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Review article

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The global cardiovascular–liver–metabolic syndemic: epidemiology, trends and challenges

Nicholas W. S. Chew[1,2,15] ✉, Anurag Mehta[3,15], Rachel Goh[2,15], Jaycie Koh[4], Yiming Chen[2], Bryan Chong[2,5], Mark Y. Chan[1,2], Muhammad Shahzeb Khan[6,7,8], Mark D. Muthiah[2,9,10], Javed Butler[6,11,16], Arun J. Sanyal[12,16] & Laurence S. Sperling[13,14,16] ✉

Abstract

The growing epidemics of metabolic-dysfunction-associated steatotic liver disease, type 2 diabetes mellitus, obesity and cardiovascular disease are inextricably linked. Cardiovascular–liver–metabolic (CLM) diseases coexist and interact to constitute a synergy of epidemics (a syndemic), with shared mechanisms and socioeconomic influences. The goal of this Review is to construct this complex public-health issue into a unified framework, using epidemiological data to illustrate the current burden of disease and the trends in the CLM syndemic and to make projections for the future. We also discuss the challenges of promoting CLM health and the need for shared solutions. The proposed micro–meso–macro framework integrates strategies to improve risk prediction and precision prevention and to disentangle the competing risks within the CLM construct (micro), while keeping communities at the heart of CLM health promotion by ensuring access to healthy foods, healthy environments and metabolic interventions (meso). In addition, we propose interventions to eliminate inequities in the social and commercial determinants of health, from communities to healthcare systems (macro). Thus, multisystem interventions could address the trajectories of the CLM disease epidemics simultaneously.

Sections

A full list of affiliations appears at the end of the paper. ✉e-mail: nicholas_ws_chew@nuhs.edu.sg; lsperli@emory.edu

Key points

- Cardiovascular–liver–metabolic (CLM) diseases represent a synergy of epidemics, or 'syndemic', underscored by cardiovascular disease, metabolic-dysfunction-associated steatotic liver disease, obesity and type 2 diabetes mellitus.
- The CLM syndemic is associated with the development of multiorgan dysfunction, underpinned by shared mechanisms and socioeconomic influences, warranting an integrated multidisciplinary approach for effective prevention and management.
- Multisystem interventions, modelled under a proposed micro–meso–macro framework, should be designed to address the trajectories of the three epidemics simultaneously.
- Our proposed framework focuses on improving risk prediction and precision prevention (micro level), ensuring accessible metabolic interventions (meso level) and targeting social and commercial determinants of health (macro level).

Introduction

Cardiovascular diseases (CVDs) are the leading cause of death globally, with an estimated 19.2 million deaths related to CVD in 2022, representing 32% of global mortality[1,2]. CVDs are primarily driven by cardiometabolic conditions, with the increasing recognition of metabolic-dysfunction-associated steatotic liver disease (MASLD) (previously termed non-alcoholic fatty liver disease (NAFLD)) as an emerging cardiovascular risk factor[3,4]. The 2023 nomenclature change from NAFLD to MASLD[5] and the recognition of the cardiovascular–liver–metabolic (CLM) axis[6,7] encapsulate the complex relationship between liver pathology and cardiometabolic diseases[5]. Approximately one in three adults worldwide have MASLD[8], with nearly two-thirds of them at an elevated risk of CVD[9,10]. In the population with MASLD, CVDs are the leading cause of death[11,12], with higher cardiac-specific mortality (4.20 deaths per 1,000 person-years) than liver-specific mortality (0.92 deaths per 1,000 person-years) or extrahepatic cancer-specific mortality (2.83 deaths per 1,000 person-years)[13].

MASLD, type 2 diabetes mellitus (T2DM), obesity and CVD often manifest sequentially or concomitantly, underpinned by shared mechanistic pathways[9,14–16]. CLM diseases constitute a 'syndemic' (a synergy of epidemics), given that they tend to coexist and interact with one another, leading to complex multiorgan dysfunction underpinned by shared societal influences[7,17]. Because CVD, MASLD and metabolic diseases are often considered in silos, we have constructed this complex public-health issue into a single syndemic framework that focuses attention on addressing these combined challenges and syndemic drivers of disease, as well as encouraging shared solutions[17].

In this Review, we use epidemiological data (Supplementary Methods) to illustrate the burden of disease and trends in the CLM syndemic and to make projections for the future. We present effective multisystem interventions across the micro, meso and macro levels of health determinants (Box 1), designed to tackle key components of this syndemic. We integrate risk-prediction and disease-prevention strategies within the CLM construct (micro), while keeping communities at the heart of CLM health by ensuring access to healthy foods, safe environments and metabolic interventions (meso) and designing interventions to eliminate inequities in access to healthcare systems (macro). With the overarching goal of promoting CLM health, strategic interventions can serve as triple-duty actions to slow the trajectories of the three epidemics simultaneously[17]. We also highlight major challenges to the improvement of CLM health (Box 2), and propose measures to chart a path forwards to confront this growing global health crisis.

Defining the CLM syndrome

Broad definition

Greater clarity on the definition of the CLM syndrome is needed to systematically identify individuals with or at risk of this disease cluster, and to establish evidence-based strategies for prevention and treatment[18]. The CLM syndrome often represents a continuum of disease and so our current understanding of its effects are heterogeneous. In its simplified form, the CLM syndrome is a constellation of interconnected conditions, including CVD, MASLD, T2DM and obesity, collectively contributing to excess morbidity, premature mortality, multiorgan disease, cardiovascular events and growing healthcare expenditure[18–23]. The definition of the CLM syndrome includes individuals at risk of, or living with, CVD potentially attributable to or complicated by MASLD or metabolic disease. This proposed definition serves as a starting point to align several concepts:

- The CLM syndemic, characterized by MASLD, obesity, T2DM and CVD
- The importance of social determinants of health in influencing the prevalence and management of the CLM syndrome
- The need for effective, multifaceted primordial and primary prevention, coupled with precision prevention, in addressing coexistent CVD and MASLD
- The call for research on the confluence and interaction of shared pathophysiological mechanisms, to facilitate novel risk stratification and interventional targets that address the CLM syndemic simultaneously[19]

Mechanisms and causality

MASLD is dominated by the multisystemic, deleterious effects of excess or dysfunctional visceral adiposity that lead to increased inflammation, oxidative stress, insulin resistance, vascular dysfunction, prothrombotic factors and atherogenic dyslipidaemia[14]. A dose–response relationship exists between MASLD and CVD, with increasing MASLD severity associated with higher incidence of cardiovascular risk factors and worsening CVD severity[20–24]. Metabolic dysfunction is the central pathomechanistic pathway in the bidirectional CLM axis[25,26]. However, MASLD pathogenesis and outcomes show considerable variation[18], underpinned by a complex interplay of factors, such as biological sex, genetic variants, multimorbidity and diverse gut microbiota composition[27–29]. The resulting subphenotypes of disease can lead to different rates of MASLD progression and responses to metabolism-based treatment[30,31]. Therefore, the heterogeneity of MASLD and metabolic disorders and their varying associations with CVD, chronic kidney disease[5,32,33], premature cognitive impairment[34,35] and cancer[36,37] should be considered.

For a nuanced understanding of the CLM syndemic, the conflicting evidence on the causal relationship between CVD and MASLD must be examined. Several studies have shown that associations between the two disease entities can be influenced by confounding or reverse causation[38]. A Mendelian randomization study demonstrated a stepwise incremental risk of ischaemic heart disease (IHD) with

increasing liver fat content and MASLD, but did not suggest causality[6]. A genome-wide association study showed that, among genetic variants associated with impaired liver triglyceride export, the alleles linked to increased hepatic fat levels were correlated with a reduced risk of IHD but an elevated risk of T2DM[39]. However, for variants associated with increased de novo lipogenesis, the alleles linked to increased hepatic fat were associated with an increased risk of IHD[39]. Other studies have shown that visceral adiposity and hepatic adipose tissue content have differential associations with CVD and T2DM outcomes[40]. Increased visceral adiposity was closely linked with the risk of CVD and T2DM, irrespective of hepatic adipose tissue content, whereas increased hepatic adipose tissue content alone was associated with an increased risk of T2DM but not CVD[41]. Therefore, more mechanistic evidence on the causative link between MASLD and CVD is needed to strengthen the proposed CLM syndemic approach[39].

The CLM syndemic

The epidemics of obesity, T2DM and MASLD in adolescents and young adults have exacerbated the growing public health concern about a CLM syndemic[42,43]. In the USA, the related surge in healthcare costs amounts to almost US $500 billion in annual direct expenditure, as well as US $1.2 trillion in annual indirect costs attributed to loss of economic productivity[44]. Years of life lost is the greatest consequence of the unfavourable cardiovascular prognosis in individuals with CLM diseases. Increased severity of obesity leads to progressively premature death, with grade III obesity associated with a median reduction in life expectancy of 8–10 years[45]. Similarly, T2DM is associated with a reduction in survival of 13–14 years, and the earlier the onset of T2DM, the greater the reduction in life expectancy[46]. Individuals with MASLD have a lifespan 4 years shorter than that of those without MASLD[47]. In 2021 alone, the CLM syndemic contributed to 21.2 million deaths and 435 million years of life lost worldwide, and has plateaued the decades-long decline in CVD mortality[48].

Importantly, social determinants of health, including unemployment, a low poverty-to-income ratio, low educational attainment levels and reduced food security, have been linked with worsening of cardiometabolic diseases[48], driving disparities in CVD and multimorbid conditions in communities with cumulative social disadvantage. Therefore, the effect of the CLM syndemic is likely to be exacerbated in low-income populations (Supplementary Table 1).

