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REVIEW

Developmental overnutrition and obesity and type 2 diabetes in offspring

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Abstract

Childhood obesity has reached pandemic proportions, and youth-onset type 2 diabetes is following suit. This review summarises the literature on the influence of developmental overnutrition, resulting from maternal diabetes, obesity, maternal dietary intake during pregnancy, excess gestational weight gain, and infant feeding practices, on the aetiology of obesity and type 2 diabetes risk during childhood and adolescence. Key goals of this review are: (1) to summarise evidence to date on consequences of developmental overnutrition; (2) describe shared and distinct biological pathways that may link developmental overnutrition to childhood obesity and youth-onset type 2 diabetes; and (3) to translate current knowledge into clinical and public health strategies that not only target primary prevention in youth, but also encourage primordial prevention during the perinatal period, with the aim of breaking the intergenerational cycle of obesity and diabetes.

Keywords Developmental programming · Lifecourse development · Obesity · Overnutrition · Review · Type 1 diabetes · Type 2 diabetes

Abbreviations

EPOCH	Exploring Perinatal Outcomes in Children
GDM	Gestational diabetes mellitus
GUTS	Growing Up Today Study
GWG	Gestational weight gain
HAPO	Hyperglycemia and Adverse Pregnancy Outcomes
HEI	Healthy Eating Index

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Introduction

The obesity pandemic has spared no age group, including young children [1]. Following in its footsteps is youth-onset type 2 diabetes, a novel paediatric condition on the rise in the USA [2] and worldwide [3]. The existence and rise in prevalence of paediatric type 2 diabetes is undoubtedly related to trends in childhood obesity given that excess adiposity is the leading risk factor for type 2 diabetes [4, 5] and emerging evidence suggest that both conditions have origins in utero [6–9]. Little remains known of specific pathways and mechanisms underlying development of youth-onset type 2 diabetes, an important first step to stemming the tide of type 2 diabetes among children and adolescents.

As depicted in Fig. 1, this review expands upon the literature surrounding developmental overnutrition, resulting from maternal diabetes, obesity, diet during pregnancy, and excess gestational weight gain, and infant feeding practices, in relation to childhood obesity and youth-onset type 2 diabetes. We start by summarising and appraising the evidence on

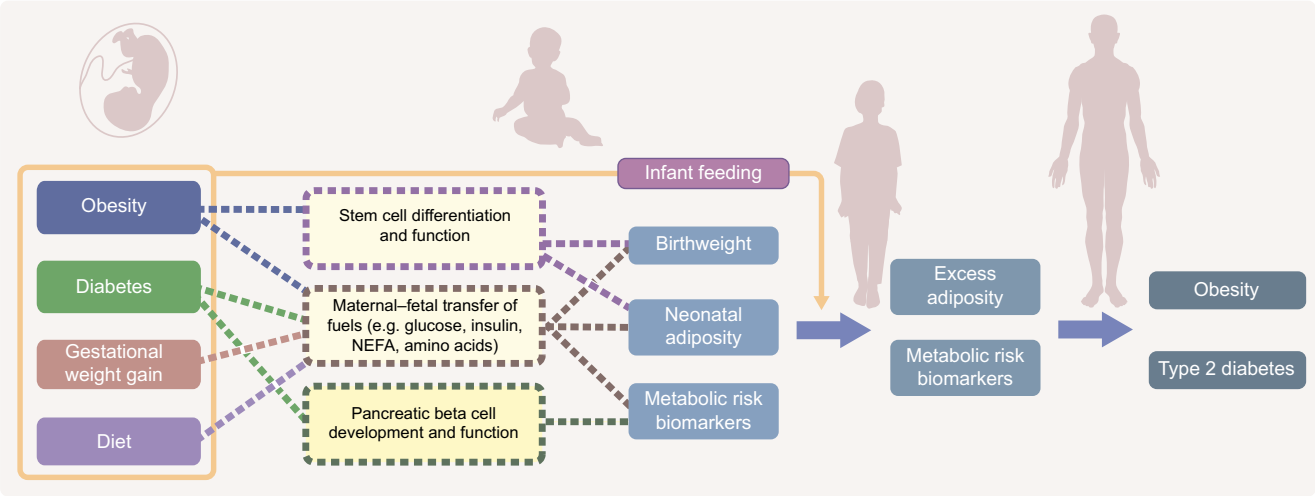

Fig. 1 Pathways through which exposure to developmental overnutrition during pregnancy (obesity, maternal diabetes, gestational weight gain, diet during pregnancy, and infant feeding) may influence the development of obesity and type 2 diabetes across the life course. Topics in boxes with a solid border are discussed in depth in this review. This figure is available as a downloadable slide

