Trends in Endocrinology & Metabolism

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REVIEWS

Opinion

Maternal Lifestyle Interventions: Targeting Preconception Health

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About one-third of women of reproductive age are obese, predisposing both mother and baby to unfavourable pregnancy outcomes and initiating an intergenerational cycle of chronic metabolic disorders. Here we summarise recent research on the influence of maternal metabolic health on offspring susceptibility to future cardiometabolic diseases. Current primary lifestyle approaches (i.e., diet and exercise interventions) to halt the succession of inherited and epigenetic metabolic abnormalities have met with limited success due to late implementation, poor adherence, and/or generic guidelines. In our opinion, such interventions must commence prior to conception to improve both maternal and child health outcomes, with new approaches urgently needed to increase adherence to primary lifestyle changes among reproductive-age women.

Highlights

Up to one-third of women of reproductive age are obese, predisposing their offspring to cardiometabolic diseases and initiating an intergenerational cycle of chronic metabolic disorders.

Epigenetic modifications in foetal tissue play a mechanistic role in metabolic disease programming through interaction of the pregnancy environment with gene function.

Primary lifestyle interventions (i.e.,diet and exercise) to improve maternal health are typically initiated in the second trimester, conferring limited benefits for mother and child.

Diet–exercise interventions should commence preconception.

Alternative approaches to current guidelines are urgently required to improve adherence and break the intergenerational cycle of inherited and epigenetic abnormalities of metabolism.

The Size of the Problem

Obesity and type 2 diabetes mellitus (T2D) are the biggest epidemics in human history [1] and the major challenge to health-care systems worldwide in the 21st century. Compared with 20 years ago, twice as many people are diagnosed with T2D, and the rapid increase in obesity and T2D among children, adolescents, and young adults predisposes future generations to increased risk for numerous chronic diseases [2]. Obesity is the result of complex interactions between genetic, environmental, and socioeconomic influences. While family history is a strong determinant for both obesity and T2D, genome-wide estimates suggest that only ~20% of obesity and T2D risk is attributable to fixed genomic variation [3,4], leaving a large part of heritability unexplained. Behavioural and environmental factors influence patterns of gene expression via gene–environment interactions and **epigenetic modifications** (see Glossary) and provide a molecular basis for the 'missing' heritability associated with the elevated risk for obesity and T2D [5]. In support of this premise, robust associations exist between susceptibility to life-long obesity, impaired glucose tolerance (IGT), and T2D in offspring and epigenetic modifications, confirming that metabolic dysfunction is transmitted across generations [6].

The importance of early human embryonic and foetal life for later increased risk of metabolic disturbances is captured in the **Developmental Origins of Health and Disease (DOHaD) hypothesis** [7]. Maternal lifestyle prior to and during pregnancy is, therefore, of paramount importance for the epigenetic mapping of the offspring [5] and underpins the intergenerational cycle of obesity, insulin resistance, and associated disorders (Figure 1).

Maternal Metabolism and Offspring Health: When Things Go Wrong

Maternal overweight and obesity are associated with a substantially higher risk of **gestational diabetes mellitus (GDM)** [8]. Both environmental factors and genetics contribute to the development of GDM, with up to 14% of live births negatively impacted by this condition [9]. Both maternal obesity and GDM are independently associated with adverse pregnancy outcomes and their combination has a greater impact than either one alone [10]. Maternal glucose

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intolerance in GDM results from peripheral insulin resistance and the failure of β-cell compensation and maternal insulin production to cope with the prevailing hyperglycaemia. Maternal glucose crosses the maternoembryonic interface, but insulin does not, leading to foetal hyperglycaemia, hyperinsulinaemia, and a vicious cycle of low-grade inflammation. Offspring exposed to untreated GDM*in utero* are insulin resistant with limited β-cell compensation compared with offspring of mothers with normal glycaemia during pregnancy [11]. GDM is independently associated with childhood IGT [11] and exposure to hyperglycaemia *in utero* is strongly related to childhood adiposity, including overweight/obesity, increased skinfold thickness and body fat, and greater waist circumference [12]. Even glucose concentrations lower than those diagnostic of GDM are associated with increased birth weight and elevated levels of cord-bloodC-peptide (reflective of the insulin-secretory activity of pancreatic β-cells, which modulates foetal growth), greater childhood adiposity, and elevated blood pressure, independent of maternal body mass index (BMI) [12–14].

Maternal Metabolism and Offspring Health: Why Things Go Wrong

Foetal exposure to maternal GDM programmes future risk of obesity, IGT, T2D, and cardiovascular disease [11–16]. Thus, epigenetic modifications in foetal tissue play a mechanistic role in metabolic disease programming through the interaction of the pregnancy environment with gene function. Such epigenetic modifications can occur via **DNA methylation**, **histone modification**, and/or alterations to **noncoding RNAs**.

Evidence supporting a role for hyperglycaemia-induced changes in the pattern of DNA methylation comes from studies of maternal and offspring cord blood. Kang *et al.* [17] collected maternal andcord blood samples from 16 pregnant women and their newborns, including eight exposed to GDM. They identified 200 loci and their corresponding genes in the maternal and cord blood that were differently methylated in women with GDM compared with women who were normoglycaemic. Bouchard *et al.* [18] found significant correlations between 2-h glucose concentrations after an oral glucose tolerance test and the degree of DNA methylation of the *leptin* gene in placenta on both the foetal and maternal side in women with GDM: higher glucose values correlated with a lower magnitude of methylation on the foetal side, but with a higher degree of methylation (and repression of gene transcription) on the maternal side. No such maternal–foetal pattern of methylation was found in healthy pregnant women.Others have identified multiple genome-wide differences in DNA methylation in foetal tissues from mothers with GDM versus healthy controls [19]. However, we currently have limited knowledge about the clinical relevance of these findings as most studies have been limited by small sample sizes and adjusted for few covariates.