Epidemiology of CLM diseases

MASLD

In 2021, approximately one in three adults worldwide (32%) were living with MASLD[8,21], amounting to 1.27 (95% uncertainty interval (UI) 1.16–1.38) billion cases worldwide (Supplementary Table 2). The prevalence of MASLD is projected to increase by 43% by 2030, to affect 47.3% of the global population[49]. The age-standardized mortality associated with MASLD increased by 5.5% between 1990 and 2021 and, by 2030, MASLD will contribute to 1.62 deaths per 100,000 of the population[49]. Similarly, the age-standardized disability-adjusted life-years (DALYs) for MASLD increased by 5.48% between 1990 and 2021, with projections for MASLD-related morbidity amounting to 41.7 DALYs per 100,000 of the population by 2030. The surge in MASLD prevalence has largely been driven by the growing global epidemics of obesity and T2DM[50], with MASLD prevalence estimated to be higher in individuals with T2DM (68.8%)[51], overweight (70.0%) and obesity (75.3%)[52] than in the general population. Although MASLD is particularly prevalent in older adults aged ≥70 years[53], this condition also poses a substantial burden (prevalence 13–30%) on adolescents and young adults (aged 15–30 years)[54,55]. MASLD-related (51.1%) and CVD-related (56.9%) morbidity is greater worldwide in men than in women[56] (Supplementary Fig. 1). Most people with MASLD have mild steatosis (accumulation of fat in liver cells), but 20–30% of those will develop fibrosis and 20–50% will progress to cirrhosis, which is a risk factor for hepatocellular carcinoma[57–59].

The burden of MASLD shows substantial inter-regional and intra-regional heterogeneity, largely attributable to socioeconomic and genetic factors as well as medical resource availability[60,61]. The burden of MASLD-related age-standardized mortality is disproportionately larger in Latin America and the Caribbean, and in North Africa and the Middle East, compared with other regions[62] (Fig. 1). Although the prevalence of MASLD is higher in regions with high sociodemographic index (SDI), which is related to a higher consumption of low-quality and ultraprocessed foods in these regions, the observed lower prevalence of MASLD in low-SDI countries might be underestimated owing to underdiagnosis and limited access to healthcare[63]. The socioeconomic realities of each region must be considered when designing targeted public-health interventions to address poverty and food insecurity and improve access to diagnostic modalities and healthcare, especially in low-to-middle-income countries[63,64].

Obesity

In 2021, obesity affected approximately one quarter of the global population[65], contributing to 3.71 million (95% UI 1.85–5.66) deaths and 128.52 million (95% UI 55.99–202.39) DALYs worldwide (Supplementary Table 2). Obesity was the greatest contributor to risk-factor-related morbidity and mortality across the CLM spectrum (Fig. 2). Between 1990 and 2021, the global burden of deaths and DALYs related to obesity increased by ≥2.5-fold[66,67]. This increase

Box 1 | A micro–meso–macro framework for the cardiovascular–liver–metabolic syndemic

Micro

- Recognizing metabolic-dysfunction-associated steatotic liver disease (MASLD) as a cardiovascular risk factor
- Disentangling competing risks
- Integrating MASLD into cardiovascular risk prediction
- Precision prevention

Meso

- Focus on obesity management and healthy lifestyle in communities
- Equitable access to metabolic pharmacotherapies

Macro

- Social determinants of health (Box 4)
- Multidisciplinary care and streamlined patient-referral algorithms
- Integrating MASLD into clinical trials of cardiovascular disease
- Addressing MASLD in global policy documents

Box 2 | Current challenges in cardiovascular–liver–metabolic health

Under-recognition
- Metabolic-dysfunction-associated steatotic liver disease (MASLD), type 2 diabetes mellitus, obesity and cardiovascular disease (CVD) constitute a synergy of epidemics
- These conditions tend to coexist and lead to complex, multiorgan dysfunction
- Cardiovascular–liver–metabolic (CLM) dysfunction is characterized by marked heterogeneity
- CLM diseases increase the risk of cardiovascular events
- The CLM syndemic has caused a plateau in the decades-long decline in CVD mortality
- Awareness of MASLD among clinicians and patients is low, and screening for this condition is uncommon

Lack of risk prediction and precision prevention
- Existing risk-stratification systems do not accurately estimate cardiovascular risk in people with MASLD
- MASLD has not been prioritized in contemporary risk-prediction models
- Challenges associated with the integration of MASLD into risk-prediction models include the lack of available and affordable biomarkers, physiological variability and the inability to distinguish stages of fibrosis or liver disease

The obesity epidemic
- Obesity affects a quarter of the global population, owing to rapid industrialization, urbanization and the epidemiological transition in lifestyle and nutrition patterns
- Implementation of effective interventions to prevent obesity remain suboptimal and inconsistent
- No region has succeeded in reversing the obesity epidemic across its population
- Barriers to effective strategies include policy inertia, ineffective political leadership, opposition from strong commercial interests and lack of enforcement for policy action

Inequitable access to metabolic pharmacotherapies
- Metabolic pharmacotherapies are under-prescribed and underutilized
- Dual treatments that target MASLD and cardiometabolic diseases, such as glucagon-like peptide 1 receptor agonists, sodium–glucose cotransporter 2 inhibitors and peroxisome proliferator-activated receptor agonists, should be considered
- Barriers to access include clinical inertia, prescribing patterns and lack of affordability

Barriers to multidisciplinary care
- Primary-care providers lack confidence in diagnosing and managing MASLD
- Non-invasive tests that can aid in risk stratification in people with CLM syndrome in the primary-care setting are scarce in low-to-middle-income regions
- A fragmented specialist framework deters the consolidation of holistic, integrated care

MASLD outcomes are not included in clinical trials of CVD
- Our knowledge of the natural history of MASLD is derived from registries of liver-biopsy data
- Evidence from prospective cohorts of patients with MASLD remains limited, which can lead to disease-spectrum bias
- MASLD is under-represented and under-reported in contemporary CVD clinical trials; these patients are usually excluded because of safety concerns

Social determinants of CLM health
- Social determinants of health (Box 4) have a strong influence on the CLM syndrome
- Social determinants of CLM health are often socioeconomically patterned
- The influence of social determinants of health begins in infancy
- Racial and ethnic disparities in CLM prevalence exist

was most pronounced in North Africa and the Middle East[68], mirroring the upwards trend in metabolic comorbidities, such as T2DM, in this region[69]. In addition, North Africa and the Middle East, as well as Central Europe, Eastern Europe and Central Asia, had the highest obesity-related age-standardized mortality in 2021 (Fig. 1). This finding is attributable to rapid urbanization in these regions, resulting in increased levels of physical inactivity with employment transitions from manual labour towards office-based, sedentary work[69]. Advances in food-processing technology and the increased accessibility, commercialization and industrialization of foods have led to substantial changes in diet and nutrition, particularly in low-to-middle-income countries. This accelerated shift from a subsistence and local diet towards ultraprocessed and nutrient-poor foods has led to increasing caloric intake and weight gain[70,71].

The concept of metabolically healthy obesity, encompassing a subgroup of individuals with obesity who do not have overt cardiometabolic abnormalities, is important. Individuals with metabolically healthy obesity have a higher risk of MASLD than metabolically healthy individuals with normal weight, but a lower risk of MASLD than those with obesity who are metabolically unhealthy[72,73]. As such, screening for MASLD is recommended in individuals with obesity, even if they seem to be metabolically healthy[72,73]. In addition, clinicians should be aware that MASLD can also occur in the absence of obesity, with global epidemiological evidence[74] demonstrating that 10–15% of individuals with MASLD have a BMI < 30 kg/m^2. Even in the absence of obesity, insulin resistance is a key pathophysiological mechanism in MASLD, with similar disease severity and clinical outcomes in people with insulin resistance with or without obesity[75,76].

Type 2 diabetes mellitus

In 2021, 506 million (95% UI 470–545 million) individuals were living with T2DM worldwide[77], affecting approximately 10.5% of adults aged 20–79 years, with a projected increase to 12.2% of the global population (an estimated 783.2 million people) by 2045 (refs. 1,78–81). T2DM contributed to 1.61 million (95% UI 1.49–1.71) deaths and 75.34 million (95% UI 63.48–90.25) DALYs worldwide in 2021 (Supplementary Table 2),

with age-standardized DALYs forecasted to increase by 22.3% between 2025 and 2050 (Figs. 3, 4 and 5).

The prevalence of MASLD in individuals with T2DM is almost double that of the general population[82,83]. In 2021, 65–70% of individuals with T2DM had MASLD, contributing to 213,480 DALYs and 10,020 deaths in these people[84–86]. T2DM accelerates the progression of MASLD, with a higher incidence of advanced fibrosis than in people with MASLD without T2DM[87]. Globally, among individuals with T2DM and MASLD, 35.54% had progression to clinically relevant fibrosis (stages F2–F4) and 14.95% had advanced fibrosis (stages F3–F4)[88]. Regional socioeconomic disparities in the prevalence of T2DM are similar to those observed for MASLD (Fig. 1).