consequences of developmental overnutrition and discussing shared and distinct biological pathways that may link developmental overnutrition to obesity and type 2 diabetes in youth. We then translate current knowledge into clinical and public health strategies that not only target primary prevention in youth, but also encourage primordial preventions during the perinatal period, with the aim of breaking the intergenerational cycle of obesity and diabetes [8, 10].

Developmental overnutrition

In utero overnutrition

Maternal diabetes

Longstanding evidence links maternal diabetes to larger offspring birth size and adiposity across life, and these associations are thought to be driven by maternal fuels: hyperglycaemia and altered lipid and/or amino acid metabolism. While earlier studies evaluated maternal diabetes as a combination of type 1, type 2 and/or gestational diabetes mellitus (GDM), more recent investigations consider diabetes subtypes and degree of hyperglycaemia, which may be more appropriate.

Maternal diabetes, fetal growth and neonatal adiposity In the 1950s, Pedersen proposed the fuel-mediated teratogenesis hypothesis, which postulated that intrauterine exposure to hyperglycaemia leads to higher birthweight and future obesity and type 2 diabetes risk [6]. This hypothesis is supported by studies showing that women with pre-existing diabetes and those who develop GDM deliver infants with higher birthweight [11–13] and fat mass [14, 15]. In a study of 195 women with GDM and 220 control individuals [15], mid-pregnancy fasting glucose was the strongest correlate of newborn fat mass, in comparison with demographic characteristics, family history and maternal anthropometry [15]. Several other studies have since identified associations of maternal hyperglycaemia with offspring adiposity at birth and beyond: (1) maternal glucose levels across all of pregnancy and in the absence of diagnosed diabetes were associated with directly measured neonatal fat mass in the Colorado-based Healthy Start Study ($n = 804$) [16]; (2) mid-pregnancy oral glucose challenge test glucose levels correlated with higher birthweight among 6854 non-diabetic pregnancies in a study conducted in Texas [17]; (3) higher mid-pregnancy oral glucose tolerance test glucose levels were associated with higher birthweight among >25,000 mother–infant pairs in the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study [18]; and (4) late pregnancy dysglycaemia among non-GDM pregnancies (HbA_{1c} ≥39 mmol/mol at delivery) predicted greater offspring weight gain during early childhood and higher BMI at age 4 years among 898 mother–child pairs in Germany [19]. Together, these findings emphasise the relevance of both degree and timing of maternal hyperglycaemia—even in the absence of frank diabetes—as determinants of offspring adiposity.

Type 1 diabetes, type 2 diabetes and GDM are each associated with altered lipid metabolism [20–22], another fuel-mediated pathway through which maternal diabetes may influence newborn adiposity [23]. In the context of GDM, maternal serum NEFA and/or triacylglycerols are associated with higher birthweight [24–26]. Findings in the general population have been mixed, with some studies suggesting that the relationship between maternal lipids and neonatal outcomes differs by pre-pregnancy weight status [27–30]. In the Healthy Heart Study [16] there was a positive association of NEFA during the second half of pregnancy with birthweight independent of pre-pregnancy BMI, but not with newborn fat

mass, among 804 mother–infant pairs. There was also a positive relationship between late pregnancy cholesterol and newborn fat mass in overweight/obese women, but not among lean women. Such findings emphasise a need to better understand how specific maternal fuels, singly and in combination with other aspects of maternal health and metabolism, may trigger fuel-mediated overnutrition.

Not surprisingly, given the interplay between lipid and amino acid metabolism [31], altered maternal serum amino acid concentrations have been observed in concomitance with maternal hyperglycaemia. In a study of 67 HAPO participants, targeted metabolomics profiling of maternal serum revealed differences in concentrations of metabolites on amino acid and macronutrient degradation pathways between BMI-matched women with high (>90th percentile) vs low fasting glucose (<10th percentile) at 28 weeks' gestation [32]. In light of the interrelationships among biochemical mechanisms of nutrient metabolism, future studies interrogating comprehensive metabolite profiles of maternal blood during pregnancy will shed light on cohesive biological pathways linking maternal hyperglycaemia to offspring health.

