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Adversity, adiposity, nutrition and metabolic well-being in multi-ethnic Asia

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Obesity, diabetes and cardiovascular disease are rising rapidly in Asia. Population-based data consistently show that Asians are at higher risk for these non-communicable diseases than their European counterparts, especially when living in urban and migrant settings. Contrary to initial hypotheses, genetic susceptibility factors only partially explain globally divergent health outcomes. In this Perspective, we discuss potential additional mechanisms to explain this divergence. We review the global disparities in the cardiometabolic disease burden and the role of genetic variation. We then summarize potential pathways linking prenatal and postnatal adversity with unfavourable nutrition, increased adiposity and altered metabolic well-being in Asian populations. In parallel, molecular epidemiological studies are providing insights into how life-course exposures and environmental adversity intersect with adverse nutrition to establish the functional genomic changes that may drive cardiometabolic risk in global Asian populations. We highlight opportunities in precision health studies to advance Asian health through the identification of underlying aetiology critical to the development of effective interventions to promote and maintain metabolic health in current and future generations of Asian individuals worldwide.

Over the past three decades, the global distribution of type 2 diabetes (T2D), hypercholesterolaemia, hypertension and cardiovascular disease (CVD) has been progressively moving towards the emerging market economies of the Asia-Pacific region[1–3]. The countries of the East, South and Southeast Asia regions (the UN definition of Asian subregions defines 'East Asian' as Chinese and other East Asian, 'South Asian' as Indian and other South Asian, and 'Southeast Asian' as Malay and other Southeast Asian ethnic groups) are now home to 296 million people living with diabetes[4], and this number is predicted to increase to 412 million by 2045 (ref. 5). Mean levels of blood pressure and total cholesterol in the population have also been rising[2]. In keeping with this, the contribution of CVD to annual mortality in Asia has grown from 20% in 1990 to 45% in 2021 (ref. 6). These figures contrast the improvements in cardiovascular risk and falling rates of CVD observed in Europe over the same period[7] (Fig. 1a).

Global disparities in the cardiometabolic disease burden

Compared to Europeans, East and South Asian individuals appear to develop T2D at lower body mass index (BMI) levels[8], with weight gain promoting greater adverse metabolic responses in South Asian compared to European men[9]. There are few comparable data for Malaysia, Indonesia or other Southeast Asian countries. Contemporary population studies also show striking differences in metabolic risk between the Asian ethnic groups, even when living in a common environment. CVD mortality appears highest in East Asians (Fig. 1a). By contrast, there is a threefold higher prevalence of T2D among people of South Asian and Southeast Asian ethnicity backgrounds compared to East Asian people when they live side by side in the city state of Singapore[10], as well as in Malaysia[11]. The prevalence of prediabetes is also elevated among Southeast and South Asian compared to East Asian migrants

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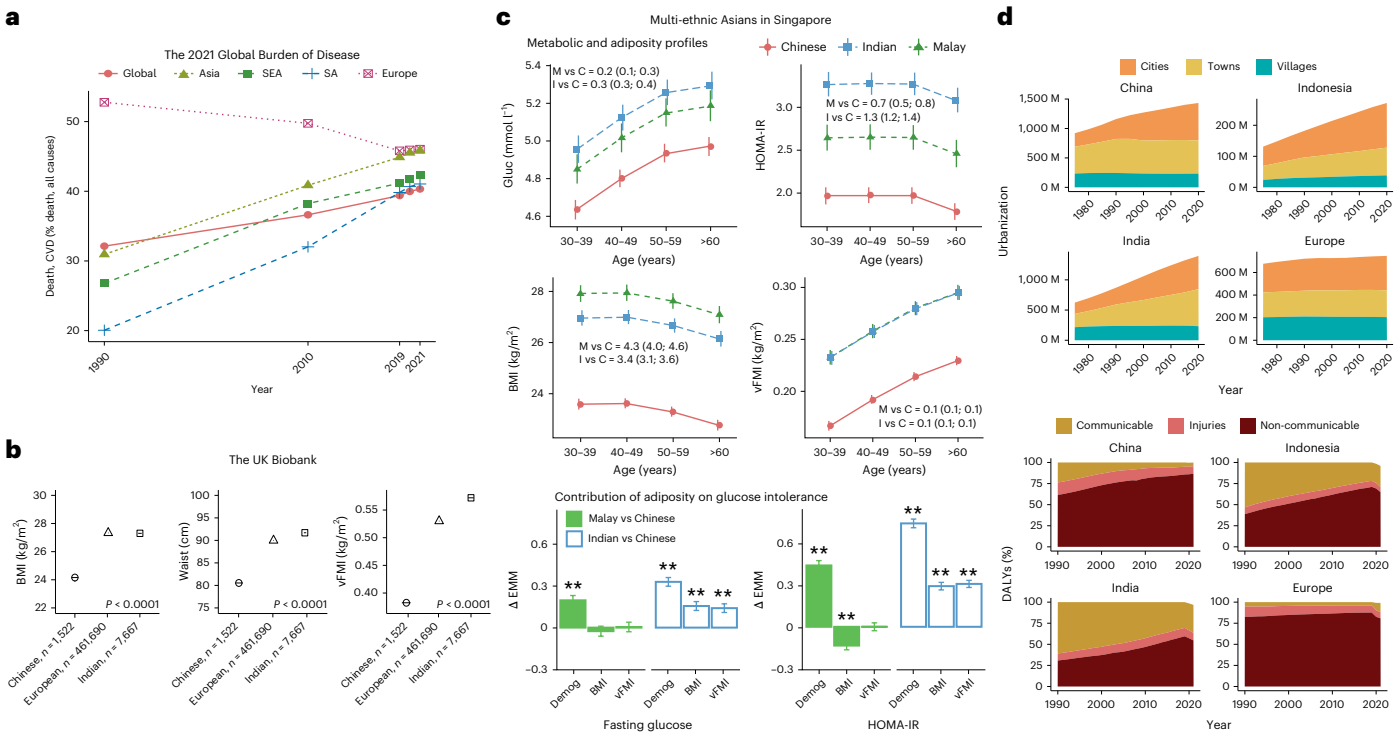

