**277**:502–7. https://doi.org/10.1016/j.atherosclerosis.2018.05.038

178. Klevmoen M, Bogsrud MP, Retterstol K, Svilaas T, Vesterbekkmo EK, Hovland A, et al. Loss of statin treatment years during pregnancy and breastfeeding periods in women with familial hypercholesterolemia. *Atherosclerosis* 2021;**335**:8–15. https://doi.org/10.1016/j.atherosclerosis.2021.09.003

179. Nordestgaard BG. Triglyceride-rich lipoproteins and atherosclerotic cardiovascular disease: new insights from epidemiology, genetics, and biology. *Circ Res* 2016;**118**:547–63. https://doi.org/10.1161/CIRCRESAHA.115.306249

180. Ginsberg HN, Packard CJ, Chapman MJ, Boren J, Aguilar-Salinas CA, Averna M, et al. Triglyceride-rich lipoproteins and their remnants: metabolic insights, role in atherosclerosis, and emerging therapeutic strategies-a consensus statement from the European Atherosclerosis Society. *Eur Heart J* 2021;**42**:4791–806. https://doi.org/10.1093/eurheartj/ehab551

181. Varbo A, Benn M, Tybjaerg-Hansen A, Nordestgaard BG. Elevated remnant cholesterol causes both low-grade inflammation and ischemic heart disease, whereas elevated low-density lipoprotein cholesterol causes ischemic heart disease without inflammation. *Circulation* 2013;**128**:1298–309. https://doi.org/10.1161/CIRCULATIONAHA.113.003008

182. Nordestgaard BG, Benn M, Schnohr P, Tybjaerg-Hansen A. Nonfasting triglycerides and risk of myocardial infarction, ischemic heart disease, and death in men and women. *JAMA* 2007;**298**:299–308. https://doi.org/10.1001/jama.298.3.299

183. Freiberg JJ, Tybjaerg-Hansen A, Jensen JS, Nordestgaard BG. Nonfasting triglycerides and risk of ischemic stroke in the general population. *JAMA* 2008;**300**:2142–52. https://doi.org/10.1001/jama.2008.621

184. Varbo A, Nordestgaard BG. Remnant cholesterol and risk of ischemic stroke in 112,512 individuals from the general population. *Ann Neurol* 2019;**85**:550–9. https://doi.org/10.1002/ana.25432

185. Wadstrom BN, Wulff AB, Pedersen KM, Jensen GB, Nordestgaard BG. Elevated remnant cholesterol increases the risk of peripheral artery disease, myocardial infarction, and ischaemic stroke: a cohort-based study. *Eur Heart J* 2022;**43**:3258–69. https://doi.org/10.1093/eurheartj/ehab705

186. Jorgensen AB, Frikke-Schmidt R, Nordestgaard BG, Tybjaerg-Hansen A. Loss-of-function mutations in APOC3 and risk of ischemic vascular disease. *N Engl J Med* 2014;**371**:32–41. https://doi.org/10.1056/NEJMoa1308027

187. Jorgensen AB, Frikke-Schmidt R, West AS, Grande P, Nordestgaard BG, Tybjaerg-Hansen A. Genetically elevated non-fasting triglycerides and calculated remnant cholesterol as causal risk factors for myocardial infarction. *Eur Heart J* 2013;**34**:1826–33. https://doi.org/10.1093/eurheartj/ehs431

188. Bhatt DL, Steg PG, Miller M, Brinton EA, Jacobson TA, Ketchum SB, et al. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. *N Engl J Med* 2019;**380**:11–22. https://doi.org/10.1056/NEJMoa1812792

189. Nicholls SJ, Lincoff AM, Garcia M, Bash D, Ballantyne CM, Barter PJ, et al. Effect of high-dose omega-3 fatty acids vs corn oil on major adverse cardiovascular events in patients at high cardiovascular risk: the STRENGTH randomized clinical trial. *JAMA* 2020;**324**:2268–80. https://doi.org/10.1001/jama.2020.22258

190. Doi T, Langsted A, Nordestgaard BG. A possible explanation for the contrasting results of REDUCE-IT vs. STRENGTH: cohort study mimicking trial designs. *Eur Heart J* 2021;**42**:4807–17. https://doi.org/10.1093/eurheartj/ehab555

191. Pradhan A D, Glynn RJ, Fruchart JC, MacFadyen JG, Zaharris ES, Everett BM, et al. Triglyceride lowering with pemafibrate to reduce cardiovascular risk. *N Engl J Med* 2022;**387**:1923–34. https://doi.org/10.1056/NEJMoa2210645

192. Jacobs DR J, Woo JG, Sinaiko AR, Daniels SR, Ikonen J, Juonala M, et al. Childhood cardiovascular risk factors and adult cardiovascular events. *N Engl J Med* 2022;**386**:1877–88. https://doi.org/10.1056/NEJMoa2109191