The process of histone acetylation regulates many cellular functions, with dysregulation of histone modification being an important factor in the pathophysiology of metabolic diseases and foetal programming. Studies of the impact of maternal obesity and GDM on histone modification are few, however, and this is a fertile area for future research. By contrast, there are extensive reports of the impact of GDM on noncoding miRNAs and their gene targets [19]. Zhu *et al.* [20] profiled the expression of plasma miRNAs in mothers with GDM and healthy controls and found 32miRNAs that were differentially expressed, with the targets of these miRNAs associated with insulin resistance and poor pregnancy outcomes (i.e., preeclampsia, emergency Caesarean section, and neonatal hypoglycaemia). A study on placentas from women with either dietary controlled GDM or GDM controlled by medication and from matched controls found differential expression of miRNAs whose targets involved mitochondrial function and glucose metabolism [21]. In that study, lower protein levels of the transcriptional coactivator **peroxisome proliferator-activated receptor gamma coactivator1 alpha (PGC1-α)** were observed in both GDM groups compared with BMI-matched controls.

Glossary

Developmental Origins of Health and Disease (DOHaD) hypothesis: proposes that environmental exposures early in embryonic and foetal life exert an important influence on future disease susceptibility.
DNA methylation: the process by which methyl groups are added to the DNA molecule. Such methylation can change the activity of the DNA segment without changing the DNA sequence. DNA typically acts to repress gene transcription when located in a gene promoter.
Epigenetic modifications: changes in gene expression that can be inherited but are not caused by changes in gene sequence.
Gestational diabetes mellitus (GDM): any glucose intolerance with the onset or first recognition during pregnancy. GDM can occur at any stage during pregnancy but is more common in the second or third trimester. The hyperglycaemia typically normalises after the birth.
Histone modifications: a post-translational modification to histone proteins that can impact gene expression by altering chromatin structure or recruiting histone modifiers.
Noncoding RNAs: functional RNA molecules transcribed from DNA that are not translated into proteins. The number of noncoding RNAs in the human genome is unknown but recent transcriptomic and bioinformatic studies suggest that there are thousands of them.
Peroxisome proliferator-activated receptor gamma coactivator 1 alpha (PGC1-α): a member of a family of transcription coactivators that plays a central role in the regulation of cellular energy metabolism. PGC1-α stimulates mitochondrial biogenesis and promotes the remodelling of skeletal muscle.f