Fig. 1 | An overview of the global and regional disparity in the cardiometabolic health burden. a, The global and regional proportion of mortality of CVD to mortality of all causes from 1990 to 2021. The 2020 and 2021 data include the COVID-19 pandemic, which may affect CVD mortality estimates[6,40]. **b**, The comparison of overall and visceral adiposity across individuals of Asian versus European ancestries in the UK (UK Biobank-approved research ID 43769). BMI and visceral fat mass index (vFMI) are expressed in kg/m^2, and waist circumference is in centimetres. Data shown as mean (95% confidence interval, CI). **c**, A comparison of representative metabolic and adiposity parameters across Chinese, Indian and Malay individuals living in shared environments in Singapore as part of the PRECISE-SG100K study[10], and the partial contribution of adiposity on the elevated burden of glucose dysregulation in Indian individuals. I vs C., Indian versus Chinese; M vs C, Malay versus Chinese, expressed as mean difference (95% CI). **d**, The longitudinal trend of urbanization and disease burden in representative Asian countries, compared with Europe. The urbanization dataset was downloaded from the European Commission[41] and Our World in Data. The global disease burden dataset was obtained from Our World in Data[42] and the Institute for Health Metrics and Evaluation[40]. 'Europe' is based on the World Health Organization definition across datasets. Communicable diseases include communicable, maternal, neonatal and nutritional diseases. The urbanization reflects domestic migration; the dataset excludes emigration that resulted in the global Asian diaspora. EMM, estimated marginal means; Gluc, fasting glucose; HOMA-IR, homeostatic model assessment for insulin resistance; SA, South Asia; SEA, Southeast Asia. vFMI was quantified by dual X-ray absorptiometry whole-body scan. Panel **c** adapted with permission from ref. 10, Elsevier.

living in the USA[12] and Canada[13]. Southeast and South Asian individuals living in Asia or abroad also have raised adiposity, blood pressure and cholesterol levels, compared with East Asian people[10,11] (Fig. 1b). The increasing disease burden in Asia over the past three decades contrasts starkly with falling incidence for diabetes and CVD in the USA and Europe (Fig. 1d).

Rising adiposity has been most marked among Asian people living in urban and migrant settings, but is now evident, and transforming health outcomes, in traditionally rural regions[14]. Excess adiposity in visceral deposits appears to have a particularly important role in cardiometabolic risk. Visceral adiposity is causally linked to insulin resistance, atherogenic dyslipidaemia, adipocytokine activation and the development of diabetes and atherosclerosis[15]. Visceral adiposity levels increased in all regions of the world over the past two decades[16], and increased visceral adiposity has made a major contribution to the secular changes in global cardiometabolic risk[17]. Anthropometric and imaging studies, including dual X-ray absorptiometry[10] and computed tomography[18] analyses, show a predisposition to visceral fat deposition in Asian populations, with evidence for higher total and visceral fat composition compared to Europeans at similar BMIs. Excess visceral fat in Asian populations closely parallels their increased prevalence of diabetes and related metabolic disturbances[10] (Fig. 1b,c). Excess adiposity explains an important fraction of the divergent metabolic health outcomes between Asian groups[8].

Genetic variation and the increased cardiometabolic risk in Asia

The presence of systematic differences in metabolic outcomes for Asian people, which are evident in diverse environmental settings, has underpinned the hypothesis that there may be genetically determined differences in susceptibility to diabetes, possibly reflecting adaptation to historic environmental pressures. This includes the classic 'thrifty gene' hypothesis[19], which suggests selection for genomic variation that enables survival through periods of low food abundance. Although an intriguing concept, such thrifty genes have proved elusive. Large-scale genetic association studies have identified thousands of common and rare variants that contribute to adiposity, CVD and diabetes and to their related endophenotypes[20–22]. However, the genetic susceptibility factors identified are typically cosmopolitan and shared across populations. For example, the most recent trans-ethnic T2D genome-wide association study (GWAS) study identified 1,289 genetic loci associated with disease, of which just six appear to be specific to Asian ancestries, and with none being specific to South Asian ancestries[23]. Furthermore, these cosmopolitan genetic variants show no evidence for a systematic increase in effect allele frequency, effect size or effect allele frequency weighted by effect size for T2D among Asian ancestries compared to European ancestries, or between Asian ethnic groups[23–25].

Polygenic risk scores (PRSs) are an alternative approach to inclusion of both common and rare genetic variants, into a summative

