A global view of hypertensive disorders and diabetes mellitus during pregnancy

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Abstract | Two important maternal cardiometabolic disorders (CMDs), hypertensive disorders in pregnancy (HDP) (including pre-eclampsia) and gestational diabetes mellitus (GDM), result in a large disease burden for pregnant individuals worldwide. A global consensus has not been reached about the diagnostic criteria for HDP and GDM, making it challenging to assess differences in their disease burden between countries and areas. However, both diseases show an unevenly distributed disease burden for regions with a low income or middle income, or low-income and middle-income countries (LMICs), or regions with lower sociodemographic and human development indexes. In addition to many common clinical, demographic and behavioural risk factors, the development and clinical consequences of maternal CMDs are substantially influenced by the social determinants of health, such as systemic marginalization. Although progress has been occurring in the early screening and management of HDP and GDM, the accuracy and long-term effects of such screening and management programmes are still under investigation. In addition to pharmacological therapies and lifestyle modifications at the individual level, a multilevel approach in conjunction with multisector partnership should be adopted to tackle the public health issues and health inequity resulting from maternal CMDs. The current COVID-19 pandemic has disrupted health service delivery, with women with maternal CMDs being particularly vulnerable to this public health crisis.

Two of the most common cardiometabolic disorders (CMDs) that occur during pregnancy are hypertensive disorders in pregnancy (HDP) and diabetes mellitus. HDP includes chronic hypertension, gestational hypertension and pre-eclampsia–eclampsia. Diabetes mellitus during pregnancy can be pre-existing type 1 diabetes mellitus or type 2 diabetes mellitus (T2DM), or gestational diabetes mellitus (GDM) that develops during pregnancy. This Review focuses on HDP and GDM. HDP and GDM share many common risk factors and similarities in their pathophysiology, including oxidative stress, inflammation and vascular endothelial dysfunction[1]; these two maternal conditions result in a large disease burden for both pregnant individuals and their offspring. Despite decreasing prevalence after years of interventions, HDP remain a leading cause of maternal mortality and morbidity globally, especially in low-income and middle-income countries (LMICs)[2–4]. The prevalence of GDM has increased dramatically over the past two decades by more than 30% in numerous countries[5–7]. These two maternal CMDs are related to substantial short-term and long-term adverse health outcomes for pregnant individuals and their offspring. Individuals with HDP or impaired glucose metabolism during pregnancy experience greater maternal mortality and morbidity rates than people with uncomplicated pregnancies. Furthermore, pregnant people with HDP or impaired glucose metabolism have an increased risk of future CMDs and premature death later in life[8–10]. Negative influences of HDP and hyperglycaemia during pregnancy on fetuses and neonates include, but are not limited to, intrauterine growth restriction (IUGR) and macrosomia, preterm birth, low birthweight and adverse outcomes later in life[11]. Notably, the burden of premature deaths from complications of CMDs in pregnancy and associated cardiovascular disease (CVD) later in life falls disproportionately upon LMICs. Several socioenvironmental factors, including poverty, air pollution, educational and sociocultural barriers, and limitations in health-care access and infrastructure[12], are responsible for such inequities in disease burden.

This Review discusses the global disease burden and risk factors for HDP and GDM, highlighting the

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Key points

- Hypertensive disorders of pregnancy (HDP) and gestational diabetes mellitus (GDM) are common cardiometabolic complications of pregnancy.
- HDP and GDM show an unevenly distributed disease burden (in terms of prevalence, disability-adjusted life years and/or maternal deaths) in low-income and middle-income countries and/or regions with low sociodemographic and human development indexes.
- In addition to common clinical, demographic and behavioural risk factors, the development and clinical consequences of HDP and GDM are substantially influenced by the socioeconomic determinants of health.
- Besides prevention and treatment at the individual level, strategies should also be made at different levels and in conjunction with multisector partnerships to improve societal and community conditions to prevent and/or manage HDP and GDM.

differences between high-income countries (HICs) and LMICs. In addition, we provide policy recommendations regarding public health interventions that can be contextualized and implemented either worldwide or regionally to help reduce the mortality and morbidity related to these maternal CMDs in an efficient and cost-effective manner. We note that, unless otherwise specified, the terms women and men refer to ciswomen and cismen.

Diagnostic criteria

HDP. Comprising chronic hypertension, gestational hypertension and pre-eclampsia–eclampsia, the precise definition and classification of HDP is evolving over time, especially for pre-eclampsia. Pre-eclampsia is not a single disorder but a variety of pathophysiological pathways that converge on a common syndromic end point, of high blood pressure occurring with proteinuria after 20 weeks of pregnancy[13]. In the past 10 years, the definition of pre-eclampsia has been extended to include individuals without proteinuria but with evidence of maternal end-organ or uteroplacental dysfunction[14]. Two of the broad definitions adopted by most clinical practice guidelines and authorities are those of the International Society for the Study of Hypertension in Pregnancy[15] and the American College of Obstetricians and Gynecologists[16] (Supplementary Table 1). The application of these broad definitions of pre-eclampsia means patients once diagnosed with gestational hypertension or chronic hypertension were recategorized as pre-eclampsia or chronic hypertension with superimposed pre-eclampsia, respectively[17–21]. This diagnostic shift will influence clinical management (for example, increased hospital admission and induction of labour)[17]. Although the debate is still ongoing on these new classification systems, studies published in 2021 revealed that a broad definition of pre-eclampsia could better identify women and babies at risk of adverse outcomes[22,23].

GDM. The diagnostic criteria for GDM have also evolved (Supplementary Table 2) These criteria are usually based on glucose thresholds for oral glucose tolerance tests. Currently, the screening and diagnostic approaches for GDM are under debate[24–32] given differences in the focus of different guidelines. For example, the ability of the diagnostic criteria to predict the risk of adverse maternal and neonatal outcomes[33–35] versus the maternal risk of developing T2DM in the future[36–38]. Adopting broad definitions of GDM might result in a considerable increase in the prevalence and incidence of GDM[26,39], with potentially increased health-care costs[40] and psychological stress in women and their families[41]. However, many researchers consider GDM treatment highly cost-effective when the benefits of future maternal T2DM and childhood obesity risk reduction are taken into account[32,42–45]. Therefore, a majority of health authorities, such as the WHO and the American Diabetes Association, have come to support the broad criteria, such as the criteria of the International Association of the Diabetes and Pregnancy Study Groups (IADPSG)[26,39].

Disease burden

HDP. HDP are among the leading causes of maternal and fetal morbidity and mortality worldwide[3], responsible for an estimated 14% of maternal deaths globally. Despite a much lower maternal mortality in HICs than in LMICs, HDP remains one of the most common causes of maternal death worldwide[2–4]. The proportion of maternal deaths from HDP was 2.8% in the UK and Ireland (2011–2013), whereas maternal mortality related to HDP ranged between 0.08 and 0.42 per 100,000 pregnancies between 2009 and 2015 (REF.[46]). The proportion of maternal deaths attributable to HDP is 7.4% in the USA, accounting for an estimated one-fifth of antenatal admissions and two-thirds of referrals to daytime assessment units[4]. In France, HDP account for one-quarter of obstetric admissions to intensive care units[4]. In contrast, in LMICs, 10–15% of direct maternal deaths are associated with HDP[3,4]. Therefore, epidemiological surveillance of HDP is crucial for perinatal health care all over the world.

