

Clinical staging to guide management of metabolic disorders and their sequelae: a European Atherosclerosis Society consensus statement

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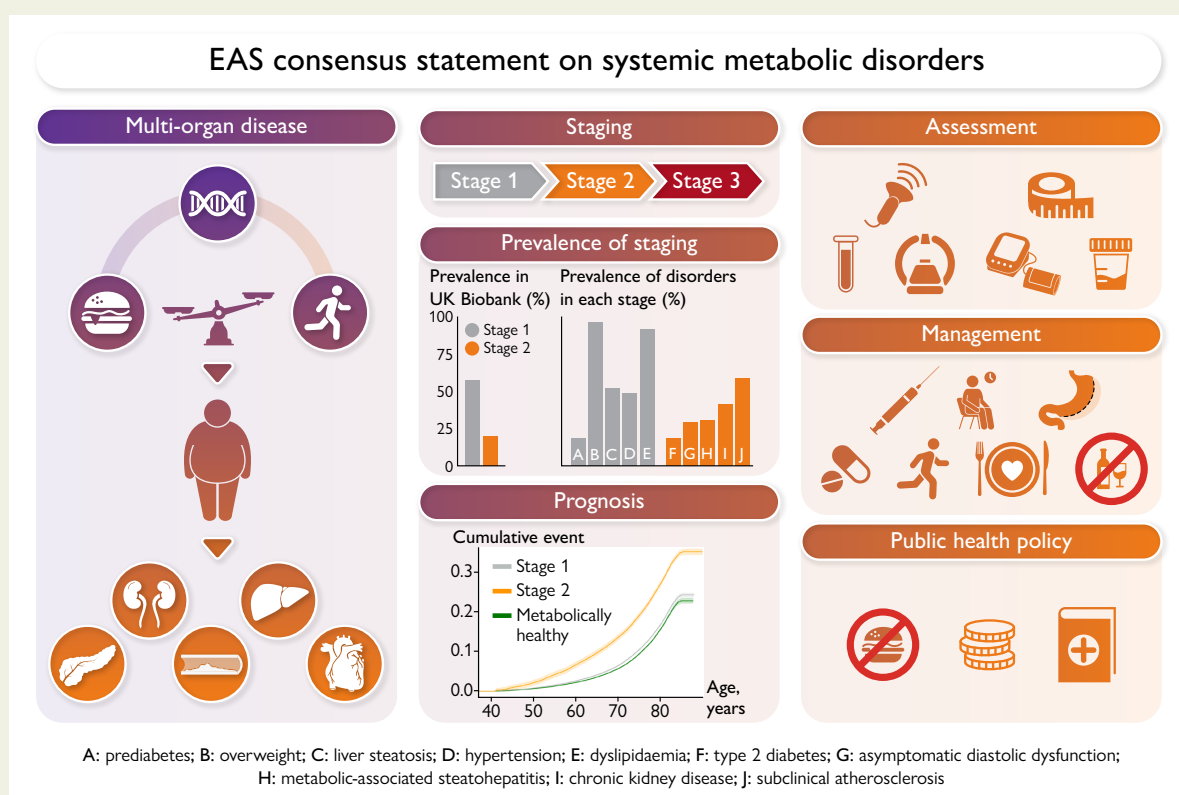
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Abstract

Obesity rates have surged since 1990 worldwide. This rise is paralleled by increases in pathological processes affecting organs such as the heart, liver, and kidneys, here termed systemic metabolic disorders (SMDs). For clinical management of SMD, the European Atherosclerosis Society proposes a pathophysiology-based system comprising three stages: Stage 1, where metabolic abnormalities such as dysfunctional adiposity and dyslipidaemia occur without detectable organ damage; Stage 2, which involves early organ damage manifested as Type 2 diabetes, asymptomatic diastolic dysfunction, metabolic-associated steatohepatitis (MASH), and chronic kidney disease (CKD); and Stage 3, characterized by more advanced organ damage affecting multiple organs. Various forms of high-risk obesity, driven by maintained positive energy balance, are the most common cause of SMD, leading to ectopic lipid accumulation and insulin resistance. This progression affects various organs, promoting comorbidities such as hypertension and atherogenic dyslipidaemia. Genetic factors influence SMD susceptibility, and ethnic disparities in SMD are attributable to genetic and socio-economic factors. Key SMD features include insulin resistance, inflammation, pre-diabetes, Type 2 diabetes, MASH, hypertension, CKD, atherogenic dyslipidaemia, and heart failure. Management strategies involve lifestyle changes, pharmacotherapy, and metabolic surgery in severe cases, with emerging treatments focusing on genetic approaches. The staging system provides a structured approach to understanding and addressing the multi-faceted nature of SMD, which is crucial for improving health outcomes. Categorization of SMD abnormalities by presence and progression is aimed to improve awareness of a multi-system trait and encourage a tailored and global approach to treatment, ultimately aiming to reduce the burden of obesity-related comorbidities.

Graphical Abstract



Keywords

Obesity • Insulin resistance/pre-diabetes • Type 2 diabetes • MASLD • Heart failure • Kidney disease

Introduction

Global obesity rates among adults have doubled between 1990 and 2022, and over a billion people worldwide today are living with obesity.¹ A large body of evidence indicates that excess adiposity, especially visceral obesity, results in several systemic abnormalities. Many of these are early markers of the future trajectory of the disease, which may

affect many organs, including the heart, liver, and kidney (and other organs, such as the brain, but these are beyond the focus of this consensus). These systemic abnormalities may progress over time, worsening prognosis and reducing life expectancy.

Although many abnormalities associated with obesity were historically considered and treated separately, it is increasingly being recognized that the various metabolic risk factors are interconnected, sometimes

with bidirectional relationships affecting disease progression. Earlier efforts to address this topic have focused on the burden and implications, which have not translated into actions and better patient care. Recent position papers have started to address this issue by proposing staging systems to describe the progression of risk and to guide the management of obesity-related metabolic complications. These include those from the European Association for the Study of Obesity (EASO)² and the Lancet Commission,³ which focus on improving the diagnosis of obesity, and from the American Heart Association,⁴ which emphasizes the contribution of the kidney. The European Atherosclerosis Society (EAS) Consensus panel convened to develop a clinically intuitive staging system based on diverse data related to the cluster of abnormalities associated with excess adiposity (*Graphical Abstract*), here termed systemic metabolic disorders (SMDs). The staging system, which is based on pathophysiology, is designed to be easily used by clinicians with actionable management for each stage designed to preserve health.

What is systemic metabolic disorder, and what causes it?

Systemic metabolic disorder comprises a cluster of metabolic abnormalities affecting multiple organs, leading to increased morbidity and mortality from both cardiovascular and non-cardiovascular causes. Systemic metabolic disorder has a heterogeneous aetiology with diverse, albeit convergent, underlying pathogenic mechanisms. These mechanisms progress to create a vicious cycle that obscures the identification of the initial pathogenic mechanisms, hindering a more holistic approach to prevention. Systemic metabolic disorder may be initiated by various aetiopathogenic factors determined by an organ's genetic-specific signature of vulnerability to an unhealthy diet and a sedentary lifestyle. Given the high prevalence of obesity, the most common determinant of SMD is a maintained positive energy balance, leading to excessive lipid accumulation and adipose tissue expansion up to an individual's predetermined threshold, after which SMD becomes manifest. However, SMD can also stem from primary defects in skeletal muscle, leading to insulin resistance, which, in turn, redistributes fuel to adipose tissue and the liver. Alternatively, initial vulnerability in the liver, where lipid homeostasis might be compromised, leads to changes in lipid/nutrient metabolic fluxes to other organs. This progressive disruption of multi-organ metabolic homeostasis sets a trajectory for SMD, evolving into a relatively dedifferentiated disorder with a progressive accumulation of comorbidities.

High-risk forms of obesity as drivers of systemic metabolic disorder

Obesity arises from a complex multi-factorial process leading to a maintained positive energy balance, culminating in the accumulation of lipids within adipocytes located beneath the skin (as subcutaneous adipose tissue) or around internal organs (as visceral adipose tissue). Efficient fat storage in subcutaneous adipose tissue initially serves as a relatively safe mechanism, shielding other organs from excessive nutrient supply.^{5–8} However, as adiposity increases, the capacity of subcutaneous adipose tissue to store and mobilize lipids may become insufficient. Consequently, fat may be redistributed to less-efficient lipid stores such as the intra-abdominal depot, liver, skeletal muscles (intramuscular fat), heart (epicardial and pericardial fat), kidneys, and beta cells in the pancreas, leading to lipotoxic insults in these ectopic deposits.^{7,9} Lipotoxicity initiates a heterogeneous, organ-specific, fibro-inflammatory response, shaping each person's unique phenotype. The severity of the lipotoxic insult, the extent of cell injury, and the

organs' resilience to inflammatory and associated fibrotic responses all influence this phenotype. The balance among these factors, whether genetic, epigenetic, or triggered by environmental exposures, can explain paradoxical phenotypes, such as people living with lower risk forms of obesity; people with metabolic dysfunction-associated steatotic liver disease (MASLD) who are resilient to progression to metabolic-associated steatohepatitis (MASH); and variability in susceptibility to develop insulin resistance, defective insulin secretion, or diabetes. Furthermore, the circadian system is tightly coupled with processes controlling sleep and metabolism, and disruption of the central and peripheral clocks might contribute to the exacerbation of obesity, nutritional fluxes, and the development of insulin resistance.¹⁰

The development of visceral obesity is secondary to the defective expandability and functionality of the subcutaneous adipose tissue.⁷ This leads to a central redistribution of lipids and lipid-induced insulin resistance, contributing to MASLD, atherogenic dyslipidaemia, endothelial dysfunction, and increased susceptibility to hypertension.¹¹ Furthermore, in the obese state, visceral adipose tissue is more susceptible to inflammatory and vasoactive cytokines, leading to increased macrophage infiltration within organs and chronic low-grade systemic fibro-inflammation, potentially amplifying the pathogenic process. Each of these factors, alone and collectively, is likely to contribute to an excess risk of atherosclerosis.¹²

Genetics

Twin and family studies show that obesity and other cardiometabolic risk factors cluster in families, suggesting that genetic factors play a significant role in disease susceptibility. Estimates of heritability range between 40% and 70% for obesity and other SMD components.^{13–16} Although rare gene mutations with large effect sizes cause extreme monogenic forms of obesity and dyslipidaemia,^{15,17} most of the variation in SMD susceptibility in the general population is attributed to many common genetic variants with small-size effects.¹⁷ Large-scale genome-wide association studies (GWASs) have identified hundreds of common variants contributing to each SMD component and its consequences.¹⁸ These studies show that although SMD components are epidemiologically related, they have unique genetic architectures; while some genetic risk loci are shared across several SMD components, others contribute to specific traits.^{19,20} This suggests a complex relationship between SMD components, with multiple distinct heritable factors contributing, independently and in concert, to disease susceptibility.

The identification of genetic underpinnings of SMD and its components has also helped to unravel the causal relationships among correlated metabolic risk factors using Mendelian randomization.^{21,22} It is also important to note that modifiable lifestyle factors, such as an unhealthy diet, lack of physical activity, and other environmental factors, may act as metabolic stressors exacerbating the genetic risk of SMD.²³

Genetic studies lend further support to the notion that visceral adipose tissue is the primary culprit driving metabolic abnormalities in SMD.^{24–26} Recent GWASs have shown that local fat depots also have a distinct genetic architecture.^{25,27} Genetic factors increasing visceral adipose tissue are associated with increased risk of hypertension, Type 2 diabetes, and dyslipidaemia, whereas genetic factors increasing gluteofemoral (hip) fat depots are associated with more favourable cardiometabolic profiles at the same level of body mass index (BMI).^{24–31}

Ethnicity

The prevalence and health burden of SMD vary substantially among racial and ethnic groups.^{32–36} This variation can be attributed partly to

socioeconomic disparities, but genetic and other individual susceptibility factors also play a significant role. For example, Asian Americans experience cardiometabolic complications at a lower BMI compared with other ethnic groups in the USA, which is likely explained by the preferential deposition of intra-abdominal fat in this population.³⁷ Moreover, South Asian ancestry confers a substantially higher risk of atherosclerotic cardiovascular disease (ASCVD) compared with other ethnicities, even after accounting for social determinants of health.³⁸ Of note, African Americans have a lower risk of steatotic liver disease compared with European and Hispanic Americans, despite a similar or even higher prevalence of obesity and insulin resistance.³⁹ In Latin America, the rising cardiometabolic risk is driven by a combination of socioeconomic disparities, rapid urbanization, and an increasing prevalence of obesity and diabetes, exacerbated by population ageing⁴⁰ and genetic predisposition.⁴¹

Systemic manifestations of systemic metabolic disorder

Systemic metabolic disorder encompasses several critical components that are commonly present but varying in intensity, especially in the early stages, before progressing towards a multi-organ systemic metabolic failure that compromises global energy homeostasis. Below, we present the main systemic manifestations of SMD that are included in our proposed staging system.

Insulin resistance, pre-diabetes, and Type 2 diabetes

Systemic insulin resistance emerges due to diminished sensitivity to insulin across one or more organs, compensated by increased plasma insulin levels to maintain euglycaemia.⁴² Insulin resistance usually precedes the onset of common forms of Type 2 diabetes, which generally manifest with peripheral and hepatic insulin resistance.⁴³ Hyperglycaemia occurs when insulin secretion from the pancreatic beta cells becomes insufficient to overcome insulin resistance.⁴⁴ Pre-diabetes is an intermediate state between normal glucose tolerance and Type 2 diabetes. Impaired fasting glucose, defined as a fasting plasma glucose level in the pre-diabetes range, is primarily associated with hepatic insulin resistance.⁴⁵ Impaired glucose tolerance, defined as a plasma glucose level 2 h after an oral glucose tolerance test (OGTT) in the pre-diabetes range, is primarily associated with muscle insulin resistance.⁴⁵

Insulin resistance, even in the absence of dysglycaemia or pre-diabetes, is predictive of several cardiometabolic traits, such as endothelial dysfunction, hypertension,⁴⁶ chronic kidney disease (CKD),⁴⁷ steatotic liver disease,⁴⁸ left ventricular diastolic dysfunction,⁴⁹ and ASCVD.^{50,51} Multiple causal mechanisms underlie these associations, including dysregulation of the sympathetic nervous system and the renin–angiotensin–aldosterone system (RAAS), maladaptive immune responses, and/or disturbed mitochondrial function, which induce tissue fibro-inflammation and oxidative stress.^{52,53} These abnormalities are further exacerbated by Type 2 diabetes, with an increased risk of ASCVD, MASLD-related cirrhosis, and heart failure.^{54–56} This phenomenon is driven by various factors, including the detrimental effects of chronic hyperglycaemia (glucotoxicity) and lipid-induced toxicity on vascular function and cardiomyocytes.⁵⁷

Metabolic dysfunction–associated steatotic liver disease

Metabolic dysfunction–associated steatotic liver disease (also known as metabolic dysfunction–associated fatty liver disease) is characterized by

a hepatic triglyceride content >5% and the presence of metabolic disturbances. It encompasses a spectrum of liver diseases progressing from the accumulation of triglycerides in hepatocytes (isolated steatosis) to liver inflammation (MASH), fibrosis, and, ultimately, cirrhosis and liver cancer in some people.⁵⁸ Mendelian randomization studies have shown that liver triglyceride content *per se* causes hepatic inflammation, fibrosis, and cancer.^{59–61} These studies also suggest that fibrosis *per se* increases insulin resistance and diabetes. Metabolic dysfunction–associated steatotic liver disease is highly associated with ASCVD and Type 2 diabetes in observational studies,⁶² which is likely explained by the substantial contribution of MASLD to atherogenic dyslipidaemia. However, Mendelian randomization analysis did not identify a causal association between genetically determined liver fat content and ischaemic heart disease.⁶³ On the other hand, secreted factors from the liver and alterations in lipid metabolism⁶⁴ might independently promote diastolic heart failure, as supported by a recent study showing that disproportionate levels of liver fat are associated with ventricular functional changes associated with heart failure.⁶⁵ A recent GWAS showed that liver fat *per se* is an independent risk factor for Type 2 diabetes but not ASCVD and that an association between liver fat and ASCVD is determined by the mechanisms that increase hepatic fat accumulation.⁶⁶ Two further studies have shown the presence of at least two types of MASLD with similar hepatic phenotype but diverging pathogenic mechanisms and clinical trajectories; one type is systemic and confers increased risk for ASCVD, heart, and kidney failure, while a second type is liver specific and protects against ASCVD.^{67,68}

Besides the quantity, the composition of hepatic lipids also influences the risk of progression of MASLD.⁶⁹ Hepatic levels of saturated, mono-unsaturated, and, to a lesser extent, polyunsaturated fatty acids are increased in those with MASLD.⁷⁰ Among sphingolipids, ceramides are present at higher levels in the liver in people with MASH,⁷¹ and targeted overexpression of acid ceramidase reduces liver steatosis in mice.⁷² Increases in hepatic sphingolipids are associated with increased oxidative stress and lipid peroxidation,⁷³ potentially important causal mediators for MASLD progression. Similarly, diacylglycerols, which are also elevated in MASLD,⁷⁰ might contribute to MASLD progression by promoting lipotoxicity.^{74–76} Future studies are needed to determine whether and how lipid quality is causally related to MASH susceptibility in humans.