Maternal diabetes and offspring obesity The relationship between maternal diabetes and offspring adiposity starts at birth and tracks across the life course. In a survey-based analysis of >14,000 US youth in the Growing Up Today Study (GUTS) [33], maternal GDM correlated with 40% higher odds of being overweight during adolescence (OR 1.4, 95% CI 1.2, 1.6). The estimate was attenuated after accounting for maternal pre-pregnancy BMI (OR 1.2, 95% CI 0.8, 1.7). In the Project Viva pre-birth cohort, among 366 boys aged 6–10 years old, the difference in fat mass between those born to mothers with GDM vs those born to normoglycaemic mothers was attenuated from 2.6 kg (95% CI 1.0, 4.2) to 2.0 kg (95% CI 0.4, 3.6) after adjusting for pre-pregnancy BMI [34]. Similarly, in 461 participants of the Exploring Perinatal Outcomes in CHildren (EPOCH) cohort, GDM exposure correlated with higher BMI, waist circumference, visceral and subcutaneous adipose tissue in offspring at age 6–13 years [35]. The investigators noted modest attenuation (i.e. by 14–42%) in estimates of interest after accounting for pre-pregnancy BMI, with some associations retaining statistical significance [35]. A recent investigation of >5000 youth in The Environmental Determinants of Diabetes in the Young (TEDDY) study reported higher odds of being overweight in 5-year-old offspring exposed to maternal GDM (OR 1.48, 95% CI 1.14, 1.92), type 1 diabetes (OR 1.60, 95% CI 1.16, 2.20) and type 2 diabetes (OR 7.39, 95% CI 2.46, 22.23) compared with their unexposed counterparts [36]; adjustment for maternal pre-pregnancy BMI attenuated all three estimates. Similarly, three meta-analyses reported that adjustment for maternal BMI attenuated, but did not completely abolish, associations of GDM with offspring obesity and abnormal glucose tolerance during childhood [37–39]. Taken together, the evidence suggests an independent effect of exposure to diabetes in utero on future adiposity and type 2 diabetes risk.

We note that although inclusion of maternal pre-pregnancy BMI in regression models exploring associations between GDM and offspring adiposity may partly account for genetic predisposition, such adjustment may also control for shared intrauterine mechanisms that lead to fetal overnutrition, since maternal glucose is elevated among overweight/obese women, even if they do not qualify as having diabetes. Use of appropriate analytical approaches (i.e. inverse probability weighting [40] to balance the distribution of pre-pregnancy BMI among women with and without GDM rather than simple adjustment, which may inadvertently block the effect of shared aetiology) and mechanistic studies, will help to ascertain the extent to which accounting for maternal BMI isolates associations of interest.

Maternal diabetes and offspring type 2 diabetes The longitudinal study of Pima Indians in the Gila River Indian Community [41] was one of the first studies to explore associations of in utero exposure to maternal diabetes (combined pre-existing type 2 diabetes and GDM) with subsequent type 2 diabetes in offspring. In this high-risk population, offspring of women with diabetes not only had higher birthweight [41], but also continued on a trajectory of higher weight-for-height through adolescence [42, 43] and had a tenfold greater risk of developing type 2 diabetes in adolescence and young adulthood [10]. Moreover, exposure to maternal diabetes was the single strongest risk factor for youth-onset type 2 diabetes (OR 10.4, 95% CI 4.3, 25.1) and accounted for most of the dramatic increase in youth-onset type 2 diabetes in this population over the last 30 years [44].

