Metabolic Imprinting and Intergenerational Cardiometabolic Risk in Human Populations: Implications for Preconception and Maternal Health

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ABSTRACT

The global rise in obesity and type 2 diabetes has been too rapid to be explained by genetic change alone, which points to developmental and environmental contributions to cardiometabolic risk. Metabolic conditions during sensitive windows, particularly preconception, pregnancy, and early postnatal life, appear to shape long-term metabolic regulation and disease susceptibility. In this narrative review, we synthesise human cohort studies, natural experiments, and experimental models, and we translate the resulting evidence into clinical and public health practice. Across human cohorts, maternal metabolic disturbances such as gestational diabetes and obesity are consistently associated with higher offspring risk of obesity, insulin resistance, and impaired glucose regulation, with adjusted estimates commonly between 1.4- and 2.0-fold. Epigenome-wide studies report differential DNA methylation in insulin-signalling, adipogenic, and energy-homeostasis pathways, lending biological plausibility, and experimental models show that transient early perturbations can durably alter metabolic physiology even after diet is later normalised. We read these converging findings as metabolic imprinting: relatively stable but potentially modifiable regulatory states, rather than deterministic germline inheritance. Set against current guidance from the ADA, FIGO, WHO, USPSTF, and ACOG, the evidence supports concrete actions across the reproductive life course, including preconception screening and weight optimisation, gestational diabetes screening and glycaemic management, appropriate gestational weight gain, and postpartum and offspring follow-up. Preconception and maternal metabolic health therefore emerge as practical, high-value targets for reducing the long-term cardiometabolic burden.

Keywords: *metabolic programming; pregnancy; gestational diabetes; obesity; epigenesis; cardiometabolic risk.*

INTRODUCTION

Population genetics alone cannot account for the rapid global rise in obesity and related metabolic disorders. Obesity prevalence has more than tripled in recent decades, and the incidence of type 2 diabetes keeps climbing across very different settings, which implies that environmental and developmental factors are central to cardiometabolic risk.[1,2,3]

Cardiometabolic disease also clusters within families and persists across generations, despite better health knowledge and public health programmes. Longitudinal cohorts repeatedly show that offspring of mothers with metabolic

disturbances, particularly gestational diabetes and obesity, carry a higher risk of obesity, insulin resistance, and impaired glucose regulation, with adjusted estimates typically 1.3- to 2.0-fold above unexposed peers.[4,5] Shared adult lifestyle alone is an unlikely explanation.

Molecular epidemiology adds plausibility. Epigenome-wide studies in mother–child cohorts find differential DNA methylation in genes governing glucose metabolism, insulin signalling, and adipogenesis in offspring exposed to adverse maternal metabolic states,[6] pointing to mechanisms that could connect early metabolic environments to long-term regulation and disease.

Developmental origins of health and disease (DOHaD) frameworks stress these early environments, yet the implications are still poorly integrated into routine cardiometabolic prevention.[7] Prenatal famine cohorts illustrate how early nutrition can leave metabolic traces detectable decades later.[8] This review uses metabolic imprinting as a pragmatic frame that draws together experimental, epidemiological, and molecular evidence, and, with an eye on clinical practice, sets out concrete preventive actions across the reproductive life course (**Figures 1** and **2**).

METHODS

We conducted a narrative review of evidence linking early-life metabolic exposures to later cardiometabolic outcomes. We prioritized systematic reviews and meta-analyses, large prospective birth and intergenerational cohorts, natural experiments such as famine cohorts, and experimental models offering mechanistic plausibility, and we drew on current clinical practice guidelines. Searches of major biomedical databases combined terms such as "metabolic programming", "metabolic imprinting", "gestational diabetes", "maternal obesity", "pregnancy", "offspring", "epigenetics", "DNA methylation", "insulin resistance", and "type 2