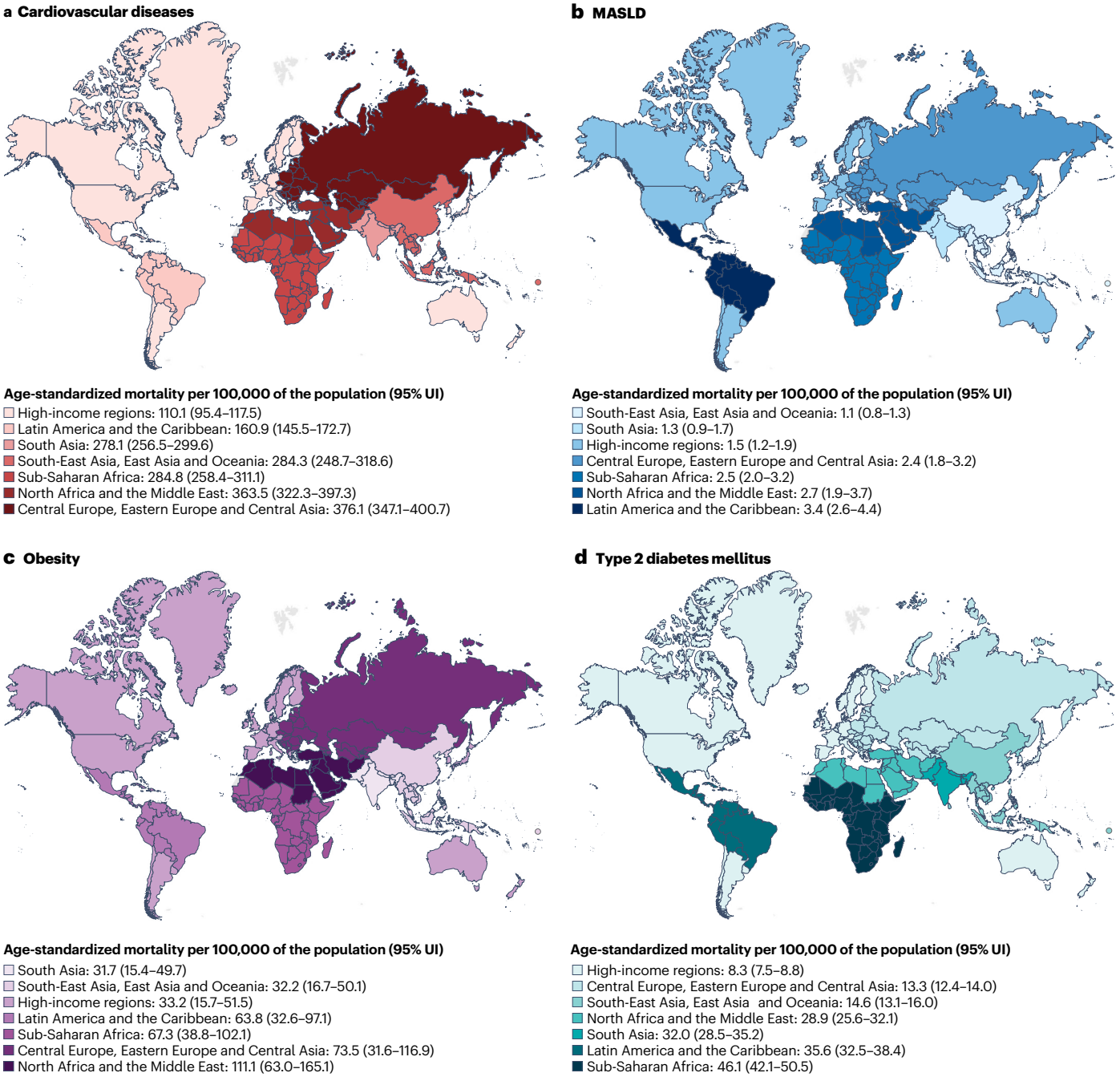

Fig. 1 | Global age-standardized mortality related to cardiovascular–liver–metabolic diseases. The cardiovascular–liver–metabolic syndemic has similar regional distributions worldwide, with a disproportionate burden of the global age-standardized mortality related to cardiovascular–liver–metabolic diseases occurring in Central Europe, Eastern Europe, Central Asia, North Africa, the Middle East and sub-Saharan Africa. **a**–**d**, Data are given per 100,000 of the population in 2021, stratified by cardiovascular diseases (**a**), metabolic-dysfunction-associated steatotic liver disease (MASLD) (**b**), obesity (**c**) and type 2 diabetes mellitus (**d**)[89,91,228,229]. UI, uncertainty interval.

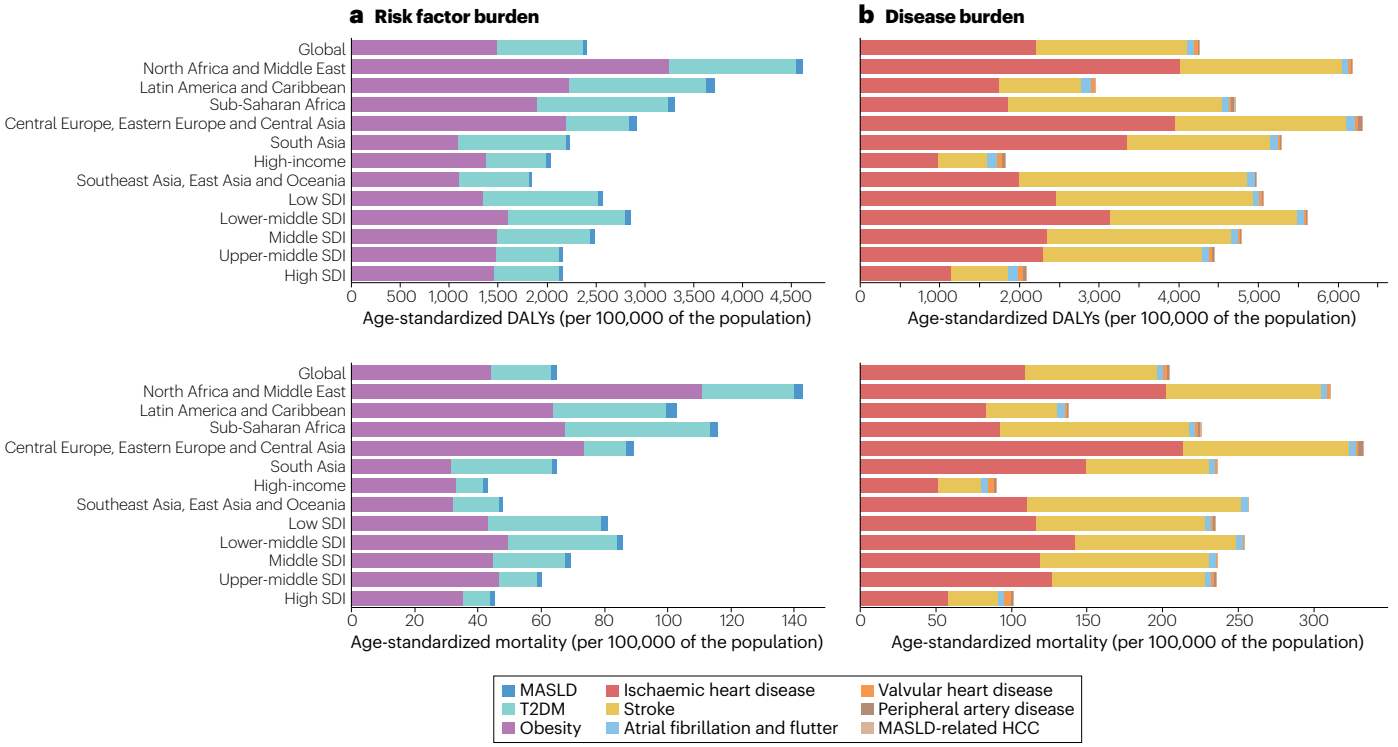

Fig. 2 | Age-standardized DALYs and mortality related to cardiovascular–liver–metabolic diseases by region. Obesity contributes to the majority of risk-factor-related morbidity and mortality worldwide, with atherosclerotic cardiovascular diseases (ischaemic heart disease and stroke) accounting for the bulk of disease-related morbidity and mortality across the cardiovascular–liver–metabolic spectrum. Data are per 100,000 of the population for cardiometabolic risk factors (**a**) and cardiovascular and liver disease (**b**) burden in 2021 (refs. 89,91,228,229). DALYs, disability-adjusted life years; HCC, hepatocellular carcinoma; MASLD, metabolic-dysfunction-associated steatotic liver disease; SDI, sociodemographic index; T2DM, type 2 diabetes mellitus.

Cardiovascular diseases

The age-standardized prevalence of CVD in 2021 was 7,178.7 (95% UI 6,696.2–7,620.7) per 100,000 of the population, with 612.06 million (95% UI 570.32–649.81) individuals with CVD worldwide. In 2021, 19.41 million (95% UI 17.78–20.67) CVD-related deaths occurred, accounting for 28.6% of all deaths, and there were 428.33 million (95% UI 403.68–453.71) CVD-related DALYs worldwide[89,90] (Supplementary Table 2). Despite prevention efforts, the rise in global CVD burden is set to persist between 2025 and 2050, with CVD prevalence forecasted to increase by 90%, CVD-related mortality by 73.4% and CVD-related DALYs by 54.7%, primarily owing to the ageing and enlarging global population[91–93]. The shift from the dominance of infectious diseases towards non-communicable diseases reflects the ongoing global epidemiological transition and will lead to an increasing number of regions with CVD as the dominant cause of death[91,92]. In 2021, the highest CVD-related age-standardized mortality was recorded in Central Europe, Eastern Europe and Central Asia, as well as North Africa and the Middle East. These regions have the largest mortality burden associated with tandem epidemics of MASLD and obesity (Fig. 1). Regions that had the highest CVD mortality also had high mortality associated with MASLD, T2DM and obesity (Supplementary Fig. 2).

Ischaemic heart disease. In 2021, the global prevalence of IHD was 254.28 million (95% UI 221.45–295.49), contributing to 8.99 million (95% UI 8.26–9.53) deaths (accounting for 13.3% of all global deaths) and 188.36 million (95% UI 177.04–198.15) DALYs[91] (Supplementary Table 2). Globally, IHD is, and will continue to be, the leading contributor to CVD-related morbidity and mortality (Fig. 2). However, with advances in IHD management, the age-standardized DALYs and mortality related to IHD are set to decrease by 41.6% and 41.8%, respectively, between 2025 and 2050 (Figs. 3, 4 and 5). The prevalence of IHD in people with MASLD is estimated to be 44.6% in 2021 (ref. 94), with a 33% higher risk of incident IHD than in those without MASLD[94]. In addition, the prevalence of IHD is greater in those with moderate-to-severe steatosis (37.5%, 95% CI 15.0–67.2%) than in those with mild steatosis (29.6%, 95% CI 13.1–54.0%)[94–96].

Geographically, Central and Eastern Europe have the highest prevalence of IHD, with several Eastern European countries, including Bulgaria, the Czech Republic, Estonia, Latvia and Lithuania, showing the largest rise in IHD prevalence in the past two decades[97]. This concerning trend mirrors the rise in metabolic risk factors, with nearly a quarter of the population in Central and Eastern Europe having metabolic syndrome[98]. The challenge will be to implement region-specific strategies for the effective treatment and prevention of IHD, tailored to low-to-middle-income countries, which have local resource constraints, complex socioeconomic environments and inherent cultural inertia[91].

Stroke. Stroke is the third-most-common cause of global mortality, contributing to 7.25 million (95% UI 6.57–7.81) deaths (10.6% of all global deaths) in 2021 (Supplementary Table 2). Age-standardized

mortality related to stroke is expected to decrease by 37.5% between 2025 and 2050 (Figs. 3, 4 and 5). The presence of MASLD increases the risk of ischaemic stroke by 18%[99], largely driven by accelerated vascular atherosclerosis and cardiac arrhythmias[100].

Stroke was the leading CVD-related cause of age-standardized mortality in sub-Saharan Africa and Southeast Asia, East Asia and Oceania in 2021 (Fig. 2). A large proportion of stroke-related deaths (86.0%, 95% CI 85.9–86.9%) occur in countries with low income, lower-middle income and upper-middle income[101], mirroring the disparate distribution of MASLD and metabolic risk factors across the SDI regions[102]. Poor quality of care for stroke[103] and low stroke awareness in the general population[104], coupled with the high burden of deleterious behavioural and metabolic comorbidities, have contributed to the double burden of stroke and MASLD in low-to-middle-income countries[105,106].