To illustrate the global prevalence of HDP, we extracted data on prevalence, death and disability-adjusted life years (DALYs) from the Institute for Health Metrics and Evaluation (IHME) Global Burden of Disease (GBD) 2019 report[47]. The GBD report estimates health loss due to 369 diseases and injuries for more than 200 countries and territories all over the world. A critical resource for informed policy making, the GBD report is aimed at improving health systems and eliminating health inequities[48]. Globally, the prevalence of HDP is 116.4 per 100,000 women of childbearing age. At the regional level, Africa had the highest prevalence of HDP, with a mean prevalence of 334.9 per 100,000 women of childbearing age, followed by Southeast Asia

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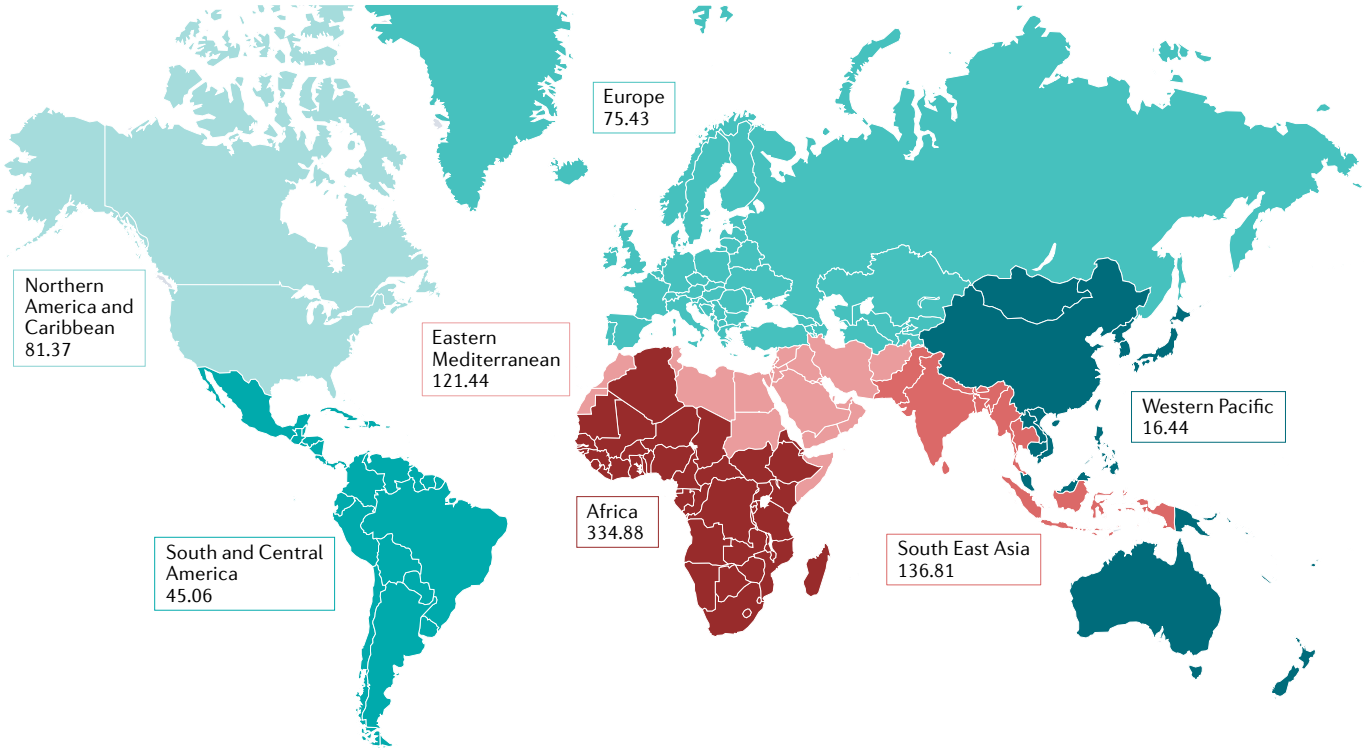

Fig. 1 | **Prevalence of hypertensive disorders of pregnancy (per 100,000 women of childbearing age) in 2019 by WHO region.** The mean prevalence of hypertensive disorders in pregnancy (HDP) shows a state of inequity among different regions worldwide. Africa has the highest mean prevalence of HDP, which is far higher than in other regions. It is followed by South East Asia and Eastern Mediterranean, which have a mean prevalence of HDP of over 0.1% among women of childbearing age. The Western Pacific has the lowest mean prevalence of HDP. Data were originally presented in REF.[48].

and the Middle East, with mean prevalences of 136.8 and 121.4 per 100,000 women of childbearing age, respectively. Conversely, the Western Pacific region had the lowest prevalence of HDP at 16.4 per 100,000 women of childbearing age (FIG. 1). A great disparity exists between HICs and LMICs regarding the disease burden of HDP (TABLE 1).

To further illustrate potential differences in disease burden of HDP at the country level, we stratified the disease burden (prevalence, DALYs and death) of HDP by country and sociodemographic index (SDI) and human development index (HDI), respectively. Countries with lower SDI and HDI generally had a greater disease burden of HDP than those with higher SDI and HDI, demonstrated by a higher prevalence, DALYs and death attributable to HDP (FIGS. 2–4). These data are consistent with those of other studies[49]. The WHO's estimate of the incidence of HDP in developing countries is 2.8% of live births, compared to an incidence of 0.4% of live births in developed countries[3]. A 2021 study investigating the epidemiological trends of HDP by using the GBD data showed that the death and incidence rates of HDP are decreasing in most countries and all regions except for those with low SDI and HDI[49].

GDM. The global prevalence of GDM has also steadily increased in the past four decades. Depending on the diagnostic criteria used, 9–25% of pregnancies are affected by GDM[50]. According to a global observational study, the prevalence of GDM ranged between 9% and 26% in 15 centres[51]. The rapid global increase in GDM occurring within the past few decades has created an emerging epidemic in both HICs and LMICs[52]. We extracted data related to pre-existing diabetes mellitus in pregnancy and GDM from the International Diabetes Federation report (10th edition)[53] (FIG. 5). Southeast Asia had the highest prevalence of GDM, with a median estimate of 25.9%, followed by the North American and Caribbean regions (median prevalence 20.7%). With a median prevalence of 14.0%, the Western Pacific had the lowest prevalence of GDM. These data are comparable to those of previous studies[7,54]. A great disparity exists between HICs and LMICs regarding the disease burden of GDM (TABLE 2). However, given different diagnostic criteria for GDM used by different countries, strict cross-country/region comparisons are difficult to interpret (FIG. 6).

Risk factors

Common risk factors. HDP and GDM share several risk factors, including advanced maternal age[55–64], overweight or obesity[56,63,65–70], nutrition (such as reduced calcium and vitamin D_3 intake[71–77]) and dietary patterns before and/or during pregnancy. For instance, a low intake of fruit, green leafy vegetables, poultry and fish, and high consumption of the Western dietary pattern (characterized by a high intake of red meat, processed meat, refined grain products, high-fat and/or high-sugar processed food) might be associated with an elevated risk of HDP and GDM[78–87] (FIG. 7).