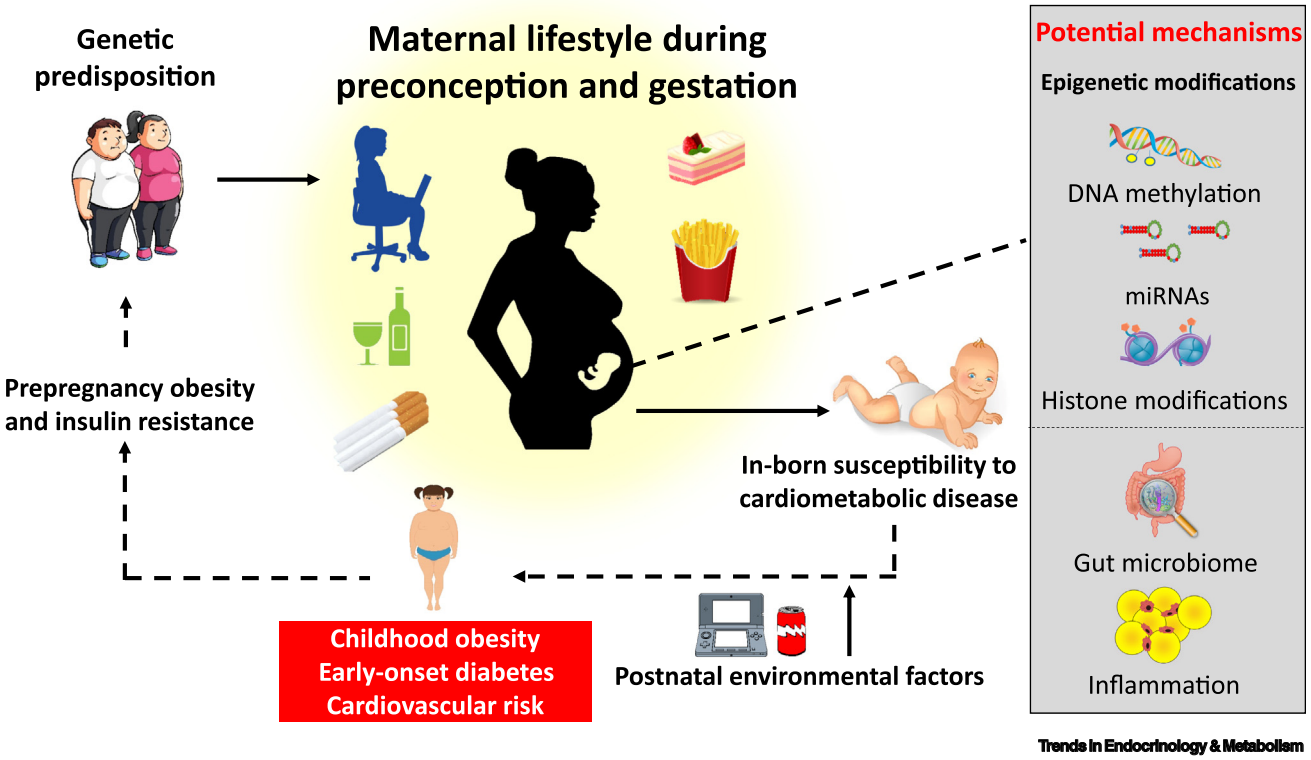

Figure 1. The Intergenerational Cycle of Chronic Cardiometabolic Disorders. Poor preconception and gestational maternal lifestyle predispose both mother and baby to unfavourable pregnancy outcomes, creating an intergenerational cycle of obesity, insulin resistance, and associated disorders.

Epigenetic modifications have their origin in poor preconception and maternal lifestyle choices with such cues exacerbating any pre-existing abnormalities in metabolism: unfavourable dietary practices combined with insufficient physical activity increase the risk of GDM-related complications. In this context, we define 'preconception' as the weeks or months from a conscious intention to conceive until conception, but acknowledge that preconception risk factors such as poor dietary quality, lack of regular physical activity, and obesity should be addressed over the preceding months and years. Diet (quality and energy content) affects multiple facets of human health and is inextricably linked to many chronic metabolic conditions. Maternal diet contributes to a foetal 'epigenetic signature' that impacts individual susceptibility to disease risk in the offspring later in life [22,23]. Diet causes profound changes in gut microbiota in pregnancy and affects the gut microbiota in newborns [24]. The initial development and maturation of the neonatal microbiota is largely determined by maternal–offspring exchanges of microbiota. An altered gut microbiota also directly influences immune cells in the gut and indirectly affects immune cells via microbial products (e.g.,lipopolysaccharides, short-chain fatty acids), impacting adipogenesis and/or insulin resistance [25]. Crusell *et al.* [26] assessed the gut microbiota composition of women with GDM in the third trimester of pregnancy and found a disrupted gut microbiota composition compared with normoglycaemic pregnant women. Differences in 'microbiota signatures' were still evident 8 months postpartum. They concluded that the composition of the gut microbiota from women with GDM, both during and after pregnancy, resembled the aberrant microbiota composition reported in non-pregnant individuals with T2D [26]. Since a growing body of evidence suggests that the period from conception through the first 2 years of life is pivotal for the formation of the gut microbiota, maternal preconception and early pregnancy

present a unique opportunity to modify the composition of the gut bacteria of both mother and offspring [24].

Too Little, Too Late: Why Current Lifestyle Interventions Are Not Working

The 2018 *Lancet* series on preconception maternal health focused scientific and media attention on the health and wellbeing of women at the time of conception, highlighting this critical period forshaping pregnancy outcomes and future maternal and child health [27–29]. The government in the UK reacted swiftly to this message, producing resources to raise public awareness on preconception care [30]. Such initiatives are to be applauded. However, there were grounds for concern. First was the limited scope of preconception strategies, with emphasis placed almost exclusively on 'improving the food environment' and little or no mention of physical activity/exercise training as a major lifestyle intervention to enhance whole-body metabolic health. Second, the scale of the initiatives was wideranging, lacking specific prescriptive recommendations that many pregnant women seek. There is limited evidence that current dietary approaches have any clinically meaningful effect on pregnancy outcomes for either the mother or the infant among women who are overweight/obese or who have already developed GDM [31,32]. Results from the majority of clinical trials show that dietary interventions are ineffective in preventing GDM [31]. There is insufficient evidence to support any single dietary intervention to offset the deleterious effects of GDM in women who already have developed this condition [32]. By contrast, preconception adherence to healthy dietary habits is associated with a lower risk of GDM [33], supporting the premise that lifestyle modification should commence before pregnancy. It is clear that merely providing women with information about dietary guidelines before or during pregnancy is totally inadequate to reduce the clinical risks associated with poor maternal metabolic health [31,32].

Regarding physical activity, European and American guidelines advocate that women should accumulate ≥150 min/week of moderate-intensity exercise (e.g.,30min of brisk walking on at least 5 days of the week) during pregnancy to help control healthy gestational weight gain and prevent GDM [34,35]. However, 85% of pregnant women fail to meet this recommendation [36]. Randomised controlled trials with a focus on exercise training in overweight/obese women during pregnancy consistently report disappointing outcomes, with little effect of exercise on maternal glycaemic control, gestational weight gain, and/or infant outcomes [37–40]. Reasons for the trivial effects in these trials are a combination of pre-existingIGT, low pre-pregnancycardiovascular fitness, and poor adherence to exercise. The exercise prescription in most studies encompasses 2–3 h of weekly moderate-intensity training, but <50% of women adhere to such protocols [41,42]. Barriers to physical activity during pregnancy include 'a lack of time','having other children', a 'lack of knowledge', and, importantly, being unclear on what type of exercise is safe to undertake [43]. Of note, patterns of pre-pregnancy physical activity is an important determinant of exercise habits during pregnancy [44]. Therefore, exercise habits need to be established early, with alternative, practical strategies to current guidelines urgently needed to increase adherence.