Hypertension

The pathophysiology of hypertension involves several inter-related factors, of which salt intake, obesity, and insulin resistance are the most relevant in the context of SMD.⁷⁷ Visceral adipose tissue produces numerous pro-oxidative and pro-inflammatory mediators that reduce insulin sensitivity predominantly in muscle and liver, thereby contributing to compensatory increased circulating insulin levels.^{78,79} However, at the level of the kidney, sensitivity to the tubular sodium-resorptive actions of insulin may be preserved. Additionally, insulin resistance results in paradoxical hyperactivity of sympathetic nerves within the kidney and increased levels of angiotensin-II and aldosterone, all of which enhance tubular sodium reabsorption in the presence of hyperinsulinaemia.^{80,81} As a result, hyperinsulinaemia can contribute to hypertension by several mechanisms that promote sodium retention by the kidney.

Obesity is also associated with the activation of RAAS and the sympathetic nervous system.^{80–82} The resulting neurohormonal activation is an essential contributor to the elevation of systemic blood pressure. Moreover, fat within and around the kidney itself causes organ compression, which increases blood pressure.⁸³ Once kidney damage

occurs in the context of obesity, these neurohormonal abnormalities, along with vascular calcification and arterial stiffness, may exacerbate hypertension by further augmenting sodium retention and increasing systemic vascular resistance.⁸⁴ Additionally, atherosclerosis can affect the kidney arteries, which, in association with flow-limiting ischaemia, can lead to resistant hypertension and kidney failure.^{85,86} Although a direct causal relationship between MASLD and hypertension has not been established, some have hypothesized that MASLD contributes to hypertension via low-grade chronic inflammation and hepatic insulin resistance.⁸⁷

Atherogenic dyslipidaemia

Most people with SMD have atherogenic dyslipidaemia, which is characterized by: (i) elevated levels of apolipoprotein B (apoB)-containing very low-density lipoproteins (VLDLs) and chylomicrons [produced by the liver and intestine, respectively, and collectively termed triglyceride-rich lipoproteins (TRLs)] and TRL remnants, (ii) an increased number of small-dense LDL particles, which are more susceptible to oxidation, and (iii) low levels of HDL-cholesterol in plasma. Atherogenic dyslipidaemia arises from a low hepatic uptake of lipoproteins, increased *de novo* lipogenesis driven by hyperinsulinaemia in the context of selective insulin resistance, insufficient fatty acid oxidation, overproduction of VLDL, impaired lipoprotein lipase (LPL)-mediated lipolysis, and reduced uptake of TRL remnants by the liver⁸⁸ (Figure 1). Increased production of chylomicrons and impaired lipolysis of chylomicron remnants contribute to postprandial dyslipidaemia.⁸⁹

The relationship between lipid abnormalities and insulin resistance is key in atherogenic dyslipidaemia. Insulin resistance causes a marked dysregulation of lipolytic activities, particularly in adipose tissue, resulting in a net increase in the release of free fatty acids (FFAs).^{90–92} Elevated FFAs, together with hyperglycaemia and hyperinsulinaemia, drive VLDL production, raising total cholesterol and triglyceride levels.^{93,94} A decrease in LPL activity further contributes to increased triglyceride levels. Cholesteryl ester transfer protein becomes activated, transferring cholesterol from HDL particles to TRLs. This process leads to the formation of small, dense HDL particles, which are cleared faster, lowering HDL levels.⁹⁵ Increased production of TRLs (both VLDL and chylomicrons) and impaired lipolysis of TRL remnants contribute to postprandial dyslipidaemia.⁸⁹ These combined changes exacerbate atherogenic risk.

Epidemiologic and genetic studies indicate that elevated levels of TRL remnants and apoB are causally related to the development of atherosclerosis.⁹⁶ Moreover, a recent study has shown that the per-particle atherogenicity of TRLs and TRL remnants appears to be greater than that of LDL,⁹⁷ which may, in part, explain the lipid-related excess risk of ASCVD beyond LDL-cholesterol. The atherogenicity of plasma triglycerides *per se* is less clear. However, epidemiological studies have shown that moderate elevation of plasma triglycerides [2.3–5.7 mmol/L (200–500 mg/dL)] is a marker of accumulation of TRL remnants and may help to identify people at higher risk for ASCVD and all-cause mortality.^{98,99} A recent study using machine learning identified plasma triglycerides, but not Type 2 diabetes, as an independent predictor of MASLD.¹⁰⁰ TRL accumulation is also a causal risk factor for

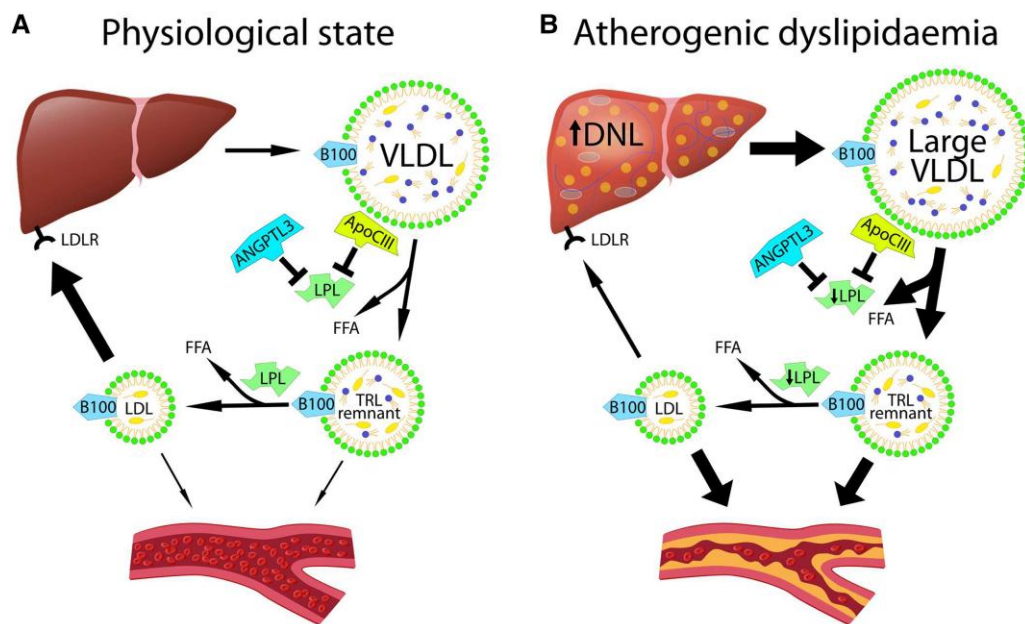


Figure 1 Overview of the development of atherogenic dyslipidaemia. (A) In the physiological state, the liver produces triglyceride-rich apolipoprotein B100-containing very low-density lipoprotein (VLDL). Triglycerides in these particles are hydrolyzed by lipoprotein lipase (LPL) to release free fatty acids (FFA). Both angiopoietin-related protein 3 (ANGPTL3) and apolipoprotein C-III (apoCIII) are endogenous inhibitors of LPL. Delipidation of VLDL results in the formation of triglyceride-rich lipoprotein (TRL) remnants, which are further delipidated to become LDLs. LDL is taken up by the liver through the LDL receptor (LDLR) and thereby removed from the circulation. (B) Atherogenic dyslipidaemia is characterized by increased hepatic *de novo* lipogenesis (DNL) and secretion of larger, more triglyceride-rich VLDL from the liver, impaired LPL-mediated lipolysis, and reduced uptake of LDL. All these factors lead to increased accumulation of TRL remnants and LDL. Both LDL and TRL remnants can transverse the endothelium and contribute to lesion initiation and progression in artery walls

low-grade inflammation,¹⁰¹ further augmenting the pro-atherogenic processes (see below).

Recent studies have highlighted a role for angiotensin-related protein 3 (ANGPTL3) and apolipoprotein C-III (apoCIII) in the development of atherogenic dyslipidaemia.^{102,103} Both proteins inhibit LPL (Figure 1), but they also have other actions in the liver and adipose tissue that are less understood.^{104,105} In the ARIC study, both plasma apoCIII and ANGPTL3 were positively and significantly correlated with TRL remnant-cholesterol and LDL-triglycerides, two biomarkers of dysfunctional triglyceride metabolism.¹⁰⁶ Of particular note, this study showed that ANGPTL3 levels were predictive of increased risk for ASCVD events, independent of traditional risk factors. Genetic studies provide further support for the role of these proteins in atherogenic dyslipidaemia. People with loss-of-function mutations in genes encoding ANGPTL3 or apoCIII experience accelerated removal of TRLs and TRL remnants during the postprandial phase.^{107,108}

Other members of the ANGPTL family are also involved in lipoprotein metabolism and insulin resistance. These include ANGPTL4, which is secreted mainly in the adipose tissue and acts as a local inhibitor of LPL, and ANGPTL8, which is secreted by the liver and adipose tissue and forms a complex with ANGPTL3 that inhibits LPL.¹⁰⁹ Mice overexpressing ANGPTL4 in adipose tissue show a predisposition to liver steatosis¹¹⁰ and ANGPTL8 levels were found to be elevated in humans with MASLD.¹¹¹ Furthermore, levels of ANGPTL4, but not ANGPTL3, are reduced by Roux-en-Y gastric bypass, possibly due to the loss of fat mass.¹¹² Taken together, these findings indicate that apoCIII and ANGPTLs contribute to the lipid and metabolic phenotypes associated with atherogenic dyslipidaemia, but their precise role remains to be determined.

Inflammation

People with visceral adiposity and insulin resistance often have an underlying pro-inflammatory phenotype that contributes to an elevated risk of ASCVD.^{113,114} Systemic inflammation is triggered by: (i) increased levels of pro-inflammatory lipid species in adipose tissue, which promote cellular stress and Toll-like receptor signalling in adipocytes and local macrophages, further promoting the recruitment of inflammatory macrophages^{115,116}; (ii) tissue hypoxia, cell death, and mechanical stress; and (iii) gut inflammation and leakage leading to the release of bacterial metabolites into the circulation.¹¹⁷ Activation of the canonical NOD, LRR, and pyrin domain-containing protein 3 (NLRP3) in inflammatory macrophages and adipocytes drives the production of pro-inflammatory cytokines such as tumour necrosis factor- α and interleukin (IL)-1, which in turn increases IL-6 production thereby promoting systemic inflammation.¹¹⁸ Similarly, excess lipid accumulation in the liver is sensed by Kupffer cells (resident macrophages) and recruited macrophages that acquire a pro-inflammatory phenotype and propagate hepatic inflammation, thereby contributing to metabolic rewiring of lipid metabolism.¹¹⁹ In addition, chronic lipotoxic stress promotes senescence in hepatocytes; MASLD severity increases in parallel with the accumulation of senescent hepatocytes, and reducing the burden of senescent hepatocytes has been shown to suppress fibro-inflammatory liver damage in mice.¹²⁰

Studies from nearly 30 years ago showed that low-grade systemic inflammation, detected either by IL-6 or the downstream biomarker high-sensitivity C-reactive protein (hsCRP), predicts incident Type 2 diabetes.^{121,122} Mendelian randomization studies provided support for a causal role of IL-6 receptor signalling in the development of coronary heart disease.¹²³ Moreover, CANTOS, a placebo-controlled, randomized trial to test canakinumab, a therapeutic monoclonal

antibody targeting IL-1 β , provided proof of concept for the inflammation hypothesis of atherothrombosis.¹²⁴ Of note, mortality was not reduced in this study, possibly due to the higher incidence of infectious complications.¹²⁴ Recent data indicate that virtually all autoimmune-inflammatory disorders, including diverse disorders such as psoriasis, rheumatoid arthritis, systemic lupus erythematosus, and inflammatory bowel disease, are associated with premature atherosclerotic events.^{125,126} Inflammation is thus well established as a crucial target for improved cardiometabolic health. However, it is important to target the immune systems in a way that prevents an increase in infections.

Heart failure

Insulin resistance, Type 2 diabetes, hypertension, atherogenic dyslipidaemia, and inflammation, all associated with obesity as noted above, increase the risk of heart failure by promoting atherosclerosis, leading to epicardial coronary artery disease and myocardial infarction. Ischaemic myocardial injury is followed by left ventricular remodelling and dilatation, promoting a decline in left ventricular ejection fraction and, subsequently, heart failure with reduced ejection fraction (HFrEF) or heart failure with mildly reduced ejection fraction (HFmrEF).