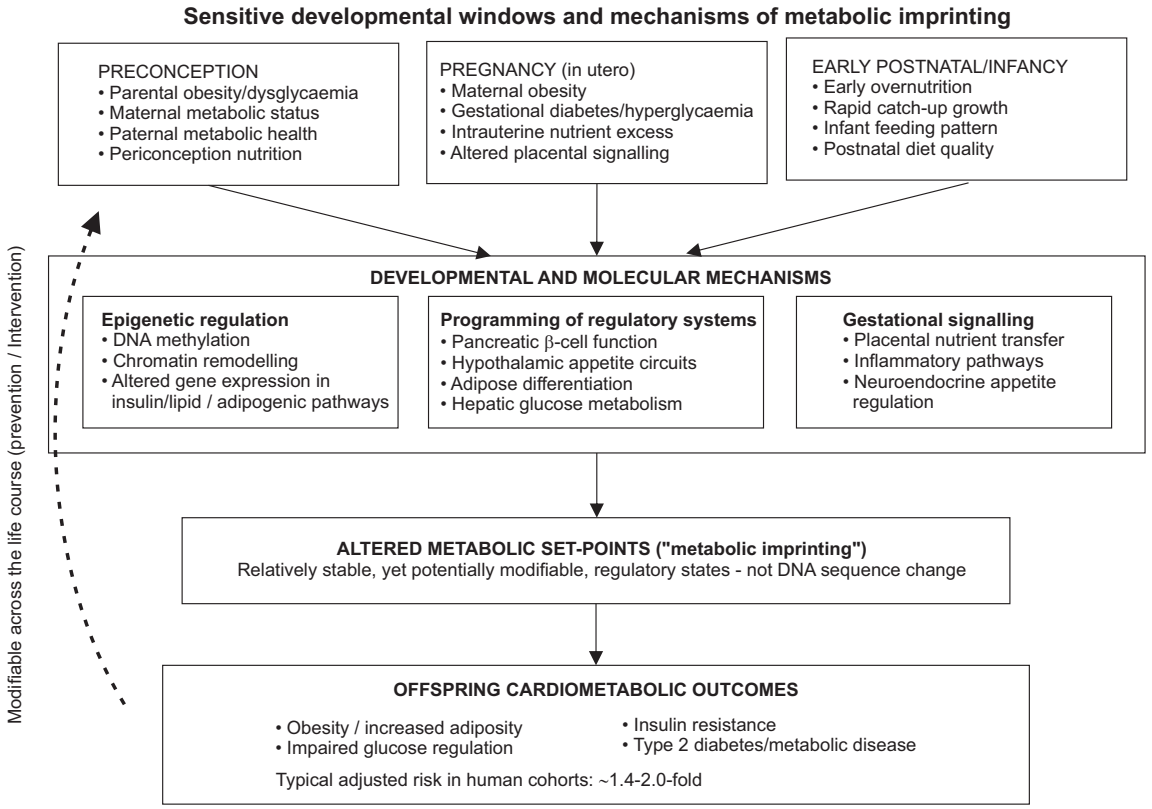

Figure 1. Sensitive developmental windows and candidate mechanisms of metabolic imprinting. Metabolic exposures during preconception, pregnancy, and early postnatal life act through epigenetic regulation, developmental programming of metabolic regulatory systems, and gestational (placental, inflammatory, and neuroendocrine) signalling to establish altered metabolic set-points. These relatively stable but potentially modifiable states are associated with offspring cardiometabolic outcomes; risk remains modifiable across the life course.

diabetes". We emphasised literature from the past decade and retained seminal studies where foundational.

CONCEPTUAL BACKGROUND: METABOLIC PROGRAMMING AND PERSISTENCE

Early metabolic environments may set durable physiological "set-points" for appetite, insulin sensitivity, energy storage, and adipose biology.[9,10,11] In fetal and early postnatal life, pancreatic beta-cell function, hypothalamic appetite circuits, adipose differentiation, and hepatic glucose metabolism all mature quickly and stay sensitive to metabolic signals, so exposures in these windows can shape both structure and later regulatory function (**Figure 1**).[1,10]

Cohort data support persistence. In utero exposure to maternal hyperglycaemia is linked to impaired glucose tolerance and insulin resistance in adolescence and adulthood, commonly 1.4- to 1.8-fold,[4] and maternal obesity tracks with higher offspring obesity and metabolic dysfunction.[12] Differential methylation in insulin-signalling, lipid-metabolism, and adipogenic genes offers one plausible route,[6] and some metabolic changes after prenatal undernutrition remain measurable decades on.[8] Persistence here is not genetic mutation or fixed inheritance. We use "intergenerational persistence" descriptively, for continuity of phenotype, since firm evidence for germline epigenetic inheritance in humans is still limited.