Investigations in lower-risk, racially diverse populations support findings from the Pima Indians. In the SEARCH for Diabetes in Youth Case–Control Study, the odds of type 2 diabetes was 7.3 (95% CI 3.2, 16.8) greater in participants whose mothers were diagnosed with diabetes during pregnancy ($n = 79$; with >90% GDM cases) than in their unexposed counterparts ($n = 190$) [45]. In addition, in utero exposure to maternal diabetes in conjunction with obesity contributed to 47% of type 2 diabetes cases in adolescent offspring of various race/ethnicities (non-Hispanic White, African American, Hispanic), suggesting that the transgenerational cycle of diabetes begetting diabetes at increasingly younger ages operates in diverse populations and race/ethnic groups. While such findings also reflect the genetic component of type 2 diabetes, the relationship between in utero exposure to maternal diabetes and future risk of type 2 diabetes is robust to adjustment for paternal diabetes and age at onset of diabetes for either parent [46]. Dabelea et al [47] showed further support for a specific intrauterine effect of maternal diabetes on offspring type 2 diabetes risk above and beyond genetics via a discordant

sibship analysis wherein the sibling born after maternal diagnosis of diabetes had threefold greater odds of type 2 diabetes than those born before diagnosis.

Pathways linking in utero overnutrition to type 2 diabetes Although excess adiposity is the leading risk factor for type 2 diabetes in adults [4, 5], whether the relationship between in utero overnutrition and youth-onset type 2 diabetes is a sole consequence of childhood obesity has garnered interest. In the Pima Indian study, acute insulin response to infused glucose was 40% lower in adults whose mothers had diabetes during pregnancy than in those whose mothers developed diabetes after delivery, despite no differences in per cent fat mass [48]. In lower-risk populations, maternal GDM has been associated with precursors of type 2 diabetes in offspring even after accounting for offspring BMI, including higher estimated insulin resistance (HOMA2-IR) among youth in EPOCH [49], and higher fasting glucose among adolescents in the Danish National Birth Cohort [50]. Similarly, in an analysis of 587 mother–offspring dyads in Denmark, Kelstrup et al found that adult offspring exposed to maternal type 1 diabetes or GDM had impaired insulin sensitivity and lower disposition index compared with adult offspring of normoglycaemic women, even after adjustment for BMI [51].

In addition to the effect of overt maternal diabetes on type 2 diabetes in offspring, a recent analysis of 4832 mother–child pairs in the HAPO Follow-Up Study revealed that the entire spectrum of maternal glycaemia (based on maternal fasting glucose levels, as well as plasma glucose levels at 1 h and 2 h post 7 g oral glucose tolerance load) was positively associated with offspring fasting glucose levels and insulin resistance at age 10–14 years, independent of maternal and child BMI and family history of diabetes [9].

Mechanisms underlying the relationship between in utero exposure to maternal diabetes and type 2 diabetes risk in offspring have been gleaned from rodent studies showing a specific detrimental effect of maternal diabetes or hyperglycaemia on offspring pancreatic beta cell development and function [52–54]. In addition, small case–control studies of mother–infant pairs with vs without GDM have noted differential expression of genes encoding the insulin receptor [55] and adiponectin [56] in cord blood, independent of maternal BMI, pointing towards epigenetic modifications of specific genes involved in glycaemic regulation as another mechanistic pathway. Further research to identify the exact mechanisms by which in utero exposure to diabetes influences risk of type 2 diabetes in offspring is needed to develop and implement effective prevention.

Maternal obesity

Vohr et al reported that maternal pre-pregnancy weight status and gestational weight gain predicted offspring fat mass at birth [57] and age 1 year [58], even among women without GDM. This positive relationship between maternal weight and offspring adiposity at birth [59] and beyond [49, 60–64] has been confirmed in numerous settings. Moreover, the consequences of pregravid adiposity are detectable across the continuum of maternal BMI and can influence offspring metabolic risk independent of offspring adiposity [64–67].

The concordance between maternal and offspring obesity can stem from genetics [68], shared environment and lifestyle [69, 70], as well as intrauterine mechanisms. The intrauterine effect of maternal obesity on offspring obesity is difficult to isolate in human studies, but animal experiments support biological plausibility. Diet-induced obesity among pregnant rodents altered offspring adipocyte metabolism to favour hypertrophy via epigenetic modifications [71–74]. Other pathways include the effect of maternal obesity on placental function [75], glycaemic regulation [76] and stem cell differentiation [77–81]. We include a brief discussion on mechanistic studies using mesenchymal stem cells in the section ‘Mechanistic studies nested within existing cohorts’; other mechanisms are reviewed elsewhere in this issue.