More recently, a unique and potent direct association between obesity and heart failure with preserved ejection fraction (HFpEF) has been identified, common in people without a history of myocardial infarction or flow-limiting epicardial coronary artery disease. Epidemiological studies have identified a robust independent relationship between increased BMI and HFpEF but not between BMI and HFrEF.^{127–130} Over 80% of people with HFpEF are overweight or living with obesity, and HFpEF is projected to become the dominant form of heart failure in the near future.^{131,132}

In contrast to atherosclerotic vascular diseases, the link between obesity and HFpEF is not explainable by traditional cardiovascular risk factors alone. Obesity contributes to HFpEF via a range of mechanisms, including harmful effects on myocardial structure and function, haemodynamic changes, neurohormonal activation, and inflammation, leading to increased left ventricular filling pressures, and through obesity-associated comorbidities such as type 2 diabetes, hypertension, coronary artery disease, and sleep apnoea (see Box 1).^{131–134}

While all people with HFpEF share haemodynamic abnormalities of increased filling pressures and resultant tissue congestion, the initiating mechanism leading to HFpEF differs. Multiple lines of evidence suggest that HFpEF results from a combination of pathophysiological phenotypes that converge to produce the common haemodynamic signature of elevated left ventricular filling pressure at rest or with exercise (see Supplementary data online, Table S1).¹³¹

Heart failure with preserved ejection fraction is more prevalent in women than in men, and compared with men, women with HFpEF tend to be more symptomatic, with more severe dyspnoea and worse overall health status. However, men with HFpEF have a higher risk of mortality and hospitalization. Some diagnostic parameters for HFpEF also differ by sex, with more frequent concentric left ventricular remodelling, more impaired left ventricular relaxation, and higher diastolic stiffness in women than men. Women also tend to have a smaller left ventricular chamber size and a higher left ventricular ejection fraction. Therefore, using sex-independent definitions of 'normal' ejection fraction results in an underestimation of left ventricular dysfunction in women.¹³²

Kidney disease

The CKD phenotype associated with SMD is characterized by a high urine albumin-to-creatinine ratio (UACR) and/or a low estimated

glomerular filtration rate (eGFR). Excess adiposity promotes kidney damage through both direct and indirect effects.^{84,135–137} Mendelian randomization analyses provide evidence for a causal link between obesity and kidney disease.¹³⁸ Histological studies show that the most common forms of CKD in people with obesity reflect overlapping pathologies associated with diabetes, hypertension, and focal segmental glomerulosclerosis.¹³⁶ The latter lesion may be directly obesity related, driven by intra-glomerular hypertension leading to enlarged hyper-filtrating glomeruli. These glomerular haemodynamic disturbances are exacerbated indirectly by diabetes and hypertension, common shared risk factors for CKD and ASCVD.¹³⁹ Additionally, excess adiposity dys-regulates the production of adipokines (e.g. leptin, resistin, and adiponectin) and pro-inflammatory mediators (e.g. tumour necrosis factor- α , IL-6, angiotensinogen, and aldosterone) that incite injury in the vasculature and kidney.^{140,141}

The American Heart Association has introduced the concept of a cardiovascular–kidney–metabolic syndrome to describe the complex pathophysiologic interactions among obesity, CKD, and total cardiovascular risk, including both ASCVD and heart failure.^{4,142} The

bidirectional association between dysfunction of the heart and the kidneys is well established.¹⁴³ Excess and dysfunctional adipose tissue, leading to inflammation and metabolic abnormalities as described in earlier sections, greatly increases the risk for developing both cardiovascular disease and CKD,¹⁴⁴ and these abnormalities have foundational pathophysiologic roles in bidirectional cardiovascular–kidney interactions. Notably, kidney dysfunction is a major driver of both ASCVD and heart failure.^{145,146} Hence, the American Heart Association has placed particular emphasis on the role of the kidney in the cardiovascular–kidney–metabolic syndrome and has introduced a staging system^{4,142} that includes designations of moderate, high, and very high-risk CKD, as defined by the Kidney Disease Improving Global Outcomes (KDIGO) heat map.¹⁴⁷

Systemic metabolic disorder staging, prevalence of systemic metabolic disorder, and risk conferred by systemic metabolic disorder

As indicated above, the individual SMD components do not appear in isolation, and there are many bidirectional associations between them. Given that a person with SMD will likely have more than one comorbidity, it is, therefore, essential to take a holistic approach to clinical management. To facilitate this process, we propose a staging system for SMD, as shown in Box 2, that we use to guide actionable management of SMD as it progresses. Stage 1 is characterized by metabolic abnormalities before organ damage, Stage 2 is characterized by early organ damage, and Stage 3 is characterized by more advanced organ damage. The defining criteria for each SMD stage are described in more detail in the next section.

To investigate the burden of SMD in the general population, we used our proposed staging system to calculate the prevalence of SMD Stages 1 and 2 in European participants of the UK Biobank (aged 40–69 years). We did not calculate the prevalence of SMD Stage 3 as the UK Biobank is a prospective cohort more suited to estimate the risk of future disease and did not include many participants with organ damage at baseline. Systemic metabolic disorder Stage 1 was observed in 58% of the population (Figure 2); the most common SMD features were overweight and dyslipidaemia (present in 96% and 91%, respectively, of those with Stage 1) followed by liver steatosis (52%) and hypertension (48%). Only 18% with Stage 1 SMD had pre-diabetes; the percentage with insulin resistance would likely be higher but proxies of this component are not available in the UK Biobank. When comparing

Box 1 Mechanisms and conditions through which obesity contributes to heart failure with preserved ejection fraction

- Myocardial stiffness and increased chamber stiffness due to structural myocardial change, which may or may not be associated with hypertension
- A pro-inflammatory state associated with visceral adiposity with resultant coronary microvascular endothelial dysfunction and increased oxidative stress, which can lead to cardiomyocyte hypertrophy and fibrosis and to interstitial fibrosis
- Increased blood volume resulting in greater cardiac filling pressures
- Increased cardiac output, stroke volume, stroke work, and hypertension, which can lead to left ventricular hypertrophy or remodelling, including both concentric and eccentric left ventricular hypertrophy/remodelling
- Right ventricular dilatation and dysfunction
- Increased epicardial fat causing right ventricular dysfunction
- Increased pericardial restraint and ventricular interdependence (mechanical factors)
- Left atrial remodelling (left atrial myopathy) and atrial fibrillation
- Increased myocardial work and decreased efficiency with increasing BMI and insulin resistance, possibly related to greater myocardial reliance on fat metabolism versus glucose oxidation
- Decreased exercise capacity (reduced peak oxygen consumption) related to decreased myocardial and skeletal muscle metabolic efficiency and increased filling pressures with exercise
- Impaired venous capacitance with resultant increased stressed blood volume resulting in increased filling pressures
- Sympathetic activation with blood volume redistribution from the splanchnic to the intravascular space
- Autonomic dysfunction leading to chronotropic incompetence
- Activation of RAAS and direct action on the adrenal gland resulting in increased release of aldosterone
- Diabetic cardiomyopathy
- Sleep apnoea, which increases risk of hypertension and atrial fibrillation
- Epicardial coronary artery disease with minor or no ischaemic myocardial damage

Box 2 Definition of each stage of systemic metabolic disorder

- Stage 1 is defined as the presence of (i) insulin resistance/pre-diabetes alone or (ii) overweight/dysfunctional adiposity and at least one of the following traits: isolated liver steatosis, hypertension, or atherogenic dyslipidaemia
- Stage 2 is defined as Type 2 diabetes, asymptomatic diastolic dysfunction, MASH/fibrosis, albuminuria or CKD Categories 1–2, or sub-clinical atherosclerosis with no history of events
- Stage 3 is defined as symptomatic HFpEF, cirrhosis/liver failure, reduced kidney function/failure and CKD Categories 3–5, or clinical manifestation of ASCVD

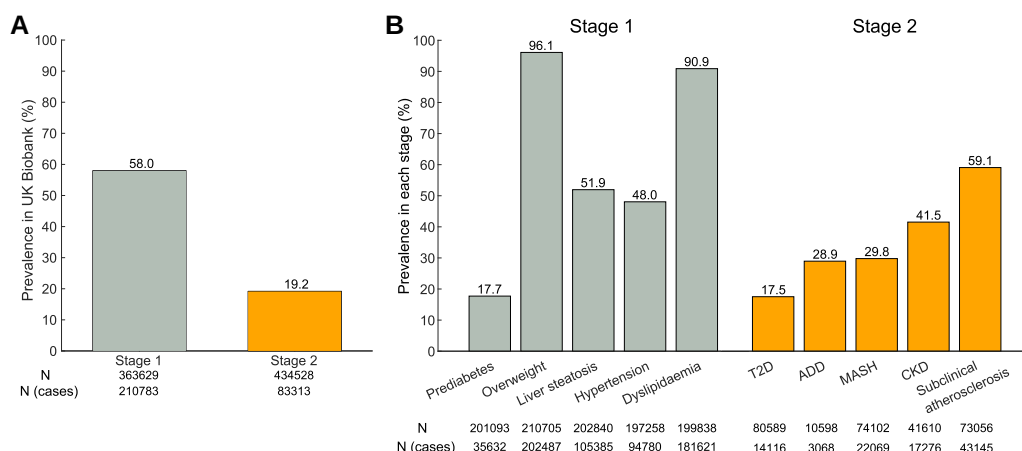


Figure 2 Prevalence of systemic metabolic disorder Stages 1 and 2 among Europeans from the UK Biobank. (A) Stage 1 was defined as individuals with pre-diabetes alone (HbA1c 39 to ≤ 47 mmol/mol; fasting insulin measurements were not available) or overweight (either body mass index ≥ 25 or waist circumference $\geq 88/102$ cm female/male) with at least one of the following conditions: liver steatosis (fatty liver index ≥ 60), hypertension (systolic blood pressure >140 or diastolic blood pressure >90 mmHg), and dyslipidaemia [non-fasting circulating triglycerides ≥ 2.0 mmol/L (177 mg/dL) or non-HDL-cholesterol ≥ 3.4 mmol/L (131 mg/dL) or apolipoprotein B ≥ 3.9 μ mol/L (100 mg/dL)]. Individuals taking anti-hyperglycaemic medications or with self-reported diabetes at baseline were excluded from Stage 1. Stage 2 was defined as individuals with at least one of the following conditions: Type 2 diabetes (HbA1c ≥ 48 mmol/mol), asymptomatic diastolic dysfunction (B-type natriuretic peptide or N-terminal-pro-B-type natriuretic peptide plasma Normalized Protein eXpression levels ≥ 95 th percentile), metabolic-associated steatohepatitis/fibrosis (Fibrotic NASH Index score >0.33), albuminuria and chronic kidney disease Categories 1–2 (estimated glomerular filtration rate ≥ 60 mL/min per 1.73 m² and urine albumin-to-creatinine ratio 3–29 mg/mmol), or atherosclerosis with no history of events ($5 \leq$ Systematic Coronary Risk Evaluation $< 10\%$ using the coefficients corresponding to low-risk individuals). Individuals who met the criteria for both stages were excluded from Stage 1. (B) Prevalence of each condition within individuals with either systemic metabolic disorder Stage 1 or 2. T2D, Type 2 diabetes; ADD, asymptomatic diastolic dysfunction; MASH, metabolic-associated steatohepatitis; CKD, chronic kidney disease.

combinations of SMD features, most people with Stage 1 SMD had both overweight and dyslipidaemia, followed by those with overweight, dyslipidaemia and liver steatosis, and overweight, dyslipidaemia, liver steatosis, and hypertension (see [Supplementary data online, Figure S1](#)).

Systemic metabolic disorder Stage 2 was observed in 19% of the European UK Biobank population; the most common SMD feature was sub-clinical atherosclerosis (present in 59% of those with Stage 2), which parallels the high prevalence of atherogenic dyslipidaemia observed in Stage 1 and is not unexpected given that ASCVD is the leading cause of death in the population, followed by CKD (present in 42% of those with Stage 2) ([Figure 2](#)). Metabolic-associated steatohepatitis and asymptomatic diastolic dysfunction were present in 30% and 29%, respectively, whereas Type 2 diabetes was only present in 18% of those with Stage 2 ([Figure 2](#)). Our observation that CKD is more prevalent than Type 2 diabetes in this population is consistent with obesity acting as a major driver of CKD. Interestingly, most early signs of organ damage were present only in one organ (see [Supplementary data online, Figure S1](#)), which is likely due to an individual predisposition to develop disease in a particular organ. The most common combination was Type 2 diabetes and MASH.

Stage 1 is likely dependent on metabolic insults that are potentially reversible by lifestyle interventions; in addition, functioning allostatic/homeostatic responses help to contain progression. Stage 2 likely represents increased inflammation and failure of allostatic/homeostatic mechanisms, leading to failure of the cells and resultant cellular injury, thus initiating fibro-inflammatory changes with some organs preferentially affected based on their genetic/epigenetic vulnerability.⁹

To validate the clinical relevance and discriminative capacity of the SMD staging, we examined the prospective association between Stages 1 and 2 and all-cause mortality over a median follow-up of

14.9 years in the UK Biobank. Stage 1 conferred a 6% prospective increase, while Stage 2 conferred a 49% increase in mortality after adjustment for sex and age ([Figure 3](#)).

Defining criteria for each stage of systemic metabolic disorder

The defining criteria for each SMD stage and the clinical variables that should be measured in a person with SMD are summarized in [Figures 4–6](#). Below, we describe the diagnostic tools and/or biomarkers that can be used to assess each SMD component.

Insulin resistance, pre-diabetes, and Type 2 diabetes

The gold standard for evaluating insulin resistance, namely the hyperinsulinaemic-euglycaemic clamp technique,¹⁴⁸ is impractical for regular large-scale clinical practice. Hence, surrogate markers for insulin resistance have been proposed, the best known of which is the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR),¹⁴⁹ calculated using the formula: [fasting plasma insulin (mU/L) $\times$ plasma fasting glucose (mmol/L)]/22.5. A value of 2.5 or higher is considered to indicate insulin resistance.¹⁵⁰ Additional surrogate markers include the triglyceride-glucose index¹⁵¹ and triglyceride to HDL-cholesterol ratio,¹⁵² both of which are associated with risk of cardiovascular disease independent of LDL-cholesterol.¹⁵³

Pre-diabetes and Type 2 diabetes can be diagnosed by measuring (i) glycated haemoglobin (HbA1c), (ii) fasting plasma glucose, or (iii) plasma

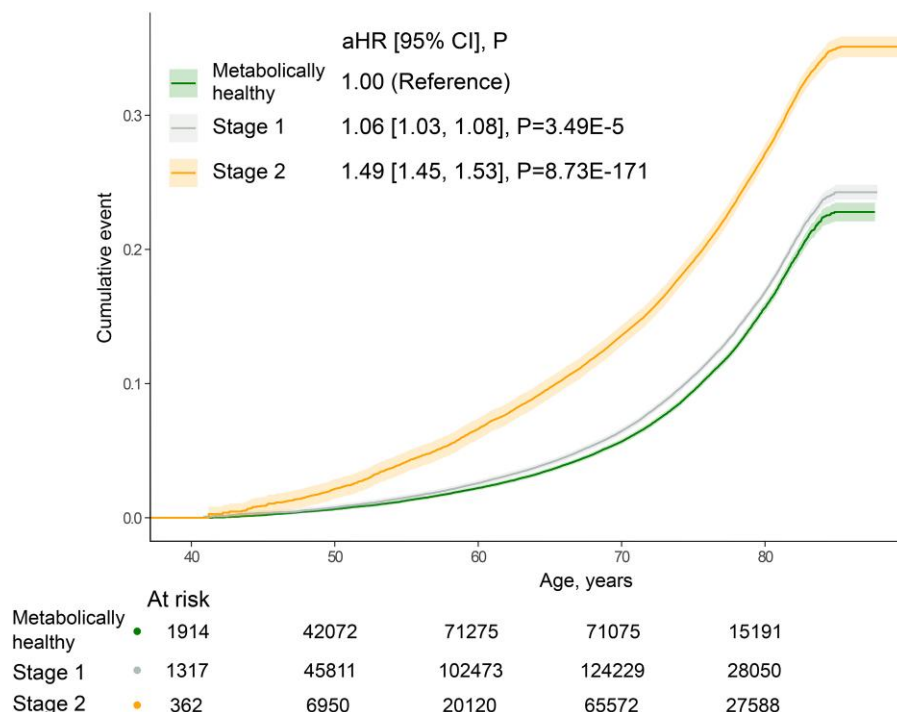


Figure 3 Kaplan–Meier estimates of cumulative events for all-cause mortality among Europeans in the UK Biobank with or without systemic metabolic disorder Stages 1 or 2. The defining criteria used here for Stages 1 and 2 are described in the legend in Figure 2. Individuals who met the criteria for both stages were excluded from Stage 1. All-cause mortality was defined using the date of death from record linkage to Hospital Episode Statistics (England and Wales) and Scottish Morbidity Records. Follow-up began at the date of baseline assessment visit and ended at the date of death, loss to follow-up, or censoring date (31 October 2022, https://biobank.ctsu.ox.ac.uk/crystal/exinfo.cgi?src=Data_providers_and_dates), whichever happened first. The median follow-up period was 14.95 years (interquartile range 14.94–14.95). Hazard ratios with 95% confidence intervals were calculated using Cox proportional hazard models for Stages 1 (grey) and 2 (orange) vs metabolically healthy (green), adjusted for age and sex. aHR, adjusted hazard ratio; CI, confidence interval.

glucose 2 h after an OGTT (Figures 4 and 5). The OGTT consists of a fasting glucose blood test followed by the consumption of a 75 g glucose drink and a diagnostic glucose blood test at 120 min. This test provides information about the pancreatic reserve to compensate for insulin resistance.