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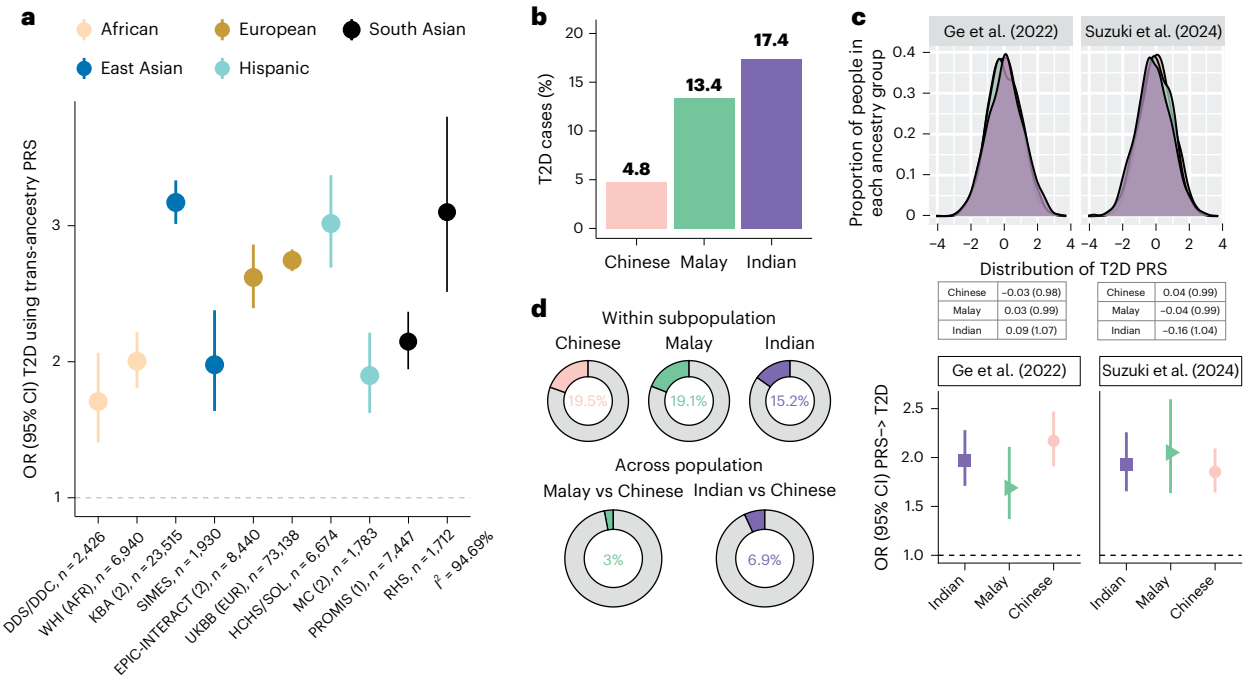

Fig. 2 | Overlaps of PRSs for T2D across global and regional ancestries. a, The odds of T2D using trans-ancestry PRSs across ten ancestry-specific cohorts, two per geographical region, recreated using supplementary tables 2 and 19 from Mahajan et al.[25]. From left to right, African: DDS/DDC, Durban Diabetes Study and Durban Diabetes Case Control; WHI, Women's Health Initiative. East Asian: KBA, Korean Biobank Array from the KoGES Consortium; SIMES, Singapore Malay Eye Study. European: EPIC-INTERACT, European Prospective Investigation into Cancer and Nutrition; UKBB, UK Biobank. Hispanic: HCHS/SOL, Hispanic Community Health Study/Study of Latinos; MC, Mexico City. South Asian: PROMIS, Pakistan Risk of Myocardial Infarction Study; RHS, Ragama Health Study. Heterogeneity test (I^2) was weighted by cohort size and adjusted for ancestral group and mean BMI of T2D cases per cohort. **b**, T2D prevalence in the PRECISE-SG100K study in Singapore[10]. **c**, The T2D PRS distribution using data from Ge et al.[27] (T.H.M., P.R.J. and J.C.C, unpublished data) or Suzuki et al.[23], expressed as a standardized z-score, and the odds of T2D PRSs in the PRECISE-SG100K study. **d**, Population attributable risk of T2D PRSs in Malay and Indian ethnic groups using data from Suzuki et al.[23], quantified by comparing individuals with top and bottom quintiles of the T2D PRSs, in contrast with the population attributable risk of T2D PRSs to the ethnic differences in T2D burden (Chinese versus Malay, Chinese versus Indian). OR, odds ratio. Panel **b** adapted with permission from ref. 10, Elsevier.

measure of genetic risk in individuals and populations. PRSs derived from multi-ancestry data provide superior disease prediction than models based on a single ancestry[26]. Emergent data show that trans-ethnic PRSs for diabetes predict diabetes risk similarly in non-African global ancestral groups, including European, South Asian and East Asian populations[27]. PRSs for T2D also do not differ systematically between Asian ethnic subgroups, despite their documented variation in diabetes prevalence[28]. Based on observed values for PRSs, and their associated risk ratios, the differences in genetic background do not explain more than a small fraction of the difference in disease burden between Asians and Europeans[25,28] (Fig. 2), or between Asian ethnic groups (Fig. 2d). Interestingly, partitioning of polygenic risk into components does suggest greater genetic predisposition towards lipodystrophy in East Asians[24], and lipodystrophy and β-cell insufficiency in South Asians, as pathways to T2D at lower BMI[29]. Thus, although genetic variation is an important determinant of T2D risk within each population group, our observations argue against genetic variation as a strong determinant of the major differences in risk between populations.

An important limitation of this Perspective is that current genome sequencing programmes relying on short-read sequencing may be inaccurate in complex regions such as repetitive DNA sequence and structural variation[30]. It does remain possible that this 'dark genome', the section of the genome that is not well assessed by short-reading sequencing, might also contain previously uncharacterized genes, gene variants of regulatory features that are both common and of high effect size. Long-read sequencing programmes of large-scale population samples are in progress in the USA, UK and Asia, and may provide useful insights on this key question[30–32].

Adverse diet underpins metabolic dysregulation in Asians

The rapid changes in population health currently observed in Asian communities highlight a key role for modifiable environmental and behavioural exposures as determinants of the rising burden of chronic disease. This view is supported by data from the Global Burden of Disease 2021 study (GBD-2021)[33] that identify dietary risk factors as the single greatest behavioural risk factor group for CVD and diabetes in East, South and Southeast Asia (Fig. 3a,b), and in contrast to the primary contribution of cigarette smoking to CVD in Europeans. Regional differences are also apparent (Fig. 3c). In East Asia, diets high in sodium are the largest dietary risk factor for CVD (226.1 versus 2.3 disability-adjusted life years (DALYs) for high processed meat consumption; Fig. 3c), reflecting the widespread use of soy sauce in Chinese, Japanese and Korean cuisines. However, the greatest dietary risk factor contributing to CVD DALYs in Southeast Asia was the low consumption of fibre (343.4 DALYs; Fig. 3c), and in South Asia it was the low consumption of fruits (403.8 DALYs; Fig. 3c).