Maternal diet during pregnancy

Macronutrient intake Studies of maternal macronutrient intake during pregnancy generally indicate that higher energy and carbohydrate intakes and lower protein intakes are associated with higher neonatal adiposity. Specifically, greater carbohydrate intake during late pregnancy was associated with higher neonatal fat mass in a study of 222 Danish mother–child pairs [82], whereas higher protein intake during mid-to-late pregnancy was associated with lower birthweight (Project Viva [83]), neonatal abdominal adiposity (the GUSTO Study [84]) and abdominal fat mass during adolescence (a Danish cohort [85]). In the Healthy Start Study, maternal intake of all energy-providing macronutrients (total fat, saturated fat, unsaturated fat, carbohydrates) except protein was associated with higher neonatal adiposity [86].

Dietary patterns The field of nutritional epidemiology recently shifted towards evaluating dietary patterns, rather than individual foods or nutrients, to reflect real-life dietary intake [87]. In the Healthy Start Study, poor diet quality during mid-pregnancy, defined as Healthy Eating Index (HEI) score ≤57, corresponded to 0.58% (95% CI: 0.07%, 1.10%) higher fat mass in newborns [88]. A pooled analysis of two cohorts (Project Viva in the USA and the Rhea cohort in Greece) found that adherence to a Mediterranean dietary pattern during mid-pregnancy predicted lower BMI, waist circumference and skinfold thicknesses in offspring across childhood [89]. Yet, a recent study of 721 overweight/obese pregnant women reported no consistent relationship of diet quality indicators, including the HEI, carbohydrate and protein intake and total energy intake, with fetal ultrasound measurements of adiposity at 28–

36 weeks' gestation [90]. While the utility of fetal ultrasounds for assessing neonatal adiposity requires validation, these findings suggest the importance of maternal pre-pregnancy weight status beyond that of diet during pregnancy.

Gestational weight gain While gestational weight gain (GWG) is not a dietary factor per se, it is a consequence of dietary intake that contributes to the gestational milieu [91–93], albeit in conjunction with the influence of pre-pregnancy weight status, and the social, genetic and physiological changes that occur during pregnancy, discussed elsewhere [94]. Both higher GWG on a continuous scale, as well as excess GWG according to current Institute of Medicine guidelines [94], have been consistently related to greater offspring adiposity from birth [95, 96] through adulthood [66, 97, 98]. Many of these studies established this association independent of pre-pregnancy BMI and shared environment/lifestyle factors [64, 97, 98]. GWG is also positively correlated with type 2 diabetes-related metabolic biomarkers in offspring, including insulin resistance and adipocytokine profile [99, 100]. In some cases, the metabolic alterations occurred in the absence of offspring obesity [64, 76].

In addition to the impact of total GWG on offspring adiposity and metabolic profile, the timing of weight gain has repercussions. Greater weight gain assessed continuously during early pregnancy has been linked to higher offspring BMI and fat mass during childhood [101, 102], whereas GWG exceeding current guidelines during the second and third trimesters correlated with greater odds of delivering a large-for-gestational age infant [103]. These discrepancies suggest a need to examine associations of GWG timing with growth trajectories rather than weight status at distinct time points.

Of note, while it is tempting to compare the effects of pre-pregnancy BMI with those of GWG on offspring health, as was done in a recent meta-analysis [104], Gillman [105] rightly pointed out that doing so may not be appropriate given that their relationships with offspring health reflect contributions from different factors at different times across a woman's lifespan. GWG occurs during pregnancy, exerting influences on offspring health through the intrauterine environment. On the other hand, pre-pregnancy BMI represents the impact of shared genes and environmental factors between mother and child, as well as a direct influence of the in utero environment and postnatal behaviours.

Postnatal overnutrition

Breastfeeding

Exclusive breastfeeding for the first 6 months of life is recommended by the World Health Organization for its protection against infant morbidity [106], benefits to maternal health [106] and potential to reduce childhood obesity [107, 108]. Although some have expressed concern regarding the safety of breastfeeding among diabetic women given the potential for higher levels of insulin and glucose in breast milk [109], studies in diverse populations (e.g. the Pima Indian study [110] and GUTS [111]) reported protective effects of breastfeeding on offspring fat distribution, metabolic traits and type 2 diabetes risk in diabetic and non-diabetic women. Beyond supporting the safety of breastfeeding, Crume et al [112] showed that breastfeeding ≥6 months mitigated the effects of GDM exposure on adiposity at age 6–13 years, suggesting a specific protective effect of breastfeeding among high-risk offspring.