In the context of obesity, pre-diabetes is an easily measurable clinical manifestation of insulin resistance. However, it is important to note that insulin resistance can exist in the absence of dysglycaemia,⁵¹ and therefore, some individuals at an early stage of SMD will not be identified when using pre-diabetes as a proxy for insulin resistance. Therefore, we recommend using HOMA-IR in addition to HbA1c to determine whether an individual is at an early stage of SMD.

Overweight/obesity

Excess adiposity is most commonly assessed using the BMI (weight in kilograms divided by height in metres squared). The World Health Organization defines overweight and obesity as BMI ≥ 25 and ≥ 30 kg/m², respectively.¹⁵⁴ However, given the increased risk of Type 2 diabetes and ASCVD in Asian people even at a BMI ≤ 25 kg/m², the American Diabetes Association guidelines in 2022 recommended that a BMI ≥ 23 kg/m² defines overweight in Asian people.¹⁵⁵ A limitation of BMI is that it does not consider the body fat distribution or the amount of free fat mass, while several anthropometric (e.g. waist circumference) and imaging measurements can be used to assess body

fat distribution.^{156,157} An analysis of pooled data from over 650 000 white adults in 2014 showed that waist circumference was positively associated with mortality at all BMI levels from 20–50 kg/m², leading to the conclusion that waist circumference should be assessed in combination with BMI to assess the risk of obesity-related premature mortality.¹⁵⁸

Given the heterogeneity of obesity and the wide variability in health outcomes for any given BMI, the Lancet Commission and the EASO recently proposed new frameworks for the diagnosis and staging of obesity that better align with current evidence.^{2,3} Both initiatives focus on obesity as an adiposity-based chronic disease and emphasize its clinical consequences. Moreover, both recognize that dysfunctional subcutaneous adipose tissue releases FFA, leading to visceral obesity and fat deposition in other ectopic depots and associated sequelae as described above.⁷ In line with this, the EASO framework states that the diagnosis of obesity should be based on the recognition of abnormal and/or excessive fat accumulation (anthropometric component) and the analysis of its present and potential effects on health (clinical component).² The framework recommends using waist-to-height ratio as the anthropometric component instead of waist circumference (in combination with BMI) as it has shown superiority as a cardiometabolic disease risk marker and is not dependent on sex-specific or ethnic differences.¹⁵⁹ The Lancet Commission used the term 'clinical obesity' to describe a situation in which symptoms and signs of excess adiposity are present and 'pre-clinical obesity' as a state of excess adiposity with

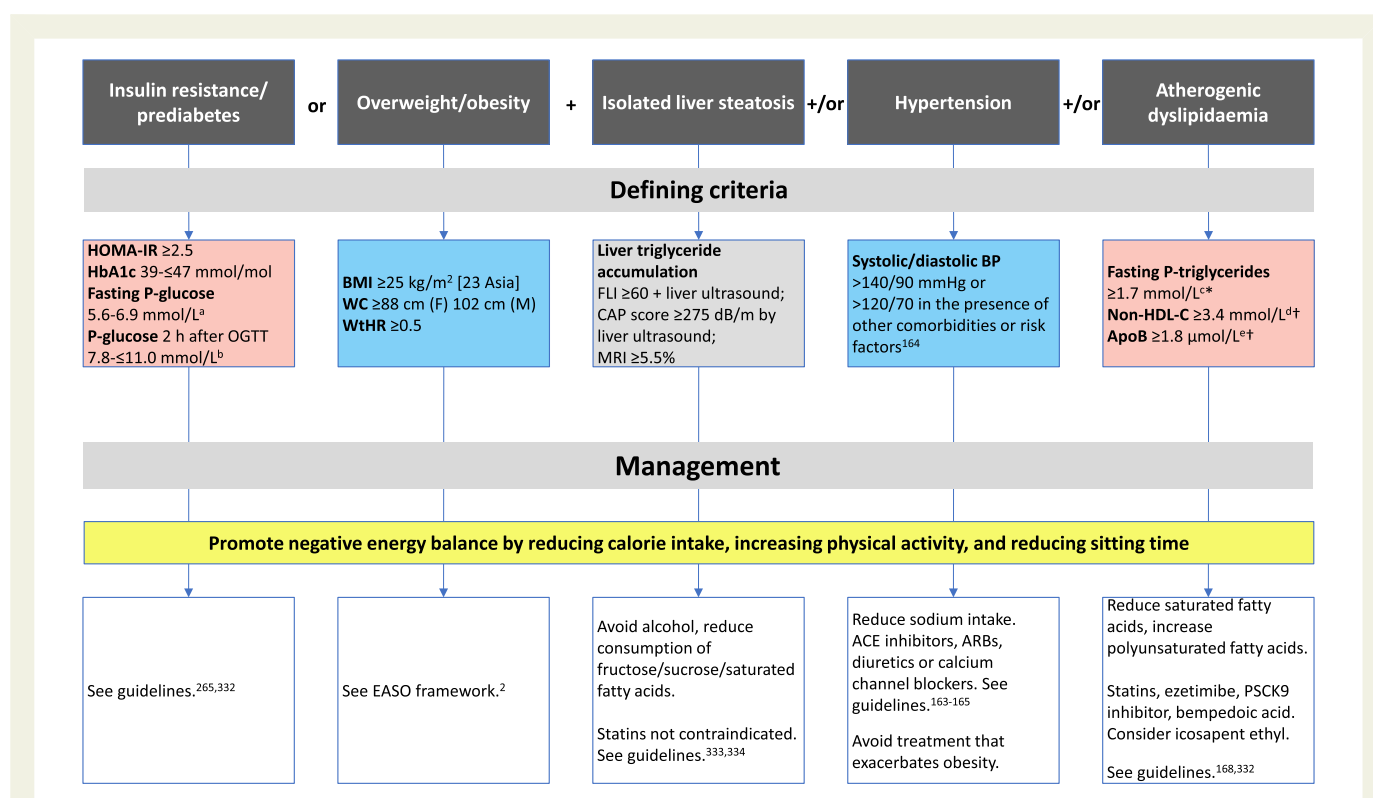


Figure 4 Defining criteria and potential management strategies for systemic metabolic disorder Stage 1. Conventional units: ^a101–124 mg/dL; ^b141 to ≤ 198 mg/dL; ^c150 mg/dL; ^d131 mg/dL; ^e100 mg/dL. *Non-fasting P-triglycerides ≥ 2.0 mmol/L (177 mg/dL). †Values shown for individuals at moderate risk of atherosclerotic cardiovascular disease. For those at high risk of atherosclerotic cardiovascular disease, lower thresholds apply: non-HDL-cholesterol ≥ 2.6 mmol/L (100 mg/dL); apolipoprotein B ≥ 1.5 μ mol/L (≥ 80 mg/dL). P, plasma; WC, waist circumference; WtHR, waist-to-height ratio; EASO, European Association for the Study of Obesity; FLI, fatty liver index; CAP, controlled attenuation parameter; MRI, magnetic resonance imaging; BP, blood pressure; C, cholesterol; ACE, angiotensin-converting enzyme; ARB, angiotensin-II receptor blocker

preserved function of other tissues and organs but with increased risk of developing clinical obesity.³ The commissioners agreed that clinical assessment of obesity should include measures of adiposity in addition to BMI (such as other anthropometric measures) to determine whether an individual has excess adiposity.³

Some advantages and disadvantages of the different methods to assess adiposity are presented in [Supplementary data online, Table S2](#). We recommend measuring BMI combined with at least one other anthropometric component, preferably the waist-to-height ratio, to diagnose excess adiposity, and cut-off points will depend on ethnicity.

Isolated liver steatosis and metabolic-associated steatohepatitis

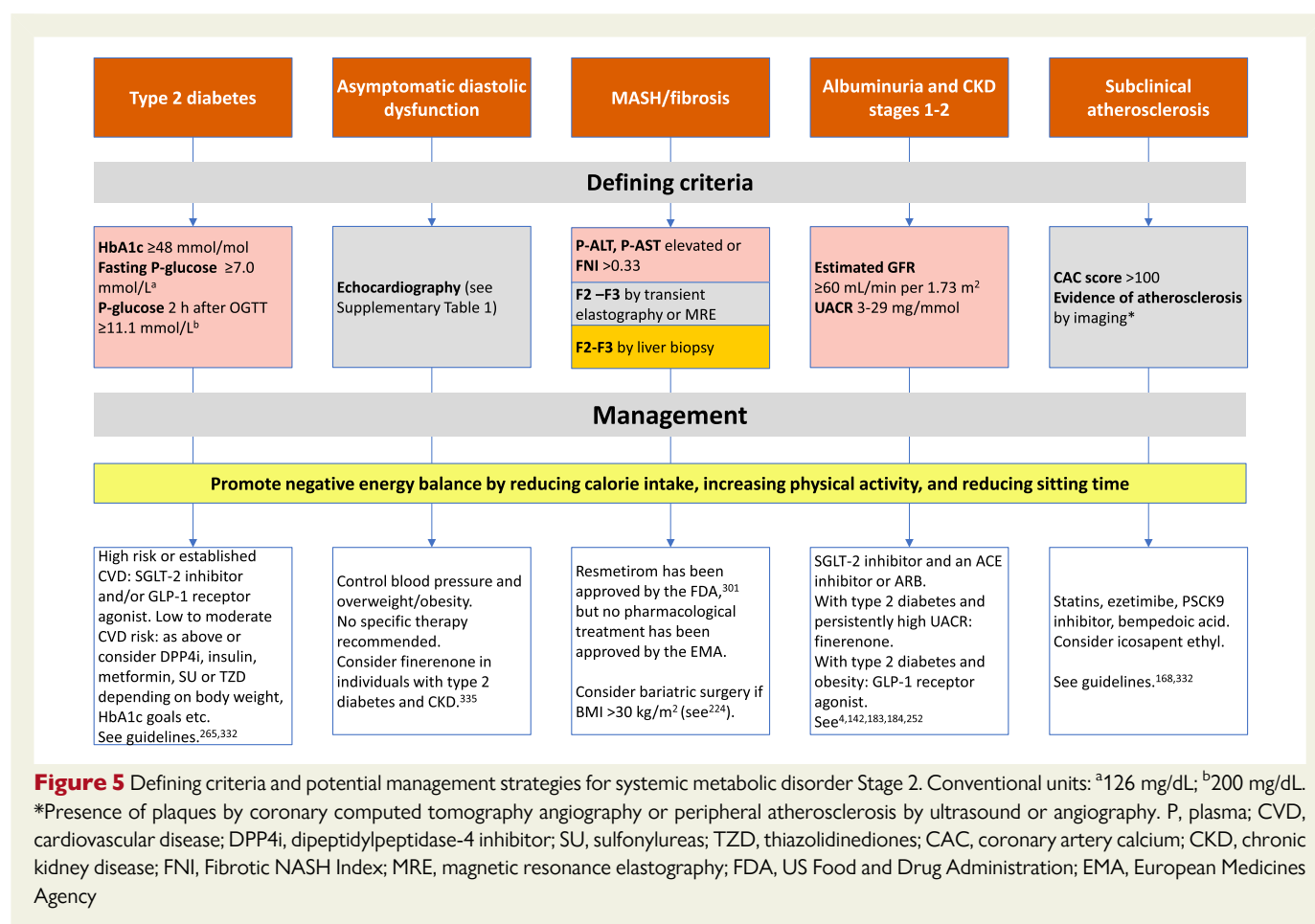
Ultrasound can determine the presence of liver steatosis. Although widely available and easy to use, this imaging method is only qualitative and has poor accuracy. The fatty liver index (FLI), which uses variables that are routinely measured in clinical practice (BMI, waist circumference, triglycerides, and gamma-glutamyl transferase), can be used to select individuals who should be referred for ultrasound.¹⁶⁰ Liver fat content can be quantitatively measured by controlled attenuation parameter, an ultrasound-based technique that is becoming more commonly available. Magnetic resonance imaging can be used to measure liver triglyceride content precisely. However, this is available only in specialized centres and does not measure qualitative changes in lipids.

Liver function and damage can be screened using traditional biochemical markers. Several tests for liver fibrosis using combinations of non-invasive markers now exist. One example is the Fibrotic NASH Index (FNI; <https://fniscore.github.io/>), which has been shown to accurately identify those with MASH and MASH regression after weight loss.^{161,162}

Liver fibrosis can be assessed by transient elastography, magnetic resonance elastography, or liver biopsy followed by histological evaluation by a pathologist. Although liver biopsy remains the gold standard to measure liver inflammation and fibrosis, this procedure is invasive, not easily standardized, and occasionally associated with complications such as bleeding.

Hypertension

Hypertension is diagnosed using widely accepted methods.¹⁶³ The 2024 European Society of Cardiology (ESC) guidelines define hypertension (as before) as systolic blood pressure (SBP) ≥ 140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg and introduce a new term: elevated blood pressure, defined as SBP 120–139 mmHg or DBP 70–89 mmHg.¹⁶⁴ This addition recognizes that the risk associated with high blood pressure is continuous and should be considered together with other risk factors to estimate cardiovascular risk.¹⁶⁴ Other guidelines state that cardiovascular risk is present in individuals with SBP 130–139 or DBP 85–89 mmHg if they have three or more other risk factors.^{163,165}



Atherogenic dyslipidaemia, atherosclerosis, and atherosclerotic cardiovascular disease

Atherogenic dyslipidaemia is diagnosed as indicated in [Figure 4](#). People can have atherogenic dyslipidaemia even when LDL-cholesterol levels are normal. A recent study using data from the UK Biobank showed that apoB, as a marker of the total number of atherogenic particles, is a more accurate marker of cardiovascular risk than is LDL-cholesterol or non-HDL-cholesterol.¹⁶⁶ Although apoB is not routinely measured in clinical practice, a growing body of evidence supports its use as a valuable tool for assessing atherogenic dyslipidaemia and the total atherogenic lipid burden,¹⁶⁷ which is of particular relevance for SMD. Furthermore, given that it does not require fasting and is relatively low cost, we strongly recommend measuring apoB and using the apoB thresholds stated in the 2019 ESC/EAS guidelines to guide clinical management.¹⁶⁸