The nuances of Asian traditional dietary practices were often lost in the global statistics: the Asia-Pacific region is home to very high diversity of traditional dietary practices, which emphasize high consumption of grains and their fermented products, soy-based or fermented soy proteins such as tofu and tempeh, locally sourced vegetables and fruits, low intake of red meat, coarse sugar, slow cooking and

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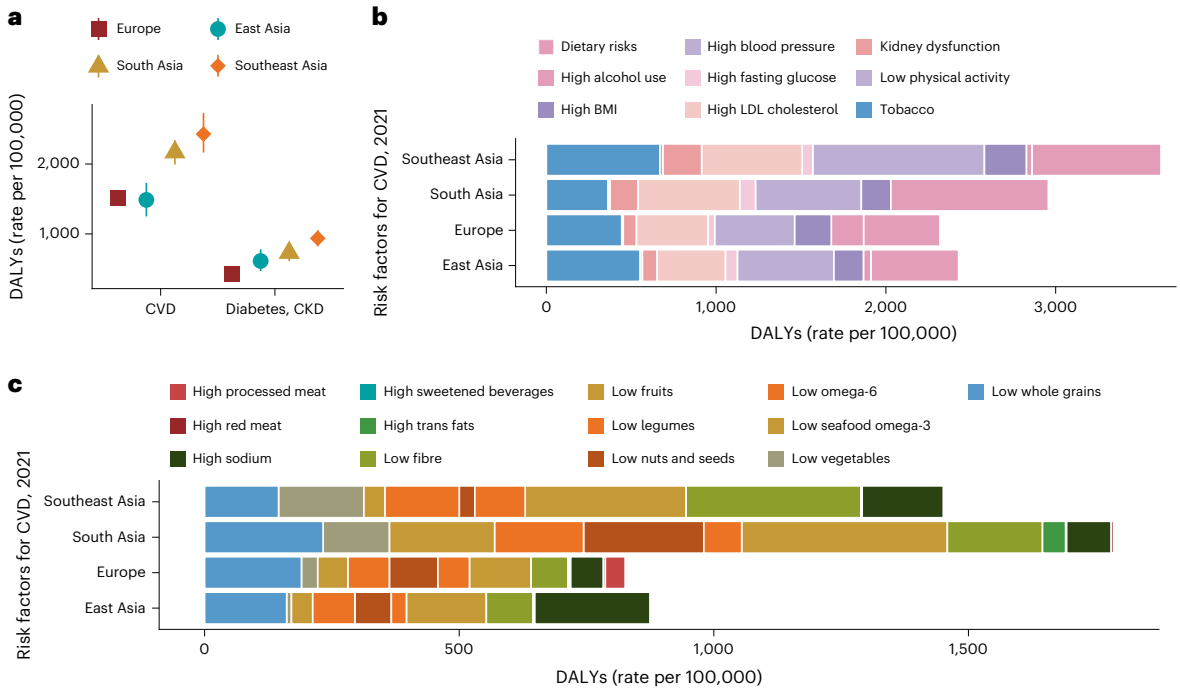

Fig. 3 | Disease risk factors contributing to the DALYs of CVD in 2021. The underlying data were extracted from the GBD-2021 study[33]. **a**, Comparison of the DALYs for CVD and diabetes and chronic kidney disease (CKD) in 2021 across regions in Asia and in Europe. **b**, The level-two breakdown of environmental and occupational, behavioural and metabolic risk factors for CVD DALYs in 2021. **c**, The level-three breakdown of dietary risk factors for CVD DALYs in 2021. All DALYs are expressed as rate per 100,000, and all panels comprise four world regions: East Asia, Europe, South Asia and Southeast Asia. LDL, low-density lipoprotein.

an incorporation of spice mixtures in both foods and beverages[34–38]. Traditional Asian dietary practices in fact incorporate the 'food as medicine' concept, historically intertwined with traditional medicine practices, including traditional Chinese medicine, Jamu and Ayurveda[34–38]. Higher consumption of traditional dietary patterns are associated with reduced obesity and a lower incidence of ischaemic heart diseases[39]. However, traditional dietary habits are becoming harder to study as they are being transformed by the rapid urbanization of Asia, accompanied by altered patterns of physical activity[40–42] (Fig. 1d). Global comparisons on the effect of specific dietary components on cardiometabolic health remain rare[43], with the findings often obscured by the collinearity between dietary habit and socio-economic deprivation[44]. Amid the broader reflection in nutrition research[45], we call for more dietary investigations in Asia-Pacific to address the regional paucity of evidence and to advance our understanding of how dietary risk factors contribute to metabolic dysregulation in Asia-Pacific.

Emergent questions for diet and metabolic health in Asia

Defining Asian-specific dietary health

One of the major challenges for global dietary data analysis is accurately quantifying diverse, culturally specific dietary practices. For example, the favourable dietary quality among South Asians as measured by the Alternative Healthy Eating Index (aHEI) in the Global Dietary Database report[46] contrasts with the high burden of T2D in this population. Established European-derived, a priori indices such as the aHEI may not fully capture the dietary variations that are common in the Southeast and South Asia; for instance, the Japanese population has high consumption of both fish and sodium, items considered as healthy and unhealthy, respectively, in the aHEI, in part reflecting the use of soy sauce for preparation and consumption of seafood in the region[47]. However, the validity and reproducibility of data-driven, a posteriori dietary patterns derived using methods such as clustering or factor analysis remained limited, owing to a lack of standardization in the types of dietary parameters included in the statistical model, choices of statistical models and criteria for evaluating validity and reproducibility[48]. This raises a critical question: how can current dietary assessment frameworks better account for regional dietary practices while retaining the robustness and validity required for global comparison? There is a need to develop high-quality dietary assessment frameworks that are both hypothesis driven and data driven, supported by both biological validations and prospective health outcomes, which incorporate Asian ingredients, cooking methods and consumption patterns.