Pregnancy is regarded as a 'teachable moment' to instil lifestyle changes, with previously inactive women being strongly encouraged to be physically active throughout pregnancy[45]. Still, we argue that it is too little and too late to initiate major lifestyle reforms during gestation. Perhaps more to the point, commencing primary lifestyle interventions much earlier will have a greater impact on maternal and offspring health outcomes [46]. In this regard, enhancing preconception health is a challenging proposition with vast potential for improvement [30]. Notwithstanding this challenge, the main goal of any intervention should be to induce rapid enhancements in maternal insulin sensitivity. Weight loss should not be the primary goal, since most women planning a

pregnancy will aim to get pregnant in a time-frame too short for substantial weight reduction. Specific diet–exercise strategies to improve insulin sensitivity are needed for women who are planning a pregnancy and these should be implemented alongside continued efforts to reverse the obesity epidemic at a population level. Below we outline two complementary primary lifestyle interventions to be initiated prior to and continued throughout pregnancy. We believe these strategies are feasible and practical and will help to break the intergenerational cycle of chronic metabolic disease states (Figure 2).

A Time to Eat and Time for Exercise

Time-Restricted Eating: A New Paradigm to Help Alleviate Disordered Metabolism

Epidemiological data demonstrate that the quality and quantity of food consumed are directly linked to human health, with current population nutrition guidelines as well as those for pregnant women emphasising food-based recommendations (i.e., the combinations and quantities of foods and nutrients consumed) as important determinants of metabolic health [47]. However, contemporary position stands make no mention of the timing of food intake during the day, which is critical for the wellbeing of an organism [48]. Objective data of the eating behaviours of women before or during pregnancy are limited [49], but recent technological advances have made it possible to capture real-time information on free-living eating patterns in humans.

Gill and Panda [50] monitored 156 adults with overweight/obesity for 3 weeks and reported that the time from the first energy intake of the day to the final eating occasion was ~15 h. There was a bias toward eating late, which was associated with reduced dietary quality, and increased intake of discretionary/comfort foods in the evening, the time at which glucose tolerance is at its nadir. Reducing the duration of food intake from >14 h/day to 10–12 h/day (time-restricted eating) for 16 weeks resulted in a 3.3-kg weight loss. There were no measures of glycaemic control in that study [50], but recent investigations of time-restricted eating report that reducing eating duration to <10 h/day improves insulin sensitivity and β-cell responsiveness [51] in men with overweight/obesity and prediabetes and lowers 24-h glucose concentrations [52] in men and

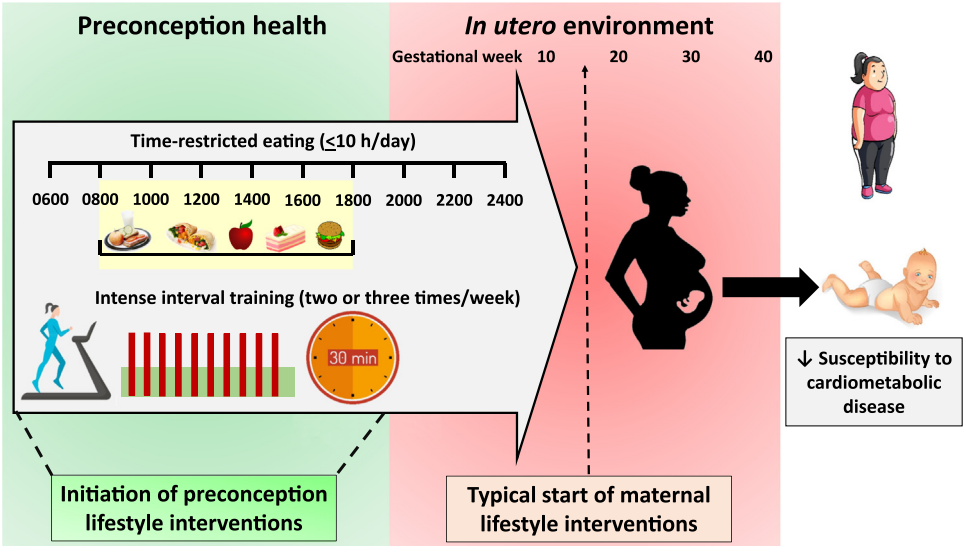

Figure 2. A Time to Eat and Time for Exercise. Novel and practical preconception and maternal lifestyle interventions could reduce the impact of maternal obesity and insulin resistance on future maternal and offspring health, thereby halting inherited and epigenetic abnormalities of metabolism.

women with overweight/obesity. These improvements in metabolic health were independent ofweight loss and/or changes to food composition. In light of this, we propose that focusing on the timing of food may be a realistic option to improve glycaemic control for women with obesity/overweight or IGT who are planning a pregnancy. Individuals with IGT who follow time-restricted eating report a lower desire to eat in the evening [51], while compared with an extended feeding pattern (14 h/day), short-termtime-restricted eating (8 h/day) improved nocturnal glycaemic control and was perceived as a practical dietary strategy in men with overweight/obesity [53]. Thus, time-restricted eating may offer a feasible and acceptable lifestyle intervention to modify eating behaviour before and potentially during pregnancy (Box 1).