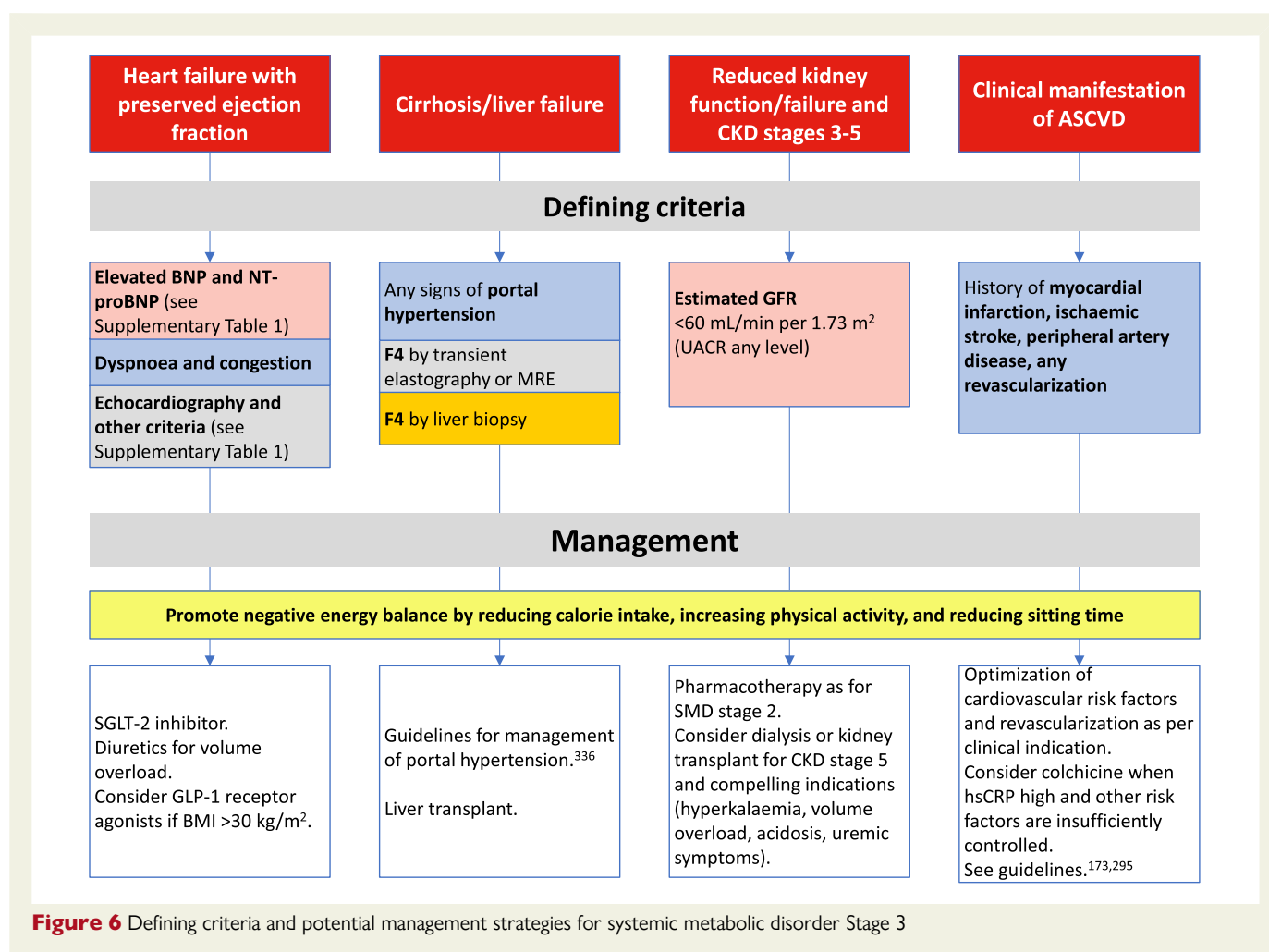
Sub-clinical atherosclerosis is prevalent in apparently healthy people in middle age due to cumulative exposure to risk factors. Risk models have been developed that combine information on conventional cardiovascular risk factors and estimate the 10-year risk of, for example: (i) death from cardiovascular disease [Systematic Coronary Risk Evaluation (SCORE)]¹⁶⁹ and (ii) fatal and non-fatal cardiovascular events (SCORE2).¹⁷⁰ Imaging studies have shown that half of men above age 40 have sub-clinical atherosclerosis,^{171,172} and thus many individuals are likely at higher risk than indicated by risk models. Measures of sub-clinical atherosclerosis may aid clinical decision-making by

helping to reclassify individuals into higher or lower risk categories than predicted by conventional factors alone. Non-invasive techniques to detect atherosclerosis include documentation of plaques by ultrasonography or coronary computed tomography (CT) angiography.¹⁷³ Coronary artery calcium (CAC), which is a relatively late occurrence in atherosclerosis, can be detected using a CT scan without contrast. A CAC score >100 is associated with $>7.5\%$ 10-year risk of ASCVD.¹⁷⁴ Peripheral atherosclerosis can be diagnosed by ultrasound or angiography. The clinical manifestation of ASCVD is defined according to the criteria listed in [Figure 6](#).

Asymptomatic diastolic dysfunction and heart failure with preserved ejection fraction

Asymptomatic left ventricular diastolic dysfunction is generally diagnosed based on specific findings on echocardiography (see [Supplementary data online, Table S1](#)).

The diagnosis of HFpEF is challenging. It requires the presence of signs and symptoms of heart failure, documented left ventricular ejection fraction $\geq 50\%$ and objective evidence of cardiac structural and/or functional abnormalities consistent with the presence of left ventricular diastolic dysfunction and raised left ventricular filling pressures, derived from echocardiographic measures, and elevated plasma levels of B-type natriuretic peptide (BNP) and its N-terminal fragment (NT-proBNP) (see [Supplementary data online, Table S1](#)).^{131,132,175–180}



The presence of echocardiographic and natriuretic peptide indicators of congestion is useful to confirm the diagnosis of HFpEF. However, their absence does not exclude HFpEF due to challenges associated with these tests, such as technical difficulties and imprecision of echocardiographic measures, especially in the presence of atrial fibrillation. More than 30% of people with HFpEF have normal natriuretic peptide values, and this is a particular issue in people living with obesity.^{178,181,182} In addition, several common conditions, including older age and CKD, can cause elevated BNP or NT-proBNP in the absence of heart failure. Moreover, approximately one-third of patients with HFpEF have normal left ventricular filling pressures at rest. Therefore, invasive haemodynamic testing and exercise testing are often necessary to determine whether or not an individual has HFpEF (see [Supplementary data online, Table S1](#)).^{131,132,175–180}

It is also important to exclude non-cardiovascular entities that may mimic HFpEF, such as kidney failure or nephrotic syndrome, liver failure, lung disease and primary pulmonary hypertension and specific cardiac diseases with similar presentation but different pathophysiology and different disease-specific therapies, such as infiltrative cardiomyopathies (especially cardiac amyloidosis), hypertrophic cardiomyopathy, pericardial disease, valvular heart disease, and high output heart failure.^{131,132}

Establishing the diagnosis of HFpEF is particularly difficult in the presence of obesity, which is often associated with symptoms of dyspnoea,

fatigue, and physical limitations even in the absence of heart failure. Moreover, in people living with obesity, echocardiography is often technically challenging, and BNP levels are typically lower and often normal even in those with HFpEF.

Albuminuria, estimated glomerular filtration rate, and chronic kidney disease

Current clinical practice guidelines, consensus statements, and advisories on CKD from KDIGO, the American Diabetes Association, and the American Heart Association, respectively, recommend testing for UACR and eGFR at least annually and more often, e.g. three to four times per year, at higher KDIGO risk categories.^{4,142,183,184} UACR and eGFR are essential to the ongoing reassessment of heart and kidney disease risks because risk-modifying therapies are to be initiated or adjusted based on risk status.

Management of systemic metabolic disorder

The primary goal of clinical management of SMD is to prevent progression and reduce the risk of end-organ damage. Successful management requires an individually tailored approach where the importance of

lifestyle changes cannot be overestimated. Our prevalence data show that over half of the UK Biobank population has Stage 1 SMD and thus clinical management should focus on: (i) reducing the number of individuals who reach this stage and (ii) preventing the transition to Stage 2 and beyond. Below we describe the latest evidence supporting the use of lifestyle changes and metabolic surgery to manage this complex multi-system condition and the currently recommended pharmacotherapy. Management strategies for each SMD stage are summarized in [Figures 4–6](#).

Lifestyle changes

Lifestyle changes to improve diet quality while reducing caloric intake and increasing energy expenditure should be considered the cornerstone of treatment for all stages of SMD. Healthy dietary patterns linked to lower cardiometabolic risk prioritize vegetables, minimally processed whole grains, healthy protein sources (primarily plant-based, fish, seafood, and low-fat or fat-free dairy), liquid plant oils, and fruit.¹⁸⁵ These patterns are low in added sugars, salt and sugary beverages.

A recent umbrella review of epidemiological meta-analyses showed that greater exposure to nutrient-poor, ultra-processed food (with high levels of sugar, salt and saturated fat and low levels of dietary fibre) is associated with adverse health outcomes, including an increased risk of cardiovascular disease-related mortality, overweight/obesity, and Type 2 diabetes.¹⁸⁶ These findings highlight the need for a major transformation of our entire economic system, starting with support for public health policies that discourage or de-incentivize consumption of ultra-processed food. Such policies would reduce the development and progression of SMD with substantial benefits for population health.

Evidence from the PREDIMED-Plus and CALERIE trials shows that calorie restriction with optimal nutritional composition can lead to reductions in body weight, visceral adiposity, inflammation, oxidative stress, and blood pressure and improvements in insulin sensitivity, glucose tolerance, and lipid metabolism in people living with both normal weight and overweight.^{187–194} Diet-induced weight loss can lead to dose-dependent remission of Type 2 diabetes,¹⁹⁵ improvements in multiple cardiometabolic and CKD risk factors,¹⁹¹ and marked reductions in liver steatosis and fibrosis.¹⁹⁶ Intermittent fasting has increased in popularity in recent years. However, a recent meta-analysis did not identify any advantage of intermittent restriction diets (combined results from time-restricted eating, alternate-day fasting, and the 5:2 diet) compared with continuous energy restriction diets.¹⁹⁷

Accumulating evidence suggests that the quality of diet (i.e. beyond the quantity of calories) influences the metabolic response to caloric reduction. Consuming a high-protein diet during weight loss therapy seems to eliminate the favourable effects of weight loss on insulin resistance.¹⁹⁸ By contrast, consuming a diverse range of foods rich in vegetable fibre, vitamins, polyunsaturated fats, phytosterols, and polyphenols while maintaining low levels of salt and saturated fatty acids—characteristic of the Mediterranean or the Nordic diet—conveys additional cardiometabolic benefits.^{199,200} The 2021 ESC guidelines recommend a healthy, more plant-based Mediterranean diet as a cornerstone of cardiovascular disease prevention in all individuals, irrespective of risk level.¹⁷³ LDL-cholesterol lowering is a primary goal in dietary interventions, and relatively small reductions [in the range of 0.15–0.50 mmol/L (5.8–19 mg/dL) with and without blood pressure lowering] that are within reach of dietary interventions have shown substantial 'dose-dependent' cardiovascular risk reductions.²⁰¹ The portfolio diet, a plant-based diet including nuts, plant protein, viscous fibre, and plant sterols, is another example of an effective strategy to lower LDL-cholesterol.²⁰²

A recent meta-analysis reveals that short-term carbohydrate restriction significantly improves cardiometabolic outcomes at the 6-month follow-up; however, these effects are not sustained beyond 12 months.²⁰³ Furthermore, total cholesterol and LDL-cholesterol have been shown to increase when carbohydrate intake falls below 40%.^{203,204} Diets with equal carbohydrate amounts but different glycaemic indexes may exert varying effects on cardiometabolic risk factors,²⁰⁵ with low glycaemic index diets promoting small yet significant improvements in people with diabetes.²⁰⁶

Engaging in regular physical activity enhances metabolic health by activating key metabolic pathways, such as glycogen synthase and LPL activity, and GLUT4 expression, independent of weight loss.²⁰⁷ Aerobic exercise in particular is effective at improving glucose tolerance and insulin sensitivity, making it a crucial component of any weight loss programme.²⁰⁸ It helps to prevent reductions in serum levels of the thyroid hormone triiodothyronine (T3) and resting metabolic rate, which are key to avoiding weight regain²⁰⁹ and countering skeletal and bone mass loss.²¹⁰ A 1-year clinical trial demonstrated that regular high-volume endurance training alone (1 h/day, 6 days a week at 71% of maximal heart rate) led to a substantial (~40%) reduction in visceral fat and marked improvements in glucose, lipid and insulin metabolism in middle-aged people.^{192,208} Aerobic exercise combined with resistance exercise also helps to prevent the loss of skeletal muscle and bone mass.²¹⁰ Reducing sedentary behaviour, i.e. reducing the awake time spent in seated, reclined or lying posture, is also essential.^{211–214}

The circadian system is tightly coupled with processes controlling sleep and metabolism, and disruption of the central and peripheral clocks might contribute to the exacerbation of obesity, nutritional fluxes and the development of insulin resistance.¹⁰

Metabolic surgery

Metabolic/bariatric surgery exerts positive effects on cardiovascular health by ameliorating obesity-related cardiovascular risk factors, including lowered blood pressure, improved lipid profiles, and enhanced glycaemic control, and can be considered in individuals living with severe obesity.

STAMPEDE was the first randomized controlled trial (RCT) in people with Type 2 diabetes to show that metabolic surgery has durable effects on glycaemic control.^{215–217} A meta-analysis of RCTs comparing surgery and (pre-incretin) medical therapy after 3 years showed better glucose control and a higher rate of diabetes remission after surgery.²¹⁸ These superior outcomes were confirmed 10 years after surgery in one RCT.²¹⁹ In a meta-analysis using patient-level survival data reconstructed from prospective controlled trials and high-quality matched cohort studies, surgery was associated with a 9.3-year increase in median life expectancy for individuals with diabetes.²²⁰

One RCT demonstrated that surgery is an effective strategy for blood pressure control in those with hypertension.²²¹ In people with MASLD, surgery resulted in the complete resolution of steatohepatitis in 84% after 1 year and the resolution of advanced liver fibrosis in 68% after 5 years.²²² In a retrospective study, surgery was associated with a reduction of the 10-year adjusted risk of incident major adverse liver and cardiovascular outcomes of 12.4% and 13.9%, respectively.²²³ An RCT recently showed 3.5 times higher resolution of steatohepatitis with no worsening of fibrosis 1 year after surgery.²²⁴

In a prospective controlled study, metabolic surgery reduced the risk of developing CKD and lowered albuminuria.²²⁵ In an RCT in people with type 2 diabetes and early-stage CKD, remission of albuminuria and CKD was more frequent after Roux-en-Y gastric bypass than after

medical treatment (82% vs 55% and 82% vs 48%, respectively).²²⁶ In a prospective cohort study, the postoperative stabilization of eGFR was linked to the reduction of insulin resistance and hyperinsulinism, with the largest effect being in a subgroup of participants with severe insulin-resistant diabetes.²²⁷

In a recent meta-analysis including 39 observational cohort studies, metabolic surgery was associated with a beneficial effect on cardiovascular mortality [hazard ratio (HR) 0.59].²²⁸ Metabolic surgery was also associated with a reduced incidence of heart failure (HR 0.50), myocardial infarction (HR 0.58), and stroke (HR 0.64). Mechanisms underlying these cardiovascular improvements are being elucidated. Beyond mere weight loss, metabolic adaptations contribute to enhanced insulin sensitivity, modulation of adipokines, and anti-inflammatory effects. Metabolic surgery also improves lipid abnormalities beyond low HDL and high triglycerides, including effects on oxidized lipoproteins, pro-protein convertase subtilisin/kexin type 9 (PCSK9), and HDL particle functionality.²²⁹ The ongoing BRAVE study (NCT04226664), a large multicentre international RCT, aims to confirm the role of surgery in the secondary prevention of major adverse cardiovascular events in individuals with obesity.

Pharmacotherapy

Glucagon-like peptide-1 receptor agonists and dual and triple peptide agonists

Glucagon-like peptide-1 (GLP-1) receptor agonists are today recognized as a class of drugs with wide-ranging therapeutic potential beyond Type 2 diabetes and obesity. Evidence supporting their benefits across a range of SMDs, including ASCVD, HFpEF, MASH, and CKD, is described in detail below. The multi-organ protective effects of these therapies appear to go beyond the 'downstream' measures of efficacy for which they were developed, namely glycaemia and weight loss.²³⁰

The first-in-class GLP-1 receptor agonist, exenatide, was exendin-based and gained Food and Drug Administration (FDA) approval in 2005 for Type 2 diabetes. The more recent GLP-1 receptor agonists are human-based, the first being liraglutide (daily dosing) and later dulaglutide and semaglutide (weekly dosing). It is now well established that GLP-1 receptor agonists not only reduce glycaemia but also promote weight loss, albeit at higher doses. Of these, semaglutide is the most potent.²³¹ The dual GLP-1 and glucose-dependent insulintropic polypeptide (GIP) receptor agonist tirzepatide has been shown to promote even greater weight loss²³² and HbA1c lowering²³³ than semaglutide in individuals who are overweight or obese with Type 2 diabetes. Topline results from a head-to-head trial (NCT05822830) show an average weight loss of 20.2% for tirzepatide vs 13.7% for semaglutide in adults who are overweight or obese but without type 2 diabetes.²³⁴ Liraglutide, semaglutide, and tirzepatide were approved by the FDA for the treatment of obesity in 2014, 2021, and 2023, respectively.