Some obstetric complications and situations, including primiparity[56,58,88–91], multifetal pregnancy[56–58,88,91] and history of GDM[56,91,92], are related to the development of HDP[16,56,65,66,88,90,91,93–97]. Other risk factors for HDP include a previous history of HDP[93,98,99], a family history of HDP[93] and pre-existing diseases, such as chronic hypertension, pregestational diabetes mellitus, thrombophilia, systemic lupus erythematosus, antiphospholipid antibody syndrome, kidney disease and obstructive sleep apnoea[16,93,94,97]. Smoking has been revealed to be a potential protective factor for HDP[100], but the evidence of the association between smoking during pregnancy and HDP remains controversial[101,102].

In terms of GDM, a previous history of GDM and a family history of diabetes mellitus might increase the risk of developing GDM in a current pregnancy[63]. Other potential risk factors include carrying a male fetus[103–106], parity[7] and polycystic ovarian syndrome[107], although some evidence is not very consistent[108]. By contrast, physical activity before and during pregnancy was reported to be associated with a decreased risk of GDM[80,109–111].

Race, ethnicity, socioeconomic and environmental factors. Debate is ongoing on the role of race and/or ethnicity in the development of maternal CMDs. Certain ethnic and racial groups have been widely reported to have a disproportionately increased disease burden of maternal CMDs. For example, African American women and Filipino women have an increased risk of developing HDP[112–114]. Higher incidence rates of HDP have also been found in Māori, Indigenous Australian, American Indian and Alaskan Native populations[94,115–117], whereas the risk of HDP in Pacific Islander populations is still controversial[118,119]. Racial and ethnic groups with an increased risk of developing GDM include Indigenous Australian, Pacific Islander, South or East Asian, Middle Eastern, Hispanic and African populations[6,120–128]. However, whether race and/or ethnicity are independent, genetically determined risk factors for maternal CMDs is controversial. Researchers have found that individuals of African Caribbean origin have a higher risk of developing HDP than white individuals, even after adjusting for markers of social deprivation[129]. Some biomarkers of disease risk have also been found to vary according to racial origin. For instance, circulating levels of placental growth factor (PlGF) in Black women and South and East Asian women are higher than in white women[130]. Some genetic variants have been reported to be associated with HDP in women with GDM[1], including the *MIR146A* rs2910164CC[131], *HNF1A* p.I27LTT[132] and *ACE* I/D polymorphism DD[133] genotypes. Of note, race can be considered as a social construct rather than a biological construct[114,134], as race is a socially derived label that can either be self-reported or assigned and might not justify any biological or genetic differences between populations[135,136]. For example, many population studies found more genetic variations within racial groups than among them[137,138].

The social determinants of health (SDOH)[139] are defined as the non-medical conditions in which people are born, grow, work, live and age, as well as the broader set of forces and systems that shape daily life conditions. According to Healthy People 2030 (REF.[140]), SDOH can be grouped into five domains: economic stability, education access and quality, health care and quality, neighbourhood and built environment, and social and community context. These factors influence health outcomes and therefore have an important influence on health inequities. The association of maternal social adversities and unfavourable pregnancy outcomes with offspring health has been widely studied and established. For example, social stress, malnutrition during pregnancy and environmental toxins have been proposed as three SDOH factors that might affect placental health[141]. In accordance with epigenetic drivers and genetic predisposition, maternal social adversities result in insidious placental changes and/or malfunction and could lead to adverse outcomes during pregnancy and beyond.

Certain racial and/or ethnic groups have an increased prevalence of maternal CMDs, but, as mentioned above, this phenomenon cannot be fully explained by genetic background. In the Generation R study[142,143] (a large population-based California cohort of singleton births)[144], Black women had an increased risk of HDP compared with white women. Higher socioeconomic status (SES), whether indicated by education or insurance status, further reduced the risk of HDP in white pregnant individuals, which in turn indirectly predicted longer gestation length. High SES is not as health-protective for Black individuals, which might be explained by structural and cultural forms of racism they experience despite their SES[144]. HDP was found to mediate the association between racial residential segregation and low birthweight among Black women in New York City, USA[145]. Furthermore, racial residential segregation was associated with higher odds of HDP in areas with higher neighbourhood poverty rates than in those with lower rates[146], which had implications for racial disparities in adverse pregnancy outcomes and CVD later in life. The stress of systemic racial disparities, such as poverty, living in racially segregated neighbourhoods, a lack of access to health-care services and experience of discrimination, can all negatively affect the health of women of certain ethnic groups, such as non-Hispanic Black women[147].

Evidence also supports associations between SDOH and diabetes mellitus-related outcomes[148]. Inequities in SDOH notably impact disparities in diabetes mellitus risk, diagnosis and outcomes[149,150], and diabetes mellitus during pregnancy is no exception[151]. Disparities

Table 1 | **The prevalence, mortality, years of life lost and disability-adjusted life years of hypertensive disorders in pregnancy**

Country category	Prevalence (per 100,000 women of childbearing age)	Mortality (per 100,000 women of childbearing age)	YLLs	DALYs
HICs	70.3	0.09	4.9	8.4
MICs	106.0	1.2	71.2	76.5
LICs	286.4	3.1	177.4	191.7
Global	116.4	1.2	70.7	76.5

DALYs, disability-adjusted life years; HICs, high-income countries; LICs, low-income countries; MICs, middle-income countries; YLLs, years of life lost. Data were originally presented in REF.[48].