Contribution of UPFs to health in Asia

Observational studies[49,50] have linked the consumption of ultra-processed foods (UPFs) with adverse health outcomes, including raised risk of T2D, CVD and mortality. This is further confirmed by a recent meta-analysis showing associations of increased UPF consumption with higher CVD risk[51]. The consumption of UPFs has also increased globally, especially in the emerging economic regions[52], albeit with regional variations. Between 2006 and 2024, the UPF sales per capita in East Asia and South and Southeast Asia have risen from 24 kg to 39 kg (~38%) and 4 kg to 11 kg (~125%), respectively, compared to a ~9% increase in North America[52]. The surge in UPF consumption is also in line with Fig. 1d. South and Southeast Asia also have the highest consumption of palm oil per capita (60% of total oil sales); palm oil contributes up to ~70% of the total ingredients in 'supermarket' UPFs[52]. Notably, Asia has had low uptake of Western-oriented, supermarket UPFs such as breakfast cereals, baked goods, spreads and carbonated soft drinks, and instead had the highest sales of ready-to-drink tea, coffee and other Asian specialty drinks[52]. This observation implies that the high palm oil consumption in Asia might have originated from unaccounted informal food sources, including street foods and other food-away-from-the-home sources that are affordable and convenient, contain suboptimal nutrition[53] and remain understudied in the Western literature.

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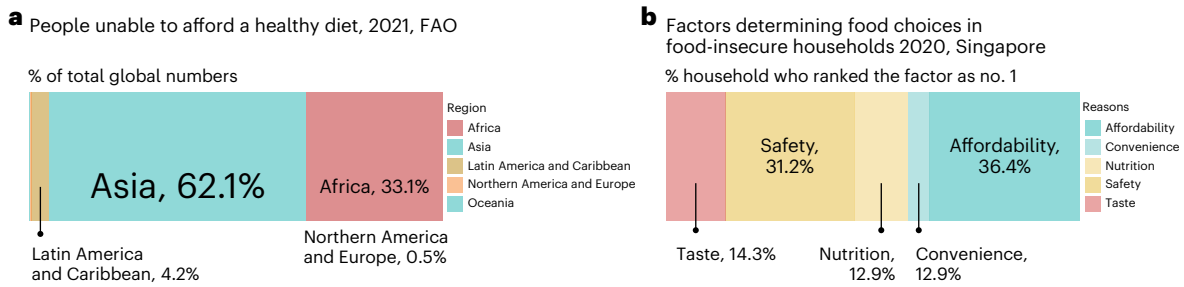

Fig. 4 | Food insecurity: the global and regional overview. a, The proportion of people who are unable to afford a healthy diet across world regions. The bar chart was recreated using the data from subsections of figure 11 of the FAO 2023 report on the state of food security and nutrition in the world[53]. **b**, The distribution of the most important factors for food choices in food-insecure households in Singapore, recreated using the data from figure 3.6 of the 2020 Hunger Report by Lien Centre for Social Innovation, Singapore[61]. Panel **b** adapted from ref. 61 under a Creative Commons license CC BY 4.0.

To date, few studies have examined the consumption of UPFs and links to adverse health outcomes in Asia[54], and there is little information to assess how Asian meals and street foods fit international food classification systems such as NOVA (Portuguese term 'nova classificação' means 'new classification'), proposed originally in Brazil and adopted in most research on UPFs to date[55]. The consumption of UPFs is also determined by the food environment, such as the density of food outlets; a recent South Asia Biobank study revealed the adverse effectof supermarket density on obesity[56]. A scoping review of 45 studies also demonstrated that eating behaviours in Southeast Asia were also driven by social, cultural and economic factors[57]. There is an urgent need to improve the understanding of Asian-specific dietary patterns and food group consumption, and the underlying eating behaviours, to unravel the relationships of these dietary exposures with the elevated cardiometabolic health burden in the Asia-Pacific region.

Food insecurity and poor dietary quality: two sides of the same coin

Food insecurity according to the Food and Agriculture Organization (FAO) is defined as "a lack of regular access to enough safe and nutritious food for normal growth and development and an active and healthy life", which may be due to the "unavailability of food and/or lack of resources to obtain food", with severity measured by the Food Insecurity Experience Scale Survey Module[58,59]. In 2022, Asia replaced Africa as the largest regional contributor to the global statistics of food insecurity, accounting for 55% (402 million) of undernourished individuals[53]. Major contributors to food insecurity in low- and middle-income countries (LMICs) include conflicts, economic pressures (including the recent effects from the COVID-19 pandemic) and weather extremes[60]. Even after accounting for the war in Ukraine in 2022, the Asia-Pacific region still accounts for 40% of global internal displacement[59], with South Asia reporting the greatest numbers of internally displaced people by natural disasters. Food insecurity driven mainly by economic shocks affects 83.9 million people globally[60]. Asia is now the highest contributor to the global statistics of people who are unable to afford a healthy diet[53] (Fig. 4a). The presence of food insecurity is highly pervasive, and evident even in stable, high-income settings. For example, despite being ranked as the most food-secure nation on the 2019 Global Food Security Index, an estimated 10% of Singaporean households experienced food insecurity at least once in the past year, especially among the minority ethnic Malay and Indian subpopulations[61].

The anticipated outcomes from severe food insecurity include an increased risk of malnutrition, driven by smaller portions, skipping meals and reduced overall food consumption. In other contexts, food insecurity can also lead to prioritization of energy-dense food sources such as UPFs, based on affordability rather than nutritional content. Affordability is a critical factor in determining food choices in food-insecure environments (Fig. 4b)[61] and globally remains the most studied food environment factor[62]. Food banks are known to have poor nutritional quality[63,64], and accessing food banks is associated with increased UPF consumption[64]. With increasing cost of living, food charities prioritized non-perishable items owing to budgetary constraints[65] and free meal programmes often serve energy-dense food owing to logistical limitation[66,67]. UPF consumption is also favoured by low-income consumers in India and Vietnam[52]. A recent meta-analysis demonstrates the association of food insecurity with 1.5 times higher likelihood of obesity[68]; food insecurity is also a risk factor for CVD outcomes[69].