Dosing schedules for the currently prescribed GLP-1/GIP receptor agonists for Type 2 diabetes and obesity are shown in Table 1. These drugs are mainly administered subcutaneously due to poor oral bio-availability, but an oral daily formulation of semaglutide is available. A recent trial showed that oral semaglutide 50 mg per day promotes similar weight reductions to those observed with subcutaneous semaglutide 2.4 mg once weekly.²³⁵ In a 68-week trial, oral semaglutide at 25 and 50 mg per day was shown to be safe and more effective in terms of both HbA1c lowering and weight loss compared with the usual 14 mg per day diabetes dose in individuals who were overweight and with diabetes.²³⁶ However, given the global shortage and cost of GLP-1 receptor agonists, the high dose required for oral administration

Table 1 Dosing schedules for the currently prescribed glucagon-like peptide-1 and glucagon-like peptide-1/glucose-dependent insulintropic polypeptide receptor agonists

Dosing schedule for Type 2 diabetes (and obesity) ^a	
GLP-1 receptor agonist	
Dulaglutide	0.75–4.5 mg once weekly
Exenatide	5–10 µg twice daily
Exenatide (extended-release)	2 mg once weekly
Liraglutide	0.6–1.8 mg once daily (3.0 mg/day for obesity)
Lixisenatide	10–20 µg once daily
Semaglutide subcutaneous	0.25–1.0 mg once weekly (2.4 mg/week for obesity)
Semaglutide tablet	3–14 mg once daily (50 mg/day for obesity)
Dual GLP-1/GIP receptor agonist	
Tirzepatide	2.5–15 mg once weekly (same for obesity)

^aAll are administered subcutaneously, with the exception of semaglutide tablet. All drugs are initiated at the lowest dose, which is then increased over several weeks to attenuate possible gastrointestinal side effects.

may limit the use of this formulation to treat obesity. A recent development of relevance is the orally available non-peptide GLP-1 receptor agonist orforglipron, which produced dose-dependent weight reductions of up to 14.7% in a Phase 2 trial.²³⁷ In this rapidly evolving field, therapies under investigation also include the so-called 'triple G' receptor agonists (GLP-1, GIP, and glucagon)²³⁸ and amylin agonists alone or combined with other gut hormone analogues,²³⁹ with the potential for even greater reductions in weight.

Definitive proof that GLP-1 receptor agonists offer cardiovascular benefits beyond glucose lowering came first from trials in populations with Type 2 diabetes for liraglutide (subcutaneous 1.8 mg once daily),²⁴⁰ semaglutide (subcutaneous 0.5 and 1 mg once weekly),²⁴¹ and dulaglutide (subcutaneous 1.5 mg once weekly).²⁴² The beneficial effects of these therapies to reduce cardiovascular events in individuals who are overweight or obese and with pre-existing cardiovascular disease but without diabetes were proven in the landmark SELECT trial for semaglutide (subcutaneous 2.4 mg once weekly vs placebo).²⁴³ Results from this trial led to the first approval by the FDA, in 2024, for an agent (semaglutide) for secondary prevention of cardiovascular disease in adults who are either overweight or obese. The dual agonist tirzepatide is currently being assessed in two cardiovascular outcome trials. The first, SURPASS-CVOT, compares once weekly subcutaneous injection of either tirzepatide up to 15 mg or dulaglutide 1.5 mg in individuals who are overweight or obese and have diabetes and established cardiovascular disease.²⁴⁴ This active comparator design, i.e. against a treatment proven to reduce cardiovascular disease rather than placebo, will provide novel insights into the role of greater weight loss and HbA1c reduction in this high-risk group.²⁴⁴ The second,

SURMOUNT-MMO (NCT05556512), is in individuals who are overweight or obese; as approximately two-thirds have cardiovascular risk factors without established cardiovascular disease, results from this trial could help to clarify the benefits of obesity management with these types of therapies in a primary prevention population.

Direct evidence of organ protection for GLP-1 receptor agonists has recently emerged. In individuals with HFpEF and obesity, semaglutide reduced heart failure symptoms and improved exercise capacity in parallel with substantial weight loss (STEP-HFpEF trial), supporting a direct role of obesity in the development of HFpEF.²⁴⁵ However, the symptomatic benefits started to appear before maximal weight loss was achieved, suggesting direct effects of GLP-1 on cardiometabolic pathways. In a similar population, tirzepatide improved symptoms of heart failure and the composite of death or heart failure hospitalization (SUMMIT trial).²⁴⁶

Given that loss of visceral adipose tissue is accompanied by loss of liver fat, the logical next step was to evaluate GLP-1 receptor agonists as a treatment for MASLD/MASH. A Phase 2 trial showed that semaglutide promotes the resolution of MASH but not regression of fibrosis.²⁴⁷ A Phase 3 trial is currently ongoing.²⁴⁸ In Phase 2 trials, tirzepatide²⁴⁹ and survodutide,²⁵⁰ a dual GLP-1 and glucagon receptor agonist, were shown to be superior to placebo in terms of resolution of MASH without worsening fibrosis. Promising clinical safety and proof-of-concept data have also been reported for HEC88473, a dual agonist for GLP-1 and fibroblast growth factor 21 (FGF21) receptors, in a Phase 1b/2a trial in individuals with MASLD and Type 2 diabetes.²⁵¹ Taken together, these data are in keeping with our clinical staging whereby early intervention with residual healing capacity may be augmented or enhanced by GLP-1/GIP receptor agonists. At the more advanced end of the spectrum with fibrosis, reversal is unlikely at present with current approaches.

Semaglutide has also been shown to reduce the risk of major kidney and ASCVD events, including cardiovascular death and death from any cause in individuals with Type 2 diabetes and CKD (FLOW trial).²⁵² A recent report showed that oral semaglutide was associated with a lower risk of major adverse cardiovascular events in individuals with Type 2 diabetes and ASCVD, CKD, or both (SOUL trial).²⁵³ Consistent with obesity being a major driver of CKD, the SELECT trial showed that semaglutide prevented CKD onset and progression in people without diabetes but with overweight or obesity and cardiovascular disease.²⁵⁴ In early 2025, semaglutide gained European Medicines Agency (EMA) and FDA approval to prevent kidney function loss, kidney failure, major ASCVD events, and cardiovascular death in adults with Type 2 diabetes and CKD. The EMA label update for semaglutide additionally includes prevention of all-cause mortality.

One consequence of the rapid weight loss induced by GLP-1 receptor agonists is loss of muscle mass, but the extent and implications of this loss are unclear. Reductions in lean mass lost (as a percentage of total weight lost) reported in clinical trials of GLP-1 receptor agonists range from below 15% up to 60%.²⁵⁵ Although the associated improvement in insulin sensitivity and lower infiltration of fat into muscles may compensate partly for the loss in strength and function, older adults with sarcopenia or those with CKD may be at higher risk of adverse effects from muscle loss.²⁵⁵ The loss of muscle mass emphasizes the notion that these drugs should be accompanied by a physical activity/exercise programme. Strength training and increased protein intake can help to reduce the potential detrimental effects of muscle loss in individuals on GLP-1 receptor agonists. Thus, despite the benefits of these therapies they must always be accompanied by lifestyle changes.

Sodium–glucose co-transporter 2 inhibitors

As a class, these drugs are effective agents for glycaemic control. They have also been shown to reduce hospitalization and cardiovascular deaths across a range of left ventricular ejection fractions in individuals with or without diabetes.²⁵⁶ Most heart failure data are available for dapagliflozin, empagliflozin, and sotagliflozin.^{257–261} Earlier initiation of sodium–glucose co-transporter 2 (SGLT2) inhibitors is warranted in individuals with heart failure, including those in hospital who have been stabilized.²⁶⁰

Sodium–glucose co-transporter 2 inhibitors have also been shown to have protective effects on major kidney and cardiovascular events, especially heart failure, in persons with CKD, with or without diabetes.^{260,262,263} Sotagliflozin has also been shown to reduce both myocardial infarction and stroke in individuals with diabetes, CKD, and cardiovascular risk factors.²⁶⁴ Current treatment recommendations consistently advise initiation of SGLT2 inhibitors in persons with CKD and an eGFR as low as 20 mL/min/1.73 m², irrespective of diabetes status.^{4,142,183,184}

Other anti-hyperglycaemic drugs

In addition to GLP-1 receptor agonists and SGLT2 inhibitors, Type 2 diabetes can be treated with metformin, sulfonylureas, meglitinides (repaglinide), acarbose, thiazolidinediones (pioglitazone), and dipeptidylpeptidase-4 inhibitors.^{54,265} Pioglitazone and metformin are insulin sensitizers and may ameliorate the adverse effects of insulin resistance on the vessel wall directly or indirectly.

Except for pioglitazone, all drugs can be combined with subcutaneous insulin treatment. While evidence supports heart and kidney protection only for GLP-1 receptor agonists and SGLT2 inhibitors, safety trials spanning the past decades indicate that other anti-hyperglycaemic drugs appear safe from a cardiovascular perspective.

Lipid-lowering medications

The primary objective of lipid-lowering medications is to lower LDL-cholesterol. However, even if the LDL-cholesterol is at goal, individuals with atherogenic dyslipidaemia will still have residual cardiovascular risk due to elevated TRLs, and the ESC/EAS guidelines recommend that non-HDL-cholesterol and apoB should be secondary targets of treatment.¹⁶⁸

High-intensity statins are the first-line therapy for achieving reductions in LDL-cholesterol, apoB, and non-HDL-cholesterol, as they have demonstrated robust benefits in numerous large-scale trials.¹⁶⁸ Contemporary approaches call for combination therapy with ezetimibe, a selective inhibitor of intestinal cholesterol absorption, followed by bempedoic acid,²⁶⁶ an oral agent that specifically inhibits ATP citrate lyase and thereby reduces cholesterol synthesis in the liver, or therapies targeting PCSK9. Proprotein convertase subtilisin/kexin type 9 inhibitors include monoclonal antibodies, such as alirocumab or evolocumab,^{267,268} and inclisiran,²⁶⁹ which relies on RNA interference mechanisms to silence hepatic PCSK9 expression. Inclisiran has been shown to promote reductions of LDL-cholesterol in the range of 50%–60% and similar reductions in apoB and non-HDL-cholesterol.²⁷⁰ Inevitably, the choice will depend upon drug availability and reimbursement in different parts of the world.

A recent open-label study in people with coronary artery disease but not diabetes showed that metformin in combination with statins reduces both the statin-induced increase in PCSK9 levels and LDL-cholesterol levels.²⁷¹ Although statins have been shown to confer a slightly increased risk of new-onset diabetes, a recent meta-analysis

indicates that the overall benefit of statin therapy in reducing cardiovascular events greatly outweighs the small increase in glycaemia.²⁷²

Fibrates are agonists of peroxisome proliferator-activated receptor- α (PPAR- α) and regulate steps in lipid and lipoprotein metabolism. Although they are effective at lowering plasma levels of triglycerides and TRLs, their benefits in reducing cardiovascular risk have not been proven. The only agent documented to lower cardiovascular risk in statin-treated individuals with elevated triglycerides is high-dose icosapent ethyl (2–4 g/day).^{273–275} Its benefits appear independent of triglyceride-lowering, but the mechanisms involved remain unclear.²⁷⁶ Furthermore, the recent PROMINENT study showed that pemafibrate, a new selective PPAR- α agonist that is effective at reducing TRLs and non-HDL-cholesterol, did not reduce either apoB levels or cardiovascular events.²⁷⁷ Thus, altering the composition of TRLs to lower triglyceride levels without enhancing the clearance of apoB-containing TRLs is unlikely to provide cardiovascular benefits.

Future therapies to treat hypertriglyceridaemia include anti-sense oligonucleotides, siRNA-based therapies, and monoclonal

antibodies targeting apoCIII and ANGPTL3; these proteins inhibit LPL (Figure 1) but likely have additional actions. Whilst these approaches reduce triglycerides dramatically in individuals with severe hypertriglyceridaemia (Table 2), further studies are needed to establish whether targeting these pathways will result in reducing the residual cardiovascular risk in individuals with SMD-related dyslipidaemia.

In people with severe hypertriglyceridaemia, it is important to lower triglycerides to reduce the risk of pancreatitis. Fenofibrate and omega-3 fatty acids, as monotherapy or in combination, can be prescribed to lower triglycerides in individuals with severe hypertriglyceridaemia [>11.4 mmol/L (1009 mg/dL)].²⁸⁵ Fenofibrate may be considered for its beneficial macro- and microvascular effects in individuals with SMD without ASCVD but elevated triglycerides [2.3–5.6 mmol/L (204–496 mg/dL)] despite LDL-lowering therapy.²⁸⁶

Finally, lipoprotein(a) is an independent risk factor for ASCVD, and it should be taken into account when estimating cardiovascular risk and treatment goals.²⁸⁷

Table 2 Emerging therapies for hypertriglyceridaemia

Drug	Dose	Mechanism of action	Comments
Volanesorsen	Subcutaneous injection of 300 mg once a week	ASO inhibiting apoCIII mRNA production	A randomized, placebo-controlled trial in 15 adults with Type 2 diabetes (HbA1c $>7.5\%$) and hypertriglyceridaemia [2.26–5.65 mmol/L (200–500 mg/dL)]; volanesorsen reduced triglyceride levels by 69% after 91 days. ²⁷⁸ Volanesorsen has been approved in EU and UK to treat familial chylomicronaemia syndrome, and it has been shown to reduce the risk of acute pancreatitis. ²⁷⁹
Olezarsen	Subcutaneous injection of 50 or 80 mg every 4 weeks	GalNAc-conjugated ASO inhibiting apoCIII mRNA production	Bridge-TIMI 73a, a randomized, placebo-controlled Phase 2b trial in 154 adults either with moderate hypertriglyceridaemia [1.69–5.63 mmol/L (150–499 mg/dL)] and elevated cardiovascular risk or with severe hypertriglyceridaemia [≥ 5.65 mmol/L (500 mg/dL)]; olezarsen reduced triglyceride levels by 53% at the highest dose and reduced the risk of acute pancreatitis. ²⁸⁰
Plozasiran	Subcutaneous injection of 10, 25, or 50 mg on Day 1 and at Week 12 (follow-up through Week 48)	siRNA inhibiting apoCIII mRNA production	SHASTA-2, a placebo-controlled, double-blind, dose-ranging, Phase 2b randomized trial in 229 adults with severe hypertriglyceridaemia [5.65–45.2 mmol/L (500–4000 mg/dL)]; plozasiran reduced triglyceride levels by 57% at the highest dose. ²⁸¹ A Phase 2b, double-blind, randomized, placebo-controlled trial in 353 adults with mixed hyperlipidaemia [triglycerides 1.69–5.63 mmol/L (150–499 mg/dL) and either LDL-cholesterol ≥ 1.8 mmol/L (70 mg/dL) or non-HDL-cholesterol ≥ 2.6 mmol/L (100 mg/dL)]; plozasiran reduced triglyceride levels by 62% at the highest dose. ²⁸²
Evinacumab	Intravenous injection of 15 mg/kg every 4 weeks	Monoclonal antibody targeting circulating ANGPTL3 protein	A randomized, placebo-controlled Phase 2 trial; evinacumab reduced triglyceride levels by 62% and 82% after 12 weeks in patients with multi-factorial chylomicronaemia syndrome (MCS) with heterozygous loss-of-function LPL pathway mutations [$n = 15$; triglycerides 11.3–26.0 mmol/L (1000–2300 mg/dL)] and MCS without LPL pathway mutations [$n = 19$; triglycerides 13.5–29.3 mmol/L (1200–2600 mg/dL)], respectively. ²⁸³
Zodasiran	Subcutaneous injection of 50, 100, or 200 mg on Day 1 and Week 12 (follow-up through Week 36)	siRNA inhibiting ANGPTL3 mRNA production	ARCHES-2, a placebo-controlled, dose-ranging Phase 2b trial in 204 adults with mixed hyperlipidaemia [triglycerides 1.69–5.63 mmol/L (150–499 mg/dL) and either LDL-cholesterol ≥ 1.8 mmol/L (70 mg/dL) or non-HDL-cholesterol ≥ 2.6 mmol/L (100 mg/dL)]; zodasiran reduced triglyceride levels by 74% after 24 weeks at the highest dose. ²⁸⁴

ASO, anti-sense oligonucleotide.