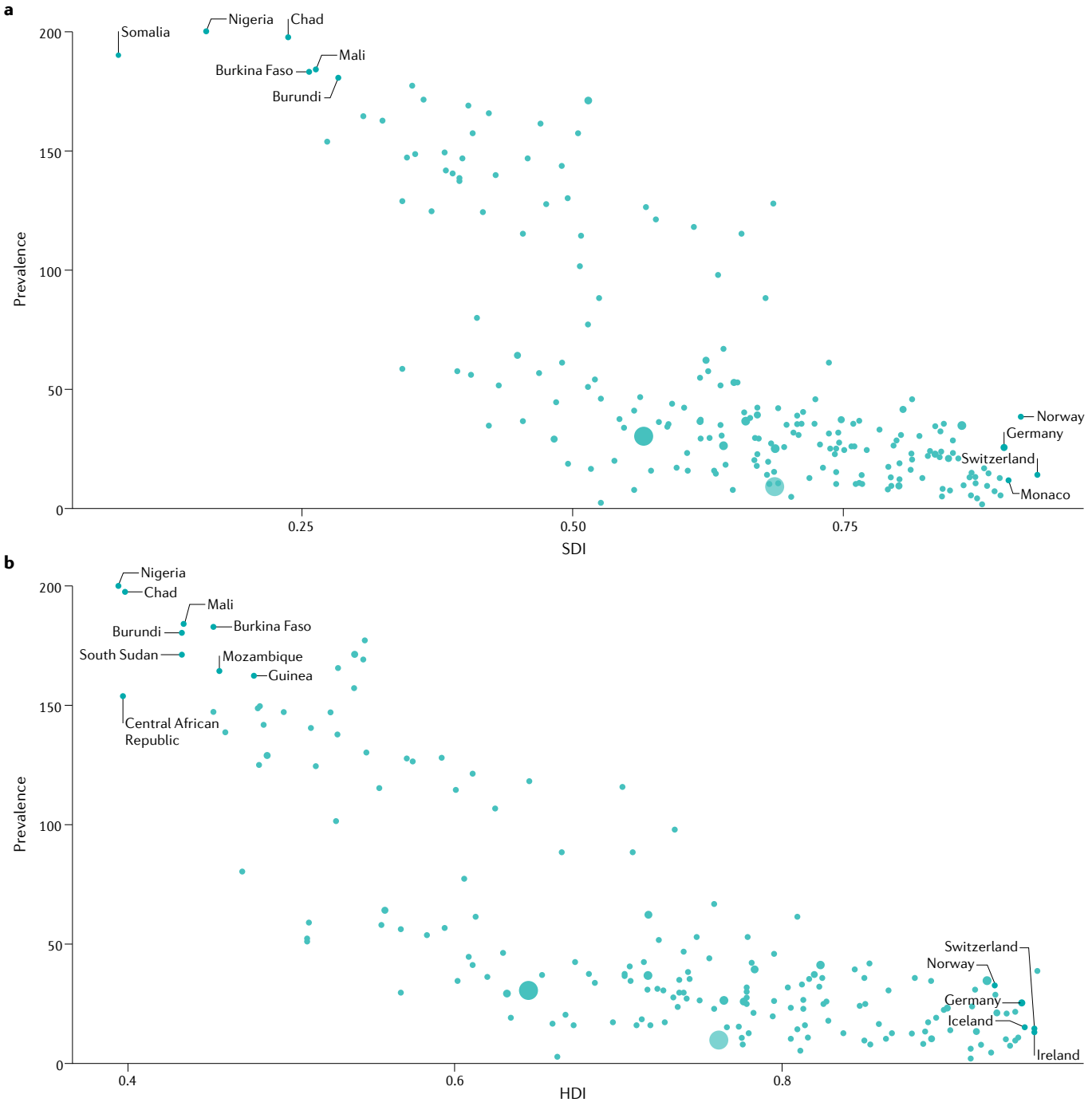

Fig. 2 | **The prevalence of hypertensive disorders of pregnancy by country and region in relation to the sociodemographic index and human development index in 2019.** Each dot indicates the prevalence of hypertensive disorders in pregnancy (HDP) in a particular country or region in relation to the sociodemographic index (SDI; part **a**) and human development index (HDI; part **b**) in 2019. The size of each dot reflects the total population of the corresponding country or region. Notable countries and regions are labelled. Countries and regions with the lowest SDI and/or HDI have the highest prevalence of HDP, including Somalia, Nigeria, Chad, Burkina Faso, Mali and Burundi. Data were originally presented in REF.[48].

in SDOH can lead to different maternal and neonatal outcomes in pregnant women with diabetes mellitus. SES factors, such as education, occupation and household income, have been reported to be associated with GDM[152], but study findings are inconsistent[6,143,153–157]. Some environmental factors, such as passive smoking[156] and exposure to persistent organic pollutants (POP) or endocrine disruptors[158,159], might contribute to an increased risk of developing GDM. A prospective study demonstrated a modest association between depressive symptoms early in pregnancy and an increased risk of incident GDM, particularly in women without obesity and women with persistent depressive symptoms throughout the first two trimesters of pregnancy[160].

The association between air pollution and maternal CMDs is a frequent topic of investigation. Several studies

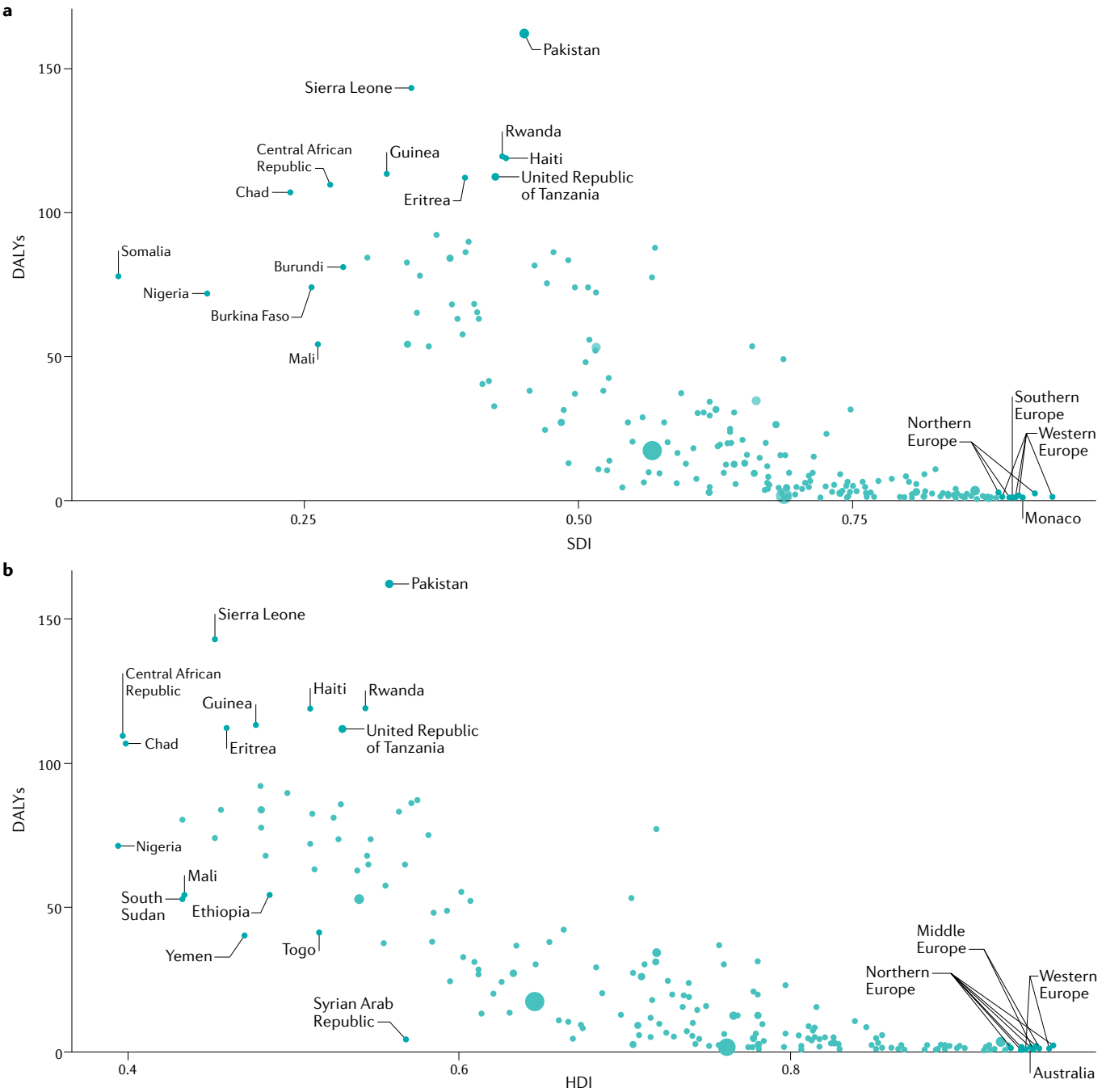

Fig. 3 | **Disability-adjusted life years attributable to hypertensive disorders of pregnancy by country and region in relation to the sociodemographic index and human development index in 2019.** Each dot indicates the disability-adjusted life years (DALYs) due to hypertensive disorders of pregnancy (HDP) in a particular country or region in relation to the sociodemographic index (SDI; part **a**) and human development index (HDI; part **b**) in 2019. The size of each dot reflects the total population of the corresponding country or region. Notable countries and regions are labelled. Countries and regions with low SDI and/or HDI have high DALYs attributable to HDP, including Pakistan, Sierra Leone, Rwanda, Haiti and Guinea. Data were originally presented in REF.[48].