Heart failure. Heart failure is estimated to affect 1–3% of the global population[107], amounting to 56.5 million (95% UI 49.7–63.7) people with heart failure in 2021 (ref. 108). North Africa and the Middle East had the highest age-standardized prevalence of heart failure (780.5 per 100,000 population)[108]. MASLD has been associated with a

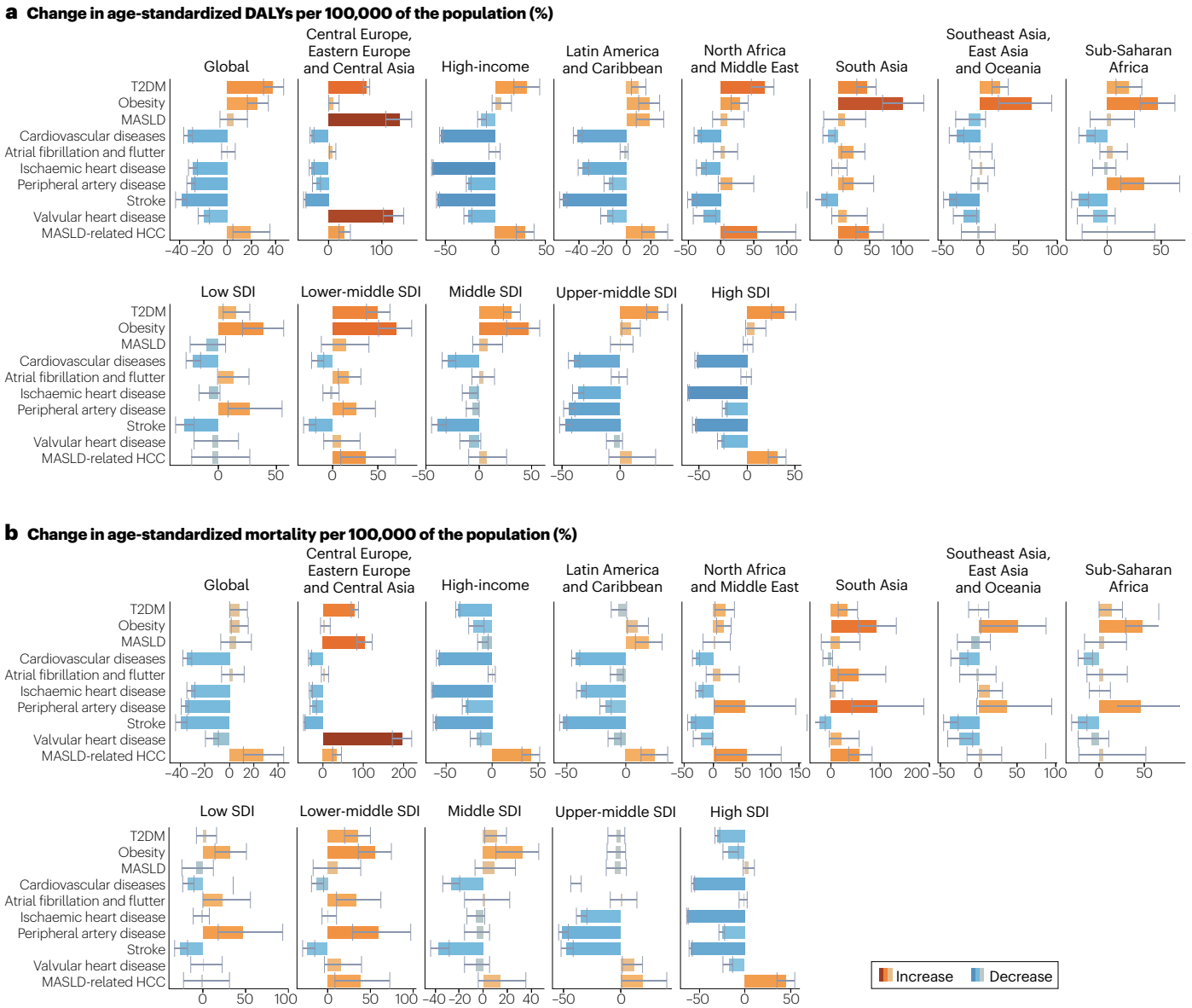

Fig. 3 | Change in age-standardized DALYs and mortality related to cardiovascular–liver–metabolic diseases by region from 1990 to 2021. Age-standardized morbidity (part **a**) and mortality (part **b**) related to cardiovascular diseases have decreased owing to medical advances, but improvements in the global trend of cardiovascular–liver–metabolic diseases are offset by the rising burden of age-standardized morbidity and mortality of upstream risk factors, such as type 2 diabetes mellitus (T2DM), obesity and metabolic-dysfunction-associated steatotic liver disease (MASLD). Data are presented per 100,000 of the population[89,91,228,229]. The error bars denote the 95% confidence interval. DALYs, disability-adjusted life years; HCC, hepatocellular carcinoma; SDI, sociodemographic index.

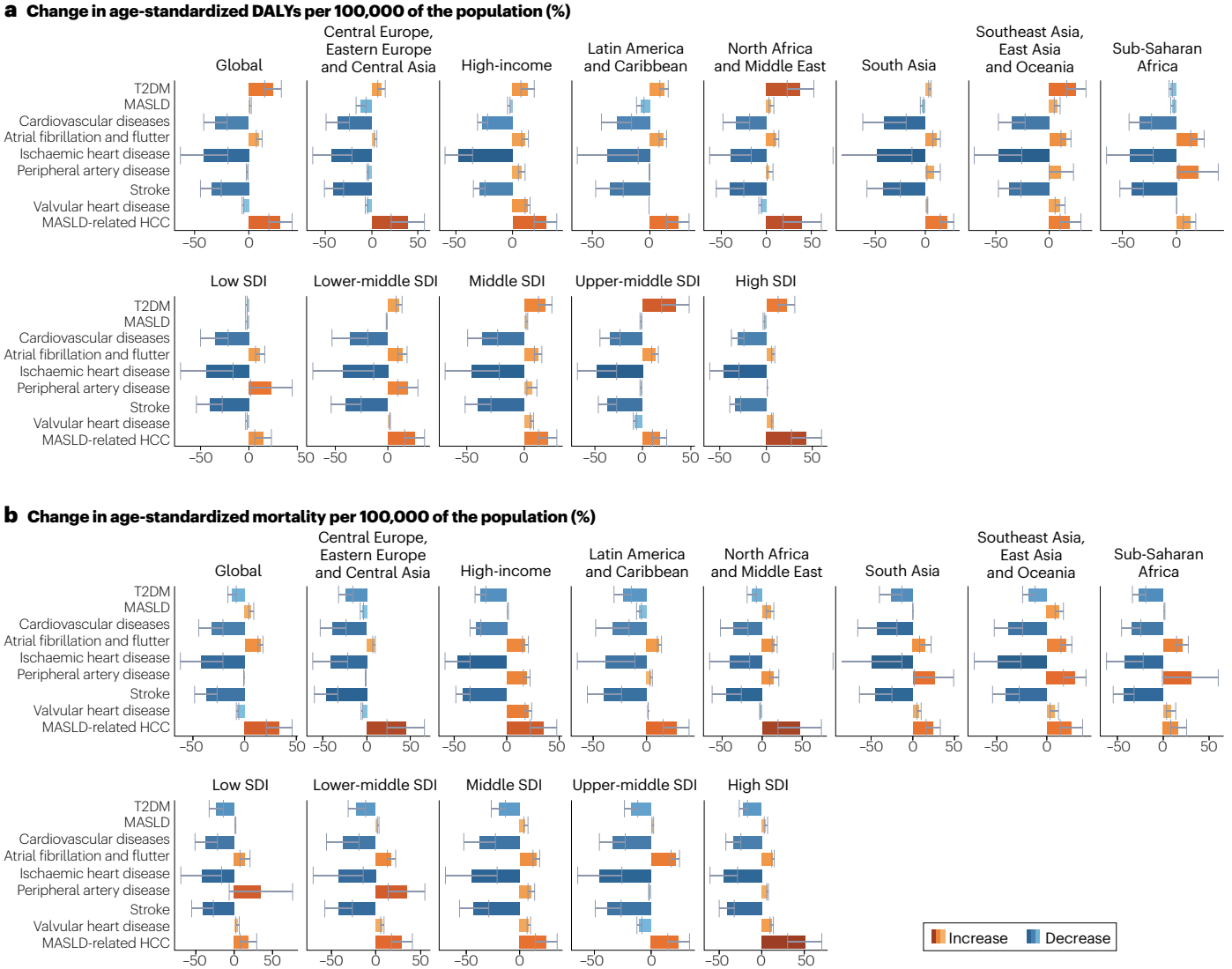

Fig. 4 | Estimated change in age-standardized DALYs and mortality related to cardiovascular–liver–metabolic diseases by region from 2025 to 2050. Forecast analysis reveals the anticipated improvements in age-standardized morbidity (part **a**) and mortality (part **b**) related to cardiovascular diseases. However, future healthcare systems will need to address the rising global burden of upstream risk factors, such as type 2 diabetes mellitus (T2DM) and metabolic dysfunction-associated steatotic liver disease (MASLD). Projected trends for obesity from 2025 to 2050 are not available. Data are presented per 100,000 of the population[89,91,228,229]. The error bars denote the 95% confidence interval. DALYs, disability-adjusted life years; HCC, hepatocellular carcinoma; SDI, sociodemographic index.

1.5-fold increase in the risk of new-onset heart failure, independent of metabolic risk factors[109]. Aetiologies of heart failure vary across the SDI, with metabolic causes (IHD and hypertensive heart disease) more prevalent in high-SDI regions[110]. Although metabolic causes are the fastest growing aetiology of heart failure in low-SDI regions, congenital and infective causes, such as rheumatic heart disease, remain substantial contributors to heart failure[111].

Other cardiovascular diseases. Atrial fibrillation, valvular heart disease and peripheral artery disease are growing drivers of cardiovascular morbidity and mortality globally (Figs. 3, 4 and 5; Supplementary Table 2). The presence of MASLD has been associated with an increased risk of incident atrial fibrillation[112], aortic valve sclerosis[113,114] and peripheral artery disease[115]. Incremental increases in the risk of these CVD subtypes have been reported in people with concomitant MASLD and T2DM[113,114,116,117].