EVIDENCE FROM EXPERIMENTAL MODELS

Experimental work isolates early metabolic exposure under controlled conditions. Foundational models showed that early metabolic disturbance can leave persistent changes in offspring insulin sensitivity, glucose metabolism, and energy homeostasis,[13,14] establishing that a transient early exposure can carry long-term consequences. Across maternal overnutrition, high-fat diet, and metabolic-dysfunction models, offspring show higher fasting glucose, lower insulin sensitivity, more adiposity, and altered energy balance, and these phenotypes frequently outlast the exposure, persisting even after diets normalise at weaning.[15,16]

Candidate mechanisms include epigenetic regulation (DNA methylation and chromatin remodelling), altered gene expression, placental signalling, inflammatory pathways, and neuroendocrine appetite control.[17,18,19] The experimental metabolic imprinting model first characterised by Vadlamudi and colleagues frames these observations well: early exposure seems to reset physiological thresholds rather than cause immediate disease, and the resulting states stay potentially modifiable.[13,15] Animal data cannot be read straight across to humans, but they give a coherent mechanistic basis that fits the human cohort patterns.[1,20]

EVIDENCE FROM HUMAN COHORTS AND NATURAL EXPERIMENTS

Human cohorts consistently tie maternal metabolic disturbance to offspring cardiometabolic outcomes. Gestational diabetes or hyperglycaemia raises offspring risk of impaired glucose regulation and insulin resistance, often 1.4- to 1.8-fold after adjustment,[4] and epigenome-wide studies find differential methylation in insulin-signalling and adipogenic pathways in exposed offspring.[6]

Natural experiments add weight. Prenatal famine exposure is associated with higher risk of obesity and impaired glucose metabolism decades later, varying by gestational timing,[8] and metabolic-pathway methylation differences have been reported long after exposure, consistent with sensitive developmental windows.[21] Intergenerational cohorts show parent–offspring associations in metabolic traits, though these may reflect shared environment, maternal physiology, and early conditions rather than confirmed germline transmission.[22,23] Systematic reviews put the increase in offspring obesity and altered glucose regulation at roughly 1.5- to 2.0-fold with maternal obesity and gestational metabolic disturbance,[5,12] plausibly through placental function and intrauterine signalling.[23,20]

SYNTHESIS OF CONVERGING EVIDENCE

Table 1 sets representative human findings alongside the experimental picture. It is meant to show conceptual alignment, not mechanistic equivalence or proof of germline inheritance.[24]

Table 1. Conceptual alignment between human metabolic cohort studies and key features of experimental metabolic imprinting

Anchor human evidence	Core human observation	Experimental feature (conceptual)	Conceptual convergence
Gestational diabetes and maternal hyperglycaemia cohorts[4,6]	Offspring show higher risk of impaired glucose regulation/ insulin resistance; differential DNA methylation in metabolic pathways.	Early metabolic disturbance produces persistent susceptibility even after later diet normalisation[15]	Early exposure may durably shift metabolic regulation without DNA sequence change.
Prenatal famine cohorts[8,21]	Increased long-term obesity / impaired glucose metabolism; timing of exposure matters; epigenetic differences persist.	Programming depends on critical windows and can persist long after exposure[17,19]	Transient early environment can influence lifelong metabolic trajectory.
Intergenerational cohorts[21,22]	Parent–offspring associations in metabolic traits / epigenetic markers; causality uncertain	Some models show multigenerational phenotypes without mutation[19]	Human data more consistent with developmental/ environmental continuity than proven germline inheritance
Maternal obesity cohorts[5,12,23]	Higher offspring obesity and metabolic dysregulation; placental/intrauterine signalling implicated	Maternal overnutrition induces persistent metabolic change[15]	Gestational metabolic state may shape offspring susceptibility