Food insecurity is thus increasingly recognized as a risk factor for excess adiposity, and adverse cardiometabolic risk. The prevalence of food insecurity mirrors the latest prevalence of the underweight and obesity double burden in 2022; India, China and Indonesia are among the countries with the largest number of underweight adults globally in 2022, and paradoxically the three Asian giants also have the highest absolute number of adults with obesity[70]. Besides obesity, it is also associated with a higher risk for symptoms of depression[61,71], with greater odds in older individuals and in male individuals, potentially leading to a vicious cycle of poor physical and mental health. Food insecurity thus emerges as an important determinant of both physical and mental health, and a potential contributor to the global disparities in chronic disease burden in LMIC settings.

Early-life nutritional adversity and adverse health outcomes

Although low birth weight (LBW, defined as <2.5 kg) has decreased in the past two decades, South Asia still reports a high global prevalence of LBW (26.4% in 2015), whereas Southeast Asia has the third-highest LBW prevalence at 12.2%[72]. Adults born with LBW are at increased risk for developing chronic diseases in later life[73]. Risks of T2D are increased among South Asians with a history of LBW, implying that fetal growth retardation may adversely affect metabolic regulation[74]. Observations that LBW is more common in LMIC settings, and predicts adverse metabolic outcomes, provides a transgenerational mechanism by which food insecurity in parents might affect the health of their offspring. Future research is required to unravel the independent effects of transgenerational programming from other postnatal environmental factors.

Early-life exposures to nutrient scarcity promote maladaptive development of pancreatic β-cell mass, leading defective insulin action and glucose intolerance in later life[19,75]. South Asian infants who were born small for gestational age also have reduced lean tissues and excess visceral fat deposition, compared with European infants[76]. Genetic variants influencing birth weight are causally linked with variants predicting glycaemic and cardiovascular traits (genetic correlation ~0.4)[77]. The variants for birth weight cluster with genes implicated with T2D, *NT5C2* (for coronary artery disease and blood pressure) and *ADRB1* (for blood pressure), glucose homeostasis and insulin signalling[77].

However, the associations with PRS for LBW are similar in both infants of South Asian and European ancestries, indicating a complementary role for other epigenetic and environmental factors such as

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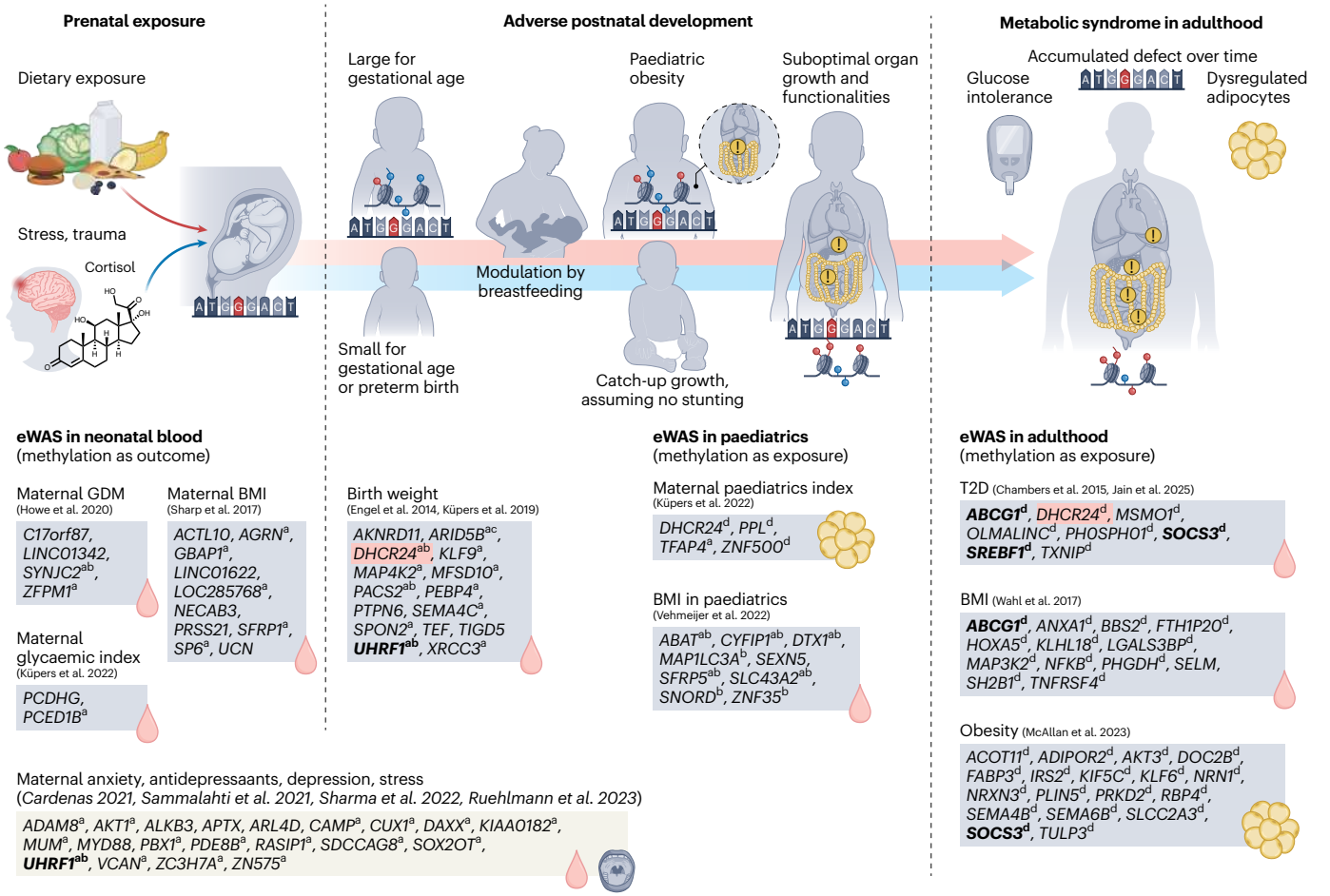