193. Duran EK, Aday AW, Cook NR, Buring JE, Ridker PM, Pradhan AD. Triglyceride-rich lipoprotein cholesterol, small dense LDL cholesterol, and incident cardiovascular disease. *J Am Coll Cardiol* 2020;**75**:2122–35. https://doi.org/10.1016/j.jacc.2020.02.059

194. Emerging Risk Factors Collaboration, Di Angelantonio E, Sarwar N, Perry P, Kaptoge S, Ray KK, et al. Major lipids, apolipoproteins, and risk of vascular disease. *JAMA* 2009;**302**:1993–2000. doi:10.1001/jama.2009.1619

195. Dugani SB, Moorthy MV, Li C, Demler OV, Alsheikh-Ali AA, Ridker PM, et al. Association of lipid, inflammatory, and metabolic biomarkers with age at onset for incident coronary heart disease in women. *JAMA Cardiol* 2021;**6**:437–47. https://doi.org/10.1001/jamacardio.2020.7073

196. Kamstrup PR, Tybjaerg-Hansen A, Nordestgaard BG. Elevated lipoprotein(a) and risk of aortic valve stenosis in the general population. *J Am Coll Cardiol* 2014;**63**:470–7. https://doi.org/10.1016/j.jacc.2013.09.038

197. Thanassoulis G, Campbell CY, Owens DS, Smith JG, Smith AV, Peloso GM, et al. Genetic associations with valvular calcification and aortic stenosis. *N Engl J Med* 2013;**368**:503–12. https://doi.org/10.1056/NEJMoa1109034

198. Kronenberg F, Mora S, Stroes ESG, Ference BA, Arsenault BJ, Berglund L, et al. Lipoprotein(a) in atherosclerotic cardiovascular disease and aortic stenosis: a European Atherosclerosis Society consensus statement. *Eur Heart J* 2022;**43**:3925–46. https://doi.org/10.1093/eurheartj/ehac361

199. Kamstrup PR, Tybjaerg-Hansen A, Steffensen R, Nordestgaard BG. Genetically elevated lipoprotein(a) and increased risk of myocardial infarction. *JAMA* 2009;**301**:2331–9. https://doi.org/10.1001/jama.2009.801

200. Kamstrup PR, Nordestgaard BG. Elevated lipoprotein(a) levels, LPA risk genotypes, and increased eisk of heart failure in the general population. *JACC Heart Fail* 2016;**4**:78–87. https://doi.org/10.1016/j.jchf.2015.08.006

201. Langsted A, Kamstrup PR, Nordestgaard BG. High lipoprotein(a) and high risk of mortality. *Eur Heart J* 2019;**40**:2760–70. https://doi.org/10.1093/eurheartj/ehy902

202. Langsted A, Nordestgaard BG, Kamstrup PR. Elevated lipoprotein(a) and risk of ischemic stroke. *J Am Coll Cardiol* 2019;**74**:54–66. https://doi.org/10.1016/j.jacc.2019.03.524

203. Clarke R, Peden JF, Hopewell JC, Kyriakou T, Goel A, Heath SC, et al. Genetic variants associated with Lp(a) lipoprotein level and coronary disease. *N Engl J Med* 2009;**361**:2518–28. https://doi.org/10.1056/NEJMoa0902604

204. Emerging Risk Factors C, Erqou S, Kaptoge S, Perry PL, Di Angelantonio E, Thompson A, et al. Lipoprotein(a) concentration and the risk of coronary heart disease, stroke, and nonvascular mortality. *JAMA* 2009;**302**:412–23. doi:10.1001/jama.2009.1063

205. O'Donoghue ML, Morrow DA, Tsimikas S, Sloan S, Ren AF, Hoffman EB, et al. Lipoprotein(a) for risk assessment in patients with established coronary artery disease. *J Am Coll Cardiol* 2014;**63**:520–7. https://doi.org/10.1016/j.jacc.2013.09.042

206. Madsen CM, Kamstrup PR, Langsted A, Varbo A, Nordestgaard BG. Lipoprotein(a)-lowering by 50 mg/dL (105 nmol/L) may be needed to reduce cardiovascular disease 20% in secondary prevention: a population-based study. *Arterioscler Thromb Vasc Biol* 2020;**40**:255–66. https://doi.org/10.1161/ATVBAHA.119.312951

207. Pare G, Caku A, McQueen M, Anand SS, Enas E, Clarke R, et al. Lipoprotein(a) levels and the risk of myocardial infarction among 7 ethnic groups. *Circulation* 2019;**139**:1472–82. https://doi.org/10.1161/CIRCULATIONAHA.118.034311