High-Intensity Training (HIT): A Time-Efficient Intervention to Help Alleviate Disordered Metabolism

Exercise training is a clinically proven, cost-effective primary intervention that delays, and in many cases prevents, the burdens associated with many lifestyle-induced chronic metabolic disorders. However, the precise type and dose of exercise to accrue health benefits is contentious, with no clear consensus for the prevention of inactivityrelated chronic diseases. Until recently, guidelines by major international authorities, including the American Diabetes Association [54], recommended that adults undertake physical activity as continuous bouts lasting a minimum of 10min to maximise cardiometabolic protection. However, by ignoring bouts <10 min, such guidelines assigned no health value to briefer, high-intensity activities. For the first time, the 2018 US physical activity guidelines explicitly removed this 10-min 'minimum bout' requirement [55], acknowledging growing scientific evidence and widespread public interest in the potential for high-intensity intermittent exercise (HIT) to induce physiological adaptations that are similar or even superior to traditional endurance exercise training in healthy individuals and those with lifestyle-induced cardiometabolic disorders.

HIT is infinitely variable, but typically defined as short (≤4 min) repeated (four to ten bouts) of intense activity interspersed with 1–3min of low-to-moderate-intensity exercise (Box 1). Various HIT protocols improve cardiorespiratory fitness in a range of clinical populations including those with cardiovascular diseases and metabolic syndrome [56,57]. In many cases, the increase in cardiometabolic fitness after HIT was superior to more time-intensive, endurance-based training. Given that a lack of time is one of the most commonly cited barriers to regular physical participation at both the population level and for pregnant women [43], these findings are important. HIT has been proven to be feasible, time effective, and enjoyable among young women with obesity [58] and women during pregnancy [59], suggesting it has the potential to increase exercise adherence in these populations. When prescribed a 10-week programme comprising three

Box 1. Practical Diet–Exercise Strategies to Improve Maternal Glycaemic Control

To be commenced preconception[a] and continued throughout pregnancy, as able.

- Time-restricted eating: a daily eating 'window' of ≤10 h.
- The timing of the eating window (i.e.,the time of the first to the last eating occasion) is flexible according to personal preferences and practicalities.
- Preconception, two or three weekly sessions of high-intensity interval training (e.g.,four to ten exercise bouts lasting a minimum of 30 s and a maximum of 4–5 min separated by 1–3 min of low-to-moderate-intensity exercise) can be an alternative exercise protocol to current, prolonged exercise prescription.
- During pregnancy, two or three weekly sessions of high-intensity interval training (e.g.,six to ten exercise bouts lasting less than 60 s interspersed with 2–3min low-intensity exercise).
- A total exercise time of <60 min/week can still confer metabolic health benefits, providing exercise is of sufficient intensity (i.e.,the maximal intensity that can be sustained for the duration and number of the prescribed workbouts).

[a]We define 'preconception' as the weeks or months from a conscious intention to conceive until conception.

weekly sessions of HIT,reproductive-age women with overweight/obesity had 85–90% adherence and a 20% improvement in insulin sensitivity [60,61]. Whether HIT can show similar adherence rates and induce similar improvements in glycaemic control in 'real-life' settings remains to be established. Reductions in body fat are also greater after HIT compared with continuous, prolonged endurance training protocols in individuals with obesity [62]. Even brief (≤15 min) HIT protocols can improve glycaemic control and cardiorespiratory fitness [63]. HIT is therefore a highly potent intervention that elicits important changes in a range of clinically relevant health outcomes in reproductive-age females.

At present, there are limited data on the effect of HIT on glycaemic control in women during pregnancy. Few studies have assessed the effect of vigorous exercise on maternal and foetal wellbeing. The impact of maternal exercise on blood flow to the uterus, the placenta, and the foetus needs further investigation, but current evidence suggests that uterine and umbilical blood flow are not compromised during or following exercise [64]. Safety issues when undertaking HIT are likely to be of concern only in previously highly trained women who continue to be able to push themselves to exercise beyond a threshold intensity at which foetal wellbeing may be compromised [65,66]. By keeping exercise bouts to <1 min, maternal heart rate does not exceed 90% of maximum heart rate, and therefore such HIT protocols are within the safety zone for foetal wellbeing [66].

To date, HIT has been investigated in only a handful of clinical trials in pregnant women [59,67,68], but results from these studies indicate clinically relevant improvements in glycaemia after training. In women with GDM,6 weeks of HIT (15–60-s workbouts separated by low-to-moderate-intensity cycling, undertaken three times per week) in combination with two self-chosenhome-based exercise sessions, improved daily postprandial glucose concentrations, in the absence of changes in glucose and insulin concentrations in response to an oral glucose tolerance test [67]. Supervised HIT (30–60-s workbouts repeated six to eight times as part of a 30–45-min moderate-intensity training session, three times per week) commenced in the first trimester of pregnancy reduced the incidence of GDM twofold among overweight or obese women [68]. These findings on HIT undertaken in pregnancy, combined with the substantial body of evidence from diseased, non-pregnant populations, suggest that HIT is a feasible, safe, and effective exercise strategy that will benefit both the mother and her offspring.