Fig. 5 | The effect of adverse prenatal and postnatal environmental exposure on disease susceptibility across the ages. Prenatal exposure might include suboptimal dietary exposure or adversity, leading to accumulated epigenetic modifications across life stages. To illustrate this, we shortlisted exemplary epigenome-wide association studies (eWAS) with $n > 1{,}000$, which investigated epigenetic markers as consequences at birth and in childhood, and as exposure in adulthood. We included key genes in eWAS of neonatal cord blood or saliva following exposure to maternal metabolic health such as BMI[98], dietary glycaemic index[99], GDM[100] or to psychological symptoms[101–104]. In childhood, we used eWAS of adipocytes following exposure to maternal glycaemic load[99], and eWAS of paediatric BMI[105]. In adulthood, we considered eWAS on blood for BMI[106] and T2D[81,107] as outcomes, and eWAS on adipocytes of individuals with obesity[108]. *UHRF1*, *SOCS3*, *SREBF1* and *ABCG1* appear more than once across study or phenotype; *DHCR24* appears across time periods. Most genes in neonatal and paediatric eWAS were also linked with T2D, adult BMI and other cardiovascular traits in the eWAS catalogue (https://www.ewascatalog.org/). Similarly, most genes in adulthood eWAS were also linked with ≥1 prenatal exposure, birth or paediatric health outcomes. ADHD, attention-deficit/hyperactivity disorder. Created in BioRender. Chambers, J. (2025) https://BioRender.com/e46cxcq.

intrauterine and postnatal nutritional environment[78]. The prevalence of hyperglycaemia in pregnancy, a marker for gestational diabetes mellitus (GDM), in South Asia was the highest globally (28.0% in 2021, compared with 12.4% in East Asian and Southeast Asian countries and 12.2% in Europe)[4]. In contrast to LBW, GDM increases birth weight and the risk of macrosomia (Fig. 5). Infants with macrosomia are also predisposed to future obesity[79] and T2D[77]. Adverse intrauterine effects of GDM on the offspring provide a further potential mechanism by which dietary adversity, obesity and T2D in adults may drive adverse metabolic health in subsequent generations (Fig. 5). Both LBW and GDM form the rapidly merging cycles of undernutrition and overnutrition[76], contributing to the double burden of malnutrition in the Asia-Pacific region[70].

Life-course exposures and environmental adversity shape metabolic pathways

The data presented above show that adversity and suboptimal nutrition may be experienced at multiple phases of the life course, and affect metabolic health in later life (Fig. 5). Molecular phenotyping studies also provide evidence of the genomic disturbances that may link unfavourable diet, metabolic dysregulation and the development of cardiometabolic disease in adults. Epigenome-wide profiling of genomic DNA reveals the presence of disturbed methylation at multiple sites that are associated with UPF consumption and other unfavourable dietary patterns[80], which precede and predict the development of T2D[81,82] and CVD[83,84]. Obesity, insulin resistance and T2D are each closely associated with perturbed methylation of *ABCG1*, which is involved in inflammatory responses to adiposity, efferocytosis (clearance of apoptotic cellular debris by macrophages or other phagocytes), cholesterol and phospholipid transport and insulin secretion[81,82]. Dysregulated methylation of *ABCG1* is also associated with circulating high-density lipoprotein cholesterol and triglycerides[85].

Mendelian randomization using suitable genetic instruments (to investigate the causality between the exposure and outcome, with less influence by confounding and reverse causation, as genetic variants are assigned randomly at conception) supports the view that

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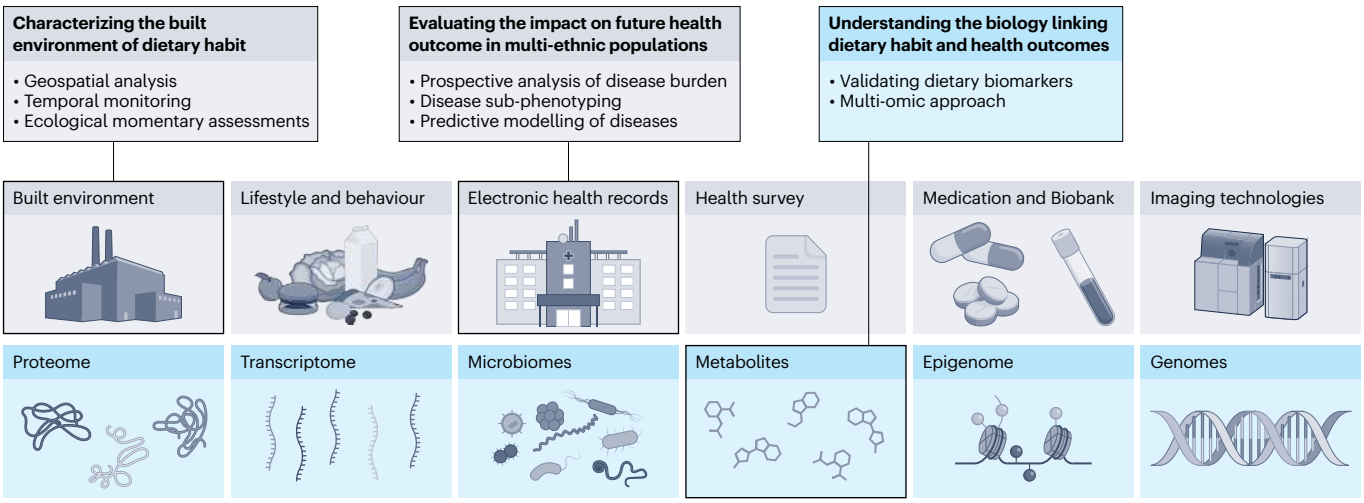

Fig. 6 | The PRECISE-SG100K study forges a roadmap for future, state-of-the-art nutritional epidemiology and nutri-omics investigation in a multi-ethnic Asian population study. The study collects an array of environmental, behavioural, physiological and clinical data. The parallel biobanking efforts with electronic health record linkage enable research ambitions including geospatial analysis, temporal monitoring, multi-omic aetiological investigations and predictive disease sub-phenotyping and modelling.

genomic regulatory features may be causally linked to the respective cardiometabolic traits, at some loci[83,86]. The identified disturbances in regulatory DNA methylation are closely linked to unfavourable dietary patterns, including lower aHEI scores[80], higher glycaemic load[87] or lower polyunsaturated fatty acids[88]. Critically, and in contrast to DNA sequence variation information, the genomic regulatory disturbances also identify and largely explain the difference in metabolic risk between populations[81,89]. Intriguingly, the methylation markers identify nuclear regulatory pathways involved in key inflammatory and metabolic pathways, including *SEL1L* (implicated in fibroblast growth factor-21)[80] and *CDCA7L*[88], providing plausible biological pathways linking food insecurity, poor diet quality and visceral adiposity to metabolic dysregulation.