208. Patel AP, Wang M, Pirruccello JP, Ellinor PT, Ng K, Kathiresan S, et al. Lp(a) (lipoprotein[a]) concentrations and incident atherosclerotic cardiovascular disease: new insights from a large national Biobank. *Arterioscler Thromb Vasc Biol* 2021;**41**:465–74. https://doi.org/10.1161/ATVBAHA.120.315291

209. Kim CJ, Kim TH, Ryu WS, Ryoo UH. Influence of menopause on high density lipoprotein-cholesterol and lipids. *J Korean Med Sci* 2000;**15**:380–6. https://doi.org/10.3346/jkms.2000.15.4.380

210. Slunga L, Asplund K, Johnson O, Dahlen GH. Lipoprotein (a) in a randomly selected 25–64 year old population: the Northern Sweden Monica study. *J Clin Epidemiol* 1993;**46**:617–24. https://doi.org/10.1016/0895-4356(93)90034-X

211. Ushioda M, Makita K, Takamatsu K, Horiguchi F, Aoki D. Serum lipoprotein(a) dynamics before/after menopause and long-term effects of hormone replacement therapy on lipoprotein(a) levels in middle-aged and older Japanese women. *Horm Metab Res* 2006;**38**:581–6. https://doi.org/10.1055/s-2006-950504

212. Derby CA, Crawford SL, Pasternak RC, Sowers M, Sternfeld B, Matthews KA. Lipid changes during the menopause transition in relation to age and weight: the study of women's health across the nation. *Am J Epidemiol* 2009;**169**:1352–61. https://doi.org/10.1093/aje/kwp043

213. Suk Danik J, Rifai N, Buring JE, Ridker PM. Lipoprotein(a), hormone replacement therapy, and risk of future cardiovascular events. *J Am Coll Cardiol* 2008;**52**:124–31. https://doi.org/10.1016/j.jacc.2008.04.009

214. Shlipak MG, Simon JA, Vittinghoff E, Lin F, Barrett-Connor E, Knopp RH, et al. Estrogen and progestin, lipoprotein(a), and the risk of recurrent coronary heart disease events after menopause. *JAMA* 2000;**283**:1845–52. https://doi.org/10.1001/jama.283.14.1845

215. Gregersen I, Hoibraaten E, Holven KB, Lovdahl L, Ueland T, Mowinckel MC, et al. Effect of hormone replacement therapy on atherogenic lipid profile in postmenopausal women. *Thromb Res* 2019;**184**:1–7. https://doi.org/10.1016/j.thromres.2019.10.005

216. Zechner R, Desoye G, Schweditsch MO, Pfeiffer KP, Kostner GM. Fluctuations of plasma lipoprotein-A concentrations during pregnancy and post partum. *Metab Clin Exp* 1986;**35**:333–6. https://doi.org/10.1016/0026-0495(86)90150-2

217. Sattar N, Clark P, Greer IA, Shepherd J, Packard CJ. Lipoprotein (a) levels in normal pregnancy and in pregnancy complicated with pre-eclampsia. *Atherosclerosis* 2000;**148**:407–11. https://doi.org/10.1016/S0021-9150(99)00296-8

218. Simony SB, Mortensen MB, Langsted A, Afzal S, Kamstrup PR, Nordestgaard BG. Sex differences of lipoprotein(a) levels and associated risk of morbidity and mortality by age: the Copenhagen General Population Study. *Atherosclerosis* 2022;**355**:76–82. https://doi.org/10.1016/j.atherosclerosis.2022.06.1023

219. Pearson GJ, Thanassoulis G, Anderson TJ, Barry AR, Couture P, Dayan N, et al. 2021 Canadian cardiovascular society guidelines for the management of dyslipidemia for the prevention of cardiovascular disease in adults. *Can J Cardiol* 2021;**37**:1129–50. https://doi.org/10.1016/j.cjca.2021.03.016

220. Cholesterol Treatment Trialists Collaboration, Fulcher J, O'Connell R, Voysey M, Emberson J, Blackwell L, et al. Efficacy and safety of LDL-lowering therapy among

men and women: meta-analysis of individual data from 174,000 participants in 27 randomised trials. *Lancet* 2015;**385**:1397–405. https://doi.org/10.1016/S0140-6736(14)61368-4

221. Navar AM, Peterson ED, Li S, Robinson JG, Roger VL, Goldberg AC, *et al.* Prevalence and management of symptoms associated with statin therapy in community practice: insights from the PALM (patient and provider assessment of lipid management) registry. *Circ Cardiovasc Qual Outcomes* 2018;**11**:e004249. https://doi.org/10.1161/CIRCOUTCOMES.117.004249

222. Bradley CK, Wang TY, Li S, Robinson JG, Roger VL, Goldberg AC, *et al.* Patient-reported reasons for declining or discontinuing statin therapy: insights from the PALM registry. *J Am Heart Assoc* 2019;**8**:e011765. https://doi.org/10.1161/JAHA.118.011765