Anti-hypertensive medications

This Consensus statement recommends anti-hypertensive therapy in line with international guidelines. The 2024 ESC guidelines recommend a target of <130/80 mmHg provided the treatment is well tolerated; these guidelines list some important exceptions and recommend the use of risk stratification.¹⁶⁴ The US guidelines also recommend treating to a target of <130/80 mmHg,¹⁶⁵ but the European Society of Hypertension (ESH) guidelines recommend a target of at least <140/90 mmHg.¹⁶³ First-line therapy for hypertension includes thiazide diuretics, calcium channel blockers, and angiotensin-converting enzyme (ACE) inhibitors or angiotensin-II receptor blockers (ARBs).^{165,288,289} For those with blood pressure >140/90 mmHg or more than 20/10 mmHg above the blood pressure target, two first-line classes of anti-hypertensive agents are recommended. Specific high-risk groups may require a more stringent target. For example, for adults with hypertension and ASCVD or a 10-year ASCVD risk of $\geq 10\%$, a target of <130/80 mmHg is recommended.¹⁶⁵ In persons with CKD, a lower target of <120/70 mmHg is recommended if it can be achieved safely.²⁸⁸ However, this lower target is not recommended by all scientific societies; the ESH guidelines, for example, recommend a less stringent target.¹⁶³

Angiotensin-converting enzyme inhibitors or ARBs (but not combined) are indicated if albuminuria or heart failure is present. Mineralocorticoid receptor antagonists are particularly effective for resistant hypertension, and beta-blockers may be preferentially used in those with HFrEF. Alpha-1 blockers are considered second- or third-line therapies that may be helpful in men with prostatism. The 2024 ESC guidelines also recommend the use of renal denervation to treat resistant hypertension in people with uncontrolled blood pressure, despite the use of three or more blood pressure-lowering drugs.¹⁶⁴

Anti-inflammatory drugs

Statin therapy lowers both atherogenic LDL-cholesterol and hsCRP, the primary biomarker for low-grade systemic inflammation.²⁹⁰ However, residual inflammatory risk after initiation of statin therapy is underappreciated and undertreated. In a recent analysis of 31 245 adults with atherosclerosis receiving guideline-directed medical care, including high-intensity statins, residual inflammatory risk (as detected by on-treatment hsCRP) was strongly associated with recurrent cardiovascular events, cardiovascular death and all-cause mortality.²⁹¹

Until recently, the only recommendations to lower inflammation were to increase exercise and improve diet. However, based on results from the CANTOS,¹²⁴ LoDoCo2,²⁹² and COLCOT²⁹³ trials,²⁹⁴ the US FDA approved low-dose colchicine as an anti-inflammatory therapy to lower cardiovascular risk. The 2021 ESC guidelines on cardiovascular disease prevention, the 2023 ESC guidelines for the management of acute coronary syndromes and the 2024 ESC guidelines for the management of chronic coronary syndromes now recommend low-dose colchicine (0.5 mg orally once daily) for secondary prevention in selected high-risk individuals with suboptimal control of risk factors.^{173,295,296} The benefit of anti-inflammatory therapies in primary prevention remains to be established from outcome trials. Even in secondary prevention, it should be noted that daily treatment with colchicine started soon after myocardial infarction and continued for a median of 3 years did not reduce the incidence of major adverse cardiovascular events in the recent CLEAR SYNERGY trial,²⁹⁷ suggesting that it does not have a role in routine treatment following a myocardial infarction. It could, however, be considered in more stable secondary prevention settings.

Ongoing trials are investigating the effects of IL-6 inhibition in the settings of CKD, dialysis, HFrEF, and acute coronary ischaemia.²⁹⁸ Proprotein convertase subtilisin/kexin type 9 inhibitors do not have substantive effects on hsCRP; however, they may have local anti-inflammatory benefits as they have been shown to reduce lipid content in the arterial wall and macrophage content within atherosclerotic plaques.^{299,300}

In usual outpatient practice, hsCRP values <1 mg/L, 1–3 mg/L, and >3 mg/L reflect lower, moderate, and higher cardiovascular risk in the context of other traditional risk markers. Among statin-treated individuals, residual inflammatory risk (defined as hsCRP >2 mg/mL) could trigger the initiation of long-term low-dose colchicine, and several ongoing trials of novel anti-inflammatory agents are using hsCRP >2 mg/L as a core enrolment criterion.

Pharmacotherapy for metabolic dysfunction-associated steatotic liver disease

Resmetirom, a beta-selective thyroid hormone receptor agonist, recently received a fast-track FDA approval as the first specific treatment for MASLD. In a Phase 3 study, resmetirom 80 mg was shown to reduce liver fibrosis at least one stage, promote resolution of MASH, and reduce levels of LDL-cholesterol levels by 14%, triglycerides by 20% and lipoprotein(a) by 30%.³⁰¹ However, evaluation of clinical event outcomes (e.g. decompensated cirrhosis, liver transplant, cardiovascular disease, and mortality) is still lacking, and resmetirom is not yet approved for MASLD in Europe.

The FGF21 analogue pegozafermin is currently in development for the treatment of severe hypertriglyceridaemia and MASLD.³⁰² In a Phase 2b trial, it has been shown to improve fibrosis in individuals with biopsy-conformed MASH and moderate or severe fibrosis.³⁰³

Convergent recommendations with other position statements

Given the recent dramatic rise in obesity and related health risks together with the recognition of metabolic heterogeneity, improved classification and management strategies for SMD are required. In our EAS consensus statement, we provide a clinically actionable framework, namely a three-stage system, based on the underlying pathophysiology of SMD. We define criteria and management strategies for each of the three stages, centred on the progression of disease across multiple organs and the importance of early treatment and of treating more than one pathology. We used our staging system to calculate the prevalence of SMD Stages 1 and 2 in European participants of the UK Biobank.

As noted earlier, other recent position papers (including those from EASO,² the Lancet Commission,³ and the American Heart Association⁴) have proposed staging systems to describe the progression of risk and to guide clinical management. The EASO presents a new framework for the diagnosis, staging and management of obesity,² and the Lancet Commission has introduced a two-stage system to differentiate between clinical and pre-clinical obesity.³ The American Heart Association has placed emphasis on the kidney by introducing the concept of the cardiovascular–kidney–metabolic syndrome; the authors present a four-stage system that aims to identify individuals at early stages of this syndrome and prevent progression to cardiovascular disease.⁴

Below we indicate how recommendations for diagnosis and management of SMD described in our EAS consensus statement align and converge with those from these recent position statements.

Redefining diagnosis of obesity

Body mass index alone does not provide information about the health status of an individual. Body mass index measurement should be combined with at least one other anthropometric component (e.g. waist circumference), and cut-off points should be appropriate for ethnicity.

Comprehensive and inter-disciplinary evaluation of other metabolic risk factors

Dysfunctional subcutaneous adipose tissue releases FFA, leading to visceral obesity and fat deposition in other ectopic depots. Central to this process is insulin resistance and accompanying atherogenic dyslipidaemia, increased blood pressure, and low-grade chronic inflammation. Collective assessment of inter-related risk factors is essential to enabling a whole-body approach to prevention. Therefore, individuals with excess adiposity should be screened before disease progression for multiple metabolic risk factors.

Recognition and management of systemic metabolic disorder as a progressive pathophysiology

The progressive pathophysiology of obesity-related metabolic complications leads to a stepwise increase in the risk of organ damage associated with later stages. The staging systems help clinicians decide how to manage SMD at the different stages, recognize that other organs might be involved, and indicate when treatment should be intensified. Lifestyle changes, focusing on improvements in the quality of diet and increased physical activity, are recognized as the cornerstone of obesity management at all stages. Multiple risk factors should be assessed at each stage and treated appropriately.

Future perspectives

Estimating the risk of systemic metabolic disorder progression

Clinical risk scores

The development of future risk scores to predict the likelihood of SMD progression may aid clinical decision-making and offer personalized approaches. Several factors should be considered. First, lifestyle variables offer the potential to identify dynamic and personalized modifiable risk factors. Second, consideration of lifetime risk and exposure will move practice towards prevention rather than treating disease. Third, a cost-effective selection of new molecular markers such as metabolites, cytokines, microRNA, or exosomes could refine the risk of sub-clinical disease. In the coming decades, big data and artificial intelligence will generate prediction tools based on pattern recognition, relying on billion-point databases across multiple different ethnicities, offering a better way to include genes, environmental exposures, and time. These are essential if the global challenges from an increase in cardio-metabolic traits are to be addressed.

The framework started by the Multi-Ethnic Study of Atherosclerosis (MESA) 20 years ago established that sub-clinical disease markers of atherosclerosis add prognostic value above traditional risk factors and are actionable.³⁰⁴ Today, in conjunction with risk scores, non-invasive vascular imaging (e.g. plaque burden and CAC) can be used to refine and personalize risk assessment.¹⁷³ While widely validated for sub-clinical coronary artery disease, the same does not yet exist for asymptomatic diastolic dysfunction.³⁰⁵ Assessing sub-clinical

markers in the myocardium (including left ventricular fibrosis) may add a new actionable dimension to the prevention of heart failure.

Polygenic risk scores

The identification of the genetic basis of SMD components through large GWAS led to the development of polygenic risk scores (PRS)—the weighted sums of disease-associated variants that quantify the overall burden of risk due to multiple risk variants across the genome inherited by each individual.¹⁷ Increasingly large GWAS over the past decade have resulted in the development of PRS for SMD components and disease outcomes, including obesity,³⁰⁶ Type 2 diabetes,³⁰⁷ hypercholesterolaemia,¹⁷ coronary artery disease,^{17,307–310} CKD,^{311,312} MASLD, and cirrhosis.^{61,67,313} These PRS have been shown to associate with large increases in the odds of metabolic abnormalities and to identify individuals at an increased risk of disease, comparable to those in carriers of monogenic variants.^{309,310,314–317} Furthermore, PRS have been shown to improve risk stratification independently of other risk factors, both genetic and non-genetic. For example, PRS were shown to identify individuals with increased risk of cardiovascular disease even among carriers of monogenic rare variants causing familial hypercholesterolaemia.³⁰⁹ Similarly, it has been shown that PRS provide independent information and can improve risk prediction compared to the use of clinical and lifestyle risk factors.^{17,23,308} A PRS for MASLD-related fibrosis has been shown to refine risk stratification and prediction calculated by non-invasive tests.³¹³

In addition, studies indicate that PRS can predict the absolute and relative benefits of pharmacological therapies and lifestyle changes.^{23,314,318} For example, in one study individuals with a high PRS for coronary artery disease (above the 90th percentile) experienced a greater risk reduction in major adverse cardiovascular events and mortality when treated with a PCSK9 inhibitor.³¹⁹ Similarly, a PRS for Type 2 diabetes was predictive of treatment responsiveness to sulfonylureas.³²⁰ Finally, since the genotype does not change throughout a lifetime, PRS, unlike clinical risk factors, can be ascertained early in life (even at birth) and can be used to identify individuals at high risk of SMD, even before overt clinical symptoms are present. Thus, PRS can potentially identify at-risk individuals at an early stage of SMD, allowing high-risk individuals to benefit from early lifestyle interventions and preventive treatments.

Although PRS are poised to improve risk prediction and outcomes via personalized treatment strategies, several challenges remain before they can be readily used in the clinic. Early PRS were developed in predominantly European populations and had diminished predictive accuracy in populations of other ancestries.³²¹ More recently, PRS developed in ancestrally diverse populations have been shown to have improved risk prediction accuracy.³⁰⁸ Moreover, PRS are usually generated by pooling together variants based on their effect on a single trait. However, the effect of variants may be discordant on outcomes, therefore nullifying the predictive value of the PRS. Partitioned PRS constructed by combining genetic variants based on physiological pathways will strengthen the predictive value.

Microbiome-based treatments

There is increasing evidence of a link between the human microbiome (particularly the gut microbiome) and host metabolism, partly mediated by diet.^{322–324} Of relevance to SMD, biomarkers of obesity, dyslipidaemia, insulin resistance, and diabetes have been shown to be associated with specific taxonomic and functional characteristics of the gut microbiome.^{325–327} Disentangling the extent to which these links are due to

nutritional differences rather than metabolism and the precise causal mechanisms remain open research areas.³²² However, increasingly large sample sizes and longitudinal intervention studies will help to answer some of the many questions in this field.

The microbiome offers potential as a therapeutic target for the prevention and treatment of SMD. Next-generation therapeutics, as well as pre-biotics, post-biotics, and a combination of these (syn-biotics), are all currently being explored in pre-clinical and clinical settings.^{328,329} Specific dietary regimes—ideally personalized to an individual's genetics and microbiome characteristics—may be able to modulate the gut microbiome to favour metabolically healthy microbial configurations.³³⁰ Microbiome re-programming can be maximized by more direct medical devices such as faecal microbiota transfer, which is under active scrutiny for metabolic disorders.³³¹ Altogether, while there are multiple promising microbiome-based potential therapeutics for metabolic diseases, all these approaches need to be further developed, standardized and validated before they are deemed clinically relevant.

Consensus key points

- Systemic metabolic disorder is complex and multi-factorial, resulting from metabolic abnormalities that affect multiple organs. It often arises due to dysfunctional excess adiposity, particularly visceral obesity, driven by an imbalance between caloric intake and energy expenditure. Systemic metabolic disorder progresses through various stages, with the initial phase driven by genetic predispositions and lifestyle factors, eventually leading to multi-organ dysfunction and increased morbidity and mortality.
- Visceral obesity is a central driver of SMD, contributing to insulin resistance, MASLD, atherogenic dyslipidaemia, hypertension, and inflammation. The accumulation of lipids in ectopic tissues such as the liver, muscles, and pancreas triggers organ-specific fibro-inflammatory responses, leading to diverse metabolic dysfunctions that increase the risk of cardiovascular and non-cardiovascular diseases.
- Genetic factors contribute to the susceptibility to SMD, with heritability estimates ranging between 40% and 70% for different components. Genetic predispositions, such as those favouring visceral fat accumulation, are associated with higher risks of conditions such as hypertension, Type 2 diabetes, and dyslipidaemia, particularly among certain ethnic groups. However, lifestyle factors can exacerbate the genetic risk of developing SMD.
- Lifestyle changes are the cornerstone of treatment for all stages and should be combined with pharmacological treatment and, in extreme cases, metabolic surgery.

Conclusions

In this Consensus article, we describe the manifestations of SMD, focusing on metabolic abnormalities affecting the liver, heart, and kidney. To combine the individual components and facilitate a holistic approach to clinical management, we propose a staging system for SMD that is based on pathophysiology and emphasizes the progression from metabolic abnormalities before organ damage (Stage 1) to early organ damage (Stage 2) and further to moderately advanced organ damage (Stage 3). We report that 58% of the European participants of the UK Biobank have Stage 1 SMD, which confers a 6% increase in all-cause mortality. In addition, a further 19% of this cohort have Stage 2 SMD, which confers a 49% increase in all-cause mortality.