LIMITS OF INTERPRETATION AND MODIFIABILITY

Most human evidence is observational, so associations cannot prove causation, and epigenetic signals may mark exposure or downstream processes rather than primary causes.[22,23] Persistence is also not irreversibility: later environments, maternal glycaemic control, and clinical care can shift risk, even if reported effects on long-term offspring outcomes vary.[25,26] Much of the heterogeneity across cohorts likely comes from differences in exposure severity, timing, treatment in pregnancy, and socioeconomic and postnatal context,[27,28] which fits reading metabolic imprinting as altered susceptibility rather than fixed fate. A workable framework should integrate the experimental, epidemiological, and molecular strands, explain persistent phenotypes, and stay cautious about causal and intergenerational claims.

CLINICAL AND PUBLIC HEALTH IMPLICATIONS

A metabolic imprinting lens moves prevention upstream, ahead of adult-only lifestyle strategies. Diet, activity, and behavioural programmes are widely used, yet obesity and metabolic disease keep rising, and interventions limited to pregnancy or early life tend to have modest or uneven long-term effects on offspring,[25] which fits the idea that programming set before and around conception adds to later risk.[1] Since higher offspring cardiometabolic risk tracks with maternal obesity and gestational diabetes,[5,12] maternal metabolic health is a logical, high-value target, with mechanistic support from links between maternal metabolic disturbance, placental function, and intrauterine signalling.[23,20] Guidelines increasingly treat care as a continuum from preconception to postpartum, and **Figure 2** maps the developmental evidence onto that continuum.

Preconception care

Preconception and early gestation look especially sensitive,[16,28] so preconception care is a practical entry point. The American Diabetes Association (ADA) recommends screening women with prior gestational diabetes for type 2 diabetes or prediabetes before conception, or before 15 weeks if not done earlier, and optimising glycaemia before pregnancy.[29] The American College of Obstetricians and Gynecologists (ACOG) similarly advises that obesity management start before pregnancy and continue postpartum.[30] The International Federation of Gynecology and Obstetrics (FIGO) "Think Nutrition First" recommendations place adolescent, preconception, and maternal nutrition, including folic acid and indicated micronutrient optimisation, within a life-course