Moving from association to causation to inform clinical care and public health practice

Life course approach

The long latency period between exposure to developmental overnutrition and future obesity/type 2 diabetes necessitates thoughtful study designs and analytical approaches to study disease aetiology, to test mechanisms and to identify opportunities for intervention. Life course epidemiology conceptual models [113] are a valuable tool for these purposes. Conceptual models not only encourage researchers to consider the web of causation among key variables, but also drive the analytical strategy. By accomplishing these tasks, researchers will better understand aetiology and mechanisms, and gain insight into modifiable determinants of type 2 diabetes across the lifespan that both coincide with and occur independently of excess adiposity.

Clever study designs and analytical strategies

Certain study designs can enhance our ability to draw causal conclusions from observational data. For instance, one could minimise the impact of genetics by comparing effect sizes for maternal vs paternal BMI [114], and/or leverage within- vs between-family comparisons [115] and sibship analyses [47, 116]. In addition, new developments in statistical techniques (i.e. inverse proportional weighting of marginal structural models [117, 118]) can enhance causal inference.

Mechanistic studies nested within existing cohorts

In the Healthy Start cohort, in vitro studies of mesenchymal stem cells harvested from cord blood in a sample of study participants provided evidence that alterations in β-catenin pathways, expression of genes involved in myocyte growth, amino acid synthesis and oxidative stress link maternal obesity to newborn adiposity and weight gain during infancy [77–81]. Such findings support biological plausibility of

observational findings of the positive correlation between maternal and child obesity in this and other cohorts.

Randomised clinical trials

Most randomised clinical trials comprising interventions focused on obesogenic conditions during pregnancy have not been effective in mitigating/reducing GDM or excess GWG [119], or preventing macrosomia [119, 120]. The limited success of these trials point towards a need for interventions prior to conception or earlier in pregnancy. Pre-conception interventions may be difficult to implement among first-time mothers given that half of pregnancies are unplanned [121], and early pregnancy interventions may be similarly challenging given that most women seek prenatal care midway through the first trimester. A potential strategy is to focus on women with a history of obesity, GDM and/or excessive GWG for surveillance and interventions prior to the next pregnancy [122]. In light of several recent studies indicating the importance of the first trimester to both maternal [123] and offspring health [101, 102], interventions on maternal behaviours to moderate weight gain during the first trimester seem promising.

There is also room for improvement in the endpoints targeted by pregnancy trials. For example, directly measured neonatal fat mass rather than birthweight is likely to be more relevant to the development of obesity and type 2 diabetes. Furthermore, longer follow-up of health outcomes beyond birth is warranted to better understand the efficacy of pregnancy trials on chronic disease risk prevention.

Finally, following findings that adequate breastfeeding limits the detrimental effects of GDM exposure [112], promoting breastfeeding among diabetic women may help to reduce obesity-related conditions in high-risk offspring, hopefully breaking the intergenerational cycle of disease.

Summary and conclusions

Youth-onset type 2 diabetes is on the rise, and trends in childhood obesity only partially explain the recent appearance of a condition that was previously confined to adults. Higher maternal BMI entering pregnancy (not simply maternal obesity), maternal hyperglycaemia (even in the absence of overt diabetes), greater GWG (not only excessive GWG according to current guidelines), and greater energy intake during pregnancy are important early-life correlates of excess adiposity and youth-onset type 2 diabetes. Importantly, maternal hyperglycaemia and GDM are associated with precursors of type 2 diabetes (e.g. insulin resistance, reduced disposition index) in offspring, starting as early as late childhood, even after accounting for current body size and/or adiposity, suggesting a specific effect of maternal hyperglycaemia on pancreatic beta cell development and function. Given the overlapping nature of these aspects of developmental overnutrition, and the shared aetiology of obesity and type 2 diabetes, future studies are warranted to disentangle pathways linking specific aspects of developmental overnutrition to obesity and type 2 diabetes risk. Accomplishment of these tasks will inform timing and targets for early interventions with potential to make measurable impacts on population health.

Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

Contribution statement WP and DD conceptualised the review. WP wrote the initial draft of the manuscript, incorporated changes suggested by co-authors, and formatted the paper for publication. DD and EO provided critical intellectual feedback. All authors approved the version of the paper to be published.

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