have shown relationships between perinatal exposure to particulate matter ≤2.5 μm in size ($PM_{2.5}$) and placental oxidative stress, DNA damage, inflammation, hypercoagulation and thrombosis[161–166], all of which are considered factors associated with the occurrence of maternal CMDs. A systematic review and meta-analysis included 11 studies and found that $PM_{2.5}$, nitrogen oxides and SO_2 exposure increased the risk of GDM[167]. Another study investigated the association between indoor air pollution and pre-eclampsia and indicated a twofold greater risk of reporting pre-eclampsia symptoms in women living in households using biomass and solid fuels than those living in households using clean fuels[168]. A systematic review was conducted on environmental contaminants and pre-eclampsia, which included studies examining POPs (six studies), drinking water contaminants (one

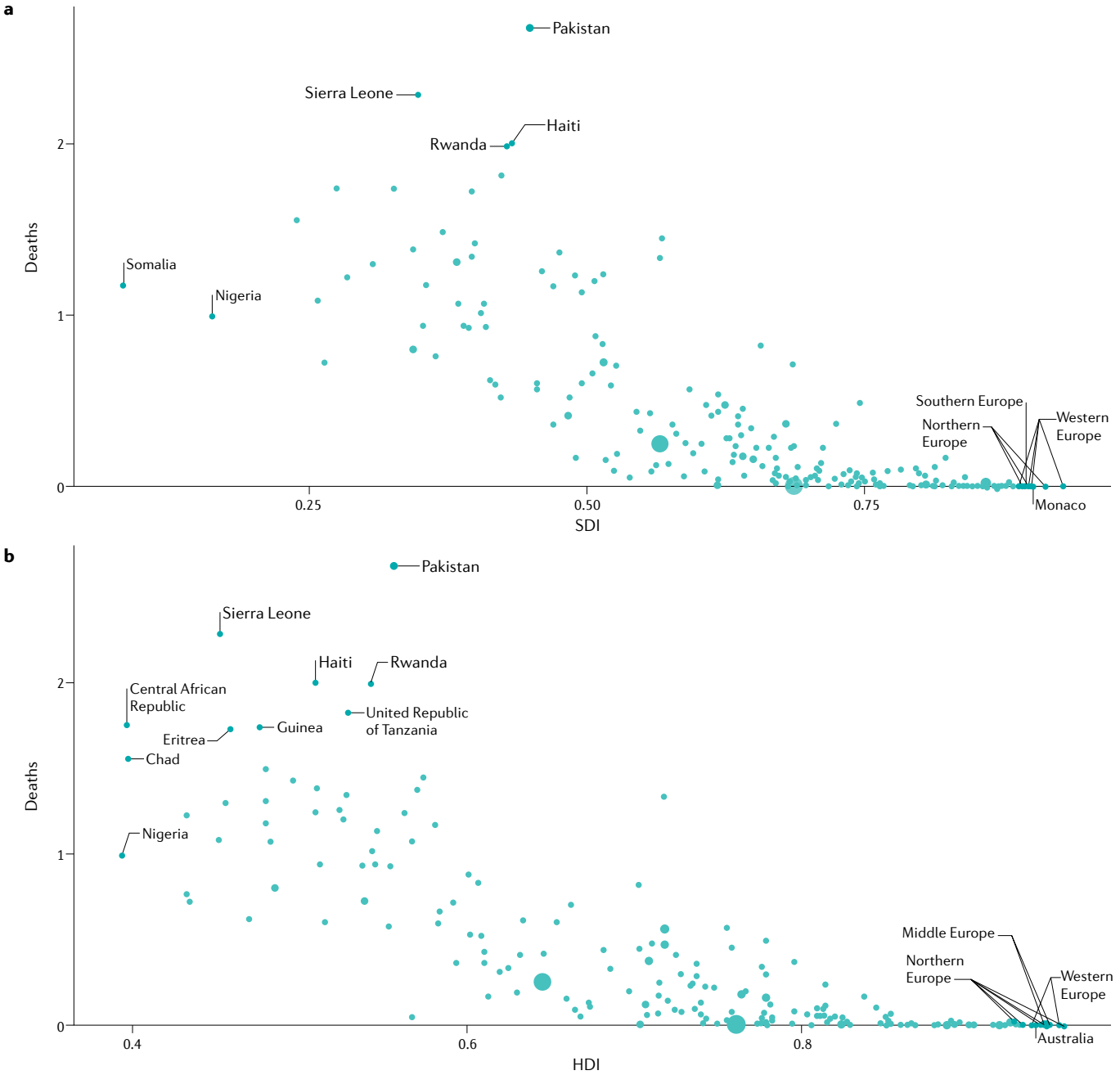

Fig. 4 | **Maternal deaths attributable to hypertensive disorders of pregnancy by country and region in relation to the sociodemographic index and human development index in 2019.** Each dot indicates the maternal deaths attributable to hypertensive disorders in pregnancy (HDP) in a particular country or region in relation to the sociodemographic index (SDI; part **a**) and human development index (HDI; part **b**) in 2019. The size of each dot reflects the total population of the corresponding country or region. Notable countries and regions are labelled. Countries and regions with low SDI and/or HDI have high numbers of maternal deaths attributable to HDP, including Pakistan, Sierra Leone, Rwanda and Haiti. Data were originally presented in REF.[48].

study), atmospheric pollutants (11 studies), metals and metalloids (six studies), and other environmental contaminants (four studies)[169]. Although definitive conclusions could not be drawn on most chemicals due to the insufficiency of investigations, nitrogen dioxide, $PM_{2.5}$ and traffic exposure were suggested to be associated with pre-eclampsia. Similarly, the impact of environmental chemicals (for example, bisphenol A, phthalates and toxic metals) on the development of GDM is not consistent among studies[170]. In general, the current evidence is highly heterogeneous. Moreover, humans are exposed to complex mixtures of various environmental contaminants, making it difficult to isolate the effect of a single chemical from those of other unknown or unmeasured co-exposures. Studies large enough to give rise to an adequate number of maternal CMD cases and equipped with robust methodology are needed to identify or confirm the relationship of maternal CMDs and