Concluding Remarks and Future Perspectives

Observational studies report epigenetic modifications in offspring of women who are obese and/or have GDM, which could, in part, explain the intergenerational cycle of obesity and insulin resistance. However, the current literature regarding the causality of these findings is scarce (see Outstanding Questions). Current lifestyle interventions aimed at breaking the intergenerational cycle of cardiometabolic disorders have met with limited success. Therefore, in a targeted effort to attenuate the transmission of poor metabolic health, we propose a paradigm shift in maternal care, with a new generation of large-scale clinical intervention studies focusing on primary prevention strategies to shape pregnancy outcomes and future child health. In our opinion, such interventions ought to include novel diet–exercise approaches to increase adherence to lifestyle changes in reproductive-age women. To improve glycaemic control before/duringpregnancy, we propose individualised time-restricted eating protocols for women in the preconception period and also throughout pregnancy. In terms of sustainability, time-restricted eating offers a practical advantage over stricter energy-restricted diet interventions, given that there are no specific limitations around energy restriction or discretionary food choices. To encourage higher rates of adherence to exercise and induce the greatest beneficial clinical effects on glycaemia, we advocate high-intensityexercise training as an enjoyable and time-efficient

Outstanding Questions

Evidence from observational studies suggests that epigenetic modifications can be an underlying mechanism for the intergenerational cycle of obesity and insulin resistance. Most of the studies in this field have small sample sizes and adjusted for few covariates, and interventional studies should determine whether these associations are causal. It is clear from both healthy and diseased populations that time-restricted eating and high-intensity interval training confer multiple health benefits; however, several unanswered questions remain before we can implement these interventions in pregnant women. Important topics that merit further investigation are listed below.

The feasibility of time-restricted eating and its efficacy in improving glycaemic control in pregnancy is currently unknown. This is an area that needs to be investigated in clinical trials.

There is insufficient evidence to recommend whether early or late time-restricted eating (i.e.,early breakfast and earlier evening meal versus later breakfast and later evening meal) confers the most beneficial effect on markers of health.

Further studies are required to assess the safety, feasibility, and efficacy of vigorous exercise on maternal and foetal wellbeing. Although small-scale, highly controlled laboratory studies report high adherence and marked effects on glycaemia after HIT, whether these effects transfer to pragmatic 'real-life' settings needs to be established.

An important next step for both time-restricted eating and HIT interventions would be to move beyond efficacy and into large-scale studies of their implementation and effectiveness, including measures of long-term adherence.

Whether the combination of time-restricted eating and exercise training confer additive or synergistic effects on glycaemic control above and beyond those induced by either intervention separately remains to be determined.

intervention to be commenced prior to and continued during pregnancy. Whether time-restricted eating is feasible in pregnancy and whether it confers additive benefits on disordered metabolism above and beyond those induced by exercise training remains to be determined experimentally (see Outstanding Questions). Multidisciplinary treatment options that target both lifestyle modifications (nutrition and physical exercise interventions) constitute the most effective approaches to break the intergenerational cycle of inherited and epigenetic abnormalities of metabolism.

Author Contributions

The authors contributed equally to the literature search, figures, data interpretation, and writing.