Challenges and future directions

Refining the micro–meso–macro framework

The CLM syndemic is expected to broaden interdisciplinary collaborations across the fields of cardiology, hepatology, endocrinology and primary care. In addition to the horizontal expansion of multidisciplinary efforts to improve CLM health, the micro–meso–macro framework needs to be refined by combining biological, clinical, epidemiological

and sociological data through powerful bioinformatic methods that effectively connect across basic, clinical, sociocultural, political and population health sciences[118]. Our understanding of the biological processes underlying CLM diseases is constantly evolving, as are the methods for characterizing, predicting and detecting the risk of CLM, which can improve precision prevention (micro). Keeping the voices of individuals and communities at the heart of CLM health promotion is crucial[118]. We must examine the dynamic interactions between wider structural factors and the local community (including specialty silos, accessibility and affordability to CLM care, food insecurity, and ethnic and sex disparities), and incorporate emerging pharmacotherapies and interventions into obesity management that are made accessible within communities (meso). At the other end of the spectrum, the role of social determinants of health (including healthcare infrastructure and socioeconomic, environmental and cultural drivers) in determining the CLM health of individuals and populations has become increasingly recognized[118]. Stakeholders should take advantage of the expanding knowledge on social epidemiology in CLM diseases to improve the implementation of structural interventions shown to benefit behaviours and health outcomes[118]. This principle extends to the wider research infrastructure, incorporating MASLD end points into randomized clinical trials of cardiometabolic diseases (macro). In the present era, where novel molecular innovations have attracted vast investments without clear models for future use[118], and developments in data science are focused on handling rapidly expanding datasets, the social and community interventions that could improve CLM health can be overlooked. However, the careful integration of these population-based strategies with technological advances, to drive health-focused developments at the micro, meso and macro levels, will be fundamental in expanding the field of CLM health[118]. Potential mitigating solutions and future directions for the current challenges in CLM health are summarized in Box 3.

Under-recognition of CLM diseases

Although the global prevalence of MASLD is substantial[13], the available (albeit limited) data point towards a low awareness of MASLD and its related complications in the general population[119,120]. A lack of awareness about CLM diseases also exists among healthcare professionals, who have adopted inconsistent approaches to diagnosis, risk assessment and referrals[121,122]. A global survey demonstrated that 64% of primary-care physicians underestimated the prevalence of MASLD[123], whereas a smaller study showed that only 46% of 250 primary-care physicians in Wisconsin, USA, performed MASLD screening in people with obesity and T2DM[124]. Herein lies the challenge, that >50% of individuals with metabolic-dysfunction-associated steatohepatitis (MASH), a more severe form of MASLD in which fat accumulation progresses to liver cell inflammation and damage, are asymptomatic, with a substantial proportion of MASH cases detected incidentally by abnormal laboratory markers[125]. The under-recognition of CLM diseases remains a major barrier to effective treatment and prevention of cardiovascular complications. A substantial proportion of people with MASLD are managed in a primary-care setting, so physicians there should be optimally positioned to identify those at an elevated risk of adverse outcomes and to facilitate early diagnosis. Resources should be streamlined to educate the public and primary-care clinicians on timely screening for CLM syndrome, especially in individuals with obesity, metabolic syndrome or T2DM and those with high cardiovascular risk[21].

Unlike chronic kidney disease, which is a well described cardiovascular-risk-enhancing factor included in the guidelines for primary prevention of CVD[126], MASLD has historically been under-recognized as a cardiovascular-risk-enhancing factor. However, the 2023 nomenclature change from NAFLD to MASLD is the first important step in shifting the diagnostic criteria towards a more comprehensive definition of the condition, acknowledging the presence of concomitant cardiometabolic diseases[5,75,127]. With the emergence of new, scalable pharmacotherapies targeting the CLM nexus, there is growing impetus for clinicians to be proactive in the recognition and management of CLM diseases to prevent cardiovascular sequelae[7]. Large-scale studies are needed to evaluate the clinical utility and cost-effectiveness of including MASLD as a cardiovascular-risk-enhancing factor that can guide management decisions on statin therapy initiation, with the greatest utility likely to be among individuals with an intermediate risk of atherosclerotic CVD[7].

Risk and prevention in CLM health

Risk prediction. The 2024 update of the PREVENT cardiovascular-risk-stratification tool includes chronic kidney disease as a risk enhancer and provides both 10-year and 30-year risk estimates for CVD, atherosclerotic CVD and heart failure[128]. With the increasing recognition of MASLD as a cardiovascular-risk enhancer, incorporating MASLD as one of the outcomes in the multivariable atherosclerotic-CVD-risk equation could be an important step in promoting CLM health, preventing atherosclerotic CVD and improving cardiovascular outcomes[18,129]. Indeed, existing risk-stratification systems, such as the Framingham Risk Score, might not accurately estimate cardiovascular risk in a cohort with MASLD, given that these models do not consider associated risk enhancers, such as insulin resistance and hypertriglyceridaemia[130]. However, the integration of MASLD (and serum-based non-invasive tests for this condition) into existing atherosclerotic-CVD-risk-prediction models presents several challenges.

Few widely available and inexpensive non-invasive tests for biomarkers of MASLD have been validated across various populations[131]. The Fibrosis-4 (FIB-4) index is the best validated screening tool for detecting advanced fibrosis, with a specificity of 98% and a sensitivity of 33%[132]. This measure outperforms other scoring systems in the identification of individuals with advanced hepatic fibrosis[5,7,133]. The FIB-4 index uses readily available clinical variables, such as age, platelet count, alanine aminotransferase and aspartate aminotransferase serum levels[134,135], with a FIB-4 score <1.3 excluding advanced fibrosis (high negative predictive value) and a FIB-4 score ≥2.67 representing a high likelihood of advanced fibrosis that warrants secondary assessment or timely hepatology referral[134]. The probability of advanced fibrosis determined by FIB-4 (score ≥2.67) has been shown to predict an increased risk of cardiovascular death and major adverse cardiovascular events in people with MASLD[136,137] and has promise in CVD-risk stratification[5,138]. However, FIB-4 score thresholds need to be used with caution because this index performs poorly in the identification of fibrosis in young adults aged ≤35 years, with current consensus recommending alternative fibrosis assessments in this age group[7,139]. In addition, given that the specificity of the FIB-4 index also decreases to 35% in those aged ≥65 years, a revised threshold of >2.0 (sensitivity 77% and specificity 70% for fibrosis) should be considered in these older people[139,140].

Emerging pharmaco-economic data for serum-based non-invasive tests are promising, suggesting that these tests are cost-effective for screening people with obesity or T2DM for the presence of a high risk of MASLD in the primary-care setting[141,142]. For example, in a UK cohort of people with T2DM, the incremental cost-effectiveness ratio

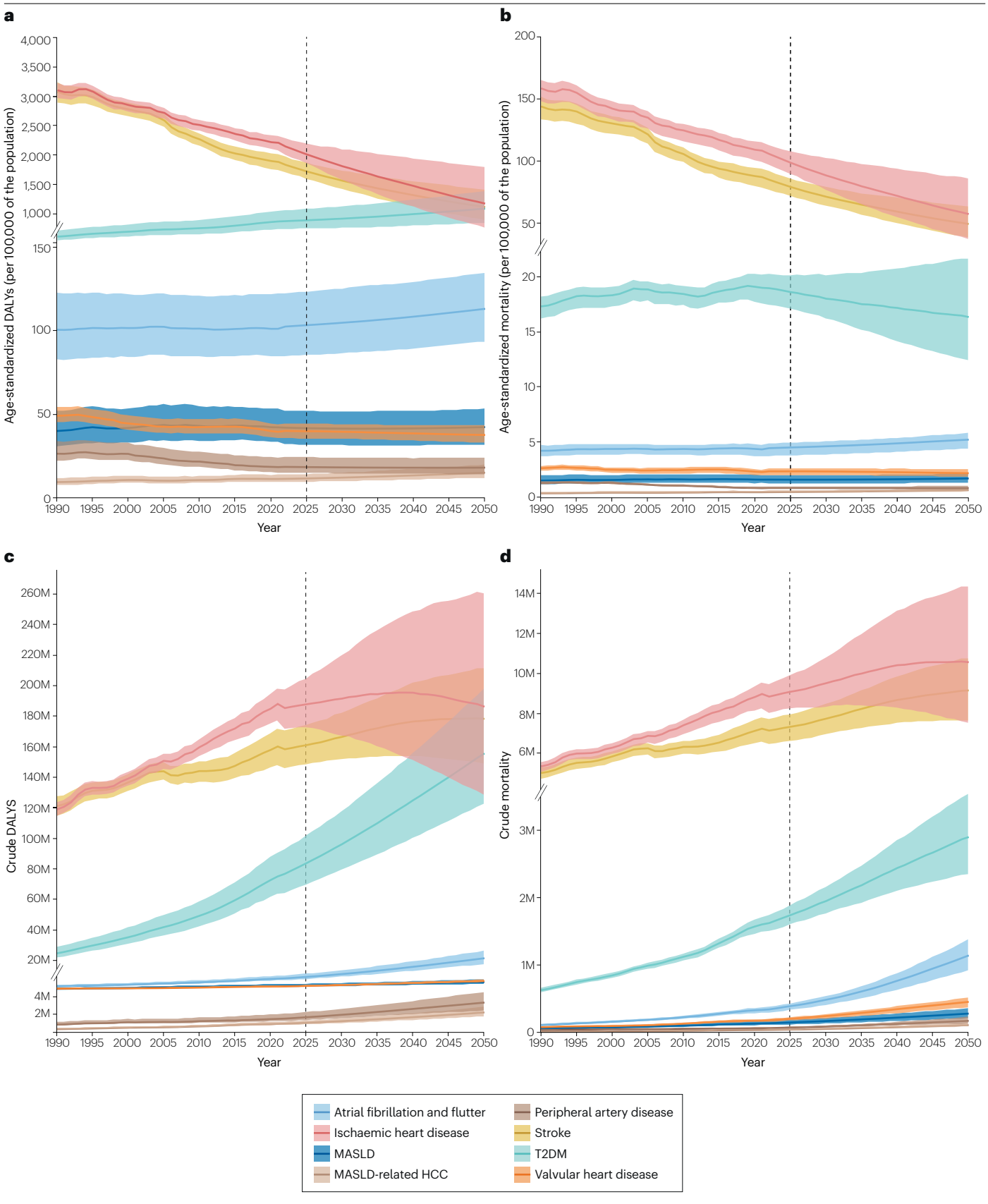
a
Age-standardized DALYs (per 100,000 of the population)
4,000
3,500
3,000
2,500
2,000
1,500
1,000
150
100
50
0
1990 1995 2000 2005 2010 2015 2020 2025 2030 2035 2040 2045 2050
Year
b
Age-standardized mortality (per 100,000 of the population)
200
150
100
50
20
15
10
5
0
1990 1995 2000 2005 2010 2015 2020 2025 2030 2035 2040 2045 2050
Year
c
Crude DALYS
260M
240M
220M
200M
180M
160M
140M
120M
100M
80M
60M
40M
20M
4M
2M
1990 1995 2000 2005 2010 2015 2020 2025 2030 2035 2040 2045 2050
Year
d
Crude mortality
14M
12M
10M
8M
6M
3M
2M
1M
0
1990 1995 2000 2005 2010 2015 2020 2025 2030 2035 2040 2045 2050
Year
Atrial fibrillation and flutter
Ischaemic heart disease
MASLD
MASLD-related HCC
Peripheral artery disease
Stroke
T2DM
Valvular heart disease