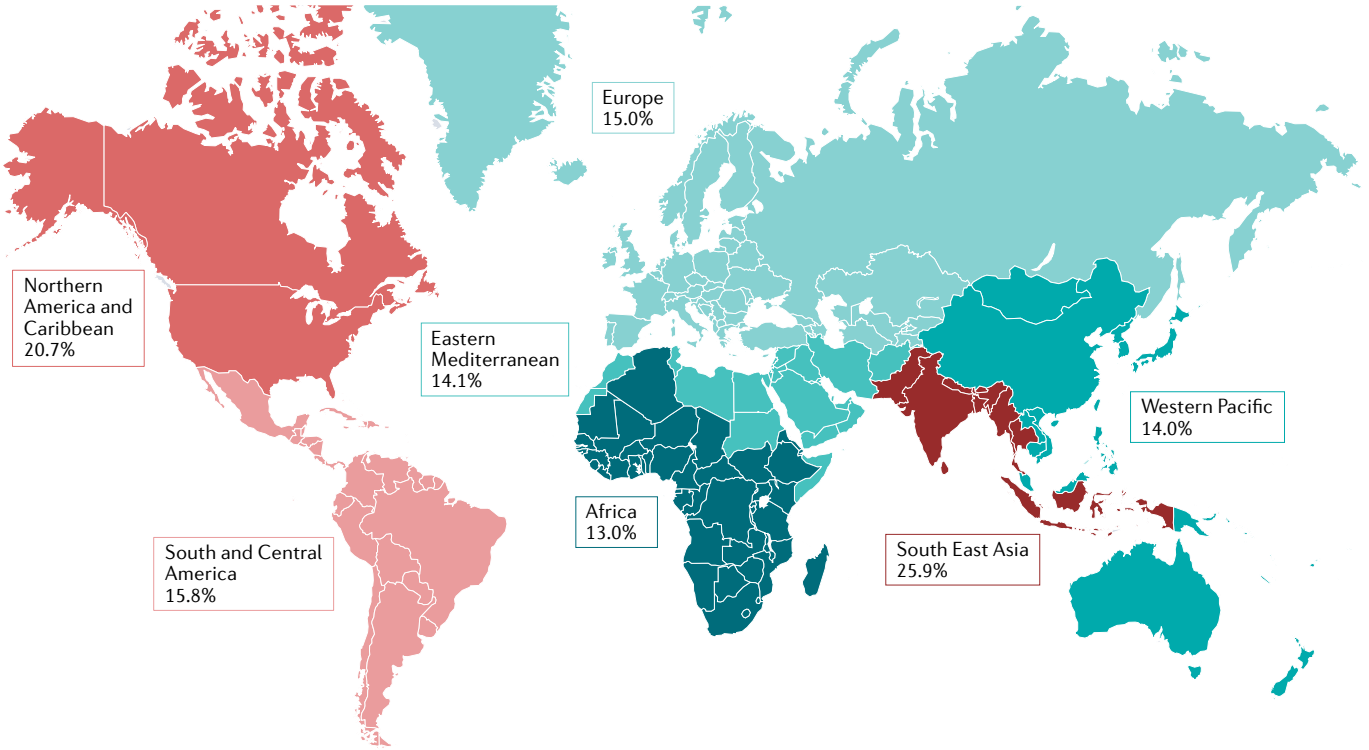

Fig. 5 | **Prevalence of gestational diabetes mellitus in 2021 by WHO region.** The mean prevalence of gestational diabetes mellitus (GDM) (the percentage of all pregnant women with GDM) shows a state of inequity among different regions worldwide. South East Asia has the highest mean prevalence of GDM, followed by North America and the Caribbean. Africa has the lowest mean prevalence of GDM. Data were originally presented in REF.[53].

environmental pollutants, to inform policy making or to develop behavioural interventions.

Clinical consequences

Maternal CMDs, such as HDP and GDM, can lead to various obstetric complications such as preterm birth, placental abruption and postpartum haemorrhage[33,171]. Furthermore, they can have negative perinatal outcomes for both the mother and the fetus or neonate, such as maternal end-organ injuries, maternal death, IUGR, large for gestational age, shoulder dystocia, hypoglycaemia, birth asphyxia, respiratory distress syndrome[33,171,172], congenital malformations in neonates[173,174], stillbirth and neonatal death. Importantly, these complications might generate long-term health problems for these mothers and their offspring.

Women with a history of HDP are more likely to have recurrent HDP in subsequent pregnancies, and this risk increases with decreasing gestational age at delivery in the index pregnancy[175]. HDP is also independently associated with a higher risk of T2DM in the future[176]. Moreover, women with a history of HDP are at a higher risk of developing hypertension, CVD and CVD-related morbidity and mortality than women with uncomplicated pregnancies[97,177–188] (Supplementary Table 3). GDM had similar effects on the risk of women developing future CVDs[189,190] (Supplementary Table 4), independent of obesity and at a fairly young age[191–194]. Women with GDM have a much higher risk of developing impaired glucose tolerance and T2DM in later life than women with uncomplicated pregnancies[7,195–201] (Supplementary Table 5). This risk is especially high for individuals with a high severity or postpartum continuation of glucose intolerance and high BMI[199–201]. The diagnosis of GDM early in pregnancy, such as during the first half of pregnancy, might increase the risk of developing diabetes mellitus later in life[202]. However, the evidence is inconsistent[203].

The theory of developmental origins of health and disease underlines the role of both prenatal and postnatal environments in shaping developmental trajectories on long-term health[204]. Available evidence has indicated, in addition to affecting the long-term health of mothers, that maternal CMDs could exert harmful health burdens on their offspring later in life. Neonates exposed to HDP might have higher blood pressure when entering adolescence than neonates from healthy pregnancies[205–208]. Evidence also exists of a link between HDP and later-life CVD and cerebrovascular disease in pregnant individuals, although it is unclear whether HDP impair the maternal CVD system and result in future CVD in these pregnant individuals, or whether they share common risk factors[209]. Maternal diabetes mellitus, regardless of the type (that is, pre-existing type 1 diabetes mellitus or T2DM, or GDM), has long-term effects on the risk of diabetes mellitus and obesity in offspring[172,210–216].

In the past decade, long-term neurological and psychiatric outcomes in neonates born to mothers with maternal CMDs have received much attention. The

offspring of women with HDP are reported to be at a greater risk of developing cognitive and psychiatric disorders, such as autism spectrum disorder (ASD), attention-deficit–hyperactivity disorder (ADHD)[217–219] or epilepsy during their later life[220]. Evidence is also emerging of the relationship between GDM and neuropsychiatric conditions in children. A 2021 systematic review found an increased risk of developing ASD but not ADHD in offspring when exposed to GDM[221]. Of note, the role of confounders, mediators and effect modifiers (for example, gestational age at birth, birthweight and SES) were not explored in many of these studies, making it difficult to interpret the current findings.

Prevention and treatment

Given the large disease burden following maternal CMDs such as HDP and GDM, for decades, researchers have explored treatments that can not only solve short-term problems but also prevent or improve long-term health outcomes for mothers with maternal CMDs and their offspring.

Treatment of maternal CMDs in the clinical setting. Currently, several treatment strategies for HDP are applied in the clinical setting, such as calcium, vitamin D or folic acid supplementation, or treatment with aspirin or anti-platelet agents (Supplementary Table 6). Other novel approaches have been investigated in clinical or preclinical studies for their benefits in preventing or treating HDP, including metformin[222–227], pravastatin[228–233], proton pump inhibitors[234–236], sulfasalazine, antioxidants (for example, melatonin, MitoQ, polyphenols, and vitamins C and E)[237], sildenafil citrate[238,239] and biological therapies (such as monoclonal antibodies)[240,241]. Placenta-specific drug delivery systems, such as the application of nanoparticles, have also been developed to prevent off-target effects from the systemic administration of certain medications. Several animal studies (most commonly using mice or rats) in this area have been performed; for example, using polyamidoamine to carry short-interfering RNA to silence the gene encoding soluble fms-like tyrosine kinase 1 (*FLT1*) and to decrease secretion of the gene product[242]. Furthermore, synthetic placental chondroitin sulfate A-binding peptide has been used to target trophoblasts[243]. Preclinical studies of monoclonal antibodies targeting tumour necrosis factor, PlGF and complement are underway as well[237]. Of note, current studies on placenta-targeted treatments, which might enable safe and efficient delivery of therapeutic drugs to improve pregnancy outcomes, mainly focus on short-term health outcomes (for example, fetal growth or birthweight)[244]. The choice of the most appropriate time point and the dosage and frequency to administer therapeutic interventions and the assessment of the long-term effects of these treatments on improving later-life health outcomes in offspring remain challenges in this area.