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References

1. Zimmet, P.Z. (2017) Diabetes and its drivers: the largest epidemic in human history? *Clin. Diabetes Endocrinol.* 3, 1
2. Zimmet, P.Z. *et al.* (2014) Diabetes: a 21st century challenge. *Lancet Diabetes Endocrinol.* 2, 56–64
3. Locke, A.E. *et al.* (2015) Genetic studies of body mass index yield new insights for obesity biology. *Nature* 518, 197–206
4. Mahajan, A. *et al.* (2018) Fine-mapping type 2 diabetes loci to single-variant resolution using high-density imputation and islet-specific epigenome maps. *Nat. Genet.* 50, 1505–1513
5. Barres, R. and Zierath, J.R. (2016) The role of diet and exercise in the transgenerational epigenetic landscape of T2DM. *Nat. Rev. Endocrinol.* 12, 441–451
6. Jaeger, K. *et al.* (2017) Transmission of metabolic dysfunction across generations. *Physiology (Bethesda)* 32, 51–59
7. Gluckman, P.D. *et al.* (2010) A conceptual framework for the developmental origins of health and disease. *J. Dev. Orig. Health Dis.* 1, 6–18
8. Chu, S.Y. *et al.* (2007) Maternal obesity and risk of gestational diabetes mellitus. *Diabetes Care* 30, 2070–2076
9. Ogurtsova, K. *et al.* (2017) IDF Diabetes Atlas: global estimates for the prevalence of diabetes for 2015 and 2040. *Diabetes Res. Clin. Pract.* 128, 40–50
10. Catalano, P.M. *et al.* (2012) The hyperglycemia and adverse pregnancy outcome study: associations of GDM and obesity with pregnancy outcomes. *Diabetes Care* 35, 780–786
11. Lowe Jr., W.L. *et al.* (2019) Hyperglycemia and Adverse Pregnancy Outcome Follow-up Study (HAPO FUS): maternal gestational diabetes mellitus and childhood glucose metabolism. *Diabetes Care* 42, 372–380
12. Lowe Jr., W.L. *et al.* (2019) Maternal glucose levels during pregnancy and childhood adiposity in the Hyperglycemia and Adverse Pregnancy Outcome Follow-up Study. *Diabetologia* 62, 598–610
13. Grunnet, L.G. *et al.* (2017) Adiposity, dysmetabolic traits, and earlier onset of female puberty in adolescent offspring of women with gestational diabetes mellitus: a clinical study within the Danish National Birth Cohort. *Diabetes Care* 40, 1746–1755
14. Tam, W.H. *et al.* (2017) *In utero* exposure to maternal hyperglycemia increases childhood cardiometabolic risk in offspring. *Diabetes Care* 40, 679–686
15. Reynolds, R.M. *et al.* (2013) Maternal obesity during pregnancy and premature mortality from cardiovascular event in adult offspring: follow-up of 1 323 275 person years. *BMJ* 347, f4539
16. Lowe Jr., W.L. *et al.* (2018) Association of gestational diabetes with maternal disorders of glucose metabolism and childhood adiposity. *JAMA* 320, 1005–1016
17. Kang, J. *et al.* (2017) Genome-wideDNA methylation variation in maternal and cord blood of gestational diabetes population. *Diabetes Res. Clin. Pract.* 132, 127–136
18. Bouchard, L. *et al.* (2010) Leptin gene epigenetic adaptation to impaired glucose metabolism during pregnancy. *Diabetes Care* 33, 2436–2441
19. Moen, G.H. *et al.* (2017) Mechanisms in endocrinology: epigenetic modifications and gestational diabetes: a systematic review of published literature. *Eur. J. Endocrinol.* 176, R247–R267
20. Zhu, Y. *et al.* (2015) Profiling maternal plasma microRNA expression in early pregnancy to predict gestational diabetes mellitus. *Int. J. Gynaecol. Obstet.* 130, 49–53
21. Muralimanoharan, S. *et al.* (2016) Mitochondrial function and glucose metabolism in the placenta with gestational diabetes mellitus: role of miR-143. *Clin. Sci. (Lond.)* 130, 931–941
22. Li, Y. (2018) Epigenetic mechanisms link maternal diets and gut microbiome to obesity in the offspring. *Front. Genet.* 9, 342
23. Tamburini, S. *et al.* (2016) The microbiome in early life: implications for health outcomes. *Nat. Med.* 22, 713–722
24. Calatayud, M. *et al.* (2019) Maternal microbiome and metabolic health program microbiome development and health of the offspring. *Trends Endocrinol. Metab.* 30, 735–744
25. Cani, P.D. *et al.* (2012) Involvement of gut microbiota in the development of low-grade inflammation and type 2 diabetes associated with obesity. *Gut Microbes* 3, 279–288
26. Crusell, M.K.W. *et al.* (2018) Gestational diabetes is associated with change in the gut microbiota composition in third trimester of pregnancy and postpartum. *Microbiome* 6, 89
27. Stephenson, J. *et al.* (2018) Before the beginning: nutrition and lifestyle in the preconception period and its importance for future health. *Lancet* 391, 1830–1841
28. Fleming, T.P. *et al.* (2018) Origins of lifetime health around the time of conception: causes and consequences. *Lancet* 391, 1842–1852
29. Barker, M. *et al.* (2018) Intervention strategies to improve nutrition and health behaviours before conception. *Lancet* 391, 1853–1864
30. Stephenson, J. *et al.* (2019) Preconception health in England: a proposal for annual reporting with core metrics. *Lancet* 393, 2262–2271
31. Tieu, J. *et al.* (2017) Dietary advice interventions in pregnancy for preventing gestational diabetes mellitus. *Cochrane Database Syst. Rev.* 1, CD006674
32. Martis, R. *et al.* (2018) Treatments for women with gestational diabetes mellitus: an overview of Cochrane systematic reviews. *Cochrane Database Syst. Rev.* 8, CD012327
33. Tobias, D.K. *et al.* (2012) Prepregnancy adherence to dietary patterns and lower risk of gestational diabetes mellitus. *Am. J. Clin. Nutr.* 96, 289–295
34. ACOG (2015) ACOG Committee Opinion No. 650: physical activity and exercise during pregnancy and the postpartum period. *Obstet. Gynecol.* 126, e135–e142
35. Royal College of Obstetricians and Gynaecologists (2015) *Physical Activity and Pregnancy*, Royal College of Obstetricians and Gynaecologists
36. Gjestland, K. *et al.* (2013) Do pregnant women follow exercise guidelines? Prevalence data among 3482 women, and prediction of low-back pain, pelvic girdle pain and depression. *Br. J. Sports Med.* 47, 515–520