We also summarize the management strategy for each stage. Lifestyle changes are effective at reducing metabolic risk factors at all stages and should be encouraged in addition to pharmacological treatment and metabolic surgery in those with severe obesity. Many of these approaches target more than one of the systemic manifestations. Due to the complex interplay of factors contributing to the development and progression of SMD, an individually tailored and multi-faceted strategy is required for effective intervention.

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Supplementary data

Supplementary data are available at *European Heart Journal* online.

Declarations

Disclosure of Interest

A.L.C. received honoraria as a consultant and speaker and/or research grants or support from: Amgen, Amgen, AstraZeneca, Daiichi Sankyo, Eli Lilly, Esperion, Ionis Pharmaceuticals, Medscape, Menarini, MSD, New Amsterdam Pharma, Novartis, Novo Nordisk, Regeneron, Sanofi, Ultragenyx, and Viatriis. A.M.D. received consultancy fees and/or research grants from Boehringer Ingelheim, HeptaBio, and Tune Therapeutics and participated in clinical trials (as a professional) for Madrigal, Hanmi, Intercept, Inventiva, and Novo Nordisk. A.M.D. has a leadership role in AASLD and the International Society for Cells of the Hepatic Sinusoid and is an Associate Editor for *Journal of Hepatology*. She has published articles with non-academic co-authors (Boehringer Ingelheim). A.V.-P. declares consultancy with Altimmune. C.J.B. declares equity interests from Novartis and Novo Nordisk, is a board member of Technoclon GmbH, and has received honoraria as a consultant or speaker and/or grants for travel and research from Amgen, Biotest AG, Daiichi Sankyo, Boehringer Ingelheim, Novartis, Oxitope, and SOBI. D.L.B. is on the advisory board for Angiowave, Bayer, Boehringer Ingelheim, CellProthera, Cereno Scientific, Elsevier Practice Update Cardiology, E-Star Biotech, High Enroll, Janssen, Level Ex, McKinsey, Medscape Cardiology, Merck, MyoKardia, NirvaMed, Novo Nordisk, PhaseBio, PLx Pharma, Stasys, and Tourmaline Bio; is on the Board of Directors for American Heart Association New York City, Angiowave (stock options), Bristol Myers Squibb (stock), DRS.LINQ (stock options), High Enroll (stock); is a consultant for Broadview Ventures, Concept Therapeutics, GlaxoSmithKline, Hims, SFJ, Summa Therapeutics, and Youngene; is on the Data Monitoring Committees for Acesion Pharma, Assistance Publique-Hôpitaux de Paris, Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO trial, funded by St. Jude Medical, now Abbott), Boston Scientific (Chair, PEITHO trial), Cleveland Clinic, Contego Medical (Chair, PERFORMANCE 2), Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine (for the ENVISAGE trial, funded by Daiichi Sankyo; for the ABILITY-DM trial, funded by Concept Medical; and for ALLAY-HF, funded by Alleviant Medical), Novartis, Population Health Research Institute, and Rutgers University (for the NIH-funded MINT Trial); has received honoraria from the American College of Cardiology (Senior Associate Editor, Clinical Trials and

News, ACC.org; Chair, ACC Accreditation Oversight Committee), Arnold and Porter law firm (work related to Sanofi/Bristol Myers Squibb clopidogrel litigation), Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute; RE-DUAL PCI clinical trial steering committee funded by Boehringer Ingelheim; AEGIS-II executive committee funded by CSL Behring), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Canadian Medical and Surgical Knowledge Translation Research Group (clinical trial steering committees), CSL Behring (AHA lecture), Cowen and Company, Duke Clinical Research Institute (clinical trial steering committees, including for the PRONOUNCE trial, funded by Ferring Pharmaceuticals), HMP Global (Editor in Chief, *Journal of Invasive Cardiology*), *Journal of the American College of Cardiology* (Guest Editor; Associate Editor), K2P (Co-Chair, inter-disciplinary curriculum), Level Ex, Medtelligence/ReachMD (CME steering committees), MJH Life Sciences, Oakstone CME (Course Director, Comprehensive Review of Interventional Cardiology), Piper Sandler, Population Health Research Institute (for the COMPASS operations committee, publications committee, steering committee, and US national co-leader, funded by Bayer), WebMD (CME steering committees), Wiley (steering committee), and other: Clinical Cardiology (Deputy Editor); named on a patent for sotagliflozin assigned to Brigham and Women's Hospital who assigned to Lexicon (neither he nor Brigham and Women's Hospital receive any income from this patent); has received research funding from Abbott, Acesion Pharma, Afimmune, Aker Biomarine, Alnylam, Amarin, Amgen, AstraZeneca, Bayer, Beren, Boehringer Ingelheim, Boston Scientific, Bristol-Myers Squibb, Cardax, CellProthera, Cereno Scientific, Chiesi, CinCor, Cleerly, CSL Behring, Faraday Pharmaceuticals, Ferring Pharmaceuticals, Fractyl, Garmin, HLS Therapeutics, Idorsia, Ironwood, Ischemix, Janssen, Javelin, Lexicon, Lilly, Medtronic, Merck, Moderna, MyoKardia, NirvaMed, Novartis, Novo Nordisk, Otsuka, Owkin, Pfizer, PhaseBio, PLx Pharma, Recardio, Regeneron, Reid Hoffman Foundation, Roche, Sanofi, Stasys, Synaptic, The Medicines Company, Youngene, and 89Bio; Royalties: Elsevier (Editor, Braunwald's Heart Disease); an is a site co-investigator for Cleerly. E.L. received honoraria as a consultant and speaker and/or received research grants from Amgen, Canadian Institutes of Health Research, HLS Therapeutics, Lib Therapeutics, Novartis, and Novo Nordisk and participated in clinical trials (as a professional) for Amgen and Boehringer Ingelheim. F.P. received consultancy fees from Eli Lilly, Ethicon, Medtronic, and Novo Nordisk.

G.F. received honoraria as a consultant and/or speaker from Lilly, Novo Nordisk, and Regeneron and is a co-chair (unpaid) of the Scientific Advisory Board of the European Association for the Study of Obesity (EASO). J.P. received research funding from the Dutch Research Council (NWO), The Netherlands Organization for Health Research and Development (ZonMW), Applied and Engineering Sciences (STW), The Dutch Topsector for Life Sciences and Health (TKI-LSH), The Californian Almond Foundation, EzCol, Newtricious, BASF, RAISIO, Upfield, and Unilever; has received reimbursement for travel and/or speaking from Unilever, Raisio, BASF, and Upfield; and is secretary of the Board from the foundation Nutrition in Transition (NIT) and is chair of the Department Nutrition and Movement Sciences of the Maastricht University. J.R.v.L. received a research grant from Novartis and is a member of the scientific advisory board of the Dutch Heart Foundation, a board member of Dutch Society Gender & Health and chair of the Dyslipidemia Working Group of the Dutch Society of Internists Vascular Medicine. K.K.R. declares stock options as part of consultancy agreement from New Amsterdam Pharma,

Scribe Therapeutics, and Pemi31. He served as a consultant and/or participated in clinical trials for Abbott Laboratories, Amarin, AstraZeneca, Bayer, Beren Therapeutics, Cleerly, Crispr, Daiichi Sankyo, Eli Lilly, Emendobio, Esperion, GSK, Kowa, MSD, New Amsterdam Pharma, Novartis, Nodthera, Novo Nordisk, Sanofi, SCRIBE, Silence Therapeutics, Ultragenyx, and Vaxxinity. He received honoraria as a speaker from Amarin, Amgen, Algorithm, Astra Zeneca, Boehringer Ingelheim, Daiichi Sankyo, Esperion, Dr Reddys, Mankind, Novartis, Novo Nordisk, Sanofi, Tecnofarma, Viatrix, and Macleod Pharma for symposia at international meetings and received research grants from Amgen, Daiichi Sankyo, Regeneron, Sanofi, and Ultragenix to Imperial College London. K.R.T. received honoraria as a consultant and/or speaker, participated in clinical trials and/or received research grants from Lilly, Boehringer Ingelheim, AstraZeneca, Bayer, Novo Nordisk, ProKidney, and Travers. She is a chair of the Diabetic Kidney Disease Collaborative, American Society of Nephrology Council on the Kidney, and American Heart Association. L.T. received honoraria as a consultant and/or speaker from Abbott, Amgen, AstraZeneca, Bayer, Daiichi Sankyo, Lilly, MSD, Pfizer, Novartis, Novo Nordisk, Sanofi, Ultragenyx, and Zentiva and participated in clinical trials for Amgen, Novo Nordisk, Novartis, MSD, and Ionis. She is the past president of the EAS and past president of the Turkish Society of Cardiology. M.A. received honoraria as a consultant and/or speaker, participated in clinical trials, and/or received travel or research grants from Alfasigma, Amarin, Amgen, Amryt, Daiichi Sankyo, Ionis/Akcea, Lilly, Novartis, Pfizer, Regeneron, Sanofi, Soby, Viatrix, and Ultragenyx. M.H. received research grants from AstraZeneca, Merck, and Novo Nordisk; consultancy fees for participation in advisory board meetings from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, Novo Nordisk, and Roche; speaker fees from AstraZeneca, Boehringer Ingelheim, Janssen, Merck, and Novo Nordisk; and holds two patents relating to glucagon-like peptides. M.R. received honoraria as a consultant and/or speaker from Novo Nordisk, Lilly, AstraZeneca, Boehringer Ingelheim, Sanofi, Sigrid Therapeutics, and Atrogi. He has also received research funding from Novo Nordisk for a project revolving around novel targets in adipocytes without any links to the present EAS consensus statement and is a member of the EASD Committee on Clinical Affairs. N.S. declares equity interests in PreBiomics (cofounder, shareholder, and consultant) and ZOE Ltd (consultant and stock option grantee) and received honoraria as a consultant for ZOE Ltd, PreBiomics, Roche, Ysopia, Alia Therapeutics, INRAE Transfert, and Freya Biosciences and as a speaker for Illumina and Tillotts Pharma. O.J. received honoraria as a consultant from Ribocure. P.M.R. has received institutional research grant support from Kowa, Novartis, Amarin, Pfizer, Esperion, Novo Nordisk, and the NHLBI; during the past 3 years has served as a consultant to Novartis, Agepha, Ardelyx, Arrowhead, AstraZeneca, CSL Behring, Janssen, Civi Biopharm, Glaxo Smith Kline, SOCAR, Novo Nordisk, Eli Lilly, New Amsterdam, Boehringer Ingelheim, Cytokinetics, Nodthera, Tourmaline Bio, and Cardio Therapeutics; has minority shareholder equity positions in Uppton, Bitterroot Bio, and Angiowave; and has received compensation for service on the Peter Munk Advisory Board (University of Toronto), the Leducq Foundation, Paris, France, and the Baim Institute (Boston, MA, USA). R.A. is a member of the board of directors for the Endocrine Society. R.F. receives research grants from the National Medical Research Council (NMRC) Singapore and the Biomedical Research Council (BMRC) Singapore and is President of the International Society of Heart Research, South East Asia Section (currently being incorporated). S.E.Q. is on the board of directors for

Abbvie; received consultancy fees from Roche, Genentech, AstraZeneca, Pfizer, Janssen and Novartis; and is a councillor of AAP. S.R. declares equity from Heptabio and a patent with US Provisional Application No. 62/908 041; received honoraria as a consultant and/or speaker from Ultragenyx, Amgen, Sanofi, Ribocure, Wave Life Sciences, AstraZeneca, Chiesi, and Novartis; received research grants from AstraZeneca; and has published articles with non-academic co-authors (AstraZeneca, related to treatments for liver disease). S.V. holds a Tier 1 Canada Research Chair in Cardiovascular Surgery and reports receiving grants and/or research support and/or speaking honoraria from Amarin, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Canadian Medical and Surgical Knowledge Translation Research Group, Eli Lilly, HLS Therapeutics, Humber River Health, Janssen, Merck, Novartis, Novo Nordisk, Pfizer, PhaseBio, S & L Solutions Event Management Inc, Sanofi, and Sun Pharmaceuticals. He is the President of the Canadian Medical and Surgical Knowledge Translation Research Group, a federally incorporated not-for-profit physician organization. The remaining authors do not have any existing or known future financial relationships or commercial affiliations to the health industry to disclose.

Data Availability

The analysis in this article was conducted under UK Biobank application number 37142. The UK Biobank data are available on application to the UK Biobank (www.ukbiobank.ac.uk/).

Appendix 1

Young EAS Fellows actively involved in the review process are as follows: Ralph K. Akyea, Centre for Academic Primary Care, Lifespan and Population Health Unit, School of Medicine, University of Nottingham, Nottingham, UK and Pelin Gölforoush, The Hatter Cardiovascular Institute, Institute of Cardiovascular Science, University College London, London, UK. Presidents of National Societies actively involved in the review process are as follows: Argentina: Argentina Lipid Society, Pablo Corral; Australia: Australian Atherosclerosis Society, Judy de Haan; Austria: Austrian Atherosclerosis Society, Dagmar Kratky; Baltic Countries: Baltic Atherosclerosis Society, Margus Viigimaa; Bosnia and Herzegovina: Association of Cardiologists in Bosnia and Herzegovina, Belma Pojskic; Cyprus: Cyprus Atherosclerosis Society, Phivos Symeonides; Czech Rep: Czech Society for Atherosclerosis, Michal Vrablik; Egypt: Egyptian Association of Vascular biology and Atherosclerosis (EAVA), Ashraf Reda; Estonia: Estonian Society of Cardiology, Märt Elmet; Finland: Finnish Atherosclerosis Society, Minna Kaikkonen-Määttä; France: New French Society of Atherosclerosis (NSFA), René Valero; Georgian: Georgian Atherosclerosis Association, Tea Gamezardashvili; Germany: DACH Society for the Prevention of Heart and Circulatory Diseases, Ulrike Schatz; Germany: Deutsche Gesellschaft zur Bekämpfung von Fettstoffwechselstörungen und ihren Folgeerkrankungen DGFF (Lipid-Liga) e.V., Oliver Weingartner; Germany: German Atherosclerosis Society, Daniel Sedding; Greece: Hellenic Atherosclerosis Society, Haralampos Milionis; Greece: Atherosclerosis Society of Northern Greece, Christodoulos Papadopoulos; Hungary: Hungarian Atherosclerosis Society, György Paragh; Iraq: The Iraqi Lipid Clinics Network, Mutaz Al-Khnifawi; Ireland: Irish Lipid Network, Vincent Maher; Italy: Italian Society for the Study of Atherosclerosis, Alberico Catapano; Korea: Korean

Society of Lipid and Atherosclerosis, Jaetaek Kim; Kyrgyzstan: Kyrgyz Atherosclerosis Society, Erkin Mirrakhimov; Mexico: Sociedad Mexicana de Nutrición y Endocrinología (SMNE), Juan Eduardo García García; Mexico: Mexican Society of Atherosclerosis—AMPAC, Juan José Parcero Valdés; Romania: Atherosclerosis Working Group of the Romanian Society of Cardiology, Dan Gaita; Romania: Atherosclerosis & Atherothrombosis Working Group within Romanian Society of Cardiology, Roxana Rimbas; Russia: Russian National Atherosclerosis Society, Marat Ezhov; Spain: Spanish Society of Arteriosclerosis, Carlos Guijarro Herráiz; Tunisia: Tunisian Heart Foundation, Habib Gamra; UK: British Atherosclerosis Society, Tomasz Guzik; and Ukraine: Ukrainian Atherosclerosis Society, Olena Mitchenko.

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