Table 2 | **Comparison of the prevalence of gestational diabetes mellitus in countries of different development levels**

Country category	Number of pregnant women	Number of GDM cases	Prevalence (%)
LICs	22,370,178	3,017,877	13.5
MICs	31,7016,513	59,085,420	18.6
HICs	61,351,133	10,012,680	16.3
Global	400,737,825	72,115,977	16.7

GDM, gestational diabetes mellitus; HICs, high-income countries; LICs, low-income countries; MICs, middle-income countries. Data were originally presented in REF.[53].

Treatments for GDM aim to achieve satisfactory glycaemic control to improve the short-term and long-term health of both mothers and babies. A wide variety of management strategies, from lifestyle interventions (such as diet and exercise) to pharmacological medications (such as metformin and insulin), have been assessed for their effectiveness and safety. A package of care (a combination of treatments starting with dietary modifications and/or exercise and/or pharmacological treatments) is effective in reducing the risk of most adverse perinatal outcomes of GDM, but the evidence is of low quality[245]. An overview of Cochrane reviews also found there is insufficient high-quality evidence about the effects of various interventions in GDM[246].

Prevention and long-term management of maternal CMDs. To date, very limited evidence exists regarding effective approaches for preventing the development of maternal CMDs and their negative health outcomes. An overview of Cochrane reviews was conducted on the effects of various interventions (diet, exercise, diet and exercise combined, dietary supplements, pharmaceutical management such as metformin, and the management of other health issues) for preventing GDM[247]. The researchers found effects only for combined diet and exercise interventions during pregnancy and supplementation with *myo*-inositol, vitamin D and treatment with metformin, but the evidence was of low to moderate quality. In another Cochrane review[248], the average risk reduction from lifestyle interventions on HDP was 0.70 (95% CI 0.40–1.22; four trials, 2,796 women; $I^2 = 79\%$; low-quality evidence). The long-term impact of lifestyle interventions on neonates, such as diabetes mellitus and adiposity in adulthood and neurosensory disability in later childhood, is rarely reported.

Lifestyle interventions include a wide variety of components (for example, education, diet, exercise and self-monitoring of blood levels of glucose). Currently, no clear evidence is available of the effectiveness of lifestyle interventions in preventing the development of HDP. Probiotic-related interventions that target the microbiota might be able to improve glycaemic control in women with GDM[249]. However, many aspects of probiotic intervention remain unclear, including the underlying mechanism, type, dose and duration of probiotics that are safe for administration during pregnancy, and whether the offspring of mothers with GDM could have long-term benefits from probiotic interventions[249,250].

Contrary to the great achievements that have been made by health professionals in understanding and managing CMDs in pregnancy, patient education lags greatly[251,252]. Self-management involving lifestyle

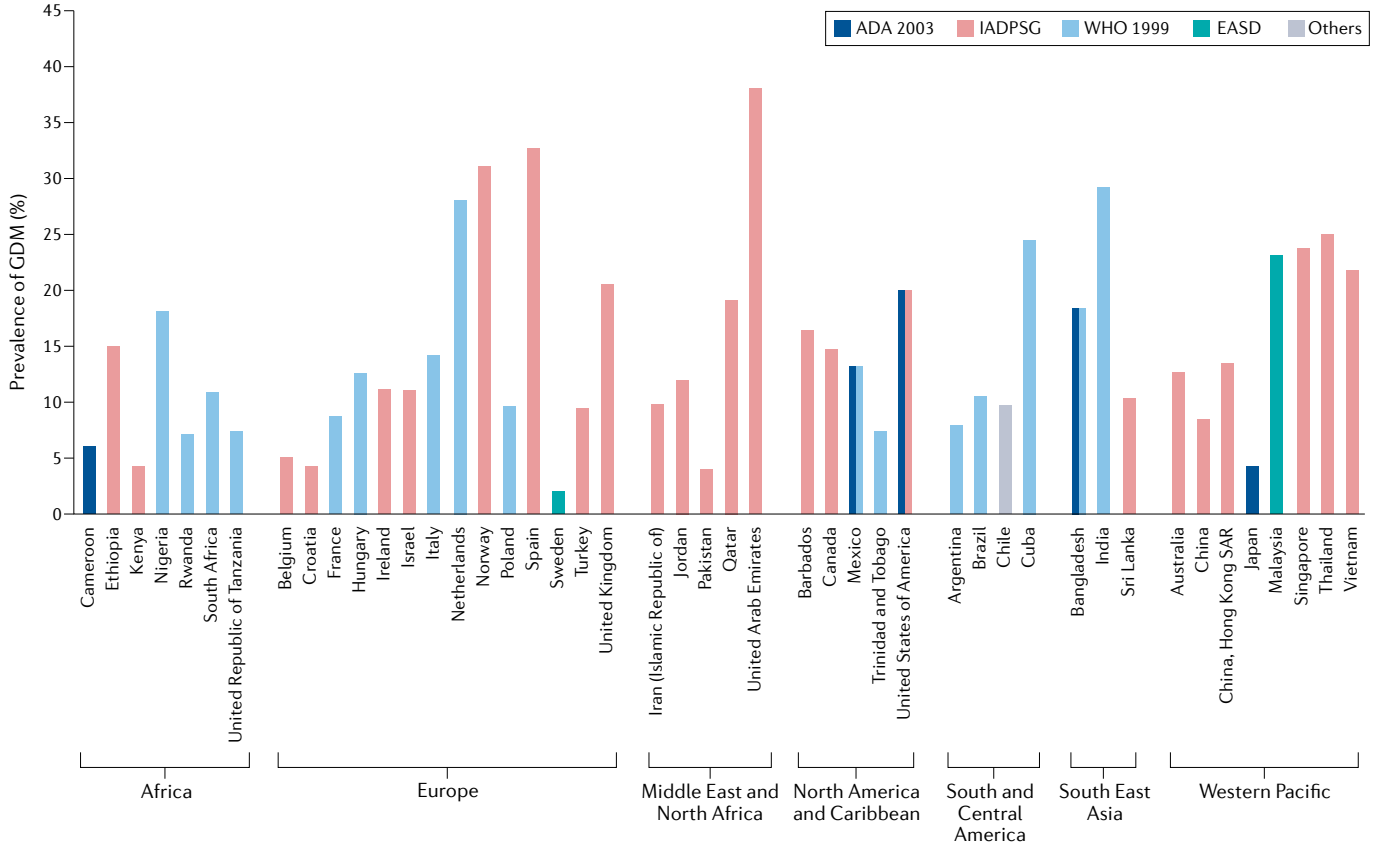

Fig. 6 | **Prevalence of gestational diabetes mellitus by WHO region.** Prevalence of gestational diabetes mellitus (GDM) in pregnant women by country according to different diagnostic criteria: American Diabetes Association (ADA), International Association of the Diabetes and Pregnancy Study Groups (IADPSG), WHO, European Association for the Study of Diabetes (EASD), and other International Classification of Diseases codes and local guidelines or criteria (Others). SAR, Special Administrative Region. Data were originally presented in REF.[53].

modification and regular glucose monitoring is crucial for the management of pre-existing diabetes mellitus in pregnancy and GDM[253]. Improved understanding of GDM, nutrition and self-management principles may result in improved glucose levels and a reduction in the number of individuals requiring insulin treatment[254–257].