37. Poston, L. *et al.* (2015) Effect of a behavioural intervention in obese pregnant women (the UPBEAT study): a multicentre, randomised controlled trial. *Lancet Diabetes Endocrinol.* 3, 767–777
38. Rono, K. *et al.* (2018) Effect of a lifestyle intervention during pregnancy – findings from the Finnish gestational diabetes prevention trial (RADIEL). *J. Perinatol.* 38, 1157–1164
39. Vinter, C.A. *et al.* (2018) Lifestyle intervention in Danish obese pregnant women with early gestational diabetes mellitus according to WHO 2013 criteria does not change pregnancy outcomes: results from the LiP (Lifestyle in Pregnancy) study. *Diabetes Care* 41, 2079–2085
40. Peaceman, A.M. *et al.* (2018) Lifestyle interventions limit gestational weight gain in women with overweight or obesity: LIFE-Moms prospective meta-analysis. *Obesity (Silver Spring)* 26, 1396–1404
41. Garnaes, K.K. *et al.* (2016) Exercise training and weight gain in obese pregnant women: a randomized controlled trial (ETIP Trial). *PLoS Med.* 13, e1002079
42. Seneviratne, S.N. *et al.* (2016) Effects of antenatal exercise in overweight and obese pregnant women on maternal and perinatal outcomes: a randomised controlled trial. *BJOG* 123, 588–597
43. Flannery, C. *et al.* (2018) Enablers and barriers to physical activity in overweight and obese pregnant women: an analysis informed by the theoretical domains framework and COM-B model. *BMC Pregnancy Childbirth* 18, 178
44. Gaston, A. and Cramp, A. (2011) Exercise during pregnancy: a review of patterns and determinants. *J. Sci. Med. Sport* 14, 299–305
45. Mottola, M.F. *et al.* (2018) 2019 Canadian guideline for physical activity throughout pregnancy. *Br. J. Sports Med.* 52, 1339–1346
46. Catalano, P. and deMouzon, S.H. (2015) Maternal obesity and metabolic risk to the offspring: why lifestyle interventions may have not achieved the desired outcomes. *Int. J. Obes.* 39, 642–649
47. Kaiser, L.L. and Allen, L. (2002) Position of the American Dietetic Association: nutrition and lifestyle for a healthy pregnancy outcome. *J. Am. Diet. Assoc.* 102, 1479–1490
48. Melkani, G.C. and Panda, S. (2017) Time-restricted feeding for prevention and treatment of cardiometabolic disorders. *J. Physiol.* 595, 3691–3700
49. Bailey, R.L. *et al.* (2019) Estimation of total usual dietary intakes of pregnant women in the United States. *JAMA Netw. Open* 2, e195967
50. Gill, S. and Panda, S. (2015) A smartphone app reveals erratic diurnal eating patterns in humans that can be modulated for health benefits. *Cell Metab.* 22, 789–798
51. Sutton, E.F. *et al.* (2018) Early time-restricted feeding improves insulin sensitivity, blood pressure, and oxidative stress even without weight loss in men with prediabetes. *Cell Metab.* 27, 1212–1221.e3
52. Jamshed, H. *et al.* (2019) Early time-restricted feeding improves 24-hour glucose levels and affects markers of the circadian clock, aging, and autophagy in humans. *Nutrients* 11, E1234
53. Parr, E.B. *et al.* (2020) A delayed morning and earlier evening time-restricted feeding protocol for improving glycemic control and dietary adherence in men with overweight/obesity: a randomized controlled trial. *Nutrients* 12, E505
54. Colberg, S.R. *et al.* (2016) Physical activity/exercise and diabetes: a position statement of the American Diabetes Association. *Diabetes Care* 39, 2065–2079
55. Piercy, K.L. *et al.* (2018) The physical activity guidelines for Americans. *JAMA* 320, 2020–2028
56. Tjonna, A.E. *et al.* (2008) Aerobic interval training versus continuous moderate exercise as a treatment for the metabolic syndrome: a pilot study. *Circulation* 118, 346–354
57. Wisloff, U. *et al.* (2007) Superior cardiovascular effect of aerobic interval training versus moderate continuous training in heart failure patients: a randomized study. *Circulation* 115, 3086–3094
58. Kong, Z. *et al.* (2016) Comparison of high-intensity interval training and moderate-to-vigorous continuous training for cardiometabolic health and exercise enjoyment in obese young women: a randomized controlled trial. *PLoS One* 11, e0158589
59. Ong, M.J. *et al.* (2016) Enhancing energy expenditure and enjoyment of exercise during pregnancy through the addition of brief higher intensity intervals to traditional continuous moderate intensity cycling. *BMC Pregnancy Childbirth* 16, 161
60. Almenning, I. *et al.* (2015) Effects of high intensity interval training and strength training on metabolic, cardiovascular and hormonal outcomes in women with polycystic ovary syndrome: a pilot study. *PLoS One* 10, e0138793
61. Kiel, I.A. *et al.* (2018) Women undergoing assisted fertilisation and high-intensity interval training: a pilot randomised controlled trial. *BMJ Open Sport Exerc. Med.* 4, e000387
62. Turk, Y. *et al.* (2017) High intensity training in obesity: a meta-analysis. *Obes. Sci. Pract.* 3, 258–271
63. Gibala, M.J. and Little, J.P. (2020) Physiological basis of brief vigorous exercise to improve health. *J. Physiol.* 598, 61–69
64. Skow, R.J. *et al.* (2019) Effects of prenatal exercise on fetal heart rate, umbilical and uterine blood flow: a systematic review and meta-analysis. *Br. J. Sports Med.* 53, 124–133
65. Szymanski, L.M. and Satin, A.J. (2012) Strenuous exercise during pregnancy: is there a limit? *Am. J. Obstet. Gynecol.* 207, 179.e1–179.e6
66. Salvesen, K.A. *et al.* (2012) Fetal wellbeing may be compromised during strenuous exercise among pregnant elite athletes. *Br. J. Sports Med.* 46, 279–283
67. Halse, R.E. *et al.* (2014) Home-based exercise training improves capillary glucose profile in women with gestational diabetes. *Med. Sci. Sports Exerc.* 46, 1702–1709
68. Wang, C. *et al.* (2017) A randomized clinical trial of exercise during pregnancy to prevent gestational diabetes mellitus and improve pregnancy outcome in overweight and obese pregnant women. *Am. J. Obstet. Gynecol.* 216, 340–351