Fig. 5 | Historical and projected trends in global DALYs and mortality related to cardiovascular–liver–metabolic diseases. Despite advances in the treatment of cardiovascular diseases, the growing crude morbidity and mortality burden related to cardiovascular–liver–metabolic diseases reflect the enlarging and ageing global population, as well as the interdependence of multisystem pathophysiological relationships. The graphs show DALYs and mortality per 100,000 of the population (panels **a** and **b**) and crude DALYs and mortality (panels **c** and **d**) with shaded 95% uncertainty interval from 1990 to 2050 attributed to the key drivers of the cardiovascular–liver–metabolic syndemic[89,91,228,229]. DALYs, disability-adjusted life years; HCC, hepatocellular carcinoma; M, million; MASLD, metabolic dysfunction-associated steatotic liver disease; T2DM, type 2 diabetes mellitus.

for the FIB-4 test was £2,059.98 per quality-adjusted life year (QALY), compared with £2,480.00 per QALY for vibration-controlled transient elastography[142] and £2,541.24 per QALY for the enhanced liver fibrosis test[142]. Sequential screening strategies, in which the FIB-4 test is combined with the enhanced liver fibrosis test or vibration-controlled transient elastography, have also been shown to be cost-saving in primary-care screening for high-risk MASLD in the UK[138].

Beyond the optimization of serum-based non-invasive tests, further refinement of the MASLD screening model should include improved systems for recall, reflex testing with specific non-invasive tests to detect fibrosis and active case finding[143,144]. In addition, other challenges include inaccuracy and sampling error in the reference standard owing to physiological variability across various populations, as well as the inability of serum-based non-invasive tests, such as the FIB-4 test, to distinguish between different stages of fibrosis or liver disease[131]. More robust, population-based studies of serum-based non-invasive tests for liver biomarkers are needed to examine the dose-dependent association between liver function and CVD and to evaluate improvements in the discrimination value and net reclassification in modified risk-assessment models[145] as well as the clinical utility and cost-effectiveness of MASLD as a risk-enhancing factor to guide treatment[18]. These risk-prediction models will need to:

- Use liver biomarkers that encapsulate the biological, clinical and epidemiological pathways that underscore the CLM nexus
- Be derived and validated in cohorts that parallel the contemporary, primary-prevention population with diverse ethnic, racial, geographical and socioeconomic backgrounds
- Include cardiovascular outcomes, such as atherosclerotic CVD, heart failure and cardiovascular mortality
- Incorporate MASLD biomarkers that are readily available in the primary-care setting for convenient implementation
- Be validated across a broad age range throughout the entire life course[7]

Competing risk. Amid the shared biological processes of the CLM syndrome, disentangling the competing risks of MASLD, obesity and the associated metabolic perturbations is vital to the integration of MASLD into cardiovascular-risk-prediction tools. The challenge with a broad CLM health construct is the analysis and selection of study outcomes. For example, an individual with advanced liver fibrosis might be at risk of cardiovascular events or death not related to the CLM syndrome, whereas an individual with mild or moderate steatosis (without fibrosis) and components of the metabolic syndrome might have an increased short-term risk of cardiovascular events or death[18]. Therefore, longitudinal studies are needed to account for the competing risks of the various components of the CLM syndrome, which can provide context and insights into mechanistic pathways that mediate each factor over time[18]. When identifying a first adverse event resulting from interacting metabolic-risk factors, adopting competing-risk methodology can help to prioritize interventions to prevent future adverse events. Adequate modelling techniques are also important in enhancing the accuracy of cardiovascular-risk prediction[146,147] and accurately estimating outcomes for the design of clinical trials and resource allocation in healthcare systems[18].

Disentangling competing risks could aid our understanding of how incorporating measures of liver steatosis, injury and fibrosis might improve cardiovascular-risk-prediction models beyond the main pillars of the metabolic syndrome and conventional measures of adiposity. However, whether the evaluation of liver steatosis is cost-effective in atherosclerotic-CVD-risk stratification, beyond the current standard of care for managing obesity and T2DM, remains to be determined. Therefore, the routine detection of liver steatosis with liver ultrasonography has not yet been recommended for atherosclerotic-CVD-risk stratification[7]. Future studies examining liver steatosis as a proxy for cardiovascular risk factor will be important[7]. The current evidence points towards an unconvincing role for mild or moderate steatosis (the first hit) in cardiovascular prognostication. However, the amplification of first-hit events, through surplus adipose tissue deposition, cytokine overproduction and oxidative stress, can lead to a self-reinforcing positive feedback that perpetuates the second hit, thereby accelerating the progression to MASH and fibrosis[148]. Liver fibrosis has been identified as a strong predictor of liver-related and cardiovascular-related outcomes[7,149]. Steatohepatitis and fibrosis are traditionally diagnosed by histology, but the use of liver biopsy is often limited by its invasiveness and the associated risk of bleeding, especially in people with CVD[7]. The use of non-invasive tests has therefore emerged as a screening tool to identify clinically significant hepatic fibrosis with the increasing availability of cost-effective indices, such as the FIB-4 index and vibration-controlled transient elastography[7].

Precision prevention. Considerable interindividual variability exists in the severity and progression of MASLD and associated CVD outcomes[28]. Therefore, precision medicine approaches are needed to identify key modifiers of health, disease and response to treatment[29,150]. Precision prevention embraces personalized prevention as well as social determinants of health. With the development and validation of interventions designed for individuals or communities at risk of CLM diseases[151], opportunities arise to improve cardiovascular and CLM health and reduce disparities[29,150,152,153]. Recognizing and quantifying the CLM 'exposome' of an individual or community, comprising various environmental, ethnic, cultural, socioeconomic, psychosocial, behavioural, biological and genetic exposures, is vital to realizing these opportunities. This knowledge can be enhanced by the understanding of gene–environment, epigenetic–environment and microbiome–environment interactions in CLM health. Several genetic polymorphisms closely linked with fatty acid metabolism, oxidative stress and liver fibrogenesis are associated strongly with increased hepatic steatosis, reduced serum triglyceride levels and susceptibility to MASLD from a young age[154,155]. The role of genetic factors in MASLD (particularly *PNPLA3*)[156,157] seems to be more prominent in lean individuals than in

Box 3 | Potential solutions and future directions for the cardiovascular–liver–metabolic syndemic

Recognition
- Recognizing metabolic-dysfunction-associated steatotic liver disease (MASLD) as a cardiovascular-risk-enhancing factor is crucial in promoting cardiovascular–liver–metabolic (CLM) health
- Interdisciplinary collaborations across the fields of cardiology, endocrinology, hepatology and primary care are crucial
- The syndemic micro–meso–macro framework (Box 1) focuses on shared challenges, drivers of disease and solutions
- Improved knowledge among healthcare providers could facilitate patient education and prevention
- Clarity on the definition of the CLM syndrome will be the next important step

Risk prediction and precision prevention
- Efforts are needed to incorporate biomarkers of MASLD and fibrosis into conventional risk models for atherosclerotic cardiovascular disease (CVD)
- The competing risks of MASLD, obesity and type 2 diabetes mellitus should be discerned when examining cardiovascular outcomes
- Precision prevention includes quantifying the individual's exposome: a combination of environmental, ethnic, cultural, socioeconomic, psychosocial, behavioural and biological exposures related to CLM health

Obesity management and healthy lifestyle in communities
- A strategy of 'think global, act local' can be applied to CLM health
- Equitable access to healthy foods and environments must be reinforced with policy regulations and economic incentives
- Strategies to reduce childhood obesity should leverage changes in local schools, grocery stores or workplaces
- Strategies to tackle commercial determinants of health are needed to ensure affordable, healthy food options
- Whole-community approaches are needed, through community capacity-building, strengthening community leadership, improving workforce skills and enhancing partnerships between research and practitioner communities
- Central actors in the network should build connections with affected communities and civil society organizations, within the multistakeholder approach

Equitable access to pharmacotherapies
- Risk-prediction models have the potential to discriminate between the risks of atherosclerotic CVD or heart failure to inform the use of sodium–glucose cotransporter 2 inhibitors and glucagon-like peptide 1 receptor agonists
- Healthcare providers and systems, insurance agencies, industry and patients should align policies and advocacy in promoting equitable access to pharmacotherapies

Healthcare systems
- Clinical management should be harmonized across primary care and cardiology, endocrinology and hepatology
- The role of a 'CLM coordinator' could encourage collaboration and support for primary-care providers and the interdisciplinary team
- Preventive medicine should be embedded within primary healthcare
- Holistic approaches should advocate for social nutrition, social prescribing and societal changes in promoting individual engagement with lifestyle changes
- Non-invasive tests would be useful to identify hepatic fibrosis in the primary-care setting and facilitate timely referrals to specialist care
- The implementation of local clinical and referral pathways for MASLD screening and management in CVD is necessary

Integrating MASLD outcomes into clinical trials of CVD
- Integrating MASLD and multiorgan outcomes into future CVD clinical trials would lead to study cohorts that are more representative of the CLM syndrome
- Wider collaboration between cardiovascular, diabetology, endocrinology and hepatology trialists should be encouraged
- The exclusion criterion of 'clinically significant liver disease' should be revised to improve trial inclusivity and the generalizability of the findings
- Examining longitudinal cardiovascular outcomes in individuals with MASLD will be beneficial

Social determinants of CLM health
- Tackling inequities in social determinants of health will require multisectoral approaches, with the involvement of political and societal stakeholders to sustain health policies and actions
- Social and structural barriers should be addressed with policies on education, food, public infrastructure and transportation, as well as the axes of inequity such as food security, socioeconomic position and disparities related to ethnicity and sex

those with overweight or obesity. Partitioned polygenic risk scores have identified the presence of at least two distinct types of MASLD[40], one that is genetically driven and liver-specific, with an increased risk of aggressive liver disease[29,158], and another that is systemic and closely linked to cardiometabolic diseases and incident CVD[29,40,158,159] As such, pathophysiological mechanisms, clinical trajectories and outcomes can differ between individuals with similar liver phenotypes at baseline, and thus great potential exists for precision medicine approaches to improve the prediction of disease progression[40].