Early-life exposure to stressful events or psychological insults may lead to aberrant programming of the hypothalamic–pituitary–adrenal axis in the offspring[90–92]. Pro-inflammatory markers are known to be elevated in adults with a history of childhood trauma[93]. Adverse changes in cardiometabolic traits and pro-inflammation following the dysregulation of 11β-hydroxysteroid dehydrogenases (11β-HSD, cortisol receptors) across tissue types have been reported in animal models in vivo[94,95]. Aberrant levels of placental 11β-HSD2, which regulates maternal–fetal transport of glucocorticoids, have been proposed as plausible markers for adverse programming in utero[96,97] (Fig. 5). Figure 5 compares the epigenetic markers observed in neonatal cord blood and saliva[98–104], or in childhood[99,105], following exposure to maternal metabolic or psychological symptoms with those observed in the epigenome-wide association studies of obesity and T2D in adulthood[81,106–108].

Glucocorticoid administration during preterm birth also increases the likelihood of adverse cardiometabolic symptoms in later life, including increased abdominal and subcutaneous fat distribution, raised blood pressure and insulin resistance[109,110] (Fig. 5). The rate of preterm birth remains disproportionately high in South Asia at 13.2 per 100 live births compared to the global 9.9 per 100 live births and has not been reduced in the past two decades[111]. Prenatal stressful events and depression are established risk factors for preterm birth and/or LBW[112]. There remains an evidence gap in the global prevalence of depression in Africa and Asia[113], but South Asian regions have the highest number of internally displaced people by natural disasters[59]. Such widespread adverse events could potentially contribute towards the preterm birth burden in the Asia-Pacific region, thereby linking early-life adversity to metabolic dysregulation.

Precision health studies in Asia and future research directions

The widely recognized under-representation of Asian individuals in longitudinal population datasets represents a major obstacle to understanding the genetic, functional and behavioural factors affecting health and well-being in global populations[114]. For instance, non-European individuals contributed to only 19% of participants in GWAS in 2016 (ref. 114), and in the International Health Cohorts Consortium registry there were altogether only <10 Asian population cohorts representing ~60% of the world population compared to 33 European cohorts[115]. A recent multi-ancestry GWAS on T2D is a case exemplar that increasing the proportion of the under-represented ancestral group (88,109 cases in East Asian groups[23], compared with 56,268 cases in the previous multi-ancestry GWAS[25]) could enable novel understanding on the aetiology of disease heterogeneity. But even in these very large exercises, South Asian groups still represented less than 8% of samples[23,24], and Southeast Asian groups were minimally represented. This motivates further collections of high-quality clinical and genomic data in multi-ethnic settings to improve understanding of the population-specific genetic factors that are actionable for disease, identify novel disease pathways, and address key questions on the contribution of genomic variation to metabolic health at population scale in the diverse Asian populations.

Emerging Asian cohorts that collect both epidemiological and biological samples, include BioBank Japan[116] (https://biobankjp.org/en/), China Kadoorie Biobank[117] (https://www.ckbiobank.org/), the Korean Genome and Epidemiology Study (KoGES) Consortium[118] (https://koges.leelabsg.org/), the PRECISE-SG100K study (Fig. 6; https://www.npm.sg/partners/precise-sg100k/, https://www.healthforlife.sg/), Taiwan Biobank[119] (https://www.biobank.org.tw/english.php) and the South Asia Biobank[120] (https://www.ghru-southasia.org/). These cohorts have pioneered the representation of East Asian, South Asian and Southeast Asian ancestries in various multi-ancestry GWAS and thus precision medicine research. Among these, the PRECISE-SG100K study, supported under the Singapore National Precision Medicine (NPM) initiative is a longitudinal multi-ethnic Asian cohort study that comprises people of Chinese, Indian and Malay ancestries living in a shared environment.

The marked heterogeneity in health outcomes across different Asian populations is often overlooked, and the ability to explore this for insights into aetiology and biomarker discovery is a unique feature

of the PRECISE-SG100K study[121–123]. Preliminary findings from the PRECISE-SG100K study have already enabled better appreciation of the contribution of Asian body composition pattern to health profile in three large Asian ancestral groups[10] and the discovery of metabolomic biomarkers of Asian food groups[124]. The study has also established common genetic variants (allele frequency > 1%) in these three ancestry groups[125] and an admixture-based estimation of severe recessive disorder genes[126]. The PRECISE-SG100K study has also successfully linked the research phenotypic data with comprehensive electronic health records in a secure environment[28] and is enabling programmes such as the health-driven design for cities (HD4) programme (https://www.cares.cam.ac.uk/research/hd4-project/; Fig. 6), which is focussed on understanding the upstream factors that shape health behaviours and outcomes in Asia.

Conclusion

We have summarized our perspective on potential pathways linking prenatal and postnatal adversity with unfavourable nutrition, increased adiposity and altered metabolic well-being in Asian populations. We also highlight the tremendous importance and potential opportunities for Asian population studies to provide new insights into the exposures and molecular pathways driving chronic disease. The ultimate goal is to harness these insights to deliver better cardiometabolic outcomes to current and future generations of Asian individuals worldwide.

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Author contributions

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Competing interests

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