Interventions for maternal CMDs from the public health perspective. CMDs in pregnancy have already become a complex public health issue since they result in an increased disease burden and generate a profound impact on health worldwide. To tackle this public health problem and reduce disparity, a multilevel approach[258] should be adopted. In addition to prevention and treatment at the individual level by addressing individual lifestyle and behavioural factors that influence health, strategies should be made at different levels and in conjunction with multisector partnerships to improve societal and community conditions by addressing the SODH.

Obesity[56,65–67] and certain dietary patterns such as the Western dietary pattern[85] are risk factors for hypertension and hyperglycaemia in pregnancy. Calcium insufficiency[71], and extremely young maternal age[55,56,58] are also recognized risk factors for HDP. Policies and measures to ensure food security, to help with dietary diversity and to delay marriage or first pregnancy (for example, until after 20 years old) might therefore help reduce the disease burden arising from CMDs in pregnancy. Although study findings have been inconsistent[6,143,153–157], poverty and poor living conditions might be associated with the development of CMDs in pregnancy[153]. Given that environmental factors such as indoor air pollution[168], passive smoking[156], POPs, and endocrine disruptors[158,159] might contribute to an increased risk of developing either HDP or GDM in pregnancy, legislation, policies, interventions and advocacy activities for smoking cessation and pollution control might lead to a decreased incidence of these two disorders.

At the community and healthcare facility level, early detection and proper management of CMDs during pregnancy, tailored to various settings and populations are crucial. In resource-limited areas where multiple clinic visits might not be possible, a point-of-care approach could be adopted. In addition, rural health workers should receive enhanced training to improve community-level detection and management of CMDs in pregnancy. For example, the community-level interventions for pre-eclampsia (CLIP) trials in Mozambique, Pakistan and India involved community engagement and task sharing with community health workers for triage and initial treatment of HDP in the local pregnant

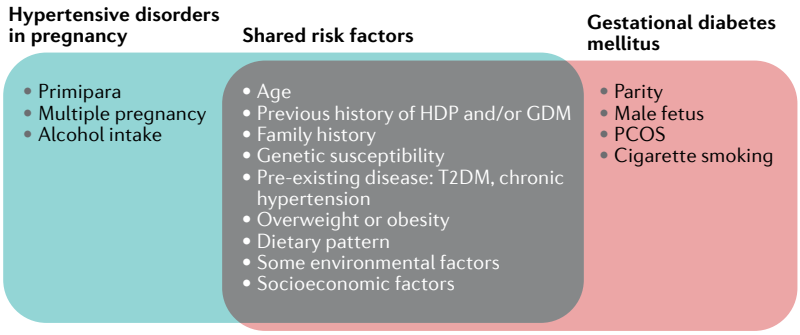

Fig. 7 | **Major risk factors for maternal cardiometabolic disorders.** Common risk factors for hypertensive disorders in pregnancy (HDP) are shown on the left, and common risk factors for gestational diabetes mellitus (GDM) are shown on the right. The overlapping area in the centre shows the risk factors shared by both HDP and GDM. PCOS, polycystic ovary syndrome; T2DM, type 2 diabetes mellitus.

population. The findings from the CLIP trials suggest that community-level interventions for women with HDP can be successfully completed by community health workers, but their numbers must be adequate to provide at least eight antenatal care contacts to reduce adverse outcomes[259]. Among women who received eight or more CLIP contacts (four in Pakistan), the probability of health system and family cost-effectiveness was ≥80%[260]. However, the CLIP study did not generate a statistically significant reduction in all-cause maternal and perinatal mortality or morbidity. This finding suggests that a focus only on community-level intervention without facility enhancement is inadequate to improve maternal and neonatal outcomes[259].

Several successful community-based GDM programmes have been conducted, some of which targeted specific at-risk groups and addressed health inequities. For instance, a programme with diabetes mellitus-specific infrastructure including certified diabetes educator visits and diabetes group visits was carried out in a high-risk population of pregnant Latino women, and demonstrated improved glycaemic control[261]. Successful community-based diabetes mellitus programmes can serve as models for programmes targeting diabetes mellitus in pregnancy. Consulting and mobilizing effective and existing community and village leadership and infrastructure enables the delivery of community-based programmes. Several key elements must be in place to implement these community-based programmes: first, a data collection and tracking system to capture and record the information from all sources of patient care, interactions and outcomes that the programme aims to achieve; second, a well-structured staff team; third, a training schedule for all who will be participating in programme delivery; fourth, health system integration via a shared electronic medical system; fifth, the identification of additional local resources that are easily available to patients to assist them in achieving their clinical and behavioural goals; and finally, ongoing communication among all parties. Furthermore, low-cost devices (such as an alert device or urinalysis device) and mobile health technologies can also have important roles in improving the outcomes of CMDs during pregnancy in remote and resource-limited areas.

The current COVID-19 pandemic has greatly disrupted health service delivery due to lockdown policies, overwhelmed health-care systems and exhausted health-care providers among other effects, such as exacerbation of poverty. Maternal and neonatal health services are no exception, particularly in resource-limited countries[262]. A prospective observational study was conducted in Nepal[263], which collected participant-level data for pregnant women enrolled in two other studies during the COVID-19 pandemic. The study found that institutional childbirth was reduced by more than half during lockdowns, along with an increase in the institutional stillbirth rate and neonatal mortality and decreased quality of care. Women with CMDs, such as HDP and GDM, in pregnancy are at a higher risk of adverse perinatal outcomes than those with uncomplicated pregnancies and require more intensive antenatal care. The COVID-19 pandemic might therefore generate large negative impacts on this population.

In terms of maternal CMDs, it was found that COVID-19 and pre-eclampsia impact perinatal outcomes (such as preterm birth, severe perinatal morbidity and mortality) in an additive fashion[264]. T2DM is one of the characteristics of patients who are at high risk of severe COVID-19 or death[265–268]. However, there are only a limited number of studies in women with GDM who are also infected with SARS-CoV-2. In the context of this and future pandemics, especially when the lockdown of general services occurs, it can be challenging for pregnant women to receive an oral glucose tolerance test and for those with hyperglycaemia in pregnancy to receive relevant health service visits for diabetes education, glucose monitoring review, fetal ultrasonography and eye testing[269]. All these factors might lead to a decreased quality of care and worsen outcomes for patients with pre-existing diabetes mellitus in pregnancy and GDM. Consequently, women with or at high risk of CMDs in pregnancy should receive special attention and preventive care during future emergencies and health service disruptions.

Conclusions

Two major maternal CMDs, HDP and GDM, are related to substantial short-term and long-term adverse health outcomes for women and their offspring. HDP and GDM have resulted in a large disease burden globally, especially among LMICs. Much progress has been made in understanding the disease burden, risk factors and clinical consequences of HDP and GDM. However, further research is needed to study the underlying pathophysiology, to develop accurate and reliable early screening and diagnostic tools, and to explore novel, effective and safe treatment strategies at the population level. Sensitive and reliable diagnostic criteria or classification lay a solid ground for epidemiology and clinical research. In addition to clinical management, a multilevel public health strategy is required to ameliorate the disease burden and to address the health inequities related to maternal CMDs.

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Z.A.B. and L.J. researched data for the article. Z.A.B., L.J., K.T. and P.v.D. contributed substantially to discussion of the content. All authors wrote the article. All authors reviewed and/or edited the manuscript before submission.

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