The fundamental influence of biological sex as a modifier of CLM-related morbidity and mortality should be considered in the approach to precision medicine[150]. The influence of sex hormones on MASLD and metabolic disorders is multifaceted, affecting factors such as adipose tissue distribution, the gut microbiome and insulin resistance[150]. Owing to the hepatoprotective effects of oestrogen, women of reproductive age have a lower risk of MASLD and fibrosis than men of the same age[150]. Sex-related differences in response to lifestyle interventions can also guide personalized prevention of CLM diseases.

For example, greater weight loss is required for MASH resolution in women than men[150].

Subphenotyping approaches have provided some evidence to improve the prediction of cardiometabolic risk in specific subpopulations of people with obesity or T2DM (such as the various categories of body-mass index, BMI)[160]. Moreover, delineating cardiometabolic-risk clusters helps to allocate individuals to specific pathophysiological risk groups, with potential benefits for prevention and treatment[160]. As our insights into CLM health continue to improve, several distinct subtypes of MASLD will probably be defined. As such, healthcare providers and policy makers should avoid a one-size-fits-all approach and embrace the tenets of precision medicine[161]. Lessons can be learnt from previous cardiometabolic approaches for risk prediction and precision prevention of obesity and T2DM[160,162]; concerted efforts to harmonize precision medicine research and standardize reporting will be crucial to enable comparisons between studies and accelerate the clinical implementation of findings[28,162].

Social determinants of CLM health

The global CLM syndemic disproportionately affects socially deprived communities[163,164], with its prevalence, severity and CLM outcomes heavily influenced by social determinants of health and socioeconomic inequities[165–173]. Social determinants of CLM health (Box 4) often overlap with cardiovascular-risk factors, such as tobacco use[174], poor nutrition[175], excessive alcohol intake and sedentary living[176,177]. These risk factors tend to co-occur, follow socioeconomic patterns and synergistically exacerbate CLM diseases[178,179], owing, in part, to the rapid urbanization and globalization that have precipitated the epidemiological and nutrition transition. Deleterious lifestyles and behaviours often go beyond individual responsibility or poor decision-making, given that they are heavily influenced by the multilayered pressures of social determinants of health. For example, the obesogenic epidemic dictates dietary choices through the presence of food deserts (regions with limited access to affordable, healthy food) and food swamps (regions with high-density food outlets selling cheap, high-calorie, nutrient-poor food)[180–182] that particularly affects socially deprived areas.

The influence of social determinants of health begins in infancy, with a heightened risk of CLM diseases in adulthood among the offspring of women with low socioeconomic levels[183,184]. Community socioeconomic deprivation is a predictor of metabolic diseases and MASH[13,171]. Individuals with a greater number of socioeconomic deprivation factors (such as use of public versus private healthcare, being foreign-born, lacking a private vehicle, or living in rented and crowded housing units) have a higher risk of CLM diseases[171,185]. Racial and ethnic disparities in CLM prevalence have also been reported. In the USA, the highest burden of MASLD and metabolic diseases are found among Hispanic people, followed by an intermediate burden in white people and the lowest burden in Black individuals[173]. In a 2024 review, the key social barriers to promoting CLM health in the USA were identified as the lack of awareness of risk factors, resulting in delayed screening and diagnosis, lack of infrastructure (such as public parks) in urban communities to promote physical activity, under-representation of specific racial groups (such as Hispanic people) in clinical trials, rising poverty and food insecurity coupled with lack of regulation of fast foods[186].

Tackling inequities in social determinants of health requires multisectoral approaches, with involvement from political and societal stakeholders to sustain effective health policies and actions to address the CLM syndrome and its upstream risk factors. Addressing the social determinants of CLM health includes macro-level policies on education, food, public infrastructure and transportation, as well as micro-level policies on the axes of inequity, such as food security, socioeconomic status and disparities relating to ethnicity and sex[187]. Strategies to incorporate MASLD and metabolic diseases into interventions and guidelines for non-communicable diseases, such as the World Health Organization's Global Action Plan for the Prevention and Control of Non-Communicable Diseases 2023–2030 (ref. 188), will be an important next step in providing the overarching framework to guide whole-society action on the CLM syndemic within the global response to non-communicable diseases[189,190]. For example, the development of the first 'fatty liver disease Sustainable Development Goal country score' in 2023 (ref. 191) provided insights into country-level preparedness for a multisectoral response to the increasing burden of MASLD. This strategic advocacy tool could guide future collaboration and action of the health and sustainable development sectors to address MASLD, both nationally and globally[191].

The multilevel macro–meso–micro framework should be incorporated into strategies targeting social and structural barriers to CLM health. Micro-level interventions include education for healthcare professionals, to ensure the timely detection of food insecurity and the linkage to appropriate community support and to reduce stigma, as well as interventions to improve nutritional literacy among

Box 4 | Social determinants of cardiovascular–liver–metabolic health

Economic stability
- Food insecurity
- Low socioeconomic status
- Lack of housing stability and quality
- Inadequate job security, working conditions and access to healthcare benefits

Education access and quality
- Low levels of education
- Poor awareness and knowledge of cardiovascular–liver–metabolic (CLM) diseases

Healthcare access and quality
- Limited access to healthcare
- Clinical inertia and prescribing patterns in CLM diseases

Neighbourhood and built environment
- Lack of access to green spaces for exercise
- Access to healthy foods
- Chronic, low-level exposure to particulate matter ($PM_{2.5}$ and PM_{10}), nitric oxides and black carbon

Social and community factors
- Migration, discrimination (for example, because of race, ethnicity, gender or religious observations) and social isolation
- Barriers to community engagement (such as language barriers) and social support
- Social stigma of CLM disease diagnosis

Refer to refs. 19,189.

healthcare professionals and the general public[189]. Meso-level strategies include social prescription for physical activities as well as community resources to address social needs (such as financial difficulties, personal safety and assistance, and education), the promotion of lifestyle modifications for patients and their families, and increasing recreational infrastructure and the access to grocery stores to promote a healthier living environment[48,192,193]. Macro-level interventions involve policy changes at the level of transnational food corporations, with improved nutritional labelling, taxes on unhealthy foods and bans or limitations on the advertisement of unhealthy food to children. Addressing MASLD in interdisciplinary clinical practice guidelines is also needed. Updated guidelines on lifestyle management in CLM disease should include the mental, social and environmental determinants of MASLD, as well as digital health interventions for CLM diseases[194].

Management of obesity in communities

Despite decades of obesity-management recommendations from national and international organizations, including the World Health Organization, the implementation of such interventions remains suboptimal and inconsistent. As a result, the prevalence of obesity has increased substantially and is now one of the leading contributors to poor health in most countries[195,196]. Global multistakeholder approaches are necessary to address the interlinked challenges of obesity, food insecurity, undernutrition and climate change[197]. Such initiatives, driven by the shared vision of promoting CLM health, can further collaborative partnerships and the pooling of resources across the public and private sectors and civil society, thus ensuring diverse policy outputs[197]. However, society is currently dominated by powerful commercial entities, whose profits are driven by unsustainable practices, entrenching power asymmetries within multistakeholder initiatives and hindering their capacity to drive systemic change in obesity prevention. No country has yet succeeded in reversing the obesity epidemic, largely owing to policy inertia, powerful opposition from strong commercial organizations to government attempts to regulate fiscal policies (such as taxes on sugary drinks), and lack of demand for policy action by the general public[17,195].

To drive transformative changes in the determinants of global CLM health, the central stakeholders (for example, the Food and Agriculture Organization of the United Nations)[197] will need to build strong connections with, and incorporate the perspectives of, the affected communities and civil society organizations[197]. A strategy of 'think global, act local' can be applied in this context, converting the global CLM health challenge into community action. Initiatives to tackle the CLM syndemic should begin at the community level, where local health authorities understand the multilevel drivers of obesity and can reorient healthcare systems to ensure equitable access to healthy foods and environments (particularly in vulnerable communities), reinforced by strict policy regulations and economic incentives. Contemporary strategies for reducing childhood obesity should start with leveraging small changes in schools, grocery stores and workplaces. These initiatives will gradually translate into wider social changes, particularly when local actions and collaborative efforts nurture cycles of mutual learning between communities[17]. Moreover, whole-community approaches have proved effective in reducing childhood obesity[198,199] by building community capacity[200], strengthening community leadership, improving workforce skills and enhancing partnerships between researchers and practitioners. Evidence-based strategies should be incentivized through community engagement, to build trust and enable tailored strategies to promote CLM health[48]. Comprehensive, systemic actions are necessary to ensure equitable access to affordable healthy food and beverages, restrict marketing of unhealthy products to young people, promote physical activity and healthy behavioural choices[17] and tackle commercial determinants of health[201]. These interventions should involve multilevel partnerships across governmental and public health agencies, insurance companies, healthcare agencies and advocacy organizations[18].

Equitable access to pharmacotherapies

Emerging metabolic pharmacotherapies that target MASLD, metabolic-risk factors and CVD have great potential to improve CLM health. Treatments that target the shared pathomechanistic pathways of MASLD and cardiometabolic diseases, such as glucagon-like peptide 1 receptor (GLP1R) agonists, sodium–glucose cotransporter 2 (SGLT2) inhibitors and pan-peroxisome proliferator-activated receptor-γ agonists, should be considered in people with T2DM, atherosclerotic CVD or target-organ damage[202]. These agents not only have beneficial effects on insulin resistance and glycaemia, but also enhance weight reduction, improve hepatic steatosis and fibrosis, and mitigate the risk of CVD. These therapeutics have been comprehensively reviewed elsewhere[7,203–205].