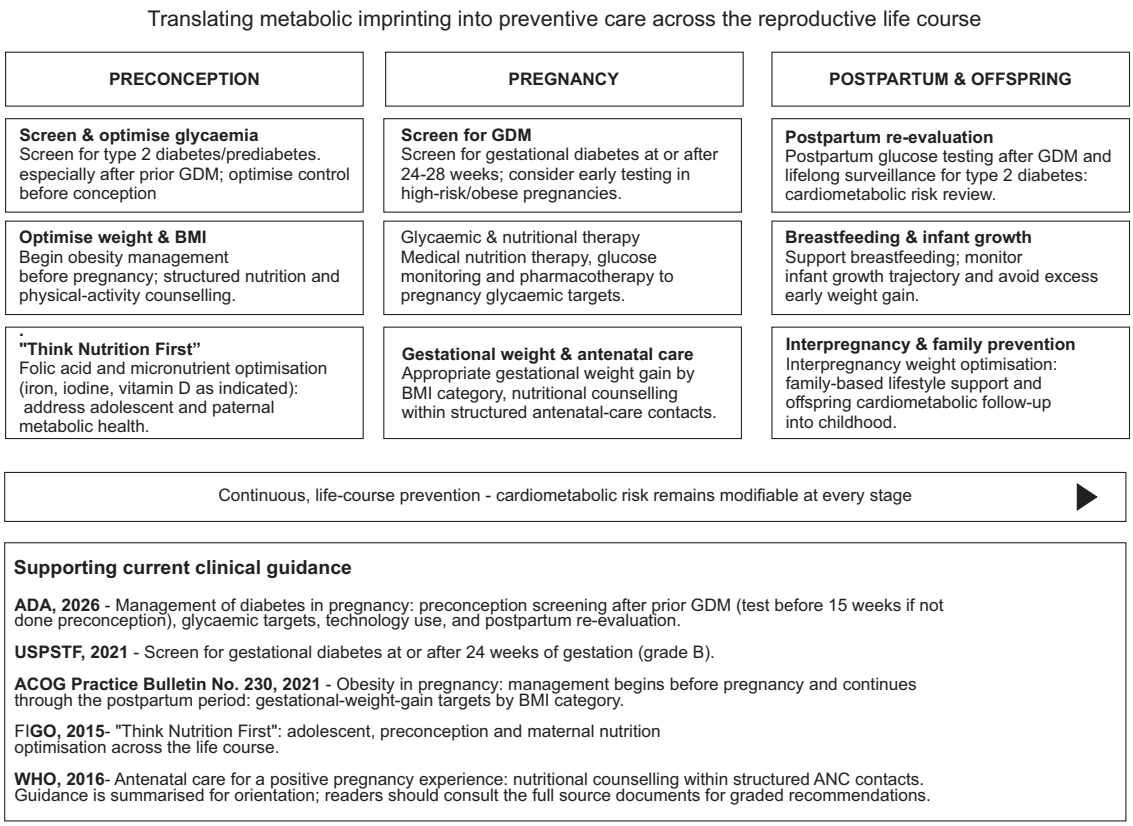

Figure 2. Translating metabolic imprinting into preventive care across the reproductive life course. Developmental evidence is mapped onto a continuum of clinical action spanning preconception, pregnancy, and the postpartum and offspring period, with supporting guidance from the ADA (2026), USPSTF (2021), ACOG Practice Bulletin No. 230 (2021), FIGO (2015), and WHO (2016). GDM, gestational diabetes mellitus; BMI, body mass index; ANC, antenatal care. The figure summarises guidance for orientation; the full source documents should be consulted for graded recommendations.

approach to intergenerational health.[31] Evidence that paternal periconception metabolic health also affects offspring widens the target beyond the mother, though the human mechanisms are still being worked out.[32,3]

Pregnancy

In pregnancy, the US Preventive Services Task Force recommends screening for gestational diabetes at or after 24 weeks (grade B),[33] with earlier testing in high-risk or obese pregnancies as the ADA and ACOG advise.[29,30] When gestational or pre-existing diabetes is present, medical nutrition therapy, glucose monitoring, and pharmacotherapy aimed at pregnancy-specific glycaemic goals lower maternal and neonatal complications.[29] Attention to gestational weight gain by body-mass-index category[30] and structured nutritional counselling within antenatal care[34] further support a healthier intrauterine environment.

Postpartum and Offspring Follow-up

The postpartum period extends the window for prevention. The ADA recommends postpartum glucose testing after gestational diabetes and lifelong surveillance for type 2 diabetes,[29] while interpregnancy weight optimisation and family-based lifestyle support can lower risk in later pregnancies and in offspring.[35,36] Breastfeeding support and tracking of infant growth address the early postnatal window that experimental models highlight.[15]

Public Health and Future Clinical Applications

At population level, folding preconception and maternal metabolic care into cardiometabolic prevention may cut long-term burden, especially where metabolic disease and social disadvantage cluster together across generations.[24,36] A developmental, intergenerational framework can sharpen prevention by naming the vulnerable windows and the points at which to act,[1,19] while keeping risk modifiable rather than predetermined.

In practice, this means building brief metabolic-risk assessment into preconception and antenatal visits, adding offspring cardiometabolic follow-up to routine care for at-risk families, and testing whether earlier, sustained action across the preconception-to-postpartum continuum yields durable intergenerational benefit.

CONCLUSION

Metabolic imprinting gives a biologically plausible way to read converging experimental, molecular, and epidemiological evidence that early-life metabolic environments leave a durable mark on metabolic regulation. Human cohorts and natural experiments link prenatal and early-life exposures to lasting cardiometabolic outcomes, and experimental models supply mechanistic plausibility for persistent change. The frame stresses developmental sensitivity and altered susceptibility, not deterministic inheritance. For practice and public health, it argues for prioritising preconception and maternal metabolic health, operationalised through current ADA, USPSTF, ACOG, FIGO, and WHO guidance across the reproductive life course, alongside continued life-course prevention. Future work should clarify mechanisms, quantify reversibility, and find interventions with durable intergenerational benefit.

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CONFLICT OF INTERESTS

The authors declare no conflict of interest.

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