Initiation of therapy with SGLT2 inhibitors, GLP1R agonists or both, on the basis of individual 10-year risk of atherosclerotic CVD or heart failure, is recommended in the American College of Cardiology/American Heart Association and European Society of Cardiology guidelines for the primary prevention of CVD[126,206]. In the era of precision medicine, risk-prediction models can help to discriminate between the absolute risks of atherosclerotic CVD and heart failure to inform a preventative strategy for the individual. Clinicians might prioritize SGLT2 inhibitors in people with CLM syndrome who have a higher risk of heart failure than atherosclerotic CVD, whereas GLP1R agonists might be selected for those at higher risk of atherosclerotic CVD than heart failure[18,207]. Importantly, more robust, long-term estimates of the net benefit of specific metabolic therapies will help to inform clinician–patient discussions to promote personalized CLM health[18].

Despite mounting evidence for the benefits on the CLM axis of glucose-lowering medications, these therapies remain underprescribed and under-used owing to clinical inertia and prescribing patterns, as well as lack of access and affordability for the patient[18,208–210]. Clinical inertia is defined as not initiating or intensifying therapy to achieve CLM targets, whereas prescribing patterns are characterized by the choice of drug classes and treatment potency. Prescribing patterns might be addressed by the use of fixed-dose combination pills, but the benefits of this approach might reach a threshold if clinical inertia persists. As such, strategies tackling clinical inertia can include CLM education, incentives for appropriate treatment initiation and intensification, and regular physician feedback[18,208–210]. All stakeholders, including healthcare professionals, healthcare systems, insurance agencies, industry and patients, should work together towards the overarching goal of aligning policies and advocacy to achieve equitable access to these evidence-based pharmacotherapies, thereby improving CLM health and alleviating global healthcare costs[18].

Multidisciplinary healthcare systems

Tackling challenges and unmet needs in the promotion of CLM health requires concerted multidisciplinary and multinational efforts from clinicians, researchers, policymakers, industry representatives and

patient advocacy groups, to improve awareness, early detection and the effectiveness of therapies, ultimately optimizing the care pathway for CLM diseases[211]. Efforts are needed to address the chasm between the provision of holistic CLM care at the population level and structural barriers that include segregated healthcare delivery systems, speciality silos, disparities in access to specialty care, clinical inertia and financial costs of developing pharmacotherapies[212].

Volume-based and value-based interdisciplinary approaches are important to harmonize clinical management across primary care and the cardiovascular, endocrinology and hepatology subspecialties to promote holistic management[213]. Moreover, the development of a 'CLM coordinator' role could support and encourage collaboration between primary-care clinicians and the interdisciplinary team, as well as easing patient navigation across the subspecialties[18,214]. The interdisciplinary care model is a shift away from the fragmented specialist framework, with the consolidation of care focused on the overall cardiometabolic milieu and on reducing the burden of incident CVD. However, multidisciplinary teamwork should not become a barrier to the delivery of care to patients, especially when simple, highly effective treatments can be provided by primary-care clinicians, who should be part of a seamless chain of care[18].

As discussed, serum-based non-invasive tests and imaging-based liver biomarkers can be useful for diagnosis, risk stratification and surveillance of disease progression and treatment response[215]. Promoting the uptake of affordable, readily available, serum-based non-invasive tests, such as the FIB-4 index, should improve the early identification of clinically significant hepatic fibrosis and streamline management, especially in regions with limited healthcare resources[216]. Primary-care and cardiometabolic services could use the FIB-4 index as a first-line strategy, in which people with a high risk of CVD with an elevated FIB-4 score (≥2.67) would undergo sequential evaluation with further imaging assessment[134,217]. Local clinical pathways for the screening of MASLD in individuals with CVDs should be implemented to develop streamlined algorithms and referral pathways to ensure that appropriate care is delivered[122].

Alongside the growing field of preventive cardiology, preventive hepatology should be recognized as an integrated transdisciplinary subspecialty in the tenets of CLM medicine[218,219]. A holistic preventive hepatology approach, focusing on prevention and management of MASLD, MASH and its associated cardiometabolic comorbidities, should be initiated at the earliest possible stage. This strategy will involve effective and sustainable healthy nutrition interventions in schools, developed and delivered in collaboration with maternal health and paediatric specialists, with the goal of mitigating childhood obesity and MASLD. Moreover, preventive hepatology clinics in tertiary-care centres, together with satellite, community-based clinics at primary-health centres, can deliver cost-effective interventions to promote awareness, education and screening of chronic liver diseases and timely management for people with MASLD[218,219]. Integrating the preventive hepatology model into primary healthcare and preventive cardiology could reduce the burden of MASLD and its complications and strengthen primary CVD prevention[218,219]. Close partnerships with community leaders, public health professionals, policymakers, governmental organizations and industry will be integral in implementing CLM health-promoting policies that balance biological perspectives and social sciences[220]. This holistic approach should include advocacy for social nutrition, social prescribing and the wider societal changes needed to promote engagement with lifestyle changes[220].

Integrating MASLD into CVD clinical trials

Although the volume of data on CLM diseases has expanded in the past decade, knowledge gaps still persist in our understanding of the natural history of MASLD and the overall MASLD burden in the general population and in high-risk CVD cohorts. Given that the majority of studies on the natural history and progression of MASLD have been derived from registries of liver biopsy data, evidence from prospective, unbiased cohorts remains limited, potentially leading to disease-spectrum bias. More research is needed on longitudinal cardiovascular outcomes in individuals with MASLD[221], with disaggregated analysis based on sex, race, ethnicity, age, socioeconomic status and other variables associated with inequities[222]. The findings from such studies will help to develop risk-prediction models and inform clinical decision-making[223–226].

To date, MASLD has been under-represented and under-reported in randomized clinical trials in people with CVD. In the SELECT trial, which investigated the effects of the GLP1R agonist semaglutide on cardiovascular outcomes in people with overweight or obesity, only 8.2% of participants had MASLD and 0.7% had MASH[14]. This prevalence of liver disease in the SELECT trial was low compared with the global prevalence of MASLD and MASH in the population with overweight or obesity[52]. Trialists should consider revising the common exclusion criterion of clinically significant liver disease, to increase the inclusivity of the trials and the generalizability of the findings to real-world populations[14,227]. We call for wider collaboration between cardiovascular, endocrinology and hepatology trialists on common trial protocols and CLM composite end points, where relevant. Integrating MASLD and multiorgan outcomes into future CVD trials would ensure that study populations are fully representative of the confluence of CLM diseases[14], facilitate drug development through multiple efficacy or safety evaluations, and expedite patient access to novel efficacious treatments. Embedding liver-related outcomes into CVD trials is also important[14]. Serum-based non-invasive tests can easily be performed in CVD trials at baseline and follow-up visits, although the confounding effects of CVD on liver enzymes should be considered[96]. Furthermore, given that cardiometabolic trials are usually large with long periods of follow-up, these studies should include participants with MASLD and incorporate liver-specific clinical outcomes (such as ascites, hepatic encephalopathy and variceal bleeding) into a multiorgan composite end point[14,227]. The occurrence of these liver-related hard end points might be sufficient in the enriched cardiometabolic population with MASLD to guide the design of future CLM trials, to determine sample size, estimate effect size and predict trends in concordance between cardiovascular and liver outcomes[14,227]. However, the use of combined cardiovascular–liver end points can pose challenges, including the adjustment for the heterogeneity of treatment effects across the liver and cardiovascular components of the composite and the differing weights of the individual cardiovascular and liver outcomes[19]. To overcome these issues, investigators could use the 'win ratio' to prioritize the order of outcome components on the basis of clinical importance, and the appropriate use of the composite outcome in trials when the investigational therapy is likely to affect the liver and heart concordantly[19].

Conclusions

The CLM syndemic is a growing global health threat that reflects the interdependence of multisystem pathophysiological relationships, nested within wider social determinants of health, and necessitates timely and proactive policy responses. A new approach to CLM health

should involve collaborative, multidisciplinary efforts to understand the root causes of these diseases and their upstream determinants, which will inform the design and implementation of effective healthcare system policy interventions. Holistic approaches to both disease prevention and management are crucial across the micro–meso–macro framework, ranging from the equitable use of cardioprotective therapies with multisystem effects, to the introduction of policies that address the social and commercial determinants of health, with the concerted goal of reducing the global impact of the CLM syndemic in communities, healthcare systems and society at large. As our understanding of the global landscape of the CLM syndrome evolves, the design of clinical trials must follow suit, allowing the inclusion of the full spectrum of people with CLM syndrome, some of whom have been traditionally under-represented in cardiovascular studies.

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Author contributions

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[1]Department of Cardiology, National University Heart Centre, National University Health System, Singapore, Singapore. [2]Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore. [3]Emory Clinical Cardiovascular Research Institute, Division of Cardiology, Department of Medicine, Emory University School of Medicine, Atlanta, Georgia, USA. [4]Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore, Singapore. [5]Ministry of Health Holdings, Singapore, Singapore. [6]Baylor Scott and White Research Institute, Dallas, TX, USA. [7]The Heart Hospital, Plano, TX, USA. [8]Department of Medicine, Baylor College of Medicine, Temple, TX, USA. [9]Division of Gastroenterology and Hepatology, Department of Medicine, National University Hospital, Singapore, Singapore. [10]National University Centre for Organ Transplantation, National University Health System, Singapore, Singapore. [11]Department of Medicine, University of Mississippi, Jackson, MS, USA. [12]Division of Gastroenterology, Hepatology and Nutrition, Department of Internal Medicine, Stravitz Sanyal Institute for Liver Disease and Metabolic Health, VCU School of Medicine, Richmond, VA, USA. [13]Division of Cardiology, Department of Medicine, Emory Clinical Cardiovascular Research Institute, Atlanta, GA, USA. [14]Emory University School of Medicine, Atlanta, GA, USA. [15]These authors contributed equally: Nicholas W. S. Chew, Anurag Mehta, Rachel Goh. [16]These authors jointly supervised this work: Javed Butler, Arun J. Sanyal, Laurence S. Sperling.